CANCER INCIDENCE AND MORTALITY ATTRIBUTABLE TO CIGARETTE SMOKING AND SECONDHAND SMOKE EXPOSURE IN ITALY

Risk and impact of tobacco control strategies

Irene Possenti



Propositions accompanying the thesis

Cancer incidence and mortality attributable to cigarette smoking and secondhand smoke exposure in Italy: risk and impact of tobacco control strategies

1) Tobacco smoking and exposure to secondhand smoke significantly increase the risk of cancer, particularly nasopharyngeal, oral and pharyngeal, and breast cancer (this thesis).

2) Despite decades of tobacco control efforts, cigarette smoking and exposure to secondhand smoke remain major public health problems in Italy (this thesis).

3) A majority of Italians support the strengthening and implementation of tobacco control policies (this thesis).

4) Public opinion is not a barrier to strengthening tobacco control policies in Italy.

5) Population attributable fractions should reflect heterogeneity in exposure rather than average exposure levels.

6) Tobacco smoking remains a major cause of cancer incidence, disability, and mortality in Italy (this thesis)

7) The healthcare costs of smoking justify stronger tobacco control policies.

8) Primary prevention remains the most cost-effective and equitable approach for reducing cancer burden, and should therefore be systematically prioritised.

9) “A cigarette is the only consumer product which when used as directed kills its consumer” (Gro Harlem Brundtland).

Irene Possenti

Maastricht, 1st October 2026

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Irene Possenti
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Cancer incidence and mortality attributable to cigarette smoking and secondhand smoke exposure in Italy

Risk and Impact of Tobacco Control Strategies

DISSERTATION

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on the authority of the Rector Magnificus, Prof. Dr. Jan Smits,
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Chapter 1

Introduction

1.1 Tobacco smoking

This section provides a global overview of tobacco smoking, from its historical roots to its current health, economic, and epidemiological impact.

1.1.1 History of tobacco

The cultivation and use of tobacco, particularly the species “Nicotiana tabacum” and “Nicotiana rustica”, have deep roots in the cultures of indigenous peoples in the Western Hemisphere. Before European contact, Native American communities had utilised these plants for thousands of years, often attributing religious and spiritual significance to tobacco [1, 2]. Tobacco was cultivated by indigenous communities using specialised agricultural techniques. Communities also cured the leaves and sometimes added lime to oral mixtures to enhance nicotine absorption [3].

The introduction of tobacco to the rest of the world from the Americas can be traced back to 11 October 1492. On this date, Christopher Columbus was given dried tobacco leaves by the Arawak people, and he subsequently transported the plant back to Europe [4]. By the late 1600s, tobacco had spread worldwide through Spanish and Portuguese trade. Governments soon exploited its fiscal value, while cigars, pipes, and snuff became the main forms of consumption [1]. Key milestones in early tobacco history are summarized in Table 1.

Table 1. Chronicle of early tobacco cultivation and use [5]

Date	Event
1492	Columbus sighted the home of the Arawaks and was offered ‘dried’ tobacco leaves.
1499	Amerigo Vespucci recorded the use of chewing tobacco on an island of Venezuela.
1545	Iroquois Indians near Montreal, Canada, were found to have smoking habits.
1556	Tobacco was first grown or became known in France.
1558	Tobacco was used in Brazil and Portugal.
1559	Tobacco was used in Spain.
1560	Nicotiana rustica was used in Central Africa.
1565	Tobacco was used in England.
1600	Tobacco was introduced to Italy, Germany, Norway, Sweden, Russia, Persia, India, Indochina, Japan, China and the west coast of Africa.

1612	John Rolfe, at Jamestown, Virginia, was the first man known to grow tobacco commercially for export.
1631	Tobacco production extended to Maryland and then gradually to other areas.
1650s	Portuguese took tobacco to South Africa and other countries. Spaniards distributed tobacco to the Philippines, Guatemala and other Central and South American countries and to the West Indies. Tobacco cultivation was begun in Indonesia. Tobacco cultivation was extended in Europe.

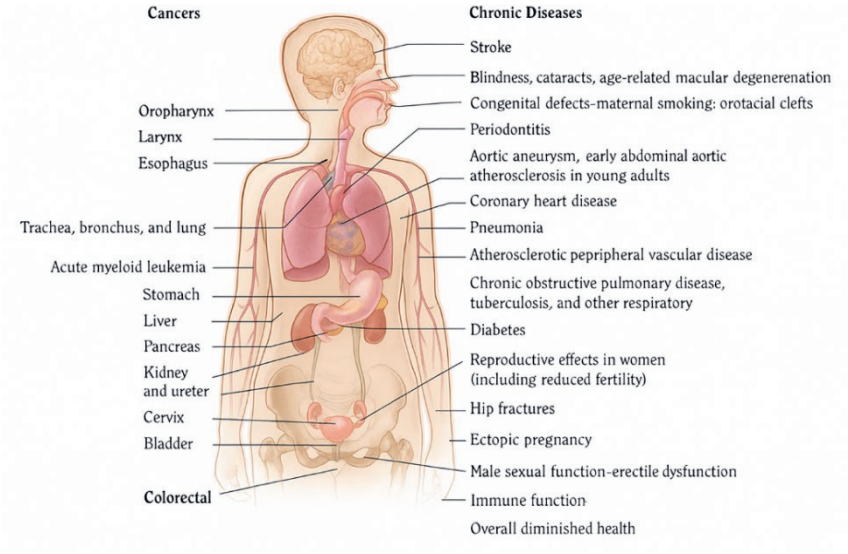
In the 19th century, advances in tobacco cultivation and processing, including the introduction of flue-cured and Burley tobacco and cigarette-making machines, reduced production costs and fuelled the rapid rise of cigarette consumption [1,5].

Concerns about the health effects of tobacco emerged in the 1920s, with growing evidence linking it to lung cancer [6]. By the 1950s, multiple studies had confirmed not only the association with lung cancer [7], as well as higher overall mortality rates among smokers [8, 9]. In response, the tobacco industry launched public relations campaigns and funded research aimed at casting doubt on these findings [1]. Concerns about the risks of passive smoking began to emerge in the 1970s [10, 11]. Once again, the tobacco industry responded by attempting to obscure and undermine the evidence [1]. By the early 1990s, tobacco smoke was recognised as a major environmental hazard, paving the way for current tobacco control policies [12,13].

1.1.2 Health consequences of tobacco smoking

Tobacco smoke contains more than 7,000 chemicals, hundreds of which are toxic and at least 70 of which are known carcinogens [14]. While tobacco use is widely recognised as a major cause of many types of cancer, its impact on health extends far beyond oncological outcomes (Figure 1).

Figure 1. The health consequences causally linked to smoking other than cancer, adapted from Surgeon General Report, 2014 [15]



One of the most devastating consequences is chronic obstructive pulmonary disease (COPD), caused by the progressive destruction of lung tissue and restricted airflow resulting from long-term exposure to tobacco smoke [16]. Smoking is the leading cause of COPD worldwide, accounting for the vast majority of cases in both middle-income and high-income countries [17]. It also exacerbates asthma, increases susceptibility to respiratory infections and impairs the lungs' natural cleaning mechanisms by damaging the cilia that line the airways and promoting the accumulation of mucus [18].

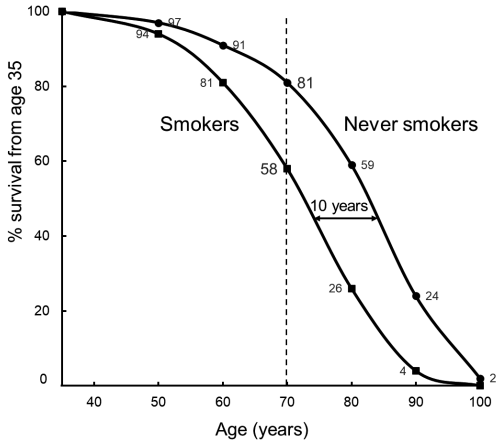
Tobacco use is also a major contributor to cardiovascular disease, promoting atherosclerosis, increasing blood pressure, and reducing oxygen transport and induces a prothrombotic state [19, 20]. This significantly raises the risk of myocardial infarction, stroke and peripheral artery disease [19].

Smoking affects fertility in both men and women, increasing the risk of pregnancy complications, reduced sperm quality and erectile dysfunction [21,22].

Other documented effects include vision problems, oral health deterioration, skin ageing, digestive disorders and an increased risk of type 2 diabetes [23–27].

The health consequences of smoking are immediate and cumulative. These consequences include increased morbidity, reduced quality of life, and premature mortality (Figure 2). Although this thesis will focus on the burden of cancer, it is important to recognise that the impact of tobacco on respiratory and cardiovascular health accounts for a significant proportion of its overall impact on public health.

Figure 2. Survival from age 35 for continuing cigarette smokers and never smokers among UK male doctors born in 1900-1930, with percentages alive at each decade of age, adapted from Doll et al., 2004 [28]



1.1.3 Economic Burden of Tobacco Use

Beyond its well-documented health consequences, tobacco use imposes a significant economic burden on societies worldwide. These costs include direct healthcare expenditures for smoking-related diseases, such as hospital care, medications and chronic disease management, as well as non-medical costs such as transportation and informal caregiving. Indirect costs arise from productivity losses due to morbidity and premature mortality, including absenteeism, presenteeism, early retirement and premature death during working age.

Globally, the economic burden of smoking is staggering. Estimates suggest that tobacco use accounted for approximately US$1.44 trillion in economic losses in 2012, equivalent to 1.8% of global GDP, with nearly 40% of this burden borne by low- and middle-income countries [29]. A comprehensive systematic review showed that smoking-related diseases were responsible for 1.5 – 6.8 % of the national health system expenditures and 0.22-0.88% of GDP of a country [30].

Understanding and quantifying these costs is essential for informing tobacco control strategies and evaluating their cost-effectiveness. Investments in prevention and cessation programs can yield substantial economic returns by reducing both healthcare expenditures and productivity losses.

1.1.4 Tobacco use worldwide

By the late 20th century, tobacco smoke had become widely recognised as a serious environmental and health hazard, prompting attention to be turned to monitoring the prevalence and impact of tobacco use worldwide. Table 2 shows the estimated prevalence of tobacco use from 2000 to 2022 across the six World Health Organization (WHO) regions, broken down by gender [31].

Table 2. Trends in prevalence of tobacco use among people aged 15 years and over, by WHO region, estimated and projected, adapted from World Health Organization, 2024 [31].

WHO Region	**2000**	**2005**	**2010**	**2015**	**2020**	**2022**
Both sexes						
African Region	17.8	15.3	13.2	11.5	10.1	9.5
Region of the Americas	26.8	23.9	21.3	19.2	17.3	16.6
South-East Asia Region	51.2	43.6	37.2	32.2	28.0	26.5
European Region	34.4	31.7	29.5	27.6	25.9	25.3
Eastern Mediterranean Region	26.9	24.3	2.0	20.1	18.7	17.9
Western Pacific Region	28.0	26.4	25.1	24.0	22.9	22.5
Global	32.7	29.3	26.4	23.9	21.7	20.9
Males						
African Region	28.7	25.1	22.2	19.7	17.6	16.6
Region of the Americas	33.9	30.4	27.4	24.8	22.6	21.7
South-East Asia Region	68.9	61.7	55.5	50.2	45.3	43.7
European Region	46.4	42.5	39.0	35.9	33.1	32.0
Eastern Mediterranean Region	43.7	40.4	37.4	34.9	33.2	31.9
Western Pacific Region	50.8	48.5	46.5	44.7	43.0	42.4
Global	49.1	45.1	41.6	38.4	35.5	34.4
Females						
African Region	7.0	5.5	4.3	3.4	2.7	2.4
Region of the Americas	19.7	17.4	15.3	13.5	12	11.4
South-East Asia Region	33.5	25.4	18.9	14.2	10.6	9.4
European Region	22.3	21.0	20.0	19.2	18.7	18.5
Eastern Mediterranean Region	10.2	8.2	6.6	5.3	4.3	4.0
Western Pacific Region	5.2	4.3	3.7	3.2	2.8	2.6
Global	16.3	13.5	11.1	9.3	7.9	7.4

The global decline in tobacco use prevalence masks substantial disparities by sex. Among men, tobacco use rates remain high despite a notable decrease: 49.1% in 2000, falling to 34.4% in 2022. Among women, tobacco use prevalence has always been lower, dropping from 16.3% in 2000 to 7.4% in 2022 [29].

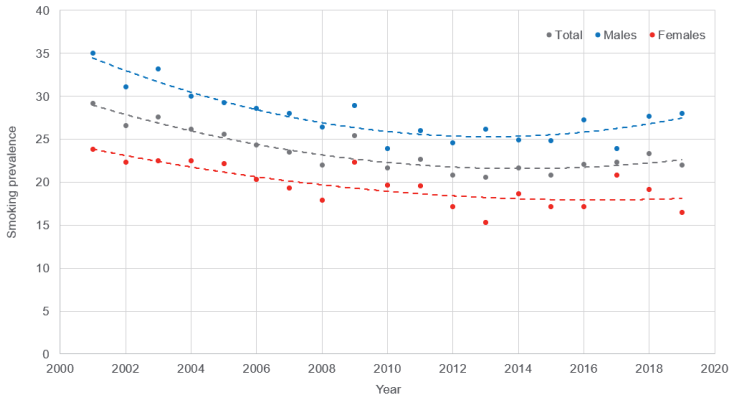
While tobacco use has declined globally, progress has been less pronounced in several European countries, including Italy, where smoking prevalence has plateaued in recent years. Understanding the Italian context is therefore essential for estimating the contemporary burden of smoking-related cancers and evaluating future tobacco control strategies.

1.1.5 The Italian context

Within the broader context of declining global tobacco use, Italy presents a case with unique trends and challenges. Over the last two decades, Italy has witnessed a substantial decline in smoking prevalence, particularly throughout the early 2000s, reaching around 20% in 2014 [32]. This reduction was largely attributed to growing public awareness of the health consequences of smoking and the enforcement of more rigorous tobacco control measures [31], particularly the adoption of a nationwide indoor smoking ban in public places and workplaces through the Legge Sirchia, introduced in 2003 [33]. However, this downward trend began to stall around 2014, marking a turning point in national tobacco use patterns (Figure 3) [34, 35]. This plateau has also been observed in data from national registries such as ISTAT, as well as European surveys including the Eurobarometer [36-38]. By 2022, smoking prevalence had risen to 24.2%, representing the most notable increase since 2009 [39].

This reversal raises concerns about the sustainability of previous public health gains. Several factors may have contributed to the recent upturn, including the introduction of novel tobacco and nicotine products, such as heated tobacco products (HTP) and electronic cigarettes (e-cig), which may have influenced both perceptions and patterns of smoking [40, 41]. Moreover, shifts in communication strategies by the tobacco industry and a potential weakening of the public health narrative may have further undermined progress.

Figure 3. Trends in the prevalence of current smokers among Italian adults aged ≥15 years, overall and by sex. Italy, 2000-2019. Adapted from Gallus, 2021 [34].



As highlighted in the literature, smoking remains more prevalent among men in Italy. Although prevalence is lower among women, it remains a persistent public health concern [32, 35, 38]. Research has also documented notable geographical and demographic disparities, with higher prevalence observed in Central Italy compared to the North and South [32, 35, 42], and smoking being more common among adults aged 25–64 than among younger and older individuals [32, 35].

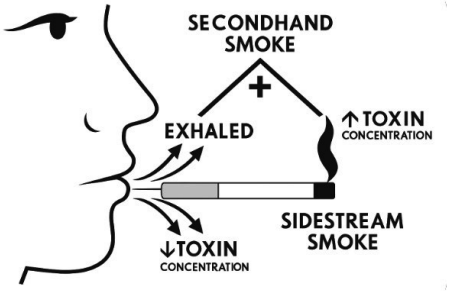
1.2 Secondhand smoke

1.2.1 Definition of secondhand smoke

Secondhand smoke (SHS) exposure is the involuntary inhalation of tobacco smoke present in the surrounding air. It is a by-product of active smoking and is also commonly been referred to as environmental tobacco smoke. Breathing SHS is also known as passive smoking or involuntary smoking [5, 43].

The process of smoking a cigarette (or other burnt tobacco products) produces three different types of tobacco smoke (Figure 4): mainstream smoke, directly inhaled by the smoker; exhaled mainstream smoke, released after inhalation; and sidestream smoke, emitted from the burning tip of the cigarette. Sidestream smoke and exhaled mainstream smoke thus jointly form SHS, which is inhaled not only by the smoker but also by people in their vicinity. Sidestream smoke makes up more than 80% of SHS [44].

Figure 4. Composition of secondhand smoke, adapted from Stepanek, 2022 [44].



SHS differs in both chemical and physical composition from active smoke, primarily due to its rapid dilution of smoke in the surrounding air [5, 45]. In addition, sidestream smoke, being generated at lower temperatures and under different conditions than mainstream smoke, contains some carcinogens and toxic substances in larger quantities [46]. The concentrations of individual components in SHS can fluctuate over time and are influenced by environmental conditions. These variations, along with representative data, have been extensively documented in field studies [43, 45, 46]. Experimental studies have also shown that sidestream smoke can be three to four times more toxic than mainstream smoke [47].

1.2.2 Health consequences of secondhand smoke exposure

SHS exposure is a well-established cause of serious health effects in both adults and children [43]. It has been classified by the International Agency for Research on Cancer (IARC) as a Group 1 carcinogen, indicating sufficient evidence of carcinogenicity in humans [48]. Like active smoking, SHS has been associated with an increased risk of several types of cancer, particularly lung cancer [5, 15]. However, the health consequences of SHS exposure extend far beyond oncological outcomes.

In adults, SHS exposure has been linked to a significantly elevated risk of cardiovascular and respiratory diseases. Even brief exposure can lead to endothelial dysfunction, increased platelet aggregation, and systemic inflammation, all of which contribute to the development of coronary heart disease and stroke [15]. Epidemiological studies have shown that non-smokers exposed to SHS have a 25–30% higher risk of developing heart disease and a 20–30% increased risk of stroke [15, 43]. Furthermore, SHS can exacerbate pre-existing respiratory conditions such as asthma and COPD, and is associated with a higher incidence of respiratory symptoms in otherwise healthy individuals [49].

The effects of SHS exposure are particularly concerning in vulnerable populations such as pregnant women and children. Prenatal exposure to SHS

has been associated with adverse pregnancy outcomes, including low birth weight, preterm delivery, and complications in fetal development [43, 50-52]. After birth, infants exposed to SHS are at increased risk of sudden infant death syndrome (SIDS), a leading cause of mortality in the first year of life [43, 49].

Children exposed to SHS are especially susceptible to its harmful effects due to their developing respiratory and immune systems. Childhood SHS exposure is causally linked to acute respiratory infections, middle ear disease, more severe asthma, and impaired lung growth, with potential long-term consequences into adulthood [15].

Given the breadth and severity of these health impacts, SHS exposure represents a major public health concern. The evidence clearly indicates that there is no safe level of exposure [15], and comprehensive tobacco control policies are essential to protect non-smokers, particularly the most vulnerable, from its harmful effects.

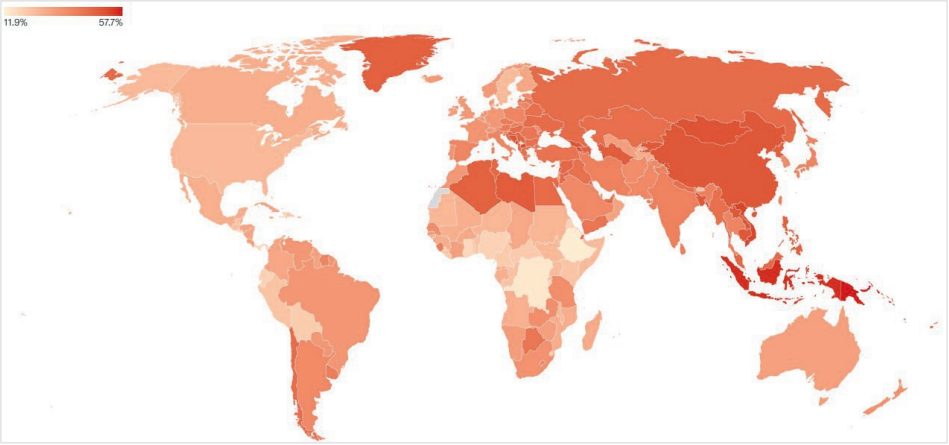
1.2.3 World prevalence of secondhand smoke exposure

Despite decades of tobacco control efforts, SHS exposure remains a widespread global health threat. According to the WHO Global Tobacco Epidemic Report 2023, approximately 1.3 million deaths per year are attributable to SHS exposure, with the burden disproportionately affecting low- and middle-income countries [53]. In these settings, weaker enforcement of smoke-free laws and higher smoking prevalence contribute to widespread SHS exposure.

Due to differences in SHS exposure definitions and data collection methods, direct prevalence estimates are often difficult to compare across countries. The GBD Study therefore uses the Summary Exposure Value (SEV), a risk-weighted measure that enables comparisons of exposure levels across regions and over time (Figure 5) [54].

The most recent analysis from GBD study estimated that in 2021, the age-standardized SEV of SHS exposure was 30.6% for males and 38.0% for females globally [54]. Although these values have slightly declined since 1990, the absolute number of deaths attributable to SHS has increased, primarily due to population growth and aging. In addition, the rate of decline has slowed in the past decade, suggesting that policy progress has stagnated in many regions, and that voluntary smoke-free rules in private settings are not yet widespread enough to compensate. The highest SHS exposure levels are observed in Asia, where women are disproportionately affected due to high male smoking prevalence and limited protection from household exposure [55].

Figure 5. Summary exposure value (SEV) of population exposed to secondhand smoke, age-standardized. Reproduced from [Su. 2025, Secondhand smoke attributable disease burden in 204 countries and territories, 1990–2021: a systematic analysis from the Global Burden of Disease Study 2021. Respir Res], licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License (http://creativecommons.org/licenses/by-nc-nd/4.0/) [54]



In the European Union, despite the implementation of smoke-free laws in public spaces across many countries, SHS exposure remains an important public health threat, estimated to be responsible for almost 24,000 deaths each year [56]. Homes remain a primary site of exposure, especially for vulnerable populations, such as children [57, 58]. According to WHO data, in some European countries, up to 60% of children are exposed to SHS at home, making domestic environments a critical source of exposure [53]. Additionally, recent data from the TackSHS project highlighted that SHS exposure is commonly reported in outdoor environments, particularly in hospitality venues, parks, and beaches, where smoking restrictions are frequently not strictly enforced or are completely absent [59-62].

This underscores the need for stronger public health campaigns and policies that promote smoke-free environments not only in public but also in private settings.

Although SHS exposure has declined globally, national data reveal considerable variability. Italy illustrates both progress and remaining gaps in protection.

1.2.4 The Italian context

Despite the progress made in tobacco control and the considerable amount of research on SHS exposure, significant gaps remain in the current knowledge base in Italy. While there is an important body of literature on SHS exposure

among children and in outdoor settings from the TackSHS project [59-61, 63], data on indoor SHS exposure in the general population are limited, with the most recent comprehensive national study based on data from 2010 [64]. That study found that 31.2% of non-smokers reported exposure to SHS in at least one setting, excluding workplaces. Specifically, 10.2% reported exposure in public places, 15.6% at home, and 17.9% in private vehicles. Among young people aged 15–24, the prevalence was even higher: 54.2% in any setting, 21.4% in public places, 27.1% at home, and 32.9% in cars. These findings highlight the persistence of SHS exposure in many environments.

In addition, a study by the Italian Centre for Disease Control (CCM) monitoring compliance with the smoking ban between 2008 and 2012 found variable enforcement across regions and settings [65]. While compliance was generally high in healthcare facilities, it was less consistent in workplaces and hospitality venues, indicating the need for stronger enforcement mechanisms and public awareness campaigns.

Overall, while Italy has made important strides in tobacco control - particularly with the 2005 national smoking ban [33] - SHS exposure remains a public health issue, especially in private and outdoor settings. The lack of recent, nationally representative data on SHS exposure in the general population underscores the need for updated surveillance efforts and targeted interventions to protect non-smokers, particularly children and young adults.

1.3 Emerging tobacco and nicotine products

1.3.1 A public health concern

Although this thesis focuses primarily on conventional cigarette smoking, the rapid proliferation of emerging nicotine and tobacco products - such as heated tobacco products (HTP) and electronic cigarettes (e-cigs) - warrants attention. These products are often proposed by industries as smoking cessation tools for adult smokers, yet growing evidence suggests they may instead contribute to nicotine dependence, and increased uptake among youth [66]. Their design, flavors, and marketing strategies often mimic consumer tech and lifestyle brands, making them especially appealing to younger demographics. Furthermore, these products are increasingly seen as contributing to the renormalization of smoking [41].

In addition, the misperception of safety surrounding these products has led to widespread passive exposure, especially in homes, schools, hospitality venues, and outdoor public spaces [67, 68].

1.3.2 Electronic cigarettes

E-cigs are electronic devices containing a liquid - a chemical mixture including propylene glycol and flavours - heated to generate an inhalable vapor, which usually contains nicotine [69].

The health effects of e-cigs are still being studied, but current evidence shows that they emit toxic substances, including formaldehyde, acetaldehyde, and heavy metals, which can damage the lungs, heart, and brain [70]. Nicotine exposure during adolescence is particularly concerning, as it can impair brain development and increase the risk of cognitive and mood disorders [71]. Moreover, e-cigs have been shown to increase the risk of cardiovascular diseases, including high heart rate, high blood pressure, and risk of myocardial infarction [72, 73]. E-cigs use might also be associated with asthma and COPD [74]. Furthermore, recent studies have revealed that there are similar epigenetic tumor biomarkers in traditional cigarette smokers and e-cigs users [75].

1.3.3 Heated tobacco products

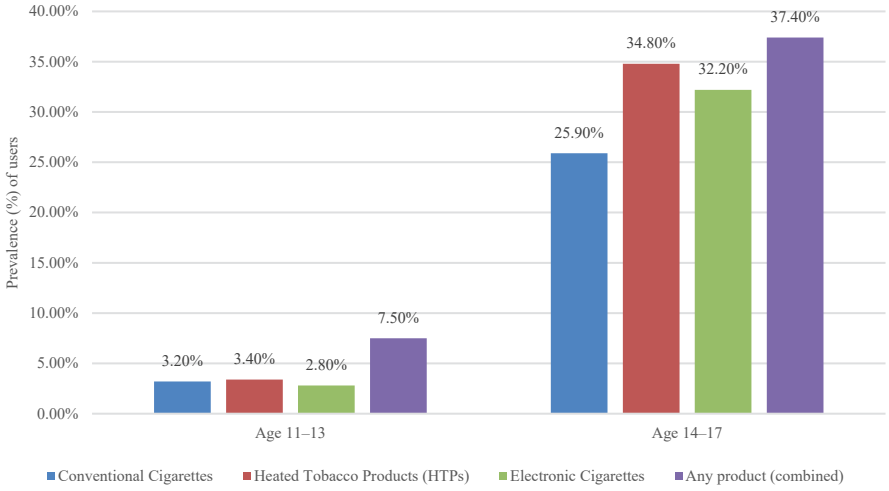
HTPs are devices that heat processed tobacco to generate an inhalable aerosol, without reaching the combustion temperatures of traditional cigarettes [76]. They can be considered as hybrid between e-cigs and conventional cigarettes: as e-cigs, they are equipped with an electronic device heating a product to generate an aerosol containing nicotine; as combusted cigarettes, the heated product is tobacco [76].

While manufacturers claim that HTPs reduce exposure to harmful chemicals, independent researchers emphasize that these products still emit nicotine and numerous toxicants, including carcinogens and respiratory irritants [77].

1.3.4 The Italian context

In Italy, the use of novel nicotine and tobacco products is steadily increasing and is particularly concerning among adolescents and young adults (Figure 6) [41, 78-80].

Figure 6. Prevalence of tobacco and nicotine product use in the previous 30 days among Italian adolescents, 2025 [79]



In addition, the phenomenon of poly-use - the combined use of traditional cigarettes and novel products - is becoming increasingly common [41, 79, 81]. This pattern raises concerns about sustained nicotine dependence, delayed smoking cessation, and increased health risks due to cumulative exposure [82, 83].

1.4 Tobacco control

1.4.1 The WHO Framework Convention on Tobacco Control

The globalisation of the tobacco epidemic in the 20th century led to a growing consensus on the need for coordinated international action.

In response, the WHO began developing the first international public health treaty under its auspices. Following several years of negotiations, the WHO Framework Convention on Tobacco Control (FCTC) was unanimously adopted by the World Health Assembly on 21 May 2003, coming into force on 27 February 2005 [76, 84]. To date, 182 countries have ratified the FCTC, making it one of the most widely embraced treaties in the history of the United Nations.

The treaty is a significant milestone in global public health, as it establishes legally binding obligations for its signatories to implement evidence-based measures to reduce the supply and demand of tobacco products.

The WHO FCTC asserts the importance of strategies to reduce both demand and supply, and provides a framework for tobacco control measures to be implemented at the national, regional and international levels. This includes actions to:

- Protect public health policies from commercial and other vested interests of the tobacco industry (Article 5.3)
- Adopt price and tax measures to reduce the demand for tobacco (Article 6)
- Protect people from exposure to tobacco smoke (Article 8)
- Regulate the contents of tobacco products (Article 9)
- Regulate tobacco product disclosures (Article 10)
- Regulate the packaging and labelling of tobacco products (Article 11)
- Warn people about the dangers of tobacco (Article 12)
- Ban tobacco advertising, promotion and sponsorship (Article 13)
- Offer people help to end their addictions to tobacco (Article 14)
- Control the illicit trade in tobacco products (Article 15)
- Ban sales to and by minors (Article 16)
- Support economically viable alternatives to tobacco growing (Article 17)

In line with the WHO FCTC, the WHO introduced the MPOWER measures in 2008 [85], a set of six cost-effective, high-impact measures designed to help countries reduce demand for tobacco. These measures include:

- Monitoring tobacco use and prevention policies;
- Protecting people from tobacco smoke;
- Offering help to quit tobacco use;
- Warning people about the dangers of tobacco;
- Enforcing bans on tobacco advertising, promotion and sponsorship;
- Raising taxes on tobacco.

1.4.2 Tobacco control in Europe

Tobacco control policies across Europe have evolved significantly over the past two decades, largely guided by the WHO FCTC and the MPOWER policy package. In the WHO European Region, most countries have adopted at least some MPOWER measures, with notable progress in areas such as smoke-free legislation, graphic health warnings, and advertising bans [85]. However, gaps remain, particularly in taxation policies, cessation support, and regulation of emerging products.

The Tobacco Control Scale (TCS) provides a comparative assessment of tobacco control implementation across 37 European countries. The score covers

eight key policy areas, reflecting the most effective tobacco control measures, including price increases through taxation, smoke-free legislation, public information campaigns, advertising bans, health warnings, and support for smoking cessation. The latest available ranking (2021) places the UK, Ireland, and France at the top, reflecting their comprehensive and well-enforced policies (Table 3) [86].

Table 3. European countries ranked by their total TCS score in 2021, adapted from Joossens, 2022 [86]

Rank 2021 (2019)	Country	Price (30)	Smoke-free places bans (22)	Budget (10)	Ad bans (13)	Health warning (10)	Treatment (10)	Illicit trade (3)	Art. 5.3 (2)	Total (100)
1 (3) ▲	Ireland	27	22	1	13	9	8	1	1	82
1 (1) –	UK	27	22	12	9	9	2	1	–	82
3 (2) ▼	France	21	18	3	11	9	6	2	1	71
4 (14) ▲	Netherlands	15	21	3	10	9	6	2	1	67
5 (8) ▲	Hungary	16	21	0	11	9	6	2	–	65
6 (5) ▼	Norway	20	17	1	13	8	3	1	0	63
7 (6) ▼	Finland	17	18	2	13	5	6	1	0	62
8 (4) ▼	Iceland	15	17	8	13	4	4	0	0	61
8 (12) ▲	Romania	18	21	0	8	5	8	1	0	61
10 (10) –	Belgium	14	16	1	10	9	7	2	0	59
11 (10) ▼	Spain	12	21	1	9	5	8	2	0	58
11 (17) ▲	Turkey	15	16	0	8	10	7	2	0	58
13 (29) ▲	Denmark	13	11	13	9	8	1	1	–	56
14 (7) ▼	Israel	16	15	0	10	6	8	0	0	55
14 (13) ▼	Greece	13	22	7	5	6	2	0	–	55
14 (17) ▲	Malta	16	16	0	11	5	5	2	–	55
17 (8) ▼	Slovenia	9	16	13	9	6	1	0	–	54
18 (15) ▼	Italy	13	18	0	9	5	6	1	0	52

18 (29) ▲	Russian Fed.	9	19	0	13	4	6	1	–	52
18 (29) ▲	Lithuania	14	15	1	10	5	5	2	0	52
21 (23) ▲	Czechia	13	15	0	8	5	6	2	0	49
21 (23) ▲	Estonia	13	15	11	5	3	2	0	–	49
21 (23) ▲	Poland	14	11	0	11	5	7	1	0	49
21 (15) ▼	Sweden	11	15	0	9	5	7	2	0	49
21 (17) ▼	Croatia	14	11	0	12	5	5	2	–	49
26 (23) ▼	Latvia	12	13	11	5	5	2	0	–	48
26 (20) ▼	Austria	11	18	0	7	5	5	2	0	48
28 (27) ▼	Cyprus	12	12	0	11	5	5	2	–	47
28 (34) ▲	Luxembourg	9	16	0	9	5	6	2	0	47
30 (20) ▼	Portugal	14	11	10	5	4	2	0	–	46
30 (32) ▲	Slovakia	11	13	9	5	6	2	0	–	46
30 (20) ▼	Ukraine	12	15	11	4	4	0	0	–	46
33 (27) ▼	Bulgaria	13	11	9	5	5	1	0	–	44
34 (36) ▲	Germany	14	11	0	6	5	5	2	0	43
35 (33) ▼	Serbia	13	11	0	9	1	3	1	0	38
36 (35) ▼	Switzerland	12	11	1	2	5	5	0	0	35
37 (new)	Bosnia & Herzegovina	14	4	0	5	0	2	0	0	25

“ –” means no information is available, “ 0 ” means insufficient to obtain one point.-1: Switzerland is the only country in this survey which has not ratified the WHO FCTC: minus one point.

Despite significant progress, tobacco control in Europe faces persistent challenges, including insufficient taxation policies, underfunded cessation services, and the growing popularity of novel nicotine products. Addressing these issues will be critical to further reducing tobacco use and its health consequences.

1.4.3 Tobacco control in Italy

Italy has historically played a leading role in tobacco control, notably becoming the first large country to implement a comprehensive indoor smoking ban in 2005, known as Sirchia's law [33]. This measure significantly reduced SHS exposure and contributed to a shift in public attitudes toward smoking. Evaluations of the law reported improvements in indoor air quality and reductions in hospital admissions for cardiovascular and respiratory conditions [33, 78]. However, the momentum of national policy innovation has slowed since then and no major national-level tobacco control measures have been introduced since [86]. As a result, SHS exposure remains a persistent public health concern, particularly in outdoor and semi-enclosed settings [62, 64, 87].

Table 4. National Tobacco Control Measures in Italy (from 2000 onwards), adapted from Istituto Superiore di Sanità, 2016 [88]

Year	Measure	Legal Reference	Summary
2003	Smoking ban in enclosed public places (“Sirchia Law”)	Law No. 3 of 16 January 2003	Banned smoking in enclosed public places and workplaces.
2004	Ban on tobacco advertising and sponsorship	Legislative Decree No. 300 of 16 December 2004	Reinforced the prohibition of advertising, sponsorship, and promotion of tobacco products in press, internet, and other media.
2012	Raised minimum age for purchasing tobacco to 18 (“Balduzzi Decree”)	Decree-Law No. 158 of 13 September 2012	Raised the minimum age for purchasing tobacco from 16 to 18; banned sales of nicotine-containing e-cigs to minors.
2013	Ban on sales of nicotine-containing e-cigs to minors	Minister of Health Ordinance, 2 April 2013	Prohibited the sale of e-cigs containing nicotine to individuals under 18.

2013	Smoking ban in schools	Decree-Law No. 104 of 12 September 2013 (Art. 4)	Extended smoking ban to outdoor areas belonging to schools; prohibited use of e-cigarettes inside schools.
2016	Packaging, warnings, sales restrictions, ban on smoking in cars	Legislative Decree No. 6 of 12 January 2016	Introduced larger pictorial health warnings, ingredient reporting requirements, stricter penalties, strengthened age restrictions, and extended smoke-free protections to vehicles with minors or pregnant women and outdoor areas of paediatric, gynaecology, obstetrics and neonatology facilities.
2020	Ban on menthol cigarettes	Legislative Decree No. 6/2016, adopted with EU Directive 2014/40/EU in 2014	Banned the placing on the market of menthol-flavoured cigarettes and other tobacco products with characterising flavours.

According to the TCS 2021, Italy has fallen from 15th to 18th place out of 37 countries [86]. Notably, the country maintained the same overall score as in the previous edition, reflecting stagnation in policy innovation and enforcement. Key weaknesses include

- Limited taxation increases on tobacco products in recent years;
- Insufficient investment in cessation services;
- Weak regulation of emerging nicotine products, such as e-cigs and HTPs;
- Inconsistent enforcement of smoke-free laws, particularly in outdoor and semi-private settings;
- Particularly active HTP lobby.

In the absence of recent national initiatives, several local jurisdictions have taken the lead in advancing tobacco control. Notably, Milan introduced a city-wide outdoor smoking ban in January 2025, prohibiting smoking in parks, public transport stops, and other high-traffic outdoor areas [89]. Other municipalities have developed targeted interventions, such as the long-standing smoke-free beach policy in Bibione, which has served as a model for promoting smoke-free tourism [90]. These subnational efforts demonstrate the potential for innovative,

context-specific policies to expand smoke-free environments and may offer valuable templates for future national strategies.

1.4.4 Future challenges and opportunities

In recent years, several legislative proposals have gained international attention for their potential to reduce tobacco initiation and consumption. These include the Smoke-Free Generation (SFG) policy, which bans the sale of tobacco to individuals born after a certain year, the Tobacco 21 (T21) policy, which raises the minimum legal age for purchasing tobacco to 21. Evidence from other high-income countries suggests that these measures are effective in curbing smoking rates and delaying initiation [91, 92].

Despite their potential benefits, the implementation, compliance with and success of these policies depend heavily on public support [33, 93, 94]. Restrictions on tobacco and nicotine access, particularly the SFG, may be perceived by the public as an infringement of personal freedom. However, recent research suggests that support for policies aimed at reducing tobacco consumption and exposure to SHS is relatively high among Italian and European populations [95, 96].

Furthermore, compliance remains a critical challenge. In Italy, even the enforcement of existing laws - such as the ban on tobacco sales to minors - is often weak. Although the legal age for purchasing tobacco is 18, violations are rarely sanctioned, and underage individuals frequently manage to obtain tobacco or nicotine products [78]. Strengthening enforcement mechanisms, including mandatory age verification and retailer accountability, would be a crucial first step in improving the effectiveness of current legislation.

Moreover, while taxation is recognized as the most effective tobacco control measure [97], Italy has not fully leveraged its potential [86]. The price elasticity of demand for cigarettes in developed countries is estimated at around −0.4, meaning that a 10% price increase leads to a 4% reduction in consumption [98]. This not only reduces smoking prevalence but also increases government revenue, as demonstrated in countries like France, where tax hikes have led to both public health gains and fiscal benefits [99].

The growing popularity of novel tobacco and nicotine products presents new challenges. These products are widely used by young people, raising concerns about nicotine addiction, dual use, and renormalization of tobacco consumption [66]. The lack of a comprehensive ban on their use in indoor public places and workplaces exposes non-users to secondhand aerosol (SHA) and facilitated widespread dual use [41]. In response to these concerns, policies banning their

use in indoor public places and workplaces, as well as prohibiting tobacco and nicotine advertising, have been proposed [100].

1.5 Tobacco related cancers

While smoking affects virtually every organ system, cancer represents one of its most important and measurable long-term consequences. Given the focus of this dissertation, the following sections concentrate on the relationship between tobacco exposure and cancer burden, with particular attention to the Italian context.

1.5.1 Biological plausibility and carcinogenic mechanisms

The causal relationship between tobacco smoking and cancer is supported by robust biological evidence. Tobacco smoke contains over 7,000 chemical compounds, of which at least 70 are known carcinogens, including polycyclic aromatic hydrocarbons (PAH), nitrosamines, and formaldehyde [15, 45].

One of the most studied carcinogens in tobacco smoke is benzo[a]pyrene, a PAH that forms DNA adducts and contributes to mutagenesis in key oncogenes and tumor suppressor genes, such as TP53 [101]. Similarly, tobacco-specific nitrosamines are potent carcinogens that have been shown to induce tumors in multiple organs in animal models and are strongly implicated in human cancers, particularly of the lung [102, 103]. Upon inhalation, carcinogens are absorbed and undergo metabolic activation, resulting in the formation of reactive intermediates capable of binding to DNA and forming DNA adducts [104]. If these adducts are not adequately repaired, they can cause miscoding during replication, leading to mutations in critical genes such as oncogenes and tumor suppressor genes [15].

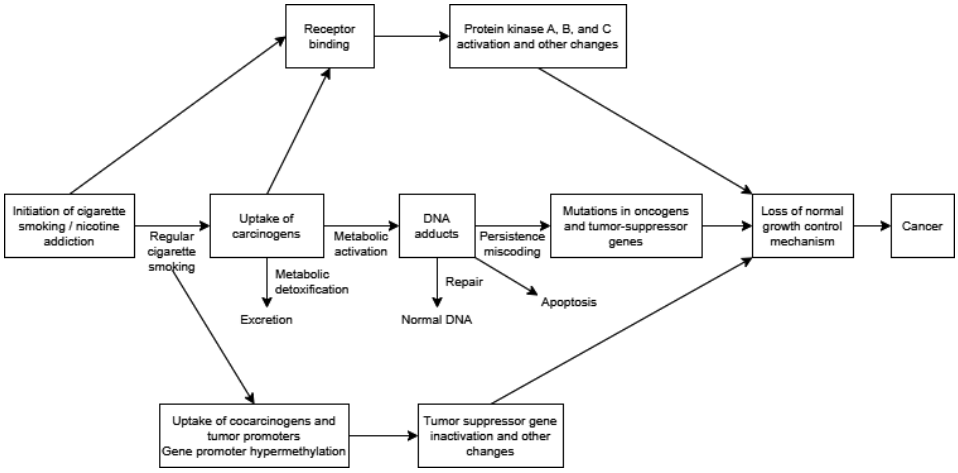
Beyond direct genotoxic effects, tobacco smoke also exerts profound influence on epigenetic regulation. Smoking has been associated with global DNA hypomethylation, site-specific hypermethylation of tumor suppressor genes, changes in histone modifications and non-coding RNA expression, contributing to disrupted normal gene and malignant transformations [105-108].

Other constituents of tobacco smoke or their metabolites may bind directly to nicotinic acetylcholine receptors and activates signaling pathways such as protein kinase A, B, and C, promoting cell survival, angiogenesis, and resistance to apoptosis, thereby facilitating malignant progression [109].

The interplay between genotoxic, epigenetic, and signalling-related mechanisms (Figure 7) provides a comprehensive biological rationale for the carcinogenicity of tobacco smoke. These molecular changes are consistent with the multistep

model of carcinogenesis and provide a mechanistic basis for the epidemiological associations between smoking and a wide range of cancers. The biological plausibility of smoking-induced carcinogenesis is thus well established, reinforcing the importance of tobacco control as a cancer prevention strategy.

Figure 7. Mechanisms linking cigarette smoking to cancer development, adapted from the Surgeon General Report, 2014 [48]



1.5.2 Methodologies to estimate tobacco-attributable morbidity and mortality

Several methodologies have been developed to estimate the burden of disease attributable to tobacco use, particularly in terms of mortality and morbidity [110]. The main methodologies used to estimate tobacco-attributable mortality are summarized in Table 5, highlighting their key features, data requirements, and limitations. A common approach involves the use of Population Attributable Fractions (PAFs), which combine data on smoking prevalence with relative risks derived from epidemiological studies. These methods are typically prevalence-based, relying on current or historical smoking patterns and disease-specific risk estimates [111-113].

One widely used method is the Peto-Lopez approach [114], which estimates tobacco-attributable mortality indirectly by using lung cancer mortality as a proxy for cumulative smoking exposure. This method is particularly useful in settings where reliable prevalence data are lacking, although it assumes a consistent relationship between lung cancer and other smoking-related diseases.

Other approaches include excess mortality models, such as those developed by Garfinkel and Rogers [115, 116], which compare observed mortality among smokers with expected mortality in non-smokers, often using cohort data.

Additionally, predictive models like the PREVENT model [117] simulate future disease burden under different tobacco control scenarios, allowing for policy impact assessment.

Each methodology has its own strengths and limitations, depending on the availability and quality of input data, the assumptions made about smoking behavior and risk, and the scope of diseases considered. The choice of method can significantly influence the estimated burden and its interpretation in public health planning.

Table 5. Methods used to estimate tobacco attributable mortality, adapted from Perez-Rios, 2008 [110]

Method Name	Key Features	Data Requirements	Limitations
Prevalence-based (Cohort Studies)	Uses smoking prevalence and relative risks from cohort studies to calculate PAFs	Smoking prevalence, cause-specific mortality, relative risks	Requires reliable prevalence and RR data; sensitive to population definitions
Prevalence-based (Case-Control Studies)	Estimates RR from case-control data; uses retrospective smoking history	Mortality data, smoking history from interviews, odds ratios	Recall bias; limited to settings with case-control data
Peto Method	Uses lung cancer mortality as proxy for smoking exposure; estimates SIR and PEF	Lung cancer mortality rates, relative risks, smoking impact ratio	Assumes consistent relationship between lung cancer and other diseases
Excess Mortality (Garfinkel)	Compares observed vs expected deaths in smokers vs non-smokers	Age- and sex-specific mortality rates for smokers and non-smokers	Requires detailed cohort data; limited generalizability
Excess Mortality (Rogers)	Combines prevalence and mortality risk rates; adjusts for smoking intensity	Smoking prevalence by intensity, mortality risks, population data	Complex modeling; requires granular smoking data
Predictive Models (Prevent)	Simulates future mortality trends under different scenarios	Demographic data, disease incidence, risk factor trends	Data-intensive; assumptions may affect accuracy

1.5.3 Epidemiological evidence of tobacco-related cancers

The epidemiological link between tobacco smoking and cancer is well established and supported by decades of research [48].

Among all malignancies, lung cancer stands out as the most strongly and consistently associated with tobacco use. According to a meta-analysis published in 2008, current smokers have a 9-fold increased risk of developing lung cancer compared to never smokers [118]. However, the risk is not uniform across all smokers, it varies substantially depending on both the intensity of smoking (e.g., number of cigarettes per day) and, more importantly, the duration of smoking over time [119, 120]. In addition, the time since smoking cessation plays a key role in modulating risk, as former smokers experience a progressive decline in lung cancer risk after quitting [121].

Other studies expanded the scope of investigation to other cancers of the respiratory tract, including the larynx, pharynx, nasal sinuses, and oral cavity, all of which showed strong associations with smoking [15]. These cancers share similar exposure pathways and are directly affected by the inhalation of tobacco smoke and its carcinogenic components.

However, the impact of tobacco smoking is not limited to the respiratory system. Extensive epidemiological evidence has demonstrated causal associations with a wide range of malignancies, including cancers of the oesophagus, pancreas, bladder, kidney, stomach, liver, cervix, colorectum, and ovary (mucinous type), as well as acute myeloid leukaemia [15]. A recent and comprehensive meta-analysis also showed the association between smoking and breast cancer risk [122]. These associations are supported by consistent findings across cohort and case-control studies, extensive dose-response relationships analysing smoking intensity, duration, and time since quitting, and strong biological plausibility.

In addition to active smoking, SHS exposure - also classified as a Group 1 carcinogen - has been causally linked to increased risk of lung cancer in non-smokers, with limited evidence for associations with cancers of the larynx, pharynx, breast, cervix, nasal cavity, nasal sinus, and nasopharynx [15, 45]. SHS contains many of the same carcinogens as mainstream smoke, and its impact is particularly concerning in settings where exposure is prolonged, such as households and workplaces.

Although the effects of cigarette smoking and SHS exposure on cancer incidence and mortality have been extensively investigated, the majority of review articles available in the scientific literature remain incomplete or methodologically limited. In particular, only a small number of meta-analyses have rigorously quantified the dose-response relationship between specific smoking variables - such as

intensity, duration, and time since quitting - and the risk of developing cancer. These parameters are essential to understand the true impact of tobacco exposure and to refine estimates of attributable cancer burden. Without detailed dose-response data, burden assessments risk underestimating or oversimplifying the complexity of smoking-related cancer risk, especially in diverse populations with varying smoking histories.

1.5.4 Incidence and burden of tobacco-related cancers in Italy

Tobacco smoking remains one of the leading preventable causes of cancer in Italy [123]. According to the latest report from the Italian Association of Medical Oncology (AIOM) “I numeri del cancro in Italia 2024”, an estimated 390,000 new cancer cases were diagnosed in the country in 2024 [124].

The most frequently diagnosed tobacco-related cancers in Italy include [124]:

- Breast cancer, with approximately 54,000 new cases;
- Colorectal cancer, with approximately 49,000 new cases;
- Lung cancer, with approximately 45,000 new cases;
- Bladder cancer, with approximately 31,000 new cases;
- Pancreatic cancer, with approximately 14,000 new cases;
- Stomach cancer, with approximately 14,000 new cases;
- Kidney cancer, with approximately 13,000 new cases.

It is important to note that not all cases of these cancers are directly attributable to smoking. Estimating the number of cases of cancer attributable to smoking requires consideration of several factors, including site-specific relative risks, the prevalence and patterns of smoking in the Italian population, and an appropriate latency period between exposure and disease onset. Accurate and meaningful burden estimates are essential for informing public health priorities and tobacco control strategies.

A recent national study estimated that 17.3% of all new cancer cases and 24.5% of all cancer deaths in Italy are attributable to tobacco smoking [125]. The burden is particularly high among men, with smoking responsible for 23.9% of incident cancers and 32.1% of cancer deaths, compared to 7.7% and 11.3%, respectively, among women.

These estimates are based on prevalence data at the population level, but do not take into account individual variations in smoking characteristics such as intensity, duration or time since cessation. These factors are known to significantly influence cancer risk. Furthermore, the relative risks employed in these models are not always derived from the most recent or context-specific

epidemiological data, which could restrict the accuracy of the attributable fraction estimates.

Given the significant impact of smoking and SHS exposure on cancer incidence and mortality rates in Italy, it is crucial to make precise, context-specific estimates of the number of cancer cases attributable to smoking in order to inform public health strategies. Accurate burden assessments enable more effective resource allocation, inform prevention and cessation programmes, and support the development of targeted policies.

1.6 Aims of the thesis

1.6.1 Conclusion from the literature and rationale

The literature reviewed above confirms the substantial burden of disease caused by tobacco use and exposure [44, 48]. However, despite the breadth of existing evidence, there are still challenges in producing updated, harmonised and context-specific estimates of the cancer burden, particularly when trying to turn epidemiological findings into actionable public health metrics.

In particular, the precise dose-response relationship between smoking, SHS exposure, and cancer risk is still not fully determined across all cancer types and smoking characteristics. Furthermore, there is a need for independent, systematic derived estimates of smoking and SHS exposure in the Italian population.

Assessing the public health impact of tobacco requires the integration of multiple complementary perspectives. Reliable estimates of the cancer burden attributable to smoking and SHS exposure rely on robust epidemiological evidence on cancer risks, accurate information on smoking behaviours and population exposure, methodological approaches capable of translating these risks into measures of disease burden, and an understanding of the health and economic consequences of tobacco use. This thesis adopts this integrated perspective to address the overarching question of how tobacco exposure contributes to the cancer burden in Italy and how this burden can be reduced through effective prevention and tobacco control strategies.

This thesis builds upon existing evidence and provides new analyses to address these gaps. The aim is to provide a comprehensive and up-to-date overview of the cancer burden attributable to cigarette smoking in Italy, achieved by integrating epidemiological data with robust analytical methods, including meta-analyses and innovative burden estimation models.

The rationale for this work is based on the need to:

1) Provide updated and accurate quantification of the association between cigarette smoking and SHS exposure and the risk of tobacco-related neoplasms;
2) Quantify the number of cases, deaths and Disability Adjusted Life Years (DALY) that could be prevented by eliminating cigarette smoking and/or SHS exposure;
3) Monitor smoking habits, SHS exposure, and support to tobacco control strategies among the Italian population.

Achieving these objectives will enhance our understanding of the real-world consequences of tobacco use and exposure to SHS. This will provide valuable insights for future research and public health planning.

This thesis is embedded within a broader research programme funded by the Italian Association for Cancer Research (AIRC), aimed at generating the epidemiological evidence required to comprehensively assess the burden of cancer attributable to smoking and SHS exposure in Italy. The programme includes systematic reviews and meta-analyses on multiple smoking-related cancer sites, the development of burden estimation methodologies, the evaluation of smoking behaviours and tobacco control measures, and the assessment of the health and economic consequences of tobacco exposure. Given the scale of this effort, which started before the beginning of this thesis and is still ongoing, it was not feasible to include all components of the programme within a single doctoral dissertation. Therefore, this thesis presents a selection of studies that contribute to different stages of this broader research agenda. Together, these studies provide complementary evidence that supports the development and application of methods to quantify the cancer burden attributable to tobacco exposure in Italy and to inform future prevention and tobacco control strategies.

1.6.2 Objectives of the thesis

The aim of this thesis is to provide new, independent epidemiological data on the cancer burden attributable to cigarette smoking and SHS exposure in Italy.

The specific objectives of this dissertation are as follows:

1) Evaluation of the association between cigarette smoking and nasopharyngeal cancer risk (Chapter 2; [126]);
2) Evaluation of the association between cigarette smoking and oral and pharyngeal cancer risk (Chapter 3; [127]);

3) Evaluation of the association between SHS exposure and the risk of breast cancer (Chapter 4; [128]);
4) Evaluation of smoking prevalence and SHS exposure in the Italian population (Chapter 5; [129]);
5) Evaluation of the Italian population's attitudes towards tobacco control policies (Chapter 6; [130]);
6) Development of a new methodology to estimate cancer incidence and mortality attributable to smoking (Chapter 7; [131]);
7) Evaluation of digestive cancer cases, deaths, and DALYs attributable to tobacco smoking in Italy (Chapter 8; [132]);
8) Evaluation of the direct economic impact of smoking-related hospitalisations in Italy (Chapter 9; [133]).

1.7 References

1. Slade J. Historical notes on tobacco. Prog Respir Res 1997; 28: 1-11.
2. Robicsek F. The Smoking Gods: Tobacco in Maya Art, History, and Religion. The University of Oklahoma Press 1978.
3. Wilbert J. Tobacco and Shamanism in South America. Yale University Press 1987.
4. IARC. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Volume 38. 1986.
5. IARC. Tobacco smoke and involuntary smoking. Vol. 83. IARC Monogr Eval Carcinog Risks Hum 2004; 1-1438.
6. Kellogg JH. Tobaccoism or How Tobacco Kills. The Modern Medicine Publishing Co. Battle Creek, Mich. 1922.
7. Doll R, Bradford Hill A. Smoking and carcinoma of the lung. Br Med J 1950; 2.
8. Doll R, Hill AB. Lung cancer and other causes of death in relation to smoking; a second report on the mortality of British doctors. Br Med J 1956; 2: 1071-1081.
9. Hammond EC, Horn D. The relationship between human smoking habits and death rates: a follow-up study of 187,766 men. J Am Med Assoc 1954; 155: 1316-1328.
10. Colley JR. Respiratory symptoms in children and parental smoking and phlegm production. Br Med J 1974; 2: 201-204.
11. Harlap S, Davies AM. Infant admissions to hospital and maternal smoking. Lancet 1974; 1: 529-532.
12. US Department of Health and Human Services PHS, Centers for Disease Control,. The Health Consequences of Involuntary Smoking: A Report of the Surgeon General. DHHS Publ No (CDC) 1986; 87-8398.
13. Glantz SA, Parmley WW. Passive smoking and heart disease. Mechanisms and risk. JAMA 1995; 273: 1047-1053.
14. Centers for Disease Control and Prevention (US). How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease. A Report of the Surgeon General. Available at https://www.ncbi.nlm.nih.gov/books/NBK53017/ (last access 19/06/2025). Atlanta (GA): Centers for Disease Control and Prevention (US) 2010.
15. U.S. Department of Health and Human Services. The Health Consequences of Smoking — 50 Years of Progress. A Report of the Surgeon General. Public Health Service, Office of the Surgeon General, Rockville, MD,2014.
16. Forey BA, Thornton AJ, Lee PN. Systematic review with meta-analysis of the epidemiological evidence relating smoking to COPD, chronic bronchitis and emphysema. BMC Pulm Med 2011; 11: 36.

17. Feng H, Li Z, Zheng R. The global burden of chronic respiratory diseases attributable to tobacco from 1990 to 2021: a global burden of disease study 2021. BMC Public Health 2025; 25: 456.
18. Jayes L, Haslam PL, Gratziou CG et al. SmokeHaz: Systematic Reviews and Meta-analyses of the Effects of Smoking on Respiratory Health. Chest 2016; 150: 164-179.
19. Rahman M, Alatiqi M, Al Jarallah M et al. Cardiovascular Effects of Smoking and Smoking Cessation: A 2024 Update. Glob Heart 2025; 20: 15.
20. Barua RS, Ambrose JA. Mechanisms of coronary thrombosis in cigarette smoke exposure. Arterioscler Thromb Vasc Biol 2013; 33: 1460-1467.
21. de Angelis C, Nardone A, Garifalos F et al. Smoke, alcohol and drug addiction and female fertility. Reprod Biol Endocrinol 2020; 18: 21.
22. Sansone A, Di Dato C, de Angelis C et al. Smoke, alcohol and drug addiction and male fertility. Reprod Biol Endocrinol 2018; 16: 3.
23. Ford PJ, Rich AM. Tobacco Use and Oral Health. Addiction 2021; 116: 3531-3540.
24. Kai JY, Zhou M, Li DL et al. Smoking, dietary factors and major age-related eye disorders: an umbrella review of systematic reviews and meta-analyses. Br J Ophthalmol 2023; 108: 51-57.
25. Li LF, Chan RL, Lu L et al. Cigarette smoking and gastrointestinal diseases: the causal relationship and underlying molecular mechanisms (review). Int J Mol Med 2014; 34: 372-380.
26. Ortiz A, Grando SA. Smoking and the skin. Int J Dermatol 2012; 51: 250-262.
27. Maddatu J, Anderson-Baucum E, Evans-Molina C. Smoking and the risk of type 2 diabetes. Transl Res 2017; 184: 101-107.
28. Doll R, Peto R, Boreham J, Sutherland I. Mortality in relation to smoking: 50 years' observations on male British doctors. BMJ 2004; 328: 1519.
29. Goodchild M, Nargis N, Tursan d'Espaignet E. Global economic cost of smoking-attributable diseases. Tob Control 2018; 27: 58-64.
30. Rezaei S, Akbari Sari A, Arab M et al. Economic burden of smoking: a systematic review of direct and indirect costs. Med J Islam Repub Iran 2016; 30: 397.
31. World Health Organization. WHO global report on trends in prevalence of tobacco use 2000–2030. Available at https://www.who.int/publications/i/item/9789240088283 (last access 16/06/2025). 2024.
32. Lugo A, Asciutto R, Pacifici R et al. Smoking in Italy 2013-2014, with a focus on the young. Tumori 2015; 101: 529-534.
33. Gallus S, Zuccaro P, Colombo P et al. Effects of new smoking regulations in Italy. Ann Oncol 2006; 17: 346-347.

34. Gallus S, Borroni E, Odone A et al. The Role of Novel (Tobacco) Products on Tobacco Control in Italy. Int J Environ Res Public Health 2021; 18.
35. Lugo A, Zuccaro P, Pacifici R et al. Smoking in Italy in 2015-2016: prevalence, trends, roll-your-own cigarettes, and attitudes towards incoming regulations. Tumori 2017; 103: 353-359.
36. European Commission. Attitudes of Europeans towards tobacco and electronic cigarettes. Available at https://europa.eu/eurobarometer/surveys/detail/2146. 2017.
37. European Commission. Special Eurobarometer 2023: Attitudes of Europeans towards tobacco and related products. Available at https://europa.eu/eurobarometer/surveys/detail/2995. 2023.
38. ISTAT. Abitudine al fumo - età dettaglio. Available at https://esploradati.istat.it/databrowser/#/it/dw/categories/IT1,Z0810HEA,1.0/HEA_STYLE/HEA_STYLE_SMOK/IT1,83_63_DF_DCCV_AVQ_PERSONE_201,1.0.
39. Istituto Superiore di Sanità. Comunicato Stampa N°39/2022 - Fumo: in Italia circa 800mila fumatori in più rispetto al 2019. Triplicato il consumo di sigarette a tabacco riscaldato. https://www.iss.it/en/comunicati-stampa/-/asset_publisher/fjTKmjJgSgdK/content/id/7146126. Published May 30, 2022. Accessed December 14, 2023.
40. Liu X, Lugo A, Davoli E et al. Electronic cigarettes in Italy: a tool for harm reduction or a gateway to smoking tobacco? Tob Control 2020; 29: 148-152.
41. Gallus S, Stival C, McKee M et al. Impact of electronic cigarette and heated tobacco product on conventional smoking: an Italian prospective cohort study conducted during the COVID-19 pandemic. Tob Control 2024; 33: 267-270.
42. Istituto Superiore di Sanità. Abitudine al fumo. Indicatori - PASSI. Available at https://www.epicentro.iss.it/passi/dati/fumo (last access 18/06/2025).
43. U.S. Department of Health and Human Services. The Health Consequences of Involuntary Exposure to Tobacco Smoke. 2006.
44. Stepanek L, Sevcikova J, Horakova D et al. Public Health Burden of Secondhand Smoking: Case Reports of Lung Cancer and a Literature Review. Int J Environ Res Public Health 2022; 19.
45. IARC. Personal habits and indoor combustions. Volume 100 E. IARC Monogr Eval Carcinog Risks Hum 2012; 1-538.
46. Jenkins RA, Tomkins B, Guerin MR. The Chemistry of Environmental Tobacco Smoke. Composition and Measurement, Second Edition. CRC Press 2000.
47. Schick S, Glantz S. Philip Morris toxicological experiments with fresh sidestream smoke: more toxic than mainstream smoke. Tob Control 2005; 14: 396-404.

48. IARC. List of Classifications, Agents classified by the IARC Monographs, Volumes 1-124. Available at https://monographs.iarc.who.int/list-of-classifications (last access 07/07/2025). 2019.
49. Flouris AD, Koutedakis Y. Immediate and short-term consequences of secondhand smoke exposure on the respiratory system. Curr Opin Pulm Med 2011; 17: 110-115.
50. Leonardi-Bee J, Britton J, Venn A. Secondhand smoke and adverse fetal outcomes in nonsmoking pregnant women: a meta-analysis. Pediatrics 2011; 127: 734-741.
51. Karumai-Mori H, Hamada H, Iwama N et al. Impact of maternal smoking and secondhand smoke exposure during singleton pregnancy on placental abruption: analysis of a prospective cohort study (the Japan Environment and Children's Study). BMJ Open 2025; 15: e089499.
52. National Cancer Institute. A Socioecological Approach to Addressing Tobacco-Related Health Disparities. National Cancer Institute Tobacco Control Monograph 22. . NIH Pub. No. 17-CA-8035A. Bethesda, MD: U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute 2017.
53. World Health Organization. WHO report on the global tobacco epidemic, 2023: protect people from tobacco smoke. https://www.who.int/publications/i/item/9789240077164. Published July 31, 2023. Accessed June 20, 2025. 2023.
54. Su Z, Xie Y, Huang Z et al. Second hand smoke attributable disease burden in 204 countries and territories, 1990-2021: a systematic analysis from the Global Burden of Disease Study 2021. Respir Res 2025; 26: 174.
55. Singh RJ, Lal PG. Second-hand smoke: a neglected public health challenge. Indian J Public Health 2011; 55: 192-198.
56. Carreras G, Lachi A, Cortini B et al. Burden of disease from second-hand tobacco smoke exposure at home among adults from European Union countries in 2017: an analysis using a review of recent meta-analyses. Prev Med 2021; 145: 106412.
57. Carreras G, Lachi A, Cortini B et al. Burden of disease from exposure to secondhand smoke in children in Europe. Pediatr Res 2021; 90: 216-222.
58. Gorini G, Carreras G. Morbidity Attributable to Second-Hand Smoke in European Children. Arch Bronconeumol 2021; 57: 455-456.
59. Henderson E, Continente X, Fernandez E et al. Secondhand smoke exposure assessment in outdoor hospitality venues across 11 European countries. Environ Res 2021; 200: 111355.
60. Henderson E, Continente X, Fernandez E et al. Secondhand smoke exposure in outdoor children's playgrounds in 11 European countries. Environ Int 2021; 149: 105775.
61. Henderson E, Continente X, Fernandez E et al. Secondhand smoke exposure and other signs of tobacco consumption at outdoor entrances of

primary schools in 11 European countries. Sci Total Environ 2020; 743: 140743.

62. Tack SHSPI, Henderson E, Lugo A et al. Secondhand smoke presence in outdoor areas in 12 European countries. Environ Res 2021; 195: 110806.
63. Apelberg BJ, Hepp LM, Avila-Tang E et al. Environmental monitoring of secondhand smoke exposure. Tob Control 2013; 22: 147-155.
64. Martinez-Sanchez JM, Gallus S, Zuccaro P et al. Exposure to secondhand smoke in Italian non-smokers 5 years after the Italian smoking ban. Eur J Public Health 2012; 22: 707-712.
65. Minardi V, Gorini G, Carreras G et al. Compliance with the smoking ban in Italy 8 years after its application. Int J Public Health 2014; 59: 549-554.
66. Scala M, Dallera G, Gorini G et al. Patterns of Use of Heated Tobacco Products: A Comprehensive Systematic Review. J Epidemiol 2025; 35: 213-221.
67. Amalia B, Fu M, Tigova O et al. Exposure to secondhand aerosol from electronic cigarettes at homes: A real-life study in four European countries. Sci Total Environ 2023; 854: 158668.
68. Amalia B, Liu X, Lugo A et al. Exposure to secondhand aerosol of electronic cigarettes in indoor settings in 12 European countries: data from the TackSHS survey. Tob Control 2021; 30: 49-56.
69. Pauly J, Li Q, Barry MB. Tobacco-free electronic cigarettes and cigars deliver nicotine and generate concern. Tob Control 2007; 16: 357.
70. Kopa-Stojak PN, Pawliczak R. Disposable electronic cigarettes - chemical composition and health effects of their use. A systematic review. Toxicol Mech Methods 2025; 35: 250-261.
71. Castro EM, Lotfipour S, Leslie FM. Nicotine on the developing brain. Pharmacol Res 2023; 190: 106716.
72. Kennedy CD, van Schalkwyk MCI, McKee M, Pisinger C. The cardiovascular effects of electronic cigarettes: A systematic review of experimental studies. Prev Med 2019; 127: 105770.
73. Tsai M, Byun MK, Shin J, Crotty Alexander LE. Effects of e-cigarettes and vaping devices on cardiac and pulmonary physiology. J Physiol 2020; 598: 5039-5062.
74. Wills TA, Soneji SS, Choi K et al. E-cigarette use and respiratory disorders: an integrative review of converging evidence from epidemiological and laboratory studies. Eur Respir J 2021; 57.
75. Song MA, Mori KM, McElroy JP et al. Accelerated epigenetic age, inflammation, and gene expression in lung: comparisons of smokers and vapers with non-smokers. Clin Epigenetics 2023; 15: 160.
76. World Health Organization. WHO report on the global tobacco epidemic 2021: addressing new and emerging products. https://www.who.int/publications/i/item/9789240032095. Published July 27, 2021. Accessed July 28, 2025. 2021.

77. World Health Organization. Heated tobacco products: summary of research and evidence of health impacts. https://www.who.int/publications/i/item/9789240042490. Published July 26, 2023. Accessed July 28, 2025. 2023.

78. Gorini G, Gallus S, Carreras G et al. Prevalence of tobacco smoking and electronic cigarette use among adolescents in Italy: Global Youth Tobacco Surveys (GYTS), 2010, 2014, 2018. Prev Med 2020; 131: 105903.

79. Istituto Superiore di Sanità. Il Rapporto Nazionale sul consumo di tabacco e nicotina: prevalenze e abitudini degli studenti/giovani consumatori. Available at chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://smettodifumare.iss.it/public-caf/Files/Rapporto%20nazionale%20tabagismo%202025.pdf. Accessed on July 30, 2025. 2025.

80. Prigitano A, Binda S, Pariani E et al. Tobacco and e-cigarette smoking habits among Italian healthcare students. Ann Ig 2020; 32: 608-614.

81. Carreras G, Minardi V, Lugo A et al. Italians are still loyal to conventional cigarettes, despite novel tobacco products. Ann Ist Super Sanita 2022; 58: 264-268.

82. Bittoni MA, Carbone DP, Harris RE. Vaping, Smoking and Lung Cancer Risk. J Oncol Res Ther 2024; 9.

83. Glantz SA, Nguyen N, Oliveira da Silva AL. Population-Based Disease Odds for E-Cigarettes and Dual Use versus Cigarettes. NEJM Evid 2024; 3: EVIDoa2300229.

84. World Health Organization. World Health Organization Framework Convention on Tobacco Control (WHO FCTC). Available online at http://www.who.int/fctc/en/. Last access July 30, 2025. 2003.

85. World Health Organization. WHO report on the global tobacco epidemic, 2025: warning about the dangers of tobacco. https://www.who.int/publications/i/item/9789240112063. Published June 23, 2025. Accessed July 30, 2025. 2025.

86. Joossens L, Olefir L, Feliu A, Fernandez E. The Tobacco Control Scale 2021 in Europe http://www.tobaccocontrolscale.org/TCS2021. Published 2022. Accessed December 21, 2023.

87. Gallus S. Second-hand smoke in Italy. Eur J Paediatr Dent 2015; 16: 257.

88. Istituto Superiore di Sanità. NORME RILEVANTI RELATIVE AI TABACCHI LAVORATI IN ITALIA (20042021). Available online at chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://www.epicentro.iss.it/ben/2021/4/volume4-2021-articolo3-aggiuntivo.pdf. Last access September 9, 2025. 2016.

89. Redazione ANSA. Milano vieta il fumo di sigaretta per strada dal primo gennaio 2025. Ansa 2024.

90. De Marco C, Ruprecht AA, Borgini A et al. Will smoking on beaches become a thing of the past? Bibione: The first smoke-free beach in Italy. Pulmonology 2023; 29: 540-542.

91. Friedman AS, Buckell J, Sindelar JL. Tobacco-21 laws and young adult smoking: quasi-experimental evidence. Addiction 2019; 114: 1816-1823.

92. The Lancet Respiratory M. The tobacco endgame: targeting the next generation. Lancet Respir Med 2023; 11: 493.

93. Hyland A, Higbee C, Borland R et al. Attitudes and beliefs about secondhand smoke and smoke-free policies in four countries: findings from the International Tobacco Control Four Country Survey. Nicotine Tob Res 2009; 11: 642-649.

94. Zhou L, Niu L, Jiang H et al. Facilitators and Barriers of Smokers' Compliance with Smoking Bans in Public Places: A Systematic Review of Quantitative and Qualitative Literature. Int J Environ Res Public Health 2016; 13.

95. Nogueira SO, Fu M, Lugo A et al. Non-smokers' and smokers' support for smoke-free legislation in 14 indoor and outdoor settings across 12 European countries. Environ Res 2022; 204: 112224.

96. Scala M, Lugo A, Gallus S. Support for smoke-free generation strategies in Italy. Lancet Reg Health Eur 2024; 44: 101013.

97. IARC. Effectiveness of Tax and Price Policies for Tobacco Control. IARC Handbooks of Cancer Prevention Volume 14. IARC 2011. Available online at: https://publications.iarc.fr/Book-And-Report-Series/Iarc-Handbooks-Of-Cancer-Prevention/Effectiveness-Of-Tax-And-Price-Policies-For-Tobacco-Control-2011. 2011.

98. Kohler A, Vinci L, Mattli R. Cross-country and panel data estimates of the price elasticity of demand for cigarettes in Europe. BMJ Open 2023; 13: e069970.

99. Devaux M, Dorfmuller Ciampi M, Guignard R et al. Economic evaluation of the recent French tobacco control policy: a model-based approach. Tob Control 2024.

100. Possenti I, Gallus S, Lugo A et al. Best practices for secondhand smoke and secondhand aerosol protection and evidence supporting the expansion of smoke- and aerosol-free environments: Recommendations from the 2nd Joint Action on Tobacco Control. Tob Prev Cessat 2024; 10.

101. Menzies GE, Reed SH, Brancale A, Lewis PD. Base damage, local sequence context and TP53 mutation hotspots: a molecular dynamics study of benzo[a]pyrene induced DNA distortion and mutability. Nucleic Acids Res 2015; 43: 9133-9146.

102. Hecht SS, Hoffmann D. Tobacco-specific nitrosamines, an important group of carcinogens in tobacco and tobacco smoke. Carcinogenesis 1988; 9: 875-884.

103. Hecht SS. DNA adduct formation from tobacco-specific N-nitrosamines. Mutat Res 1999; 424: 127-142.

104. Phillips DH, Venitt S. DNA and protein adducts in human tissues resulting from exposure to tobacco smoke. Int J Cancer 2012; 131: 2733-2753.

105. Fasanelli F, Baglietto L, Ponzi E et al. Hypomethylation of smoking-related genes is associated with future lung cancer in four prospective cohorts. Nat Commun 2015; 6: 10192.

106. Jin T, Hao J, Fan D. Nicotine induces aberrant hypermethylation of tumor suppressor genes in pancreatic epithelial ductal cells. Biochem Biophys Res Commun 2018; 499: 934-940.

107. Liu F, Killian JK, Yang M et al. Epigenomic alterations and gene expression profiles in respiratory epithelia exposed to cigarette smoke condensate. Oncogene 2010; 29: 3650-3664.

108. Zong D, Liu X, Li J et al. The role of cigarette smoke-induced epigenetic alterations in inflammation. Epigenetics Chromatin 2019; 12: 65.

109. Chen RJ, Chang LW, Lin P, Wang YJ. Epigenetic effects and molecular mechanisms of tumorigenesis induced by cigarette smoke: an overview. J Oncol 2011; 2011: 654931.

110. Perez-Rios M, Montes A. Methodologies used to estimate tobacco-attributable mortality: a review. BMC Public Health 2008; 8: 22.

111. Shultz JM, Novotny TE, Rice DP. Quantifying the disease impact of cigarette smoking with SAMMEC II software. Public Health Rep 1991; 106: 326-333.

112. Centers for Disease C, Prevention. Annual smoking-attributable mortality, years of potential life lost, and economic costs--United States, 1995-1999. MMWR Morb Mortal Wkly Rep 2002; 51: 300-303.

113. Forastiere F, Perucci CA, Arca M, Axelson O. Indirect estimates of lung cancer death rates in Italy not attributable to active smoking. Epidemiology 1993; 4: 502-510.

114. Peto R, Lopez AD, Boreham J et al. Mortality from tobacco in developed countries: indirect estimation from national vital statistics. Lancet 1992; 339: 1268-1278.

115. Rogers RG, Hummer RA, Krueger PM, Pampel FC. Combining Prevalence and Mortality Risk Rates: The Case of Cigarette Smoking. Popul Dev Rev 2005; 31: 259-292.

116. Garfinkel L. Cancer mortality in nonsmokers: prospective study by the American Cancer Society. J Natl Cancer Inst 1980; 65: 1169-1173.

117. Bronnum-Hansen H, Juel K. Estimating mortality due to cigarette smoking: two methods, same result. Epidemiology 2000; 11: 422-426.

118. Gandini S, Botteri E, Iodice S et al. Tobacco smoking and cancer: a meta-analysis. Int J Cancer 2008; 122: 155-164.

119. Doll R, Peto R. Cigarette smoking and bronchial carcinoma: dose and time relationships among regular smokers and lifelong non-smokers. J Epidemiol Community Health (1978) 1978; 32: 303-313.

120. Remen T, Pintos J, Abrahamowicz M, Siemiatycki J. Risk of lung cancer in relation to various metrics of smoking history: a case-control study in Montreal. BMC Cancer 2018; 18: 1275.

121. Reitsma M, Kendrick P, Anderson J et al. Reexamining Rates of Decline in Lung Cancer Risk after Smoking Cessation. A Meta-analysis. Ann Am Thorac Soc 2020; 17: 1126-1132.
122. Scala M, Bosetti C, Bagnardi V et al. Dose-response Relationships Between Cigarette Smoking and Breast Cancer Risk: A Systematic Review and Meta-analysis. J Epidemiol 2023; 33: 640-648.
123. Collaborators GBDCRF. The global burden of cancer attributable to risk factors, 2010-19: a systematic analysis for the Global Burden of Disease Study 2019. Lancet 2022; 400: 563-591.
124. AIOM. I Numeri del Cancro in Italia 2024. Available at https://www.aiom.it/i-numeri-del-cancro-in-italia/. Last access August 5, 2025. 2024.
125. Collatuzzo G, Malvezzi M, Mangiaterra S et al. Cancers attributable to tobacco smoking in Italy in 2020. Cancer Epidemiol 2024; 92: 102623.
126. Possenti I, Martini A, Bagnardi V et al. Association between cigarette smoking and nasopharyngeal cancer risk: a meta-analysis. Rhinology 2025; 63: 13-21.
127. Possenti I, Miotti S, Gallus S et al. Smoking and Oral and Pharyngeal Cancer: A Meta-Analysis. Oncology Reviews 2025; 19.
128. Possenti I, Scala M, Carreras G et al. Exposure to second-hand smoke and breast cancer risk in non-smoking women: a comprehensive systematic review and meta-analysis. Br J Cancer 2024; 131: 1116-1125.
129. Possenti I, Scala M, Odone A et al. Prevalence of Cigarette Smoking and Secondhand Smoke Exposure in Italy in 2024. Tumori Journal 2025; 111: 478-486.
130. Possenti I, Scala M, Girvalaki C, et al. Attitudes towards tobacco and nicotine control policies in Italy: insights from a 2024 national survey. Nicotine Tob Res, 2026.
131. Possenti I, Gallus S, Scala M et al. Estimating cancer cases and deaths attributable to smoking and secondhand smoke exposure at national level: a methodology based on individual-level data. Submitted to Lancet Regional Health - Europe 2026.
132. Possenti I, Gallus S, Odone A et al. Evaluation of digestive cancer cases, deaths, and DALYs attributable to tobacco smoking in Italy. Submitted to The Lancet Gastroenterology & Hepatology 2026.
133. Possenti I, Scala M, Rognoni M et al. Analysis of the direct economic impact of smoking-related hospitalisations in Italy. Tob Induc Dis 2024; 22.

Chapter 2

Association between cigarette smoking and nasopharyngeal cancer risk: a meta-analysis

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2.1 Abstract

Introduction: Nasopharyngeal cancer (NPC) is a relatively rare yet aggressive malignancy, primarily affecting regions of East and Southeast Asia. This study aims at providing an up-to-date quantification of the association between cigarette smoking and NPC risk, overall and by histological subsites.

Methods: We conducted a systematic review and meta-analysis of case-control and cohort studies on the association between cigarette smoking and NPC risk published up to May 2023. The methodology used is original and efficient and includes both a comprehensive umbrella review and a traditional review. We estimated pooled relative risks (RR) of NPC according to smoking status, intensity, duration, and time since quitting.

Results: Among 46 eligible articles, 40 original studies were included in this meta-analysis. Compared with never smokers, the pooled RR of NPC was 1.61 for current, 1.28 for former, and 1.62 for ever smokers. The RR for ever compared with never smokers was 2.37 for squamous cell NPC and 1.06 for undifferentiated NPC. NPC risk significantly increased linearly with smoking intensity and duration, and decreased linearly with increasing time since quitting.

Conclusion: This meta-analysis confirms the link between tobacco smoking and NPC, highlighting the significant risk posed even by moderate cigarette consumption. Additionally, our findings underscore the differential risk between squamous cell and undifferentiated subtypes of NPC, shedding light on the distinct implications for NPC prevention strategies.

2.2 Introduction

Nasopharyngeal cancer (NPC) is a malignant neoplasm that arises from the epithelial cells of the nasopharynx. Its incidence is relatively limited, with less than two cases diagnosed per 100,000 people per year worldwide [1]. However, its geographical distribution varies widely, with the highest incidence in Southeast Asian regions, where the age-standardized rate stands at 4.7 cases per 100,000 individuals [2]. NPC has a significant impact on patients' quality of life and is known to be quite aggressive, with an estimated 5-year survival rate of 63% [3].

Several risk factors have been identified for the development of NPC. Among these, extensive research has focused on factors such as Epstein-Barr virus infection, genetic predisposition, alcohol consumption, and exposure to environmental toxins [2, 4-6]. In addition, cigarette smoking is recognized as a major risk factor associated with cancers of the respiratory tract, including the nasopharynx [7-9]. The composition of cigarette smoke encompasses several hazardous chemicals, many of which are recognized carcinogens. When inhaled, these substances enter the upper respiratory tract, can induce DNA damage and promote the progression of cancer cells [10].

Despite extensive research, there are still major gaps in the understanding of the etiology of NPC. In addition, although the association between cigarette smoking and cancers of the respiratory tract is well-established, the precise role of smoking in cancers of different sites within the respiratory tract remains unclear. In fact, most of the recent studies investigating cancer risks associated with cigarette smoking treat NPC exclusively as part of the cancers of the head and neck, the upper aerodigestive tract, or the pharynx [11, 12]. The complex aetiology of NPC, which distinguishes it from other cancers, requires separate consideration and investigation, particularly in examining different histological subtypes.

The primary objective of this meta-analysis is to quantify the precise magnitude of the association between cigarette smoking and NPC risk, thus filling the existing gap from recent meta-analyses on this topic. In addition, this meta-analysis aims to unravel the association of interest using dose-response analyses with smoking intensity, duration and time since quitting, and performing stratified analyses, with specific stratifications including sex, geographical area, and cancer subtype.

2.3 Methods

The current meta-analysis is part of a series of systematic reviews and meta-analyses investigating the association between cigarette smoking and secondhand smoke (SHS) exposure and cancer risk [13-18]. The present analysis is specifically focused on NPC. This analysis uses an innovative methodology that combines umbrella and traditional review approaches [19]. In our umbrella review, we systematically identified all relevant meta-analyses, pooled analyses and reviews that examined the association between cigarette smoking and the risk of NPC. We then used a traditional review process to identify original studies published after the most recent comprehensive review. Our study protocol is registered in the International Prospective Register of Systematic Reviews (PROSPERO; registration number: CRD42017063991).

This approach provides a comprehensive overview of the existing evidence and allows studies identified through different search strategies, databases, and eligibility criteria to be captured. In this way, it efficiently builds upon the work already conducted by previous research groups and maximizes the likelihood of identifying relevant studies that may not be retrieved through a single de novo search strategy.

However, relying exclusively on published reviews may lead to the omission of recently published studies and limits the possibility of applying a consistent set of eligibility criteria across all available evidence. Therefore, a complementary traditional systematic review was conducted to identify additional eligible studies published before or after the most recent available meta-analysis and to ensure that all studies meeting the predefined inclusion criteria were considered.

By combining these approaches, it was possible to maximize the completeness of evidence retrieval, evaluate the consistency of previous evidence syntheses, and produce an updated quantitative estimate based on all eligible studies available at the time of the review. Previous reviews adopting a similar strategy have shown that systematically screening the studies included in existing systematic reviews and meta-analyses can identify a substantial number of additional eligible articles, including many studies published before the search date of the most recent review but not captured by its original search strategy [13-18].

The review was conducted in accordance with the PRISMA 2020 guidelines whenever applicable. Due to the combined umbrella review and traditional review design, a conventional PRISMA flowchart could not be fully applied, as the study identification and selection process differed from that of a standard systematic review. A completed PRISMA checklist is provided in the Annex 1.

2.3.1 Search strategy

In the first stage, we conducted an umbrella review focusing on the association between smoking and SHS exposure and cancer risk across different anatomical sites. Using a thorough literature search of multiple databases, including PubMed/MEDLINE, Embase, the Institute for Scientific Information Web of Science and the Cochrane Database of Systematic Reviews, we identified all relevant meta-analyses, pooled analyses and systematic reviews on the association between cigarette smoking and SHS exposure and cancer risk up to October 12 2022.

The umbrella review identified 57 reports (Supplementary Table 1), which included systematic reviews, meta-analyses, pooled analyses or reports from international agencies, regarding the association between cigarette smoking and SHS exposure and the risk of cancers located anywhere in the upper aero-digestive tract. From these reports, all original articles that specifically addressed NPC were extracted, resulting in the identification of 72 non-duplicate original publications on tobacco smoking and the risk of NPC. These articles were thoroughly screened from their full text using the eligibility criteria described in the following section, resulting in the exclusion of 33 articles that were identified as ineligible (Supplementary Table 2).

In the subsequent phase of our search, we conducted a literature search to encompass all original studies published between January 2016 (i.e., the beginning of the year previous to the publication date of the most recent and comprehensive review available on the topic [8]) and May 31 2023. The search string involved combinations of MeSH and text words related to NPC and tobacco or smoking (Supplementary Box 1). After excluding duplicate publications and ineligible articles, the literature update resulted in 11 additional original publications on cigarette smoking and the risk of NPC.

By merging the original articles identified in the umbrella review and the literature update, a total of 46 non-duplicate publications were considered eligible (Supplementary Figure 1).

2.3.2 Eligibility criteria

To be included in the present meta-analysis, studies were required to meet specific eligibility criteria: i) be either case-control studies (including nested case-control studies or pooled analyses of case-control studies) or cohort studies (including case-cohort studies or pooled analyses of cohort studies); ii) be published as original articles in the English language; iii) provide data pertaining to the general population; iv) provide information on the association between cigarette smoking and the risk of NPC; v) report risk estimates, including risk

ratios, odds ratios, hazard ratios, or mortality rate ratios - all referred to as relative risk (RR) - for at least one variable among smoking status (current, former, and/or ever), intensity, duration, and time since quitting, compared with never or current cigarette smokers, and the corresponding 95% confidence intervals (CI), or provide sufficient information to calculate them.

2.3.3 Data extraction

In the data extraction phase, information was systematically collected from each eligible study, including both general and study-specific details. Data extracted included: general publication information (e.g., first author, year of publication, and journal), study characteristics (e.g., country in which the study was conducted, study name, study design, and sample size), details of the statistical model used for RR estimates (including covariates considered), and RRs with corresponding 95% CIs and, where available, numbers of cases and controls (or persons at risk/person-years for cohort studies) for different exposure categories.

Where appropriate, we used the technique for aggregating non-independent estimates described by Hamling and colleagues [20]. This approach involved modifying the reference category or collapsing RRs from two or more categories in cases where the reference group remained the same across categories.

2.3.4 Statistical analysis

We calculated pooled RRs for current, former, and ever smokers compared with never smokers. These estimates were performed both overall and stratified by study design (i.e., cohort and case-control studies). We used random-effects meta-analytic models to account for the heterogeneity of risk estimates [21].

Study quality was assessed by two authors (AL and IP) using the Newcastle-Ottawa Scale (NOS) [22]. NOS score ranges between 0 (poor quality) and 9 (good quality) and consider information on three broad categories: selection (maximum 4 points), comparability (maximum 2 points) and outcome for case-control or exposure for cohort studies (maximum 3 points). In this meta-analysis, high-quality studies were defined as those with NOS scores ≥7. To ensure the completeness and comprehensiveness of our study, no low-quality study was excluded from the meta-analysis.

Heterogeneity was assessed using the $\chi 2$ test, and inconsistency was quantified using the I2 statistic, which represents the proportion of total variation attributable to between-study variance [23]. We carried out stratified analyses based on various study and population characteristics, such as cancer subsite, sex, study design, type of control (for case-control studies), endpoint (for cohort studies),

tertiles of the number of cases, presence of any adjustment, study quality, geographic area, income group, and year of publication.

To investigate publication bias, we examined funnel plots [24] and employed Egger's test for funnel plot asymmetry [25].

We examined both linear and nonlinear associations between smoking intensity (for current vs. never smokers), smoking duration (for current vs. never smokers), and time since quitting (for former vs. current smokers) and the log RR of NPC. Dose-response relationships were evaluated using a one-stage random-effects dose-response model [26]. Non-linear coefficients were subjected to the Wald test for statistical significance. When linearity was rejected, non-linear relationships were modelled using restricted cubic splines with three knots at fixed percentiles of exposure (10%, 50%, and 90%) [14, 27]. Exposure levels for each category were determined as the midpoint between upper and lower bounds; for open-ended upper categories, exposure levels were set at 1.2 times the lower bound [19, 28, 29].

In cases where the numbers of cases and/or controls in specific exposure categories were not available in the original study publication, we estimated the covariance between log RRs by considering the total number of cases and/or controls in the study, weighted by the average percentage distribution of subjects pooled from all other studies [30].

All statistical analyses were performed using R software version 4.2.2 (R Development Core Team, 2017), particularly leveraging the "meta" and "dosresmeta" packages [30, 31].

2.4 Results

2.4.1 Study selection and description

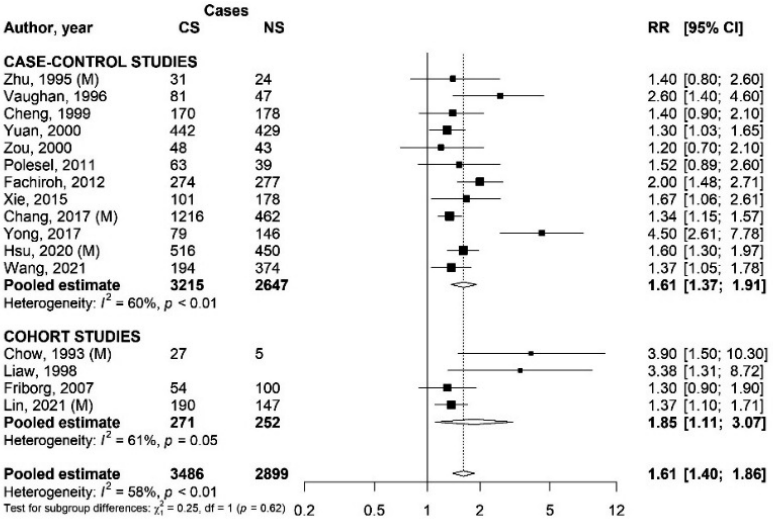
Among the initially identified 46 eligible articles exploring the relationship between cigarette smoking and NPC risk, 38 were identified from existing reviews and meta-analyses identified in the umbrella review and 8 were newly identified studies retrieved in the traditional review [32-39]. From these articles, 6 were excluded during the study selection process due to duplicated data (Supplementary Table 2). Consequently, a total of 40 studies (33 case-control and 7 cohort studies) were included in the present systematic review and meta-analysis (Supplementary Table 3 and Supplementary Table 4). The selected studies covered the period from 1982 to 2021 and included more than 15,000 NPC cases. Among them, 16 studies provided a measure of the association (or

data to calculate it) for current smokers, 15 for former smokers, and 37 studies for ever smokers, as compared with never smokers. Additionally, 17 studies reported RR estimates for smoking intensity (including 5 among current smokers), 15 for smoking duration (including 5 among current smokers), and 8 for time since quitting. Publications containing data that were partially excluded from the present meta-analysis, with the corresponding reasons of exclusion, are described in Supplementary Table 5. The quality score of included case-control and cohort studies are shown in Supplementary Table 6 and Supplementary Table 7, respectively. Overall, 11 (33%) case-control and 5 (71%) cohort studies were scored as of high quality (i.e., NOS≥7).

2.4.2 Quantitative data synthesis

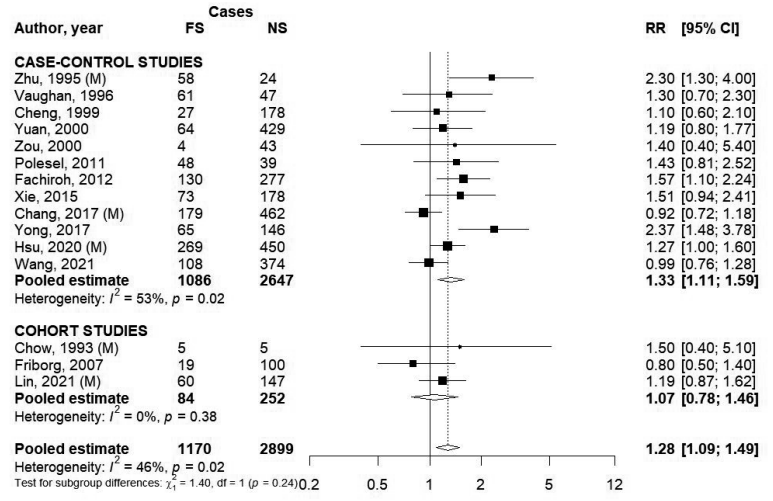
The pooled RR of NPC for current smokers compared to never smokers was 1.61 (95% CI: 1.40-1.86), and was non-significantly lower in case-control (RR: 1.61; 95% CI: 1.37-1.91) than in cohort (RR: 1.85; 95% CI: 1.11-3.07) studies (Figure 1). Corresponding RR estimates for former smokers compared to never smokers were 1.28 (95% CI: 1.09-1.49) overall, 1.33 (95% CI: 1.11-1.59) in case-control studies, and 1.07 (95% CI: 0.78-1.46) in cohort studies (Figure 2). The pooled RR for ever smokers compared to never smokers was 1.62 (95% CI: 1.41-1.87) overall, 1.64 (95% CI: 1.41-1.91) in case control and 1.46 (95% CI: 1.00-2.12) in cohort studies (Supplementary Figure 2).

Figure 1. Forest plot of study-specific and pooled relative risk (RR) of nasopharyngeal cancer (NPC) for current cigarette smokers (CS) versus never smokers (NS), by study design.



CI: confidence interval; M: males.

Figure 2. Forest plot of study-specific and pooled relative risk (RR) of nasopharyngeal cancer (NPC) for former cigarette smokers (FS) versus never smokers (NS), by study design.



CI: confidence interval; M: males.

The pooled RRs for specific cancer subsites are detailed in Table 1 and in Supplementary Tables 3 and 4. Compared with never smokers, the RR for differentiated squamous cell carcinoma of the nasopharynx was 4.79 (95% CI: 2.50-9.20; n=2) for current smokers, 1.75 (95% CI: 0.91-3.34; n=2) for former smokers, and 2.37 (95% CI: 1.69-3.32; n=5) for ever smokers. The RR for undifferentiated NPC was 0.92 (95% CI: 0.36-2.34; n=2) for current smokers, 1.36 (95% CI: 0.88-2.10; n=2) for former smokers, and 1.06 (95% CI: 0.78-1.44; n=4) for ever smokers.

Possible sources of heterogeneity were investigated through stratified analyses (Table 1 and Supplementary Figure 5). Among current smokers, significant differences have been observed according to endpoint (RRs of NPC were 1.35 in cohort studies on incidence and 3.42 in cohort studies on mortality, p<0.01). Among former smokers, significant differences were observed according to number of cases (RRs of NPC were 1.75 for studies with less than 151 cases, 1.40 in studies with a number of cases between 150 and 700, and 1.09 in studies with more than 700 cases; p=0.03), adjustments (RRs of NPC were 2.14 for studies with non-adequate adjustments and 1.28 for studies with adequate adjustments; p=0.01), and geographic area (RRs of NPC were 1.72 in studies conducted in North America, 1.43 in a study conducted in Europe, and 1.22 in studies conducted in Asia; p=0.03). Among ever smokers, a significant difference was observed according to type of controls in case-control studies (RRs of NPC were 1.33 for studies with hospital controls and 1.77 for studies with population controls; p=0.02).

Table 1. Pooled relative risk (RR) and corresponding 95% confidence interval (CI) for nasopharyngeal cancer (NPC) risk for current, former, and ever cigarette smokers vs. never cigarette smokers, overall and in strata of selected characteristics.

Strata	Current smokers				Former smokers				Ever smokers			
	N. studies	Pooled RR (95% CI)	p-value*	p-value#	N. studies	Pooled RR (95% CI)	p-value*	p-value#	N. studies	Pooled RR (95% CI)	p-value*	p-value#
Total	16	1.61 (1.40-1.86)	-	<0.01	15	1.28 (1.09-1.49)	-	0.03	37	1.62 (1.41-1.87)	-	<0.01
Type of study												
Case-control	12	1.61 (1.37-1.91)	<0.01	<0.01	12	1.33 (1.11-1.59)	0.24	0.02	33	1.64 (1.41-1.91)	0.57	<0.01
Cohort	4	1.85 (1.11-3.07)		0.05	3	1.07 (0.78-1.46)		0.38	4	1.46 (1.00-2.12)		0.09
Histological Type												

SQC NPC	2	4.79 (2.50-9.20)	-	0.45	2	1.75 (0.91-3.34)	-	0.63	5	2.37 (1.69-3.32)	-	0.85
UD NPC	2	0.92 (0.36-2.34)		0.11	2	1.36 (0.88-2.10)		0.83	4	1.06 (0.78-1.44)		0.23
Sex												
Men	5	1.43 (1.28-1.61)	0.89	0.59	5	1.23 (1.06-1.42)	0.32	0.54	9	1.41 (1.29-1.53)	0.46	0.55
Women	2	1.38 (0.79-2.40)		0.94	2	0.88 (0.46-1.68)		0.17	4	1.95 (0.82-4.62)		0.02
Type of controls[a]												
Hospital	4	1.53 (1.33-1.77)	0.46	0.79	4	1.24 (1.03-1.48)	0.38	0.44	9	1.33 (1.17-1.52)	0.02	0.24
Population	8	1.77 (1.24-2.53)		<0.01	8	1.41 (1.12-1.77)		0.20	22	1.77 (1.46-2.13)		<0.01
Endpoint[b]												
Incidence	2	1.35 (1.12-1.63)	<0.01	0.81	2	1.03 (0.71-1.50)	0.38	0.20	3	1.48 (0.91-2.41)	0.85	0.04
Mortality	3	3.42 (1.93-6.06)		0.93	1	1.50 (0.42-5.36)		-	1	1.64 (0.64-4.20)		-
Number of cases[c]												
<151	4	1.52 (1.12-2.06)	0.15	0.22	4	1.75 (1.22-2.53)	0.03	0.67	14	1.93 (1.41-2.62)	0.31	<0.01
151-700	6	1.97 (1.41-2.76)		<0.01	6	1.40 (1.07-1.83)		0.03	14	1.61 (1.33-1.96)		<0.01
≥701	6	1.40 (1.27-1.54)		0.33	5	1.09 (0.92-1.29)		0.26	9	1.41 (1.10-1.81)		<0.01
Adjustments[d]												
Non-adequate	4	2.80 (1.43-5.46)	0.07	<0.01	3	2.14 (1.41-3.24)	0.01	0.64	7	1.64 (0.99-2.74)	0.99	<0.01
Adequate	12	1.49 (1.35-1.64)		0.01	12	1.28 (1.09-1.49)		0.18	30	1.64 (1.44-1.87)		<0.01
Study Quality												
Low (NOS<7)	7	1.86 (1.40-2.47)	0.07	<0.01	7	1.42 (1.13-1.77)	0.27	0.13	22	1.55 (1.29-1.87)	0.37	<0.01
High (NOS≥7)	9	1.41 (1.28-1.55)		<0.01	8	1.20 (1.01-1.44)		0.15	15	1.75 (1.46-2.10)		<0.01
Geographic area[e]												
North America	3	2.24 (1.28-3.90)	0.46	0.14	3	1.72 (1.09-2.71)	0.03	0.38	6	1.99 (1.56-2.53)	0.10	0.81
Europe	1	1.52 (0.89-2.60)		-	1	1.43 (0.81-2.52)		-	2	1.46 (1.46-2.23)		<0.01
Asia	12	1.56		<0.01	11	1.22		0.03	29	1.64		0.54

		(1.34-1.81)				(1.03-1.44)				(1.37-1.96)		
Income group[f]												
High income	7	1.70 (1.38-2.10)	0.67	0.16	7	1.36 (1.04-1.78)	0.54	0.20	11	1.63 (1.35-1.97)	0.98	0.32
Middle or low income	9	1.59 (1.28-1.98)		<0.01	8	1.23 (1.01-1.50)		0.03	26	1.63 (1.35-1.96)		<0.01
Year of publication												
≤2000	7	1.66 (1.25-2.21)	0.99	<0.01	6	1.39 (1.05-1.83)	0.03	0.51	13	1.58 (1.32-1.89)	0.76	0.20
2001-2014	3	1.62 (1.62-2.17)		0.33	3	1.24 (0.82-1.88)		0.10	12	1.57 (1.13-2.17)		<0.01
≥2015	6	1.66 (1.24-2.23)		<0.01	6	1.25 (0.98-1.58)		<0.01	12	1.75 (1.39-2.21)		<0.01

* p-value for heterogeneity across strata.

p-value for heterogeneity within strata.

[a] Type of controls for case-control studies only. Studies considering both studies with hospital and with population controls were not included.

[b] Endpoint for cohort studies only. Studies providing RRs for both incidence and mortality were considered in both categories.

[c] Studies in which the number of cases was not reported were excluded.

[d] Estimates adjusted for, at least, age, sex, and at least one of the following variables: alcohol consumption, Epstein-Barr Virus infection, race, diet, and family history of NPC, and exposure to pollutants (e.g., air pollution, radon, asbestos).

[e] Studies conducted in multiple countries from different geographic areas were not included. No studies from Africa, South America, or Oceania.

[f] Studies conducted in multiple countries with different income groups were not included.

NOS: Newcastle Ottawa Scale; SQC: squamous cell; UD: undifferentiated.

2.4.3 Publication bias

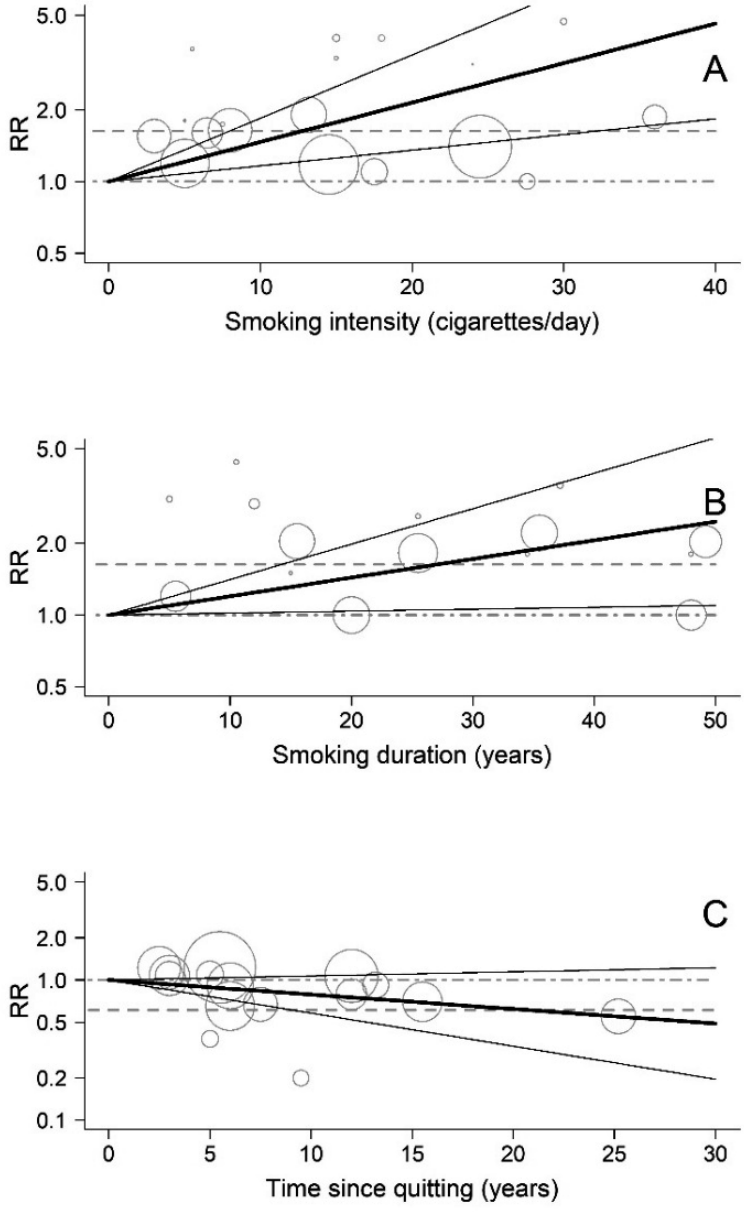
Evidence of possible publication bias emerged for the analysis of current compared with never smokers both from the visual inspection of the funnel plot (Supplementary Figure 6, panel A) and from the Egger's test (p=0.02), while there was no evidence of publication bias in either former or ever smokers (Supplementary Figure 6, panels B and C; p=0.15 and p=0.11, respectively).

2.4.4 Dose-response analysis

Figure 3 shows the dose-response relationships between smoking intensity, duration, and time since quitting in relation to the risk of NPC. A linear increase

in NPC risk was observed with increasing smoking intensity among current smokers (RRs were 1.47; 95% CI: 1.16-1.84 for 10 cigarettes per day and 2.14; 95% CI: 1.35-3.40 for 20 cigarettes per day; Figure 3, panel A). The risk of NPC also increased linearly with increasing duration of smoking: RRs were 1.44 (95% CI: 1.04-1.99) for 20 years and 2.06 (95% CI: 1.08-3.94) for 40 years of smoking (Figure 3, panel B). A non-significant inverse linear association was observed between time since quitting smoking and the risk of NPC, with the RR for former smokers compared with current smokers being 0.79 (95% CI: 0.58-1.06) after 10 years and 0.62 (95% CI: 0.34-1.14; Figure 3, panel C) after 20 years. Thus, the risk for former compared to current smokers after 20 years since smoking cessation is equivalent to the risk for never compared to current smokers (RR=0.62).

Figure 3. Relative risk (RR) for the dose-response relationships between cigarette smoking intensity, duration, and time since quitting and nasopharyngeal cancer.



A: cigarette smoking intensity (based on 5 studies); B: cigarette smoking duration (based on 5 studies); C: time since quitting (based on 8 studies).

——— Linear model;

——— 95% confidence interval of the linear models;

– · – · – RR for the reference category (never smokers in A and B, current smokers in C);

– – – – RR for current vs. never cigarette smokers (A and B) former vs. current cigarette smokers (C);

◯ RR for various exposure categories in each study included in the analysis. The area of the circle is proportional to the precision (i.e. to the inverse variance) of the RR.

2.5 Discussion

This systematic review and meta-analysis provides up-to-date and comprehensive evidence on the association between cigarette smoking and NPC risk. It includes 46 eligible articles and uses data from 40 original articles and more than 15,000 NPC cases. Pooled risk estimates showed a 61% and 28% increased NPC risk in current and former smokers, respectively. Dose-response analyses revealed that the risk of NPC increased linearly with the intensity and duration of the smoking habit.

The most recent meta-analysis focusing on NPC alone, and not as part of the head and neck or the upper aerodigestive tract, found a 59% excess risk of NPC associated with smoking [8]. Notably, our study, which included twice as many articles, strengthens the robustness of these findings.

Our analysis revealed a significant association only between smoking and differentiated squamous cell NPC, whereas no such association was observed for undifferentiated NPC. This finding, which is consistent with previous meta-analyses on NPC [8, 9], is also aligned with patterns observed for other cancer sites, such as lung and oesophageal cancer, for which higher RRs of cancer associated with smoking were observed for squamous cell carcinoma compared with other histological subtypes [40]. Undifferentiated carcinoma accounts for more than 95% of the NPC cases in high-incidence regions, such as Asia, whereas squamous cell NPC is predominant in low-incidence regions, such as North America [41]. Furthermore, undifferentiated NPC is more strongly correlated with Epstein-Barr virus infection [42], suggesting distinct etiological pathways for this subtype. Despite potential limitations in our stratified analyses due to the limited number of studies providing stratified analyses for histological subtypes, the results suggest different risk profiles across NPC histologies, highlighting the need for further research to elucidate these complex interactions.

Most of the studies included in the meta-analysis were from Asian countries, where the incidence of NPC is 4 to 5 times higher than those observed in Europe or North America [1]. Significant heterogeneity in risk estimates across geographic area emerged among former smokers, with the lowest risk found in

the studies conducted in Asia. Non-significantly lower RRs for studies conducted in Asia compared to studies conducted in North America were also observed among current and ever smokers. This phenomenon, previously noted by Xue and colleagues [9], may be attributed to the varying histological subtypes in high- and low-risk areas, particularly to the higher prevalence of undifferentiated NPC, which appears to be less associated with smoking, in high-risk areas, such as Asia. These results also suggest that smoking does not act synergistically with factors contributing to the higher occurrence of NPC in Eastern populations, such as Epstein-Barr Virus infection.

The dose-response analyses carried out showed linear associations for smoking intensity and duration with NPC risk. These findings are generally consistent with those emerging from previously published meta-analyses, which were however based on smaller numbers of studies [8, 9]. A non-significant inverse linear dose-response association between time since quitting smoking and NPC risk emerged, with the risk of a former smoker reaching that of a never smoker after 20 years since quitting smoking. This result, which was not analysed in previous meta-analyses, sheds light on the beneficial impact of smoking cessation on NPC risk. Given the limited number of studies contributing to this analysis, its interpretation underscores the need for further research to clarify the role of smoking cessation in reducing NPC risk.

Our systematic review and meta-analysis has several strengths. The innovative methodology used to identify original articles based on a combination of umbrella and traditional reviews [15] allowed the inclusion of more than 40 epidemiological studies investigating the association between cigarette smoking and NPC risk, making this meta-analysis the most comprehensive on the topic. Notably, while the most recent NPC-specific meta-analysis identified 21 eligible studies up to its search date [8], our combined umbrella and traditional review approach identified 36 eligible studies published within the same time period. This highlights the ability of the adopted combined strategy to improve the completeness of evidence retrieval. The screening process of all the retrieved publications was carefully carried out to avoid data overlap. A comprehensive quality assessment of the included studies was performed using the NOS [22]. No significant differences in NPC among current, former, and never smokers were found according to study quality as measured by the NOS.

The limitations of this work are those typical of meta-analyses of epidemiological studies. Case-control and cohort studies are prone to selection and recall bias. Differential misclassification of exposure may have occurred since information on smoking status, smoking intensity and duration, and time since quitting was self-reported in all studies. We assumed that the impact of these biases was limited. In fact, the risk estimates were not significantly heterogeneous across study

design. It has also been observed that smokers may be over-represented among hospital-based controls, biasing the association towards the null [43]. Our results support this hypothesis, showing a weaker association in hospital-based studies compared with population-based case-control studies.

Consistent heterogeneity between studies was found for each smoking status. This may be the result of pooling data from studies conducted with different methodologies, using different definitions of smoking, and including subjects with different characteristics and background risk levels. We accounted for heterogeneity between studies using random-effects models, although these models did not completely resolve heterogeneity. We examined possible sources of heterogeneity in risk estimates through stratified analyses according to histological subtype of cancer, socioeconomic status, and study characteristics. However, these variables only partially explained the observed heterogeneity.

In conclusion, this meta-analysis confirms the association between cigarette smoking and NPC, and shows that even moderate cigarette consumption can significantly increase the risk. These findings underscore the need for continued research to identify risk factors associated with the high prevalence of undifferentiated NPC in high-incidence regions, such as Eastern Asia. In addition, these results are important to reduce the burden of NPC and highlight the importance of distinguishing between histological subtypes in NPC risk assessment and prevention. People should avoid smoking, and current smokers should quit to reduce the risk.

2.6 Contribution to the overall thesis framework

This chapter contributed to the broader objective of generating robust epidemiological evidence on smoking-related cancer risks. Together with the analyses presented in the following chapters, it helped strengthen the evidence base required for subsequent burden estimation exercises. While nasopharyngeal cancer represents only one smoking-related malignancy, the methodological approach adopted here forms part of a wider research programme aimed at quantifying the cancer burden attributable to tobacco exposure. The next chapter expands this work by examining the association between cigarette smoking and oral and pharyngeal cancers, thereby further enriching the epidemiological evidence needed for burden estimation.

2.7 References

1. Ferlay J, Ervik M, Lam F et al. Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. Available at https://gco.iarc.who.int/today (last access 8th March 2024) 2024.
2. Chen YP, Chan ATC, Le QT et al. Nasopharyngeal carcinoma. Lancet 2019; 394: 64-80.
3. American Cancer Society. Survival Rates for Nasopharyngeal Cancer. Available at https://www.cancer.org/cancer/types/nasopharyngeal-cancer/detection-diagnosis-staging/survival-rates.html (last access 20th September 2023). 2022.
4. Carpen T, Gille E, Hammarstedt-Nordenvall L et al. Occupational risk variation of nasopharyngeal cancer in the Nordic countries. BMC Cancer 2022; 22: 1130.
5. Chen L, Gallicchio L, Boyd-Lindsley K et al. Alcohol consumption and the risk of nasopharyngeal carcinoma: a systematic review. Nutr Cancer 2009; 61: 1-15.
6. Zeng YX, Jia WH. Familial nasopharyngeal carcinoma. Semin Cancer Biol 2002; 12: 443-450.
7. IARC. Tobacco smoke and involuntary smoking. Vol. 83. IARC Monogr Eval Carcinog Risks Hum 2004; 1-1438.
8. Long M, Fu Z, Li P, Nie Z. Cigarette smoking and the risk of nasopharyngeal carcinoma: a meta-analysis of epidemiological studies. BMJ Open 2017; 7: e016582.
9. Xue WQ, Qin HD, Ruan HL et al. Quantitative association of tobacco smoking with the risk of nasopharyngeal carcinoma: a comprehensive meta-analysis of studies conducted between 1979 and 2011. Am J Epidemiol 2013; 178: 325-338.
10. IARC. Personal habits and indoor combustions. Volume 100 E. IARC Monogr Eval Carcinog Risks Hum 2012; 1-538.
11. Di Credico G, Edefonti V, Polesel J et al. Joint effects of intensity and duration of cigarette smoking on the risk of head and neck cancer: A bivariate spline model approach. Oral Oncology 2019; 94: 47-57.
12. Chang CP, Chang SC, Chuang SC et al. Age at start of using tobacco on the risk of head and neck cancer: Pooled analysis in the International Head and Neck Cancer Epidemiology Consortium (INHANCE). Cancer Epidemiol 2019; 63: 101615.
13. Botteri E, Borroni E, Sloan EK et al. Smoking and colorectal cancer risk, overall and by molecular subtypes: a meta-analysis. Am J Gastroenterol 2019; 115: 1940-1949.
14. Lugo A, Peveri G, Bosetti C et al. Strong excess risk of pancreatic cancer for low frequency and duration of cigarette smoking: A comprehensive review and meta-analysis. Eur J Cancer 2018; 104: 117-126.

15. Lugo A, Peveri G, Gallus S. Should we consider gallbladder cancer a new smoking-related cancer? A comprehensive meta-analysis focused on dose-response relationships. Int J Cancer 2019; 146: 3304-3311.
16. Possenti I, Scala M, Carreras G et al. Exposure to second-hand smoke and breast cancer risk in non-smoking women: a comprehensive systematic review and meta-analysis. In press. Br J Cancer 2024.
17. Rota M, Possenti I, Valsassina V et al. Dose-response association between cigarette smoking and gastric cancer risk: a systematic review and meta-analysis. Gastric Cancer 2024; 27: 197-209.
18. Scala M, Bosetti C, Bagnardi V et al. Dose-response relationships between cigarette smoking and breast cancer risk: a systematic review and meta-analysis. Journal of Epidemiology 2023.
19. Lugo A, Bosetti C, Peveri G et al. Dose-response relationship between cigarette smoking and site-specific cancer risk: protocol for a systematic review with an original design combining umbrella and traditional reviews. BMJ Open 2017; 7: e018930.
20. Hamling J, Lee P, Weitkunat R, Ambuhl M. Facilitating meta-analyses by deriving relative effect and precision estimates for alternative comparisons from a set of estimates presented by exposure level or disease category. Stat Med 2008; 27: 954-970.
21. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986; 7: 177-188.
22. Wells GA, Shea B, O'Connell D et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses (accessed 23 November 2023). 2014.
23. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002; 21: 1539-1558.
24. Peters JL, Sutton AJ, Jones DR et al. Contour-enhanced meta-analysis funnel plots help distinguish publication bias from other causes of asymmetry. J Clin Epidemiol 2008; 61: 991-996.
25. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315: 629-634.
26. Crippa A, Discacciati A, Bottai M et al. One-stage dose-response meta-analysis for aggregated data. Stat Methods Med Res 2019; 28: 1579-1596.
27. Desquilbet L, Mariotti F. Dose-response analyses using restricted cubic spline functions in public health research. Stat Med 2010; 29: 1037-1057.
28. Bagnardi V, Rota M, Botteri E et al. Alcohol consumption and site-specific cancer risk: a comprehensive dose-response meta-analysis. Br J Cancer 2015; 112: 580-593.
29. Berlin JA, Longnecker MP, Greenland S. Meta-analysis of epidemiologic dose-response data. Epidemiology 1993; 4: 218-228.
30. Crippa A, Orsini N. Multivariate Dose-Response Meta-Analysis: The dosresmeta R Package. Journal of Statistical Software 2016; 72.

31. Balduzzi S, Rucker G, Schwarzer G. How to perform a meta-analysis with R: a practical tutorial. Evid Based Ment Health 2019; 22: 153-160.

32. Ban EZ, Lye MS, Chong PP et al. Haplotype CGC from XPD, hOGG1 and ITGA2 polymorphisms increases the risk of nasopharyngeal carcinoma in Malaysia. PLoS One 2017; 12: e0187200.

33. Chang ET, Liu Z, Hildesheim A et al. Active and Passive Smoking and Risk of Nasopharyngeal Carcinoma: A Population-Based Case-Control Study in Southern China. Am J Epidemiol 2017; 185: 1272-1280.

34. Hsu WL, Chien YC, Huang YT et al. Cigarette smoking increases the risk of nasopharyngeal carcinoma through the elevated level of IgA antibody against Epstein-Barr virus capsid antigen: A mediation analysis. Cancer Med 2020; 9: 1867-1876.

35. Hu T, Lin CY, Xie SH et al. Smoking can increase nasopharyngeal carcinoma risk by repeatedly reactivating Epstein-Barr Virus: An analysis of a prospective study in southern China. Cancer Med 2019; 8: 2561-2571.

36. Oudjehih M, Deltour I, Bouhidel ML et al. Smokeless Tobacco Use, Cigarette Smoking, and Upper Aerodigestive Tract Cancers: A Case-Control Study in the Batna Region, Algeria, 2008-2011. Tob Use Insights 2020; 13: 1179173x20902239.

37. Singh SA, Ghosh SK. Polymorphisms of XRCC1 and XRCC2 DNA Repair genes and Interaction with Environmental Factors Influence the Risk of Nasopharyngeal Carcinoma in Northeast India. Asian Pac J Cancer Prev 2016; 17: 2811-2819.

38. Singh SA, Ghosh SK. Metabolic Phase I (CYPs) and Phase II (GSTs) Gene Polymorphisms and Their Interaction with Environmental Factors in Nasopharyngeal Cancer from the Ethnic Population of Northeast India. Pathol Oncol Res 2019; 25: 33-44.

39. Wang L, Mai ZM, Ngan RK et al. Dose-Response Reduction in Risk of Nasopharyngeal Carcinoma From Smoking Cessation: A Multicenter Case-Control Study in Hong Kong, China. Front Oncol 2021; 11: 699241.

40. Lubin JH, Cook MB, Pandeya N et al. The importance of exposure rate on odds ratios by cigarette smoking and alcohol consumption for esophageal adenocarcinoma and squamous cell carcinoma in the Barrett's Esophagus and Esophageal Adenocarcinoma Consortium. Cancer Epidemiol 2012; 36: 306-316.

41. Chang ET, Adami HO. The enigmatic epidemiology of nasopharyngeal carcinoma. Cancer Epidemiol Biomarkers Prev 2006; 15: 1765-1777.

42. Tsao SW, Tsang CM, Pang PS et al. The biology of EBV infection in human epithelial cells. Semin Cancer Biol 2012; 22: 137-143.

43. Sadetzki S, Bensal D, Novikov I, Modan B. The limitations of using hospital controls in cancer etiology--one more example for Berkson's bias. Eur J Epidemiol 2003; 18: 1127-1131.

Annex Chapter 2

PRISMA checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Pag 46
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Pag 47
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Pag 48
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Pag 48
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Pag 50-51
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Pag 50
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Suppl
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Pag 50
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Pag 51
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Pag 51

Section and Topic	Item #	Checklist item	Location where item is reported
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Pag 51
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Pag 51
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Pag 51-52
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Pag 51-52
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Pag 52
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Pag 51-52
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Pag 51-52
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Pag 51
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Pag 51
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Pag 52
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	NA
RESULTS			

Section and Topic	Item #	Checklist item	Location where item is reported
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Pag 52-53
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Suppl
Study characteristics	17	Cite each included study and present its characteristics.	Suppl
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Suppl
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Pag 53-54, Suppl
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Suppl
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Pag 53-54, Suppl
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Pag 55-56, Suppl
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Pag 55-56
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Suppl
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	NA
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Pag 59
	23b	Discuss any limitations of the evidence included in the review.	Pag 60-61

Section and Topic	Item #	Checklist item	Location where item is reported
	23c	Discuss any limitations of the review processes used.	Pag 60-61
	23d	Discuss implications of the results for practice, policy, and future research.	Pag 61
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Pag 49
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Pag 49
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Online pub
Competing interests	26	Declare any competing interests of review authors.	Online pub
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Online pub

Supplementary Materials available online at:
https://www.rhinologyjournal.com/Abstract.php?id=3239

Chapter 3

Smoking and Oral and Pharyngeal Cancer: A Meta-Analysis

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Oncology Reviews: 2026;19: 1672607.

3.1 Abstract

Introduction: Oral cavity and pharyngeal cancer (OPC) affects over 580,000 people globally each year, with tobacco and alcohol being key risk factors. This meta-analysis quantifies the excess risk of OPC associated with cigarette smoking and its patterns.

Methods: We carried out a systematic review and meta-analysis of case-control and cohort studies assessing the association between cigarette smoking and OPC risk, including articles published up to February 2025. Using a combined umbrella and traditional review approach, we estimated pooled relative risks (RR) by smoking status, intensity, duration, and time since quitting.

Results: Out of 137 eligible articles, 115 original studies were included in this meta-analysis. Relative to never smokers, the pooled risk of OPC was 3.58 (95% CI: 3.03–4.24; n=54) among current smokers, 1.61 (95% CI: 1.44–1.81; n=53) among former smokers, and 2.45 (95% CI: 2.19–2.75; n=80) among ever smokers. Subsite-specific analyses showed RRs of 3.39 (95% CI: 2.64–4.35; n=25) for oral cancer and 4.24 (95% CI: 2.96–6.09; n=18) for pharyngeal cancer in current versus never smokers. Risk rose steeply with both smoking intensity and duration, doubling after 6 cigarettes per day or 7 years of smoking, before reaching a plateau around an RR of 5 at 20 cigarettes per day or 20 years. The risk declined nonlinearly with longer time since quitting, with a 50% reduction observed within seven years of cessation.

Conclusion: Our findings reaffirm the substantial impact of smoking on OPC risk and stress the need for efforts to avoid smoking initiation and support cessation.

3.2 Introduction

The annual worldwide incidence of oral cavity cancer is estimated at almost 400,000 cases, while pharyngeal cancer (excluding nasopharyngeal cancer) accounts for almost 200,000 new cases each year [1]. In terms of mortality, an estimated 188,230 deaths occur annually due to oral cavity cancer, while pharyngeal cancer (excluding nasopharyngeal cancers) is associated with approximately 93,185 deaths per year [1]. Nearly two-thirds of all new cases of oral cavity and pharyngeal cancer (OPC) each year arise in Asian countries, with the highest numbers reported in Sri Lanka, Indonesia, India, Pakistan and Bangladesh [2].

Several risk factors for the development of OPC have been identified in the scientific literature. Among these, the most studied are tobacco use and alcohol consumption [3, 4]. Other important risk factors for OPC are the use of betel, a substance derived from the betel palm, which is widespread in South East Asia and increases the risk of OPC by more than 4 times [5], and human papillomavirus (HPV) infection. HPV infection has been estimated to increase the risk of OPC by more than 60% [6]. In contrast, regular consumption of fruit and vegetables has been identified as a protective factor, reducing the risk of OPC by approximately 25% [7].

Trends in the disease in recent years have been influenced by changes in the lifestyles of different populations. In southern European men, where alcohol and tobacco consumption has declined since the mid-1980s, mortality from OPC has declined steadily over the years. In contrast, in Central and Eastern European countries, where consumption of these substances has remained high, deaths have increased in recent decades [8]. In Asian countries, the number of OPC cases remains constant and very high [9], partly due to the large consumption of betel among the population [10].

Although the association between smoking and OPC is well established in literature, there is a lack of recent meta-analyses that focus on these cancer sites individually, rather than grouping them under the broader categories of head and neck cancer or upper aerodigestive tract cancer [11, 12].

The primary aim of this meta-analysis is to provide a precise quantification of the association between cigarette smoking and OPC risk, thereby addressing the gap left by recent meta-analyses on the topic. An additional goal is to compare subgroups based on sex, geographic area, and cancer anatomical subtype, amongst others, and to evaluate dose-response relationships, including smoking intensity, duration, and time since quitting.

3.3 Methods

This work is part of a broader series of systematic reviews and meta-analyses investigating the link between cigarette smoking, secondhand smoke (SHS) exposure, and cancer risk [13-22]. To ensure we identified all relevant original studies efficiently and thoroughly, we used a two steps approach [15]. As a first step, we carried out an umbrella review to comprehensively identify meta-analyses, pooled analyses, and reviews that had examined the link between cigarette smoking and the risk of OPC. From these meta-analyses, pooled analyses and reviews, we extracted the original studies included in the identified reviews, allowing us to gather all high-quality evidence already available. Following this, a traditional review was undertaken to identify original studies published after the most recent comprehensive review. The study protocol is available in PROSPERO (registration number CRD42017063991).

The review was conducted in accordance with the PRISMA 2020 guidelines whenever applicable. Due to the combined umbrella review and traditional review design, a conventional PRISMA flowchart could not be fully applied, as the study identification and selection process differed from that of a standard systematic review. A completed PRISMA checklist is provided in the Annex 1.

The search strategy, inclusion criteria, and data extraction procedures are detailed in Annex.

We computed pooled relative risks (RR) for current, former, and ever smokers versus never smokers, both overall and separately by study type (cohort and case-control).

All analyses were performed using R software version 4.2.2 (R Development Core Team, 2017), utilizing the "meta" and "dosresmeta" packages for statistical computations.

3.4 Results

3.4.1 Study selection and description

Out of 137 eligible original articles, 22 were excluded as their participants overlapped with those reported in other included studies (Supplementary Table 2). Consequently, 115 original studies—comprising 87 case-control and 28 cohort designs—fulfilled the inclusion criteria and were incorporated into this meta-analysis (Supplementary Tables 3 and 4). These studies, published between 1969 and 2024, encompassed data on over 40,000 cases of oral or pharyngeal cancer. Of these, 64 studies provided data specifically for oral cancer,

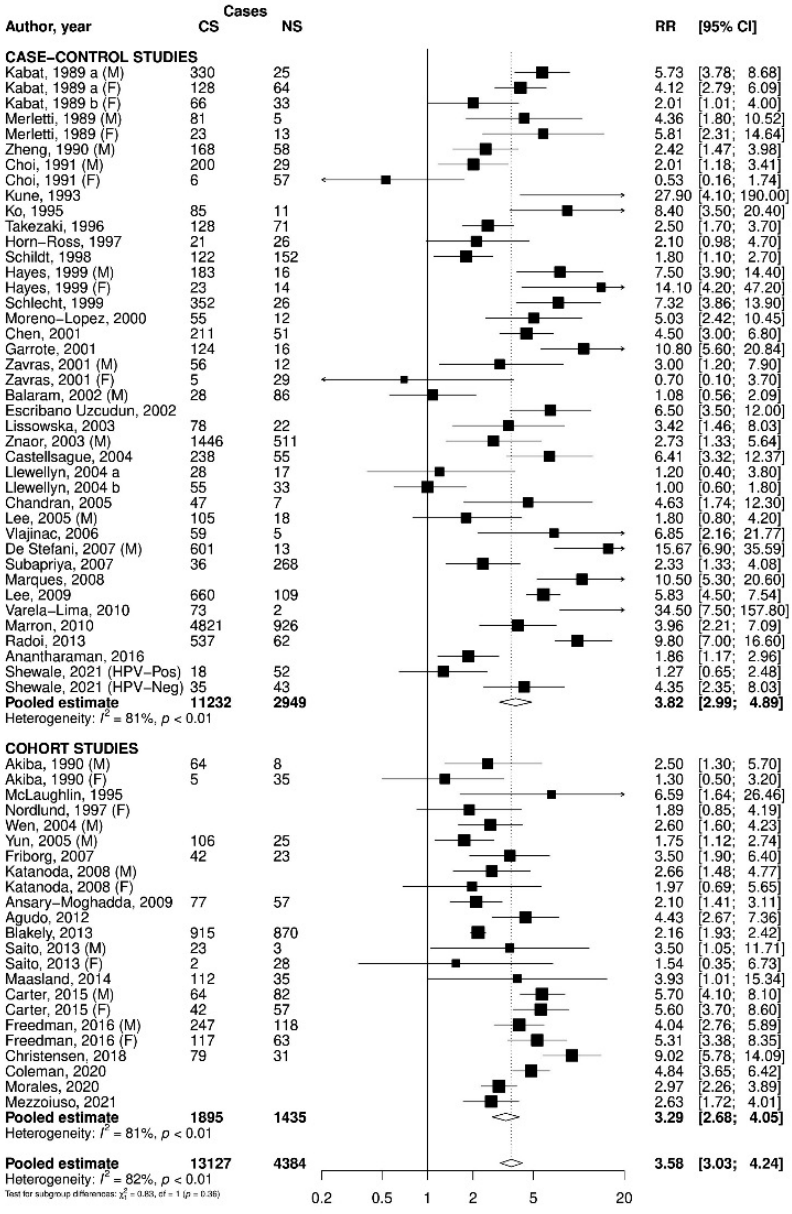
49 for pharyngeal cancer, and 36 studies provided only combined data for both anatomical subtypes.

A total of 54 studies on OPC reported risk estimates (or data allowing their calculation) for current smokers, 53 for former smokers, and 80 for ever smokers, all compared to never smokers. Additionally, 43 studies provided RR by smoking intensity (including 20 among current smokers), 30 by smoking duration (10 among current smokers), and 22 by time since quitting. Publications partially excluded from this meta-analysis, along with reasons for exclusion, are detailed in Supplementary Table 5. Quality assessments for case-control and cohort studies are presented in Supplementary Tables 6 and 7, respectively, identifying 11 high-quality case-control and 14 high-quality cohort studies.

3.4.2 Quantitative data synthesis

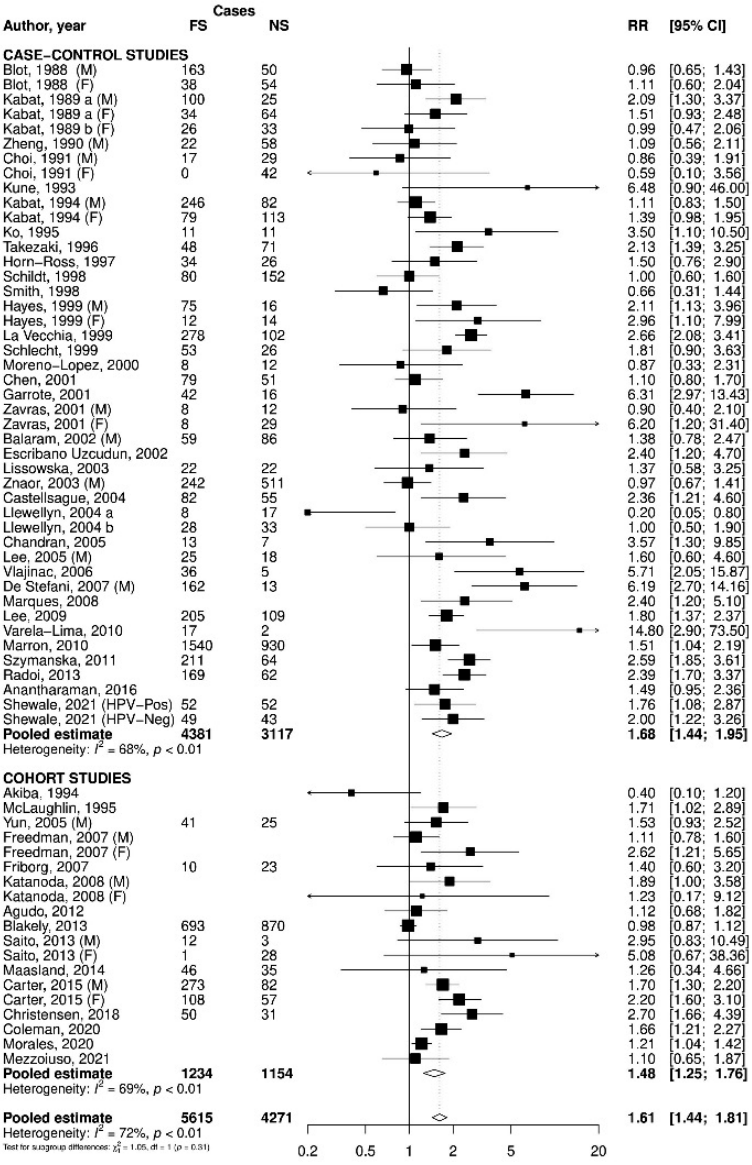
The overall pooled RR of OPC for current smokers compared to never smokers was 3.58 (95% CI: 3.03-4.24), with case-control studies reporting a RR of 3.82 (95% CI: 2.99-4.89) and cohort studies 3.29 (95% CI: 2.68-4.05) (Figure 1). For former smokers versus never smokers, the pooled RR was 1.61 (95% CI: 1.44-1.81), with estimates of 1.68 (95% CI: 1.44-1.95) in case-control and 1.48 (95% CI: 1.25-1.76) in cohort studies (Figure 2). Among ever smokers, the overall RR was 2.45 (95% CI: 2.19-2.75), with 2.55 (95% CI: 2.21-2.94) in case-control and 2.15 (95% CI: 1.81-2.54) in cohort studies (Supplementary Figure 2). Significant heterogeneity was observed across all pooled estimates.

Figure 1. Forest plot of study-specific relative risks (RR) and pooled relative risk (RR) of oral and pharyngeal cancer for current cigarette smokers (CS) versus never smokers (NS), overall and stratified by study design.



CI: confidence interval; F: females; HPV+: Human Papillomavirus test positive subjects; HPV -: Human Papillomavirus test negative subjects; M: males.

Figure 2. Forest plot of relative risks (RR) of oral and pharyngeal cancer for former cigarette smokers (FS) versus never smokers (NS), overall and stratified by study design.



CI: confidence interval; F: females; HPV+: Human Papillomavirus test positive subjects; HPV -: Human Papillomavirus test negative subjects; M: males.

3.4.3 Stratified Analyses

The RRs stratified by anatomical subtype are reported in Supplementary Figures 3-5 for oral cavity cancer (3.39 for current and 1.41 for former smokers) and in Supplementary Figures 6-8 for pharyngeal cancer (4.24 for current and 1.94 for former smokers.

In the anatomical subtype analysis, the RR for oral cavity cancer was 3.39 (95% CI: 2.64-4.35; n=25; Supplementary Figure 3) for current smokers, 1.41 (95% CI: 1.20-1.66; n=23; Supplementary Figure 4) for former smokers, and 2.18 (95% CI: 1.89-2.52; n=47; Supplementary Figure 5) for ever smokers. For pharyngeal cancer, the RR was 4.24 (95% CI: 2.96-6.09; n=18; Supplementary Figure 6) in current smokers, 1.94 (95% CI: 1.41-2.67; n=18; Supplementary Figure 7) for former smokers, and 3.25 (95% CI: 2.56-4.14; n=30; Supplementary Figure 8) for ever smokers. Regarding pharyngeal subsites, the RR for oropharyngeal cancer was 3.20 (95% CI: 2.25-4.55; n=5) for current smokers and , 2.31 (95% CI: 1.26-4.23; n=4) for former smokers, and 2.94 (95% CI: 2.02-4.29; n=12) for ever smokers. The RR for hypopharyngeal cancer was 4.21 (95% CI: 0.78-22.59; n=2) for current smokers and, 1.80 (95% CI: 0.20-16.00; n=2) for former smokers, and 3.95 (95% CI: 2.56-6.08; n=8) for ever smokers.

Regarding histological subtype, the RR for squamous cell carcinoma of the oral cavity and pharynx was 3.31 (95% CI: 2.07-5.30; n=11) among current smokers, 1.86 (95% CI: 1.16-2.99; n=9) for former smokers, and 2.28 (95% CI: 1.71-3.03; n=17) for ever smokers, all compared to never smokers (Table 1).

Potential heterogeneity was further investigated through stratified analyses. For current smokers, marked geographic differences emerged, with the highest RRs observed in South America (10.02) and Oceania (6.44), intermediate values in North America (5.01), Europe (3.59), and Africa (4.63, single study), and the lowest in Asia (2.26; p for interaction subgroup differences <0.01). In case-control studies of former smokers, risk estimates varied by control type, being higher in studies with hospital controls (1.90) than in those with population controls (1.35). According to endpoint in cohort studies, significantly higher RR estimates were observed in studies analysing mortality than incidence, both for former and for ever smokers (RRs were 1.89 for mortality and 1.14 for incidence for former smokers, and 2.69 for mortality and 1.83 for incidence for ever smokers; p for interaction subgroup differences <0.01).A significant difference was also observed among ever versus never smokers according to HPV serology (RRs were 3.28 for subjects with HPV negative serology and 1.35 for those with HPV positive serology; p-value for subgroup difference=0.02). Stratified analyses based on NOS quality scores, distinguishing high-quality studies (NOS ≥ 7) from lower-quality ones (NOS < 7), revealed no meaningful differences in OPC risk

estimates for current, former, or ever smokers versus never smokers. Similarly, no significant variation emerged when stratifying by NOS quality score, sex, sample size, adequacy of confounder adjustment, geographic region, income level, or publication year.

Table 1. Pooled relative risk (RR) and corresponding 95% confidence interval (CI) for oral and pharyngeal (OPC) risk for current, former, and ever cigarette smokers vs. never cigarette smokers, overall and in strata of selected characteristics.

Strata	Current smokers				Former smokers				Ever smokers			
	N. studies	Pooled RR (95% CI)	p-value[a]	p-value[b]	N. studies	Pooled RR (95% CI)	p-value[a]	p-value[b]	N. studies	Pooled RR (95% CI)	p-value[a]	p-value[b]
Total	54	3.58 (3.03-4.24)	-	<0.01	53	1.61 (1.44-1.81)	-	<0.01	80	2.45 (2.19-2.75)	-	<0.01
Histological Type												
Squamous cell	11	3.31 (2.07-5.30)	-	<0.01	9	1.86 (1.16-2.99)	-	<0.01	17	2.28 (1.71-3.03)	-	<0.01
Anatomical Subtype												
Oral cavity	25	3.39 (2.64-4.35)	-	<0.01	23	1.41 (1.20-1.66)	-	<0.01	47	2.18 (1.89-2.52)	-	<0.01
Pharynx	18	4.24 (2.96-6.09)	-	<0.01	18	1.94 (1.41-2.67)	-	<0.01	30	3.25 (2.56-4.14)	-	<0.01
Oropharynx	5	3.20 (2.25-4.55)	-	0.07	4	2.31 (1.26-4.23)	-	0.12	12	2.94 (2.02-4.29)	-	<0.01
Hypopharynx	2	4.21 (0.78-22.59)	-	0.11	2	1.80 (0.20-16.00)	-	<0.01	8	3.95 (2.56-6.08)	-	<0.01
Type of study												
Case-control	36	3.82 (2.99-4.89)	0.36	<0.01	38	1.68 (1.44-1.95)	0.31	<0.01	62	2.55 (2.21-2.94)	0.13	<0.01
Cohort	18	3.29 (2.68-4.05)		<0.01	15	1.48 (1.25-1.76)		<0.01	18	2.15 (1.81-2.54)		<0.01
Sex												
Women	16	2.77 (1.89-4.07)	0.77	<0.01	14	1.50 (1.17-1.93)	0.38	0.06	17	2.05 (1.51-2.77	0.36	<0.01
Men	22	2.98 (2.27-3.89)		<0.01	20	1.28 (1.00-1.65)		<0.01	29	2.47 (1.91-3.19)		<0.01

Type of controls[c]											
Hospital	21	3.93 (2.83-5.46)	0.76	<0.01	26	1.90 (1.55-2.32)	0.04	<0.01	33	2.47 (2.03-3.00)	0.58	<0.01
Population	11	3.59 (2.23-5.78)		<0.01	10	1.35 (1.04-1.75)		<0.01	22	2.72 (2.03-3.66)		<0.01
Endpoint[d]												
Incidence	9	3.00 (2.35-3.82)	0.45	<0.01	9	1.14 (0.99-1.31)	<0.01	0.12	13	1.83 (1.54-2.17)	<0.01	<0.01
Mortality	9	3.51 (2.53-4.86)		<0.01	6	1.89 (1.63-2.20)		0.66	6	2.69 (2.13-3.40)		0.08
HPV status												
Negative		-				-			4	3.28 (1.77-6.08)	0.02	<0.01
Positive									4	1.35 (0.90-2.02)		0.20
Number of cases[e]												
<126	20	3.11 (2.38-4.06)	0.43	<0.01	17	1.59 (1.06-2.38)	0.12	<0.01	27	2.34 (1.86-2.94)	0.16	<0.01
126-374	17	4.00 (2.89-5.54)		<0.01	16	1.89 (1.62-2.22)		0.04	29	2.29 (1.86-2.82)		<0.01
≥375	15	3.89 (2.82-5.11)		<0.01	19	1.49 (1.27-1.76)		<0.01	21	2.92 (2.42-3.51)		<0.01
Adjustments[f]												
Non-adequate	20	3.42 (2.67-4.38)	0.67	<0.01	17	1.49 (1.23-1.80)	0.32	<0.01	38	2.40 (2.01-2.86)	0.82	<0.01
Adequate	34	3.68 (2.93-4.62)		<0.01	36	1.68 (1.45-1.94)		<0.01	42	2.46 (2.13-2.84)		<0.01
Adjustment for betel quid or tobacco chewing [g]												
Non-adjusted	9	2.26 (1.91-2.68)	0.81	0.42	8	1.47 (1.11-1.94)	0.11	0.18	20	2.20 (1.76-2.77)	0.44	<0.01
Adjusted	5	2.45 (1.31-4.59)		<0.01	4	1.36 (0.87-2.12)		0.15	14	2.53 (1.95-3.28)		0.003
Study Quality												
Low (NOS<7)	43	3.64 (2.94-4.50)	0.91	<0.01	41	1.67 (1.45-1.92)	0.31	<0.01	62	2.48 (2.16-2.85)	0.58	<0.01
High (NOS≥7)	11	3.70 (3.00-4.58)		<0.01	12	1.47 (1.20-1.79)		<0.01	16	2.32 (1.94-2.78)		0.05
Geographic area[h]												
North America	11	5.01 (3.96-6.35)	<0.01	<0.01	14	1.60 (1.35-1.90)	0.28	<0.01	15	2.47 (2.06-2.96)	0.25	<0.01
Europe	19	3.59 (2.63-4.89)		<0.01	18	1.59 (1.24-2.04)		<0.01	18	2.58 (1.88-3.55)		<0.01
Asia	14	2.26		0.08	12	1.41		0.11	34	2.33		<0.01

		(1.91-2.67)			(1.12-1.78)			(1.97-2.77)	
South America	3	10.02 (6.68-15.03)	0.35	3	2.91 (1.44-5.88)	0.07	4	5.12 (2.85-9.19)	0.17
Oceania	2	6.44 (0.54-76.97)	<0.01	2	1.93 (0.33-11.42)	0.06	2	3.87 (0.38-39.30)	0.02
Africa	1	4.63 (1.74-12.31)	-	1	3.57 (1.30-9.83)	-	3	2.19 (0.88-5.45)	0.10
Income group[i]									
High income	42	3.60 (3.01-4.31)	<0.01	43	1.54 (1.37-1.73)	<0.01	52	2.46 (2.16-2.79)	<0.01
			0.50			0.07			0.83
Middle or low income	8	4.47 (2.48-8.05)	<0.01	8	2.38 (1.51-3.77)	<0.01	26	2.38 (1.86-3.05)	<0.01
Year of publication									
<2000	15	3.41 (2.49-4.66)	<0.01	17	1.44 (1.19-1.74)	<0.01	24	2.46 (1.91-3.17)	<0.01
2000-2009	23	3.35 (2.50-4.49)	<0.01	21	1.74 (1.35-2.25)	<0.01	23	2.48 (1.96-3.13)	<0.01
			0.57			0.35			0.99
≥2010	15	4.06 (3.11-5.231)	<0.01	15	1.70 (1.42-2.04)	<0.01	33	2.43 (2.09-2.83)	<0.01

[a] p-value for heterogeneity across strata.

[b] p-value for heterogeneity within strata.

[c] Type of controls for case-control studies only. Studies considering both studies with hospital and with population controls were not included in this stratification.

[d] Endpoint for cohort studies only. Studies providing RRs for both incidence and mortality, separately, were considered in both categories.

[e] Studies in which the number of cases was not reported were not included in this stratification.

[f] Estimates adjusted for, at least, age, sex, and alcohol consumption.

[g] Restricted to studies conducted in Asia

[h] Studies conducted in multiple countries from different geographic areas were not included in this stratification.

[i] Studies conducted in multiple countries with different income groups were not included in this stratification.

NOS: Newcastle Ottawa Scale.

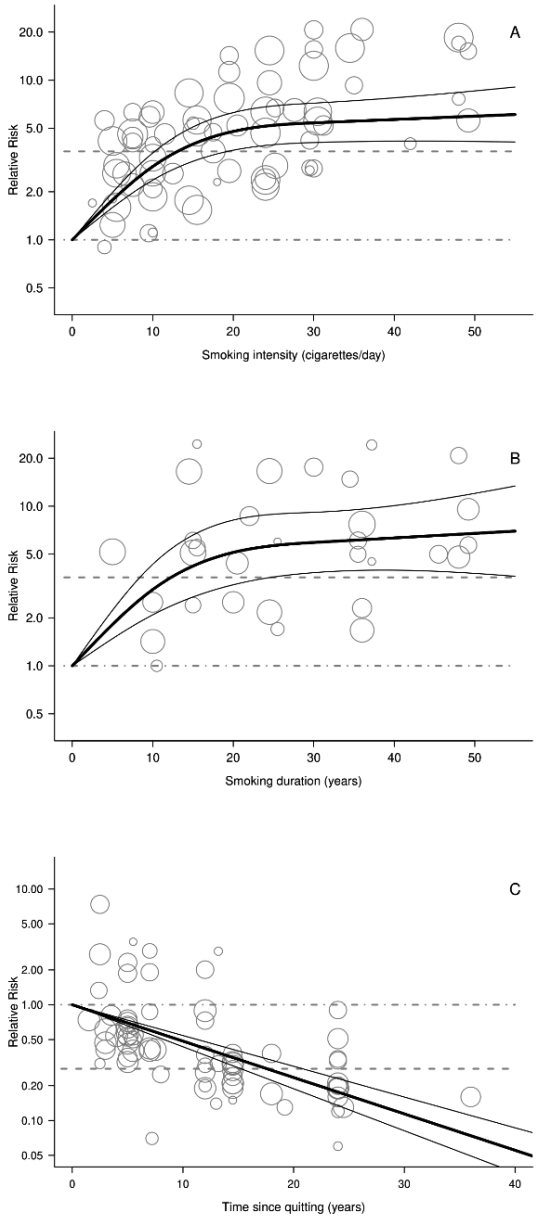
3.4.4 Publication bias

No indication of publication bias was observed for current smoking and OPC risk, based on both funnel plot inspection (Supplementary Figure 9; panel A) and Egger's test (p = 0.06). In contrast, evidence of bias emerged for former and ever smokers (p = 0.01 and p = 0.03; panels B and C, respectively). Adjusted pooled estimates obtained using the Duval and Tweedie trim-and-fill method are reported in Supplementary Table 8.

3.4.5 Dose-response analysis

Figure 3 illustrates the dose–response relationships between smoking intensity (panel A), duration (panel B), and time since quitting (panel C) and OPC risk. Among current smokers, OPC risk rose nonlinearly with intensity, increasing sharply between 5–10 and 20 cigarettes/day before plateauing. Estimated RRs were 1.98 (95% CI: 1.74–2.25) for six, 2.88 (95% CI: 2.37–3.50) for ten, and 4.78 (95% CI: 3.64–6.27) for 20 cigarettes/day (estimated using the curve functions reported in Supplementary Box 2). A nonlinear trend was also observed for smoking duration, with RRs of 2.01 (95% CI: 1.62–2.51) after seven, 2.64 (95% CI: 1.96–3.57) after ten, and 5.10 (95% CI: 3.27–7.96) after 20 years. Conversely, OPC risk declined with time since quitting, with the RR halving within seven years (0.51; 95% CI: 0.42–0.59) and approaching that of never smokers after 18 years (0.28; 95% CI: 0.17–0.33).

Figure 3. Relative risk (RR) curves illustrating the dose-response relationships between cigarette smoking and oral and pharyngeal cancer risk: (A) smoking intensity (current vs never smokers); (B) smoking duration (current vs never smokers); and (C) time since quitting smoking (former vs current smokers).



A: cigarette smoking intensity (based on 20 studies); B: cigarette smoking duration (based on 10 studies); C: time since quitting (based on 21 studies).

——— Restricted cubic spline from random-effects dose-response models (A and B) or linear model (C);
——— 95% confidence interval of the spline models;
– · – · – RR for the reference category (never smokers in A and B, current smokers in C);
– – – – RR for current vs. never cigarette smokers (A and B) former vs. current cigarette smokers (C);
◯ RR for various exposure categories in each study included in the analysis. The area of the circle is proportional to the precision (i.e. to the inverse variance) of the RR.

3.5 Discussion

This systematic review and meta-analysis offers the most up-to-date and comprehensive evidence on the relationship between cigarette smoking and oral and pharyngeal cancer (OPC). Drawing on 137 eligible publications and 115 original studies covering more than 40,000 OPC cases, our results indicate that current smokers have over a threefold higher risk of OPC compared with never smokers, while former smokers retain a 60% increased risk. Dose-response analyses demonstrated that OPC risk more than doubles with as few as six cigarettes per day or after only seven years of smoking. The risk declines substantially after quitting, with former smokers reaching half the risk within seven years of cessation.

From a public health perspective, the strong association between smoking and OPC risk underscores the need for reinforced tobacco control measures. In particular, tailored smoking cessation programs and awareness campaigns should be prioritized, especially in regions with the highest disease burden. Increasing tobacco prices through taxation represents one of the most effective strategies to reduce smoking prevalence and related health risks, particularly among young people and low-income populations [23]. These interventions are essential to prevent OPC and other smoking-related cancers.

The most recent and comprehensive meta-analysis focusing on the association between smoking and the risk of OPC, which was published in 2009, reported an increased risk (RR 3.41) similar to that found in our study [24]. That meta-analysis included 25 original articles; therefore our study, which is based on about 50% more articles, strengthens the robustness of these findings.

By relating our RR estimates for current vs never and former vs never smokers, we obtain a former vs current RR of 0.45. This estimate aligns closely with the RR of 0.44 reported in a recent meta-analysis on smoking cessation [25], further reinforcing the consistency of our findings and strengthening benefits of quitting smoking.

Our stratified analysis by anatomical subtype showed differences in the risk of OPC associated with cigarette smoking. For current smokers compared with never smokers, the pooled RR of oral cancer was 3.39, which is similar to the 3.43 RR reported in the 2008 meta-analysis conducted by Gandini et al. [4]. Although more recent meta-analyses have examined the association between smoking and oral cancer, they have focused on specific populations or histological subtypes, limiting the generalisability of their findings [26, 27]. On the other hand, the association between smoking and pharyngeal cancer has been less extensively investigated in previous meta-analyses, with the only one reporting an RR for pharyngeal cancer being Gandini's 2008 study [4]. Notably, the RR reported in this meta-analysis (RR 6.76) was significantly higher than our estimate (RR 4.24), but it was based on only seven studies, while we found 43 studies investigating pharyngeal cancer. It has been hypothesized that the higher risk associated with smoking for pharyngeal cancer compared to oral cancer is due to the aerodynamics of respiratory flow in the upper airway, as hypothesized in a previous study [28]. By providing an updated and comprehensive quantification of risk estimates for both cancer subtypes, this meta-analysis fills a critical gap in the literature.

Further stratification of pharyngeal cancer into oropharyngeal and hypopharyngeal cancer showed pooled RRs of 2.94 and 3.63, respectively, for ever versus never smokers. A previous meta-analysis investigating this difference reported a higher RR for oropharyngeal than hypopharyngeal cancer [29]. However, its estimates were based on a much smaller number of studies (3 for oropharynx and 2 for hypopharynx) compared to our analysis (12 and 8, respectively). Notwithstanding this, evidence remains scarce, with estimates for current and former smokers based on only two studies. The limited data on these subtypes highlights a critical gap in the literature. The previously hypothesised association between airflow dynamics and higher smoking-related risk in the oropharynx compared with the oral cavity [28] may also explain the difference between subtypes, as the oropharynx, being closer to the oral cavity, may reflect a decreasing exposure gradient along the airway. The limited data on these subtypes highlights a critical gap in the literature and affects the generalizability of our results, underscoring the need for additional well-designed studies focusing specifically on oropharyngeal and hypopharyngeal cancers.

To our knowledge, this is the first meta-analysis to provide risk estimates for oral and pharyngeal squamous cell carcinoma associated with smoking. The risks we found for current, former, and ever smokers for the oral and pharyngeal squamous cell carcinoma appear to be quite similar to the overall estimates for OPC. This observation contrasts with findings for other cancer sites, such as nasopharynx and lung, where higher risks associated with smoking have been documented for squamous cell carcinoma [18, 30, 31]. The lack of such difference in our results may indicate a more uniform carcinogenic effect of smoking throughout the oral cavity and pharynx, suggesting the need for further investigation into the underlying biological mechanisms and potential risk factors contributing to this phenomenon.

Our analysis shows significant differences in the risks of OPC for different endpoints in cohort studies, with higher RR estimates for mortality compared to incidence. The increased mortality risk associated with smoking suggests that not only the incidence, but also the prognosis of individuals diagnosed with these cancers is worse in smokers than in never smokers, highlighting the urgent need for effective cessation strategies and early detection in this high-risk population.

When we stratified by HPV serological status, we found that the risk associated with smoking was substantially higher among HPV-negative individuals than among HPV-positive individuals. HPV infection is one of the main etiological factors for cancers of the oral cavity and pharynx, particularly tumours arising in the oropharynx [6]. Consequently, in HPV-positive individuals, tobacco smoking's relative contribution to cancer risk may appear diluted, as HPV-driven oncogenic pathways tend to dominate tumour development [32]. Importantly, just few studies provided the stratification by HPV serological status. Future studies should therefore consider HPV status in their analyses and stratify or adjust for it appropriately, as failure to do so may mask important differences in risk magnitude across subgroups.

Significant geographic variations in risk estimates were observed for current smokers, with the lowest risks reported in studies from Asia. Non-significantly lower RRs were found in Asia compared with other regions also among former and ever smokers. These findings are in line with a previous meta-analysis focused exclusively on oral cancer, which reported an RR of 1.88 in Asia, compared with 3.62 in Africa, 7.65 in the Americas, and 3.12 in Europe [33]. Given that around two-thirds of all OPC cases occur in Asia [2], it is important to investigate other risk factors for OPC that are particularly prevalent in this region, such as betel quid and areca-nut consumption, which play a major roles in OPC etiology and may confound the association with smoking [5]. For instance, use of areca nut has been linked with oral cancer risks of approximately 7.9 in South-Central Asia [34]. However, in our stratified analysis restricted to Asian studies,

no significant differences emerged in the pooled risk estimates between studies that adjusted for betel quid or tobacco chewing and those that did not, suggesting that these factors may not fully explain the lower RRs observed in Asian populations. In addition, the lower RR observed in Asia compared with other areas may indicate Other regional factors, such as differences in smoking habits and cultural patterns on tobacco use, including the frequent use of bidis [35], could result in lower exposure to mainstream smoke compared with manufactured cigarettes and partially explain the observed geographic difference. Genetic or epigenetic factors specific to Asian populations may also modulate susceptibility to the carcinogenic effects of tobacco. In fact, some studies have identified gene-environment interactions and biomarker profiles unique to Asian populations that may influence OPC risk [36, 37], potentially attenuating the carcinogenic impact of smoking on the oral cavity and pharynx. In contrast, the exceptionally high RRs reported in Africa, Oceania, and South America are likely influenced by the limited number of available studies, which may distort overall risk estimates. This underlines the clear need for further research in these areas in order to better characterise the epidemiology of smoking-related cancers and to inform more accurate and region-specific public health strategies. Moreover, when using relative risks to estimate population attributable fractions (PAF) for OPC, region-specific RRs should be applied, as pooling global estimates may dilute the PAFs in Western regions where smoking-related risks are substantially higher.

The dose-response analysis revealed a nonlinear association for smoking intensity, with a steep increase in risk up to 20 cigarettes per day, followed by a plateau. This highlights the fact that even smoking a small number of cigarettes per day, e.g. six, is sufficient to double the risk of OPC. A similar nonlinear pattern was observed for smoking duration, with the risk doubling after as little as seven years. time since quitting showed an inverse nonlinear relationship with OPC risk: the risk was halved within seven years of cessation and approached that of never smokers after 18 years. This finding, consistent with results from a recent meta-analysis [25], carries strong public health implications, underscoring the importance of quitting as early as possible. A significant and relevant decrease in OPC risk is observed even for few years since smoking cessation, thus suggesting that quitting smoking is always beneficial.

Our systematic review and meta-analysis present several notable strengths. By combining an umbrella review with a traditional review [15], we applied an efficient and effective methodology that enabled the inclusion of over 100 epidemiological studies on cigarette smoking and OPC risk, making this the most comprehensive meta-analysis to date on the topic. Careful screening of all retrieved publications was conducted to prevent data overlap. Study quality was thoroughly assessed using the NOS [38]. Although no study was excluded in

order to preserve comprehensiveness, stratified analyses by NOS score showed no significant differences in OPC risk estimates for current, former, and ever smokers. Furthermore, we applied flexible random-effects models with restricted cubic splines [39] to capture the dose–response relationships for smoking intensity, duration, and time since quitting, providing a more precise characterization of risk patterns.

This study shares the common limitations of meta-analyses based on epidemiological research. Both case-control and cohort designs are susceptible to selection and recall biases. Since smoking status, intensity, duration, and cessation time were self-reported across all studies, some degree of differential misclassification of exposure may have occurred. We believe the impact of these biases to be limited, as risk estimates did not vary significantly by study design. While it has been suggested that hospital-based controls may over-represent smokers - potentially biasing results toward the null [40] - our findings do not support this, given the absence of significant differences by control type in case-control studies. However, our results do not support this hypothesis, as no significant differences according to type of controls emerged among case-control studies. Substantial heterogeneity was observed across all smoking status analyses, likely reflecting variation in study methodologies and participant characteristics. Although random-effects models were applied to address this heterogeneity, it was not fully eliminated. Stratified analyses considering cancer anatomical subtypes, socioeconomic factors, and study features were conducted to explore potential sources of heterogeneity, but these factors only partly accounted for the observed variability. Finally, evidence of publication bias was detected in the analyses on former and ever smokers. To account for this, we applied the trim-and-fill method [41], which slightly lowered the pooled relative risk estimates, suggesting that selective publication of positive findings may have partially inflated the observed associations.

In conclusion, this meta-analysis reaffirms the strong association between cigarette smoking and the risk of OPC, demonstrating that even a moderate smoking intensity and a short smoking duration can substantially elevate this risk. These findings emphasise the urgent need for immediate, coordinated action from policymakers, healthcare professionals, and researchers to curb smoking-related cancer risks. Strengthening prevention policies, ensuring sustained investment in tobacco control, and promoting cessation at both individual and population levels are essential steps to reduce the future burden of OPC through prevention efforts to avoid smoking initiation and strategies to support smoking cessation among smokers.

3.6 Contribution to the overall thesis framework

This chapter further expanded the epidemiological evidence on the relationship between cigarette smoking and cancer by focusing on oral and pharyngeal cancers. In addition to confirming the increased risk among smokers, the review provided detailed dose-response estimates according to smoking intensity, duration, and time since cessation.

Together with the evidence presented in the previous chapter, this work strengthens the epidemiological foundation required to quantify the cancer burden attributable to tobacco exposure. Moreover, the dose-response estimates generated by this study contribute to the broader evidence base used for the development and application of the burden estimation methodology presented later in the thesis, including the assessment of digestive cancers attributable to smoking in Italy. The next chapter extends this investigation to secondhand smoke (SHS) exposure, addressing an additional and often overlooked source of tobacco-related cancer risk

3.7 References

1. Bray F, Laversanne M, Sung H et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2024; 74: 229-263.
2. Abati S, Bramati C, Bondi S et al. Oral Cancer and Precancer: A Narrative Review on the Relevance of Early Diagnosis. Int J Environ Res Public Health 2020; 17.
3. Bagnardi V, Rota M, Botteri E et al. Alcohol consumption and site-specific cancer risk: a comprehensive dose-response meta-analysis. Br J Cancer 2015; 112: 580-593.
4. Gandini S, Botteri E, Iodice S et al. Tobacco smoking and cancer: a meta-analysis. Int J Cancer 2008; 122: 155-164.
5. Gupta R, Mariano LC, Nethan ST et al. Risk Reversal of Oral, Pharyngeal and Oesophageal Cancers after Cessation of Betel Quid Users: A Systematic Review and Meta-Analysis. Ann Glob Health 2022; 88: 5.
6. Giraldi L, Collatuzzo G, Hashim D et al. Infection with Human Papilloma Virus (HPV) and risk of subsites within the oral cancer. Cancer Epidemiol 2021; 75: 102020.
7. Warnakulasuriya S. Global epidemiology of oral and oropharyngeal cancer. Oral Oncol 2009; 45: 309-316.
8. Bosetti C, Carioli G, Santucci C et al. Global trends in oral and pharyngeal cancer incidence and mortality. Int J Cancer 2020; 147: 1040-1049.
9. Chaturvedi AK, Anderson WF, Lortet-Tieulent J et al. Worldwide trends in incidence rates for oral cavity and oropharyngeal cancers. J Clin Oncol 2013; 31: 4550-4559.
10. Gunasekera SK, Perera KA, Fernando C, Udagama PV. A shifting paradigm in the aetiology of oral and pharyngeal cancer in Sri Lanka: a case-control study providing serologic evidence for the role of oncogenic HPV types 16 and 18. Infect Agent Cancer 2015; 10: 12.
11. Chang CP, Chang SC, Chuang SC et al. Age at start of using tobacco on the risk of head and neck cancer: Pooled analysis in the International Head and Neck Cancer Epidemiology Consortium (INHANCE). Cancer Epidemiol 2019; 63: 101615.
12. Di Credico G, Edefonti V, Polesel J et al. Joint effects of intensity and duration of cigarette smoking on the risk of head and neck cancer: A bivariate spline model approach. Oral Oncology 2019; 94: 47-57.
13. Botteri E, Borroni E, Sloan EK et al. Smoking and Colorectal Cancer Risk, Overall and by Molecular Subtypes: A Meta-Analysis. Am J Gastroenterol 2020; 115: 1940-1949.
14. Liu X, Peveri G, Bosetti C et al. Dose-response relationships between cigarette smoking and kidney cancer: A systematic review and meta-analysis. Crit Rev Oncol Hematol 2019; 142: 86-93.

15. Lugo A, Bosetti C, Peveri G et al. Dose-response relationship between cigarette smoking and site-specific cancer risk: protocol for a systematic review with an original design combining umbrella and traditional reviews. BMJ Open 2017; 7: e018930.
16. Lugo A, Peveri G, Bosetti C et al. Strong excess risk of pancreatic cancer for low frequency and duration of cigarette smoking: A comprehensive review and meta-analysis. Eur J Cancer 2018; 104: 117-126.
17. Malevolti MC, Maci C, Lugo A et al. Second-hand smoke exposure and cervical cancer: a systematic review and meta-analysis. J Cancer Res Clin Oncol 2023; 149: 14353-14363.
18. Possenti I, Romelli, M., Carreras, G., Biffi, A., Bagnardi, V., Specchia, C., Gallus, S., Lugo, A.,. Association Between Secondhand Smoke Exposure and Lung Cancer Risk in Never Smokers: A Systematic Review and Meta-Analysis. Eur Resp Rev (Submitted) 2024.
19. Possenti I, Martini A, Bagnardi V et al. Association between cigarette smoking and nasopharyngeal cancer risk: a meta-analysis. Rhinology 2025; 63: 13-21.
20. Possenti I, Scala M, Carreras G et al. Exposure to secondhand smoke and breast cancer risk in non-smoking women: a comprehensive systematic review and meta-analysis - In press. British Journal of Cancer 2023.
21. Rota M, Possenti I, Valsassina V et al. Dose-response association between cigarette smoking and gastric cancer risk: a systematic review and meta-analysis. Gastric Cancer 2024; 27: 197-209.
22. Scala M, Bosetti C, Bagnardi V et al. Dose-response Relationships Between Cigarette Smoking and Breast Cancer Risk: A Systematic Review and Meta-analysis. J Epidemiol 2023; 33: 640-648.
23. Chaloupka FJ, Straif K, Leon ME, Working Group IAfRoC. Effectiveness of tax and price policies in tobacco control. Tob Control 2011; 20: 235-238.
24. Ansary-Moghaddam A, Huxley RR, Lam TH, Woodward M. The risk of upper aero digestive tract cancer associated with smoking, with and without concurrent alcohol consumption. Mt Sinai J Med 2009; 76: 392-403.
25. Khalifeh M, Ginex P, Boffetta P. Reduction of head and neck cancer risk following smoking cessation: a systematic review and meta-analysis. BMJ Open 2024; 14: e074723.
26. Mello FW, Melo G, Pasetto JJ et al. The synergistic effect of tobacco and alcohol consumption on oral squamous cell carcinoma: a systematic review and meta-analysis. Clin Oral Investig 2019; 23: 2849-2859.
27. Petti S, Masood M, Scully C. The magnitude of tobacco smoking-betel quid chewing-alcohol drinking interaction effect on oral cancer in South-East Asia. A meta-analysis of observational studies. PLoS One 2013; 8: e78999.

28. Maasland DH, van den Brandt PA, Kremer B et al. Alcohol consumption, cigarette smoking and the risk of subtypes of head-neck cancer: results from the Netherlands Cohort Study. BMC Cancer 2014; 14: 187.
29. Prasad JB, Dhar M. Risk of major cancers associated with various forms of tobacco use in India: a systematic review and meta-analysis. Journal of Public Health (Germany) 2019; 27: 803-813.
30. Khuder SA. Effect of cigarette smoking on major histological types of lung cancer: a meta-analysis. Lung Cancer 2001; 31: 139-148.
31. Pesch B, Kendzia B, Gustavsson P et al. Cigarette smoking and lung cancer--relative risk estimates for the major histological types from a pooled analysis of case-control studies. Int J Cancer 2012; 131: 1210-1219.
32. Applebaum KM, Furniss CS, Zeka A et al. Lack of association of alcohol and tobacco with HPV16-associated head and neck cancer. J Natl Cancer Inst 2007; 99: 1801-1810.
33. Sadri G, Mahjub H. Tobacco smoking and oral cancer: a meta-analysis. J Res Health Sci 2007; 7: 18-23.
34. Warnakulasuriya S, Chen THH. Areca Nut and Oral Cancer: Evidence from Studies Conducted in Humans. J Dent Res 2022; 101: 1139-1146.
35. Rahman M, Sakamoto J, Fukui T. Bidi smoking and oral cancer: a meta-analysis. Int J Cancer 2003; 106: 600-604.
36. Bau DT, Liu TY, Tsai CW et al. A Genome-Wide Association Study Identified Novel Genetic Susceptibility Loci for Oral Cancer in Taiwan. Int J Mol Sci 2023; 24.
37. Rapado-Gonzalez O, Salta S, Lopez-Lopez R et al. DNA methylation markers for oral cancer detection in non- and minimally invasive samples: a systematic review. Clin Epigenetics 2024; 16: 105.
38. Wells GA, Shea B, O'Connell D et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses (accessed 23 November 2023). 2014.
39. Crippa A, Discacciati A, Bottai M et al. One-stage dose-response meta-analysis for aggregated data. Stat Methods Med Res 2019; 28: 1579-1596.
40. Sadetzki S, Bensal D, Novikov I, Modan B. The limitations of using hospital controls in cancer etiology--one more example for Berkson's bias. Eur J Epidemiol 2003; 18: 1127-1131.
41. Duval S, Tweedie R. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics 2000; 56: 455-463.

Annex Chapter 3

Search strategy

As a first step, we conducted an umbrella review focusing on the association between smoking and SHS exposure and cancer risk in different anatomical sites. We performed a literature search of PubMed/MEDLINE, Embase, the Institute for Scientific Information Web of Science, and the Cochrane Database of Systematic Reviews, in order to identify relevant meta-analyses, pooled analyses, and systematic reviews on the association between cigarette smoking and SHS exposure and cancer risk up to 12 October 2022.

The umbrella review identified 61 reports on the association between cigarette smoking and the risk of cancers located anywhere in the upper aerodigestive tract (Supplementary Table 1), including systematic reviews, meta-analyses, pooled analyses, or reports from international agencies. All original articles addressing OPC were extracted from these reports, resulting in the identification of 195 non-duplicate original publications on tobacco smoking and the risk of OPC. We included cancers of the oral cavity (ICD-10: C00-C09), oropharynx (ICD-10: C10), and hypopharynx (ICD-10: C13). Given the complex aetiology of nasopharyngeal cancer (ICD-10: C11), which distinguishes it from other pharyngeal cancers, considering it within the analysis of overall pharyngeal sites is not appropriate. Therefore, articles that focused only on nasopharyngeal cancer were excluded and analysed in a separate meta-analysis [1]. Selected articles on OPC were screened based on their full text using the eligibility criteria described in the following section, resulting in the exclusion of 94 articles identified as ineligible (Supplementary Table 2).

In the following phase of our search, we conducted a traditional literature search in PubMed/MEDLINE and Embase that included all original studies published between January 2008 (i.e., the beginning of the year of the search string of the most recent and comprehensive review available on the topic [2]) and 5 February 2025. Our search string included combinations of MeSH terms and text words related to OPC and tobacco or smoking (Supplementary Box 1). After excluding duplicate publications and ineligible articles, the literature update resulted in 43 original publications on cigarette smoking and the risk of OPC. Six articles retrieved during the conduction of previous systematic reviews on other cancer sites were also added.

By merging the original articles identified in the umbrella review and the traditional review, a total of 137 non-duplicate publications were considered eligible (Supplementary Figure 1).

Eligibility criteria

To be included in this meta-analysis, studies had to meet specific eligibility criteria: i) be either case-control studies (including nested case-control studies or pooled analyses of case-control studies) or cohort studies (including case-cohort studies or pooled analyses of cohort studies); ii) be published as original articles in the English language; iii) provide data on the general population; iv) provide information on the association between cigarette smoking and the risk of oral cancer, pharyngeal (excluding nasopharyngeal) cancer, or both combined; (v) report risk estimates, including risk ratios, odds ratios, hazard ratios, or mortality rate ratios - all referred to as relative risk (RR) - for at least one variable among smoking status (current, former, and/or ever smokers), intensity, duration, and time since quitting, compared with never or current cigarette smokers, and the corresponding 95% confidence intervals (CI), or provide sufficient information to calculate them.

Data extraction

Information, including both general and study-specific details, was systematically collected from each eligible study during the data extraction phase. Data extracted included: general publication information (e.g., first author, year of publication, and journal), study characteristics (e.g., country in which the study was conducted, study name, study design, and sample size), details of the statistical model used for RR estimates (including covariates considered), and RRs with corresponding 95% Cis. Where available, data on the number of cases and persons at risk/person-years (for cohort studies) or the number of controls (for case-control studies) were extracted for each smoking exposure category (e.g., never, current, former, or ever smokers). Where available, numbers of cases and controls (or persons at risk/person-years for cohort studies) for each smoking exposure category (e.g., never, current, former, or ever smokers) and for dose-response analyses (e.g., categories of smoking intensity, duration, or time since quitting).

Where appropriate, we used the technique described by Hamling and colleagues for aggregating non-independent estimates [3]. This approach involved modification of the reference category or collapsing of RRs from two or more categories in studies where the reference group was the same across categories. Where RRs were reported separately for different anatomical subsites of OPC, we used the method described by Rucker and colleagues [4] to obtain a single RR for overall OPC.

Statistical analysis

To account for heterogeneity of risk estimates, we used random effects meta-analytic models [5].

Heterogeneity was assessed using the χ2 test, and inconsistency was quantified using the I2 statistic, which represents the proportion of total variation attributable to between-study variance [6]. We carried out stratified analyses based on various study and population characteristics, such as cancer anatomical and histological subtype, sex, study design, type of control (for case-control studies), endpoint (for cohort studies), tertiles of the number of cases, presence of adequate adjustments, study quality, geographic area, income group, and year of publication.

Study quality was assessed using the Newcastle-Ottawa Scale (NOS) [7]. The NOS score ranges from 0 (poor quality) to 9 (good quality) and considers information on three broad categories: selection (maximum 4 points), comparability (maximum 2 points), and outcome for case-control or exposure for cohort studies (maximum 3 points). In this meta-analysis, high-quality studies were defined as those with NOS scores ≥7. To ensure the completeness and comprehensiveness of our study, no low-quality study was excluded from the meta-analysis.

To investigate publication bias, we examined funnel plots [8] and employed Egger's test for funnel plot asymmetry [9].

We examined both linear and nonlinear associations between smoking intensity (for current vs. never smokers), smoking duration (for current vs. never smokers), and time since quitting (for former vs. current smokers) and the log RR of OPC. Dose-response relationships were evaluated using a one-stage random-effects dose-response model [10]. Nonlinear coefficients were subjected to the Wald test for statistical significance. When linearity was rejected, nonlinear relationships were modelled using restricted cubic splines with three knots at fixed percentiles of exposure (10%, 50%, and 90%) [11, 12]. Exposure levels for each category were determined as the midpoint between upper and lower bounds; for open-ended upper categories, exposure levels were set at 1.2 times the lower bound [13, 14].

When the number of cases and/or controls for a specific exposure category was not available in the original published studies, we estimated the covariance between log RR by considering the total number of cases and/or controls in the studies, weighted by the average percentage distribution of subjects pooled from all other studies [15].

PRISMA checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Pag 70
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Pag 71
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Pag 72
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Pag 72
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Annex
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Annex
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Suppl
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Annex
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Annex
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Annex
	10b	List and define all other variables for which data were sought (e.g. participant and intervention	Annex

Section and Topic	Item #	Checklist item	Location where item is reported
		characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Annex
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Pag 73, Annex
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Annex
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Annex
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Annex
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Annex
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Annex
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Annex
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Annex
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	NA
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in	Pag 73-74

Section and Topic	Item #	Checklist item	Location where item is reported
		the search to the number of studies included in the review, ideally using a flow diagram.	
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Suppl
Study characteristics	17	Cite each included study and present its characteristics.	Suppl
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Suppl
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Pag 75-76, Suppl
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Suppl
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Pag 75-76, Suppl
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Pag 78-81
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Pag 78-81
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Suppl
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	NA
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Pag 84
	23b	Discuss any limitations of the evidence included in the review.	Pag 84
	23c	Discuss any limitations of the review processes used.	Pag 88
	23d	Discuss implications of the results for practice, policy, and future research.	Pag 88

Section and Topic	Item #	Checklist item	Location where item is reported
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Pag 73
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Pag 73
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Online pub
Competing interests	26	Declare any competing interests of review authors.	Online pub
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Online pub

References

1. Possenti I, Martini A, Bagnardi V et al. Association between cigarette smoking and nasopharyngeal cancer risk: a meta-analysis. Rhinology 2025; 63: 13-21.
2. IARC. Personal habits and indoor combustions. Volume 100 E. IARC Monogr Eval Carcinog Risks Hum 2012; 1-538.
3. Hamling J, Lee P, Weitkunat R, Ambuhl M. Facilitating meta-analyses by deriving relative effect and precision estimates for alternative comparisons from a set of estimates presented by exposure level or disease category. Stat Med 2008; 27: 954-970.
4. Rucker G, Cates CJ, Schwarzer G. Methods for including information from multi-arm trials in pairwise meta-analysis. Res Synth Methods 2017; 8: 392-403.
5. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986; 7: 177-188.
6. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002; 21: 1539-1558.
7. Wells GA, Shea B, O'Connell D et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses (accessed 23 November 2023). 2014.
8. Peters JL, Sutton AJ, Jones DR et al. Contour-enhanced meta-analysis funnel plots help distinguish publication bias from other causes of asymmetry. J Clin Epidemiol 2008; 61: 991-996.
9. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315: 629-634.
10. Crippa A, Discacciati A, Bottai M et al. One-stage dose-response meta-analysis for aggregated data. Stat Methods Med Res 2019; 28: 1579-1596.
11. Desquilbet L, Mariotti F. Dose-response analyses using restricted cubic spline functions in public health research. Stat Med 2010; 29: 1037-1057.
12. Lugo A, Peveri G, Bosetti C et al. Strong excess risk of pancreatic cancer for low frequency and duration of cigarette smoking: A comprehensive review and meta-analysis. Eur J Cancer 2018; 104: 117-126.
13. Bagnardi V, Rota M, Botteri E et al. Alcohol consumption and site-specific cancer risk: a comprehensive dose-response meta-analysis. Br J Cancer 2015; 112: 580-593.
14. Berlin JA, Longnecker MP, Greenland S. Meta-analysis of epidemiologic dose-response data. Epidemiology 1993; 4: 218-228.
15. Crippa A, Orsini A.,. Multivariate Dose-Response Meta-Analysis: The dosresmeta R Package. 2016.

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Chapter 4

Exposure to secondhand smoke and breast cancer risk in non-smoking women: a comprehensive systematic review and meta-analysis

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4.1 Abstract

Through the use of an innovative method to identify original publications, we conducted meta-analysis of all epidemiological studies evaluating the association between SHS exposure and breast cancer risk among female non-smokers published in English up to October 2022. Pooled relative risks (RR) were obtained through the use of random-effects models. Dose-response relationships were derived using log-linear functions. Out of 73 identified eligible studies, 63 original articles were included in the meta-analysis. The pooled RR for breast cancer for overall exposure to SHS was 1.24 (95% confidence interval, CI, 1.15-1.34, number of articles, n=52). Regarding the setting of exposure, RRs were 1.17 (95% CI 1.08-1.27, n=39) for SHS exposure at home, 1.03 (95% CI 0.98-1.08, n=37) at workplace, 1.24 (95% CI 1.11-1.37, n=16) at home or workplace, and 1.45 (95% CI 1.16-1.80, n=13) for non-specified settings. The risk of breast cancer increased linearly with higher duration (95% CI 1.04-1.59 for 40 years of SHS exposure, n=12), intensity (95% CI 1.14-1.67 for 20 cigarettes of SHS exposure per day, n=6), and pack years (95% CI 0.92-2.45 for 40 SHS pack years, n=6) of SHS exposure. This meta-analysis shows a statistically significant excess risk of breast cancer in women exposed to SHS.

4.2 Introduction

According to the World Health Organization (WHO), breast cancer is globally the most frequently diagnosed malignancy, with estimated 2.3 million new cases in 2020 [1, 2]. Breast cancer is also the most commonly diagnosed cancer among young women, accounting for one-third of cancer diagnoses in women under the age of 50 [1]. Breast cancer is the leading cause of cancer deaths among women, accounting for around 15% of all female cancer deaths [1].

Several non-modifiable risk factors for the development of breast cancer have been identified, such as advanced age and specific genetic mutations [3]. Moreover, some reproductive factors have been highlighted, such as nulliparity, short duration of breastfeeding, and late age at menopause [4, 5]. Modifiable risk factors for breast cancer include alcohol intake [6, 7], low levels of physical activity [8], being overweight or obese after menopause [9], and use of combined oestrogen and progesterone contraceptives or hormone replacement therapies [10, 11]. Importantly, a direct association between active cigarette smoking and breast cancer risk has been established [12, 13].

Secondhand smoke (SHS) exposure occurs when people involuntary inhale tobacco smoke that is present in the surrounding air. SHS has been classified as a human carcinogen by the International Agency for Research on Cancer (IARC) [12], it has been listed as a toxic air pollutant by the California Environmental Protection Agency (CalEPA) [14], and is considered by the WHO as one of the world major health threats, causing each year approximately 1.2 million deaths [15]. There is valid biological rationale to suspect that exposure to carcinogens in tobacco smoke may lead to the development of breast cancer [16]. After nicotine and other carcinogenic components of cigarette smoke reach the breast [17], they can be activated by several enzymes, such as the CYP and N-acetyltransferase 2 (NAT2), and give rise to DNA adducts [16].

The possible association between SHS exposure and breast cancer risk is a widely controversial topic in the scientific literature, with several papers leading to divergent conclusions. An early meta-analysis conducted by the CalEPA indicated the evidence for SHS exposure and breast cancer risk as “consistent with a causal association in younger primarily premenopausal women” [14]. Similarly, according to the Canadian Expert Panel on Tobacco Smoke and Breast Cancer Risk, “the relationship between SHS and breast cancer in younger, primarily premenopausal women is consistent with causality” [18]. On the other hand, IARC defined the evidence for an association as “inconsistent”, also for pre-menopausal women [12, 19]. Furthermore, a report by the U.S. Public Health Service stated that “the evidence is suggestive but not sufficient to infer a causal relationship between exposure to secondhand tobacco smoke and breast cancer” [16]. The most recent meta-analyses on the topic, whose strings were conducted

in 2014, 2015, and 2022 and which included 15, 47, and 39 studies, respectively, concluded that SHS is associated with breast cancer among women, although caution in interpreting results was suggested due to the high heterogeneity of the estimates [20-22]. After these publications, additional studies have been made available and we therefore found it necessary to update the evidence on the topic.

In the present meta-analysis, we aim to provide the most up-to-date and comprehensive estimate of the association between SHS exposure and the risk of breast cancer in non-smoking women [23]. In addition, we provide dose-response relationships with duration, intensity, and pack-years of SHS exposure and stratified analyses for menopausal status, NAT2 polymorphism, and the presence of oestrogen (ER) and progesterone receptors (PR).

4.3 Methods

The present study is part of a series of systematic reviews and meta-analyses on the association between cigarette smoking or SHS exposure and cancer risk [13, 23-27]. It employs an innovative methodology for identifying original articles, that relies on a combination of umbrella and traditional reviews, which has already been described in previous publications [23, 25]. The study protocol was registered in the International Prospective Registry of Systematic Reviews (PROSPERO; registration number: CRD42017063991).

The review was conducted in accordance with the PRISMA 2020 guidelines whenever applicable. Due to the combined umbrella review and traditional review design, a conventional PRISMA flowchart could not be fully applied, as the study identification and selection process differed from that of a standard systematic review. A completed PRISMA checklist is provided in the Annex 1.

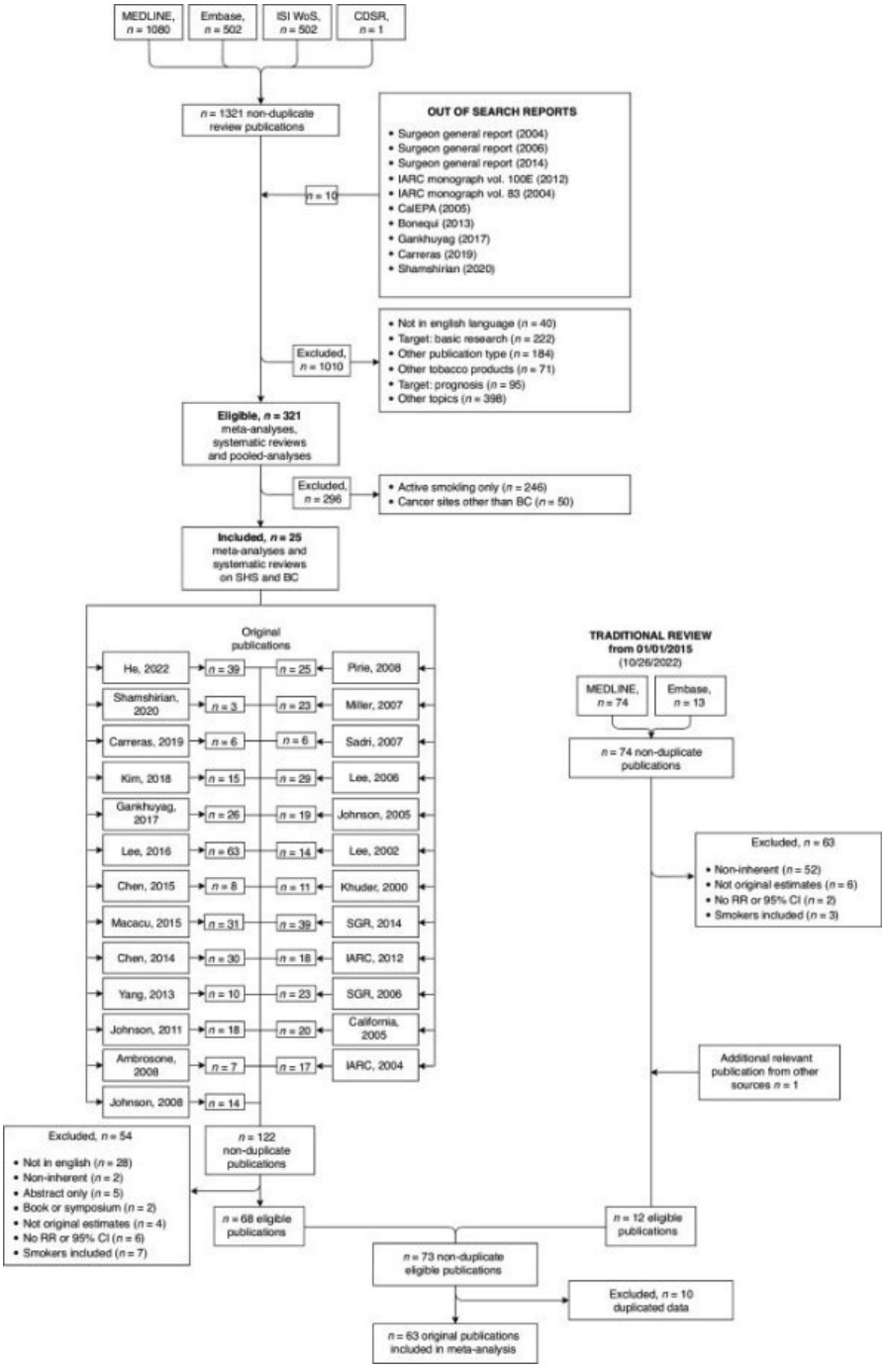
2.3.1 Search strategy

During the first phase of the search strategy, we conducted an umbrella review on active smoking and SHS exposure and the risk of cancer at any site. We ran a comprehensive literature search through four distinct scientific databases (PubMed/MEDLINE, Embase, Institute for Scientific Information Web of Science, and Cochrane Database of Systematic Reviews) to identify all meta-analyses, pooled analyses, and systematic reviews on the association between smoking or SHS exposure and cancer risk. The original search was conducted on the 27th of April 2017 [23] and was subsequently updated on the 14th of January 2020 [13] and on the 12th of October 2022. Among 321 eligible meta-analyses, pooled analyses, systematic reviews, and reports, 25 were retrieved on the association between SHS exposure and breast cancer risk (Supplementary Table 1). From the previously mentioned 25 reports, we identified 122 non-duplicate original

publications on the association between SHS exposure and breast cancer risk (Figure 1). These articles were screened for eligibility on the basis of their full text using the eligibility criteria described in the following section, leading to the exclusion of 54 papers (Supplementary Table 2).

In a second step, we carried out a traditional literature search on PubMed/MEDLINE and Embase, in order to identify all original studies on the topic that were published in English between 2015 (i.e., the search date of the last and most comprehensive review available on the issue [22]) and the 26th of October 2022. The search string included combinations of MeSH terms and free text on breast cancer and SHS (Supplementary Box 1) and resulted in a total of 74 non-duplicate original publications. After the exclusion of ineligible publications, the update of the scientific literature led to 12 original articles on the association between SHS exposure and breast cancer risk. Overall, these two steps of the search strategy resulted in a total of 73 non-duplicate articles being considered as eligible.

Figure 1. Flowchart for the selection of the original studies on the association between secondhand (SHS) exposure and breast cancer risk included in the review and meta-analysis.



4.3.2 Eligibility criteria

To be considered eligible in the present meta-analysis, studies had to: (i) be published as an original article in English; (ii) be a case-control study (including nested case-control studies or pooled analyses of case-control studies) or a cohort study (including case-cohort studies or pooled analyses of cohort studies); (iii) provide information on the association between exposure to SHS and risk of female malignant breast cancer only in the subgroup of never or non-smoking adult women; (iv) either report risk estimates, including risk ratios, odds ratios, hazard ratios, or mortality ratios – as of now all named as relative risks (RR) – for SHS exposure in at least one setting or source, or SHS exposure duration (years of exposure), intensity (number of cigarettes per day to which one is exposed) or pack-years, using as comparison group women not exposed to SHS, and corresponding 95% confidence intervals (CI), or provide sufficient information to calculate them. As an exception to the fourth criterion, if a study was conducted on a population of women with a prevalence of smokers lower than 5%, it was included in the analysis even if it did not report association measures specifically for never or non-smokers. No restriction was applied according to outcome assessment (either histologically confirmed or from cancer registries or medical records or death certificates).

4.3.3 Data Extraction

For each eligible study, we collected general information on the publication (e.g., first author, year of publication, and journal), the study (e.g., country of study implementation, study design, calendar period of study conduction, and sample size), the setting of SHS exposure (e.g., at home, at workplace, or in public places), the source of SHS exposure (e.g., in childhood or from partner), the model used for RR estimates (including adjusting variables), the RRs with corresponding 95% CIs, and, when available, the number of cases and controls (or at-risk subjects/person-years for cohort studies) for the various exposure categories. When necessary, we used the Hamling's method [28] to change the reference category or to collapse the RRs of two or more categories with the same reference group. When several RRs were reported separately for different types of breast cancer (e.g., ER positive or negative cancers), we used the method described by Rucker and colleagues [29] to obtain a single RR for overall breast cancer. RRs were also extracted by subgroup (e.g., menopausal status), if available.

4.3.4 Statistical analysis

Pooled RRs for the association between SHS exposure and risk of breast cancer were estimated considering different settings or sources of SHS exposure: at home, at workplace, at home or workplace, from partner, during childhood, and

in non-specified settings. The latter source also includes those exposures defined through general questions such as: “Are you exposed to secondhand smoke in at least one setting?” or “Have you ever been exposed to SHS in any setting?”. We also performed an overall analysis by considering one risk for each original article. When more than one source or setting of SHS exposure was provided in the same article, we prioritized them in the following order: 1) in non-specified settings with clarification about weekly or daily minimum duration of exposure (in terms of hours per day/week); 2) at home or at workplace; 3) at home (excluding exposure from partner only); 4) from partner; and 5) in non-specified settings without clarification about minimum duration of exposure. From this overall analysis, we excluded studies exclusively focused on childhood exposure to SHS.

Pooled estimates were obtained using random-effects models to account for heterogeneity in risk estimates [30]. Heterogeneity between studies was assessed using the X^2 test, and inconsistency was measured using the I^2 statistic, which represents the proportion of the total variation attributable to variance between studies [31]. We conducted stratified analyses for overall SHS exposure according to different study, population, cancer, and genetic characteristics (i.e., study design, geographic area, type of control, endpoint, year of publication, income group, presence of adjusting variables, number of cases, menopausal status, presence of ER or PR, and NAT2 polymorphism). Heterogeneity between strata was assessed using the Q test for subgroup differences, assuming a random effect model.

To assess publication bias, we examined funnel plots [32] and applied Egger's test for funnel plot asymmetry [33].

We estimated linear dose-response relationships between duration, intensity, and pack-years of overall SHS exposure and the log RR for breast cancer, after having tested the statistical significance of linearity using the Wald's test.

All statistical analyses were performed using R software version 4.2.2 (R Development Core Team, 2022) and, specifically, the “meta” [34] and “dosresmeta” packages [35].

4.4 Results

4.4.1 Study selection and description

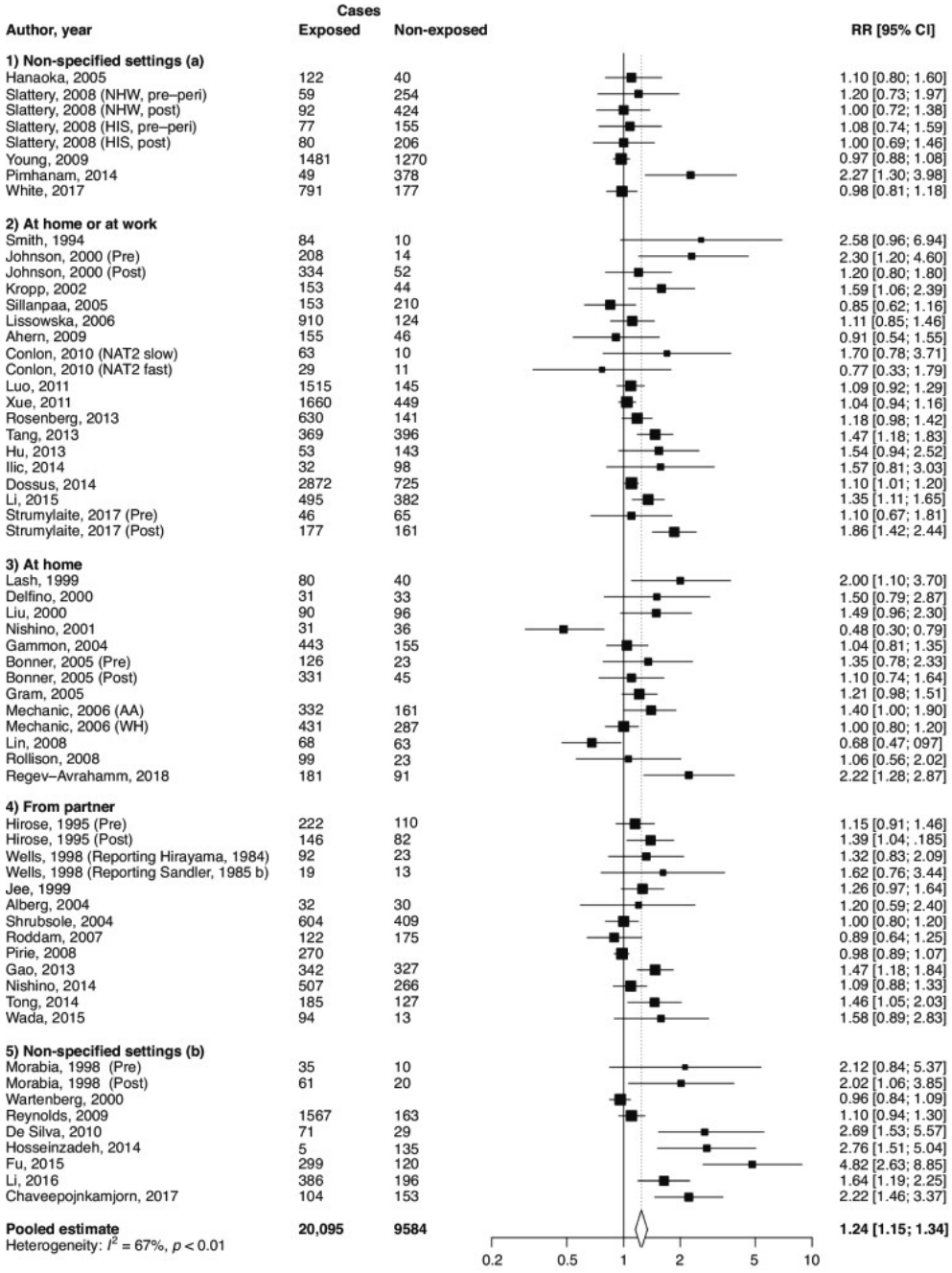
Among the 73 identified eligible articles, 10 were excluded because they reported duplicate data (Supplementary Table 3), which left 63 studies for the present meta-analysis. The main characteristics of the included case-control (n=47, 73%)

and cohort (n=17, 27%) studies are summarized in Supplementary Table 4 and Supplementary Table 5, respectively (one article included both a case-control study and a cohort study [36]). Studies were published between 1984 and 2022 and included more than 30,000 breast cancer cases. Thirty-seven studies (62%) provided a measure of the association for SHS exposure at home (including exposure from the partner), 15 for exposure at workplace (24%), 16 for exposure at home or workplace (25%), and 13 for exposure in non-specified settings (21%). In addition, 19 studies (30%) reported the association between childhood SHS exposure and the risk of breast cancer. The definitions used to assess SHS exposure varied widely between the articles and are detailed in Supplementary Tables 6 and 7. Publications containing data that were partially excluded from the present meta-analysis, with the corresponding reasons of exclusion, are described in Supplementary Table 8.

4.4.2 Quantitative data synthesis

In the overall analysis (i.e., considering one source or setting of exposure for each article), the pooled RR for breast cancer for women ever exposed to SHS compared with non-exposed ones was 1.24 (95% CI 1.15-1.34; Figure 2), and was significantly higher in case-control (RR: 1.35; 95% CI 1.23-1.48) than in cohort (RR: 1.06; 95% CI 1.01-1.11) studies (p-value of heterogeneity between study designs <0.01).

Figure 2. Forest plot of the overall analysis* and pooled relative risk (RR) of breast cancer for women exposed to secondhand smoke (SHS) compared with non-exposed women by setting or source of exposure.



AA: African-American ethnicity; CI: confidence intervals, HIS: Hispanic ethnicity, NHW: non-Hispanic women of Caucasian ethnicity; Pre: pre-menopausal women; Pre-peri: pre- or peri-menopausal women; Post: post-menopausal women, RR: relative risk, WH: White ethnicity.

a: Including clarifications about weekly or daily minimum duration of exposure; b: Without clarifications about weekly or daily minimum duration of exposure.

* Considering one source or setting of exposure for each article

Table 1 shows the RRs for the association between SHS exposure and breast cancer in strata of selected characteristics. Regarding different exposure settings, the pooled RRs for breast cancer were 1.17 (95% CI 1.08-1.27) at home (Supplementary Figure 1), 1.03 (95% CI 0.98-1.08) at workplace (Supplementary Figure 2), 1.24 (95% CI 1.11-1.37) at home or workplace (Supplementary Figure 3), and 1.45 (95% CI 1.16-1.80) in non-specified settings (Supplementary Figure 4). Pooled RR for SHS exposure in non-specified settings was significantly lower in studies considering at least a weekly or daily exposure (RR: 1.01; 95% CI 0.93-1.09) than in studies considering any exposure without clarification on the duration of the exposure (RR: 1.91; 95% CI 1.35-2.70; p<0.01; data not shown). Pooled RRs were 1.16 (95% CI 1.05-1.29) for partner-only exposure (Supplementary Figure 5) and 1.05 (95% CI 1.00-1.10) for SHS exposure during childhood (Supplementary Figure 6). Significant differences in the association between overall SHS exposure and breast cancer risk were observed by the type of controls in case-control studies (RRs were 1.55 among studies with hospital-based controls and 1.22 among studies with population-based control; p<0.01), income group (RRs were 1.70 for middle and 1.13 for high-income countries; p<0.01), geographic area (RRs were 1.05 for North and Central America, 1.23 for Europe, and 1.44 for Asia; p<0.01), year of publication (RRs were 1.26 among studies published before 2005, 1.03 among studies published between 2005 and 2011, and 1.53 among studies published after 2011; p<0.01), presence of adjustment for alcohol consumption (RRs were 1.13 in studies adjusting for alcohol consumption and 1.45 in studies not adjusting for alcohol consumption), and number of cases (RRs were 1.46 among studies with less than 151 cases, 1.33 among studies with a number of cases between 151 and 600, and 1.11 among studies with more than 600 cases; p<0.01). No significant differences emerged for the effect of SHS exposure on breast cancer risk according to presence of any type of adjustment, adequate adjustments, menopausal status, NAT2 polymorphism, ER status, and PR status (Table 1). The analysis on pre-menopausal women did not reveal differences in the association among pre-menopausal women when comparing studies assessing lifetime exposure to the overall pool of studies (RRs were 1.24 for studies on pre-menopausal women assessing lifetime exposure and 1.21 for all studies on pre-menopausal women; Supplementary Table 9 and Supplementary Figure 7).

Table 1. Pooled relative risk (RR) and corresponding 95% confidence interval (CI) for breast cancer for ever exposed to secondhand smoke (SHS) versus never exposed to SHS, overall and in strata of selected characteristics.

Strata	N. studies	Pooled RR (95% CI)	p-value[a]	p-value[b]
Total	52	1.24 (1.15-1.34)		<0.01
Settings of SHS exposure				
At home[c]	37	1.17 (1.08-1.27)	NA	<0.01
At workplace	15	1.03 (0.98-1.08)		0.05
At home or workplace	16	1.24 (1.11-1.37)		<0.01
Non-specified	13	1.45 (1.16-1.80)		<0.01
Specific sources				
From partner	17	1.16 (1.05-1.29)	NA	<0.01
During childhood	19	1.05 (1.00-1.10)		0.02
Geographic area[d]				
Northern and central America	19	1.05 (1.00-1.10)	<0.01	0.40
Europe	12	1.23 (1.04-1.44)		<0.01
Asia	22	1.44 (1.21-1.70)		0.02
Income group[e]				
High-income	38	1.13 (1.06-1.20)	<0.01	<0.01
Middle-income	14	1.70 (1.41-2.04)		<0.01
Study design				
Case-control	37	1.35 (1.23-1.48)	<0.01	<0.01
Cohort	15	1.06 (1.01-1.11)		<0.01
Type of controls[f]				
Hospital	14	1.55 (1.34-1.79)	0.01	<0.01
Population	23	1.22 (1.10-1.36)		<0.01
Endpoint[g]				
Incidence	13	1.14 (0.99-1.32)	0.54	<0.01
Mortality	2	1.04 (0.79-1.36)		0.19
Year of publication				
<2005	16	1.26 (1.09-1.46)		<0.01
2005-2011	18	1.03 (0.98-1.07)	<0.01	0.18
≥2012	18	1.53 (1.31-1.77)		<0.01
Adjustment				
Crude	4	1.51 (1.05-2.17)	0.28	<0.01
Adjusted	48	1.22 (1.14-1.32)		<0.01
Adjusted for alcohol consumption				
Not adjusted	23	1.45 (1.26-1.67)	<0.01	<0.01
Adjusted	29	1.13 (1.05-1.22)		<0.01
Adjustments				
Non-adequate	39	1.29 (1.17-1.42)	0.17	<0.01

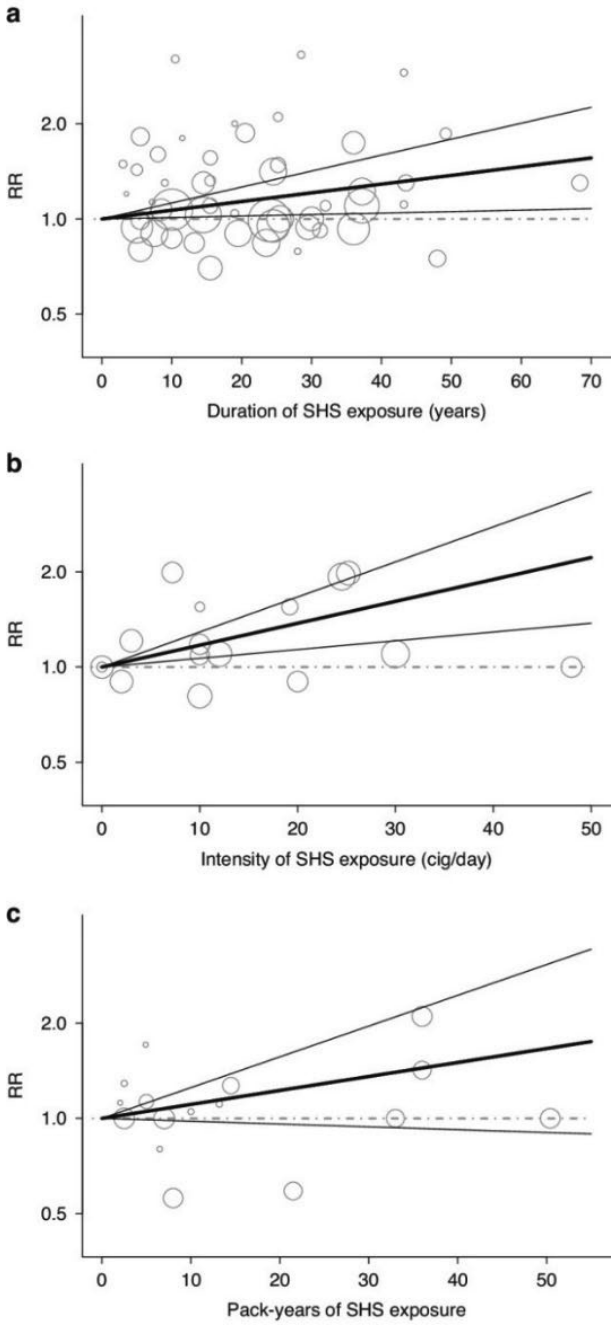
Adequate[h]	13	1.16 (1.03-1.31)		<0.01
Number of cases				
≤150	17	1.46 (1.20-1.75)		<0.01
151-600	18	1.33 (1.11-1.58)	<0.01	<0.01
≥601	17	1.11 (1.05-1.17)		<0.01
Menopausal status				
Post-menopause	27	1.14 (1.05-1.25)	0.43	<0.01
Pre-menopause	27	1.21 (1.09-1.34)		<0.01
Estrogen Receptor				
Positive	10	1.20 (1.05-1.38)	0.95	<0.1
Negative	9	1.21 (1.02-1.44)		0.12
Progesterone Receptor				
Positive	7	1.19 (1.06-1.39)	0.82	0.12
Negative	8	1.21 (1.08-1.31)		0.18
NAT2				
Slow	6	1.63 (1.22-2.19)	0.89	0.72
Fast	6	1.70 (1.03-2.81)		0.03

NAT2: N-acetyltransferase 2. [a]p-value for heterogeneity across strata; [b]p-value for heterogeneity within strata; [c]Including exposure from partner; [d]No studies from Africa or South America; [e]No studies from low-income countries; [f]Type of controls for case-control studies only; [g]Endpoint for cohort studies only; [h] Estimates adjusted at least for age, family history of breast cancer, body mass index or weight, parity, and alcohol consumption.

4.4.3 Dose-response analysis

The risk of breast cancer increased linearly with the duration of SHS exposure (RRs: 1.13; 95% CI 1.02-1.26 for 20 years of SHS exposure and 1.29; 95% CI 1.04-1.59 for 40 years of SHS exposure; based on 12 studies; Figure 3, Panel A). The risk also increased linearly with the intensity of SHS exposure (RRs: 1.08; 95% CI 1.03-1.13 for 5 cigarettes of exposure per day and 1.38; 95% CI 1.14-1.67 for 20 cigarettes of exposure per day; based on 6 studies; Figure 3, Panel B) and pack-years (RRs: 1.23; 95% CI 0.96-1.56 for 20 pack-years and 1.50; 95% CI 0.92- 2.45 for 40 pack years; based on 6 studies; Figure 3, Panel C).

Figure 3. Relative risk (RR) for the dose-response relationships between secondhand smoke (SHS) exposure duration, intensity, and pack years, and the risk of breast cancer: (panel A) Years of SHS exposure; (panel B) Cigarettes per day (cig/day) of SHS exposure; (panel C) Pack-years of SHS exposure.



——— Linear model from a random-effects dose-response model;

——— 95% confidence interval of the linear model;

– · – · – RR for non-exposed women;

◯ RR for various exposure categories in each study included in the analysis. The area of the circle is proportional to the precision (i.e., to the inverse variance) of the RR.

4.4.4 Publication bias

Evidence of publication bias was found in the overall analysis, with a p-value for the Egger's test lower than 0.01 (Supplementary Figure 8, panel A), and for the majority of the settings of SHS exposure (Supplementary Figure 8, panels B-G).

4.5 Discussion

This systematic review provides the most up-to-date and comprehensive knowledge on the association between SHS exposure and breast cancer risk, including 73 eligible articles and using data from 63 original articles and 35,302 breast cancer cases. The corresponding meta-analysis showed an overall significant 24% excess risk of breast cancer in non-smoking women exposed to SHS compared with non-exposed ones, and a significant increased risk for women exposed to SHS at home, at home and workplace, and in non-specified settings. Moreover, we found that the risk of breast cancer linearly increased with increasing duration, intensity, and pack-years of SHS exposure. Our review, in agreement with findings of the most recent meta-analyses on the topic [20-22], provides a definite answer to the open question on the role of SHS exposure on breast cancer risk.

It is well-established that alcohol drinking is one of the biggest avoidable risk factors for breast cancer. A comprehensive meta-analysis found that moderate alcohol consumption (i.e., at least 12.5 g per day of alcohol) increased the risk of breast cancer by 23% [6]. For this reason, quitting alcohol drinking or reducing alcohol consumption is today considered one of the main strategies to prevent breast cancer risk [37]. With an excess risk of 24% for women exposed to SHS, our meta-analysis places SHS exposure among the main modifiable lifestyle-related risk factors for the development of breast cancer. This is particularly relevant given the relatively high frequency of SHS exposure, affecting globally 35% of women [38], much higher than the estimate of 25% of women who consume alcoholic beverages [39].

Our RR estimate for SHS exposure appears of a higher magnitude than the most recent estimate of the association between active smoking and breast cancer risk (i.e., RR=1.09) [13]. However, the populations of the reference category of the two estimates are different (non-smokers and non-exposed to SHS vs never smokers), thus complicating the comparison between the two estimates [40]. Particularly, in evaluating the association between active smoking and breast cancer risk, never smokers exposed to SHS are included in the reference category, thus increasing the risk of that group. Neglecting this aspect may lead to an underestimation of the true risks associated with active smoking. Moreover, a higher recall bias for SHS exposure, rather than active smoking, has been suggested [41]. Finally, it is possible that the intensity of smoking consumption in terms of cigarettes per day in female current smokers is relatively low, whereas the intensity of SHS exposure might be relatively high. For example, a large Chinese study showed a median SHS exposure of more than 3 hours per day in the control group [42].

Our meta-analysis identified significant differences in risk estimates between study designs, with cohort studies showing a lower pooled RR compared with case-control studies. However, the association remained statistically significant in cohort studies, reporting a 6% increased risk of breast cancer in non-smoking women exposed to SHS. A possible explanation for this difference is that the magnitude of the misclassification of SHS exposure may be more pronounced in cohort studies. In fact, cohort studies often rely on a single-point assessment of SHS exposure, thus lacking comprehensive information about previous lifetime SHS exposure or repeated assessments during follow-up [43]. This can lead to important misclassification of SHS exposure. Given the relatively high prevalence of exposure to SHS in the population, the misclassification of exposed women as non-exposed ones can substantially dilute observed risks [44] and may therefore contribute to the underestimation of the pooled RR observed in cohort studies. On the other hand, a different recall bias between cancer cases and healthy subjects is expected to affect more frequently case-control rather than cohort studies. This might result in an overestimation of the RR observed in case-control studies.

Regarding the setting of SHS exposure, we found a significant increased risk of breast cancer for women exposed at home, at home or at workplace, and in non-specified settings, while a non-significant association has been observed with SHS exposure at workplace alone. The latter result confirms the findings from the most recent meta-analyses on the topic [20, 22] and suggests that SHS exposure in other settings, such as at home, may play a larger role in the development of breast cancer. This meta-analysis also found a significant 16% increased risk of breast cancer in women exposed to SHS from a partner and a borderline significant 5% increased risk in women exposed to SHS during childhood. This

latter finding is in line with the results of the most recent meta-analyses on the topic, which found a significant association between childhood exposure and breast cancer risk [20, 22].

Some authors have suggested that NAT2-related gene polymorphism and SHS exposure may interact in the development of breast cancer [45, 46]. To our knowledge, our meta-analysis is the first to provide summary estimates of the evidence for the association between SHS exposure and breast cancer risk stratified by NAT2 polymorphism. No meaningful differences were observed between different polymorphisms of NAT2, with three studies providing higher RRs associated with fast NAT2 acetylators, two studies giving higher RRs for slow NAT2 acetylators, and one study reporting similar RRs for the two polymorphisms.

Moreover, it has been hypothesized that DNA methylation modification in blood could represent a causal pathway linking cigarette smoke and breast cancer risk, particularly ER-positive breast cancer risk [47]. Several other authors have suggested that the association between SHS and breast cancer may vary depending on hormone receptor status [48-50]. This notwithstanding, we did not find significant differences concerning ER and PR status by pooling the RRs of 10 and 8 studies, respectively. However, as these results are based on few and conflicting studies, future evaluations are needed to provide further evidence on the issue.

Since it has been hypothesized that SHS exposure may have a greater effect on the risk of breast cancer among pre- than post-menopausal women [14, 18], we conducted a stratified analysis according to menopausal status based on 27 articles. Although our meta-analysis did not find a significant difference according to menopausal status (p=0.43), the excess risk was higher in pre- compared to post-menopausal women (21% vs 14%). RR estimates were statistically significant in both strata of menopausal status. This finding is in contrast with the results of some previous meta-analyses, reporting that passive smoking increased the risk of breast cancer in pre-menopausal women, but had no effect on the incidence in post-menopausal ones. However, estimates for these studies were based on a more limited number of studies [20, 22]. We also did not find evidence of a difference in risk for studies on pre-menopausal women assessing lifetime exposure to SHS. Although the CalEPA and the U.S. Surgeon Generals reports found higher RR estimates for this category of women [14, 51], results from 12 studies identified in the present systematic review do not support this evidence. This might be at least partially due to differences in the hierarchy used to choose one source of exposure from each study. In addition, recent studies may have influenced the results of this stratified analysis.

Our study found a linear dose-response relationship between the duration of SHS exposure and the risk of breast cancer, showing that women exposed to SHS for more than 40 years had a 30% increased risk of breast cancer compared with non-exposed ones. This result is highly consistent with a recent meta-analysis which found an increased risk of breast cancer by 35% for women exposed for more than 30 years, concluding that a longer duration of SHS exposure was positively related to the increased incidence of breast cancer [20]. We also found that intensity and pack-years of SHS exposure increased linearly the risk of breast cancer. However, these findings are based on six studies only. Moreover, questions used to collect information on the intensity of SHS exposure were heterogeneous and thus difficult to be combined. These results should therefore be confirmed by future studies.

Our meta-analysis has several strengths. First of all, the innovative methodology used to identify original articles, which involved a combination of umbrella and traditional reviews, allowed us to incorporate data from 73 eligible studies investigating the link between SHS and breast cancer risk. This meta-analysis is therefore the most exhaustive available on the topic, including a very large sample size. Additionally, we implemented a rigorous screening process of the publications to prevent data overlap. Another strength is related to the examination of different settings and sources of exposure, which allows for a more comprehensive understanding of the relationship between SHS and breast cancer. Furthermore, we investigated dose-response relationships, in order to better explain the observed associations.

Limitations of this meta-analysis include the presence of heterogeneity between studies, which was found for almost all sources of exposure. This could be due to the combination of data from studies that were conducted with different methods, had different definitions of SHS exposure, and included individuals with different characteristics and background risks. To account for this heterogeneity, we employed random-effects models, which provide more cautious estimates but do not completely eliminate heterogeneity. Additionally, we examined potential sources of heterogeneity by conducting stratified analyses based on factors such as the study design, population, and cancer characteristics. Moreover, the potential misclassification of SHS exposure in the included studies may have affected the precision of our estimates.

Our systematic review is part of a series of comprehensive systematic reviews on the association between cigarette smoking and SHS exposure and cancer risk at several sites [13, 23, 25-27]. Consistently with previously conducted reviews, we decided not to assess quality of eligible studies. In fact, the recommended tool to evaluate the quality of observational studies (i.e., case-control and cohort studies) is the Newcastle-Ottawa Quality Assessment Scale (NOS) [52], which

more likely detects the quality of the report rather than the quality of the study. Moreover, the scoring of most of its items is somewhat subjective, and, in the case of large established cohort studies, often requires the evaluation of methods described in protocols or previous publications. We therefore preferred to conduct stratified analyses according to objective study quality parameters, including the presence of adjustments for confounding factors and the study population size, based on the number of breast cancer cases. Considering these measures, the high-quality studies (those providing adjusted estimates, particularly adjusted for alcohol consumption, and those with larger size) showed lower but still statistically significant excess breast cancer risks.

In conclusion, our meta-analysis provides comprehensive and up-to-date evidence that SHS exposure represents a significant risk factor for the development of breast cancer among non-smoking women. The strength, consistency, temporality, dose-response relationship, and biological plausibility of the observed association, as supported by the Bradford Hill criteria, collectively suggest a causal link between SHS exposure and breast cancer risk [53]. These findings may be relevant in raising awareness among the general population and health professionals about the risks of SHS exposure, especially at home and in other private settings, and in promoting smoke-free interventions, such as smoke-free homes. SHS exposure should be listed among the main avoidable risk factors for breast cancer in order to gather major support for health promotion, health education intervention, and policies.

4.6 Contribution to the overall thesis framework

This chapter extended the investigation from active smoking to secondhand smoke (SHS) exposure, addressing an important component of tobacco-related cancer burden that is often overlooked in burden estimation studies. By providing updated evidence on the association between SHS exposure and breast cancer risk, the study generated quantitative risk estimates that can be incorporated into burden estimation models.

Together with the findings of the previous chapters, this work contributed to the development of the methodological framework presented later in the thesis, demonstrating how epidemiological evidence can be translated into measures of attributable burden. In particular, the study provided an opportunity to apply and test the proposed approach in the context of SHS-related cancer burden. The next chapter shifts the focus from risk estimation to population exposure, presenting updated data on smoking habits and SHS exposure in Italy, which represent essential inputs for burden estimation studies.

4.7 References

1. Ferlay J, Colombet M, Soerjomataram I, Parkin DM, Pineros M, Znaor A, et al. Cancer statistics for the year 2020: An overview. Int J Cancer. 2021.
2. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71(3):209-49.
3. Boffetta P, La Vecchia C. Neoplasms. In: Detels R, Beaglehole R, Lansang M, editors. Oxford Textbook of Public Health 5th Edition. New York:: Oxford University Press; 2009. p. 997-1020.
4. Collaborative Group on Hormonal Factors in Breast Cancer. Menarche, menopause, and breast cancer risk: individual participant meta-analysis, including 118 964 women with breast cancer from 117 epidemiological studies. Lancet Oncol. 2012;13(11):1141-51.
5. Ewertz M, Duffy SW, Adami HO, Kvåle G, Lund E, Meirik O, et al. Age at first birth, parity and risk of breast cancer: a meta-analysis of 8 studies from the Nordic countries. Int J Cancer. 1990;46(4):597-603.
6. Bagnardi V, Rota M, Botteri E, Tramacere I, Islami F, Fedirko V, et al. Alcohol consumption and site-specific cancer risk: a comprehensive dose-response meta-analysis. Br J Cancer. 2015;112(3):580-93.
7. Hamajima N, Hirose K, Tajima K, Rohan T, Calle EE, Heath CW, Jr., et al. Alcohol, tobacco and breast cancer--collaborative reanalysis of individual data from 53 epidemiological studies, including 58,515 women with breast cancer and 95,067 women without the disease. Br J Cancer. 2002;87(11):1234-45.
8. Steindorf K, Ritte R, Eomois PP, Lukanova A, Tjonneland A, Johnsen NF, et al. Physical activity and risk of breast cancer overall and by hormone receptor status: the European prospective investigation into cancer and nutrition. Int J Cancer. 2013;132(7):1667-78.
9. Reeves GK, Pirie K, Beral V, Green J, Spencer E, Bull D, et al. Cancer incidence and mortality in relation to body mass index in the Million Women Study: cohort study. BMJ. 2007;335(7630):1134.
10. Chlebowski RT, Manson JE, Anderson GL, Cauley JA, Aragaki AK, Stefanick ML, et al. Estrogen plus progestin and breast cancer incidence and mortality in the Women's Health Initiative Observational Study. J Natl Cancer Inst. 2013;105(8):526-35.
11. Morch LS, Hannaford PC, Lidegaard O. Contemporary Hormonal Contraception and the Risk of Breast Cancer. N Engl J Med. 2018;378(13):1265-6.
12. IARC. Personal habits and indoor combustions. Volume 100 E. IARC Monogr Eval Carcinog Risks Hum. 2012:1-538.
13. Scala M, Bosetti C, Bagnardi V, Possenti I, Specchia C, Gallus S, et al. Dose-response relationships between cigarette smoking and breast

cancer risk: a systematic review and meta-analysis. Journal of Epidemiology. 2023.

14. California Environmental Protection Agency. Proposed Identification of Environmental Tobacco Smoke as a Toxic Air Contaminant. California Environmental Protection Agency. 2005.
15. World Health Organization. WHO report on the global tobacco epidemic, 2015: raising taxes on tobacco. 2015.
16. U.S. Department of Health and Human Services. The Health Consequences of Smoking — 50 Years of Progress. A Report of the Surgeon General. Rockville, MD: Public Health Service, Office of the Surgeon General; 2014.
17. Thompson PA, DeMarini DM, Kadlubar FF, McClure GY, Brooks LR, Green BL, et al. Evidence for the presence of mutagenic arylamines in human breast milk and DNA adducts in exfoliated breast ductal epithelial cells. Environ Mol Mutagen. 2002;39(2-3):134-42.
18. Collishaw NB, N.F.; Cantor, K.P.; Hammond, S.K.; Johnson, K.C. Canadian Expert Panel on Tobacco Smoke and Breast Cancer Risk. Toronto: Ontario Tobacco Research Unit. 2009.
19. IARC. Tobacco smoke and involuntary smoking. Vol. 83. IARC Monogr Eval Carcinog Risks Hum. 2004:1-1438.
20. He Y, Si Y, Li X, Hong J, Yu C, He N. The relationship between tobacco and breast cancer incidence: A systematic review and meta-analysis of observational studies. Front Oncol. 2022;12:961970.
21. Kim AS, Ko HJ, Kwon JH, Lee JM. Exposure to Secondhand Smoke and Risk of Cancer in Never Smokers: A Meta-Analysis of Epidemiologic Studies. International journal of environmental research and public health. 2018;15(9).
22. Lee PN, Hamling JS. Environmental tobacco smoke exposure and risk of breast cancer in nonsmoking women. An updated review and meta-analysis. Inhalation toxicology. 2016;28(10):431-54.
23. Lugo A, Bosetti C, Peveri G, Rota M, Bagnardi V, Gallus S. Dose-response relationship between cigarette smoking and site-specific cancer risk: protocol for a systematic review with an original design combining umbrella and traditional reviews. BMJ Open. 2017;7(10):e018930.
24. Botteri E, Borroni E, Sloan EK, Bagnardi V, Bosetti C, Peveri G, et al. Smoking and Colorectal Cancer Risk, Overall and by Molecular Subtypes: A Meta-Analysis. Am J Gastroenterol. 2020;115(12):1940-9.
25. Lugo A, Peveri G, Bosetti C, Bagnardi V, Crippa A, Orsini N, et al. Strong excess risk of pancreatic cancer for low frequency and duration of cigarette smoking: A comprehensive review and meta-analysis. Eur J Cancer. 2018;104:117-26.
26. Malevolti MC, Lugo A, Scala M, Gallus S, Gorini G, Lachi A, et al. Dose-risk relationships between cigarette smoking and cervical cancer: a systematic review and meta-analysis. Eur J Cancer Prev. 2022.

27. Santucci C, Bosetti C, Peveri G, Liu X, Bagnardi V, Specchia C, et al. Dose-risk relationships between cigarette smoking and ovarian cancer histotypes: a comprehensive meta-analysis. Cancer Causes Control. 2019;30(9):1023-32.
28. Hamling J, Lee P, Weitkunat R, Ambuhl M. Facilitating meta-analyses by deriving relative effect and precision estimates for alternative comparisons from a set of estimates presented by exposure level or disease category. Stat Med. 2008;27(7):954-70.
29. Rucker G, Cates CJ, Schwarzer G. Methods for including information from multi-arm trials in pairwise meta-analysis. Res Synth Methods. 2017;8(4):392-403.
30. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7(3):177-88.
31. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21(11):1539-58.
32. Peters JL, Sutton AJ, Jones DR, Abrams KR, Rushton L. Contour-enhanced meta-analysis funnel plots help distinguish publication bias from other causes of asymmetry. J Clin Epidemiol. 2008;61(10):991-6.
33. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315(7109):629-34.
34. Balduzzi S, Rucker G, Schwarzer G. How to perform a meta-analysis with R: a practical tutorial. Evid Based Ment Health. 2019;22(4):153-60.
35. Crippa AON. Multivariate Dose-Response Meta-Analysis: The dosresmeta R Package. Journal of Statistical Software. 2016;72.
36. Wells AJ. Re: "Breast cancer, cigarette smoking, and passive smoking". Am J Epidemiol. 1998;147(10):991-2.
37. WHO. Alcohol is one of the biggest risk factors for breast cancer. Available online at: https://www.who.int/europe/news/item/20-10-2021-alcohol-is-one-of-the-biggest-risk-factors-for-breast-cancer (accessed 03 March 2023). 2021.
38. Oberg M, Jaakkola MS, Woodward A, Peruga A, Pruss-Ustun A. Worldwide burden of disease from exposure to second-hand smoke: a retrospective analysis of data from 192 countries. Lancet. 2011;377(9760):139-46.
39. G. B. D. Alcohol Collaborators. Alcohol use and burden for 195 countries and territories, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet. 2018;392(10152):1015-35.
40. Dossus L, Boutron-Ruault MC, Kaaks R, Gram IT, Vilier A, Fervers B, et al. Active and passive cigarette smoking and breast cancer risk: results from the EPIC cohort. Int J Cancer. 2014;134(8):1871-88.
41. Reynolds P. Smoking and breast cancer. Journal of mammary gland biology and neoplasia. 2013;18(1):15-23.

42. Shrubsole MJ, Gao YT, Dai Q, Shu XO, Ruan ZX, Jin F, et al. Passive smoking and breast cancer risk among non-smoking Chinese women. Int J Cancer. 2004;110(4):605-9.

43. Johnson KC, Wells AJ. Active and passive smoking in breast cancer. Epidemiology. 2002;13(6):745-6.

44. Rothman KJ, Greenland S. Modern Epidemiology. 2nd ed. Philadelphia: Lippincott-Raven. 1998.

45. Chang-Claude J, Kropp S, Jager B, Bartsch H, Risch A. Differential effect of NAT2 on the association between active and passive smoke exposure and breast cancer risk. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2002;11(8):698-704.

46. Millikan RC, Pittman GS, Newman B, Tse CK, Selmin O, Rockhill B, et al. Cigarette smoking, N-acetyltransferases 1 and 2, and breast cancer risk. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 1998;7(5):371-8.

47. Tang H, Yang D, Han C, Mu P. Smoking, DNA Methylation, and Breast Cancer: A Mendelian Randomization Study. Front Oncol. 2021;11:745918.

48. Gram IT, Wiik AB, Lund E, Licaj I, Braaten T. Never-smokers and the fraction of breast cancer attributable to second-hand smoke from parents during childhood: the Norwegian Women and Cancer Study 1991-2018. International journal of epidemiology. 2022;50(6):1927-35.

49. Morabia A, Bernstein M, Ruiz J, Heritier S, Diebold Berger S, Borisch B. Relation of smoking to breast cancer by estrogen receptor status. Int J Cancer. 1998;75(3):339-42.

50. Strumylaite L, Kregzdyte R, Poskiene L, Bogusevicius A, Pranys D, Norkute R. Association between lifetime exposure to passive smoking and risk of breast cancer subtypes defined by hormone receptor status among non-smoking Caucasian women. PloS one. 2017;12(2):e0171198.

51. U.S. Department of Health and Human Services. The Health Consequences of Involuntary Exposure to Tobacco Smoke: A Report of the Surgeon General. Atlanta, GA: Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2006.

52. Zeng X, Zhang Y, Kwong JS, Zhang C, Li S, Sun F, et al. The methodological quality assessment tools for preclinical and clinical studies, systematic review and meta-analysis, and clinical practice guideline: a systematic review. J Evid Based Med. 2015;8(1):2-10.

53. Hill AB. The Environment and Disease: Association or Causation? Proc R Soc Med. 1965;58(5):295-300.

Annex Chapter 4

PRISMA Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Pag 102
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Pag 103
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Pag 104
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Pag 105
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Pag 108
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Pag 105-106
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Suppl
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Pag 105-108
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Pag 108
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Pag 108

Section and Topic	Item #	Checklist item	Location where item is reported
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Pag 108
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	NA
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Pag 109
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Pag 108-109
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Pag 108
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Pag 109
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Pag 109
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Pag 109
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Pag 109
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Pag 109
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	NA
RESULTS			

Section and Topic	Item #	Checklist item	Location where item is reported
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Pag 109-110
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Suppl
Study characteristics	17	Cite each included study and present its characteristics.	Suppl
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	NA
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Pag 111, Suppl
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	NA
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Pag 111, Suppl
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Pag 113-114
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Pag 113-114
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Suppl
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	NA
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Pag 116
	23b	Discuss any limitations of the evidence included in the review.	Pag 119
	23c	Discuss any limitations of the review processes used.	Pag 119

Section and Topic	Item #	Checklist item	Location where item is reported
	23d	Discuss implications of the results for practice, policy, and future research.	
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Pag 105
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Pag 105
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Original pub
Competing interests	26	Declare any competing interests of review authors.	Original pub
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Original pub

Supplementary Materials available online at:
https://pmc.ncbi.nlm.nih.gov/articles/PMC11443041/

Chapter 5

Prevalence of Cigarette Smoking and Secondhand Smoke Exposure in Italy in 2024

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5.1 Abstract

Background: Despite past progress, smoking and secondhand smoke (SHS) remain major public health concerns in Italy. The absence of recent regulations and the spread of novel products highlight the need for continued monitoring.

Methods: We conducted a nationally representative survey in Italy in 2024 using face-to-face interviews on 3125 participants aged 15 years and older. Smoking prevalence, daily SHS exposure in indoor settings and their relationship with sociodemographic and behavioral factors were analysed using unconditional multiple logistic regression models.

Results: In 2024, 26.6% of Italian adults reported to be current conventional cigarette smokers (31.5% in men and 22.3% in women), 11.7% former smokers, and 61.7% never smokers. Compared to never, current smoking was more common among middle age groups (adjusted odds ratio; aOR=2.00; 95% confidence intervals; CI: 1.5–2.6 for individuals aged 25–64 compared with <25 years) and was related to higher levels of education (p for trend=0.008). Current smoking was also more frequent among users of electronic cigarettes (e-cigs; aOR=25.5; 95% CI: 10.8-60.2) and heated tobacco products (HTP; aOR=100.3; 95% CI: 35.4-284.2). Among nonsmokers, 16.3% reported daily indoor exposure to SHS, mainly at work (6.4%) and in other indoor places (7.1%). Daily exposure at home and in private and public transport was 4.3%, 4.3% and 1.4%, respectively. Being exposed to SHS decreased significantly with age (p for trend<0.001).

Conclusion: This study highlights that smoking prevalence remains high and that SHS exposure continues to represent a significant public health concern in Italy. The results underline the need to update and enforce evidence-based tobacco control measures.

5.2 Introduction

Cigarette smoking is the leading preventable cause of mortality and morbidity worldwide, with a devastating impact on public health. Tobacco consumption is estimated to be responsible for about 8 million deaths per year, of which about 1 million are attributable to exposure to secondhand smoke (SHS) [1, 2]. Tobacco use also remains a major public health challenge in Italy. Indeed, it is estimated that more than 70,000 deaths are attributable to tobacco use each year in Italy [3]. In addition, smoking poses a significant economic burden on the Italian healthcare system, with hospital admissions attributable to this risk factor exceeding €1.5 billion annually [4].

Over the past two decades, Italy has experienced a significant decline in smoking prevalence, particularly in the early 2000s, driven by increased awareness of the associated health risks and the implementation of stricter tobacco control policies. Since 2014, however, an interruption of the positive trend has been observed [5]. In 2022, the prevalence of cigarette smoking had risen to 24.2%, the first significant increase since 2009 [6]. In parallel, Italy has been a pioneer in the fight against SHS exposure. In 2005, it became the first large country in the world to enact comprehensive smoke-free legislation banning smoking in indoor public places, including restaurants, bars and workplaces [7]. Although tobacco control policies have been successful [8], no new national measures have been implemented in Italy since 2005 [9], and SHS exposure remains an important public health issue [10-12]. Local jurisdictions have implemented noteworthy policies, such as outdoor smoking ban in Milan since January 2025 [13], or smoke-free beach areas in selected beaches, such as in Bibione [14]. These initiatives represent important steps toward expanding smoke-free environments in Italy and could serve as valuable models for national-level policies.

On the other hand, the growing popularity of electronic cigarettes (e-cig) and heated tobacco products (HTP) is raising concerns about the renormalization of smoking and tobacco use [15]. These products are particularly widespread among young people, increasing the risk of nicotine addiction and long-term health consequences [16]. While often marketed as less harmful alternatives, there is no conclusive scientific evidence proving that e-cigs and HTPs carry a lower health risk than traditional cigarettes [17].

Despite the progress made in tobacco control and the considerable amount of research on smoking prevalence and SHS exposure, significant gaps remain in the current knowledge base in Italy. The most recently published comprehensive data on smoking prevalence from Italy date from 2023 and do not explore factors associated with smoking habits [18]. Furthermore, while there is a considerable amount of research on SHS exposure among children and in outdoor settings

[12, 19-21], data on indoor SHS exposure in general population remain scarce, with the most recent published comprehensive study using data from 2010 [11].

These figures highlight the need for continued monitoring and updated data on both active smoking and SHS exposure in Italy. Given the observed stalling in smoking prevalence decline and persistent SHS exposure, there is an urgent need to better understand current trends. This study aims to provide an updated assessment of the prevalence of smoking and SHS exposure in Italy, with a focus on stratified analyses by demographic characteristics. This study seeks to fill critical knowledge gaps in order to guide future public health strategies and interventions.

5.3 Methods

The data used in this study come from a cross-sectional survey conducted between March and September 2024. The sample was composed of 3125 participants (1515 men and 1610 women), representative of the Italian population aged 15 and over in terms of sex, age, geographic area, and socioeconomic characteristics.

The study used a multistage representative sampling approach to select participants. First, municipalities were sampled from all 20 Italian regions, stratified by region and municipality size. Next, a random sample of electoral districts was drawn within each selected municipality. Finally, individuals were randomly selected from the electoral lists, further stratified by sex and age. To capture young people aged 15-17 who were not on the electoral rolls, a quota sampling method based on sex and exact age was employed. If a selected participant was unavailable or declined to participate, he or she was replaced with an individual who matched the sex, age group, and area of residence (same municipality and same district). This substitution process was designed to preserve the representativeness of the final sample.

Interviews were conducted by trained interviewers using a structured questionnaire administered through computer-assisted face-to-face interviews at participants' homes. The questionnaire collected general sociodemographic information, smoking status, and number of cigarettes smoked per day. Participants' level of education was classified as low for those who completed middle school or less, intermediate for high school graduates, and high for university graduates or beyond. Never smokers were defined as individuals who reported having smoked fewer than 100 cigarettes in their lifetime. Former smokers were those who had smoked 100 or more cigarettes in their lifetime but had not smoked for at least one year. Current smokers were defined as those

who reported having smoked 100 or more cigarettes in their lifetime and who were currently smoking cigarettes or had quit within the past year. In addition to conventional cigarette smoking status (hereafter referred to as “smoking”), the questionnaire also collected information on the use of electronic cigarettes (e-cig) and heated tobacco products (HTP). Individuals were categorised as e-cig users if they reported current use (daily or occasional) of any type of e-cig, including disposable, cartridge-based or rechargeable e-cigs containing nicotine salts. For HTP use, individuals were categorised as users if they reported current use (daily or occasional) of any type of HTP, such as IQOS or Glo.

The study also investigated SHS exposure from conventional cigarettes in indoor settings. Nonsmokers (former and never smokers combined) were asked about their exposure to SHS in five different indoor settings: at home, at work (or at school for students), on public transport (e.g., trains, trams, buses and underground trains), in private cars, and in “other indoor settings” (e.g., bars, restaurants, cafeterias and other leisure venues). Participants reported the average amount of time (in minutes per day) they were exposed to SHS in each of the five indoor settings during an average working and non-working day. Nonsmokers were classified as “daily exposed to SHS” if they reported being exposed for at least one minute per day during working and/or non-working day in any indoor setting. Otherwise, they were classified as “non-exposed to SHS”.

5.3.1 Statistical Analysis

Statistical weights were generated and used in phase of data analysis to ensure representativeness of the Italian population aged 15 years and over. Descriptive statistics were used to describe the main results, including percentage prevalence and the corresponding 95% confidence intervals (CI) for categorical variables and mean and standard deviation (SD) for continuous variables. To explore how selected sociodemographic characteristics are independently related with different smoking outcomes and to identify target subpopulation for prevention strategies, while reducing the influence of potential shared associations with third variables that could distort the observed relationships, we used unconditional multiple logistic regression models including terms for sex, age, level of education, and geographic area. We estimated the adjusted odds ratios (aOR) and corresponding 95% CIs for current smokers versus never smokers, former smokers vs current smokers, and nonsmokers daily exposed to SHS in indoor settings vs nonsmokers non-exposed to SHS in indoor settings.

All statistical analyses were conducted using SAS version 9.4 statistical package (SAS Institute).

5.4 Results

In 2024, 61.7% of Italian adults aged 15 years and over described themselves as never smokers, 11.7% as former smokers, and 26.6% as current smokers (31.1% of men and 22.3% of women; Table 1). The proportions of current and former smokers were higher among men (31.3% and 15.1%, respectively) than among women (22.3% and 8.5%, respectively). Male current smokers reported smoking a higher number of cigarettes per day (14.0 cigarettes per day; SD=6.2) than female ones (12.4 cigarettes per day; SD=5.7). In 2024, 16.3% of nonsmokers in Italy reported a daily exposure to SHS in at least one indoor setting, 17.7% in men and 15.1% in women. Indoor SHS exposure from conventional cigarettes was 4.3% at home (4.3% among men and 4.2% among women), 6.4% in workplaces (7.6% among men and 5.4% among women), 1.4% in public transports (1.1% among men and 1.7% among women), 4.3% in private transports (4.6% among men and 4.1% among women), and 7.1% in other indoor settings (7.7% among men and 6.6% among women).

Table 1. Smoking status and secondhand smoke (SHS) exposure in the Italian population aged ≥15 years, overall and by sex, Italy, 2024.

	Total (N=3125)	Men (N=1515)	Women (N=1610)
Smoking status, % (95% CI)			
Never smokers	61.7 (60.0-63.4)	53.7 (51.2-56.2)	69.2 (67.0-71.5)
Former smokers	11.7 (10.6-12.9)	15.1 (13.3-16.9)	8.5 (7.2-9.9)
Current smokers	26.6 (25.0-28.1)	31.1 (28.8-33.5)	22.3 (20.3-24.3)
Mean cigarettes/day (SD)	13.3 (6.0)	14.0 (6.2)	12.4 (5.7)
Daily SHS exposure in indoor settings, % of exposed (95% CI) among nonsmokers [a]			
Any indoor setting	16.3 (14.8-17.8)	17.7 (15.4-20.0)	15.1 (13.1-17.0)
Home	4.3 (3.4-5.1)	4.3 (3.1-5.6)	4.2 (3.1-5.3)
Workplace	6.4 (5.4-7.4)	7.6 (6.0-9.2)	5.4 (4.2-6.7)
Public transport	1.4 (0.9-1.9)	1.1 (0.4-1.7)	1.7 (1.0-2.4)
Private transport	4.3 (3.5-5.2)	4.6 (3.4-5.9)	4.1 (3.0-5.2)
Other indoor settings	7.1 (6.0-8.1)	7.7 (6.0-9.3)	6.6 (5.2-8.0)

CI: confidence intervals; SD: standard deviation; [a] never and former smokers combined

The analysis of determinants for current smoking is described in Table 2. Men were significantly more likely to be current smokers than women (aOR=1.78, 95% CI: 1.52-2.13). Compared with those aged 25 years or younger, the frequency of current smokers was significantly higher among those aged 25-64 (aOR=1.99; 95% CI: 1.50-2.3), whereas no significant difference was observed for those aged 65 years or older (aOR=1.27; 95% CI: 0.92-1.76; p for trend=0.400). Individuals with intermediate (aOR=1.61; 95% CI: 1.30-2.00) or high (aOR=1.40; 95% CI: 1.05-1.85) education were significantly more likely to be current smokers than those with low education (p for trend=0.008). Geographical differences were observed, with higher odds of current smoking in southern Italy and the islands (aOR=1.50; 95% CI: 1.24-1.82) compared with northern Italy. Current smoking was strongly related with use of novel nicotine and tobacco products, with significantly higher odds for e-cig users (aOR=25.49; 95% CI: 10.80-60.16) and HTP users (aOR=100.25; 95% CI: 35.36-284.23) compared with non-users. Among e-cig users and HTP users, 87.8% and 92.5% respectively reported being current smokers.

Table 2. Adjusted odds ratios* (aOR) of current smokers vs never smokers (excluding former smokers), according to selected characteristics, Italy, 2024.

	N	N (%) never smokers	N (%) current smokers	Current smokers vs never smokers [a] aOR (95% CI)
Total	3125	1928 (61.7)	830 (26.6)	-
Sex				
Women	1610	1114 (69.2)	359 (22.3)	Ref
Men	1515	814 (53.7)	472 (31.1)	1.78 (1.52-2.13)
Age (years)				
<25	353	275 (77.9)	74 (20.8)	Ref
25-44	808	486 (60.1)	263 (32.6)	1.92 (1.41-2.61)
45-64	1104	624 (56.5)	341 (30.9)	2.03 (1.51-2.73)
≥65	860	543 (63.2)	152 (17.7)	1.27 (0.92-1.76)
p for trend				*0.400*
Level of education				
Low	973	639 (65.7)	183 (18.9)	Ref
Intermediate	1676	992 (59.2)	504 (30.1)	1.61 (1.30-2.00)
High	476	297 (62.4)	143 (30.1)	1.40 (1.05-1.85)

p for trend				*0.008*
Geographic area				
Northern Italy	1454	953 (65.5)	360 (24.8)	Ref
Central Italy	623	366 (58.7)	159 (25.5)	1.20 (0.95-1.50)
Southern Italy and islands	1048	610 (58.2)	312 (29.8)	1.50 (1.24-1.82)
E-cig use				
Non-user	3054	1922 (62.9)	768 (25.2)	Ref
User	71	6 (8.4)	62 (87.8)	25.49 (10.80-60.16)
HTP use				
Non-user	2985	1924 (64.5)	702 (23.5)	Ref
User	139	4 (2.7)	129 (92.5)	100.25 (35.36-284.23)

[a] Excluding n=366 former smokers; CI: confidence intervals; E-cig: electronic cigarette; HTP: heated tobacco product.
* Odds ratios were estimated with unconditional multiple logistic regression models after adjustment for age, sex, level of education, and geographic area.
Estimates in bold are statistically significant at 0.05 level.
Percentages do not sum to 100% because former smokers were excluded from the analysis.

The aORs for being a former smoker compared with a current smoker (i.e., having quit smoking among ever smokers) are shown in Supplementary Table 1. Men were more likely to be former smokers than women (aOR=1.32; 95% CI: 1.01-1.72). The odds of being a former smoker increased with age (p for trend<0.001) and decreased with education (p for trend<0.001). HTP use (aOR=0.19; 95% CI: 0.08-0.41) and e-cig use (aOR=0.16; 95% CI: 0.05-0.53) were significantly related with a lower likelihood of having quit smoking compared with non-users. Among ever users of e-cigs and HTPs, 10 and 15, respectively, were former smokers (totalling 18 individuals without overlap).

Supplementary Table 2 explores the relationship between socio-demographic and behavioural factors and current cigarette smoking among young adults aged 15-24 years. In this subgroup, no significant relationship was observed between sex and current smoking. Geographical differences were observed among the youngest, with higher odds of current smoking in southern Italy and the islands (aOR=1.93; 95% CI: 1.07-3.48) compared with northern Italy. In the youngest age

group, current smoking was strongly related with use of novel nicotine and tobacco products, with significantly higher odds for e-cig users (aOR=16.27; 95% CI: 3.06-86.70) and HTP users (aOR=110.83; 95% CI: 19.15-641.39) compared with non-users.

Table 3 shows the relationship between different demographic and socioeconomic factors and daily exposure to SHS in any indoor setting. No significant associations emerged between sex and SHS exposure. The odds of exposure to SHS decreased significantly with age, with the aOR being 0.55 (95% CI: 0.38-0.79) for those aged 45-64 years and 0.54 (95% CI: 0.37-0.78) for those aged 65 years and over, compared with those aged 25 years or less (p for trend<0.001). No significant relationship was observed between educational level and SHS exposure (p for trend=0.181). Individuals from central Italy (aOR=2.60; 95% CI: 1.92-3.52) and from southern Italy and the islands (aOR=2.81; 95% CI: 2.14-3.68) were significantly more likely to be exposed to SHS than those from northern Italy.

Table 3. Adjusted odds ratios* (aOR) of exposure to secondhand smoke (SHS) in any indoor setting vs non-exposure, among nonsmokers, according to selected characteristics, Italy, 2024

	N	N (%) Exposed	aOR (95% CI)
Total	2294	373 (16.3)	-
Sex			
Women	1251	188 (15.1)	Ref
Men	1043	185 (17.7)	1.23 (0.98-1.56)
Age (years)			
<25	280	63 (22.5)	Ref
25-44	544	109 (20.1)	0.83 (0.58-1.21)
45-64	763	108 (14.2)	0.55 (0.38-0.79)
≥65	707	93 (13.1)	0.54 (0.37-0.78)
p for trend			*<0.001*
Level of education			
Low	789	121 (15.4)	Ref
Intermediate	1172	185 (15.8)	1.17 (0.89-1.56)
High	333	67 (20.2)	1.27 (0.88-1.83)
p for trend			0.181
Geographic area			
Northern Italy	1094	107 (9.8)	Ref
Central Italy	465	98 (21.2)	2.60 (1.92-3.52)

Southern Italy and islands	736	168 (22.8)	2.81 (2.14-3.68)

CI: confidence intervals.

* Odds ratios were estimated with unconditional multiple logistic regression models after adjustment for age, sex, level of education, and geographic area. Estimates in bold are statistically significant at 0.05 level.

5.5 Discussion

This cross-sectional study, conducted in 2024 on a representative sample of over 3000 Italians, found that about one in four Italians were current smokers. In addition, among nonsmokers, one in six reported daily exposure to secondhand smoke (SHS) in indoor settings.

Since the early 2000s, Italy has consistently seen a significant decline in smoking prevalence, driven by increased awareness of health risks and stronger tobacco control policies, reaching around 20% in 2014 [5]. However, this positive trend seems to have stalled in the last decade [22, 23], as reflected in official ISTAT and Eurobarometer data [24-26]. Our results, together with previous surveys using analogous methods [5, 22, 23], confirm that the downward trend in smoking prevalence has ceased, and even suggest a possible increase in conventional smoking. This is also confirmed by cigarette sales data, which recorded an increase in 2024.

Compared to other European countries, Italy has historically exhibited some distinctive patterns in cigarette smoking. Less recent studies have shown Italy to be one of the countries with the lowest smoking prevalence, likely due in part to historically low smoking rates among women [27, 28]. However, according to the present study and the most recent data, Italy's current smoking prevalence (27%) is now beginning to surpass the EU average (24%) [24]. This suggests the need to strengthen cessation efforts and support smoking cessation services in order to accelerate progress in tobacco and nicotine control.

The urgent need for new and more effective tobacco control measures is further highlighted by the recent increase in the average number of cigarettes smoked per day, which rose to 13.3 cigarettes in 2024. This level corresponds to the average observed in 2015 [23], and represents a notable increase from the 11.5 cigarettes per day recorded in 2022 [6].

Sex and age differences in smoking prevalence provide additional insights into the tobacco consumption landscape in Italy. Consistently with results from prior Italian and European studies [6, 25], men maintain higher smoking rates compared to women. However, the proportion of female smokers and their daily

cigarette consumption have seen a concerning rise in recent years [5, 6, 22, 29], highlighting the need for targeted interventions to counteract this trend. The results confirm that older age groups exhibit a higher prevalence of smoking compared to younger cohorts [5, 22]. However, the escalating use of novel tobacco products among youth is particularly concerning, as these devices may foster nicotine addiction and renormalize smoking behavior, potentially serving as a gateway to conventional tobacco and thereby increasing long-term cigarette smoking rates [22, 30-32].

Smoking prevalence resulted higher in the central, southern and island regions of Italy than in the north. These differences may reflect differences in cultural attitudes or in the implementation and enforcement of tobacco control policies. Further research is needed to better understand these regional differences and develop targeted interventions. Although our multivariable models adjusted for educational level, residual confounding cannot be completely ruled out. Given the well-known economic and cultural differences between northern and southern Italy, regional variations in smoking prevalence may be partly attributable to unmeasured aspects of socioeconomic status or other contextual factors correlated with both education and geographic area.

The analysis revealed that socio-economic level, as measured specifically by educational level, is related with smoking behaviour, with individuals with intermediate and high levels of education showing higher smoking rates. This pattern does not reflect the conventional inverse gradient typically observed in Europe [33], nor does it align with earlier Italian data [5, 22]. However, it is similar with more recent findings from other Mediterranean populations, such as Greece and Spain [33, 34]. This may reflect a different stage of the tobacco epidemic in Mediterranean countries compared with the rest of Europe. However, this finding should be interpreted with caution, as residual confounding by age cannot be ruled out.

The use of novel products, such as e-cigarettes and heated tobacco products, was associated with a higher likelihood of cigarette smoking and a lower likelihood of quitting smoking. This is further supported by the strikingly low number of former smokers among ever users of these products – only 0.05% of the population. This finding suggests that only a negligible fraction of people could have successfully used these devices to quit smoking, reinforcing important concerns about their promotion as smoking cessation tools. Indeed, several studies have observed that smokers who use novel products are less likely to quit smoking [30, 35]. Furthermore, evidence from studies conducted in Italy suggests that these products may even act as a gateway to cigarette smoking, especially among young people [16, 30]. These results highlight the need for new tobacco control strategies aimed to regulate novel products.

An additional analysis focused on young people aged 15–24, who are a key target group for tobacco and nicotine prevention. Compared to data from over a decade ago (2013–2014), the prevalence of smoking in this age group has slightly increased, rising from 19.9% to 20.8% [5]. This increase is primarily due to a rise of cigarette smoking among young women, whose smoking prevalence increased from 18.0% to 20.7%, whereas the prevalence among young men has remained essentially unchanged. This pattern might be a reflection of targeted marketing strategies employed by the tobacco industry. Throughout history, the tobacco industry has positioned smoking as a symbol of independence or modernity, particularly appealing to young women. Moreover, the strong association between smoking and the use of e-cigs and HTPs among young people highlights the increasing influence of these novel products on tobacco-related behaviours. This is in stark contrast with the narrative that portrays these products as cessation tools for long-term smokers.

The proportion of people reporting indoor exposure to SHS in this study is lower than both the last Eurobarometer report [25] and a 2012 study [11], which reported exposure between 20 and 30%. However, differences in the way the questions are asked, particularly when they involve subjective assessments of exposure, could be a significant challenge in comparing results. In addition, the use of a threshold of only one minute/day to define SHS exposure might be considered too sensitive. Nevertheless, we found that changing the threshold for SHS exposure had only a minimal impact on prevalence estimates (total SHS exposure was 15.0 % using a threshold of one hour/week instead of 16.3% using one minute/day). A study based on 2017-2018 data, which used the same questions and thresholds as our survey, found that one in four nonsmoking Italians was exposed to SHS [36]. This may indicate that recent initiatives aiming at protect people from harmful effects of SHS, such as the European Directive 40/2014 (Legislative Decree 6/2016) adopted in 2016 [37], which bans smoking in cars in the presence of minors, have had a positive impact, although there is still much work to be done. The fact that workplaces and other indoor settings, such as bars and restaurants, are the most common settings for SHS exposure is striking, as it suggests that the Sirchia Law, which bans smoking in indoor public places, is not being fully respected. This highlights the need for stricter enforcement of the law to protect people from harmful exposure to tobacco smoke in workplaces and leisure venues [38]. It should be noted that our study did not assess exposure to aerosols from other tobacco and nicotine products, which appears to be increasingly widespread [39]. Given the rising popularity of electronic cigarettes and heated tobacco products, future research should consider monitoring exposure to these aerosols.

SHS exposure was highest among younger individuals, which is especially concerning given its heightened harm at a young age. Previous studies have

shown that early exposure to SHS can have long-term negative effects on respiratory and cardiovascular health [40], as well as influence attitudes toward active smoking [41]. This underscores the need for targeted strategies to protect younger populations from exposure, including stricter enforcement of existing regulations and awareness campaigns on the risks of SHS.

Exposure to SHS resulted more common in the central, southern and island regions of Italy. This is consistent with the latest PASSI surveillance data, which highlight lower compliance with indoor smoking bans in these areas compared to northern regions [42]. The regional variation may be due to cultural factors and is of particular concern given the well-documented health risks of SHS exposure, including its association with breast and lung cancer [43, 44]. These findings highlight the need for targeted strategies to raise awareness and reduce exposure, particularly in these areas, in order to mitigate the harmful effects of SHS.

The study has several limitations that should be considered. First, its cross-sectional design precludes the ability to infer causality, allowing only the identification of relationships. Second, the self-reported nature of the data introduces the potential for information bias, such as underreporting of smoking habits. This concern is particularly relevant for SHS exposure, as the subjective nature of the questions may make comparisons with other populations particularly challenging. However, the face-to-face interview approach with trained interviewers helped to minimise this bias. Despite limited information on non-respondents, the rigorous sampling strategy and the substitution method employed ensured the representativeness of the final sample. Another limitation is that SHS exposure was assessed exclusively with reference to exposure to conventional cigarette smoke, without including exposure to secondhand aerosol from novel nicotine products such as e-cigs and HTPs. This limits the comprehensiveness of our estimates of secondhand exposure. Future studies should incorporate specific measures of secondhand aerosol exposure, to better reflect the evolving landscape of tobacco and nicotine use and its potential public health impact. Furthermore, our study lack data on smoking prevalence and SHS exposure among children and adolescents under 15 years of age, since these annual surveys are aimed at providing information on smoking habits in the Italian adult population. These data are however available in multiple surveillance systems available at a national level. Since this age group represents a critical population for tobacco and nicotine control efforts, future research should prioritize the youth population to better understand smoking initiation and inform targeted prevention strategies. Finally, while the sample size was sufficient to estimate overall prevalence with a small standard error, it was inadequate to provide precise estimates for smaller subpopulations. Conversely, a key strength of the study is the representativeness of the sample, which ensures the

generalizability of the findings to the Italian adult population. Additionally, the use of the same standardized survey instrument and methodology allows for appropriate comparisons to be made with previous and future studies.

5.6 Conclusion

In conclusion, this study provides valuable insights into the current situation of smoking and SHS exposure in Italy, highlighting the persistently high prevalence of current smoking and ongoing challenges related to SHS exposure. These findings suggest that existing tobacco control measures may need to be updated and enforced to effectively address emerging issues, such as the increased use of novel nicotine products. Given the strong association observed between the use of e-cigs or HTPs and cigarette smoking, our findings raise important concerns about the current role of these products in supporting smoking cessation and underscore the importance of closely monitoring their impact on smoking patterns in the population. Moreover, we recommend the implementation of new policies and interventions, such as enforcing stricter regulations on novel products and strengthening public awareness campaigns, particularly in areas where SHS exposure remains high. These targeted interventions are essential to reduce the burden of tobacco-related disease and protect public health.

5.7 Contribution to the overall thesis framework

While the previous chapters focused on generating epidemiological evidence on tobacco-related cancer risks, this chapter addresses another key component of burden estimation: population exposure. Accurate estimates of smoking prevalence and SHS exposure are essential inputs for quantifying the number of cancers attributable to tobacco exposure.

By providing updated and independent estimates of smoking habits and SHS exposure in the Italian population, this study contributes to reducing an important source of uncertainty in burden calculations. These data form a critical link between epidemiological risk estimates and their application to the Italian population. The next chapter complements this perspective by examining public attitudes towards tobacco control policies, providing insight into the social and policy context in which future prevention strategies may be implemented.

5.8 References

1. Global Burden of Disease Risk Factors Collaborators. Global burden and strength of evidence for 88 risk factors in 204 countries and 811 subnational locations, 1990-2021: a systematic analysis for the Global Burden of Disease Study 2021. Lancet 2024; 403: 2162-2203.
2. World Health Organization. WHO report on the global tobacco epidemic, 2023: protect people from tobacco smoke. Available online at https://www.who.int/publications/i/item/9789240077164. 2022.
3. Gallus S, Muttarak R, Martinez-Sanchez JM et al. Smoking prevalence and smoking attributable mortality in Italy, 2010. Prev Med 2011; 52: 434-438.
4. Possenti I, Scala M, Rognoni M et al. Analysis of the direct economic impact of smoking-related hospitalizations in Italy. Tob Induc Dis 2024; 22.
5. Lugo A, Asciutto R, Pacifici R et al. Smoking in Italy 2013-2014, with a focus on the young. Tumori 2015; 101: 529-534.
6. Istituto Superiore di Sanità. Comunicato Stampa N°39/2022 - Fumo: in Italia circa 800mila fumatori in più rispetto al 2019. Triplicato il consumo di sigarette a tabacco riscaldato. https://www.iss.it/en/comunicati-stampa/-/asset_publisher/fjTKmjJgSgdK/content/id/7146126. Published May 30, 2022. Accessed December 14, 2023.
7. Gallus S, Zuccaro P, Colombo P et al. Effects of new smoking regulations in Italy. Ann Oncol 2006; 17: 346-347.
8. Gorini G, Chellini E, Galeone D. What happened in Italy? A brief summary of studies conducted in Italy to evaluate the impact of the smoking ban. Ann Oncol 2007; 18: 1620-1622.
9. Joossens L, Olefir L, Feliu A, Fernandez E. The Tobacco Control Scale 2021 in Europe http://www.tobaccocontrolscale.org/TCS2021. Published 2022. Accessed December 21, 2023.
10. Gallus S. Second-hand smoke in Italy. Eur J Paediatr Dent 2015; 16: 257.
11. Martinez-Sanchez JM, Gallus S, Zuccaro P et al. Exposure to secondhand smoke in Italian non-smokers 5 years after the Italian smoking ban. Eur J Public Health 2012; 22: 707-712.
12. Tack SHS Project Investigators, Henderson E, Lugo A et al. Secondhand smoke presence in outdoor areas in 12 European countries. Environ Res 2021; 195: 110806.
13. Redazione ANSA. Milano vieta il fumo di sigaretta per strada dal primo gennaio 2025. Ansa 2024.
14. De Marco C, Ruprecht AA, Borgini A et al. Will smoking on beaches become a thing of the past? Bibione: The first smoke-free beach in Italy. Pulmonology 2023; 29: 540-542.
15. Caouette JD, Epstein M, Halvorson MA et al. Co-occurring Change in Electronic Nicotine Delivery System (ENDS) and Cigarette Harm Perceptions and Use in Young Adults. Nicotine Tob Res 2025.

16. Liu X, Lugo A, Davoli E et al. Electronic cigarettes in Italy: a tool for harm reduction or a gateway to smoking tobacco? Tob Control 2020; 29: 148-152.
17. Glantz SA, Nguyen N, Oliveira da Silva AL. Population-Based Disease Odds for E-Cigarettes and Dual Use versus Cigarettes. NEJM Evid 2024; 3: EVIDoa2300229.
18. Mastrobattista L, Palmi I. Il Rapporto Nazionale sul Tabagismo. Available online at //efaidnbmnnnibpcajpcglclefindmkaj/https://smettodifumare.iss.it/public-caf/Files/Rapporto%20Nazionale%20Tabagismo%202023.pdf. 2023.
19. Henderson E, Continente X, Fernandez E et al. Secondhand smoke exposure in outdoor children's playgrounds in 11 European countries. Environ Int 2021; 149: 105775.
20. Henderson E, Continente X, Fernandez E et al. Secondhand smoke exposure assessment in outdoor hospitality venues across 11 European countries. Environ Res 2021; 200: 111355.
21. Henderson E, Continente X, Fernandez E et al. Secondhand smoke exposure and other signs of tobacco consumption at outdoor entrances of primary schools in 11 European countries. Sci Total Environ 2020; 743: 140743.
22. Gallus S, Borroni E, Odone A et al. The Role of Novel (Tobacco) Products on Tobacco Control in Italy. Int J Environ Res Public Health 2021; 18.
23. Lugo A, Zuccaro P, Pacifici R et al. Smoking in Italy in 2015-2016: prevalence, trends, roll-your-own cigarettes, and attitudes towards incoming regulations. Tumori 2017; 103: 353-359.
24. European Commission. Attitudes of Europeans towards tobacco and electronic cigarettes. Available at https://europa.eu/eurobarometer/surveys/detail/2146. 2017.
25. European Commission. Special Eurobarometer 2023: Attitudes of Europeans towards tobacco and related products. Available at https://europa.eu/eurobarometer/surveys/detail/2995. 2023.
26. ISTAT. Abitudine al fumo - età dettaglio. Available at https://esploradati.istat.it/databrowser/#/it/dw/categories/IT1,Z0810HEA,1.0/HEA_STYLE/HEA_STYLE_SMOK/IT1,83_63_DF_DCCV_AVQ_PERSONE_201,1.0.
27. Gallus S, Lugo A, Liu X et al. Who Smokes in Europe? Data From 12 European Countries in the TackSHS Survey (2017-2018). J Epidemiol 2021; 31: 145-151.
28. Fernandez E, Lugo A, Clancy L et al. Smoking dependence in 18 European countries: Hard to maintain the hardening hypothesis. Prev Med 2015; 81: 314-319.
29. Trama A, Boffi R, Contiero P et al. Trends in lung cancer and smoking behavior in Italy: an alarm bell for women. Tumori 2017; 103: 543-550.

30. Gallus S, Stival C, McKee M et al. Impact of electronic cigarette and heated tobacco product on conventional smoking: an Italian prospective cohort study conducted during the COVID-19 pandemic. Tob Control 2024; 33: 267-270.
31. Singh S, Windle SB, Filion KB et al. E-cigarettes and youth: Patterns of use, potential harms, and recommendations. Prev Med 2020; 133: 106009.
32. World Health Organization. Report on the Global Tobacco Epidemic 2019: Offer Help to Quit Tobacco Use. Available online at https://www.who.int/teams/health-promotion/tobacco-control/who-report-on-the-global-tobacco-epidemic-2019. 2019.
33. Casetta B, Videla AJ, Bardach A et al. Association Between Cigarette Smoking Prevalence and Income Level: A Systematic Review and Meta-Analysis. Nicotine Tob Res 2017; 19: 1401-1407.
34. Rachiotis G, Barbouni A, Katsioulis A et al. Prevalence and determinants of current and secondhand smoking in Greece: results from the Global Adult Tobacco Survey (GATS) study. BMJ Open 2017; 7: e013150.
35. Scala M, Dallera G, Gorini G et al. Patterns of use of heated tobacco products: a comprehensive systematic review. J Epidemiol 2025.
36. Lugo A, Tack SHS Project Investigators. Esposizione al fumo passivo in ambienti chiusi tra i non fumatori europei: risultati del Progetto TackSHS. Available at https://www.tabaccologiaonline.it/article/view/76/133. Tabaccologia 2022.
37. European Parliament. DIRECTIVE 2014/40/EU OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 3 April 2014. Available at https://health.ec.europa.eu/system/files/2016-11/dir_201440_en_0.pdf. 2014.
38. Possenti I, Gallus S, Lugo A et al. Best practices for secondhand smoke and secondhand aerosol protection and evidence supporting the expansion of smoke- and aerosol-free environments: Recommendations from the 2nd Joint Action on Tobacco Control. Tob Prev Cessat 2024; 10.
39. Amalia B, Liu X, Lugo A et al. Exposure to secondhand aerosol of electronic cigarettes in indoor settings in 12 European countries: data from the TackSHS survey. Tob Control 2021; 30: 49-56.
40. U.S. Department of Health and Human Services. The Health Consequences of Involuntary Exposure to Tobacco Smoke. 2006.
41. Yang X, Yan Z, Xu G et al. How secondhand smoke exposure affects tobacco use and smoking susceptibility of adolescents: Sex and school differences. Tob Induc Dis 2021; 19: 68.
42. Istituto Superiore di Sanità. Sorveglianza PASSI. I dati per l'Italia. Fumo passivo. Available at https://www.epicentro.iss.it/passi/dati/fumoPassivo. 2023.
43. Possenti I, Romelli M, Carreras G et al. Association between second-hand smoke exposure and lung cancer risk in never-smokers: a systematic review and meta-analysis. Eur Respir Rev 2024; 33.

44. Possenti I, Scala M, Carreras G et al. Exposure to second-hand smoke and breast cancer risk in non-smoking women: a comprehensive systematic review and meta-analysis. Br J Cancer 2024; 131: 1116-1125.

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Chapter 6

Attitudes towards tobacco and nicotine control policies in Italy: insights from a 2024 national survey

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Nicotine and Tobacco Research

6.1 Abstract

Introduction: This study assesses the Italian population's support for innovative tobacco control policies, which aim at reducing use of nicotine-containing products and exposure to secondhand smoke and aerosol.

Methods: A cross-sectional study was conducted in 2024 among a representative sample of 3,125 Italian adults. We assessed support on banning tobacco sales to people born after a certain year (Smoke-Free Generation, SFG), raising the minimum age for purchasing tobacco to 21 years (Tobacco 21, T21), substantially increasing tobacco taxation, banning electronic cigarettes (e-cigarette) and heated tobacco products (HTP) in indoor public places and workplaces, and prohibiting tobacco and e-cigs advertising.

Results: Support for tobacco control policies was 67.0% for the SFG policy, 72.9% for the T21 policy, 61.5% for a tax increase, 80.8% for a ban on indoor e-cigarette and HTP use in public places and 81.7% in workplaces respectively, and 78.2% for an advertising ban for all nicotine products. Support for all policies increased with age (p-values for trend ranging from <0.001 to 0.037) and was significantly lower among current smokers (support ranging from 17.9% to 59.7%). E-cigarette users showed lower support for a SFG (32.4%) and advertising bans (41.4%), while HTP users were less supportive of all policies except the T21 policy (support ranging from 13.2% to 43.9%).

Conclusion: In Italy, strong public support exists for new tobacco control laws, especially among never smokers and non-users of novel products. However, also a considerable proportion of current smokers, e-cigarette and HTP users support these policies. Policymakers can confidently advance these strategies, while public campaigns should target less supportive groups.

6.2 Introduction

Cigarette smoking is a leading cause of preventable mortality and morbidity worldwide, responsible for about 8 million deaths annually, including 1 million due to secondhand smoke (SHS) [1, 2]. In Italy, tobacco use is responsible for more than 70,000 deaths per year, representing 15% of all deaths [3]. The economic burden of smoking is also significant, with smoking-related hospital admissions costing more than €1.5 billion annually [4].

Italy was a pioneer in the fight against tobacco and SHS exposure, becoming the first large country to introduce comprehensive smoke-free legislation in 2003 banning smoking in indoor public places such as restaurants, bars and workplaces [5]. Since then, however, no relevant national tobacco control policy has been introduced. The Tobacco Control Scale (TCS), which quantifies the implementation of tobacco control policies based on World Bank and World Health Organization (WHO) recommendations, testifies the stagnation of Italian tobacco control policies [6]. In the latest TCS ranking, Italy placed 18th among 37 European countries, with a score of 52 out of 100, a drop of three places compared to the previous edition. Notably, Italy scored particularly low on cigarette pricing (13 points out of 30), as cigarette prices in Italy remain relatively low, around six euros per pack, compared to countries like France and the United Kingdom, where they can cost up to twice as much [7]. In addition, although current regulations in Italy explicitly prohibit the sale of tobacco and nicotine products to minors, enforcement appears inconsistent, and underage access remains a critical issue. Despite the legal framework designed to protect youth, evidence suggests that minors still manage to obtain and use these products, highlighting the urgent need for more effective enforcement strategies [8].

Legislative proposals such as banning the sale of tobacco to people born after a certain year (Smoke-Free Generation policy, SFG), raising the minimum age for purchasing tobacco to 21 years (Tobacco 21 policy, T21), and increasing taxes on conventional cigarettes are gaining international attention and have been demonstrated to be effective in reducing tobacco initiation and consumption in other developed countries [9-11]. Despite the potential benefits of these policies, their implementation, compliance and success depend heavily on public support [5, 12, 13]. Laws that restrict access to tobacco, particularly the SFG, may be perceived by the public as an infringement of personal freedom. However, recent research suggests that support for policies aimed at reducing tobacco consumption and SHS exposure is relatively high in the Italian and European populations [14, 15].

The growing popularity of electronic cigarettes (e-cigarettes) and heated tobacco products (HTP) has raised concerns about the renormalization of tobacco use and dual use [16]. These products are widely used by young people, potentially

leading to nicotine addiction and long-term health consequences [17]. These products are marketed as potentially less harmful alternatives, however independent research is cautious about this “harm reduction” claim [18]. The lack of a complete ban on these products in indoor public places and workplaces means that people are exposed to potentially harmful substances of the secondhand aerosol (SHA). In addition, this regulatory gap has led to widespread dual use, where people smoke conventional cigarettes outdoors and use e-cigarette and HTP indoors or in settings where conventional smoking is prohibited [19]. Recent evidence suggests that this pattern of consumption may be particularly harmful [18, 20]. In response to these concerns, policies banning their use in indoor public places and workplaces, as well as prohibiting tobacco and e-cigarette advertising, have been proposed to prevent further normalization of tobacco consumption and reduce SHA exposure [21].

Despite some recent research [14, 15], there is an important gap in the existing research on support for new policies conducted on representative samples of the Italian population. Furthermore, the current literature lacks studies that thoroughly examine the determinants of support for specific tobacco control policies. This gap limits the understanding of the socio-demographic dynamics that influence public opinion on such regulations. A better understanding of these factors is crucial for promoting effective policies and gaining the public support needed to implement new tobacco control measures in Italy.

Recognizing the importance of public opinion, this study aims to assess the levels of support for potential tobacco control legislation in Italy using a representative sample of the Italian population. Particularly, this analysis will focus on the SFG policy initiative, the T21 policy, the tax increase on conventional cigarettes, the ban on e-cigarette and HTP use in indoor public places and workplaces respectively, and the ban on tobacco and e-cigarette advertising. Furthermore, we intend to investigate socio-demographic determinants that influence individuals' support to specific tobacco control measures.

6.3 Methods

The data used in this study come from a cross-sectional survey conducted between March and September 2024 by the Istituto di Ricerche Farmacologiche Mario Negri (IRFMN), with fieldwork performed by DOXA. The sample comprised of 3125 participants (1515 men and 1610 women) representative of the Italian population aged 15 and over in terms of sex, age, geographical area and socio-economic characteristics. The Ethics Committee of Istituto Neurologico Carlo Besta–Milano acknowledged the collection of anonymous data in face-to-face population-based, observational, cross-sectional studies (File number 37, 2017).

For participants aged 15 to 17 years, informed verbal consent was explicitly obtained from a parent or legal guardian prior to the interview, along with presentation and signature of the written information sheet, which was retained by the survey team.

Participants were selected using a multi-stage sampling technique to ensure representativeness. First, municipalities in all 20 Italian regions were selected on the basis of the size of the region and the municipality. Next, a random selection of electoral districts within each municipality was made. Individuals were then randomly selected from the electoral lists to ensure stratification by sex and age. For young people aged 15-17 who were not on the electoral rolls, a quota sampling approach was used, focusing on both sex and exact age. If a selected participant was unavailable or declined to participate, he or she was replaced with an individual who matched the sex, age group, and area of residence (same municipality and same district). This substitution process was designed to preserve the representativeness of the final sample.

Interviews were conducted by trained interviewers using a structured questionnaire administered via computer-assisted face-to-face interviews in participants' homes (CAPI mode). The questionnaire collected general socio-demographic information, smoking status, and use of novel nicotine containing product (e-cigarette and HTP). Participants' level of education was classified as low for those who completed middle school or less, intermediate for high school graduates, and high for university graduates or beyond. Never smokers were defined as individuals who reported having smoked fewer than 100 cigarettes in their lifetime. Former smokers were those who had smoked 100 or more cigarettes in their lifetime but had quit smoking from at least one year. Current smokers were defined as those who reported having smoked 100 or more cigarettes in their lifetime and who were currently smoking cigarettes or had quit within the past year. In addition to smoking status, the questionnaire also collected information on the use of e-cigarette and HTP use. Individuals were categorised as e-cigarette users if they reported current use (daily or occasional) of any type of e-cigarettes, including disposable, cartridge-based or rechargeable e-cigarettes containing nicotine salts. Individuals who reported not using any type of e-cigarette are hereafter referred to as “non-users of e-cigarettes”. For HTP use, individuals were categorised as users if they reported current use (daily or occasional) of any type of HTP, such as IQOS or Glo. Individuals who reported not using any type of HTP are hereafter referred to as “non-users of HTPs”.

A specific section of the questionnaire was dedicated to collect information regarding attitudes towards proposed tobacco control policies, including: i) Smoke-Free Generation Initiative policy (SFG): prohibiting tobacco and nicotine products sales to individuals born after a certain date (e.g., a lifetime ban on the

sale of tobacco and nicotine products to people born after 1 January 2010), thereby restricting access to tobacco and nicotine throughout their lifetime; ii) Tobacco 21 policy (T21): raising the legal age of sale of tobacco and nicotine products from 18 to 21 years; iii) Increase tobacco taxation: increasing excise duties/taxes on conventional cigarettes, raising the cost of a cigarette pack from around €6 to €10, and use the revenue to support smoking cessation (e.g., free access to smoking cessation services or free pharmacological therapies) or fund research; iv) Indoor ban of new products: banning the use of e-cigs and HTPs in indoor public places (e.g., public transport, clubs, bars, restaurants); v) Workplace indoor ban of new products: banning the use of e-cigarettes and HTPs in indoor workplaces; and vi) Advertising ban: banning advertisements for tobacco products and e-cigs, including on social networks. For each proposed regulation, participants were asked to express their level of support or opposition using the following response options: strongly in favour, in favour, against, strongly against, or does not know /does not state (Supplementary Box 1).

Data Analysis

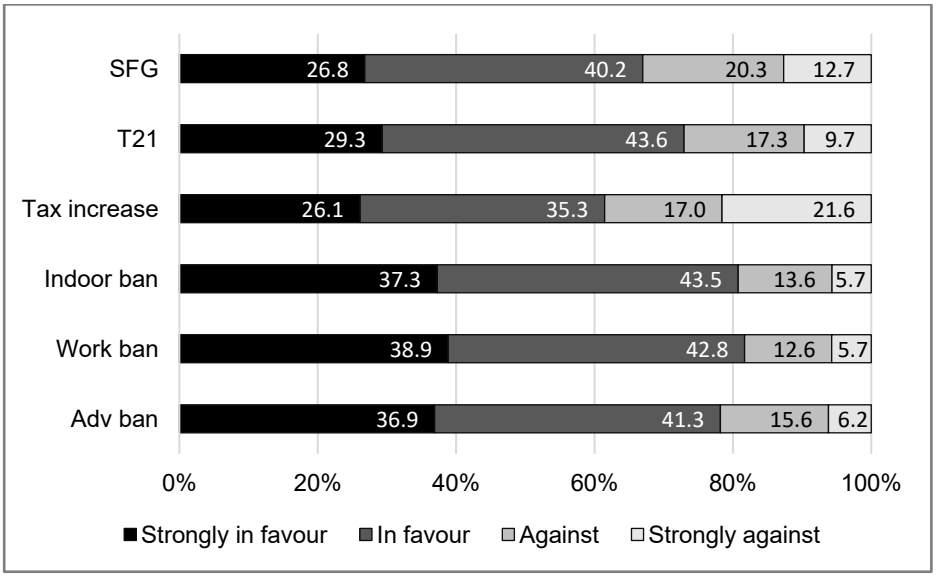
Data processing included the generation of statistical weights to ensure the representativeness of the Italian population aged 15 years and over. Descriptive statistics were used to summarise the main findings. We estimated adjusted odds ratios (aOR) and corresponding 95% confidence intervals (CI) for support (in favour or strongly in favour) of the six proposed tobacco control policies based on sociodemographic and behavioural factors. aORs were estimated using unconditional multiple logistic regression models, adjusted for sex, age, educational level and geographical area. All the variables included in the analyses were complete, with no missing values. Therefore, no imputation or specific handling of missing data was required.

All statistical analyses were performed using the SAS statistical package, version 9.4 (SAS Institute) [22].

6.4 Results

Figure 1 shows the percentages of respondents according to their support to each of the six tobacco control policies. The overall percentage of favourable responses (“in favour” or “strongly in favour”) was 67.0% for the SFG policy, 72.9% for the T21 policy, 61.5% for the tax increase measure, 80.8% for the indoor ban on e-cigs and HTPs, 81.7% for the workplace ban on these products, and 78.2% for the advertising ban of all tobacco products and e-cigs.

Figure 1. Percent (%) distribution of support for selected inadequately adopted tobacco control policies in a representative cross-sectional sample of 3125 Italian adults. Italy, 2024.



SFG: smoke-free generation; T21: Tobacco 21; Tax increase: Increase excise duties/taxes on conventional cigarettes, raising the cost of a pack from about €6 to €10; Indoor ban: Ban the use of e-cigarettes and heated tobacco in indoor public places; Work ban: Ban the use of e-cigarettes and heated tobacco in indoor workplaces; Adv ban: Ban advertisements for tobacco products and electronic cigarettes, including on social networks. Full questions available in Supplementary Box 1. Percentages are calculated excluding responses "Does not know/does not state".

Regarding the SFG policy, people aged 25-44 years (aOR=1.75, 95% CI: 1.31-2.34), 45-64 years (aOR=1.92, 95% CI: 1.45-2.53), and ≥65 years (aOR=1.74, 95% CI: 1.30-2.33) were significantly more likely to support the policy than younger participants aged <25 years (p for trend =0.001; Table 1). Current smokers (aOR=0.19, 95% CI: 0.16-0.23), former smokers (aOR=0.72, 95% CI: 0.55-0.95) were less likely to support the SFG compared with never smokers. Both e-cigarette users (aOR=0.55, 95% CI: 0.32-0.96) and HTP users (aOR=0.57, 95% CI: 0.38-0.87) showed reduced support compared with non-users of e-cigarettes and non-users of HTPs. For the T21 policy, the support was higher in participants aged 25-44 years (aOR=2.49, 95% CI: 1.85-3.35), 45-64 years (aOR=3.14, 95% CI: 2.36-4.18), and ≥65 years (aOR=2.81, 95% CI: 2.08-3.79) compared to those aged <25 years (p for trend <0.001). Current smokers (aOR=0.18, 95% CI: 0.15-0.22) and former smokers (aOR=0.63, 95% CI: 0.47-0.85) were significantly less likely to support this measure compared with never

smokers. For the tax increase policy, an increasing support was observed with increasing age of participants (p for trend=0.037). Current smokers (aOR=0.06, 95% CI: 0.04-0.07) and former smokers (aOR=0.50, 95% CI: 0.39-0.66) were significantly less supportive towards increasing tobacco taxation, as were HTP users (aOR=0.48, 95% CI: 0.27-0.84). No statistically significant differences were observed in support of these measures according to participants' sex and level of education.

Table 1. Support for tobacco control policies (smoke-free generation, SFG; Tobacco 21, T21; and Tax increase) in a representative sample of 3125 Italian adults, overall and according to socio-demographic and behavioural characteristics. Italy, 2024.

	N	SFG			T21			Tax increase[a]		
		In favour %[b]	aOR[c] (95% CI)	*p-value*	In favour %[b]	aOR[c] (95% CI)	*p-value*	In favour %[b]	aOR[c] (95% CI)	*p-value*
Total	3125	67.0	-	-	72.9	-	-	61.5	-	-
Sex										
Men	1515	66.7	Ref		70.0	Ref		58.0	Ref	
Women	1610	67.2	0.86 (0.73-1.01)	*0.069*	75.7	1.12 (0.94-1.33)	*0.212*	64.7	1.01 (0.84-1.20)	*0.959*
Age (years)										
<25	353	59.3	Ref		58.0	Ref		62.2	Ref	
25-44	808	65.4	1.75 (1.31-2.34)	*<0.001*	71.2	2.49 (1.85-3.35)	*<0.001*	56.7	1.14 (0.83-1.58)	*0.426*
45-64	1104	67.5	1.92 (1.45-2.53)	*<0.001*	75.0	3.14 (2.36-4.18)	*<0.001*	60.0	1.34 (0.98-1.83)	*0.064*
≥65	860	70.9	1.74 (1.30-2.33)	*<0.001*	78.0	2.81 (2.08-3.79)	*<0.001*	67.6	1.35 (0.98-1.86)	*0.069*
p for trend			*0.001*			*<0.001*			*0.037*	
Education[d]										
Low	973	72.0	Ref		77.1	Ref		66.5	Ref	
Intermediate	1676	64.5	0.87 (0.71-1.07)	*0.176*	70.1	0.87 (0.70-1.08)	*0.207*	59.4	0.99 (0.79-1.23)	*0.892*
High	476	65.5	0.83 (0.63-1.10)	*0.187*	74.8	1.03 (0.77-1.38)	*0.851*	58.6	0.91 (0.68-1.22)	*0.523*
p for trend			*0.153*			*0.933*			*0.554*	
Smoking status										
Never	1928	76.7	Ref		82.4	Ref		79.6	Ref	
Current	830	41.1	0.19 (0.16-0.23)	*<0.001*	48.8	0.18 (0.15-0.22)	*<0.001*	17.9	0.06 (0.04-0.07)	*<0.001*
Former	366	74.2	0.72	*0.022*	78.7	0.63	*0.003*	68.1	0.50	*<0.001*

			(0.55-0.95)			(0.47-0.85)			(0.39-0.66)	
E-cigarette use[e]										
Non-user	3054	67.8	Ref		73.7	Ref		62.4	Ref	
User	71	32.4	0.55 (0.32-0.96)	*0.036*	43.0	0.67 (0.40-1.11)	*0.124*	23.6	0.96 (0.50-1.83)	*0.896*
HTP use[f]										
Non-user	2985	68.6	Ref		74.5	Ref		63.8	Ref	
User	139	31.2	0.57 (0.38-0.87)	*0.008*	40.5	0.69 (0.47-1.01)	*0.057*	13.2	0.48 (0.27-0.84)	*0.010*

[a]Increase excise duties/taxes on conventional cigarettes, raising the cost of a pack from about €6 to €10, full question available in Supplementary Box 1; [b]Respondents answering to be "in favour" or "strongly in favour". Percentages are calculated excluding responses "Does not know/does not state" (which ranged from 1.6% to 5.1%); [c]aORs are estimated with unconditional logistic regression models adjusted for sex, age, education, geographical area and smoking status; [d] Level of education was classified as low for those who completed middle school or less, intermediate for high school graduates, and high for university graduates or beyond; [e] Individuals who reported not using any type of e-cigarette are referred to as non-users; [f] Individuals who reported not using any type of HTP are referred to as non-users; CI: confidence interval; HTP: heated tobacco product.

Support for a ban on e-cigarette and HTPs use in indoor public places was significantly higher among older participants (Table 2). Older people were more likely to support the indoor ban compared to participants aged <25 years (p for trend <0.001). Current smokers and HTP users were significantly less supportive of the indoor ban (aOR=0.18, 95% CI: 0.15-0.23, and aOR=0.42, 95% CI: 0.29-0.61, respectively). Participants aged 25-44 years (aOR=1.41, 95% CI: 1.00-1.98), 45-64 years (aOR=1.58, 95% CI: 1.14-2.19) and ≥65 years (aOR=1.60, 95% CI: 1.13-2.26) showed higher support for banning e-cigarette and HTP use in indoor workplaces compared to those aged <25 years (p for trend =0.012). Current smokers (aOR=0.16, 95% CI: 0.13-0.20) and HTP users (aOR=0.42, 95% CI: 0.29-0.62) were significantly less supportive of this policy. Participants aged 45-64 years (aOR=1.95, 95% CI: 1.43-2.65) and those aged ≥65 years (aOR=2.03, 95% CI: 1.46-2.83) were more in favour of the advertising ban than those aged <25 years (p for trend <0.001). Individuals with higher level of education were more likely to support the measure (aOR=1.41, 95% CI: 1.03-1.93) than those with lower level education. Current smokers (aOR=0.21, 95% CI: 0.17-0.26) and former smokers (aOR=0.64, 95% CI: 0.47-0.89) were less likely to support the advertising ban, and both e-cigarette users (aOR=0.45, 95% CI: 0.27-0.76) and HTP users (aOR=0.48, 95% CI: 0.33-0.71) were also significantly less supportive. No statistically significant differences in support of the three policies were observed according to sex.

Table 2. Support for tobacco control policies (indoor ban of electronic cigarettes, e-cigarette, and heated tobacco products; ban of e-cigs and HTPs in workplaces; and advertising ban of e-cigarettes and HTPs) in a representative sample of 3125 Italian adults, overall and according to socio-demographic and behavioural characteristics. Italy, 2024.

		Indoor ban			Work ban			Adv ban		
	N	In favour %[a]	aOR[b] (95% CI)	*p-value*	In favour %[a]	aOR[b] (95% CI)	*p-value*	In favour %[a]	aOR[b] (95% CI)	*p-value*
Total	3125	80.8	-	-	81.7	-	-	78.2	-	-
Sex										
Men	1515	78.9	Ref		79.7	Ref		76.2	Ref	
Women	1610	82.5	1.04 (0.86-1.26)	*0.709*	83.5	1.07 (0.87-1.30)	*0.534*	80.1	1.03 (0.85-1.24)	*0.783*
Age (years)										
<25	353	76.6	Ref		78.3	Ref		72.8	Ref	
25-44	808	78.3	1.40 (1.00-1.94)	*0.047*	79.6	1.41 (1.00-1.98)	*0.048*	72.5	1.20 (0.88-1.64)	*0.260*
45-64	1104	80.5	1.62 (1.19-2.23)	*0.003*	81.6	1.58 (1.14-2.19)	*0.006*	80.1	1.95 (1.43-2.65)	*<0.001*
≥65	860	85.1	1.83 (1.30-2.57)	*<0.001*	85.2	1.60 (1.13-2.26)	*0.009*	83.5	2.03 (1.46-2.83)	*<0.001*
p for trend			*<0.001*			*0.012*			*<0.001*	
Education[d]										
Low	973	82.9	Ref		83.5	Ref		80.6	Ref	
Intermediate	1676	79.2	1.04 (0.82-1.32)	*0.741*	80.7	1.06 (0.83-1.35)	*0.660*	76.2	1.01 (0.80-1.27)	*0.964*
High	476	82.1	1.26 (0.91-1.75)	*0.167*	81.4	1.11 (0.80-1.54)	*0.533*	80.5	1.41 (1.03-1.93)	*0.034*
p for trend			*0.198*			*0.526*			*0.055*	
Smoking status										
Never	1928	88.7	Ref		89.9	Ref		86.3	Ref	
Current	830	59.7	0.18 (0.15-0.23)	*<0.001*	59.5	0.16 (0.13-0.20)	*<0.001*	57.5	0.21 (0.17-0.26)	*<0.001*
Former	366	86.5	0.74 (0.53-1.04)	*0.086*	88.7	0.84 (0.58-1.21)	*0.345*	82.5	0.64 (0.47-0.89)	*0.007*

E-cigarette use[e]										
Non-user	3054	81.3	Ref		82.3	Ref		79.0	Ref	
User	71	58.9	0.85 (0.51-1.42)	*0.532*	57.5	0.77 (0.47-1.29)	*0.324*	41.4	0.45 (0.27-0.76)	*0.003*
HTP use[f]										
Non-user	2985	82.5	Ref		83.5	Ref		79.9	Ref	
User	139	43.0	0.42 (0.29-0.61)	*<0.001*	43.9	0.42 (0.29-0.62)	*<0.001*	41.8	0.48 (0.33-0.71)	*<0.001*

[a]Respondents answering to be “in favour” or “strongly in favour”. Percentages are calculated excluding responses “Does not know/does not state” (which ranged from 1.6% to 5.1%); [b]aORs are estimated with unconditional logistic regression models adjusted for sex, age, education, geographical area and smoking status; [d] Level of education was classified as low for those who completed middle school or less, intermediate for high school graduates, and high for university graduates or beyond; [e] Individuals who reported not using any type of e-cigarette are referred to as non-users; [f] Individuals who reported not using any type of HTP are referred to as non-users; CI: confidence interval; HTP: heated tobacco product.

6.5 Discussion

In this study conducted on a nationally representative sample of Italian adults, we observed broad support (62% to 82%) for all the proposed tobacco control policies. Measures focused on discouraging the use of conventional cigarettes among young people with initiatives such as the SFG policy, T21 and tax increases were supported by 62% to 73% of respondents. Measures focusing on novel tobacco and nicotine products such as indoor and workplace bans of novel tobacco and nicotine products and bans on their advertising, were supported by 78% to 82% of respondents. Across all the proposed regulations support was higher among older adults and never smokers and lower, but still not negligible, among younger respondents and current smokers. These results indicate that there is a significant opportunity for the implementation of tobacco control measures in Italy, and policymakers can rely on the support of a broad base of the population, including those directly affected by these regulations.

The high level of support towards the SFG policy suggests that concerns about individual choice and generational equity are balanced by the willingness to protect future generations from the harms of tobacco and nicotine addiction [23]. The support was particularly strong among older people and non-smokers, suggesting that these groups perceive such regulation as an essential measure to protect public health and future generations. The high support could be due to an increased awareness of the health risks of smoking, but also to the fact that

this regulation would not directly affect the behaviour of adult respondents. Given the substantial support observed, the SFG initiative could be established as a long-term strategic objective. Meanwhile, the immediate reinforcement of existing age-related sales bans could serve as the first concrete policy action.

Similarly, as T21 directly restricts tobacco sales to people under 21, older adults are not directly subject to these restrictions and may therefore see the policy as a protective measure for younger people. This measure is particularly relevant, as most smokers start before the age of 21, and delaying smoking initiation can significantly reduce the likelihood of long-term addiction [24]. Even stricter enforcement of the existing ban on sales to minors under 18 would be beneficial, as many people take up smoking before reaching adulthood [25]. The findings on SFG and T21 are consistent with a previous study conducted in a large convenience sample of Italian adults, which found slightly higher support for these measures (74% for SFG, 82% for T21) [15]. The lack of a representative sample in that study could explain the higher support observed. In the present study, we confirm the strong support for SFG and T21 in face-to-face interviews in a representative sample of the Italian population. This high level of support provides political momentum to advance T21 legislation in Italy. Implementation could be accompanied by targeted communication efforts aimed at young adults, with the aim of building understanding and compliance.

The proposal for a substantial increase in tobacco taxation, raising the cost of a pack from about €6 to €10 and allocating the revenue thus generated to smoking cessation support, was supported by an outstanding three out of five respondents, with lower support among current and former smokers, consistent with the notion that those who actively consume tobacco are more sensitive to price increases. Indeed, evidence from the literature shows that increasing the price of cigarettes is one of the most effective measure to reduce smoking prevalence and consumption [26]. Public support in this area could be used to advocate for fiscal policies aimed at reducing consumption while generating resources for cessation services and prevention campaigns. The high level of support overall may also be due to an understanding that price increases would lead to increased revenues that could then be reinvested in public health initiatives. In fact, it has been shown that an increase in prices would lead to higher revenue, which could be therefore reinvested in public health efforts [26]. Concerns have been raised about the disproportionate financial burden of price increases on lower-socioeconomic (SES) groups. However, an increase in prices does not necessarily imply that tax increases are also disproportionately burdensome on lower-SES populations. In fact, tobacco use among individuals of lower-SES is more responsive to changes in price, while higher-SES populations exhibit less sensitivity. As a result, a tax increase that raises tobacco prices will lead to the largest declines in smoking among lower-SES individuals,

placing a greater burden on higher-SES consumers [27]. At the same time, the reduction in consumption in lower-SES groups would lead to a reduction in smoking-related diseases and the associated costs borne by individuals.

The literature has consistently shown that both T21 and price increases are effective in reducing smoking initiation and promoting smoking cessation. Indeed, studies indicate that raising the legal age for purchasing tobacco to 21 could significantly decrease the likelihood of young adults starting to smoke [28], while substantial increases in tobacco prices have been linked to lower consumption rates and higher cessation rates, especially among youth and lower-income groups [29]. Given the proven effectiveness and broad public support, these policies could be considered strong candidates for implementation within a comprehensive tobacco control strategy in Italy.

The promotion of smoke and aerosol-free environments is essential to protect public health and reduce the harm caused by tobacco and nicotine products. Equalizing legislation for novel products with conventional cigarettes is crucial for public health protection [21]. In this context, around four out of five respondents were in favour of banning e-cigarettes and HTPs from indoor public places and indoor workplaces. This high level of support not only reflects concerns about public health due to exposure to HTP aerosol but also suggests a general discomfort, particularly among people who do not use e-cigarettes or HTPs, with being exposed to SHA [30, 31]. Support for both measures was significantly higher among older participants and non-smokers, who are usually less accustomed to these new products [32]. Older people may also recall more vividly the implementation of the comprehensive 2005 smoke-free legislation and recognise its effectiveness in reducing exposure to tobacco smoke and SHS [33], which may strengthen their support for extending similar restrictions to novel tobacco and nicotine products. HTP users were less likely to support these measures as they directly restrict the use of such products. However, still over 40% of HTP users and over half of e-cigarette users supported these measures, along with over 80% of other respondents, indicating potential for these laws to gain widespread support. These results provide a compelling rationale for revising current legislation to include novel products within existing indoor smoking bans. This would restore clarity to the regulations and address the growing public concern about exposure to SHA.

In Italy, tobacco products are currently banned from advertising in accordance with Directive 2003/33/EC of the European Parliament and of the Council of 26 May 2003 [34]. However, this regulation does not cover novel devices, allowing their promotion through various channels [35]. In addition, these products are theoretically proposed as cessation aids for long-term smokers, but their advertising strategies -through colours, flavours, and branding- attract younger

populations of never smokers, thus increasing the number of nicotine dependent consumers [36]. In this context, the proposed ban on advertising of HTPs and e-cigarettes was supported by about four out of five respondents. This finding may reflect a shared belief in the negative impact of tobacco marketing on public health, as well as a consensus that reducing exposure to tobacco advertising can help reduce smoking consumption. Conversely, current smokers, former smokers and both e-cigarette and HTP users were less favourable towards the advertising ban, possibly because they are more accustomed to tobacco advertising. Results indicate that extending the advertising ban to all tobacco and nicotine products, would be supported and could limit the appeal of these products among youth. Public health authorities should monitor compliance and adapt messaging to counter industry marketing narratives.

This study has some limitations. Although the sample size was sufficient to provide overall estimates with small standard errors, it was inadequate to provide precise estimates for smaller subpopulations. In particular, the results for e-cigarette and HTP user subgroups should be interpreted with caution due to the relatively small sample sizes of the subgroups, which may limit the power to detect statistically significant associations. The sampling method involved a substitution process whereby unavailable individuals were replaced with matched newly recruited participants. The unknown response and substitution rates represent a limitation; however, this substitution process was designed to ensure the final sample was still representative. The representativeness of the sample is a key strength, as it supports the generalisability of our findings to the general Italian population. The cross-sectional design of this study precludes any causal inference between the observed associations and, as with all survey-based studies, the reliance on self-reported demographic data may introduce reporting bias. Data on smoking status, e-cigarette use and HTP use are also self-reported and are therefore subject to potential misclassification bias. Despite limited information on non-respondents, the rigorous sampling strategy and the substitution method employed ensured the representativeness of the final sample. This, together with the multivariate analyses, strengthens the credibility of our results. The data on attitudes towards the investigated tobacco control policies may be affected by social desirability bias, whereby respondents tend to answer questions in a way that they perceive to be politically or socially correct. However, the level of support was high enough to justify the implementation of the policies in question, even when accounting for social desirability bias. Moreover, a larger survey conducted via Computer-Assisted Web Interviewing (i.e., not face-to-face and therefore unaffected by social desirability bias) found even higher levels of support for the SFG and T21 policies, confirming widespread support among the Italian population [15].

In Italy, a substantial majority of the population - including a non-negligible proportion of tobacco and nicotine product users - supports a wide range of tobacco control measures. The high level of support for the SFG and T21 initiatives suggests that fully enforcing the existing law banning sales to minors - possibly with the addition of penalties for adults who supply tobacco or nicotine to minors - could be a crucial step in protecting young people, especially given the current nicotine use emergency among youth. The win-win strategy of raising tobacco prices through increased taxation is proving to be a popular option, but its great potential remains actually unexploited. Public support in this area could be used to advocate for fiscal policies aimed at reducing consumption while generating resources for cessation services and prevention campaigns. Finally, the support for extending existing tobacco policies to cover e-cigarettes and HTPs suggests that policymakers should feel confident about implementing these measures. Notably, equalizing the legislation of novel tobacco and nicotine products to conventional cigarettes could address regulatory gaps and respond to issues on their normalization. Importantly, implementing these regulations aligns with the objectives of Europe's Beating Cancer Plan, contributing to the creation of a Tobacco-Free Generation by 2040. To strengthen policy effectiveness, tailored actions should be directed at groups showing lower levels of support. Among tobacco and nicotine consumers, communication strategies should emphasise the personal and public health benefits of regulation (e.g., benefits of cessation, reduced addiction and health risks, cleaner indoor environments). Healthcare providers, peer-focused campaigns, and targeted digital media could play a pivotal role in enhancing acceptance among these groups. For younger individuals, school-based programmes, social media campaigns, and stricter enforcement around points of sale could help to improve understanding and adherence. These tailored strategies, alongside broader public awareness initiatives, can increase support among less favourable subgroups while enhancing the population-level impact of the proposed regulations.

6.6 Contribution to the overall thesis framework

While the previous chapters focused on generating epidemiological evidence and exposure estimates, this chapter addresses the policy and behavioural dimensions of tobacco control. Quantifying the burden attributable to tobacco exposure is essential to identify the magnitude of the problem, but reducing that burden ultimately depends on the implementation and public acceptance of effective tobacco control measures.

By evaluating attitudes towards existing and novel tobacco control policies in Italy, this study provides evidence on the societal context in which prevention

strategies are developed and implemented. These findings complement the epidemiological and burden estimation components of the thesis by helping to assess the feasibility and potential acceptability of interventions aimed at reducing future tobacco-related cancer burden.

The next chapter builds on the epidemiological and behavioural evidence presented so far by introducing a novel methodology to estimate the cancer burden attributable to smoking, integrating smoking status, intensity, duration, and cessation into a single analytical framework.

6.7 References

1. Collaborators GBDRF. Global burden and strength of evidence for 88 risk factors in 204 countries and 811 subnational locations, 1990-2021: a systematic analysis for the Global Burden of Disease Study 2021. Lancet 2024; 403: 2162-2203.
2. World Health Organization. WHO report on the global tobacco epidemic, 2023: protect people from tobacco smoke. https://www.who.int/publications/i/item/9789240077164. Published July 31, 2022. Accessed September 19, 2024.
3. Gallus S, Muttarak R, Martinez-Sanchez JM et al. Smoking prevalence and smoking attributable mortality in Italy, 2010. Prev Med 2011; 52: 434-438.
4. Possenti I, Scala M, Rognoni M et al. Analysis of the direct economic impact of smoking-related hospitalizations in Italy. Tob Induc Dis 2024; 22.
5. Gallus S, Zuccaro P, Colombo P et al. Effects of new smoking regulations in Italy. Ann Oncol 2006; 17: 346-347.
6. Joossens L, Olefir L, Feliu A, Fernandez E. The Tobacco Control Scale 2021 in Europe http://www.tobaccocontrolscale.org/TCS2021. Published 2022. Accessed December 21, 2023.
7. Devaux M, Dorfmuller Ciampi M, Guignard R et al. Economic evaluation of the recent French tobacco control policy: a model-based approach. Tob Control 2024.
8. Cerrai S, Benedetti E, Colasante E et al. E-cigarette use and conventional cigarette smoking among European students: findings from the 2019 ESPAD survey. Addiction 2022; 117: 2918-2932.
9. Statement on Tobacco 21 from the European Respiratory Society Tobacco Control Committee. Available at: https://erj.ersjournals.com/content/61/3/2300134 [Last access 24 April 2024].
10. Friedman AS, Buckell J, Sindelar JL. Tobacco-21 laws and young adult smoking: quasi-experimental evidence. Addiction 2019; 114: 1816-1823.
11. The Lancet Respiratory M. The tobacco endgame: targeting the next generation. Lancet Respir Med 2023; 11: 493.
12. Hyland A, Higbee C, Borland R et al. Attitudes and beliefs about secondhand smoke and smoke-free policies in four countries: findings from the International Tobacco Control Four Country Survey. Nicotine Tob Res 2009; 11: 642-649.
13. Zhou L, Niu L, Jiang H et al. Facilitators and Barriers of Smokers' Compliance with Smoking Bans in Public Places: A Systematic Review of Quantitative and Qualitative Literature. Int J Environ Res Public Health 2016; 13.
14. Nogueira SO, Fu M, Lugo A et al. Non-smokers' and smokers' support for smoke-free legislation in 14 indoor and outdoor settings across 12 European countries. Environ Res 2022; 204: 112224.

15. Scala M, Lugo A, Gallus S. Support for smoke-free generation strategies in Italy. Lancet Reg Health Eur 2024; 44: 101013.
16. Caouette JD, Epstein M, Halvorson MA et al. Co-occurring Change in Electronic Nicotine Delivery System (ENDS) and Cigarette Harm Perceptions and Use in Young Adults. Nicotine Tob Res 2025.
17. Liu X, Lugo A, Davoli E et al. Electronic cigarettes in Italy: a tool for harm reduction or a gateway to smoking tobacco? Tob Control 2020; 29: 148-152.
18. Glantz SA, Nguyen N, Oliveira da Silva AL. Population-Based Disease Odds for E-Cigarettes and Dual Use versus Cigarettes. NEJM Evid 2024; 3: EVIDoa2300229.
19. Gallus S, Lugo A, Stival C et al. Electronic Cigarette Use in 12 European Countries: Results From the TackSHS Survey. J Epidemiol 2023; 33: 276-284.
20. Bittoni MA, Carbone DP, Harris RE. Vaping, Smoking and Lung Cancer Risk. J Oncol Res Ther 2024; 9.
21. Possenti I, Gallus S, Lugo A et al. Best practices for secondhand smoke and secondhand aerosol protection and evidence supporting the expansion of smoke- and aerosol-free environments: Recommendations from the 2nd Joint Action on Tobacco Control. Tob Prev Cessat 2024; 10.
22. SAS Institute (2010) STAT-SAS, Version 9.4. SAS Institute, Cary, North Carolina.
23. Berrick AJ. The tobacco-free generation proposal. Tob Control 2013; 22 Suppl 1: i22-26.
24. Ali FRM, Agaku IT, Sharapova SR et al. Onset of Regular Smoking Before Age 21 and Subsequent Nicotine Dependence and Cessation Behavior Among US Adult Smokers. Prev Chronic Dis 2020; 17: E06.
25. Gorini G, Gallus S, Carreras G et al. Prevalence of tobacco smoking and electronic cigarette use among adolescents in Italy: Global Youth Tobacco Surveys (GYTS), 2010, 2014, 2018. Prev Med 2020; 131: 105903.
26. IARC. Effectiveness of Tax and Price Policies for Tobacco Control. IARC Handbooks of Cancer Prevention Volume 14. IARC 2011. Available online at: https://publications.iarc.fr/Book-And-Report-Series/Iarc-Handbooks-Of-Cancer-Prevention/Effectiveness-Of-Tax-And-Price-Policies-For-Tobacco-Control-2011. 2011.
27. Chaloupka FJ, Yurekli A, Fong GT. Tobacco taxes as a tobacco control strategy. Tob Control 2012; 21: 172-180.
28. Cox DW, Rodriguez L, Grigg J, Tobacco Control Committee of the European Respiratory S. Statement on Tobacco 21 from the European Respiratory Society Tobacco Control Committee. Eur Respir J 2023; 61.
29. Chaloupka FJ, Straif K, Leon ME, Working Group IAfRoC. Effectiveness of tax and price policies in tobacco control. Tob Control 2011; 20: 235-238.
30. Ghazi S, Song MA, El-Hellani A. A scoping review of the toxicity and health impact of IQOS. Tob Induc Dis 2024; 22.

31. Zervas EN, Matsouki N, Tsipa CF, Katsaounou PA. Particle emissions from heated tobacco products. Tob Prev Cessat 2024; 10.

32. Gallus S, Stival C, Carreras G et al. Use of electronic cigarettes and heated tobacco products during the Covid-19 pandemic. Sci Rep 2022; 12: 702.

33. Gallus S. Second-hand smoke in Italy. Eur J Paediatr Dent 2015; 16: 257.

34. European Union. Directive 2003/33/EC of the European Parliament and of the Council of 26 May 2003 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the advertising and sponsorship of tobacco products (Text with EEA relevance). Available at https://eur-lex.europa.eu/eli/dir/2003/33/oj. 2003.

35. Abroms LC, Duan Z, Bar-Zeev Y et al. Impact of exposures to Heated Tobacco Products in the media and through social connections on product perceptions and use. Tob Prev Cessat 2024; 10.

36. Cerrai S, Potente R, Gorini G et al. What is the face of new nicotine users? 2012-2018 e-cigarettes and tobacco use among young students in Italy. Int J Drug Policy 2020; 86: 102941.

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Chapter 7

Estimating cancer cases and deaths attributable to smoking and secondhand smoke exposure at national level: a methodology based on individual-level data

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7.1 Abstract

Introduction: Prevalence-based methods estimate smoking-attributable cancer cases using exposure prevalence, relative risks (RRs), and incidence/mortality rates, but they cannot capture heterogeneity in smoking behaviour. We developed a new method based on individual-level data (ILD) to address this limitation, applied it to real-world data as a proof-of-concept example on breast cancer, and compared its performance with that of a traditional prevalence-based approach.

Methods: The ILD approach estimates population attributable fractions (PAFs) within a representative sample of the target population. Each ever smoker is assigned a single cancer-specific RR summarising smoking history (status, intensity, duration, and time since quitting), derived from dose–response RRs from meta-analyses. These excess risks are used to compute smoking PAFs, then applied to national cancer counts. The same procedure can estimate the burden attributable to secondhand smoke (SHS) among never smokers. We applied this method to estimate breast cancer cases attributable to smoking and SHS in Italy in 2022 and compared results with those from a prevalence-based method.

Results: We analysed data from a representative sample of the Italian population aged 14 and over, comprising 54,407 women. Using the ILD method, we estimated that 1,205 incident breast cancer cases were attributable to active smoking and 1,554 to SHS exposure, for a total of 2,759 attributable cases. The prevalence-based method yielded 2,692 attributable cases (1,359 attributable to smoking and 1,333 to SHS exposure).

Conclusions: Our findings highlight a substantial burden of breast cancer attributable to both active smoking and SHS exposure, yielding estimates that are similar with those obtained through prevalence-based methods. The ILD approach, by incorporating detailed dose–response information, provides subgroup-sensitive estimates and can be particularly useful when applied to populations or subgroups with non-standard or heterogeneous smoking patterns. However, its application requires detailed exposure data and entails higher analytical complexity than traditional methods.

7.2 Introduction

Tobacco smoking is a major cause of premature death and disability worldwide, responsible for an estimated 8 million deaths annually, including over 1 million deaths due to exposure to secondhand smoke (SHS) [1, 2]. In the 20th century alone, tobacco use was responsible for more than 100 million deaths worldwide [3]. Estimating the burden of smoking and SHS exposure is essential to assess the true public health impact and to guide policy, resource allocation and targeted interventions to prevent smoking-related diseases and mitigate their widespread effects.

Several methods have been developed to estimate cases and deaths of various diseases attributable to smoking. The most widely used approaches are the prevalence-based methods, such as the one based on Levin's formula [4]. This method estimates the attributable number of cases or deaths by combining exposure (i.e., smoking or SHS exposure prevalence) data with relative risks (RR) of tobacco-related diseases and then applies the obtained population attributable fraction (PAF) to national disease-specific incident and mortality data. Other prevalence-based methods include the prevalence-based analysis in case-control studies [5] and the basic model [6].

While prevalence-based methods provide important insights, they also have several limitations, particularly in their ability to capture the full complexity of smoking-related features [7]. The use of aggregate prevalence estimates may overlook differences in smoking patterns and differences across sociodemographic subgroups or the impact of changes in smoking behaviour over time. Particularly, they do not adequately account for factors such as duration of smoking or time since quitting (TSQ), which are critical for accurate estimates of tobacco-attributable mortality and morbidity. This raises the need to explore new possibilities for methodological advancements. Such efforts are crucial to improving the accuracy of these estimates and supporting the development of more effective public health strategies. More precise estimates also allow policymakers to prioritize prevention in the most affected subgroups.

For these reasons, we aim to develop a new method that uses individual-level data (ILD) to provide a more flexible estimate of cancer cases and deaths attributable to cigarette smoking and SHS exposure. Unlike traditional prevalence-based methods, which assign the same average risk to entire subgroups, the ILD method assigns cancer-specific RRs at individual level by jointly incorporating heterogeneity in smoking behaviour, including intensity, duration, and TSQ. This allows for a more nuanced and potentially valid assessment of the smoking- and SHS-attributable burden. In this article, we also provide a practical application of this method by estimating breast cancer cases attributable to smoking and SHS exposure in Italy for the year 2022. We selected

breast cancer as a proof-of-concept because it is the most frequently diagnosed cancer in Italy among women [8], ensuring high public-health relevance. Importantly, the association between smoking (active and SHS exposure) and breast cancer has been only recently consolidated by comprehensive meta-analyses [9, 10]. These syntheses also provide the granular dose-response relationships needed to perform a method that jointly integrates smoking and SHS exposure status and characteristics (intensity, duration, TSQ, and SHS intensity). Furthermore, we compare the results obtained with those obtained applying a prevalence-based method to the same data [4], chosen as it requires the same set of data as our ILD approach.

7.3 Methods

The core idea of the method proposed in this paper is to estimate the population attributable fraction (PAF) within a representative sample of the target population, by directly estimating the number of predicted cancer cases attributable and not attributable to smoking or SHS exposure within the sample, by considering all the relevant smoking-related characteristics of individual-level participants. This PAF is then applied to the number of observed cancer cases in the target population, taking into account an appropriate latency period.

The ILD method can be applied not only to estimate the number of cancer cases attributable to smoking, but also smoking-attributable deaths or disability-adjusted life years (DALYs). For simplicity of presentation, throughout the description of the methods we refer to the estimation of the number of cases. We present below the methodology for, respectively, active smoking and SHS exposure.

Active smoking

The first step of the ILD method assigns each individual of the sample a cancer-specific RR based on their smoking status and characteristics - specifically, smoking intensity (i.e., number of cigarettes smoked per day) and duration (i.e., years of smoking) for ever smokers, and TSQ (i.e., time since quitting smoking, in years) for former smokers. Such individual RRs are computed starting from estimates available from previously published meta-analyses providing dose-response associations between the corresponding smoking-related variables and site-specific cancer risk.

For each individual i, according to their smoking status, the individual cancer-specific RR is defined as follows:

$$\begin{cases} RR_i = 1 & i\ never\ smoker \\ RR_i = \{1 + [(RR_{curr} - 1) * x_i * y_i]\} & i\ current\ smoker \\ RR_i = \{1 + [(RR_{curr} - 1) * x_i * y_i]\} * \left\{1 - \left[\left(1 - \frac{RR_{ex}}{RR_{curr}}\right) * z_i\right]\right\} & i\ former\ smoker \end{cases} \quad (1)$$

where:

- RR_{curr} is the RR for current vs. never smokers;
- RR_{ex} is the RR for former vs. never smokers
- x_i is the percent variation of RR of dose-specific smoking intensity for current smokers (RR_{id}, obtained from the dose-risk curve) from the RR associated with the mean smoking intensity value (RR_{im}, calculated among studies from which the intensity curve is derived)

$$x_i = 1 - (\frac{RR_{im} - RR_{id}}{RR_{im} - 1})$$

- y_i is the percent variation of RR of dose-specific smoking duration for current smokers (RR_{dd}, obtained from the dose-risk curve) from the RR associated with the mean smoking duration value (RR_{dm}, calculated among studies from which the duration curve is derived)

$$y_i = 1 - \left(\frac{RR_{dm} - RR_{dd}}{RR_{dm} - 1}\right)$$

- z_i is the percent variation of RR of dose-specific TSQ for former smokers (RR_{td}, obtained from the dose-risk curve) from the RR associated with the mean TSQ value (RR_{tm}, calculated among studies from which the TSQ curve is derived)

$$z_i = 1 - \left(\frac{RR_{tm} - RR_{td}}{RR_{tm} - 1}\right)$$

This approach allows the RR for current and former versus never smokers to be weighted according to individual smoking-related characteristics, thereby incorporating heterogeneity in exposure into the overall risk estimation.

To ensure epidemiological plausibility, we imposed a directional constraint on the final individual RR for former smokers. Specifically, for cancer sites in which former smoking is associated with an increased risk (i.e., $RR_{ex} > 1$), individual RR estimates for former smokers falling below 1 are set to 1. Conversely, for cancer sites in which former smoking is associated with a reduced risk (i.e., $RR_{ex} < 1$), individual RR estimates for former smokers exceeding 1 are set to 1. This constraint was applied only to the final relative risk estimate for former smokers.

Let denote p as the specific cancer incidence probability for a never smoker. In the absence of smoking, each individual in the sample would have probability p of cancer incidence, and the predicted number of cancer cases in the sample would be equal to $p * n$, where n represents the sample size. In the presence of smoking, the specific cancer incidence probability for each individual is $p * RR_i$ (note that RR_i is set to one for never smokers). Consequently, the predicted number of cancer cases (C_TOT_PRED) can be obtained by summing, for each individual, the product of their RR_i and p:

$$C\_TOT\_PRED = \sum_{i=1}^{n} p * RR_i = p * \sum_{i=1}^{n} RR_i \qquad (2)$$

The predicted number of cancer cases in the sample population that would not have occurred in the absence of smoking, which can also be defined as the predicted excess number of cancer cases attributable to smoking (C_SMOK _PRED), is calculated as:

$$C\_SMOK\_PRED = \left(\sum_{i=1}^{n} p * RR_i\right) - p * n = p * \left[\left(\sum_{i=1}^{n} RR_i\right) - n\right] \qquad (3)$$

The PAF is calculated as the ratio between the predicted excess number of cancer cases due to smoking to the predicted total number of cases in the sample population. This formula is conceptually similar to the categorical exposure-based PAF [11], with the key difference that it is applied at the individual level rather than to exposure subgroups.

$$PAF_{smoking} = \frac{C\_SMOK\_PRED}{C\_TOT\_PRED} = \frac{p * [(\sum_{i=1}^{n} RR_i) - n]}{p * \sum_{i=1}^{n} RR_i} = \frac{(\sum_{i=1}^{n} RR_i) - n}{\sum_{i=1}^{n} RR_i} \qquad (4)$$

By multiplying the estimated smoking PAF and the number of specific cancer cases that occurred in the target population in a given year, accounting for an appropriate latency period, it is possible to estimate the number of cancer cases attributable to smoking in the target population.

To quantify the uncertainty around these estimates, it is essential to account both for the variability in the risk estimates derived from meta-analyses - including the RRs for current and former smokers and the dose–response parameters - and for the sampling variability associated with the representative sample drawn from the target population. To simultaneously incorporate both sources of uncertainty in calculating Confidence Intervals (CI), we propose an approach that combines Monte Carlo simulations with bootstrap resampling, as described in detail in the *Supplementary Materials*.

Secondhand smoke exposure

The number of cancer cases attributable to SHS exposure is calculated among never smokers, only, as the impact of smoking could mask the effect due to SHS [12]. The first step assigns each individual of the sample a cancer-specific RR based on their SHS exposure and characteristics, specifically SHS exposure intensity in terms of number of cigarettes a person is exposed to daily. Such individual RRs are computed starting from estimates available from previously published meta-analyses providing dose-response associations between the SHS intensity and site-specific cancer risk.

For each never smoker i, according to their status of exposure to SHS, the individual cancer-specific RR is defined as follows:

$$\begin{cases} RR_i = 1 & i \text{ not exposed to SHS} \\ RR_i = \{1 + [(RR_{SHS} - 1) * w_i]\} & i \text{ exposed to SHS} \end{cases} \quad (5)$$

where:

- RR_{SHS} is the RR of never smokers exposed to SHS vs. never smokers not exposed to SHS
- w_i is the percent variation of RR of dose-specific SHS intensity for exposed to SHS (RR_{sd}, obtained from the dose-risk curve) from the RR associated with the mean SHS intensity value (RR_{sm} calculated among studies from which the SHS intensity curve is derived)

$$w_i = 1 - \left(\frac{RR_{sm} - RR_{sd}}{RR_{sm} - 1}\right)$$

This allows the RR for SHS exposure to be weighted based on the intensity of exposure.

Based on calculated individual SHS RRs, we applied calculations analogous to those described for active smoking (Formulas 2-4) to estimate the PAF for SHS, obtaining that

$$PAF_{SHS} = \frac{C\_SHS\_PRED}{C\_TOT\_PRED} = \frac{(\sum_{i=1}^{n} RR_i) - n}{\sum_{i=1}^{n} RR_i} \quad (6)$$

Note that, in this case, n represents the number of never smokers in the sample. C_SHS_PRED represents the number of predicted cancer cases attributable to SHS in the sample.

As with active smoking, the number of cancer cases attributable to SHS among never smokers in a target population can be estimated by multiplying the SHS

exposure PAF by the number of cancer cases in the target population of never smokers for a given year, accounting for latency. If information on smoking status of cancer cases in the target population is not available, it is possible to estimate the SHS exposure PAF on the complete sample size and applying it to the overall number of cancer cases in target population.

Dose-response variables related to active smoking and SHS exposure are incorporated into the formula only when considered reliable. If the dose-response relationships for a given variable is deemed unreliable, the corresponding percent variation (i.e., x_i, y_i, w_i or z_i) is not used in the RR estimation. The criteria used to define the reliability of these dose-response variables are described in the Supplementary Materials.

PAFs for smoking and SHS exposure can be computed overall or stratified by age group and/or sex, and then applied to the corresponding subgroups of cancer cases. The age- and sex-stratified formulas for PAFs are reported in the Supplementary Material.

Notably, the structure of the methodology allows for the possibility of negative PAFs, in case smoking or SHS exposure are protective factors for the risk of a specific cancer-site or disease. Specifically, formulas (4) and (6) yield negative values when the individual RR assigned to exposed individuals is less than 1. In such cases, the exposure is associated with a protective effect, and the resulting PAF can be applied to estimate the proportion of cases, deaths, or DALYs prevented due to the exposure. Although this scenario is usually not expected in the context of tobacco smoking and cancer, our framework is designed to accommodate such instances and provide coherent estimates in either direction of association.

To calculate CIs, the same approach described in the *Supplementary Material* for active smoking can be applied to SHS exposure, allowing for the incorporation of uncertainty from both the RR estimates and the sampling variability.

Materials

To implement the ILD method for estimating the number of cancer cases attributable to smoking and SHS exposure, we rely on three key data sources.

- data on smoking behaviour from a representative sample of the target population (collected with a defined time lag to account for the latency period between exposure and cancer onset);
- RRs of specific cancer sites associated with active smoking and SHS exposure, as well as dose-response relationships for smoking intensity, duration, and TSQ, and SHS exposure intensity;

- national cancer incidence or mortality data of the target population.

In the example employed in this article, we aimed at estimating the number of breast cancer cases attributable to smoking and SHS exposure in the Italian population in 2022. Data sources required to employ the method and specific sources used in the example are summarized in Table 1.

Anonymized data at individual-level on smoking status, intensity, duration, TSQ, and exposure to SHS and SHS intensity were obtained from a nationally representative health survey conducted in 2013 by the Italian National Institute of Statistics (ISTAT) [13]. The decision to use data from 2013 was driven by the availability of complete data at individual level and the need to allow for an adequate latency period. Moreover, this latency period is consistent with published PAF studies for breast cancer that adopt a latency of about 10 years [14, 15]. The survey by ISTAT used in this application was designed to be nationally representative through a two-stage stratified sampling design: municipalities were sampled within strata defined by region and settlement size, and households/individuals were then selected within these municipalities. Data collection occurred in four quarterly waves (March, June, September, December) to minimize seasonal variation. The sampling plan ensures coverage across all Italian regions and alignment with key demographic margins, including age and sex distributions [13]. The final dataset includes individuals from 49,800 households across 1,400 municipalities, providing broad geographic and demographic representativeness. The survey included detailed information on tobacco use and exposure among 104,086 individuals aged ≥14 years. For the present analysis, we restricted the sample to female participants (n=54,407). Smoking status was assessed using the question “Do you currently smoke?”. Participants who answered “Yes” were classified as current smokers, those who answered “No, but I used to smoke” were classified as former smokers, and those who answered “No, I have never smoked” were classified as never smokers. Current and former smokers were asked how many cigarettes they smoked per day and at what age they started smoking. Former smokers were also asked to report the age at which they quit smoking. Exposure to SHS among never smokers was assessed through the question “How often are you exposed to tobacco smoke in indoor environments?”. For each of the following locations - home, workplace, public places and car - participants could choose one of the following options: “Never or almost never”, “Less than one hour per day”, “From one to five hours per day”, and “More than five hours per day”. To quantify SHS exposure, we assigned a midpoint value in minutes to each response category (30 minutes/day for “Less than one hour per day”, 180 minutes/day for “From one to five hours per day”, and 420 minutes/day for “More than five hours per day”), a widely used procedure for approximating continuous exposure in categorical dose–response analyses [16, 17]. We summed the values across the four

locations to obtain the total number of minutes of SHS exposure per day. Responses of “Never or almost never” were assigned a value of zero minutes. Those who reported this response in all four settings were classified as non-exposed. The sum of minutes of exposure in all settings was then divided by five - a commonly reported average time to smoke a single cigarette [18] - to estimate the number of cigarettes to which an individual was daily exposed. While this assumption is not based on precise conventions, it provides a pragmatic approach in the absence of more detailed data; however, when available, direct information on the number of cigarettes smoked per day should be preferred. A sensitivity analysis with different conversion factors from minutes of exposure to cigarettes per day (4, 5, or 6 minutes per cigarette) is also proposed.

RRs of breast cancer associated with active smoking, SHS and dose–response relationships were derived from the two most recent and comprehensive meta-analyses available on the topic, one focused on active smoking and the other on SHS exposure [9, 10]. These studies provided risk estimates and dose–response functions for key exposure characteristics, including smoking intensity, duration, TSQ, and SHS exposure levels. The meta-analysis on active smoking reported a pooled RR of breast cancer of 1.07 for current smokers and 1.08 for former smokers, compared to never smokers [10]. The meta-analysis on the relationships between SHS exposure and breast cancer risk among never smokers provided a RR of 1.24 [9]. Full dose-response functions for smoking intensity, duration, TSQ, and SHS intensity are provided in Supplementary Table 1.

The number of incident breast cancer cases in Italy in 2022 was retrieved from the European Cancer Information System (ECIS), which provides regularly updated estimates of cancer incidence and mortality across European countries based on population-based cancer registries and epidemiological models [8]. According to ECIS, approximately 58,160 new breast cancer cases were estimated in Italy in 2022, of which 57,490 among women.

Table 1 – Data sources required to apply the individual level data (ILD) method to estimate cancer burden attributable to smoking and second-hand smoke (SHS) in Italy in 2022, and specific sources used in the example.

Data source	Required data	Possible sources	Sources used in the present example
Individual-level data (ILD)	Smoking status, intensity, duration, time since quitting, SHS exposure, SHS intensity	Nationally representative cross-sectional surveys	ISTAT, 2013 health survey [13]
RRs and dose-risk functions	RRs for smoking status and SHS exposure; dose–risk functions for smoking intensity, duration, time since quitting, and SHS intensity	Published meta-analyses	Scala et al. 2023 (active smoking) [10], Possenti et al. 2024 (SHS exposure) [9]
Cancer burden data	Total number of cancer cases, deaths, or DALYs, preferably stratified by age and sex	National cancer registries and other official sources (e.g., WHO, GBD, national statistical agencies, scientific literature)	ECIS, breast cancer incidence in Italy, 2022 [8]

GBD: Global Burden of Disease; DALYs: disability-adjusted life-years; ECIS: European Cancer Information System; ISTAT: Italian National Institute of Statistics; RR: relative risk; WHO: World Health Organization.

Statistical analysis

We applied the proposed ILD method described above to estimate the number of breast cancer cases attributable to active smoking and SHS exposure in the Italian population in 2022. As a worked example, a step-by-step application of the proposed method to estimate breast cancer cases attributable to active smoking is presented in detail in the *Supplementary Material*. Due to the unreliability of the TSQ dose–response curve, percentage variations related to TSQ were not applied in the estimation of individual RRs among former smokers (see *Supplementary Material* for further details). For comparison purposes, we also estimated the number of attributable cases using a prevalence-based method

based on Levin's formula applied to the same data sources, but using aggregated exposure prevalence in the target population and pooled RRs from the literature [4]. For both methods, we calculated PAFs and attributable cases stratified by age. To this aim, the sample size was divided into three age groups: ≤40 years, 41-60 years, and >60 years. These estimates were then applied to breast cancer case counts in 2022, which were stratified by age at diagnosis into the following categories: <50 years, 50–69 years, and ≥70 years. CIs for the estimates were calculated for both approaches. For the ILD method, we applied the procedure described in the *Supplementary Material*, which integrates Monte Carlo simulations and bootstrap resampling, performing one million iterations to account for both parameter uncertainty and sampling variability. For the prevalence-based approach using Levin's formula, CIs were derived from Monte Carlo simulations based on 1,000 iterations [19].

All statistical analyses were performed using SAS (SAS version 9.4, SAS Institute) and R (R version 4.4.3).

7.4 Results

Description of the sample

The analysis included a total of 54,407 Italian women aged 14 years and older (mean age 51 years, standard deviation; SD=19.97). Among these, 15.4% were current smokers, 16.1% were former smokers, and 68.5% reported they have never smoked. Among never smokers, 86.9% have never been exposed to SHS and 13.1% were exposed to SHS, with 7.7% exposed less than one hour per day, 3.8% between 1 and 5 hours, and 1.6% more than 5 hours daily. Overall, smoking prevalence was highest in middle-aged women, while SHS exposure was more prevalent in the youngest group. Detailed demographic and smoking-related characteristics of the sample stratified by age are summarized in Table 2.

Table 2. Smoking characteristics of the study sample of women aged ≥14 years (n = 54,407), stratified by age groups (Italy, 2013)

	Age ≤40 years (n=17,501)	Age 41-60 years (n=18,269)	Age >60 years (n=18,637)	Total (n=54,407)
Smoking status, n (%)				
Never smokers	12,453 (71.2)	10,905 (59.7)	13,897 (74.6)	37,255 (68.5)
Former smokers	1,970 (11.3)	3,582 (19.6)	3,231 (17.3)	8,783 (16.1)

Current smokers	3,078 (17.6)	3,782 (20.7)	1,509 (8.1)	8,369 (15.4)
Mean intensity in cigarettes/day (SD) [a]	9.20 (6.41)	11.36 (7.51)	11.14 (8.20)	10.67 (7.47)
Mean smoking duration in years (SD) [a]	11.01 (6.55)	24.56 (11.08)	34.33 (15.22)	23.27 (14.43)
Mean TSQ smoking in years (SD) [b]	5.03 (4.77)	14.80 (9.79)	20.80 (13.27)	14.82 (11.99)
Daily SHS exposure in indoor settings, n (%) [c]				
Not exposed	14,416 (82.4)	16,322 (89.3)	17,517 (94.0)	32,378 (86.9)
<1 hours/day	1,808 (10.3)	1,154 (6.3)	659 (3.5)	2,884 (7.7)
1-5 hours/day	890 (5.1)	553 (3.0)	320 (1.7)	1,415 (3.8)
>5 hours/day	387 (2.2)	240 (1.3)	141 (0.8)	578 (1.6)
Mean SHS exposure intensity in cigarettes/day (SD) [d]	21.5 (21.7)	21.1 (21.4)	22.2 (22.4)	21.5 (21.8)

SD: standard deviation; SHS: secondhand smoke; TSQ: time since quitting;
[a] among ever smokers (i.e., current and former smokers combined);
[b] among former smokers;
[c] among never smokers;
[d] among never smokers exposed to SHS
No missing values were registered for smoking status, smoking duration and TSQ, while 16 missing values were found for smoking intensity and 8 for SHS exposure.

Results with Individual-Level Data (ILD) method

The formulas (1-6) described in the Methods section were applied to estimate individual RRs associated with smoking and SHS exposure. Individual RRs for current smokers ranged between 1.00 and 1.77 (SD=0.06), with the average RR being 1.06 compared to never smokers, and individual RRs for former smokers ranged between 1.00 and 1.63 (SD=0.06), with the average RR being 1.06 compared to never smokers. Among never smokers exposed to SHS, the

individual RRs ranged between 1.06 and 2.37 (SD=0.41) and the average RR was 1.33 compared to non-exposed to SHS.

Using formula (4), adapted for age-stratified estimates, PAFs for smoking were estimated at 0.74% (95% CIs: 0.57%-0.96%) for the youngest age group, 2.57% (95% CIs: 2.06%-3.12%) for the middle age group, and 2.22% (95% CIs: 1.78%-2.69%) for the oldest age group. Applying this PAF to the estimated number of breast cancer cases among Italian women in 2022, it was found that 76 (95% CIs: 59-99) cases of breast cancer were attributable to active smoking among people aged 49 years or younger, 586 (95% CIs: 469-710) cases among people aged 50–69 years, and 543 (95% CIs: 435-657) cases among people aged 70 years or older. Overall, it was estimated that 1,205 (95% CIs: 1,040-1,370) breast cancer cases were attributable to active smoking, representing 2.10% (95% CIs: 1.81%-2.38%) of all breast cancer cases.

Using formula (6), the age-stratified PAFs for SHS exposure were estimated in the entire sample, resulting in a value of 5.25% (95% CIs: 3.25%-7.60%) for the lowest age group, 2.71% (95% CIs: 1.66%-3.98%) for the intermediate age group, and 1.62% (95% CIs: 0.98%-2.43%) for the highest age group. Applying this PAF to the estimated number of breast cancer cases among women in 2022 yielded 540 (95% CIs: 335-783) cases attributable to SHS exposure among people aged 49 years or younger, 616 (95% CIs: 378-906) cases among people aged 50-69 years, and 397 (95% CIs: 239-593) cases among people aged 70 years or older. Overall, it was estimated that 1,553 (95% CIs: 1,164-1,942) breast cancer cases were attributable to SHS exposure, corresponding to 2.70% (95% CIs: 2.02%-3.38%) of all breast cancer cases.

Results from the sensitivity analysis for SHS exposure using different conversion factors from minutes of exposure to cigarettes per day (4, 5, or 6 minutes per cigarette) are reported in *Supplementary Table 2*, with total PAF estimates ranging from 2.11 (6 minutes/cigarette) to 4.08% (4 minutes/cigarette).

The total number of breast cancer cases attributable to smoking and SHS exposure was estimated at 2,758 (95% CIs: 2,335-3,181), corresponding to 4.80% (95% CIs: 4.06%-5.53%) of all breast cancer cases.

Results from Levin's formula

To compare our results with those obtained using alternative approaches, we applied a prevalence-based approach to the same sample population and cancer incidence estimates. Applying the obtained PAFs to the estimated number of breast cancer cases among Italian women in 2022, we obtained 1,359 (95% CIs: 1,265-1,650) breast cancer cases attributable to active smoking and 1,333 (95%

CIs: 1,057-1,794) to SHS exposure, for a total of 2,692 (95% CIs: 2,472-3,294) cases.

Table 3 reports a comparison between the two methods.

Table 3. Comparison of population attributable fractions (PAFs) and attributable cases of breast cancer by age group, estimated using individual-level data (ILD) method (the proposed method) and a prevalence-based (PB) method.

	Cancer cases	PAF[a] % (95% CIs)		Attributable cancer cases n (95% CIs)	
		ILD method	PB method	ILD method	PB method
Active smoking					
<50 years	10,299	0.74 (0.57-0.96)	2.19 (1.64-2.58)	76 (59-99)	225 (169-266)
50-69 years	22,768	2.57 (2.06-3.12)	2.93 (2.30-3.58)	586 (469-710)	667 (524-815)
≥70 years	24,423	2.22 (1.78-2.69)	1.91 (1.55-2.32)	543 (435-657)	467 (379-567)
Total	57,490	2.10 (1.81-2.38)	2.36 (2.20-2.87)	1,205 (1,040-1,370)	1,359 (1,265-1,650)
SHS exposure					
<50 years	10,299	5.25 (3.25-7.60)	4.05 (2.53-5.60)	540 (335-783)	416 (261-577)
50-69 years	22,768	2.71 (1.66-3.98)	2.50 (1.52-3.43)	616 (378-906)	570 (246-781)
≥70 years	24,423	1.62 (0.98-2.43)	1.42 (0.87-2.02)	397 (239-593)	347 (212-493)
Total	57,490	2.70 (2.02-3.38)	2.32 (1.84-3.12)	1,553 (1,164-1,942)	1,333 (1,057-1,794)
Active smoking + SHS exposure		4.80 (4.06-5.53)	4.69 (4.30-5.73)	2,758 (2,335-3,181)	2,692 (2,472-3,294)

[a] The age groups used to estimate PAFs and attributable cases differ in order to account for the latency period. PAFs were calculated from smoking data extracted from the sample stratified by the following age groups: ≤40 years, 41-60 years, and >60 year.

95% CIs: 95% Confidence Intervals; SHS: secondhand smoke.

7.5 Discussion

Brief recall of the method

In this paper, we propose an individual-level data (ILD) method to estimate the number of cancer cases attributable to active smoking and/or SHS exposure. This approach combines data at individual-level from a nationally representative survey with the most up-to-date RR estimates from the scientific literature.

Unlike approaches based on aggregate population prevalence of smoking status, the proposed ILD method uses individual microdata from a nationally representative survey and estimates the smoking and SHS associated RRs for each individual, based on their specific smoking characteristics. Specifically, the method calculates weighted RRs by incorporating dose-response relationships for both active smoking status and SHS exposure, thus accounting for variations in smoking intensity, duration, TSQ, and intensity of SHS exposure. This weighting allows a more precise estimation of the individual excess risk attributable to tobacco exposure. These weighted RRs are then used to estimate PAFs, which are finally applied to total number of cancer cases, deaths or DALYs.

Comments on results from practical application

In a practical application of this method, we estimated the number of female breast cancer cases in Italy in 2022 that were attributable to active smoking and SHS exposure. By applying the age-specific PAFs to national cancer incidence estimates, we identified more than 1,200 breast cancer cases attributable to active smoking and more than 1,500 cases attributable to SHS exposure, for a total of almost 3,000 attributable cases. The overall PAFs were 2.10% for active smoking and 2.70% for SHS exposure. These findings emphasise the significant impact of tobacco smoking on breast cancer incidence, with similar contributions from active smoking and SHS exposure. Notably, the substantial proportion of cases attributable to SHS exposure underscores the need for stronger public health measures aimed at reducing involuntary exposure to tobacco smoke. This highlights that prevention efforts should not only focus on reducing active smoking but also prioritize policies that protect non-smokers from SHS exposure.

Comparison with prevalence-based method

To illustrate the advantages of the proposed ILD method, we compared the results obtained for breast cancer with those derived using a prevalence-based method, applied using the same original sample, the same meta-analytic RRs for

smoking and SHS exposure, and the same number of incident breast cancer cases. For this comparison, attributable fractions were estimated considering only smoking status and exposure to SHS prevalence, without incorporating dose-response information and using exclusively aggregated data. The prevalence-based approach yielded population PAFs of 2.36% for active smoking and 2.32% for SHS exposure, corresponding to 1,359 and 1,333 attributable cases, respectively. As expected, these estimates are slightly different from those obtained using the proposed ILD method. This difference likely reflects the inability of the prevalence-based method to capture the different risk associated with varying levels of exposure, which is instead accounted for in the ILD approach. In fact, the prevalence-based method averages risk across the population, thereby underestimating the contribution of heavier or longer-duration smokers, while the ILD method explicitly captures this variations, leading to higher and arguably more realistic burden estimates. In our sample, current smokers reported a lower mean smoking intensity (~11 cigarettes/day) than that of the populations included in the meta-analyses used to derive the pooled RRs (~16 cigarettes/day). Applying a single status-based RR therefore leads to a relative overestimation of the attributable burden for active smoking. Conversely, never-smokers exposed to SHS in our dataset reported slightly higher exposure intensity (mean ~22 cigarettes/day equivalent) compared with the reference populations used to derive pooled SHS RRs (~20 cigarettes/day equivalent), resulting in an underestimation of the SHS-attributable burden when using prevalence-based RRs. Age-related differences and within-stratum heterogeneity in smoking and SHS characteristics likely contribute to these discrepancies. The ILD approach captures such variability by construction, while prevalence-based status RRs do not. Particularly, when stratified by age, the prevalence-based method based on Levin's formula estimated a higher number of smoking attributable cases in the youngest age group, and lower numbers in the older groups, compared to our method. This is mainly due to the fact that the prevalence-based approach does not account for smoking duration [4], which tends to increase with age and substantially contributes to a higher risk in older age groups.

Notably, confidence intervals (CI) obtained using the ILD method were slightly wider than those derived from Levin's formula. This reflects the incorporation of uncertainty from multiple parameters, including sampling, dose–response relationships, and relative risks, rather than relying solely on population-level prevalence and summary RRs. CIs estimation was implemented using a bootstrap–Monte Carlo approach to propagate uncertainty from both risk estimates and sampling variability. While this provides a transparent and reproducible solution for a novel method, alternative approaches could be explored in future work to refine uncertainty quantification. In addition, future

developments could include advanced uncertainty and sensitivity analyses to quantify the relative contribution of each input parameter to PAF variability, using methods such as global sensitivity analysis (GSA) described by Saltelli et al. [20] to identify inputs with minimal influence and guide model simplification or prioritization in data collection.

While other prevalence-based approaches exist, we focused on Levin's method because it is one of the most widely applied in the literature and, crucially, it uses the same input data as ILD. This ensured that any differences observed could be attributed to the methodological aspects rather than to the underlying data.

Comparison with results from Carreras

Another useful point of comparison is provided by a previous European-level study by Carreras et al. That study estimated that 2.6% of breast cancer cases were attributable to active smoking and 1.0% to SHS exposure [21]. While our estimate for active smoking (2.10%) is in agreement with the European estimate, our analysis yielded a notably higher figure for SHS exposure (3.01%). This discrepancy can be largely explained by the different RR used. The European study was based on an earlier, less comprehensive meta-analysis, which reported a lower RR for SHS exposure (1.07) [22], than the more recent, extensive evidence used in our analysis (RR = 1.24) [9]. This difference underscores how the choice of risk estimates, particularly for exposures with evolving evidence, can substantially influence the magnitude of the attributable burden.

Strengths

One of the main strengths of our approach is the use of data on smoking behaviour at individual-level. By capturing heterogeneity at the individual level in smoking-related variable (intensity, duration, and TSQ), it enables for a flexible and valid estimation of PAFs. In contrast, traditional approaches, although adaptable through stratification, apply aggregated prevalence-based estimates to grouped populations [4, 23], which can obscure important heterogeneities and lead to biased burden estimates. Even with stratification by smoking-related characteristics (e.g., intensity or duration), the reliance on aggregated data limits the ability to fully represents the complexity of individual exposure patterns, whereas the ILD framework preserves it.

Another key advantage of our approach lies in its ability to incorporate several dose-response information into the estimation of smoking and SHS attributable burden, thus representing an improvement over existing method. In fact, other frameworks, such as the Global Burden of Disease (GBD) study, usually rely on a single dose-response variable for current smokers, most commonly pack-years

[24-26]. Although methodologically valid, the use of pack-years cannot fully disentangle the contributions of smoking intensity and duration [27, 28]. The use of pack-years has been criticized for conflating intensity and duration, implicitly assuming they contribute equally to risk, whereas evidence, especially for lung cancer, indicates that duration has a stronger effect [28-31]. Moreover, RRs for pack-years are less frequently reported and often based on fewer studies, which may limit their robustness. When only pack-years are available, however, the ILD method can still be applied using this measure, thus preserving the benefits of individual-level analysis even in less detailed datasets. By incorporating separate dose-response relationships for intensity, duration and TSQ (and, when available, dose-response information for SHS exposure), our ILD method more accurately reflects the complexity of smoking exposure, offering a richer and more biologically coherent estimation of attributable risk. This also makes the ILD framework particularly useful for populations whose smoking patterns differ substantially from those represented in the meta-analytical sources used to derive pooled RRs, as it allows the attributable burden to reflect the actual distribution of exposure rather than relying on assumptions of comparability between populations.

An additional strength of our ILD method lies in its hybrid structure: although it incorporates dose-response variables, it does not rely exclusively on them. Instead, it uses RRs estimates by smoking status as a starting point. These estimates are usually widely available and typically more robust, being derived from a larger body of epidemiologic evidence. Dose-response information is then used to weight these baseline risks at the individual level, enabling more refined estimates without compromising the robustness of the initial parameters.

A further important feature of our approach lies in its flexibility and adaptability for subgroup estimation. By using data at individual-level, it is possible to easily estimate PAFs that are stratified by relevant demographic characteristics, such as age and sex. While, for certain tobacco-related outcomes, sex- and age-stratified RRs exist and can be used to derive stratified PAFs, such estimates rarely encompass the full set of exposure dimensions needed for nuanced burden estimation. Thus, the ILD method provides a more in-depth understanding of the burden of cancer and can help identify subgroups that are disproportionately affected by tobacco exposure. For instance, the duration of smoking tends to increase with age. Failure to consider this factor could result in an overestimation of the attributable burden in younger age groups and an underestimation in older age groups. Integrating dose-response relationships for multiple exposure characteristics allows the model to provide a more accurate risk estimation across different strata. This makes the approach particularly valuable for informing age- and sex-specific prevention strategies, and it can be readily stratified by any

characteristic available in the source dataset (e.g., education, region, socioeconomic status, or comorbidities), as appropriate.

Furthermore, this method is not restricted to cancer outcomes, as it can also be applied to other tobacco-related diseases, including cardiovascular and respiratory conditions. Crucially, this framework can also be adapted to other risk factors whenever relevant exposure characteristics are available at an individual level, making it a flexible tool for estimating disease burden across a variety of exposures and health outcomes. Besides, the method can accommodate both harmful and protective associations between exposures and diseases.

Finally, the proposed ILD method enables the assessment of the cancer burden related not only to active smoking but also to SHS exposure. Incorporating SHS into the analysis is essential to capture the full spectrum of tobacco-related risks and to support public health policies.

Limitations

One key limitation of this approach is its reliance on large and detailed data at individual-level from a nationally representative sample. Such data may not always be easily available, particularly in low-resource settings or for specific populations. Importantly, where detailed inputs are unavailable, the ILD framework can be implemented with simplified inputs (for example, only with pack-years). Moreover, because the ILD framework explicitly combines multiple inputs, the resulting uncertainty can be larger than in prevalence-based summaries, reflecting the propagation of uncertainty from each component.

Moreover, it can be challenging to find data that appropriately account for a latency period between exposure and disease onset. However, the need to account for a latency period may be questioned, both because the ILD method already incorporates information on smoking duration, and because observational data from which RR are calculated often do not reflect a complete latency period. In addition, applying the method to diseases with shorter latencies, such as cardiovascular diseases, justifies using recent data.

Furthermore, the accuracy and reliability of the results depend heavily on the quality of these data. This requires careful validation and data cleaning to ensure that key variables are correctly recorded and suitable for analysis. However, the use of cross-sectional data represents a more feasible option compared with other approaches that rely on longitudinal data from cohort studies, such as the basic model and the Rogers's method [6, 32]. These alternative methods require long-term follow-up or detailed case ascertainment and exposure reconstruction, which are often more resource-intensive and less frequently available at the population level.

At the same time, it should be acknowledged that both smoking status and exposure to SHS are generally self-reported. This may introduce measurement error, including recall bias and misclassification of exposure. Such limitations are inherent to survey-based data and to PAF methods that rely on them. Particularly, self-reported smoking may be affected by under-reporting due to social desirability and stigma [33]. Consequently, exposure prevalence may be underestimated, which would likely attenuate the estimated smoking- and SHS-attributable burden. Moreover, exposures are measured at a single point in time. This implies an assumption of temporal stability (e.g., smoking frequency and SHS exposure do not change meaningfully within individuals), which may not hold over the life course and can lead to exposure misclassification.

Like Levin's formula [4], our method assumes a constant baseline risk (p) of developing the disease in all individuals, regardless of their age, sex or other characteristics. In practice, stratifying by age and sex can mitigate this limitation to some extent, although residual heterogeneity in baseline risk across population subgroups may still remain.

Another issue regards the uncertainty surrounding the RRs used, particularly for dose-response variables. Even using estimates based on high-quality and comprehensive meta-analyses, RRs may still be affected by heterogeneity across studies, publication bias or residual confounding factors.

Moreover, the calculation of individual RRs relies on the assumption that the RR associated with the average value of the dose-response variable (calculated among studies from which the specific dose-response curve is derived) is truly representative of all studies included in the meta-analysis. However, only a subset of original studies typically reports detailed dose-response data, and this subset may not be representative of the full body of evidence considered in the meta-analyses, thus biasing individual-level RR estimates.

Another inherent limitation of our approach, common across most burden-of-disease methods [23, 25, 34], is the assumption that the exposure of interest (i.e., cigarette smoking) acts independently of other risk factors. This is a strong assumption, particularly for cancers with a multifactorial etiology such as breast cancer, for which reproductive, hormonal, genetic and lifestyle factors also play an important role. The use of RR estimates derived from meta-analyses of studies that are largely adjusted for key factors helps to mitigate the extent of this issue. However, residual confounding and interactions with other determinants cannot be entirely excluded. In principle, the ILD framework could be extended to incorporate additional individual-level risk factors, when both exposure data and compatible dose–response estimates are available, allowing a more comprehensive assessment of their joint and relative contributions. Such

extensions could represent a valuable direction for future methodological development.

In summary, from a practical perspective, the ILD approach could be particularly useful when the goal is to obtain more precise estimates or to highlight differences across age, sex, socioeconomic groups, or other relevant subgroups, thereby identifying populations at higher risk or more responsive to prevention strategies. It is also well suited for populations with non-standard, heterogeneous, or atypical smoking and SHS exposure patterns. In contrast, traditional prevalence-based methods may remain preferable in settings where only aggregated exposure data are available or where input data are limited.

7.6 Conclusions

In conclusion, the approach proposed in this paper offers a flexible and detailed method for estimating the burden of cancer attributable to tobacco exposure, by incorporating dose-response relationships. It allows for a precise quantification of the impact of both active smoking and SHS exposure. This method can be adapted to different population subgroups, supporting targeted public health strategies and priority setting.

7.7 Contribution to the overall thesis framework

This chapter represents the methodological core of the thesis. The preceding chapters generated the key components required for burden estimation, including epidemiological evidence on smoking- and SHS-related cancer risks, dose–response relationships, and population-level exposure data. Building upon this evidence, this chapter introduces a novel methodology to estimate the cancer burden attributable to tobacco exposure at the individual level.

A major strength of this approach is its ability to integrate smoking status, intensity, duration, and time since cessation into a single analytical framework, thereby capturing the heterogeneity of smoking-related cancer risk more accurately than conventional methods. By translating epidemiological evidence into population-attributable fractions that can be applied to national data, this framework provides a bridge between risk estimation and public health impact assessment.

The next chapter demonstrates the practical application of this methodology by estimating the incidence, mortality, and DALYs attributable to tobacco smoking for digestive cancers in Italy.

7.8 References

1. Collaborators GBDRF. Global burden and strength of evidence for 88 risk factors in 204 countries and 811 subnational locations, 1990-2021: a systematic analysis for the Global Burden of Disease Study 2021. Lancet 2024; 403: 2162-2203.
2. World Health Organization. WHO report on the global tobacco epidemic, 2023: protect people from tobacco smoke. https://www.who.int/publications/i/item/9789240077164. Published July 31, 2023. Accessed June 20, 2025. 2023.
3. Jha P. Avoidable global cancer deaths and total deaths from smoking. Nat Rev Cancer 2009; 9: 655-664.
4. Levin ML. The occurrence of lung cancer in man. Acta Unio Int Contra Cancrum 1953; 9: 531-541.
5. Niu SR, Yang GH, Chen ZM et al. Emerging tobacco hazards in China: 2. Early mortality results from a prospective study. BMJ 1998; 317: 1423-1424.
6. Forastiere F, Perucci CA, Arca M, Axelson O. Indirect estimates of lung cancer death rates in Italy not attributable to active smoking. Epidemiology 1993; 4: 502-510.
7. Perez-Rios M, Montes A. Methodologies used to estimate tobacco-attributable mortality: a review. BMC Public Health 2008; 8: 22.
8. European Commission. ECIS - European Cancer Information System. Estimates of cancer incidence and mortality in 2022, for all countries. Available at https://ecis.jrc.ec.europa.eu/ (last access 27/05/2025).
9. Possenti I, Scala M, Carreras G et al. Exposure to second-hand smoke and breast cancer risk in non-smoking women: a comprehensive systematic review and meta-analysis. Br J Cancer 2024; 131: 1116-1125.
10. Scala M, Bosetti C, Bagnardi V et al. Dose-response Relationships Between Cigarette Smoking and Breast Cancer Risk: A Systematic Review and Meta-analysis. J Epidemiol 2023; 33: 640-648.
11. Shield KD, Parkin DM, Whiteman DC et al. Population Attributable and Preventable Fractions: Cancer Risk Factor Surveillance, and Cancer Policy Projection. Curr Epidemiol Rep 2016; 3: 201-211.
12. Öberg M, Jaakkola MS, Prüss-Üstün A et al. Second-Hand Smoke: Assessing the Environmental Burden of Disease at National and Local Levels. WHO Environmental Burden of Disease Series, No. 18. Geneva, Switzerland: World Health Organization 2010.
13. ISTAT. INDAGINE STATISTICA MULTISCOPO SULLE FAMIGLIE. Condizioni di salute. Available at https://www.istat.it/microdati/condizioni-di-salute-e-ricorso-ai-servizi-sanitari-anni-1994-2005/. 2013.
14. van Gemert WA, Lanting CI, Goldbohm RA et al. The proportion of postmenopausal breast cancer cases in the Netherlands attributable to lifestyle-related risk factors. Breast Cancer Res Treat 2015; 152: 155-162.

15. Parkin DM. 1. The fraction of cancer attributable to lifestyle and environmental factors in the UK in 2010. Br J Cancer 2011; 105 Suppl 2: S2-5.

16. Il'yasova D, Hertz-Picciotto I, Peters U et al. Choice of exposure scores for categorical regression in meta-analysis: a case study of a common problem. Cancer Causes Control 2005; 16: 383-388.

17. Qi X, Guo H, Artem Z, Wang W. An Interval-Valued Data Classification Method Based on the Unified Representation Frame. IEEE Access 2020; 17002-17012.

18. Zhang T, Chillrud SN, Yang Q et al. Characterizing peak exposure of secondhand smoke using a real-time PM(2.5) monitor. Indoor Air 2020; 30: 98-107.

19. Lee S, Moon S, Kim K et al. A Comparison of Green, Delta, and Monte Carlo Methods to Select an Optimal Approach for Calculating the 95% Confidence Interval of the Population-attributable Fraction: Guidance for Epidemiological Research. J Prev Med Public Health 2024; 57: 499-507.

20. Saltelli A, Ratto M, Andres T et al. Global Sensitivity Analysis. The Primer. John Wiley & Sons, Ltd 2008.

21. Carreras G, Lachi A, Boffi R et al. Burden of disease from breast cancer attributable to smoking and second-hand smoke exposure in Europe. Int J Cancer 2020; 147: 2387-2393.

22. Macacu A, Autier P, Boniol M, Boyle P. Active and passive smoking and risk of breast cancer: a meta-analysis. Breast Cancer Res Treat 2015; 154: 213-224.

23. Shultz JM, Novotny TE, Rice DP. Quantifying the disease impact of cigarette smoking with SAMMEC II software. Public Health Rep 1991; 106: 326-333.

24. Collaborators GBDT. Spatial, temporal, and demographic patterns in prevalence of smoking tobacco use and attributable disease burden in 204 countries and territories, 1990-2019: a systematic analysis from the Global Burden of Disease Study 2019. Lancet 2021; 397: 2337-2360.

25. Siemiatycki J, Karp I, Sylvestre MP, Pintos J. Estimating the proportion of cases of lung cancer legally attributable to smoking: a novel approach for class actions against the tobacco industry. Am J Public Health 2014; 104: e60-66.

26. Ai F, Zhao J, Yang W, Wan X. Estimating smoking-attributable lung cancer mortality in Chinese adults from 2000 to 2020: a comparison of three methods. BMC Cancer 2024; 24: 47.

27. Lubin JH, Caporaso NE. Cigarette smoking and lung cancer: modeling total exposure and intensity. Cancer Epidemiol Biomarkers Prev 2006; 15: 517-523.

28. Peto J. That the effects of smoking should be measured in pack-years: misconceptions 4. Br J Cancer 2012; 107: 406-407.

29. Potter AL, Xu NN, Senthil P et al. Pack-Year Smoking History: An Inadequate and Biased Measure to Determine Lung Cancer Screening Eligibility. J Clin Oncol 2024; 42: 2026-2037.
30. Remen T, Pintos J, Abrahamowicz M, Siemiatycki J. Risk of lung cancer in relation to various metrics of smoking history: a case-control study in Montreal. BMC Cancer 2018; 18: 1275.
31. Doll R, Peto R. Cigarette smoking and bronchial carcinoma: dose and time relationships among regular smokers and lifelong non-smokers. J Epidemiol Community Health (1978) 1978; 32: 303-313.
32. Rogers RG, Hummer RA, Krueger PM, Pampel FC. Combining Prevalence and Mortality Risk Rates: The Case of Cigarette Smoking. Popul Dev Rev 2005; 31: 259-292.
33. Wong SL, Shields M, Leatherdale S et al. Assessment of validity of self-reported smoking status. Health Rep 2012; 23: 47-53.
34. Peto R, Lopez AD, Boreham J et al. Mortality from tobacco in developed countries: indirect estimation from national vital statistics. Lancet 1992; 339: 1268-1278.

Supplementary Materials Chapter 7

Criteria for reliability of dose–response curves

Dose-response functions are incorporated into the main formula only when deemed reliable. The rationale for excluding certain dose-response estimates stems from the need for consistency between the relative risks (RRs) derived from these functions and the corresponding overall RRs for smoking status (i.e., current or former smokers) or secondhand smoke (SHS) exposure reported in the same meta-analysis.

In particular, a dose–response relationship is considered unreliable if it yields RR estimates for the average level of a smoking and SHS-related variable (e.g., intensity, duration, time since quitting, or SHS intensity) that are markedly inconsistent with the RR reported for the corresponding smoking status. This approach is based on the premise that overall RRs by smoking status or SHS exposure are typically derived from a larger body of evidence, whereas dose-response estimates are often based on a smaller subset of studies, since they are not always consistently reported in original articles.

To operationalize this, a dose-response curve is considered unreliable if:

> (i) it does not yield, for any dose of the smoking-related variable, a RR equal to that reported for the corresponding smoking status (i.e., “current” for smoking intensity and duration, “former” for time since quitting, and “exposed” for SHS intensity) in the same meta-analysis;
>
> (ii) the dose value corresponding to the RR for smoking status or SHS falls outside the range of one third to five thirds the average dose value reported in the original studies (calculated among studies from which the specific dose-response curve is derived)

For example, in the calculation of breast cancer cases and considering smoking intensity, the average number of cigarettes smoked per day among current smokers in the studies included in the meta-analysis on breast cancer from which the specific dose-risk curve is derived is 16. A dose-response intensity curve is therefore considered unreliable if:

(i) it does not yield a RR equal to that reported for current smokers (1.07) at any level of intensity;

> (ii) the intensity value corresponding to the RR for current smokers falls outside the range of 5.3 to 26.7 cigarettes per day (i.e., one third to five

thirds of the mean intensity value in the studies from which the intensity curve is derived).

Adapted PAF formula for age- and sex-stratified estimates

To account for differences across demographic subgroups, the formulas for the population attributable fraction (PAF) can be adapted to allow stratification by age and sex. This stratified version of the formula enables more accurate estimation of the disease burden attributable to smoking and SHS exposure within each subgroup, which can then be summed to obtain overall estimates.

Particularly, to estimate smoking PAF for sex j and age-group k, it is possible to use the following formula:

$$PAF_{smoking}\,(jk) = \frac{\sum_{i=1}^{n_{jk}} RR_i - n_{jk}}{\sum_{i=1}^{n_{jk}} RR_i} \qquad (4*)$$

Where n_{jk} represents the number of participants of sex j and age-group k and RR_i are the individual RRs calculated using formula (1).

Note that individual RRs are assigned based on overall dose-risk characteristics (smoking status, intensity, duration, and TSQ) derived from published meta-analysis, without stratification by age or sex.

Therefore, age- and sex-specific PAFs can be applied to the number of observed cancer cases or deaths in the sample to obtain the number of cases or deaths attributable to smoking within each subgroup. These can then be summed to obtain the total number of cases or deaths attributable to smoking.

Analogously, the SHS exposure PAF for sex j and age-group k, it is possible to use the following formula:

$$PAF_{SHS}\,(jk) = \frac{\sum_{i=1}^{n_{jk}} RR_i - n_{jk}}{\sum_{i=1}^{n_{jk}} RR_i} \qquad (6*)$$

Where n_{jk} represents the number of never smokers of sex j and age-group k.

Also in this case, individual RRs are assigned based on overall dose-risk characteristics (SHS exposure and intensity) derived from published meta-analysis, without stratification by age or sex.

Therefore, age- and sex-specific PAFs can be applied to the number of observed cancer cases or deaths in the sample to obtain the number of cases or deaths attributable to smoking within each subgroup. These can then be summed to obtain the total number of cases or deaths attributable to smoking.

Bootstrap and Monte Carlo Simulation for Confidence Intervals Estimation

To comprehensively account for both sampling variability and uncertainty in the input parameters, a two-stage simulation approach is proposed, combining bootstrap resampling and Monte Carlo simulations.

1. Bootstrap Resampling

Generate *n* bootstrap samples from the original dataset by random sampling with replacement [1]. Each bootstrap sample represents a possible realization of the underlying population, capturing the variability due to sampling.

2. Monte Carlo Simulation within Each Bootstrap Sample

Within each bootstrap sample, perform a Monte Carlo simulation [2]. In each simulation, independently sample all input variables required to estimate the individual RRi, including RR for current smokers (RRcurr), RR for former smokers (RRex), and the variables used to calculate the modifiers xi, yi, and zi. The distributions used for these variables should reflect their respective uncertainties, as derived from the literature or empirical data.

3. Calculation of PAF

Within each iteration, calculate the individual RR for each subject and subsequently compute the PAF for the simulated sample.

4. Aggregation of Results

This process yields a total of *n* PAF estimates. The empirical distribution of these PAFs is then used to derive point estimates (e.g., the median) and 95% confidence intervals (e.g., the 2.5th and 97.5th percentiles), thus reflecting both sources of uncertainty.

Assumption of Independence: In the Monte Carlo simulation, all input variables used to estimate RRi are sampled independently. This includes RR for current and former smokers, as well as the variables used to calculate the modifiers. While this assumption simplifies the simulation process, it is unlikely to hold in reality. Modeling the joint distribution of these variables would require detailed

empirical data on their correlations, which are often unavailable or difficult to estimate reliably. In the absence of such information, assuming independence allows the simulation to proceed while still capturing a substantial portion of the uncertainty.

Choice of number of iterations: The parameter *n*, representing the total number of iterations, determines the precision and stability of the resulting estimates. If the method accounted only for sampling variability, a value of $n \geq 1000$ would generally be sufficient to ensure reliable confidence intervals in bootstrap iterations. However, since this approach also incorporates uncertainty in the input parameters through Monte Carlo simulation within each bootstrap sample, a larger number of iterations is recommended. Specifically, setting $n \geq 1000 \times 1000$ (one million iterations) allows for a more comprehensive propagation of both sources of uncertainty, resulting in smoother empirical distributions and more robust interval estimates.

By integrating both bootstrap and Monte Carlo methods, this approach enables a robust and transparent estimation of the PAF and its uncertainty, ensuring that both sampling error and parameter uncertainty are fully propagated and reflected in the final results.

Supplementary Table 1. Dose-response breast cancer RRs associated with dose-specific smoking intensity, duration, time since quitting (TSQ), and secondhand smoke (SHS) intensity [3, 4] and corresponding percent variation[a]

	Intensity (cig/day)		Duration (years)		TSQ (years)		SHS intensity (cig/day)	
Dose	RR[b]	Percent variation	RR[b]	Percent variation	RR[c]	Percent variation[d]	RR[e]	Percent variation
0	1.00	0.00	1.00	0.00	1.00	0.00	1.00	0.00
1	1.01	0.06	1.01	0.04	1.00	0.06	1.02	0.04
2	1.01	0.12	1.01	0.09	1.00	0.13	1.03	0.09
3	1.02	0.18	1.02	0.13	1.00	0.19	1.05	0.13
4	1.02	0.24	1.02	0.17	0.99	0.25	1.07	0.17
5	1.03	0.30	1.03	0.22	0.99	0.31	1.09	0.22
6	1.04	0.36	1.04	0.26	0.99	0.38	1.11	0.26
7	1.04	0.43	1.04	0.30	0.99	0.44	1.13	0.31
8	1.05	0.49	1.05	0.35	0.99	0.50	1.15	0.36
9	1.05	0.55	1.05	0.39	0.99	0.57	1.17	0.41
10	1.06	0.61	1.06	0.44	0.99	0.63	1.19	0.46
11	1.07	0.68	1.07	0.48	0.99	0.69	1.21	0.51
12	1.07	0.74	1.07	0.53	0.98	0.75	1.23	0.56
13	1.08	0.81	1.08	0.58	0.98	0.81	1.25	0.61
14	1.08	0.87	1.08	0.62	0.98	0.88	1.27	0.66
15	1.09	0.93	1.09	0.67	0.98	0.94	1.29	0.72
16	1.10	1.00	1.10	0.71	0.98	1.00	1.31	0.77
17	1.10	1.07	1.10	0.76	0.98	1.06	1.34	0.83
18	1.11	1.13	1.11	0.81	0.98	1.12	1.36	0.88
19	1.12	1.20	1.12	0.86	0.97	1.19	1.38	0.94
20	1.12	1.26	1.12	0.90	0.97	1.25	1.41	1.00
21	1.13	1.33	1.13	0.95	0.97	1.31	1.43	1.06
22	1.14	1.40	1.14	1.00	0.97	1.37	1.46	1.12
23	1.14	1.47	1.14	1.05	0.97	1.43	1.48	1.18
24	1.15	1.54	1.15	1.10	0.97	1.49	1.51	1.24
25	1.16	1.60	1.16	1.15	0.97	1.55	1.53	1.31
26	1.16	1.67	1.16	1.20	0.97	1.61	1.56	1.37
27	1.17	1.74	1.17	1.25	0.96	1.68	1.59	1.44
28	1.18	1.81	1.18	1.30	0.96	1.74	1.61	1.51
29	1.18	1.88	1.18	1.35	0.96	1.80	1.64	1.57
30	1.19	1.95	1.19	1.40	0.96	1.86	1.67	1.64
31	1.20	2.03	1.20	1.45	0.96	1.92	1.70	1.71
32	1.20	2.10	1.20	1.50	0.96	1.98	1.73	1.79
33	1.21	2.17	1.21	1.55	0.96	2.04	1.76	1.86
34	1.22	2.24	1.22	1.60	0.96	2.10	1.79	1.93
35	1.22	2.31	1.22	1.65	0.95	2.16	1.82	2.01
36	1.23	2.39	1.23	1.71	0.95	2.22	1.85	2.09
37	1.24	2.46	1.24	1.76	0.95	2.28	1.88	2.16
38	1.25	2.53	1.25	1.81	0.95	2.34	1.91	2.24

39	1.25	2.61	1.25	1.86	0.95	2.40	1.95	2.33
40	1.26	2.68	1.26	1.92	0.95	2.46	1.98	2.41
41	1.27	2.76	1.27	1.97	0.95	2.52	2.02	2.49
42	1.27	2.84	1.27	2.03	0.95	2.58	2.05	2.58
43	1.28	2.91	1.28	2.08	0.94	2.64	2.09	2.66
44	1.29	2.99	1.29	2.14	0.94	2.70	2.12	2.75
45	1.30	3.07	1.30	2.19	0.94	2.76	2.16	2.84
46	1.30	3.14	1.30	2.25	0.94	2.82	2.20	2.93
47	1.31	3.22	1.31	2.30	0.94	2.88	2.23	3.03
48	1.32	3.30	1.32	2.36	0.94	2.94	2.27	3.12
49	1.33	3.38	1.33	2.41	0.94	3.00	2.31	3.22
50	1.33	3.46	1.33	2.47	0.94	3.06	2.35	3.31
51	1.34	3.54	1.34	2.53	0.93	3.11	2.39	3.41
52	1.35	3.62	1.35	2.59	0.93	3.17	2.43	3.51
53	1.36	3.70	1.36	2.64	0.93	3.23	2.47	3.62
54	1.37	3.78	1.37	2.70	0.93	3.29	2.52	3.72
55	1.37	3.86	1.37	2.76	0.93	3.35	2.56	3.83
56	1.38	3.94	1.38	2.82	0.93	3.41	2.60	3.94
57	1.39	4.03	1.39	2.88	0.93	3.47	2.65	4.05
58	1.40	4.11	1.40	2.94	0.93	3.53	2.69	4.16
59	1.41	4.19	1.41	3.00	0.92	3.58	2.74	4.27
60	1.41	4.28	1.41	3.06	0.92	3.64	2.79	4.39
61	1.42	4.36	1.42	3.12	0.92	3.70	2.84	4.51
62	1.43	4.45	1.43	3.18	0.92	3.76	2.89	4.63
63	1.44	4.53	1.44	3.24	0.92	3.82	2.94	4.75
64	1.45	4.62	1.45	3.30	0.92	3.87	2.99	4.87
65	1.46	4.71	1.46	3.36	0.92	3.93	3.04	5.00
66	1.46	4.79	1.46	3.42	0.92	3.99	3.09	5.13
67	1.47	4.88	1.47	3.49	0.91	4.05	3.14	5.26
68	1.48	4.97	1.48	3.55	0.91	4.11	3.20	5.39
69	1.49	5.06	1.49	3.61	0.91	4.16	3.25	5.53
70	1.50	5.15	1.50	3.68	0.91	4.22	3.31	5.66
71	1.51	5.24	1.51	3.74	0.91	4.28	3.37	5.80
72	1.52	5.33	1.52	3.81	0.91	4.34	3.42	5.95
73	1.52	5.42	1.52	3.87	0.91	4.39	3.48	6.09
74	1.53	5.51	1.53	3.94	0.91	4.45	3.54	6.24
75	1.54	5.60	1.54	4.00	0.90	4.51	3.60	6.39
76	1.55	5.69	1.55	4.07	0.90	4.57	3.67	6.54
77	1.56	5.78	1.56	4.13	0.90	4.62	3.73	6.70
78	1.57	5.88	1.57	4.20	0.90	4.68	3.79	6.85
79	1.58	5.97	1.58	4.27	0.90	4.74	3.86	7.01
80	1.59	6.07	1.59	4.33	0.90	4.79	3.92	7.18
81	1.60	6.16	1.60	4.40	0.90	4.85	3.99	7.34
82	1.61	6.26	1.61	4.47	0.90	4.91	4.06	7.51
83	1.61	6.35	1.61	4.54	0.90	4.96	4.13	7.68
84	1.62	6.45	1.62	4.61	0.89	5.02	4.20	7.86
85	1.63	6.55	1.63	4.68	0.89	5.08	4.27	8.04

86	1.64	6.64	1.64	4.75	0.89	5.13	4.35	8.22
87	1.65	6.74	1.65	4.82	0.89	5.19	4.42	8.40
88	1.66	6.84	1.66	4.89	0.89	5.24	4.50	8.59
89	1.67	6.94	1.67	4.96	0.89	5.30	4.58	8.78
90	1.68	7.04	1.68	5.03	0.89	5.36	4.66	8.97
91	1.69	7.14	1.69	5.10	0.89	5.41	4.74	9.17
92	1.70	7.24	1.70	5.18	0.88	5.47	4.82	9.37
93	1.71	7.34	1.71	5.25	0.88	5.52	4.90	9.57
94	1.72	7.45	1.72	5.32	0.88	5.58	4.99	9.78
95	1.73	7.55	1.73	5.39	0.88	5.64	5.07	9.99
96	1.74	7.65	1.74	5.47	0.88	5.69	5.16	10.21
97	1.75	7.76	1.75	5.54	0.88	5.75	5.25	10.42
98	1.76	7.86	1.76	5.62	0.88	5.80	5.34	10.65
99	1.77	7.97	1.77	5.69	0.88	5.86	5.43	10.87
100	1.78	8.07	1.78	5.77	0.87	5.91	5.52	11.10

[a] Percent variation are calculated from the RR associated with the average dose value (calculated among studies from which the specific dose-response curve is derived). The average smoking intensity was calculated at 16 cigarettes per day, the average smoking duration at 22 years, the average TSQ among former smokers at 16 years, and the average exposure to SHS at 20 cig/day.

[b] RR for current vs. never smokers

[c] RR for former vs. current smokers

[d] Since the RR for TSQ among former smokers never reaches the value of the RR for former vs. current smokers (1.01) [4] the dose-response curve for TSQ is considered unreliable. Consequently, related percentage variations are not employed in estimating individual RRs (see *Criteria for Reliability of Dose–Response Curves* for further details)

[e] RR for never smokers exposed to SHS vs. never smokers not exposed to SHS

Step-by-step application of the method to estimate breast cancer cases attributable to active smoking

Step 1: Using formula (1), assign each individual in the sample a RR associated with their smoking habits.

For example, a current smoker *i* who smokes 20 cigarettes per day from 30 years will have:

$$RR_i = \{1 + [(RR_{curr} - 1) * x_i * y_i]\}$$
$$= \{1 + [(1.07 - 1) * 1.26 * 1.40]\} = 1.12$$

Where:

- RR_{curr} = 1.07 [4];
- $x_i = 1 - (\frac{RR_{im} - RR_{id}}{RR_{im} - 1}) = 1 - (\frac{RR_{i(16)} - RR_{i(20)}}{RR_{i(16)} - 1}) = 1 - (\frac{1.10 - 1.12}{1.10 - 1}) = 1.26$;
- $y_i = 1 - (\frac{RR_{dm} - RR_{dd}}{RR_{dm} - 1}) = 1 - (\frac{RR_{d(22)} - RR_{d(30)}}{RR_{d(22)} - 1}) = 1 - (\frac{1.14 - 1.19}{1.14 - 1}) = 1.40$.

$RR_{i(x)}\ and\ RR_{d(y)}$ represents 20042021the dose-specific RRs corresponding to an intensity dose x and a duration dose y, respectively.

Percent variation are calculated from the RR associated with the average dose value (calculated among studies from which the specific dose-response curve is derived). The average smoking intensity was calculated at 16 cigarettes per day and the average smoking duration at 22 years.

Dose-specific RRs are reported in Supplementary Table 1.

Please note that small differences may arise because values are shown rounded to the second decimal place.

ID	Status	RR from status	Intensity	x_i	Duration	y_i	TSQ	z_i	Individual RR
1	Never	1	0	NA	0	NA	0	NA	1.00
2	Current	1.07	20	1.26	30	1.40	0	NA	1.12
3	Former	1.08	15	0.93	24	1.10	11	0.69	1.08
…	…	…	…	…	…	…	…	…	…
54,407	Never	1	0	NA	0	NA	0	NA	1.00

Step 2: For each age group, calculate the PAF as the ratio of the predicted excess number of cancer cases due to smoking to the predicted total number of cases in the sample population, using formula (4).

$$PAF_{smoking} = \frac{(\sum_{i=1}^{n} RR_i) - n}{\sum_{i=1}^{n} RR_i}$$

Age group	$\sum_{i=1}^{n} RR_i$	n	PAF
<50	17,631.12	17,501	0.73%
50-69	18,751.60	18,269	2.57%
70+	19,061.16	18,637	2.22%

Step 3: For each age group, calculate the number of breast cancer cases attributable to smoking by multiplying the estimated smoking PAF by the number of breast cancer cases occurred.

Age group	PAF	Breast cancer cases	Breast cancer cases attributable to smoking
<50	0.74%	10,299	76
50-69	2.57%	22,758	586
70+	2.22%	24,423	543

Step 4: Calculate the total number of breast cancer cases that can be attributed to smoking by adding together the number of cases in each age group.

$$Total\ breast\ cancer\ cases\ attributable\ to\ smoking = 77 + 586 + 543 = 1{,}205$$

Step 5: Calculate the total PAF by dividing the total number of breast cancer cases attributable to smoking by the total number of breast cancer cases.

$$PAF = 1{,}205/(10{,}299 + 22{,}758 + 24{,}423) = 1{,}205/57{,}490 = 2.10\%$$

Supplementary Table 2. Sensitivity analysis of population attributable fractions (PAF) estimates for secondhand smoke (SHS) exposure using different conversion factors from minutes of exposure to cigarettes per day (4, 5, or 6 minutes per cigarette).

	Cancer cases	PAF		
		4 minutes/cigarette	5 minutes/cigarette	6 minutes/cigarette
SHS exposure				
<50 years	10,299	7.77	5.25	4.11
50-69 years	22,768	4.10	2.71	2.11
≥70 years	24,423	2.51	1.62	1.26
Total	57,490	4.08	2.70	2.11

References

1. Efron B. Bootstrap methods: Another look at the jackknife. The Annals of Statistics 1979; 7: 1-26.
2. Metropolis N, Ulam S. The Monte Carlo method. J Am Stat Assoc 1949; 44: 335-341.
3. Possenti I, Scala M, Carreras G et al. Exposure to second-hand smoke and breast cancer risk in non-smoking women: a comprehensive systematic review and meta-analysis. Br J Cancer 2024; 131: 1116-1125.
4. Scala M, Bosetti C, Bagnardi V et al. Dose-response Relationships Between Cigarette Smoking and Breast Cancer Risk: A Systematic Review and Meta-analysis. J Epidemiol 2023; 33: 640-648.

Chapter 8

Smoking-attributable burden of digestive tract cancers in Italy: a comprehensive analysis using an individual-level approach

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8.1 Abstract

Background: Digestive tract cancers represent a major health burden in Italy. To provide updated estimates of the fraction attributable to cigarette smoking, this study evaluates smoking-attributable cases, deaths, and disability-adjusted life years (DALY) for oral and pharyngeal, oesophageal, gastric, and colorectal cancers using an individual-level data (ILD) approach that incorporates detailed smoking characteristics.

Methods: We used ILD from a nationally representative Italian survey (n=104,086), which were combined with cancer-site-specific relative risks (RR) and dose-response functions from recent meta-analyses. Using the ILD approach, each survey participant was assigned a cancer-site-specific RR based on smoking status, intensity, duration, and time since quitting. Excess risks were used to compute age- and sex-stratified smoking population-attributable fractions (PAF), then applied to national cancer incidence, mortality, and DALYs data in 2022.

Results: We estimated that, in 2022, cigarette smoking accounted for 10,578 incident cases, 5,730 deaths, and 111,806 DALYs from digestive tract cancers in Italy, corresponding to PAFs of 13.6% (95% confidence interval; CI: 12.2-15.0), 14.6% (95% CI: 13.1-16.1), and 15.3% (95% CI: 14.2-16.5), respectively. The highest relative burden was observed for oral and pharyngeal cancers (PAF for incidence 34.3%, 95% CI: 30.4-38.1), followed by oesophageal (PAF for incidence 23.9%, 95% CI: 19.8-28.0), gastric (PAF for incidence 19.8%, 95% CI: 18.4-21.1), and colorectal cancers (PAF for incidence 9.0%, 95% CI: 7.1-10.9). PAFs were consistently higher among men and varied substantially by age group.

Conclusions: Cigarette smoking remains a major contributor to the burden of digestive tract cancers in Italy, accounting for nearly one-seventh of all cases, deaths, and DALYs. Differences by cancer site, sex, and age highlight the need for strengthened tobacco control measures, effective cessation support, and approaches to promote early detection in older adults.

8.2 Introduction

Digestive tract cancers, including oral cavity and pharynx, oesophagus, gastric, and colorectal cancers, account for a substantial share of the global cancer burden. In 2022, these malignancies collectively represented almost four million of new cases and nearly one-fourth of cancer-related deaths worldwide [1]. In Italy, colorectal cancer alone accounted for about 55,000 new cases and 24,000 deaths in 2023, while gastric cancer contributed roughly 13,500 cases and 10,000 deaths [2]. Cancers of the oral cavity, pharynx, and oesophagus together accounted for almost 10,000 cases and over 5,000 deaths [2]. According to the Global Burden of Disease Study, in Italy, these four cancer sites cause annually more than 700.000 disability-adjusted life years (DALY) lost [3].

Digestive tract cancers are influenced by a combination of genetic predisposition and lifestyle-related exposures [4, 5]. Among modifiable factors, diet, obesity, and alcohol consumption play an important role, particularly in the development of gastric and colorectal cancers [5, 6]. Moreover, tobacco smoking stands out as one of the most significant and well-documented risk factors across these malignancies [7]. Its impact is particularly pronounced for cancers of the oral cavity and pharynx, where a recent meta-analysis reported a relative risk (RR) of 3.58 for current smokers [8]. Substantial associations have also been observed for oesophageal cancer (RR 2.68) [9] and gastric cancer (RR 1.53) [10], while even colorectal cancer shows a modest but significant increase in risk (RR 1.14) among current smokers [11]. In addition, the risk of digestive cancer risk increases with smoking intensity and duration, and decreases progressively with time since quitting (TSQ).

Worldwide, tobacco smoking is estimated to account for almost 42% of oral cavity and pharyngeal cancers, around 35% of oesophageal cancers, and smaller but meaningful shares of gastric (11%) and colorectal cancers (5%) [3, 12]. In Italy, recent estimates show that smoking was responsible for approximately 39% of oral cavity cancers, 62% of pharyngeal cancers, and 31% of oesophageal cancers in 2020, while the attributable fraction was lower for gastric (8%) and colon (5%) and rectal (12%) cancers [13]. Despite these advances, most burden studies, including the mentioned analysis, rely on aggregated prevalence-based approaches and often use outdated RRs. In addition, these methods typically consider smoking status only, overlooking key exposure variables such as intensity, duration, and TSQ, which are known to importantly influence the risk [13].

To address these gaps, we apply a recently developed method that integrates multiple smoking-related measures at the individual level (intensity, duration, and TSQ) into the estimation process [14]. This approach enables a precise and valid calculation of population attributable fractions (PAF) by capturing heterogeneity

in exposure patterns. By applying this method to Italian data, this study aims to provide a comprehensive, precise and site-specific evaluation of burden of digestive tract cancers attributable to tobacco smoking, offering important evidence to inform national tobacco control strategies.

8.3 Methods

Materials

To estimate smoking-attributable cancer burden, we applied the Individual-Level Data (ILD) method, an approach recently developed by our group [14]. This method combines individual smoking histories, including smoking status, intensity, duration, and time since quitting (TSQ) to calculate individual-specific relative risks (RR). These individual RRs are then used to estimate population attributable fractions (PAFs) and to derive the number of smoking-attributable cases, deaths, and DALYs. To apply the ILD method for estimating cancer cases, deaths, and DALYs attributable to smoking, we used three main data sources:

- individual-level data on smoking behaviour (i.e., smoking status, intensity, duration, and TSQ) from a nationally representative sample, collected with an appropriate time lag to account for the latency between exposure and cancer onset;

- RRs of specific cancer sites associated with active smoking, as well as dose-response relationships for smoking intensity, duration, and TSQ;

- national incidence, mortality, and DALYs data of the target population.

In particular, anonymized data at individual-level on smoking status, intensity, duration, and TSQ were obtained from a nationally representative health survey conducted in 2013 by the Italian National Institute of Statistics (ISTAT) [15]. The survey included detailed information on tobacco use and exposure among 104,086 individuals aged ≥14 years. Smoking status was assessed using the question “Do you currently smoke?”. Participants who answered “Yes” were classified as current smokers, those who answered “No, but I used to smoke” were classified as former smokers, and those who answered “No, I have never smoked” were classified as never smokers. Current and former smokers were asked how many cigarettes they smoked per day (used as smoking intensity) and at what age they started smoking (used to derive smoking duration). Former smokers were also asked to report the age at which they quit smoking (used as TSQ).

RRs for specific digestive tract cancers by smoking status and dose-response functions, including smoking intensity, duration, and TSQ, were derived from the most recent and comprehensive meta-analyses available on the topics [8-11].

RRs for current and former smokers vs never smokers and full dose-response functions for smoking intensity, duration, and TSQ extracted from meta-analyses are provided in Supplementary Table 1 and 2.

The number of incident digestive tract cancer cases and deaths in Italy were retrieved from the European Cancer Information System (ECIS), which provides regularly updated estimates of cancer incidence and mortality across European countries based on population-based cancer registries and epidemiological models [2]. According to ECIS, in 2022 77,768 new cases and 39,193 deaths were estimated for digestive tract cancers in Italy. DALYs lost attributable to digestive tract cancers in Italy were obtained from the Global Burden of Disease (GBD) study [3]. Since DALYs estimates for 2022 were not available, we used 2023 values as a proxy for 2022, assuming minimal variation between consecutive years. According to GBD, in 2023 in Italy there were 727,449 DALYs for digestive tract cancers. Age- and sex-stratified incident cases, deaths, and DALYs of specific digestive tract cancers in the Italian population are reported in Supplementary Table 3.

Statistical Analysis

The details of the ILD method are described in detail in Possenti et al. [14]. In brief, the method assigns each participant a cancer-specific RR derived from a continuous dose-response function that jointly incorporates smoking intensity, duration, and, for former smokers, time since quitting. Particularly, intensity and duration contribute defining the individual's cumulative smoking exposure, which is mapped onto the dose-response curve for current smokers. For former smokers, this risk is then modified using a time since quitting decay function, which progressively reduces the excess risk according to the meta-analytic evidence for each cancer site. This approach allows us to compute a participant-specific RR that reflects their complete smoking trajectory rather than relying on broad smoking categories. Functions used to derive the individual RRs are detailed in Supplementary Box 1.

The predicted age- and sex-stratified PAFs in the sample were obtained by comparing the sum of individual RRs to the expected sum under no exposure (i.e., all RRs = 1). The PAFs were then applied to observed cancer cases, deaths, and DALYs in the target population. Uncertainty was addressed through Monte Carlo simulations [16] combined with bootstrap resampling [17].

All statistical analyses were performed using R (R version 4.4.3).

8.4 Results

Description of the sample

The analysis included a total of 104,086 Italian individuals aged 14 years and older (mean age 49.94 years, standard deviation; SD=19.64). Among these, 19.7% were current smokers, 22.1% were former smokers, and 54.0% reported they have never smoked. Among ever smokers, average smoking intensity was 13.57 cigarettes/day (SD=9.57) and average smoking duration was 24.99 years (SD=14.73). Among former smokers, average time since quitting was 16.29 years (SD=12.48). Detailed distributions stratified by age and sex are provided in Supplementary Table 4.

Smoking-attributable burden of digestive tract cancers

When considering all digestive tract cancers combined (oral and pharyngeal, oesophageal, gastric, and colorectal cancers), cigarette smoking was responsible for 10,578 (95% CIs 9,477-11,679) incident cases, 5,730 (95% CIs 5,127-6,325) deaths, and 111,806 (95% CIs 103,266-120,346) DALYs in Italy in 2022. These figures correspond to overall PAFs of 13.6% (95% CIs 12.2-15.0) for incidence, 14.6% (95% CIs 13.1-16.1) for mortality, and 15.3% (95% CIs 14.2-16.5) for DALYs (Table 1 and Figure 1).

Cancer-site-specific estimates showed that smoking had the greatest impact on oral and pharyngeal cancers, with 2,400 cases (95% CIs 2,132-2,667), 989 deaths (95% CIs 851-1,126), and 25,115 DALYs (95% CIs 22,501-27,729) attributable to smoking (PAFs: 34.3%, 32.7%, and 37.3%, respectively). For oesophageal cancer, smoking accounted for 592 (95% CIs 490-693) cases, 469 (95% CIs 373-565) deaths, and 12,299 (95% CIs 10,543-14,056) DALYs (PAFs: 23.9%, 22.4%, and 26.0%, respectively). Gastric cancer showed 2,667 (95% CIs 2,490-2,845) cases, 1,982 (95% CIs 1,844-2,120) deaths, and 36,826 (95% CIs 34,512-39,140) DALYs attributable to smoking (PAFs: 19.8%, 20.00%, and 19.2%, respectively). Finally, for colorectal cancer, smoking was responsible for 4,919 (95% CIs 3,870-5,967) cases, 2,290 (95% CIs 1,732-2,849) deaths, and 37,566 (95% CIs 29,973-45,159) DALYs (PAFs: 9.0%, 9.5%, and 8.9%, respectively).

When stratifying by sex, PAFs were consistently higher among males across all cancer sites. According to different age groups, the highest PAFs were observed in the 50-69 age group for all cancer sites in females (36.5% for oral and pharyngeal cancer, 24.9% for oesophageal cancer, 12.1% for gastric cancer, and 4.8% for colorectal cancer) and for oral and pharyngeal and oesophageal cancer in males (52.9% and 39.1%, respectively). Conversely, for gastric and colorectal cancer among males, the highest PAFs were observed in the 70+ age group

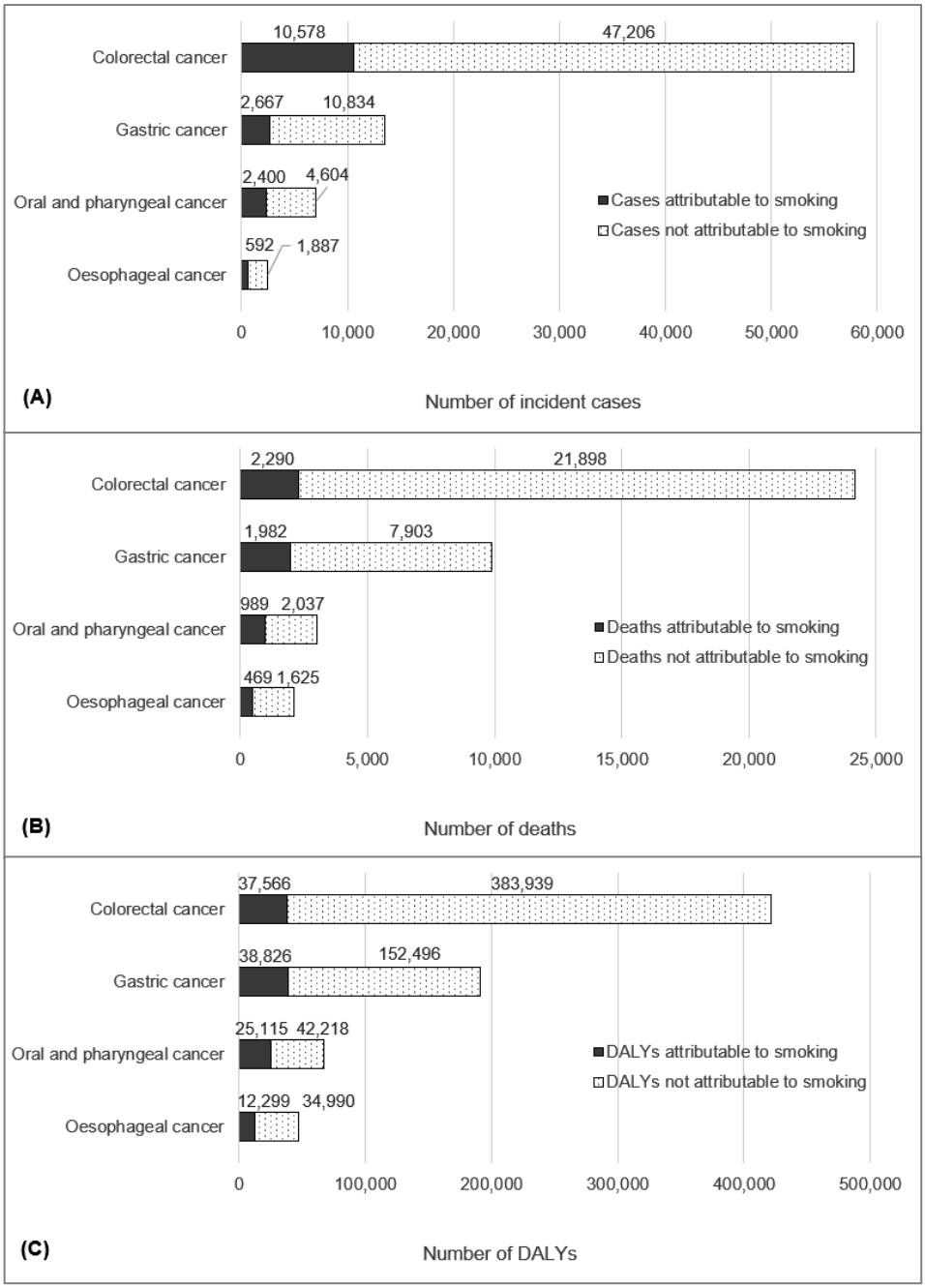
(28.9% and 15.4%, respectively). Detailed results stratified by age and sex are provided in Supplementary Table 5.

Table 1. Smoking-attributable cases, deaths, disability-adjusted life years (DALY), and population attributable fractions (PAF) for digestive tract cancers (Italy, 2022)

	Attributable cases		**Attributable deaths**		**Attributable DALYs**	
Cancer site	**n (95% CI)**	**PAF, % (95% CI)**	**n (95% CI)**	**PAF, % (95% CI)**	**n (95% CI)**	**PAF, % (95% CI)**
Oral cavity and pharynx	2,400 (2,132-2,667)	34.3 (30.4-38.1)	989 (851-1,126)	32.7 (28.1-37.2)	25,115 (22,501-27,729)	37.3 (33.4-41.2)
Oesophagus	592 (490-693)	23.9 (19.8-28.0)	469 (373-565)	22.4 (17.8-27.0)	12,299 (10,543-14,056)	26.0 (22.3-29.7)
Stomach	2,667 (2,490-2,845)	19.8 (18.4-21.1)	1,982 (1,844-2,120)	20.0 (18.7-21.4)	36,826 (34,512-39,140)	19.2 (18.0-20.5)
Colorectum	4,919 (3,870-5,967)	9.0 (7.1-10.9)	2,290 (1,732-2,849)	9.5 (7.2-11.8)	37,566 (29,973-45,159)	8.9 (7.1-10.7)
All digestive tract cancers	10,578 (9.477-11,679)	13.6 (12.2-15.0)	5,730 (5,127-6,325)	14.6 (13.1-16.1)	111,806 (103,266-120,346)	15.3 (14.2-16.5)

95% CI: 95% confidence intervals.

Figure 1. Smoking-attributable cases (panel A), deaths (panel B), and disability-adjusted life years (DALY; panel C) for digestive tract cancers (Italy, 2022)



8.5 Discussion

Our study estimated the burden of digestive tract cancers attributable to cigarette smoking in Italy in 2022. According to our results, smoking was responsible for almost a seventh of this burden, equating to over 10,000 new cases, 5,000 deaths and 100,000 DALYs lost.

Site-specific comparisons provide further insight into the burden attributable to smoking, with oral and pharyngeal cancers showing the highest relative smoking-attributable burden, followed by oesophageal, gastric, and colorectal cancers. Our estimates are broadly consistent with those reported by the Global Burden of Disease (GBD) study, which shows similar ranking of sites and PAFs values [3]. A recent analysis by Collatuzzo et al. [13] reported PAFs of approximately 39-62% for cancers of the oral cavity and pharynx, 31% for oesophageal cancer, 8% for gastric cancer and 5-12% for colorectal cancer. Compared with these figures, our estimates were slightly lower for oral and pharyngeal cancers (≈35%), similar for oesophageal (≈25%) and colorectal cancer (≈9%), and substantially higher for gastric cancer (≈20%). In general, differences between estimates may reflect different methodological approaches, including how heterogeneity in exposure and smoking patterns is accounted for, as well as different choice of RRs from meta-analyses. In particular, the marked difference for gastric cancer may be explained by the substantially lower RR for current vs never smokers used in Collatuzzo's analysis (RR = 1.25), compared with our analysis (RR = 1.53). Collatuzzo's RR is based on the StoP Project pooled-analysis [18], while ours is taken from a recent comprehensive meta-analysis [10], encompassing the Stop Project and more than 200 other observational studies and thus providing a more precise estimate. However, it should be noted that comprehensive meta-analyses incorporate evidence from around the world, including Asian populations, where RRs for cancers of the oral cavity, pharynx and oesophagus are typically lower than those reported in European studies. As a consequence, the use of globally pooled estimates may lead to an underestimation of the smoking-attributable burden when applied to a European population such as Italy.

When stratified by sex, PAFs were consistently higher among males across all cancer sites, reflecting the historically greater prevalence and intensity of smoking among men in Italy [19, 20]. In absolute terms, the numbers of attributable cases, deaths and DALYs were also higher among males. This was due to a combination of higher smoking exposure and the fact that men are more frequently affected by these cancers [2].

In females, the highest PAFs were observed in individuals aged 50-69 years across all sites, which is consistent with the later diffusion of smoking among women in Italy [21] and the consequent concentration of cumulative exposure in

that birth cohort. In males, the highest PAFs occurred in the 50-69 age group for oral and pharyngeal and for oesophageal cancers, whereas for gastric and colorectal cancers they peaked in the over-70s age group. This discrepancy likely reflects the greater reduction in risk after quitting smoking for oral, pharyngeal and oesophageal cancer compared to gastric and colorectal cancers. As older age groups include a higher proportion of male former smokers, PAFs decrease more markedly for cancers where quitting substantially lowers risk, such as oral, pharyngeal and oesophageal cancers [8, 9]. Conversely, for gastric and colorectal cancers, where the risk persists for longer after quitting, the highest PAFs for males are observed in the oldest age group [10, 11].

When comparing smoking-attributable cases, deaths, and DALYs across cancer sites, notable differences and similarities emerged. Colorectal cancer ranked first for all indicators, with substantially more cases and deaths than gastric cancer (≈5,000 cases for colorectal cancer vs. ≈2,500 cases for gastric cancer), which ranked second, yet similar DALYs (≈38,000 DALYs for colorectal cancer vs. ≈37,000 DALYs for gastric cancer). This could be due to the higher proportion of advanced-stage cases for gastric cancer, which cause greater functional impairment and symptom burden, while colorectal cancer benefits from widespread screening programs that enable earlier detection and less severe disease stages [22]. Oral and pharyngeal cancers and gastric cancer showed comparable numbers of cases (≈2,400 cases for oral and pharyngeal vs. ≈2,700 for gastric cancer), but gastric cancer had more than twice as many deaths (≈989 deaths for oral and pharyngeal vs. ≈1,982 deaths for gastric cancer), consistent with its higher mortality [23]. Finally, oesophageal cancer displayed a unique pattern, with a very similar number of cases and deaths (≈600 cases vs. ≈500 deaths), highlighting its extremely high fatality rate [24]. These contrasts illustrate how incidence, mortality, and DALYs capture different dimensions of disease burden and why all three indicators are needed for a comprehensive assessment.

Our findings have important implications for cancer prevention and control strategies. The significant impact of smoking on digestive tract cancers highlights the importance of strengthening tobacco control policies and cessation programmes. Given the high PAFs for oral, pharyngeal and oesophageal cancers, targeted interventions could significantly reduce the incidence and mortality of these cancers. Furthermore, the continued risk of gastric and colorectal cancers even after quitting smoking highlights the importance of early detection and screening in older populations. Integrating smoking cessation support into routine healthcare and cancer screening programmes could be highly beneficial in reducing both cancer incidence and long-term disability.

In the Italian context, these findings are particularly relevant. Italy was among the first European countries to adopt a comprehensive national smoke-free law with

the 2003 “Sirchia Law”, which substantially reduced exposure to second-hand smoke and contributed to lowering smoking prevalence [25]. However, since then, few significant national tobacco control measures have been introduced, and progress in taxation, cessation support, and regulation of new nicotine products has remained limited. As a result, smoking decline stopped and prevalence remains high, with approximately one in four adults still smoking cigarettes in 2024 [20].

This study has several strengths. Firstly, it uses a methodological approach that considers heterogeneity in smoking patterns by taking into account intensity, duration and time since quitting at an individual level, rather than applying uniform exposure categories. This enables more accurate estimation of risk and attributable burden, reflecting real-world variability in smoking behaviours. Secondly, the analysis is based on updated national data and provides stratification by sex and age, offering detailed insights that can inform targeted prevention strategies. Thirdly, the use of comprehensive and updated meta-analyses to derive RRs ensures that the estimates are based on the best available evidence. Finally, including multiple burden indicators (cases, deaths and DALYs) enables a comprehensive assessment of smoking's impact on digestive tract cancers.

However, some limitations should be acknowledged. Firstly, estimates rely on self-reported smoking data, which may introduce misclassification. Such misclassification may arise from recall errors, social desirability bias, or inconsistent reporting across surveys, and is generally expected to be non-differential with respect to cancer outcomes. This would likely attenuate the true associations and lead to conservative PAF estimates [26]. Secondly, residual confounding by other risk factors cannot be excluded. Alcohol consumption, dietary patterns, and socioeconomic status are all associated with both smoking and digestive tract cancer risk [27, 28], and imperfect adjustment for these factors may influence the estimated attributable fractions. However, the use of RRs derived from comprehensive meta-analyses mitigates this concern, as the majority of primary studies included in these meta-analyses adjust for the major confounders. Furthermore, the analysis focuses exclusively on cigarette smoking and does not account for other tobacco and nicotine products, nor exposure to secondhand smoke, both of which may contribute to the overall cancer burden. Additionally, DALYs were derived from modelled disability weights and life expectancy, which may vary depending on the source. Moreover, in estimating PAFs for incidence, mortality and DALYs, we used the same cancer-specific RRs derived from meta-analyses and prevalently relying on incidence data. Although separate estimates for incidence and mortality have been explored in previous works [8-11], differences were generally small and often based on a much more limited number of mortality studies, leading to greater uncertainty. Particularly,

applying incidence-based RRs to mortality could possibly yields conservative estimates, since any additional smoking-related deterioration in prognosis would increase mortality RRs rather than reduce them. Using incidence-based RRs for all three outcomes is therefore consistent with standard epidemiological practice and with established burden-of-disease approaches. Finally, as with all burden studies, causal assumptions are based on epidemiological evidence, but cannot be verified directly using the available data. Despite these limitations, the strengths of the approach enhance the validity and applicability of the findings for public health planning.

In conclusion, cigarette smoking remains a relevant factor in the burden of digestive tract cancers in Italy, accounting for almost a fifth of cases, deaths, and DALYs. The greatest impact was seen with oral and pharyngeal cancers, followed by oesophageal, gastric, and colorectal cancers, with notable differences observed by sex and age group. These findings emphasise the importance of tobacco control and cessation strategies in reducing cancer incidence and mortality, and highlight the need for an integrated approach that also addresses early detection.

8.6 Contribution to the overall thesis framework

This chapter represents the practical application of the methodological framework developed in the previous chapter. By combining individual-level risk estimates with Italian population data, it provides updated estimates of cancer incidence, mortality, and DALYs attributable to tobacco smoking, demonstrating how epidemiological evidence can be translated into meaningful public health metrics.

Beyond quantifying the current burden of tobacco-related cancers in Italy, this chapter illustrates the added value of the proposed methodology in producing more refined and context-specific burden estimates. It therefore represents the culmination of the epidemiological, behavioural, and methodological work presented throughout the thesis.

The following chapter extends the assessment of tobacco-related burden by examining its economic consequences, providing a complementary perspective on the societal impact of smoking in Italy.

8.7 References

1. Bray F, Laversanne M, Sung H et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2024; 74: 229-263.
2. European Commission. ECIS - European Cancer Information System. Estimates of cancer incidence and mortality in 2022, for all countries. Available at https://ecis.jrc.ec.europa.eu/ (last access 27/05/2025).
3. Institute for Health Metrics and Evaluation (IHME). GBD Compare. Seattle, WA: IHME, University of Washington. Available at http://vizhub.healthdata.org/gbd-compare (Accessed 19/01/2026)
4. Cai X, Li X, Liang C et al. The effect of metabolism-related lifestyle and clinical risk factors on digestive system cancers in East Asian populations: a two-sample Mendelian randomization analysis. Sci Rep 2024; 14: 9474.
5. Jin G, Lv J, Yang M et al. Genetic risk, incident gastric cancer, and healthy lifestyle: a meta-analysis of genome-wide association studies and prospective cohort study. Lancet Oncol 2020; 21: 1378-1386.
6. Murphy N, Moreno V, Hughes DJ et al. Lifestyle and dietary environmental factors in colorectal cancer susceptibility. Mol Aspects Med 2019; 69: 2-9.
7. Danpanichkul P, Suparan K, Pang Y et al. Mortality of Gastrointestinal Cancers Attributable to Smoking, Alcohol, and Metabolic Risk Factors, and its Association With Socioeconomic Development Status 2000-2021. Am J Med 2025; 138: 800-808 e802.
8. Possenti I, Miotti S, Gallus S et al. Smoking and oral and pharyngeal cancer: a meta-analysis. Oncol Rev 2025; 19: 1672607.
9. Teshima A, Possenti I, Bertacchi D et al. Evaluating the Effect of Cigarettes Smoking on Oesophageal Cancer Risk: A Systematic Review and Meta-Analysis with Dose-response Relationships European Journal of Public Health (Under Review) 2026.
10. Rota M, Possenti I, Valsassina V et al. Dose-response association between cigarette smoking and gastric cancer risk: a systematic review and meta-analysis. Gastric Cancer 2024; 27: 197-209.
11. Botteri E, Borroni E, Sloan EK et al. Smoking and Colorectal Cancer Risk, Overall and by Molecular Subtypes: A Meta-Analysis. Am J Gastroenterol 2020; 115: 1940-1949.
12. Gbd Lip O, Pharyngeal Cancer C, Cunha ARD et al. The Global, Regional, and National Burden of Adult Lip, Oral, and Pharyngeal Cancer in 204 Countries and Territories: A Systematic Analysis for the Global Burden of Disease Study 2019. JAMA Oncol 2023; 9: 1401-1416.
13. Collatuzzo G, Malvezzi M, Mangiaterra S et al. Cancers attributable to tobacco smoking in Italy in 2020. Cancer Epidemiol 2024; 92: 102623.
14. Possenti I, Gallus S, Scala M et al. Estimating cancer cases and deaths attributable to smoking and secondhand smoke exposure at national level: a methodology based on individual-level data with proof-of-concept

application to breast cancer in Italy in 2022. Lancet Regional Health Europe (Under Review) 2026.

15. ISTAT. INDAGINE STATISTICA MULTISCOPO SULLE FAMIGLIE. Condizioni di salute. Available at https://www.istat.it/microdati/condizioni-di-salute-e-ricorso-ai-servizi-sanitari-anni-1994-2005/. 2013.
16. Metropolis N, Ulam S. The Monte Carlo method. J Am Stat Assoc 1949; 44: 335-341.
17. Efron B. Bootstrap methods: Another look at the jackknife. The Annals of Statistics 1979; 7: 1-26.
18. Praud D, Rota M, Pelucchi C et al. Cigarette smoking and gastric cancer in the Stomach Cancer Pooling (StoP) Project. Eur J Cancer Prev 2018; 27: 124-133.
19. Lugo A, Asciutto R, Pacifici R et al. Smoking in Italy 2013-2014, with a focus on the young. Tumori 2015; 101: 529-534.
20. Possenti I, Scala M, Odone A et al. Prevalence of cigarette smoking and secondhand smoke exposure in Italy in 2024. Tumori 2025; 111: 478-486.
21. Di Novi C, Marenzi A. The smoking epidemic across generations, genders, and educational groups: A matter of diffusion of innovations. Econ Hum Biol 2019; 33: 155-168.
22. Cardoso R, Guo F, Heisser T et al. Proportion and stage distribution of screen-detected and non-screen-detected colorectal cancer in nine European countries: an international, population-based study. Lancet Gastroenterol Hepatol 2022; 7: 711-723.
23. Farinati F, Pelizzaro F. Gastric cancer screening in Western countries: A call to action. Dig Liver Dis 2024; 56: 1653-1662.
24. Li J, Xu J, Zheng Y et al. Esophageal cancer: Epidemiology, risk factors and screening. Chin J Cancer Res 2021; 33: 535-547.
25. Gallus S, Zuccaro P, Colombo P et al. Effects of new smoking regulations in Italy. Ann Oncol 2006; 17: 346-347.
26. Lash T, Fink A, Fox M. Misclassification. Applying Quantitative Bias Analysis to Epidemiologic Data. Statistics for Biology and Health. Springer, New York, NY 2009.
27. Ferraroni M, Negri E, La Vecchia C et al. Socioeconomic indicators, tobacco and alcohol in the aetiology of digestive tract neoplasms. Int J Epidemiol 1989; 18: 556-562.
28. Jardim SR, de Souza LMP, de Souza HSP. The Rise of Gastrointestinal Cancers as a Global Phenomenon: Unhealthy Behavior or Progress? Int J Environ Res Public Health 2023; 20.

Supplementary Materials Chapter 8

Supplementary Table 1. Relative risks (RR) and 95% confidence intervals (CI) for current and former vs never smokers extracted from meta-analyses

Cancer Site [ref]	**RR (95% CI) for current vs never smokers**	**RR (95% CI) for former vs never smokers**
Oral and pharyngeal cancer [1]	3.58 (3.03-4.24)	1.61 (1.44-1.81)
Oesophageal cancer [2]	2.68 (2.37-3.03)	1.71 (1.54-1.90)
Gastric cancer [3]	1.53 (1.44-1.62)	1.30 (1.23-1.37)
Colorectal cancer [4]	1.14 (1.10-1.18)	1.17 (1.15-1.20)

Supplementary Table 2. Dose-response functions for digestive tract cancers RRs associated with dose-specific smoking intensity, duration, and time since quitting [1-4]

Dose	Intensity (cigarettes/day)				Duration (years)				Time since quitting (years)			
	OPC	OC	GC	CC	OPC	OC	GC	CC	OPC	OC	GC	CC
1	1.13	1.10	1.04	1.01	1.11	1.03	1.01	1.00	0.93	0.96	0.99	1.01
2	1.26	1.20	1.09	1.01	1.23	1.05	1.03	1.01	0.87	0.93	0.97	1.03
3	1.42	1.32	1.13	1.02	1.36	1.08	1.04	1.01	0.80	0.89	0.96	1.04
4	1.59	1.44	1.18	1.03	1.50	1.11	1.06	1.02	0.75	0.86	0.94	1.05
5	1.78	1.57	1.22	1.03	1.66	1.13	1.07	1.02	0.70	0.82	0.93	1.07
6	1.98	1.70	1.27	1.04	1.83	1.16	1.08	1.03	0.65	0.79	0.92	1.08
7	2.19	1.84	1.32	1.05	2.01	1.19	1.10	1.03	0.60	0.76	0.90	1.08
8	2.41	1.98	1.36	1.05	2.21	1.22	1.11	1.04	0.56	0.73	0.89	1.09
9	2.65	2.13	1.41	1.06	2.42	1.25	1.13	1.04	0.52	0.71	0.88	1.09
10	2.88	2.26	1.45	1.07	2.64	1.29	1.14	1.05	0.49	0.68	0.87	1.09
11	3.11	2.40	1.49	1.08	2.88	1.32	1.16	1.05	0.45	0.65	0.85	1.09
12	3.34	2.52	1.52	1.08	3.12	1.35	1.18	1.05	0.42	0.63	0.84	1.09
13	3.56	2.64	1.55	1.09	3.38	1.39	1.19	1.06	0.39	0.60	0.83	1.08
14	3.78	2.75	1.58	1.10	3.63	1.42	1.21	1.06	0.36	0.58	0.82	1.07
15	3.98	2.85	1.61	1.11	3.89	1.46	1.22	1.07	0.34	0.56	0.81	1.06
16	4.17	2.94	1.63	1.11	4.15	1.50	1.24	1.07	0.31	0.54	0.79	1.05
17	4.34	3.01	1.65	1.12	4.41	1.54	1.26	1.08	0.29	0.52	0.78	1.04
18	4.50	3.08	1.66	1.13	4.65	1.57	1.28	1.08	0.27	0.50	0.77	1.02
19	4.65	3.13	1.68	1.14	4.89	1.61	1.29	1.09	0.25	0.48	0.76	1.01
20	4.78	3.18	1.69	1.14	5.10	1.66	1.31	1.09	0.24	0.46	0.75	0.99
21	4.89	3.21	1.69	1.15	5.30	1.70	1.33	1.10	0.22	0.44	0.74	0.97
22	4.99	3.24	1.70	1.16	5.48	1.74	1.35	1.10	0.20	0.43	0.73	0.95
23	5.08	3.25	1.70	1.17	5.63	1.79	1.36	1.11	0.19	0.41	0.72	0.94
24	5.15	3.26	1.71	1.17	5.77	1.83	1.38	1.11	0.18	0.39	0.71	0.92
25	5.22	3.26	1.71	1.18	5.88	1.88	1.40	1.12	0.16	0.38	0.70	0.90
26	5.27	3.26	1.70	1.19	5.97	1.93	1.42	1.12	0.15	0.37	0.69	0.88
27	5.31	3.25	1.70	1.20	6.03	1.98	1.44	1.13	0.14	0.35	0.68	0.87
28	5.35	3.24	1.70	1.21	6.08	2.03	1.46	1.13	0.13	0.34	0.67	0.85
29	5.38	3.23	1.70	1.21	6.10	2.08	1.48	1.14	0.12	0.32	0.66	0.83
30	5.41	3.21	1.69	1.22	6.10	2.13	1.50	1.14	0.11	0.31	0.65	0.82
31	5.43	3.20	1.69	1.23	6.08	2.19	1.52	1.15	0.11	0.30	0.64	0.80

32	5.46	3.18	1.68	1.24	6.04	2.24	1.54	1.15	0.10	0.29	0.63	0.78
33	5.49	3.17	1.68	1.25	5.98	2.30	1.56	1.16	0.09	0.28	0.62	0.77
34	5.51	3.15	1.68	1.25	5.91	2.36	1.58	1.16	0.09	0.27	0.61	0.75
35	5.54	3.14	1.67	1.26	5.83	2.42	1.60	1.17	0.08	0.26	0.60	0.74
36	5.56	3.12	1.67	1.27	5.73	2.48	1.63	1.17	0.07	0.25	0.59	0.72
37	5.59	3.11	1.67	1.28	5.62	2.54	1.65	1.18	0.07	0.24	0.59	0.71
38	5.62	3.09	1.66	1.29	5.50	2.61	1.67	1.18	0.06	0.23	0.58	0.69
39	5.64	3.08	1.66	1.30	5.38	2.67	1.69	1.19	0.06	0.22	0.57	0.68
40	5.67	3.06	1.66	1.31	5.25	2.74	1.72	1.20	0.06	0.21	0.56	0.67
41	5.70	3.05	1.65	1.31	5.12	2.81	1.74	1.20	0.05	0.20	0.55	0.65
42	5.73	3.03	1.65	1.32	4.98	2.89	1.76	1.21	0.05	0.20	0.55	0.64
43	5.75	3.02	1.64	1.33	4.85	2.96	1.79	1.21	0.04	0.19	0.54	0.63
44	5.78	3.01	1.64	1.34	4.71	3.03	1.81	1.22	0.04	0.18	0.53	0.62
45	5.81	2.99	1.64	1.35	4.57	3.11	1.84	1.22	0.04	0.17	0.52	0.60
46	5.84	2.98	1.63	1.36	4.44	3.19	1.86	1.23	0.04	0.17	0.52	0.59
47	5.86	2.96	1.63	1.37	4.31	3.27	1.89	1.23	0.03	0.16	0.51	0.58
48	5.89	2.95	1.63	1.38	4.18	3.36	1.91	1.24	0.03	0.16	0.50	0.57
49	5.92	2.93	1.62	1.39	4.06	3.44	1.94	1.24	0.03	0.15	0.49	0.56
50	5.95	2.92	1.62	1.40	3.94	3.53	1.97	1.25	0.03	0.14	0.49	0.55
51	5.98	2.91	1.62	1.41	3.82	3.62	1.99	1.26	0.02	0.14	0.48	0.53
52	6.01	2.89	1.61	1.41	3.71	3.71	2.02	1.26	0.02	0.13	0.47	0.52
53	6.04	2.88	1.61	1.42	3.60	3.81	2.05	1.27	0.02	0.13	0.47	0.51
54	6.06	2.86	1.61	1.43	3.49	3.90	2.07	1.27	0.02	0.12	0.46	0.50
55	6.09	2.85	1.60	1.44	3.39	4.00	2.10	1.28	0.02	0.12	0.45	0.49
56	6.12	2.84	1.60	1.45	3.29	4.11	2.13	1.28	0.02	0.11	0.45	0.48
57	6.15	2.82	1.59	1.46	3.19	4.21	2.16	1.29	0.02	0.11	0.44	0.47
58	6.18	2.81	1.59	1.47	3.10	4.32	2.19	1.29	0.02	0.11	0.43	0.46
59	6.21	2.80	1.59	1.48	3.01	4.43	2.22	1.30	0.01	0.10	0.43	0.46
60	6.24	2.78	1.58	1.49	2.92	4.54	2.25	1.31	0.01	0.10	0.42	0.45
61	6.27	2.77	1.58	1.50	2.83	4.66	2.28	1.31	0.01	0.09	0.41	0.44
62	6.30	2.76	1.58	1.51	2.75	4.78	2.31	1.32	0.01	0.09	0.41	0.43
63	6.33	2.74	1.57	1.52	2.67	4.90	2.34	1.32	0.01	0.09	0.40	0.42
64	6.36	2.73	1.57	1.53	2.59	5.03	2.37	1.33	0.01	0.08	0.40	0.41
65	6.39	2.72	1.57	1.54	2.51	5.15	2.41	1.34	0.01	0.08	0.39	0.40
66	6.42	2.70	1.56	1.55	2.44	5.29	2.44	1.34	0.01	0.08	0.39	0.40
67	6.45	2.69	1.56	1.56	2.37	5.42	2.47	1.35	0.01	0.07	0.38	0.39
68	6.48	2.68	1.56	1.57	2.30	5.56	2.51	1.35	0.01	0.07	0.38	0.38
69	6.52	2.66	1.55	1.58	2.23	5.70	2.54	1.36	0.01	0.07	0.37	0.37
70	6.55	2.65	1.55	1.59	2.16	5.85	2.58	1.37	0.01	0.07	0.36	0.37
71	6.58	2.64	1.55	1.61	2.10	6.00	2.61	1.37	0.01	0.06	0.36	0.36
72	6.61	2.63	1.54	1.62	2.04	6.15	2.65	1.38	0.01	0.06	0.35	0.35
73	6.64	2.61	1.54	1.63	1.98	6.31	2.68	1.38	0.01	0.06	0.35	0.34
74	6.67	2.60	1.54	1.64	1.92	6.47	2.72	1.39	0.00	0.06	0.34	0.34
75	6.70	2.59	1.53	1.65	1.86	6.63	2.76	1.40	0.00	0.05	0.34	0.33
76	6.74	2.58	1.53	1.66	1.81	6.80	2.79	1.40	0.00	0.05	0.33	0.32
77	6.77	2.56	1.53	1.67	1.75	6.98	2.83	1.41	0.00	0.05	0.33	0.32
78	6.80	2.55	1.52	1.68	1.70	7.15	2.87	1.42	0.00	0.05	0.32	0.31
79	6.83	2.54	1.52	1.69	1.65	7.34	2.91	1.42	0.00	0.05	0.32	0.30
80	6.87	2.53	1.52	1.70	1.60	7.52	2.95	1.43	0.00	0.05	0.32	0.30
81	6.90	2.52	1.51	1.72	1.55	7.72	2.99	1.43	0.00	0.04	0.31	0.29
82	6.93	2.50	1.51	1.73	1.51	7.91	3.03	1.44	0.00	0.04	0.31	0.29
83	6.97	2.49	1.51	1.74	1.46	8.12	3.07	1.45	0.00	0.04	0.30	0.28
84	7.00	2.48	1.50	1.75	1.42	8.32	3.11	1.45	0.00	0.04	0.30	0.28
85	7.03	2.47	1.50	1.76	1.38	8.54	3.15	1.46	0.00	0.04	0.29	0.27
86	7.07	2.46	1.50	1.77	1.34	8.75	3.20	1.47	0.00	0.04	0.29	0.26
87	7.10	2.44	1.49	1.79	1.30	8.98	3.24	1.47	0.00	0.03	0.29	0.26
88	7.13	2.43	1.49	1.80	1.26	9.21	3.28	1.48	0.00	0.03	0.28	0.25
89	7.17	2.42	1.49	1.81	1.22	9.44	3.33	1.49	0.00	0.03	0.28	0.25
90	7.20	2.41	1.48	1.82	1.19	9.68	3.37	1.49	0.00	0.03	0.27	0.24
91	7.24	2.40	1.48	1.83	1.15	9.93	3.42	1.50	0.00	0.03	0.27	0.24
92	7.27	2.39	1.48	1.85	1.12	10.18	3.47	1.51	0.00	0.03	0.27	0.23

93	7.31	2.37	1.47	1.86	1.09	10.44	3.51	1.51	0.00	0.03	0.26	0.23
94	7.34	2.36	1.47	1.87	1.05	10.71	3.56	1.52	0.00	0.03	0.26	0.23
95	7.38	2.35	1.47	1.88	1.02	10.99	3.61	1.53	0.00	0.03	0.25	0.22
96	7.41	2.34	1.46	1.90	0.99	11.27	3.66	1.53	0.00	0.02	0.25	0.22
97	7.45	2.33	1.46	1.91	0.96	11.55	3.71	1.54	0.00	0.02	0.25	0.21
98	7.48	2.32	1.46	1.92	0.93	11.85	3.76	1.55	0.00	0.02	0.24	0.21
99	7.52	2.31	1.45	1.94	0.91	12.15	3.81	1.55	0.00	0.02	0.24	0.20
100	7.56	2.30	1.45	1.95	0.88	12.46	3.86	1.56	0.00	0.02	0.24	0.20

CC: colorectal cancer; OC: oesophageal cancer; OPC: oral and pharyngeal cancer; GC: gastric cancer.

Supplementary Box 1. Functions used to derive cancer-site specific individual relative risks (RRi) [5]

Never smokers	$RR_i = 1$
Current smokers	$RR_i = \{1 + [(RR_{curr} - 1) * x_i * y_i]\}$
Former smokers	$RR_i = \{1 + [(RR_{curr} - 1) * x_i * y_i]\} * \left\{1 - \left[\left(1 - \frac{RR_{ex}}{RR_{curr}}\right) * z_i\right]\right\}$

where:

- RR_{curr} is the RR for current vs. never smokers
- RR_{ex} is the RR for former vs. never smokers
- x_i is the percent variation of RR of dose-specific smoking intensity for current smokers (RR_{id}, obtained from the dose-risk curve) from the RR associated with the mean smoking intensity value (RR_{im}, calculated among studies from which the intensity curve is derived)

$$x_i = 1 - (\frac{RR_{im} - RR_{id}}{RR_{im} - 1})$$

- y_i is the percent variation of RR of dose-specific smoking duration for current smokers (RR_{dm}, obtained from the dose-risk curve) from the RR associated with the mean smoking duration value (RR_{dd}, calculated among studies from which the intensity curve is derived)

$$y_i = 1 - \left(\frac{RR_{dm} - RR_{dd}}{RR_{dm} - 1}\right)$$

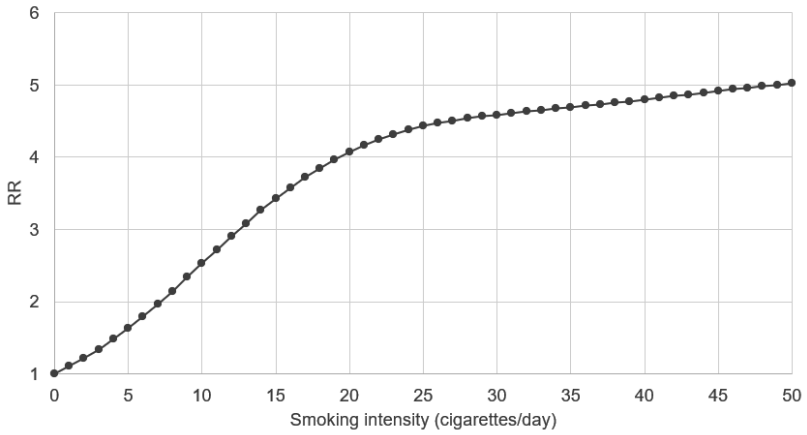
- z_i is the percent variation of RR of dose-specific time since quitting for former smokers (RR_{tm}, obtained from the dose-risk curve) from the RR associated

with the mean time since quitting value (RR_{td}calculated among studies from which the time since quitting curve is derived)

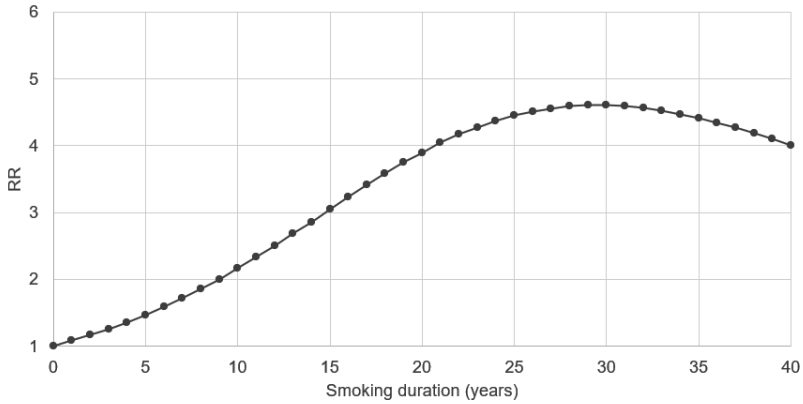
$$z_i = 1 - \left(\frac{RR_{tm} - RR_{td}}{RR_{tm} - 1}\right)$$

To facilitate the interpretation of the individual-level dose-response function used in the ILD method, we provide, as an example, graphical representations of how the RR of oral and pharyngeal cancer varies as a function of smoking intensity, duration, and time since quitting. These plots are based on the same exposure-response equations described above and illustrate how each smoking dimension contributes to the individual RR while holding the other dimensions constant.

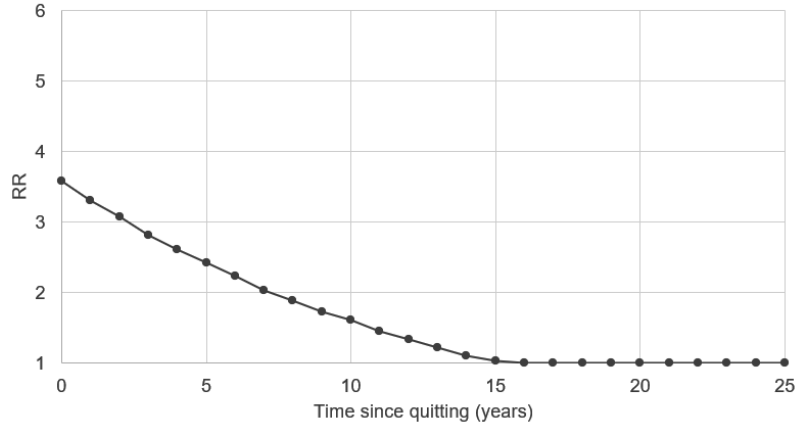
Supplementary Figure 1. Individual relative risk (RR) of oral and pharyngeal cancer for current smokers as a function of smoking intensity (at fixed smoking duration values)



Supplementary Figure 2. Individual relative risk (RR) of oral and pharyngeal cancer for current smokers as a function of smoking duration (at fixed smoking intensity values)



Supplementary Figure 3 - Individual relative risk (RR) of oral and pharyngeal cancer for former smokers as a function of time since quitting (at fixed smoking intensity and duration values)



Supplementary Table 3. Number of incident cases, deaths and disability-adjusted life years (DALY), stratified by sex and age-group, for each specific site of digestive tract cancers. Italy (2022)

	Incident cases [6]			**Deaths [6]**			**DALYs [7]**		
	Males	Females	Total	Males	Females	Total	Males	Females	Total
Oral and pharyngeal cancer									
<50 years	512	183	695	111	36	147	4550	1,832	6,382

50-69 years	2,212	741	2,953	839	251	1,090	26,164	8,252	34,416
≥70 years	1,709	1,647	3,356	949	840	1,789	16,434	10,101	26,535
Total	4,433	2,571	7,004	1,899	1,127	3,026	47,148	20,185	67,333
Oesophageal cancer									
<50 years	76	24	100	55	9	64	2,658	633	3,291
50-69 years	772	242	1,014	547	150	697	18,388	4,420	22,808
≥70 years	889	476	1,365	862	471	1,333	14,647	6,543	21,190
Total	1,737	742	2,479	1,464	630	2,094	35,693	11,596	47,289
Gastric cancer									
<50 years	191	165	356	137	94	231	8,064	5,732	13,796
50-69 years	2,281	1,193	3,474	1,324	646	1,970	45,559	23,678	69,237
≥70 years	5,256	4,415	9,671	4,227	3,457	7,684	62,688	45,601	108,289
Total	7,728	5,773	13,501	5,688	4,197	9,885	116,311	75,011	191,322
Colorectal cancer									
<50 years	1,124	1,023	2,147	270	224	494	14,333	10,978	25,311
50-69 years	9,475	7,382	16,857	2,559	1,928	4,487	89,917	60,510	150,427
≥70 years	18,626	17,154	35,780	10,153	9,054	19,207	132,757	113,010	245,767
Total	29,225	25,559	54,784	12,982	11,206	24,188	237,007	184,498	421,505

Supplementary Table 4. Smoking characteristics of the study sample of individuals aged ≥14 years (n = 104,086), stratified by sex and age groups (Italy, 2013) [8]

	Age ≤40 years (n=35,183)	**Age 41-60 years (n=35,572)**	**Age >60 years (n=33,331)**	**Total (n=104,086)**
Males				
Never smokers, n (%)	10,006 (57.2)	6,683 (38.6)	4,713 (32.1)	21,402 (39.3)
Former smokers, n (%)	2,208 (12.6)	5,354 (30.9)	7,697 (52.4)	15,259 (28.0)
Current smokers, n (%)	5,468 (31.3)	5,266 (30.4)	2,284 (15.5)	13,018 (23.9)
Mean intensity in cigarettes/day (SD) [a]	12.24 (7.88)	16.04 (9.77)	17.90 (11.5)	15.65 (10.20)
Mean smoking duration in years (SD) [a]	12.09 (6.79)	25.91 (10.40)	36.51 (14.71)	25.96 (14.86)
Mean TSQ smoking in years (SD) [b]	4.92 (4.63)	14.10 (9.37)	22.76 (13.07)	17.14 (12.69)
Females				
Never smokers, n (%)	12,453 (71.2)	10,905 (59.7)	13,897 (74.6)	37,255 (68.5)
Former smokers, n (%)	1,970 (11.3)	3,582 (19.6)	3,231 (17.3)	8,783 (16.1)
Current smokers, n (%)	3,078 (17.6)	3,782 (20.7)	1,509 (8.1)	8,369 (15.4)
Mean intensity in cigarettes/day (SD) [a]	9.20 (6.41)	11.36 (7.51)	11.14 (8.20)	10.67 (7.47)

Mean smoking duration in years (SD) [a]	11.17 (6.46)	24.63 (11.02)	34.36 (15.19)	23.40 (14.36)
Mean TSQ smoking in years (SD) [b]	5.03 (4.77)	14.80 (9.79)	20.80 (13.27)	14.82 (11.99)
Total				
Never smokers, n (%)	22,459 (64.3)	17,588 (49.5)	18,610 (66.3)	58,657 (54.0)
Former smokers, n (%)	4,178 (12.0)	8,936 (25.1)	10,928 (39.5)	24,042 (22.1)
Current smokers, n (%)	8,546 (24.5)	9,048 (25.4)	3,793 (13.7)	21,387 (19.7)
Mean intensity in cigarettes/day (SD) [a]	11.03 (7.48)	14.11 (9.20)	15.70 (10.98)	13.57 (9.57)
Mean smoking duration in years (SD) [a]	11.72 (6.68)	24.38 (10.68)	35.82 (14.90)	24.99 (14.73)
Mean TSQ smoking in years (SD) [b]	4.97 (4.70)	14.38 (9.55)	22.18 (13.16)	16.29 (12.48)

SD: standard deviation; TSQ: time since quitting;

[a] among ever smokers (i.e., current and former smokers combined);

[b] among former smokers;

No missing values were registered for smoking status and time since quitting, while 399 missing values were registered for smoking intensity and 230 missing values were registered for smoking duration.

Supplementary Table 5. Smoking-attributable number of cases, deaths, disability-adjusted life years (DALY), and population attributable fractions (PAF) for digestive tract cancers stratified by sex and age groupa (Italy, 2022)

Cancer site		PAF (95 % CI)	Cases (95 % CI)	Deaths (95 % CI)	DALYS (95 % CI)
Oral and pharyngeal cancer	Males				
	<50	32.9 (27.8-38.0)	168 (142-195)	36 (31-42)	1,495 (1,264-1,730)
	50-69	52.9 (47.5-58.2)	1,170 (1,050-1,286)	444 (398-488)	1,3836 (12,417-15214)
	70+	30.2 (18.3-43.6)	516 (313-745)	286 (174-414)	4,960 (3,011-7,164)
	Total	41.8 (36.2-47.4) [b]	1,854 (1,606-2,101)	767 (638-895)	20,290 (17,776-22,805)
	Females				
	<50	17.6 (14.3-21.2)	32 (26-39)	6 (5-8)	322 (262-387)
	50-69	36.5 (31.4-41.7)	270 (232-309)	91 (79-105)	3,008 (2,589-3,440)
	70+	14.8 (10.0-21.3)	244 (164-351)	124 (84-179)	1,495 (1,008-2,151)
	Total	21.2 (17.3-25.2) [b]	546 (445-647)	222 (173-271)	4,825 (4,109-5,540)
Oesophageal cancer	Males				
	<50	22.2 (18.9-25.5)	17 (14-19)	12 (10-14)	590 (503-678)
	50-69	39.1 (35-43.4)	302 (270-335)	214 (192-237)	7,195 (6,438-7,982)
	70+	18.9 (9.8-31)	168 (87-275)	163 (85-267)	2,764 (1,441-4,535)
	Total	28.0 (22.3-33.7) [b]	487 (387-586)	389 (295-483)	10,549 (8,818-12,280)
	Females				
	<50	11 (9.2-12.9)	3 (2-3)	1 (1-1)	70 (58-82)
	50-69	24.9 (21.6-28.4)	60 (52-69)	37 (32-43)	1,101 (955-1,257)
	70+	8.9 (5.6-13.5)	42 (27-64)	42 (26-64)	580 (366-885)
	Total	14.2 (11.4-16.9) [b]	105 (85-126)	80 (61-99)	1,751 (1,450-2,051)
Gastric cancer	Males				
	<50	7.6 (6.5-8.8)	14 (12-17)	10 (9-12)	611 (522-706)
	50-69	22.1 (19.5-24.7)	504 (445-563)	292 (259-327)	10,064 (88,98-11,253)
	70+	28.9 (26.1-31.9)	1,521 (1,370-1,677)	1,223 (1,102-1,349)	18,142 (16,336-20,004)
	Total	26.4 (24.3-28.5)	2,039 (1,875-2,204)	1,526 (1,398-1,654)	28,817 (26,636-30,998)
	Females				
	<50	3.8 (3.2-4.4)	6 (5-7)	4 (3-4)	217 (183-251)
	50-69	12.1 (11.3-14.9)	144 (135-178)	78 (73-96)	2,858 (2,685-3,523)

	70+	10.8 (9.5-12.3)	478 (418-543)	374 (327-425)	4,934 (4,314-5,609)
	Total	10.9 (9.7-12)	628 (562-694)	456 (405-506)	8,009 (7,237-8,781)
Colorectal cancer	Males				
	<50	2.9 (2.4-3.5)	33 (27-40)	8 (6-10)	419 (341-506)
	50-69	10.1 (7.9-12.7)	957 (747-1,206)	258 (202-326)	9,082 (7,085-11,446)
	70+	15.4 (10.5-21.2)	2,870 (1,959-3,941)	1,565 (1,068-2,148)	20,458 (13,966-28,091)
	Total	13.2 (9.7-16.7) [b]	3,860 (2,843-4,877)	1,831 (1,287-2,375)	29,958 (22,566-37,350)
	Females				
	<50	1.4 (1.2-1.6)	14 (12-17)	3 (3-4)	154 (133-180)
	50-69	4.8 (3.8-6.2)	357 (281-460)	93 (73-120)	2,923 (2,305-3,770)
	70+	4 (2.9-5.7)	688 (503-979)	363 (265-517)	4,532 (3,311-6,453)
	Total	4.1 (3.1-5.1) [b]	1,059 (804-1,313)	459 (331-587)	7,608 (5,875-9,341)

95% CI. 95% Confidence intervals.

[a] The age groups used to estimate PAFs and attributable cases differ in order to account for the latency period. PAFs were calculated from smoking data extracted from the sample stratified by the following age groups: ≤40 years, 41-60 years, and >60 year; [b] Total PAFs non-stratified by age group are reported for incident cases.

References

1. Possenti I, Miotti S, Gallus S et al. Smoking and oral and pharyngeal cancer: a meta-analysis. Oncol Rev 2025; 19: 1672607.
2. Teshima A, Possenti I, Bertacchi D et al. Evaluating the Effect of Cigarettes Smoking on Oesophageal Cancer Risk: A Systematic Review and Meta-Analysis with Dose-response Relationships European Journal of Public Health (Under Review) 2026.
3. Rota M, Possenti I, Valsassina V et al. Dose-response association between cigarette smoking and gastric cancer risk: a systematic review and meta-analysis. Gastric Cancer 2024; 27: 197-209.
4. Botteri E, Borroni E, Sloan EK et al. Smoking and Colorectal Cancer Risk, Overall and by Molecular Subtypes: A Meta-Analysis. Am J Gastroenterol 2020; 115: 1940-1949.
5. Possenti I, Gallus S, Scala M et al. Estimating cancer cases and deaths attributable to smoking and secondhand smoke exposure at national level: a methodology based on individual-level data with proof-of-concept application to breast cancer in Italy in 2022. Lancet Regional Health Europe (Under Review) 2026.
6. European Commission. ECIS - European Cancer Information System. Estimates of cancer incidence and mortality in 2022, for all countries. Available at https://ecis.jrc.ec.europa.eu/ (last access 27/05/2025).
7. Institute for Health Metrics and Evaluation (IHME). GBD Compare. Seattle, WA: IHME, University of Washington. Available at http://vizhub.healthdata.org/gbd-compare (Accessed 19/01/2026)
8. ISTAT. INDAGINE STATISTICA MULTISCOPO SULLE FAMIGLIE. Condizioni di salute. Available at https://www.istat.it/microdati/condizioni-di-salute-e-ricorso-ai-servizi-sanitari-anni-1994-2005/. 2013.

Chapter 9

Analysis of the direct economic impact of smoking-related hospitalisations in Italy

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9.1 Abstract

Introduction: Tobacco-related diseases have a substantial economic impact in terms of medical expenses, loss of productivity, and premature death. Tobacco use is estimated to be responsible for more than 90,000 deaths each year in Italy. We aimed to evaluate the annual direct economic impact on the National Health System of hospitalisations attributable to tobacco smoking in Italy.

Methods: We analysed data from all the hospitalisations of patients aged 30 and over occurred in Italy for 12 selected tobacco-related diseases during 2018. These diseases included: oropharyngeal cancer, oesophageal cancer, gastric cancer, lung cancer, pancreatic cancer, bladder cancer, laryngeal cancer, ischaemic heart disease, stroke, disease of arteries, arterioles, and capillaries, pneumonia and influenza, and chronic obstructive pulmonary disease. We obtained information on 984,322 hospital discharge records, which included the direct costs of each hospitalisation. Using relative risk estimates from the scientific literature, we computed the population attributable fraction for various tobacco-related diseases to estimate the economic impact attributable to tobacco smoking.

Results: One third of all hospitalisations occurred in 2018 in Italy among people aged 30 and over for 12 tobacco-related diseases were found to be attributable to smoking, accounting for a total cost of €1.64 billion. Among the diseases considered, those with the highest expenditures attributable to tobacco smoking were ischaemic heart disease, cerebrovascular disease, and lung cancer, accounting for €556, €290, and €229 million, respectively.

Conclusions: Tobacco has a substantial economic impact in Italy, accounting for around 6% of the total cost of hospitalisations in 2018. This figure is expected to be largely underestimated due to several conservative assumptions adopted in the statistical analyses. It is imperative to prioritize comprehensive tobacco control measures to counteract the huge healthcare costs due to tobacco smoking.

9.2 Introduction

Tobacco smoke contains over 7,000 chemicals, of which at least 250 are known to be harmful for health and 69 are known carcinogens [1,2]. Despite widespread knowledge of the diseases caused by tobacco smoking, including cancer, ischaemic heart disease (IHD), stroke, and chronic obstructive pulmonary disease (COPD), it remains the main avoidable risk factor, representing a serious public health problem with millions of people continuing to smoke globally [3].

Tobacco smoking is the second leading cause for premature death and disability worldwide, with an estimated 8 million deaths per year attributable to its use, including more than 1 million deaths attributable to exposure to secondhand smoke (SHS) [3,4]. It is estimated that there were more than 100 million tobacco-related deaths worldwide in the 20th century, and if current trends continue, the projected number of tobacco-related deaths in the 21st century could reach 1 billion [5].

The global economic expenditure attributable to tobacco smoking, which includes both direct health expenditure and indirect costs from productivity loss, is estimated at $1.4 trillion per year, or 1.8% of global gross domestic product (GDP) [4,6]. Global health expenditure attributable to tobacco-related diseases was calculated at $422 billion in 2012, representing 5.7% of global health expenditure [6]. The economic cost of tobacco smoking in the United States exceeded $600 billion in 2018, including more than $230 billion in direct healthcare expenditures and more than $370 billion in indirect expenditures due to productivity loss. Of these indirect costs, $185 billion were due to smoking-related illnesses, $180 billion to smoking-related premature deaths, and $7 billion to premature deaths from SHS exposure [1,7-9].

In Italy it is estimated that 96,000 deaths per year are attributable to tobacco smoking, representing 15% of all deaths (20.6% of all deaths in men and 7.9% of all deaths in women) [10]. It has also been estimated that, without the implementation of effective tobacco control measures, nearly 300,000 lives would be prematurely lost from smoking by 2040 [11]. Smoking prevalence in Italy has been declining for a long time, but from 2013 the decrease has faltered and there has been a worrying shift in the trend, with the prevalence of current smokers rising up to 24.2% in 2022, the first increase since 2009 [3,12]. The rise in smoking prevalence is partly due to the lack of adoption of effective tobacco control policies in Italy [13] and to the introduction of novel nicotine-containing products, such as electronic cigarettes and heated tobacco products [14]. These novel products, which have become extremely popular in Italy, particularly among younger people, have obstructed tobacco control, leading to a renormalisation of the smoking habit [14,15].

In Italy, healthcare services are provided by both public and private hospitals. Public hospitals are funded and managed by the government, offering public medical services to all citizens and residents, typically free of charge or with minimal out-of-pocket expenses. The cost of treatment in public hospitals is covered by the National Health System, ensuring universal access to healthcare services. In contrast, private hospitals, alongside public treatments covered by the National Health System, may offer private higher-cost treatment options, often with more amenities and comfort, but patients bear the full cost unless covered by private insurance.

This article examines the direct economic impact of tobacco-related hospitalisations on the National Health System in Italy. Previous information on smoking-related expenditure in Italy is limited. The most recent data on the issue are from 2009 and show that smoking-related diseases account for 6.3% of the total expenditure in the Italian National Health System [16].

9.3 Methods

The data used in this study were provided by the Italian Ministry of Health and were extracted from the Italian National Hospital Discharge Database (Hospital Discharge Records – Schede di Dimissione Ospedaliera, SDO), an electronic database with complete coverage of discharges from all public and private hospitals in Italy. Hospital discharge reports from the SDO were anonymised and included relevant information from the patients' medical records, including personal data (i.e., sex, date and place of birth, and region of residence), organisational arrangements of the stay (i.e., admission unit, months of hospitalisation and discharge, length of stay, and cost of the hospitalisation), and clinical information (e.g., main diagnosis, five secondary diagnoses, and discharge modalities).

Hospitalisation costs were expressed in euros and calculated according to the Diagnosis Related Groups (DRG) system used by the Italian National Health Service. Main and secondary diagnoses were classified according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) [17].

The data provided by the Italian National Health Service covered all hospitalisations in 2018 for patients aged 30 years and older with one of 14 selected diseases as their main diagnosis. We excluded two of the selected diseases (peptic ulcer and renal pelvic cancer), resulting in the following 12 tobacco-related diseases: oropharyngeal cancer (ICD-9-CM: 141, 143-146, 148, 149), oesophageal cancer (150), gastric cancer (151), lung cancer (162),

pancreatic cancer (157), bladder cancer (188), laryngeal cancer (161), IHD (410-414), stroke (430-438), diseases of arteries, arterioles, and capillaries (440-448, hereafter referred to as arteriosclerosis), pneumonia and influenza (480-487), and COPD (490-492, 496). In addition, hospital discharge reports with any tobacco-related cancer as a secondary diagnosis and a cancer-related treatment as main diagnosis (e.g., chemotherapy or radiotherapy) were also included in the analyses. This exception was based on the recognition that the costs associated with these treatments were directly attributable to the underlying tobacco-related cancer, registered as secondary diagnosis.

The number of hospitalisations and total costs were obtained for each of the 12 tobacco-related diseases considered in this study. To compute each disease-specific Population Attributable Fraction (PAF), the following formula was applied to each sex and age subgroup [18]:

$$PAF = \frac{((p0 + p1 * RR1 + p2 * RR2) - 1)}{(p0 + p1 * RR1 + p2 * RR2)}$$

where p0, p1, and p2 represent the prevalence of never smokers, current smokers, and former smokers, respectively, and RR1 and RR2 are the disease-specific relative risks (RR) for current smokers and former smokers, respectively, compared with never smokers.

Data on the prevalence of never, former, and current smokers in each sex and age subgroup were obtained from the 2003 survey conducted by the Italian National Institute of Statistics (ISTAT) and are shown in *Supplementary Table 1* [19]. We assumed a 15-year lag between smoking and the onset of tobacco-related disease because of the expected long latency of several diseases, including cancer [20]. Disease-specific RRs for current and former smokers compared with never smokers were derived from previously conducted meta-analyses and are detailed in *Supplementary Table 2*. Additionally, sensitivity analyses were performed using different RRs, derived from a pooled analysis [21].

The number of hospitalisations and costs attributable to tobacco smoking were therefore calculated using the following formulas:

$$Attributable\ hospitalizations = \sum_i \sum_j \sum_k PAF_{ijk} * number\ of\ hospitalizations_{ijk}$$

$$Attributable\ costs = \sum_i \sum_j \sum_k PAF_{ijk} * total\ costs_{ijk}$$

Where i stands for sex, j for age groups, and k for specific disease.

Analyses were performed using STATA, version 17 (StataCorp, College Station, Texas 77845, USA).

9.4 Results

A total of 984,322 hospital discharge reports were included in the analysis, representing all the hospitalisations of patients aged 30 and over with one of the 12 considered tobacco-related diseases in Italy in 2018. These hospitalisations had a cumulative cost of €4,937 billion. Supplementary Figure 1 shows the hospitalisation rates per million inhabitants by main diagnosis. Among these tobacco-related diseases, the most frequent hospitalisations were for IHD, stroke, and pneumonia and influenza, accounting for 263,214, 251,090, and 135,782 hospitalisations, respectively (Table 1). Among tobacco-related cancers, bladder cancer accounted for the highest number of hospitalisations (77,961), followed by lung cancer (68,284 hospitalisations) and pancreatic cancer (24,507 hospitalisations).

Table 1. Hospitalisations and expenditures, total and attributable to smoking, stratified by disease (Italy, 2018)

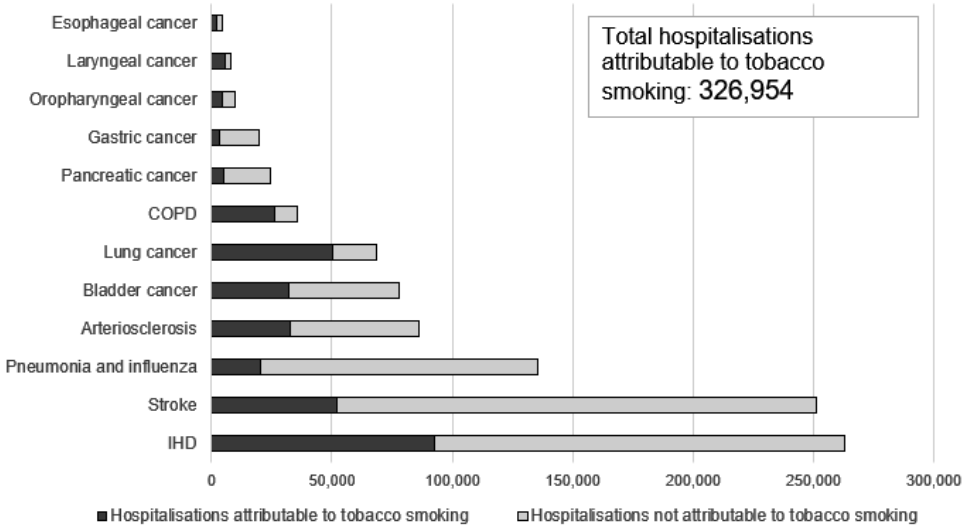
Disease	Total number of hospitalisations	PAF hospitalisations	Attributable hospitalisations	Total expenditure	PAF expenditure	Attributable expenditure
Oropharyngeal cancer	9,742	43.72%	4,259	€ 46,308,439	43.87%	€ 20,313,925
Esophageal cancer	4,505	41.76%	1,881	€ 22,684,856	41.91%	€ 9,507,821
Gastric cancer	19,869	17.69%	3,514	€ 118,904,756	17.63%	€ 20,962,538
Pancreatic cancer	24,507	19.52%	4,783	€ 123,040,960	19.67%	€ 24,199,247
Laryngeal cancer	7,754	74.77%	5,798	€ 42,172,339	74.70%	€ 31,504,228

Lung cancer	68,284	73.67%	50,308	€ 310,464,131	73.76%	€ 228,996,823
Bladder cancer	77,961	41.55%	32,396	€ 252,928,438	41.69%	€ 105,201,584
IHD	263,214	35.29%	92,900	€ 1,544,608,137	36.02%	€ 556,423,694
Stroke	251,090	20.70%	51,986	€ 1,347,555,704	21.53%	€ 290,079,568
Arteriosclerosis	86,132	37.76%	32,523	€ 560,205,936	38.67%	€ 216,617,474
Pneumonia and influenza	135,782	14.80%	20,102	€ 481,093,909	15.01%	€ 72,201,303
COPD	35,482	74.70%	26,504	€ 87,645,877	75.41%	€ 66,096,567
Total	984,322	33,27%	326,954	€ 4,937,613,482	33.31%	€ 1,642,104,772

Attributable expenditure: expenditure (€) attributable to tobacco smoking, Attributable hospitalisations: number of hospitalisations attributable to tobacco smoking, COPD: chronic obstructive pulmonary disease, IHD: ischaemic heart disease, PAF: Population Attributable Fraction

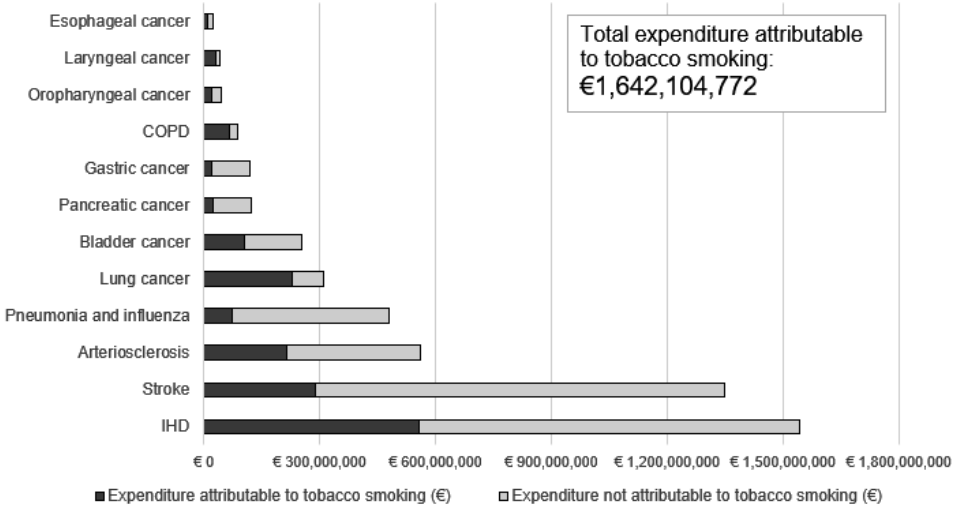
Out of 984,322 hospitalisations, 326,954 were found to be directly attributable to tobacco smoking, accounting for 33% of the total number of hospitalisations considered (Table 1). Among the tobacco-related diseases considered, the highest PAF values, which represent the proportions of hospitalisations for the disease attributable to tobacco smoking, were observed for laryngeal cancer, with smoking contributing to approximately 75% of the reported hospitalisations, followed by COPD (75%) and lung cancer (74%). Among all hospitalisations for the considered tobacco-related cancers, 48% were found to be attributable to tobacco smoking. The highest number of hospitalisations attributable to tobacco smoking was observed for IHD, with 92,900 hospitalisations, followed by stroke with 51,986 hospitalisations, and lung cancer with 50,308 hospitalisations (Figure 1). Tobacco smoking was responsible for 40% and 22% of the considered hospitalisations in men and women, respectively, while in both sexes the age group most affected by smoking was the 60-69 years age group, in which 42% of the analysed hospitalisations (86,955 out of 209,482) were attributable to tobacco smoking (Table 2).

Figure 1. Disease-specific number of hospitalisations attributable and not attributable to tobacco smoking (Italy, 2018)



COPD: chronic obstructive pulmonary disease, IHD: ischaemic heart disease

Figure 2. Disease-specific expenditure attributable and not attributable to tobacco smoking (Italy, 2018)



COPD: chronic obstructive pulmonary disease, IHD: ischaemic heart disease

In total, the cumulative expenditure attributable to tobacco smoking reached €1.64 billion, accounting for approximately 33% of the total healthcare expenditure associated with the hospitalisations analysed. The highest healthcare expenditure attributable to tobacco smoking was observed for IHD, with costs of €556 million, followed by stroke with €290 million, and lung cancer with €229 million (Figure 2 and Table 1). Tobacco smoking was responsible for 40% and 22% of the expenditure in men and women, respectively, while the age group most affected by smoking was the 60-69 age group, in which 41% of the expenditure (457,539 out of 1,123,058 thousand of €) were attributable to tobacco smoking (Table 3).

Table 2. Hospitalisations, total and attributable to smoking, stratified by sex and age group (Italy, 2018)

	Males			Females			Total		
Age group (years)	Tot H	Attr H	PAF	Tot H	Attr H	PAF	Tot H	Attr H	PAF
30-34	2,352	380	16.13%	1,785	236	13.25%	4,137	616	14.89%
35-39	4,110	1,352	32.90%	2,927	650	22.18%	7,037	2,002	28.45%
40-49	26,426	10,236	38.73%	13,675	3,694	27.01%	40,101	13,930	34.74%
50-59	77,598	32,458	41.83%	32,749	10,954	33.45%	110,347	43,412	39.34%
60-69	148,437	66,122	44.55%	61,045	20,833	34.13%	209,482	86,955	41.52%
70-79	201,098	83,645	41.59%	102,975	26,809	26.03%	304,073	110,454	36.32%
80+	155,776	52,376	33.62%	153,368	17,207	11.22%	309,144	69,583	22.51%
Total	615,797	246,569	40.04%	368,524	80,383	21.81%	984,321	326,952	33.22%

Attr H: number of hospitalisations attributable to tobacco smoking; PAF: Population Attributable Fraction; Tot H: total number of hospitalisations.

In the sensitivity analyses performed using different RRs, the number of hospitalisations attributable to smoking increased to 373,621, representing 38% of the total number of hospitalisations considered. Similarly, the cumulative expenditure attributable to smoking increased to €1,842 million, representing 37% of the total healthcare expenditure associated with the analysed hospitalisations (Supplementary Table 3).

Table 3. Expenditure (in thousands of €), total and attributable to smoking, stratified by sex and age group (Italy, 2018)

	Males			Females			Total		
Age group (years)	Tot Exp	Attr Exp	PAF	Tot Exp	Attr Exp	PAF	Tot Exp	Attr Exp	PAF
30-34	11,136	1,882	16.90%	7,855	1,051	13.38%	18,991	2,932	15.44%
35-39	21,132	7,214	34.14%	12,930	2,909	22.49%	34,062	10,693	29.87%
40-49	147,493	57,283	38.84%	69,169	18,252	26.39%	216,662	75,535	34.86%
50-59	438,397	180,732	41.23%	165,966	53,490	32.23%	604,363	234,222	38.76%
60-69	813,345	355,596	43.72%	309,713	101,943	32.92%	1,123,058	457,539	40.74%
70-79	1,058,798	431,524	40.85%	521,216	130,817	25.10%	1,580,014	562,341	35.59%
80+	704,347	231,284	32.84%	656,116	68,127	10.38%	1,360,463	299,411	22.01%
Total	3,194,648	1,276,515	39.61%	1,742,965	376,589	21.61%	4,937,613	1,642,673	33.27%

Attr Exp: expenditure attributable to tobacco smoking (in thousands of €), PAF: Population Attributable Fraction, Tot Exp: total expenditure (in thousands of €).

9.5 Discussion

This study provides valuable insights into the analysis of the burden of tobacco-related hospitalisations and associated healthcare costs in Italy. By analysing a comprehensive dataset of almost 1 million hospital discharge reports for 12 selected tobacco-related diseases in 2018, we found that tobacco smoking was responsible for a third of the hospitalisations and expenditures associated with these diseases, amounting to more of 320,000 hospitalisations and more than €1.64 billion.

The diseases with the highest Population Attributable Fraction (PAF) in our study were chronic obstructive pulmonary disease (COPD), laryngeal cancer, and lung cancer, with smoking contributing to approximately three out of four hospitalisations for each of these diseases. Our findings are partly aligned with those of two similar studies conducted in the UK and Switzerland, which found that lung cancer and COPD were among the diseases with the highest proportion attributable to smoking [22,23]. However, direct comparisons between studies should be made with caution because of differences in country-specific smoking prevalence and methodologies applied, including the reporting of combined

results for several tobacco-related cancers and not for laryngeal cancer, separately.

Our study revealed a substantial burden of tobacco-related hospitalisations in Italy. In particular, if tobacco smoking was eliminated, more than 300,000 hospitalisations could be prevented each year. Among the 12 tobacco-related diseases considered, the highest numbers of hospitalisations attributable to tobacco were observed for IHD, stroke, and lung cancer. These findings reflect the significant impact of smoking on cardiovascular diseases and respiratory conditions.

In addition, our study revealed important sex differences, with a higher proportion of hospitalisations and expenditure attributable to tobacco smoking observed in men than in women. Overall, the number of hospital admissions and expenditure due to smoking is three times higher in men than in women. This is in line with previous studies conducted in European countries, although they focused on mortality rather than hospitalisation [22,23]. Possible factors contributing to this difference include higher smoking prevalence rates and intensity of the smoking habit in men than women.

The results highlight that tobacco smoking has a substantial economic impact in Italy, accounting for one third of the direct expenditure for hospitalisations for the tobacco-related diseases considered. This finding is consistent with a 2017 study conducted in Switzerland, which reported that tobacco smoking accounted for 28% of the expenditure related to tobacco-related diseases [22]. Examining the total cost of hospitalisations in Italy in 2018 [24], our findings indicate that tobacco smoking accounts for at least 5.9% of the total expenditure.

The estimated expenditure to hospitalisation attributable to tobacco smoking in our study is substantially underestimated. First, our analysis focused on only 12 specific tobacco-related diseases, opting for a conservative selection. However, recent literature has identified a total of 56 smoking-related diseases [25]. Notably, our selection of diseases, although conservative, still accounts for a substantial proportion, approximately 85%, of the global deaths attributed to tobacco smoking as calculated by the Global Burden of Disease Study [26], suggesting that we have captured a substantial, albeit not completely exhaustive, proportion of the total hospitalisations attributable to smoking. Despite this, our analysis did not encompass several common and costly diseases that have been demonstrated to be linked to smoking, such as breast and colorectal cancer [21,27,28], which stand as the two most frequently diagnosed cancers in Italy [29]. We also did not include diabetes, prostate cancer, and liver cancer, all established to be linked with smoking [21]. Therefore, the economic impact of smoking on the healthcare system is likely to be greater when considering the

broader range of tobacco-related diseases. Second, our analysis was mainly limited to hospitalisations for smoking-related diseases as the main diagnosis. This approach did not consider hospitalisations where a tobacco-related disease was listed as a secondary diagnosis. As smoking may contribute to the severity and complications of several health conditions, this approach may have underestimated the true economic expenditure attributable to tobacco smoking. Third, we calculated hospitalisations and costs directly attributable to active smoking and did not include an assessment of the impact of exposure to SHS, which would provide a more complete understanding of the total burden of tobacco-related diseases in non-smokers. Notably, recent meta-analyses have shown significant associations between SHS exposure and the risk of cervical and breast cancer [30,31]. However, the health burden from SHS is expected to be relatively low, as it is estimated to account for less than 10% of the disability-adjusted life years attributable to active smoking in Italy [32]. Future studies should focus on estimating the direct economic costs attributable to SHS exposure in the non-smoking population.

It should also be noted that the costs estimated in our study represent only a fraction of the healthcare costs attributable to tobacco smoking. In fact, hospitalisations account for less than a quarter of the total costs incurred by the Italian National Health System, and we expect tobacco smoking to have a substantial impact on the costs of outpatient services, drugs, and other healthcare resources [28]. Moreover, our analysis focuses on the direct economic impact of tobacco-related hospitalisations on the National Health System and does not take into account out-of-pocket expenditure incurred by individuals. This omission is particularly relevant for private hospitalisations, where patients bear the full cost of treatment. Future research should address this limitation by incorporating out-of-pocket costs to provide a more comprehensive understanding of the economic impact of tobacco-related morbidity. The non-inclusion of private hospitalisations, which do not affect the National Health System, may also have led to an underestimation of the number of hospitalisations attributable to smoking. However, it is important to note that private hospitalisations represent only a small proportion of total hospitalisations in Italy. In addition, we did not account for the burden of indirect costs. Indirect costs, including productivity losses due to premature mortality or disability, informal care for people with tobacco-related illnesses, and the costs of tobacco-related fires and sickness absence, are important components in assessing the overall economic impact of smoking on society. A recent study revealed that smoking costs England £49.2 billion each year in lost productivity and service costs, along with an additional £25.9 billion lost in quality-adjusted life years due to premature death from smoking [33]. These findings underscore the importance of incorporating such indirect costs in future studies to provide a more comprehensive assessment of the economic burden of tobacco smoking in Italy.

In addition, several other limitations should be taken into account when interpreting the results of this study. First, several assumptions were made in the calculation of the PAFs. Particularly, the appropriateness of the relative risks (RR) employed warrants consideration, as specific RR estimates for Italy would be ideal. However, the evidence used is derived from comprehensive meta-analyses and systematic reviews encompassing diverse populations, including Europe. It is also worth noting that results from sensitivity analyses suggest that the choice of RR may have led to an underestimation of the number of hospitalisations and attributable costs. Moreover, unmeasured factors, such as socioeconomic status and lifestyle habits, may influence both smoking behavior and hospitalization rates, potentially biasing our results. Finally, it should be noted that the results of our study are specific to the Italian context and may not be directly generalisable to other countries. Differences in health care systems, smoking prevalence, health care practices and socioeconomic factors between countries may limit the applicability of our results to other countries.

In conclusion, given the substantial burden of tobacco-related hospitalisations and associated costs, it is essential to prioritise comprehensive tobacco control measures to reduce smoking prevalence. One particularly effective strategy is to increase tobacco excise taxes. Indeed, it is well established that in high-income countries increases in taxation – and prices – reduce consumption while increasing revenues [34,35]. Particularly, it has been estimated that a 10% increase in prices would result in a 4% decrease in consumption [35,36]. Furthermore, given the fact that these costs are borne by the regions, whereas taxes on cigarette sales are collected by the Italian State, it might be worth exploring the possibility of giving the regions more control over tobacco taxation.

9.6 Contribution to the overall thesis framework

This chapter complements the epidemiological and burden estimation analyses presented throughout the thesis by assessing the economic consequences of tobacco use in Italy. While the previous chapter quantified the health burden attributable to smoking in terms of cancer cases, deaths, and DALYs, this study translates part of that burden into healthcare costs, providing an additional perspective on the societal impact of tobacco exposure.

Together, the findings presented across the thesis highlight how smoking and secondhand smoke affect the Italian population from epidemiological, behavioural, clinical, and economic perspectives. By integrating these complementary dimensions, the thesis provides a more comprehensive assessment of the burden attributable to tobacco and reinforces the value of

evidence-based tobacco control policies aimed at reducing both health and economic costs.

9.7 References

1. U.S. Department of Health and Human Services. The Health Consequences of Smoking — 50 Years of Progress. A Report of the Surgeon General. Rockville, MD: Public Health Service, Office of the Surgeon General; 2014.
2. National Cancer Institute. Harms of Cigarette Smoking and Health Benefits of Quitting. https://www.cancer.gov/about-cancer/causes-prevention/risk/tobacco/cessation-fact-sheet. Published December 19, 2017. Accessed December 22, 2023.
3. G. B. D. Risk Factors Collaborators. Global burden of 87 risk factors in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet. 2020;396(10258):1223-1249. doi: 10.1016/S0140-6736(20)30752-2.
4. World Health Organization. WHO report on the global tobacco epidemic, 2021: addressing new and emerging products. https://www.who.int/publications/i/item/9789240032095. Published July 27, 2021. Accessed December 22, 2023.
5. Jha P. Avoidable global cancer deaths and total deaths from smoking. Nat Rev Cancer. 2009;9(9):655-664. doi: 10.1038/nrc2703.
6. Goodchild M, Nargis N, Tursan d'Espaignet E. Global economic cost of smoking-attributable diseases. Tob Control. 2018;27(1):58-64. doi: 10.1136/tobaccocontrol-2016-053305.
7. Shrestha SS, Ghimire R, Wang X, Trivers KF, Homa DM, Armour BS. Cost of Cigarette Smoking–Attributable Productivity Losses, U.S., 2018. Am J Prev Med. 2022;63(4):478-485. doi: 10.1016/j.amepre.2022.04.032.
8. Max W, Sung HY, Shi Y. Deaths from secondhand smoke exposure in the United States: economic implications. Am J Public Health. 2012;102(11):2173-2180. doi: 10.2105/AJPH.2012.300805.
9. Xu X, Shrestha SS, Trivers KF, Neff L, Armour BS, King BA. U.S. healthcare spending attributable to cigarette smoking in 2014. Prev Med. 2021;150:106529. doi: 10.1016/j.ypmed.2021.106529.
10. OECD., Policies. EOohSa. Italy: Country Health Profile 2021, State of Health in the EU. OECD Publishing, Paris/European Observatory on Health Systems and Policies, Brussels. 2021.
11. Levy D, Gallus S, Blackman K, Carreras G, La Vecchia C, Gorini G. Italy SimSmoke: the effect of tobacco control policies on smoking prevalence and smoking attributable deaths in Italy. BMC Public Health. 2012;12:709. doi: 10.1186/1471-2458-12-709.
12. Istituto Superiore di Sanità. Comunicato Stampa N°39/2022 - Fumo: in Italia circa 800mila fumatori in più rispetto al 2019. Triplicato il consumo di sigarette a tabacco riscaldato. https://www.iss.it/en/comunicati-stampa/-/asset_publisher/fjTKmjJgSgdK/content/id/7146126. Published May 30, 2022. Accessed December 14, 2023.

13. Joossens L, Olefir L, Feliu A, Fernandez E. The Tobacco Control Scale 2021 in Europe. http://www.tobaccocontrolscale.org/TCS2021. Published 2022. Accessed December 22, 2023. Brussels: Smoke Free Partnership, Catalan Institute of Oncology.
14. Gallus S, Stival C, McKee M, Carreras G, Gorini G, Odone A, et al. Impact of electronic cigarette and heated tobacco product on conventional smoking: an Italian prospective cohort study conducted during the COVID-19 pandemic. Tob Control. 2022. doi: 10.1136/tc-2022-057368.
15. Gallus S, Borroni E, Odone A, van den Brandt PA, Gorini G, Spizzichino L, et al. The Role of Novel (Tobacco) Products on Tobacco Control in Italy. Int J Environ Res Public Health. 2021;18(4). doi: 10.3390/ijerph18041895.
16. GHK. A study on liability and the health costs of smoking. https://health.ec.europa.eu/system/files/2016-11/tobacco_liability_final_en_0.pdf. Published April, 2012. Accessed December 22, 2023. London, GHK.
17. National Center for Health Statistics. ICD-9-CM: International classification of diseases, 9th revision, clinical modification. https://www.cdc.gov/nchs/icd/icd9cm.htm#:~:text=ICD%2D9%2DCM%20is%20the,10%20for%20mortality%20coding%20started. Accessed December 22, 2023.
18. Mansournia MA, Altman DG. Population attributable fraction. BMJ. 2018;360:k757. doi: 10.1136/bmj.k757.
19. ISTAT. I.Stat - your direct access to the Italian Statistics. Available at http://dati.istat.it/?lang=en. Accessed December 14, 2023.
20. Lipfert FW, Wyzga RE. Longitudinal relationships between lung cancer mortality rates, smoking, and ambient air quality: a comprehensive review and analysis. Crit Rev Toxicol. 2019;49(9):790-818. doi: 10.1080/10408444.2019.1700210.
21. Carter BD, Abnet CC, Feskanich D, Freedman ND, Hartge P, Lewis CE, et al. Smoking and mortality--beyond established causes. N Engl J Med. 2015;372(7):631-640. doi: 10.1056/NEJMsa1407211.
22. Farcher R, Syleouni ME, Vinci L, Mattli R. Burden of smoking on disease-specific mortality, DALYs, costs: the case of a high-income European country. BMC Public Health. 2023;23(1):698. doi: 10.1186/s12889-023-15535-9.
23. Allender S, Balakrishnan R, Scarborough P, Webster P, Rayner M. The burden of smoking-related ill health in the UK. Tob Control. 2009;18(4):262-267. doi: 10.1136/tc.2008.026294.
24. Ragioneria Generale dello Stato. Il monitoraggio della spesa sanitaria. Available at https://www.rgs.mef.gov.it/VERSIONE-I/attivita_istituzionali/monitoraggio/spesa_sanitaria/index.html Published 2019. Accessed December 20, 2023.
25. Chan KH, Wright N, Xiao D, Guo Y, Chen Y, Du H, et al. Tobacco smoking and risks of more than 470 diseases in China: a prospective cohort study.

Lancet Public Health. 2022;7(12):e1014-e1026. doi: 10.1016/S2468-2667(22)00227-4.

26. G. B. D. Risk Factors Collaborators. GBD Compare. https://vizhub.healthdata.org/gbd-compare/. Accessed January 31, 2024. 2019.
27. Scala M, Bosetti C, Bagnardi V, Possenti I, Specchia C, Gallus S, et al. Dose-response Relationships Between Cigarette Smoking and Breast Cancer Risk: A Systematic Review and Meta-analysis. J Epidemiol. 2023;33(12):640-648. doi: 10.2188/jea.JE20220206.
28. Botteri E, Borroni E, Sloan EK, Bagnardi V, Bosetti C, Peveri G, et al. Smoking and Colorectal Cancer Risk, Overall and by Molecular Subtypes: A Meta-Analysis. Am J Gastroenterol. 2020;115(12):1940-1949. doi: 10.14309/ajg.0000000000000803.
29. AIOM. I NUMERI DEL CANCRO IN ITALIA 2022. https://www.aiom.it/wp-content/uploads/2022/12/2022_AIOM_NDC-web.pdf. Published 2022. Accessed December 20, 2023.
30. Malevolti MC, Maci C, Lugo A, Possenti I, Gallus S, Gorini G, et al. Second-hand smoke exposure and cervical cancer: a systematic review and meta-analysis. J Cancer Res Clin Oncol. 2023;149(15):14353-14363. doi: 10.1007/s00432-023-04841-9.
31. Possenti I, Scala M, Carreras G, Bagnardi V, Bosetti C, Gorini G, et al. Exposure to secondhand smoke and breast cancer risk in non-smoking women: a comprehensive systematic review and meta-analysis - In press. British Journal of Cancer. 2023.
32. Collaborators GBDRF. Global burden of 87 risk factors in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet. 2020;396(10258):1223-1249. doi: 10.1016/S0140-6736(20)30752-2.
33. ASH. New figures show smoking costs billions more than tobacco taxes as consultation on creating a smokefree generation closes. https://ash.org.uk/media-centre/news/press-releases/new-figures-show-smoking-costs-billions-more-than-tobacco-taxes-as-consultation-on-creating-a-smokefree-generation-closes. Published December 6, 2023. Accessed December 21, 2023.
34. Gallus S, Lugo A, La Vecchia C, Boffetta P, Chaloupka FJ, Colombo P, et al. Pricing Policies And Control of Tobacco in Europe (PPACTE) project: cross-national comparison of smoking prevalence in 18 European countries. Eur J Cancer Prev. 2014;23(3):177-185. doi: 10.1097/CEJ.0000000000000009.
35. IARC. Effectiveness of Tax and Price Policies for Tobacco Control. https://publications.iarc.fr/Book-And-Report-Series/Iarc-Handbooks-Of-Cancer-Prevention/Effectiveness-Of-Tax-And-Price-Policies-For-Tobacco-Control-2011. Published 2011. Accessed December 22, 2023. IARC Handbooks of Cancer Prevention. 2011;14.

36. Gallus S, Fernandez E, Townsend J, Schiaffino A, La Vecchia C. Price and consumption of tobacco in Italy over the last three decades. Eur J Cancer Prev. 2003;12(4):333-337. doi: 10.1097/00008469-200308000-00015.

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Chapter 10

Discussion

10.1 Main findings

This thesis provides an updated and comprehensive assessment of the association between cigarette smoking and secondhand smoke (SHS) exposure, and cancer risk. It also evaluates the resulting health and economic impact in Italy. By integrating evidence from systematic reviews and meta-analyses, national surveillance data on smoking behaviours and public attitudes, and innovative methodological approaches to burden estimation, this work offers a multidimensional perspective on the impact of tobacco use and exposure.

The main findings confirm the central role of tobacco as a leading and still insufficiently controlled risk factor for cancer, while highlighting relevant site-specific associations, persistent exposure patterns in the Italian population, and substantial preventable burdens in terms of cancer incidence, mortality, healthcare costs, and disability.

10.1.1 Association between tobacco and cancer risk

The meta-analytical evidence presented in this work strengthens the causal link between active smoking and cancers of the upper aerodigestive tract. In particular, for nasopharyngeal cancer, pooled estimates indicated a 61% increased risk among current smokers and a 28% increased risk among former smokers [1]. Current smokers showed a more than twofold increased risk of oral and pharyngeal cancers, and former smokers exhibited a 61% increased risk compared to never smokers [2].

The results consistently indicate that tobacco-related cancer risk is strongly influenced by exposure characteristics, including intensity, duration, and time since cessation, across cancer sites and different smoking patterns [1, 2]. The gradual reduction in risk observed among former smokers, which is consistent with findings from many other cancer sites, highlights the tangible benefits of smoking cessation [3-5]. The observed dose-response relationships with smoking intensity and duration further support the cumulative nature of tobacco-related carcinogenesis, being consistent with both biological plausibility and previous epidemiological findings [6, 7].

Beyond well-established smoking-related cancers, this thesis report on SHS exposure as an independent carcinogenic risk factor, particularly for cancer sites where the epidemiological evidence has historically been inconsistent or less extensively investigated [6, 8, 9]. A comprehensive systematic review and meta-analysis of the association between SHS exposure and breast cancer risk revealed a 24% excess risk among never smoking women exposed to SHS, together with linear dose-response relationships for duration, intensity, and

cumulative exposure [10]. These findings support the causal interpretation of this association.

10.1.2 Tobacco use and public perception in Italy

In Italy, tobacco use remains widespread despite long-standing tobacco control measures. After a significant decline following the introduction of the national indoor smoking ban ('Sirchia Law') in 2005 [11], smoking prevalence stagnated since 2014 [12, 13]. Subsequently, it increased again in 2022, reaching 24% [14].

Analyses conducted within this thesis indicate a further increase in smoking prevalence in 2024, with around 27% of adults classified as current smokers in the general population and a mean daily consumption of approximately 13 cigarettes per day among current smokers [15]. Exposure to SHS also remains substantial, with around 16% of non-smokers reporting daily indoor exposure. Findings also suggest that involuntary exposure predominantly persists in settings not fully covered by existing legislation, such as private homes, vehicles, and some workplaces.

At the same time, analyses of public attitudes reveal strong support among the population for the strengthening of tobacco control policies. In 2024, a clear majority of Italian adults expressed support for key measures, with approval levels ranging from around 60% for fiscal interventions, such as huge tobacco tax increases, to over 70% for age-based restrictions. These included raising the legal age for tobacco purchases to 21 and introducing Smoke-Free Generation policies. Even higher levels of support were observed for regulatory measures aimed at protecting non-smokers, with over 80% in favour of banning e-cigarettes (e-cig) and heated tobacco products (HTP) in indoor public places and workplaces, and close to 80% in favour of comprehensive bans on tobacco advertising and promotion [16].

Overall, these findings depict a context in which high and persistent levels of tobacco exposure coexist with widespread public support for ambitious tobacco control strategies. These observations provide essential background for the evaluation of tobacco control strategies discussed in the subsequent sections.

10.1.3 Methodological innovation

A key contribution of this thesis is the development of a methodological approach to quantify cancer burden attributable to tobacco smoking that incorporate heterogeneity in individual smoking patterns.

Specifically, the analyses integrate smoking status with key exposure dimensions - intensity, duration, and time since cessation - through dose-response functions derived from updated meta-analytical evidence [17].

This approach provides a granular representation of risk across the population, showing how cancer risk varies not only between smokers and never smokers but also within these groups according to different smoking characteristics. By aggregating individual excess risks, this framework is used to estimate population attributable fractions (PAF) and national cancer burden using individual-level exposure profiles. The same analytical framework can be extended to exposure to SHS exposure and diseases other than cancer.

Overall, the methodological approach adopted in this thesis underpins the epidemiological and burden estimates presented in the subsequent chapter, providing a consistent link between detailed exposure assessment and population-level impact.

10.1.4 Impact of tobacco on healthcare and disease burden

The analyses presented in this thesis document a substantial impact of tobacco smoking on cancer burden and healthcare utilisation in Italy.

Estimates based on national data indicate that a large proportion of cancer incidence, mortality, and disability is attributable to cigarette smoking, with particularly high PAFs observed for cancers of the digestive tract, including oral cavity and pharynx, oesophagus, stomach and colorectum. For these sites, smoking accounts for around a seventh of cases, deaths, and Disability-Adjusted Life Years (DALYs), reflecting both the strength of the association and the high prevalence of exposure in the population [18].

In addition to the oncological burden, this thesis highlights the significant pressure exerted by smoking on the Italian healthcare system. Analyses of hospital discharge records show that approximately one third of hospitalisations for selected smoking-related diseases in adults are attributable to tobacco smoking, corresponding to a direct cost of about €1.6 billion in a single year [19]. Cardiovascular diseases, chronic respiratory conditions, and lung cancer account for the largest share of these smoking-attributable hospital costs, underscoring the multi-system impact of tobacco beyond cancer.

Importantly, the burden estimates presented in this work are likely conservative. These considerations suggest that the true impact of tobacco on population health and healthcare resources in Italy extends beyond the quantifications reported here.

Overall, the findings of this thesis indicate that tobacco smoking continues to generate a substantial and largely preventable burden on both population health and the healthcare system.

10.2 Advancement in knowledge

This thesis makes significant contributions to four interlocking areas of research: (i) it clarifies site-specific associations for cancer outcomes that were previously underexplored or inconsistently reported; (ii) it delivers updated, country-specific insights into smoking, SHS exposure, and attitudes towards potential tobacco control policies in Italy; (iii) it develops an innovative methodological framework that integrates individual smoking patterns with meta-analytical dose-response evidence to derive precise burden estimates; and (iv) it assembles these strands into a coherent picture of tobacco-attributable burden in Italy that is directly relevant for evaluation and planning purposes.

10.2.1 Novel associations and underexplored cancer sites

The first area of advancement relates to cancer sites for which previous syntheses were limited by heterogeneous endpoints or the absence of comprehensive dose-response modelling. Treating nasopharyngeal cancer as an independent outcome rather than a component of the broader “head and neck” grouping enables this work to quantify robust associations for current and former smokers, and to document clear dose-risk patterns for intensity and duration. Similarly, the synthesis of oral and pharyngeal cancer evidence is updated and harmonised, confirming risks exceeding twofold among current smokers and a substantial residual risk after cessation.

Regarding involuntary exposure, this thesis provides conclusive evidence on an association that had remained historically contested and methodologically fragmented [6, 8]. The comprehensive systematic review and meta-analysis on SHS and breast cancer in never smokers synthesises the most complete body of data to date, demonstrating a consistent excess risk with clear dose-response relationships. Taken together with established mechanistic plausibility and causal criteria from authoritative evaluations [6], these results resolve the residual uncertainty surrounding the carcinogenic relevance of SHS for breast cancer.

10.2.2 Population-level insights

A second advancement lies in providing contemporary, country-specific evidence for Italy, integrating behavioural data with attitudes towards potential new tobacco control policies. Earlier national sources documented the stagnation of smoking

trends after 2014 and the modest increase observed in 2022 [12-14]. By analysing data from 2024, this thesis provides an updated national overview and demonstrates that smoking and SHS exposure are still widespread and unevenly distributed across different demographic groups.

The scientific contribution extends beyond describing prevalence. This thesis demonstrates how behavioural patterns intersect with public attitudes, revealing that a clear majority of adults supports the strengthening of tobacco control regulations. Support encompasses fiscal measures, age-based restrictions such as Tobacco-21 and Smoke-Free Generation, and the extension of smoke-free environments to e-cigs and HTPs and are coherent with previous findings on a non-representative sample of the Italian population [20].

Taken together, these findings offer a fuller and current picture of tobacco use and social norms in Italy. This strengthens the evidence base needed to understand which interventions are likely to be both effective and acceptable to the public.

10.2.3 Methodological contributions

A third advancement of this thesis concerns how risk and attributable burden are estimated, by developing an innovative method that addresses some limitations of conventional prevalence-based models [21]. Such approaches typically fail to capture the substantial heterogeneity in smoking patterns because they apply average relative risks to broad smoking categories.

This thesis develops and applies a framework based on individual-level relative risks, constructed from smoking status, intensity, duration, and time since cessation, and calibrated using relative risks and dose-response relationships derived from comprehensive meta-analyses. This enables the risk to vary continuously across individuals, providing a realistic representation of exposure trajectories.

Within this framework, PAFs are derived by aggregating individual excess risks, rather than combining prevalence with a single summary relative risk. This yield estimates that better reflect the actual distribution of smoking patterns and the temporal dynamics of exposure and risk. The same structure can be seamlessly extended to SHS exposure and to site-specific dose-response, supporting consistent modelling across cancer types while respecting aetiologic differences.

Together, these methodological contributions produce more nuanced and internally coherent estimates of tobacco-attributable burden.

10.2.4 Comprehensive burden estimation

Finally, this thesis brings together site-specific risk and dose-response relationships, updated Italian exposure data and empirically observed costs, providing decision-ready estimates of the burden of tobacco-attributable cancer.

In terms of oncology, the thesis provides updated estimates showing that tobacco substantially contributes to cancer incidence, mortality and DALYs in Italy, particularly by providing updated PAFs for digestive tract cancers. From an economic perspective, the evaluation of Italian hospitalisations reveals that approximately one-third of admissions for major smoking-related diseases can be directly attributed to smoking. This equates to around €1.64 billion in direct hospital expenditure alone and indicates that tobacco smoking accounts for at least 5.9% of the total National Health System expenditure.

10.3 Conclusions, implications and key considerations

The findings of this thesis should not be viewed as a collection of independent studies, but rather as complementary components of a broader framework aimed at understanding and quantifying the cancer burden attributable to tobacco exposure in Italy. The work progressed through four interconnected stages. First, updated epidemiological evidence was generated to quantify the association between smoking, SHS exposure, and cancer risk. Second, population-level information on smoking behaviours, SHS exposure, and attitudes towards tobacco control policies was collected to characterize the Italian context in which tobacco-related disease occurs. Third, these data were integrated into an innovative methodological framework capable of translating individual exposure histories into population-level burden estimates. Finally, this framework was applied to quantify the health and economic consequences of tobacco exposure in Italy.

Taken together, these components provide a more complete understanding of tobacco-related burden than any individual approach could achieve in isolation. Epidemiological evidence identifies the risks, behavioural data describe the distribution of exposure, methodological advances translate these risks into attributable burden, and economic analyses quantify the societal consequences. This integrated perspective creates a comprehensive evidence base to support tobacco control policies and cancer prevention strategies in Italy.

10.3.1 Public health implications

The findings of this thesis confirm that tobacco use and SHS exposure remain major, preventable causes of cancer burden in Italy, with particularly high PAFs

for digestive tract cancers. Importantly, the work also establishes SHS as a carcinogenic exposure relevant to breast cancer among never smokers, a dimension largely absent from current prevention frameworks. From a public health perspective, this poses SHS protection to a core component of women's cancer prevention, alongside well-recognised determinants such as alcohol consumption [22, 23]. It also highlights the need to address environments in which SHS exposure is most frequent, including homes, private vehicles, and semi-private settings where regulation and enforcement are minimal.

These findings also highlight the importance of prioritising risk communication and lifestyle-focused prevention strategies. This will ensure that awareness of the dangers of active smoking and SHS is fully integrated into population-level health promotion efforts.

Overall, the results reinforce the fact that meaningful reductions in cancer incidence, mortality and healthcare costs are achievable through comprehensive lifestyle-related prevention approaches, including strengthened public information, increased awareness of SHS risks and targeted support for groups with the highest exposure. Therefore, addressing tobacco use and SHS exposure should remain a core priority within the national public health agenda to support equitable and sustained improvements in population health.

10.3.2 Policy recommendations

A key message of this thesis is that high levels of smoking and SHS exposure in Italy coexist with widespread public support for stronger tobacco control measures. This indicates both an epidemiological need and a social readiness to adopt more restrictive and efficient measures that can meaningfully reduce tobacco-attributable harm.

The first priority should be to close remaining exposure gaps, particularly in settings where involuntary exposure persists despite existing protections [24]. Extending smoke-free rules to all nicotine-delivery products, including e-cigs and HTPs, would ensure regulatory coherence with current patterns of use and strengthen protection in indoor public places and workplaces. Equally important is the effective enforcement of existing measures. The persistence of SHS exposure in semi-private and outdoor high-density settings demonstrates that legal provisions alone are insufficient without systematic, well-resourced implementation.

Preventing initiation remains essential, especially in light of plateauing prevalence trends. The strong public support observed for Tobacco-21 and Smoke-Free Generation proposals suggests that Italy is well positioned to implement measures aimed at curbing uptake among adolescents and young

adults. These interventions align with international best practice and would complement exposure-based protections [25-27].

Fiscal policy remains one of the most powerful tools available [28]. Sustained increases in tobacco excise taxation would reduce consumption and deter people from taking up smoking, while also helping to offset the substantial healthcare costs attributable to smoking. Therefore, price measures carry both preventive and economic benefits for the National Health Service.

Overall, the evidence suggests that Italy has a clear opportunity to strengthen its tobacco control strategy. Consistently enforcing existing laws while adopting targeted measures supported by the population would provide a solid foundation for reducing tobacco-attributable disease in the coming years.

Finally, given the emerged profile of risk and exposure, incorporating structured advice on tobacco and SHS into routine prevention and screening programmes would offer an immediate and feasible opportunity to strengthen population-level cancer prevention.

10.3.3 Limitations of the present work

Several limitations should be considered when interpreting the findings of this thesis. First, the results are largely based on observational and meta-analytical evidence, which limits causal inference. Although consistency across studies, dose-response relationships, and biological plausibility support the robustness of the associations, residual confounding cannot be fully excluded. In addition, heterogeneity in study design, exposure assessment, and confounder adjustment across included studies may have influenced pooled estimates.

Second, estimates of smoking behaviour and SHS exposure rely mainly on self-reported data, which are subject to recall and social desirability biases. Misclassification of exposure, particularly under-reporting, may therefore have occurred and would likely lead to conservative estimates of prevalence and risk.

Third, the burden estimation approach is based on several assumptions, including the specification of dose-response relationships, the modelling of risk reduction after smoking cessation, and the transferability of RRs to the Italian context. While these assumptions are grounded in the best available evidence, uncertainty in the input parameters inevitably affects burden estimates.

Further limitations relate to data availability and representativeness. National data may not fully capture informal settings of SHS exposure, emerging patterns of novel nicotine-product use, or sub-population variability. Moreover, economic

estimates are limited to selected diseases and direct hospital costs, likely underestimating the total societal burden.

Finally, generalizability may be limited to settings with similar smoking patterns, healthcare systems, and tobacco-control histories, limiting direct transferability to substantially different contexts.

10.3.4 Research gaps and future directions

From a methodological perspective, the individual-level burden framework developed in this thesis offers several avenues for expansion. It can be applied to all tobacco-related cancer sites, particularly those of the respiratory tract, to derive site-specific PAFs that fully incorporate exposure heterogeneity. The framework can also be extended to incorporate co-exposures, multi-product use and time-dependent policy scenarios, providing a more flexible basis for future decision-analytic models. Integrating economic and quality-of-life outcomes would further enhance the relevance of such models for public health and health system planning.

Future research should aim to characterise smoking trajectories over time, including transitions between exclusive smoking, dual use and consumption of multiple products, and generate independent evidence on the long-term health effects of novel nicotine products. Such evidence is essential not only for understanding their contribution to population risk but also for enabling, in the future, robust PAF estimates for e-cigs, HTPs, and other emerging devices, which is currently not possible due to the scarcity of high-quality epidemiological data.

A final priority concerns SHS exposure. As demonstrated in this thesis, SHS significantly contributes to the cancer burden, including the risk of breast cancer among never smokers. However, scientific literature still lacks harmonised and standardised definitions of exposure. Improved SHS monitoring would strengthen exposure assessment, support equity-focused protection and improve future burden estimation.

10.3.5 Final reflections

By integrating epidemiological evidence, behavioural and policy indicators, methodological innovation, and burden and cost estimation, this thesis moves beyond the description of tobacco-related risks and provides a unified framework for understanding, quantifying, and reducing the cancer burden attributable to tobacco exposure in Italy. The enduring burden attributable to tobacco, together with the demonstrated public support for stronger protections, indicate that substantial progress is feasible. Prioritising SHS protection, preventing initiation in younger generations, and using taxation to curb consumption while relieving

the health-system load are immediate, evidence-aligned steps. The tools and results presented here can support Italy in accelerating reductions in tobacco-attributable harm through informed, implementable, and publicly supported strategies.

10.4 References

1. Possenti I, Martini A, Bagnardi V et al. Association between cigarette smoking and nasopharyngeal cancer risk: a meta-analysis. Rhinology 2025; 63: 13-21.
2. Possenti I, Miotti S, Gallus S et al. Smoking and Oral and Pharyngeal Cancer: A Meta-Analysis. Oncology Reviews 2025; 19.
3. Liu X, Peveri G, Bosetti C et al. Dose-response relationships between cigarette smoking and kidney cancer: A systematic review and meta-analysis. Crit Rev Oncol Hematol 2019; 142: 86-93.
4. Lugo A, Peveri G, Bosetti C et al. Strong excess risk of pancreatic cancer for low frequency and duration of cigarette smoking: A comprehensive review and meta-analysis. Eur J Cancer 2018; 104: 117-126.
5. Rota M, Possenti I, Valsassina V et al. Dose-response association between cigarette smoking and gastric cancer risk: a systematic review and meta-analysis. Gastric Cancer 2024; 27: 197-209.
6. IARC. Personal habits and indoor combustions. Volume 100 E. IARC Monogr Eval Carcinog Risks Hum 2012; 1-538.
7. U.S. Department of Health and Human Services. The Health Consequences of Smoking — 50 Years of Progress. A Report of the Surgeon General. Public Health Service, Office of the Surgeon General, Rockville, MD,2014.
8. IARC. Tobacco smoke and involuntary smoking. Vol. 83. IARC Monogr Eval Carcinog Risks Hum 2004; 1-1438.
9. U.S. Department of Health and Human Services. The Health Consequences of Involuntary Exposure to Tobacco Smoke. 2006.
10. Possenti I, Scala M, Carreras G et al. Exposure to second-hand smoke and breast cancer risk in non-smoking women: a comprehensive systematic review and meta-analysis. Br J Cancer 2024; 131: 1116-1125.
11. Martinez-Sanchez JM, Gallus S, Zuccaro P et al. Exposure to secondhand smoke in Italian non-smokers 5 years after the Italian smoking ban. Eur J Public Health 2012; 22: 707-712.
12. Gallus S, Borroni E, Odone A et al. The Role of Novel (Tobacco) Products on Tobacco Control in Italy. Int J Environ Res Public Health 2021; 18.
13. Lugo A, Asciutto R, Pacifici R et al. Smoking in Italy 2013-2014, with a focus on the young. Tumori 2015; 101: 529-534.
14. Istituto Superiore di Sanità. Comunicato Stampa N°39/2022 - Fumo: in Italia circa 800mila fumatori in più rispetto al 2019. Triplicato il consumo di sigarette a tabacco riscaldato. https://www.iss.it/en/comunicati-stampa/-/asset_publisher/fjTKmjJgSgdK/content/id/7146126. Published May 30, 2022. Accessed December 14, 2023.
15. Possenti I, Scala M, Odone A et al. Prevalence of cigarette smoking and secondhand smoke exposure in Italy in 2024. Tumori 2025; 111: 478-486.

16. Possenti I, Scala M, Girvalaki C et al. Attitudes towards tobacco and nicotine control policies in Italy: insights from a 2024 national survey. Submitted to Nicotine and Tobacco Research 2026.
17. Possenti I, Gallus S, Scala M et al. Estimating cancer cases and deaths attributable to smoking and secondhand smoke exposure at national level: a methodology based on individual-level data. Submitted to Lancet Regional Health - Europe 2026.
18. Possenti I, Gallus S, Odone A et al. Evaluation of digestive cancer cases, deaths, and DALYs attributable to tobacco smoking in Italy. Submitted to The Lancet Gastroenterology & Hepatology 2026.
19. Possenti I, Scala M, Rognoni M et al. Analysis of the direct economic impact of smoking-related hospitalizations in Italy. Tob Induc Dis 2024; 22.
20. Scala M, Lugo A, Gallus S. Support for smoke-free generation strategies in Italy. Lancet Reg Health Eur 2024; 44: 101013.
21. Perez-Rios M, Montes A. Methodologies used to estimate tobacco-attributable mortality: a review. BMC Public Health 2008; 8: 22.
22. Bagnardi V, Rota M, Botteri E et al. Alcohol consumption and site-specific cancer risk: a comprehensive dose-response meta-analysis. Br J Cancer 2015; 112: 580-593.
23. WHO. Alcohol is one of the biggest risk factors for breast cancer. Available online at: https://www.who.int/europe/news/item/20-10-2021-alcohol-is-one-of-the-biggest-risk-factors-for-breast-cancer (accessed 03 March 2023). 2021.
24. Possenti I, Gallus S, Lugo A et al. Best practices for secondhand smoke and secondhand aerosol protection and evidence supporting the expansion of smoke- and aerosol-free environments: Recommendations from the 2nd Joint Action on Tobacco Control. Tob Prev Cessat 2024; 10.
25. Friedman AS, Buckell J, Sindelar JL. Tobacco-21 laws and young adult smoking: quasi-experimental evidence. Addiction 2019; 114: 1816-1823.
26. Hyland A, Higbee C, Borland R et al. Attitudes and beliefs about secondhand smoke and smoke-free policies in four countries: findings from the International Tobacco Control Four Country Survey. Nicotine Tob Res 2009; 11: 642-649.
27. The Lancet Respiratory Medicine. The tobacco endgame: targeting the next generation. Lancet Respir Med 2023; 11: 493.
28. IARC. Effectiveness of Tax and Price Policies for Tobacco Control. IARC Handbooks of Cancer Prevention Volume 14. IARC 2011. Available online at: https://publications.iarc.fr/Book-And-Report-Series/Iarc-Handbooks-Of-Cancer-Prevention/Effectiveness-Of-Tax-And-Price-Policies-For-Tobacco-Control-2011. 2011.

Summary

Background and rationale

Tobacco smoking remains one of the leading preventable causes of cancer worldwide and continues to represent a major public health challenge in Italy. Although the carcinogenicity of active smoking is well established, important gaps persist in the quantification of site specific risks, the role of secondhand smoke (SHS), and the specific estimation of the population burden attributable to tobacco exposure. In addition, stagnating trends in smoking prevalence, the emergence of novel nicotine products, and evolving public attitudes towards tobacco control policies highlight the need for updated and integrated evidence to inform prevention strategies in Italy.

In response to this background, this PhD thesis aims to provide a comprehensive assessment of cancer risk and burden attributable to cigarette smoking and SHS exposure in Italy, combining updated epidemiological evidence, national data on exposure and attitudes, and methodological innovation in burden estimation.

Association between tobacco exposure and cancer risk

The thesis provides updated meta-analytical evidence confirming the strong association between active smoking and cancers of the upper aerodigestive tract. For nasopharyngeal cancer, pooled estimates presented in Chapter 2 showed a significantly increased risk among both current and former smokers, with clear dose-response relationships according to smoking intensity and duration. Similarly, Chapter 3 showed that smoking was associated with more than a twofold increased risk of oral and pharyngeal cancers among current smokers and a 60% increased risk for former smokers. Across sites, the analyses consistently demonstrated the cumulative and time dependent nature of tobacco related carcinogenesis, with progressive risk reduction following smoking cessation.

Beyond active smoking, a major contribution of this thesis concerns involuntary exposure. A comprehensive systematic review and meta-analysis presented in Chapter 4 provided strong evidence of an association between SHS exposure and breast cancer risk among never smoking women. The synthesis demonstrated a significant excess risk together with linear dose-response relationships for duration, intensity, and cumulative exposure, addressing long standing discrepancies in the literature. These findings suggest that SHS is an important preventable carcinogenic exposure in women's health.

Tobacco use, secondhand smoke exposure, and public attitudes in Italy

Using recent national data, Chapter 5 documents that tobacco use remains widespread in Italy despite decades of tobacco control efforts. Analyses

conducted within this work indicate that approximately one quarter of Italian adults are current smokers, with a substantial average daily cigarette consumption.

Exposure to SHS also remains common, with a meaningful proportion of non-smokers reporting daily indoor exposure, particularly in settings not fully covered by existing legislation, such as private homes, vehicles, and some workplaces. These patterns suggest persistent gaps in population protection.

At the same time, Chapter 6 provides evidence of broad public support for strengthening tobacco control policies in Italy. A clear majority of adults expressed support for fiscal measures, age-based restrictions such as Tobacco 21 and Smoke Free Generation proposals, and the extension of smoke free environments to electronic cigarettes (e-cig) and heated tobacco products (HTP). This combination of high exposure and strong public support highlights an important context for future tobacco control efforts.

Methodological innovation in burden estimation

A key contribution of this thesis is the development and application of a novel methodological framework to estimate cancer burden attributable to tobacco smoking, presented in Chapter 7. Traditional burden estimates typically rely on average relative risks applied to broad exposure categories, which do not fully capture heterogeneity in smoking histories or the time dependent reduction in risk after cessation.

In contrast, this thesis constructs individual level relative risks based on smoking status, intensity, duration, and time since cessation, calibrated using dose-response relationships from updated meta-analyses. Population attributable fractions (PAF) are then derived by aggregating individual excess risks, allowing the burden to reflect the true distribution of exposure in the population. This approach provides a realistic and flexible representation of risk and can be extended to SHS exposure and multiple cancer sites.

Health and economic burden of tobacco smoking

Applying this framework to national data, Chapter 8 quantifies a substantial burden of cancer attributable to tobacco smoking in Italy. High PAFs were observed for cancers of the digestive tract, including oral cavity and pharynx, oesophagus, stomach, and colorectum.

Beyond cancer, the thesis documents a considerable impact of smoking on healthcare utilisation in Chapter 9. Approximately one third of hospitalisations for

selected smoking related diseases were attributable to tobacco smoking, corresponding to direct hospital costs of about €1.64 billion in a single year.

Public health and policy implications

From a public health perspective, the findings underscore that tobacco use and SHS exposure remain central, preventable determinants of cancer burden in Italy. The identification of SHS as a breast cancer risk factor highlights the importance of protecting women from involuntary exposure and integrating SHS awareness into cancer prevention strategies alongside other lifestyle determinants such as alcohol consumption.

The coexistence of high smoking and SHS prevalence with strong public support for tobacco control indicates that meaningful reductions in burden are achievable. Strengthening enforcement of existing measures, preventing initiation among younger generations, and reducing exposure through comprehensive approaches remain key priorities.

Limitations

The findings of this thesis should be interpreted in light of some limitations, including the reliance on observational and self-reported data and the assumptions underlying burden estimation. Consequently, the estimated risks and population burdens are likely conservative approximations of the true impact of tobacco exposure.*Conclusions*

In summary, this thesis provides an integrated and updated assessment of tobacco attributable cancer risk and burden in Italy. By combining refined epidemiological evidence, contemporary national data, and methodological innovation, it moves beyond descriptive estimates to deliver decision relevant evidence. The results demonstrate that tobacco smoking and SHS exposure continue to generate a substantial and largely preventable burden on population health and the healthcare system, while also highlighting clear opportunities for prevention. The analytical framework and findings presented in this work can support more effective, equitable, and evidence based tobacco control strategies in Italy.

Riassunto

Contesto e razionale

Il fumo di tabacco rimane una delle principali cause prevenibili di tumore in tutto il mondo e continua a rappresentare una sfida importante per la salute pubblica in Italia. Sebbene la cancerogenicità del fumo attivo sia ben consolidata, permangono importanti lacune nella quantificazione dei rischi specifici per sede, nel ruolo del fumo passivo e nella stima specifica del carico di popolazione attribuibile all'esposizione al tabacco. Inoltre, il ristagno delle tendenze nella prevalenza dei fumatori, l'emergere di nuovi prodotti a base di nicotina e l'evoluzione delle opinioni della popolazione generale nei confronti delle politiche di controllo del tabagismo evidenziano la necessità di dati aggiornati e integrati per orientare in modo efficace le strategie di prevenzione in Italia.

In questo contesto, la presente tesi di dottorato mira a fornire una valutazione completa del rischio di tumore e del carico attribuibile al fumo di sigaretta e all'esposizione al fumo passivo in Italia, combinando dati epidemiologici aggiornati, dati nazionali sull'esposizione e sugli atteggiamenti della popolazione, insieme a innovazioni metodologiche nella stima del carico di malattia.

Associazione tra esposizione al tabacco e rischio di tumore

La tesi fornisce evidenze meta-analitiche aggiornate che confermano la forte associazione tra fumo attivo e il rischio di tumori del tratto aerodigerente superiore. Per il tumore rinofaringeo, le stime aggregate presentate nel Capitolo 2 hanno mostrato un aumento significativo del rischio sia tra i fumatori attuali che tra gli ex fumatori, con chiare relazioni dose-risposta rispetto all'intensità e alla durata del fumo. Analogamente, il Capitolo 3 ha mostrato che il fumo di sigaretta è associato a un aumento di oltre il doppio del rischio di tumori del cavo orale e della faringe nei i fumatori attuali e a un aumento del 60% del rischio negli ex fumatori. In tutti i siti tumorali considerati, le analisi hanno mostrato in modo coerente la natura cumulativa e dipendente dal tempo della carcinogenesi correlata al tabacco, con una progressiva riduzione del rischio dopo la cessazione del fumo.

Oltre al fumo attivo, un contributo importante di questa tesi riguarda l’analisi dell'esposizione involontaria a fumo passivo. Una revisione sistematica e meta-analisi completa presentata nel Capitolo 4 ha fornito evidenze robuste sull’associazione tra esposizione al fumo passivo e il rischio di tumore della mammella tra le donne che non hanno mai fumato. La sintesi ha dimostrato un eccesso di rischio consistente e relazioni dose-risposta lineari per la durata, l'intensità e l'esposizione cumulativa al fumo passivo, contribuendo a chiarire le incongruenze riportate da precedenti studi presenti nella letteratura scientifica.

Nel complesso, questi risultati collocano il fumo passivo come un'esposizione cancerogena rilevante e prevenibile per la salute delle donne.

Consumo di tabacco, esposizione al fumo passivo e opinione pubblica in Italia

Utilizzando dati nazionali recenti, il Capitolo 5 documenta come il consumo di tabacco rimanga ampiamente diffuso in Italia, nonostante decenni di sforzi e di interventi per il controllo del tabagismo. Le analisi condotte indicano che circa un quarto degli adulti italiani è attualmente fumatore, con un consumo medio giornaliero di sigarette piuttosto elevato.

Anche l'esposizione al fumo passivo rimane diffusa, con una percentuale significativa di non fumatori che riferisce un'esposizione quotidiana in ambienti chiusi, in particolare in contesti non completamente coperti dalla legislazione vigente, come abitazioni private, veicoli e alcuni luoghi di lavoro. Questi pattern suggeriscono persistenti lacune nella protezione della popolazione e sottolineano la necessità di interventi più mirati per ridurre l'esposizione al fumo passivo.

Allo stesso tempo, il Capitolo 6 evidenzia un ampio sostegno pubblico al rafforzamento delle politiche di controllo del tabagismo in Italia. Una netta maggioranza degli adulti si dichiara favorevole ad un inasprimento delle misure fiscali, a restrizioni basate sull'età, come le proposte Tobacco 21 e Smoke Free Generation, e all'estensione alle sigarette elettroniche e ai prodotti del tabacco riscaldato dei divieti di fumo in ambienti in cui è già vietato fumare sigarette tradizionali. La combinazione fra livelli elevati di fumo ed esposizione al fumo passivo e forte sostegno pubblico evidenzia un contesto importante per i futuri sforzi di controllo del tabagismo.

Innovazione metodologica nella stima del danno attribuibile

Un contributo fondamentale di questa tesi è lo sviluppo e l'applicazione di un nuovo quadro metodologico per la stima del danno attribuibile al fumo di tabacco, presentato nel Capitolo 7. I metodi tradizionali si basano in genere sui rischi relativi medi applicati ad ampie categorie di esposizione, che non tengono pienamente conto dell'eterogeneità delle abitudini di fumo o della riduzione del rischio nel tempo dopo la cessazione.

Al contrario, questa tesi ha permesso di costruire un metodo che utilizza rischi relativi a livello individuale basati sullo stato di fumatore, sull'intensità, sulla durata e sul tempo trascorso dalla cessazione, calibrati utilizzando relazioni dose-risposta provenienti da meta-analisi recenti e complete. Le frazioni attribuibili alla popolazione vengono quindi stimate aggregando gli eccessi di rischio a livello individuale, consentendo alla stima del carico attribuibile di riflettere la reale distribuzione dell'esposizione nella popolazione. Questo

approccio fornisce una rappresentazione realistica e flessibile del rischio e può essere esteso sia all'esposizione al fumo passivo che a più sedi tumorali.

Impatto sanitario ed economico del fumo di tabacco

Applicando questo metodo ai dati nazionali italiani, il Capitolo 8 quantifica un impatto sostanziale del carico dei tumori attribuibile al fumo di tabacco in Italia. Sono stati osservate frazioni attribuibili di popolazione elevate per i tumori dell'apparato digerente, compresi quelli del cavo orale e della faringe, dell'esofago, dello stomaco e del colon-retto.

Oltre all'ambito oncologico, il Capitolo 9 documenta anche un impatto considerevole del fumo sull'utilizzo dell'assistenza sanitaria. Circa un terzo dei ricoveri ospedalieri per patologie correlate al fumo è risultato essere direttamente attribuibile al fumo di tabacco, con un costo ospedaliero diretto di circa 1,64 miliardi di euro in un solo anno.

Implicazioni per la salute pubblica e le politiche

Dal punto di vista della salute pubblica, i risultati sottolineano come il consumo di tabacco e l'esposizione al fumo passivo continuino a rappresentare fattori centrali e prevenibili del carico di tumori in Italia. L'identificazione dell'esposizione al fumo passivo come fattore di rischio per il tumore alla mammella evidenzia l'importanza di proteggere le donne dall'esposizione involontaria e di integrare la consapevolezza dei rischi legati al fumo passivo nelle strategie di prevenzione oncologica insieme ad altri fattori modificali legati agli stili di vita, come il consumo di bevande alcoliche.

La coesistenza di un'elevata prevalenza del fumo e dell'esposizione al fumo passivo, insieme a un forte sostegno pubblico per il rafforzamento delle misure di controllo del tabagismo, indica che esistono ampie opportunità per ottenere riduzioni significative del carico di malattia. Il rafforzamento dell'applicazione delle misure già in vigore, la prevenzione dell'iniziazione al fumo tra le giovani generazioni e la riduzione dell'esposizione al fumo passivo attraverso approcci globali rimangono priorità fondamentali.

Limitazioni

I risultati di questa tesi devono essere interpretati alla luce di alcune limitazioni, tra cui l'affidamento su dati osservazionali e auto-riportati e le assunzioni alla base delle stime di carico attribuibile. Di conseguenza, i rischi stimati e il carico di malattia attribuibile sono probabilmente approssimazioni conservative dell'impatto reale dell'esposizione al tabacco.

Conclusioni

In sintesi, questa tesi fornisce una valutazione integrata e aggiornata del rischio di tumore attribuibile al tabagismo e del relativo impatto in Italia. Combinando evidenze epidemiologiche avanzate, dati nazionali aggiornati e innovazioni metodologiche, il lavoro va oltre le stime descrittive per fornire informazioni rilevanti e utili al processo decisionale. I risultati dimostrano che il fumo di tabacco e l'esposizione al fumo passivo continuano a generare un impatto sostanziale, e in gran parte prevenibile, sulla salute della popolazione e sul sistema sanitario, evidenziando al contempo chiare opportunità di prevenzione. Il quadro analitico e i risultati presentati in questa tesi possono supportare la definizione di strategie di controllo del tabagismo più efficaci, eque e basate su solide basi scientifiche nel contesto italiano.

Samenvatting

Achtergrond en motivering

Het roken van tabak blijft wereldwijd een van de belangrijkste vermijdbare oorzaken van kanker en vormt nog steeds een grote uitdaging voor de volksgezondheid in Italië. Hoewel het kankerverwekkende effect van actief roken algemeen erkend is, bestaan er nog steeds belangrijke hiaten in de kennis. Zo is er beperkte duidelijkheid over locatiespecifieke risico's, de rol van passief roken en de precieze ziektelast die aan tabaksblootstelling kan worden toegeschreven.

Daarnaast daalt het percentage rokers in Italië de laatste jaren nog maar nauwelijks: waar het vroeger duidelijk afnam, lijkt die daling nu af te vlakken. In combinatie met de opkomst van nieuwe nicotineproducten en veranderende publieke opvattingen over tabaksontmoedigingsbeleid onderstreept dit de noodzaak van geactualiseerde en geïntegreerde gegevens. Deze zijn essentieel om effectieve preventiestrategieën te ontwikkelen.

Tegen deze achtergrond heeft dit proefschrift tot doel een uitgebreide beoordeling te geven van het risico op kanker en de daarmee gepaard gaande lasten die toe te schrijven zijn aan het roken van sigaretten en de blootstelling aan passief roken in Italië. Hierbij wordt gebruikgemaakt van geactualiseerde epidemiologische gegevens, nationale gegevens over blootstelling en attitudes, en vernieuwende methoden voor het schatten van de lasten.

Verband tussen blootstelling aan tabak en het risico op kanker

Het proefschrift levert geactualiseerd meta-analytisch bewijs dat het sterke verband tussen actief roken en kanker van de bovenste lucht- en spijsverteringswegen bevestigt. Voor nasofaryngeale kanker, in Hoofdstuk 2 toonden gepoolde schattingen aan zowel huidige als voormalige rokers een verhoogd risico hadden, met duidelijke dosis-responsrelaties op basis van de intensiteit en duur van het roken. Hoofdstuk 3 liet eveneens zien dat roken samenhing met een meer dan verdubbeld risico op mond- en keelkanker bij huidige rokers en een 60% hoger risico bij voormalige rokers. Over alle locaties heen lieten de analyses consequent zien dat tabaksgerelateerde een het cumulatief en tijdsafhankelijk proces is, met een geleidelijke afname van het risico na stoppen met roken.

Naast actief roken besteedt dit proefschrift ook veel aandacht voor onvrijwillige blootstelling. In Hoofdstuk 4 leverde een uitgebreid systematisch overzicht en meta-analyse leverden overtuigend bewijs voor een verband tussen blootstelling aan passief roken en het risico op borstkanker bij vrouwen die nooit hebben gerookt. De synthese liet een verhoogd risico zien, samen met lineaire dosis-responsrelaties voor duur, intensiteit en cumulatieve blootstelling, en droeg daarmee bij aan het verklaren van langdurige inconsistenties in de literatuur.

Deze bevindingen onderstrepen dat passief roken een van de belangrijkste vermijdbare carcinogene blootstellingen is voor de gezondheid van vrouwen.

Tabaksgebruik, passief roken en publieke attitudes in Italië

Op basis van recente nationale gegevens toont Hoodfdstuk 5 aan dat tabaksgebruik in Italië nog steeds wijdverbreid is, ondanks decennia van inspanningen om tabaksgebruik terug te dringen. Uit analyses die in het kader van dit onderzoek zijn uitgevoerd, blijkt dat ongeveer een kwart van de Italiaanse volwassenen momenteel rookt, met een aanzienlijk gemiddeld dagelijks sigarettenverbruik.

Blootstelling aan passief roken kwam nog steeds veel voor: een aanzienlijk deel van de niet-rokers gaf aan dagelijks binnenshuis te worden blootgesteld, met name in omgevingen die niet volledig onder de bestaande wetgeving vallen, zoals privéwoningen, voertuigen en sommige werkplekken. Deze patronen wijzen op aanhoudende hiaten in de bescherming van de bevolking.

Tegelijkertijd toont Hoodfstuk 6 aan dat er brede publieke steun voor het versterken van het tabaksontmoedigingsbeleid in Italië. Een duidelijke meerderheid van de volwassenen sprak zich uit voor fiscale maatregelen, leeftijdsgebonden beperkingen zoals de voorstellen van Tobacco 21 en Smoke Free Generation, en de uitbreiding van rookvrije omgevingen naar elektronische sigaretten en verwarmde tabaksproducten. Deze combinatie van hoge blootstelling en sterke publieke steun benadrukt een belangrijke context voor toekomstige inspanningen op het gebied van tabaksontmoediging.

Methodologische innovatie bij het schatten van lasten

Een belangrijke bijdrage van dit proefschrift is de ontwikkeling en toepassing van een nieuw methodologisch kader voor het schatten van de kankerlast die toe te schrijven is aan tabaksgebruik. Dit kader wordt geïntroduceerd en toegepast in Hoofdstuk 7. Traditionele schattingen van de last zijn doorgaans gebaseerd op gemiddelde relatieve risico's die worden toegepast op brede blootstellingscategorieën. Hierdoor wordt onvoldoende rekening gehouden met de heterogeniteit in rookgeschiedenis en de tijdsafhankelijke vermindering van het risico na het stoppen met roken.

In tegenstelling hiermee worden in deze thesis relatieve risico’s op individueel niveau geschat op basis van rookstatus, intensiteit, duur en tijd sinds stoppen met roken, gekalibreerd met dosis-responsrelaties uit geactualiseerde meta-analyses. Vervolgens worden populatie-attributieve fracties (PAF) afgeleid door individuele excessrisico's te combineren, waardoor de geschatte ziektelast beter aansluit bij de werkelijke verdeling van blootstelling in de populatie. Deze

benadering levert een realistische en flexibele weergave van het risico en kan worden uitgebreid naar blootstelling aan passief roken en verschillende kankerlocaties.

Gezondheids- en economische last van tabaksgebruik

Door toepassing van deze methodologie in Hoofdstuk 8 kwantificeert het proefschrift de aan tabaksgebruik toe te schrijven kankerlast voor specifieke kankerlocaties in Italië.Daarbij werden hoge PAF's waargenomen voor kankers van het spijsverteringskanaal, waaronder de mondholte en keelholte, slokdarm, maag en dikke darm.

Naast kanker beschrijft Hoofdstuk 9 ook de aanzienlijke impact van roken op het gebruik van gezondheidszorg. Ongeveer een derde van de ziekenhuisopnames voor met roken geassocieerde ziekten was toe te schrijven aan tabaksgebruik, wat overeenkomt met directe ziekenhuiskosten van ongeveer 1,64 miljard euro in één jaar.

Implicaties voor de volksgezondheid en het beleid

Vanuit volksgezondheidsperspectief onderstrepen de bevindingen dat tabaksgebruik en passief roken belangrijke, vermijdbare determinanten blijven van de kankerlast in Italië.De identificatie van passief roken als risicofactor voor borstkanker onderstreept het belang van het beschermen van vrouwen tegen onvrijwillige blootstelling, en van het integreren van bewustwording hierover in kankerpreventiestrategieën, naast andere leefstijlfactoren zoals alcoholgebruik.

Het naast elkaar bestaan van een hoge prevalentie van roken en passief roken en een sterke publieke steun voor tabaksontmoediging suggereert dat een aanzienlijke vermindering van de lasten mogelijk is. Het versterken van de handhaving van bestaande maatregelen, het voorkomen van het beginnen met roken onder jongere generaties en het verminderen van blootstelling via een alomvattende aanpak blijven belangrijke prioriteiten.

Limitaties

De bevindingen van dit proefschrift dienen te worden geïnterpreteerd in het licht van enkele beperkingen, waaronder het gebruik van observationele en zelfgerapporteerde gegevens en de aannames die ten grondslag liggen aan de ziektelastschattingen. Hierdoor moeten de geschatte risico’s en de aan tabaksblootstelling toe te schrijven ziektelast worden beschouwd als conservatieve benaderingen van de werkelijke impact.

Conclusies

Samenvattend biedt dit proefschrift een geïntegreerde en geactualiseerde beoordeling van het aan tabak toe te schrijven kankerrisico en de daarmee samenhangende last in Italië. Door epidemiologisch bewijs, actuele nationale gegevens en methodologische innovatie te combineren, gaat het verder dan beschrijvende schattingen en levert het beleidsrelevant bewijs. De resultaten tonen aan dat tabaksgebruik en blootstelling aan passief roken een aanzienlijke en grotendeels vermijdbare last blijven vormen voor de volksgezondheid en het gezondheidszorgstelsel, maar wijzen ook op duidelijke mogelijkheden voor preventie. Het analytische kader en de bevindingen uit dit proefschrift kunnen bijdragen aan effectievere, rechtvaardigere en op bewijs gebaseerde strategieën voor tabaksontmoediging in Italië.

Impact Statement

During this PhD, the findings of the included studies have been disseminated to a wide audience, including researchers, students, practitioners, policy stakeholders, and the general public, through multiple channels.

Peer-reviewed publications

During this PhD, the scientific outputs generated through the eight studies included in the thesis have generated substantial peer-reviewed dissemination, contributing directly to the international literature on tobacco epidemiology, secondhand smoke (SHS) exposure, methodological innovations in burden estimation, and tobacco control. Six of the eight manuscripts have already been accepted or published in peer-reviewed journals [1-6], demonstrating the scientific relevance and quality of the work. The manuscript presenting the new methodological framework presented in Chapter 7 is currently undergoing a second round of peer-review at Lancet Regional Health - Europe, reflecting the work's scientific robustness and its relevance within the European public health research landscape [7]. The eighth manuscript has also been submitted to an important indexed journal [8]. Together, these publications have contributed to shaping scientific discussions on tobacco-related cancer risk, burden estimation, and prevention priorities by providing updated risk estimates, national exposure data, and transparent methodological approaches, and have been used as reference points in ongoing debates on tobacco control within the Italian and international research community.

Importantly, the findings from the study on smoking-attributable healthcare costs have also been presented to institutional stakeholders in a dedicated presentation at the Italian Senate, thereby directly informing policy-oriented discussions on the economic impact of smoking.

These publications demonstrate the advances that the thesis has delivered in multiple domains. These include updated and harmonised meta-analytical evidence on the carcinogenic effects of tobacco and SHS exposure, contemporary estimates of smoking and involuntary exposure in Italy, and the development of an individual-level framework for estimating cancer burden attributable to smoking. The publication record therefore reflects not only the breadth of research undertaken but also its capacity to inform diverse fields, from cancer epidemiology to behavioural surveillance and health-system evaluation.

Together, these peer-reviewed contributions form the scientific basis of the thesis, ensuring its findings are accessible, verifiable and reusable by researchers, clinicians, decision-makers and public health institutions.

Oral speeches

During the PhD, the thesis findings were actively disseminated at leading national and European scientific events, enabling direct engagement with researchers, practitioners and policy-adjacent audiences. The results on the burden of tobacco on the healthcare system (Chapter 9) were first presented as a poster at the 2023 European Conference on Tobacco or Health (ECToH) in Madrid, and were subsequently presented as oral communications at the 2024 XX National Congress of the Italian Society of Tobaccology (SITAB) in Rimini and the 2025 European Network for Smoking and Tobacco Prevention (ENSP) Conference in Belgrade. This process enabled the work to evolve from receiving initial feedback from peers to being discussed more widely among clinicians, public health professionals, and tobacco control advocates, thereby strengthening the external validation of the methodology and its applicability to health system planning.

Complementing these contributions, the analyses in Chapter 6, including support for measures such as Tobacco-21, Smoke-Free Generation, and the extension of smoke-free environments to electronic cigarettes and heated tobacco products, were presented as a poster at the World Conference on Tobacco Control 2025 in Dublin, reaching a global audience of experts.

Additionally, the results from Chapters 4 and 7 concerning the methodological framework for estimating individual-level burden and the systematic review and meta-analysis on SHS exposure and the risk of breast cancer, respectively, were presented as an oral communication at the 2025 XX National SITAB Congress in Pisa. This provided an opportunity to introduce the methodological innovation to a national audience of epidemiologists and tobacco control practitioners and to discuss the implications of SHS exposure for women's cancer prevention.

Across these meetings, the presentations facilitated rigorous question-and-answer exchanges, fostered connections for future collaboration and helped to align the thesis outputs with ongoing European debates on prevention priorities, SHS protection and the evaluation of policy feasibility.

Press releases and media coverage

A further dimension of dissemination throughout this PhD has been the substantial engagement with the national press and media outlets, which has significantly broadened the reach of the research beyond academic and professional audiences. In particular, the study presented in Chapter 9, received extensive visibility in the Italian context and was featured by several of the most prominent Italian newspapers and media networks, including Il Sole 24 Ore, Repubblica, and ANSA, among others [9-11]. This wide circulation contributed to bringing the economic implications of tobacco use, quantified through smoking-attributable hospitalisations and direct healthcare costs, into the public

discourse, increasing visibility of smoking-attributable healthcare costs among policymakers and the general public.

Media engagement extended also to the work reported in Chapter 4, which was highlighted in a dedicated press release by the Italian Association on Cancer Research (AIRC; Fondazione AIRC per la Ricerca sul Cancro) [12]. By presenting the findings in an accessible format and emphasising the public health relevance of SHS exposure, particularly for women who have never smoked, this coverage has helped to raise awareness of a carcinogenic risk that is not widely recognised.

Overall, press releases and media reporting were crucial in raising public awareness of scientific evidence by bringing key findings on smoking-attributable healthcare costs and SHS related cancer risks to national newspapers, news agencies, and institutional communication channels, thereby reaching journalists, policy stakeholders, healthcare professionals, and the general public. This visibility facilitated informed public debate, increased recognition of tobacco as a preventable driver of cancer and healthcare expenditure, and amplified the relevance of the research within Italy's health-policy and cancer-prevention landscape.

Podcast and Radio communication

Podcasts and radio outreach provided an additional avenue of dissemination, offering the opportunity to translate scientific concepts into formats accessible to a broader and more diverse public.

During the PhD, I took part in a live radio interview on Giornale Radio [13], focusing specifically on the findings of the study presented in Chapter 9, which quantified the economic impact of smoking on hospitalisations and direct healthcare costs in Italy. This format enabled the dissemination of the thesis results to an even wider audience, reaching individuals who do not usually engage with traditional academic or online scientific content.

At the same time, I had the opportunity to develop a three-episode podcast series entitled Tobacco-Free Talks, which was published on YouTube. The series was designed to communicate key issues related to tobacco, nicotine products, and cancer prevention through an engaging and conversational style [14-16]. It originated during an exchange period at the ENSP in Brussels, part of the European Commission project EUREST-RISE [17], where I could draw on the organisation's experience in evidence-based communication. While the podcasts did not focus exclusively on the findings of my PhD research, they provided a valuable platform for presenting selected results. These included insights on SHS exposure, women's health, and the burden of tobacco-related cancers, presented

within a broader narrative aimed at improving health literacy and dispelling misconceptions about tobacco use. Podcast episodes were presented and discussed in several middle and high-school settings, supporting health education activities and stimulating informed debate among adolescents, a key target group for primary prevention.

Through the radio segment and podcast series, the research gained greater visibility beyond academic and institutional contexts, encouraging more informed public discussion about tobacco, cancer prevention and the societal implications of smoking and SHS exposure in the general population.

Presentations and engagement with young audiences

In addition to academic and media dissemination, part of the impact of this PhD was realised through direct educational activities involving adolescents and educators working in school settings.

Recently, I took part as a speaker in a training programme for early-childhood educators held in Naples, where I delivered educational content on the concept of addiction, its behavioural and social determinants, and its relevance for prevention at early ages. This experience allowed the translation of scientific knowledge into pedagogical perspectives, supporting educators in addressing prevention-related topics in an age-appropriate manner.

Furthermore, I participated in a prevention-focused meeting at a secondary school, where I had the opportunity to engage directly with students and answer to their questions regarding the relationship between smoking, cancer risk, and disease prevention. The interaction with students highlighted both a strong interest in health-related topics and the importance of clear, evidence-based communication tailored to young audiences. The experience gained throughout the PhD proved essential in facilitating informed discussion and addressing misconceptions around smoking and cancer.

Together, these activities contributed to strengthening health education and awareness among young people and educators, reinforcing the role of scientific expertise in supporting early prevention efforts and informed dialogue in school environments.

Overall impact of the research

Overall, the dissemination activities undertaken during this PhD have had a broad and multidimensional impact, reaching scientific, professional, institutional and public audiences.

Peer-reviewed publications ensured the core findings were integrated into the international evidence base, making them available to researchers, clinicians, and public health agencies. Presenting scientific work at major national and European conferences enabled direct engagement with experts in epidemiology, tobacco control and health system planning. These events facilitated constructive discussion, supported methodological refinement and increased the visibility of the work within the European tobacco control community.

Media coverage and press releases further extended the reach of the research, bringing key findings into the public domain. This raised awareness among decision-makers, journalists and citizens of the health and societal implications of tobacco exposure. Podcasts and radio interviews provided an additional means of engaging the public, translating complex scientific concepts into accessible information for non-specialist audiences and raising awareness of the harms associated with tobacco. Finally, the dissemination activities also included direct educational engagement with adolescents and educators.

Taken together, these dissemination efforts helped ensure that the knowledge generated throughout the PhD reached scientific, policy, and public audiences. This creates a strong foundation for the future impact of the thesis, which is explored in the following section.

Future impact of the generated knowledge

The evidence generated in this PhD has strong potential to shape future developments in research, surveillance, and cancer-prevention practice. The refined site-specific risk estimates, including those on SHS exposure and breast cancer risk, provide a robust scientific basis that can be integrated into national prevention programmes and targeted communication strategies, particularly those aimed at women and younger individuals. In this context, further school-based meetings and educational activities are also planned, with the aim of continuing to translate scientific evidence into age-appropriate prevention messages and to support informed discussion among adolescents.

The individual-level burden framework developed in this thesis is designed to be applied to all cancer sites causally associated with smoking and SHS, and, as evidence grows, can be readily adapted to estimate the burden attributable to novel nicotine products. This flexibility positions the framework as a tool that can support national burden estimation, scenario modelling, and policy evaluation, particularly in settings lacking individual-level exposure integration.

Importantly, the thesis also provides timely insights for the Italian policy landscape. Currently, Italy is experiencing a national signature campaign that proposes increasing the price of all smoking and nicotine inhalation products by

5 euros. This campaign is led by major cancer and public health organisations. The updated risk evidence, burden estimates and public support data produced in this PhD provide metrics that can be used to contextualise and evaluate such initiatives, informing discussions on the expected population impact and potential reductions in smoking prevalence and SHS exposure.

Overall, the knowledge developed in this thesis provides a scientifically robust foundation for future progress in cancer prevention, burden estimation and policy analysis, thereby supporting Italy's efforts to reduce tobacco-related harm.

References

1. Possenti I, Martini A, Bagnardi V et al. Association between cigarette smoking and nasopharyngeal cancer risk: a meta-analysis. Rhinology 2025; 63: 13-21.
2. Possenti I, Miotti S, Gallus S et al. Smoking and Oral and Pharyngeal Cancer: A Meta-Analysis. Oncology Reviews 2025; 19.
3. Possenti I, Scala M, Carreras G et al. Exposure to second-hand smoke and breast cancer risk in non-smoking women: a comprehensive systematic review and meta-analysis. Br J Cancer 2024; 131: 1116-1125.
4. Possenti I, Scala M, Girvalaki C et al. Attitudes towards tobacco and nicotine control policies in Italy: insights from a 2024 national survey. Submitted to Nicotine and Tobacco Research 2026.
5. Possenti I, Scala M, Odone A et al. Prevalence of cigarette smoking and secondhand smoke exposure in Italy in 2024. Tumori 2025; 111: 478-486.
6. Possenti I, Scala M, Rognoni M et al. Analysis of the direct economic impact of smoking-related hospitalizations in Italy. Tob Induc Dis 2024; 22.
7. Possenti I, Gallus S, Scala M et al. Estimating cancer cases and deaths attributable to smoking and secondhand smoke exposure at national level: a methodology based on individual-level data. Submitted to Lancet Regional Health - Europe 2026.
8. Possenti I, Gallus S, Odone A et al. Evaluation of digestive cancer cases, deaths, and DALYs attributable to tobacco smoking in Italy. Submitted to The Lancet Gastroenterology & Hepatology 2026.
9. Redazione Roma. Il fumo costa in ricoveri 1,64 miliardi. L'Istituto Mario Negri: imporre accise. Available online at https://www.ilsole24ore.com/art/il-fumo-costa-ricoveri-164-miliardi-l-istituto-mario-negri-imporre-accise-AGFwFBY. Il Sole 24 ORE 2024.
10. Fumo, i costi dei ricoveri ospedalieri pesano per 1,6 miliardi di euro l'anno sulle casse dello Stato. Available online at https://www.repubblica.it/salute/2024/06/12/news/fumo_costi_danni_salute-423218654/. Repubblica 2024.
11. Redazione ANSA. Il fumo pesa sui ricoveri per 1,64 miliardi l'anno. Available online at https://www.ansa.it/canale_saluteebenessere/notizie/medicina/2024/06/12/il-fumo-pesa-sui-ricoveri-per-164-miliardi-lanno_d60e2f2d-ec03-4d67-a12f-a867f3bd76e7.html. ANSA 2024.
12. Il fumo passivo aumenta il rischio di tumore al seno. Available online at https://www.airc.it/traguardi-dei-ricercatori/il-fumo-passivo-aumenta-il-rischio-di-tumore-al-seno. AIRC 2024.
13. Giornale Radio. Availlable online at https://giornaleradio.fm/.
14. ENSP Bruxelles. Tobacco-free Talks Ep.1 (ITA): Sanremo ha smesso di fumare? Available online at https://www.youtube.com/watch?v=fcT8LJdqmbs. 2025.

15. ENSP Bruxelles. Tobacco-free Talks Ep.2 (ITA): Nuovi prodotti, facciamo chiarezza. Available online at https://www.youtube.com/watch?v=kHBA87jHZqo. 2025.
16. ENSP Bruxelles. Tobacco-free Talks Ep.3 (ITA): Ambiente, animali, sfruttamento: i danni meno noti del tabacco. Available online at https://www.youtube.com/watch?v=yENSlkNy8bs. 2025.
17. EUREST-RISE: An innovative networking and training MSCA on European Tobacco Control. Available at https://www.eurest-project.eu/.

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About the author

Irene Possenti was born in Brescia, Italy, on December 2nd, 1998. She obtained her Bachelor's degree in Statistics and Information Management from the University of Milan-Bicocca in 2020, followed by a Master's degree in Statistical Sciences from the Alma Mater Studiorum - University of Bologna in 2022. In the same year, she began her PhD in Epidemiology and Public Health at Maastricht University (School of CAPHRI).

Throughout her doctoral training, she has developed a strong scientific profile in the field of cancer epidemiology, with a particular focus on preventable risk factors, most notably cigarette smoking and secondhand smoke exposure, and their impact on human health. During her PhD, she authored over fifteen peer-reviewed publications, with several additional manuscripts currently under review or in press, contributing methodological, epidemiological, and public-health insights to the international literature.

Her research work has also enabled her to actively promote the importance of healthy lifestyles and primary prevention, both within Italy and internationally, through scientific dissemination and communication initiatives.

Alongside her PhD, Irene Possenti's role at the Mario Negri Institute allowed her to participate in several national and international collaborative research projects, supported by the European Commission, the Italian Ministry of Health, and major Italian cancer charities including the Italian Association for Cancer Research (AIRC) and the Italian League Against Cancer (LILT). These experiences further strengthened her expertise in epidemiology and public health and fostered collaborations across multidisciplinary research environments.

List of publications

1. Possenti I, Martini A, Bagnardi V et al. Association between cigarette smoking and nasopharyngeal cancer risk: a meta-analysis. Rhinology 2025; 63: 13-21.
2. Possenti I, Miotti S, Gallus S et al. Smoking and Oral and Pharyngeal Cancer: A Meta-Analysis. Oncology Reviews 2025; 19.
3. Possenti I, Scala M, Carreras G et al. Exposure to second-hand smoke and breast cancer risk in non-smoking women: a comprehensive systematic review and meta-analysis. Br J Cancer 2024; 131: 1116-1125.
4. Possenti I, Scala M, Odone A et al. Prevalence of Cigarette Smoking and Secondhand Smoke Exposure in Italy in 2024. Tumori Journal 2025; 111: 478-486.
5. Possenti I, Scala M, Girvalaki C, et al. Attitudes towards tobacco and nicotine control policies in Italy: insights from a 2024 national survey. Nicotine Tob Res, 2026.
6. Possenti I, Gallus S, Scala M et al. Estimating cancer cases and deaths attributable to smoking and secondhand smoke exposure at national level: a methodology based on individual-level data. Submitted to The Lancet Regional Health - Europe 2026.
7. Possenti I, Gallus S, Odone A et al. Evaluation of digestive cancer cases, deaths, and DALYs attributable to tobacco smoking in Italy. Submitted to The Lancet Gastroenterology & Hepatology 2026.
8. Possenti I, Scala M, Rognoni M et al. Analysis of the direct economic impact of smoking-related hospitalizations in Italy. Tob Induc Dis 2024; 22.

