INTERNATIONAL SMOKING-RELATED BURDEN OF CANCER AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE AT THE TURN OF THE TWENTY-FIRST CENTURY

Geographic and temporal variations within Europe and the United States

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Een internationale studie van tabak gerelateerde last door kanker en chronisch obstructief longlijden

Geografische variatie binnen Europa en de Verenigde Staten

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"J'irai au bout de mes rêves,
Tout au bout de mes rêves.
J'irai au bout de mes rêves,
Où la raison s'achève,
Tout au bout de mes rêves.
J'irai au bout de mes rêves. »

Jean-Jacques Goldman (pop singer) 1982

To Raphaël, Aldébaran, Iris and Eridan

CONTENTS

1

Introduction

1.1 BACKGROUND

The discovery of the link between lung cancer, chronic obstructive pulmonary disease and tobacco: a brief history

While the 1964 Report of the US Surgeon General[1] is often regarded as a turning point in the recognition that cigarette smoking causes several cancers and chronic obstructive pulmonary disease (COPD), the evidence took time to build and was much disputed along the way. Before the twentieth century, lung cancer was a rare disease[2] (around 1 death per 100 000).[3] In 1900, an increase in lung cancer mortality was noted by vital statisticians.[1] The possible association between lung cancer and tar — highly used in road construction and known to cause skin cancer in mice — was presented in 1926 by De Vries, a Dutch pathologist, at the first World Congress on Cancer Control, in New York. He had observed increases in the proportion of lung cancer deaths in his autopsies, from 1% in 1901 to 10% in 1925.[4]

Lung cancer was not yet a concern, and cigarettes were not suspected, probably because most men of higher socioeconomic status smoked, including doctors and scientists. In 1929, in Germany, and 2 years later in the Netherlands – based on autopsies — it was declared plausible that smoking caused lung cancer. The first case-control study was published in 1939 by Müller from the Cologne Hospital.[5] He showed that lung cancer patients were far more likely to have smoked compared with cancer-free controls. Around that time, increases in lung cancer incidence and mortality became more conspicuous, with around 10 men out of 100 000 dying from lung cancer in the US (Figure 1).[6] In this country, it corresponded to less than 3 000 deaths per year, with women contributing very little.[1]

This was only the dawn of massive cigarette smoking in the US, made possible by the invention of the cigarette rolling machine in the 1880s (Figure 2), pushed by advertising and what would become modern marketing.

Likewise, in England and Wales, there was a fifteenfold increase in the number of deaths from lung cancer between 1922 and 1947.[3] This led Hill and Doll to conduct a study on 1,732 cancer patients and 743 controls on exposure to smoking, car and fuel fumes, and occupational exposure. They concluded that smoking was an important factor in the cause of carcinoma of the lung.[3] In 1948, Wassink, a Dutch surgical oncologist, linked smoking and cancer based on smoking patterns of patients with lung cancer versus those with skin cancer.[7] Notwithstanding those alarming news, smoking remained almost universal in industrialized countries, at least among men. In the Netherlands, 90% of men[8] and 30% of women[9] smoked in 1958. One year

earlier, at the urge of the US general Surgeon General, a study group on smoking and health, composed of members of the American Cancer Society, the American Heart Association, the National Cancer Institute, and the National Heart Institute, concluded, based on 16 studies from 5 countries that:[10]

- Lung cancer occurs five to fifteen times more frequently among smokers than nonsmokers;
- One of every ten men who smoked more than two packs of cigarettes a day died of lung cancer;
- Smoking cessation reduces the risk of lung cancer occurrence.

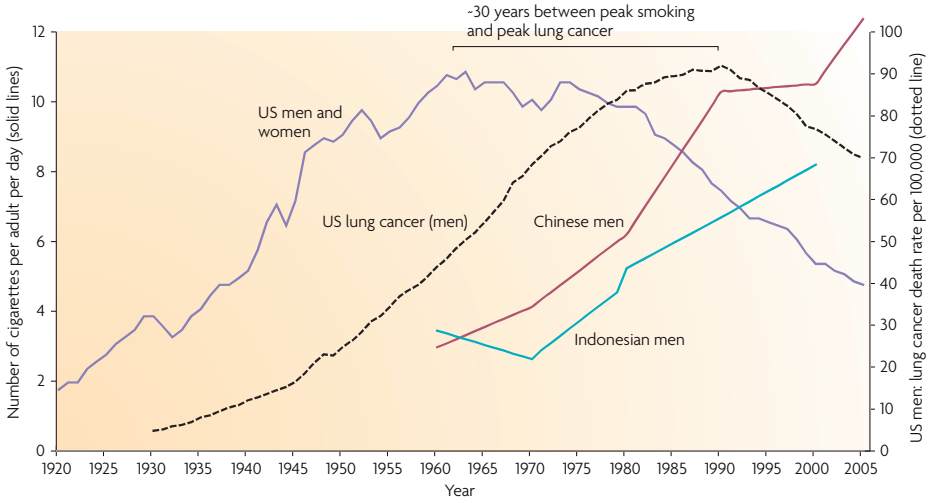

Figure 1. Trends in cigarette consumption and male lung cancer rates, 1920–2005.
Source:[6]

At that point, the tobacco industry was already toiling to create and maintain doubt over the causal relationship between cigarette smoking and lung cancer.[10] In 1959, the Cancer Prevention Study I (CPS I) recruited one million people in the US to examine the association of tobacco use with cancer and other causes of death.[11] By virtue of its large sample size, CPS I offered solid quantification of some mortality risks — including lung cancer and COPD — in relation to smoking.[11] In the meantime, the extraordinary rise in lung cancer deaths remained unabated: 18 000 deaths in 1950, 27 000 deaths in 1955, reaching 41 000 deaths in 1962, in the US.[1] Similarly, rapid increases in deaths from chronic bronchitis and emphysema were observed in the US: from 2 300 in 1945 to 15 000 in 1962.[1] The Surgeon General's report,[1] released in 1964, was the decisive milestone in the ever growing evidence that smoking was causally related to several diseases, including lung cancer and chronic bronchitis (a term then used for the disease now generally referred to as COPD). That year, 68% of

the male and 32% of the female US population was smoking cigarettes, adding up to nearly 70 million people.[1]

Since then, the list of diseases linked to smoking – although continuously contested[12] – has expanded to include nearly all organs (Figure 3). In the latest report released in 2014,[13] fifty years after the first Surgeon General's report, 12 cancers were confirmed to be linked to cigarette smoking: oropharynx, larynx, esophageal, lung, stomach, liver, pancreas, kidney and ureter, cervix uteri, urinary bladder and acute myeloid leukemia. In 2004, the International Agency for Research on Cancer (IARC) had established a few more smoking-related cancers:[14] oral cavity, nasopharynx, hypopharynx, nasal cavity, paranasal sinuses and ovary.

Figure 2. Cigarette rolling machine. Circa 1880. Louisiana State University Rural life museum. Baton Rouge, Louisiana, USA.

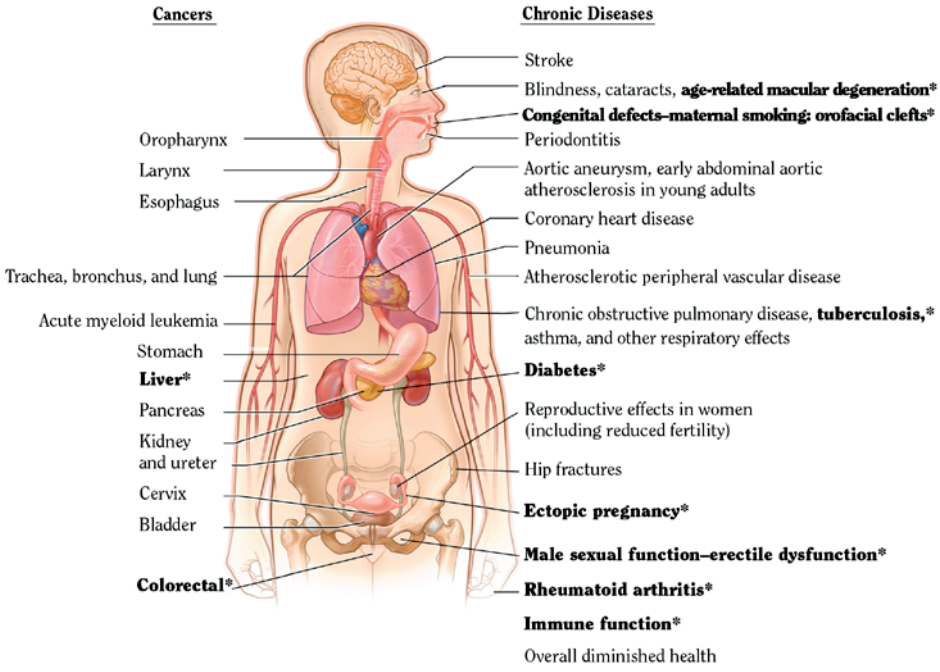

Figure 3. The health consequences causally linked to tobacco smoking.
Sources: USDHHS 2004, 2006, 2012, in 2014 Surgeon General's report.[13] Note: conditions in bold and followed by an asterisk are new diseases that have been added as causally linked to smoking in the 2014 report.

Water-pipes, a common way of smoking tobacco in North Africa and Southwest Asia, and increasingly popular in the US, expose to the same toxicants and carcinogens as cigarette — plus high levels of carbon monoxide and polycyclic aromatic hydrocarbons from the burning charcoal.[15] Cigars and pipes cause cancer as well.[16] Secondhand tobacco smoke induces lung cancer[14] and other smoking-related diseases commonly diagnosed among smokers. In total, 15% of lung cancer cases among individuals who have never smoked in the UK in 2010 were due to exposure to secondhand smoke.[17] Finally, smokeless tobacco causes cancer of the oral cavity, esophagus, and pancreas.[14]

However, the chapter on the list of diseases triggered by tobacco, whether smoked or smokeless, might not be closed yet. Indeed, new evidence shows that even more cancers[18] and more diseases[19] could be caused by cigarette smoking. Also, the mechanistic link between lung cancer and COPD is being further investigated.[20]

In the next chapters, the burden of smoking-related cancers and COPD at the turn of the twenty-first century, and their relationship with smoking will be examined. Given the gender differences in smoking prevalence, both burdens will be studied by sex.

The burden of smoking-related cancers

Between 2000–2007, tobacco use has been associated with 5–6 million deaths per year worldwide, around 15% of which are cancer deaths.[6]

Lung cancer represents the main smoking-related diagnosed cancer and has been the most commonly diagnosed cancer worldwide for several decades.[21] Seventy-one percent of lung cancer deaths worldwide are attributable to smoking[22] (75% in the US).[23] Because of the strong causal relation between smoking and lung cancer, its disease patterns and trends are more influenced by changes in smoking prevalence than those of other smoking-related cancers. Other risk factors of lung cancer (Table 1) include outdoor and indoor air pollution, radon, and occupational exposure. They play a more important role in lung cancer occurrence in populations with low smoking prevalence. Globally, about a quarter of lung cancer cases occurs in people who have never smoked (only 10-15% in Europe and the US).[24] In Eastern Asia, lung cancer is common in non-smoking women, likely as a result of exposure to indoor air pollution, genetic susceptibility of some Asian populations, and cooking oil heating (oil heated to high temperatures in woks for stir-frying food emits volatile carcinogens) in some regions.[25]

Table 1. Risk factors of lung cancer

Tobacco smoking, including secondhand smoke
Radon
Occupational exposure to polycyclic aromatic hydrocarbons, certain metals, asbestos, crystalline silica, and wood dust
Outdoor air pollution, specifically to particulate matter and diesel engine exhaust
Indoor air pollution, including emissions from household combustion of coal, and cooking oil heating
Genetic factors
COPD

Sources[25-27]

Worldwide, there were an estimated 1.8 million new lung cancer cases (13% of all cancer diagnoses) and 1.6 million deaths (19% of all cancer deaths) in 2012.[21] The annual number of deaths is close to the number of new cases due to the poor prognosis of patients with lung cancer, even in high income countries (5-year relative survival of 19% in 2005–2009 in the US and 15% in the Netherlands).[28]

Lung cancer incidence and mortality rates vary 80–fold from one country to another.[21] Incidence and mortality rates are higher in men than in women, reflecting historical differences in smoking behavior. The global maps presented in Figure 4a show the lung cancer mortality in each sex. On the one hand, in men (Figure 4A), the highest lung cancer incidence rates are in Europe, Eastern Asia, and Northern America. Among women, the highest lung cancer rates are in Northern America, Northern and Western Europe, Australia/New Zealand, and Eastern Asia (Figure 4)Figure 4B. These are the regions where smoking prevalence has been the highest or still is.[29] On the other hand, rates are low in Africa, parts of Asia and Latin America.

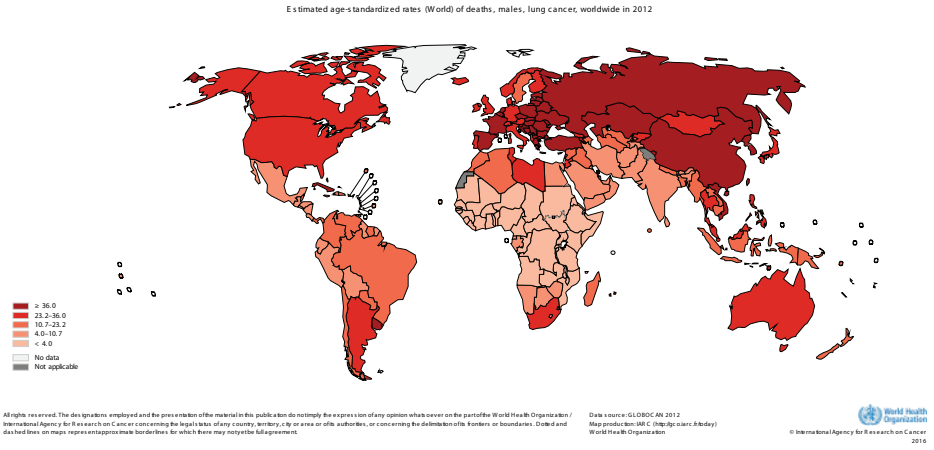

Figure 4a. Estimated age-standardized (world) lung cancer mortality rate in men in 2012.
Source: http://globocan.iarc.fr/

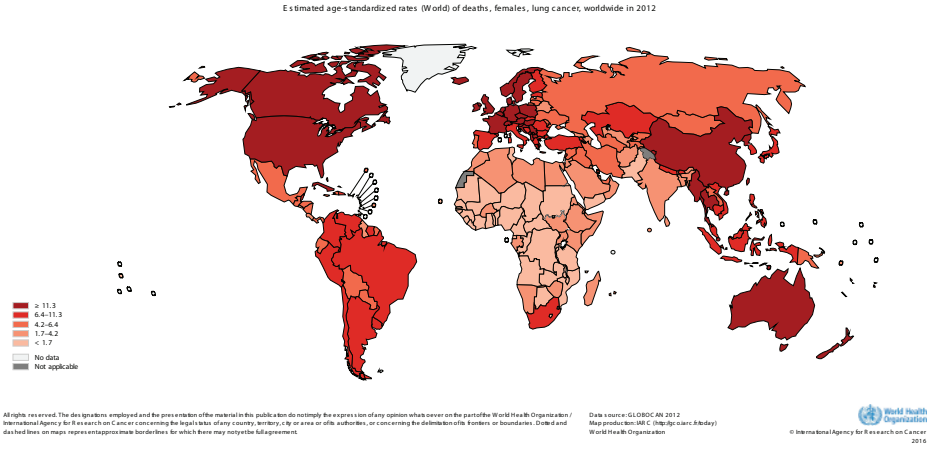

Figure 4b. Estimated age-standardized (world) lung cancer mortality rate in women in 2012.
Source: http://globocan.iarc.fr/

If the distribution of the lung cancer mortality depicted on the worldwide maps shadows the differences in prevalence of lung cancer risk factors (mainly smoking) within countries, lung cancer incidence and mortality rates also vary at sub-national level. For instance, lung cancer rates are higher in the Netherlands in regions where tobacco-transformation industries are established[30] and in the US in states[31] where tobacco is grown.

Women started to massively smoke cigarettes later than men, after new cigarettes (filtered, 'light' and 'low tar') had been made available on the market. Those new

cigarettes, marketed as 'safer', generated as many lung cancer cases, but different types of lung cancer (more on this in chapter 2.2). In the US, cigarette smoking peaked during World War II among men born the 1920s, and approximately ten years later among women born in the 1930s.

According to the Surgeon General, smoking causes 11 types of cancer besides lung cancer.[13] The risk of lung cancer diagnosis among current or former smokers is generally higher than for other tobacco-related cancers.[32] The risks of cancer diagnosis in former and current cigarette smokers as compared to never smokers in smoking-related disease is similar to the risk of cancer.[32] For instance, the risk of dying from liver cancer for current and former smokers compared with never smokers (around 2 and 1.3, respectively) is similar to the risk of dying from stroke. The risk of cancer diagnosis and cancer death are lower in former than current smokers. For example, current male smokers have 25 times more chances die from lung cancer than never smokers, and former male smokers have 7 times more chances die from lung cancer than never smokers (Table 2).

Table 2. Mortality risk estimates in former and current cigarette smokers as compared to never smokers, for smoking-related cancers and chronic diseases

	Men		Women	
	Former	Current	Former	Current
Cancer				
Lung	6.8	25.3	6.8	22.9
Laryngeal	2.4	13.9	11.6	103.8
Oral cavity and Pharyngeal	1.7	5.7	2.2	5.6
Esophageal	2.6	3.9	2.2	5.1
Bladder	2.4	3.9	2.3	3.9
Liver	1.5	2.3	1.1	1.8
Stomach	1.5	1.9	1.1	1.7
Acute myeloid leukemia	1.4	1.9	1.1	1.1
Kidney, Renal pelvis, Ureter	1.5	1.8	1.2	1.2
Pancreatic	1.0	1.6	1.2	1.9
Colorectal	1.2	1.4	1.2	1.6
Cervical	-	-	1.1	1.6
Other non-communicable diseases				
COPD	7.5	27.8	9.2	25.0
Ischemic heart disease	1.5	2.6	1.6	3.0
Stroke	1.2	1.9	1.2	2.1

Sources: [13, 19,33]

The population attributable fraction (PAF) of tobacco smoking in cancer was computed by Parkin for the UK (Table 3).[17] For example, 71% of esophageal cancer cases in women were explained by smoking.

Table 3. Proportion of cancer cases attributable to smoking in 2010 in the UK and cancer deaths attributable to smoking in 2011 in the US

	Incidence (UK)[a17]		Mortality (US)[23]	
	Men (%)	Women (%)	Men (%)	Women (%)
Lung	85	80	83	76
Laryngeal	79	79	72	93
Oral cavity and Pharyngeal	70	55	49	43
Esophageal	63	71	52	44
Bladder	38	34	47	41
Liver	27	15	28	14
Stomach	26	15	26	11
Acute myeloid leukemia	19	6	23	3
Kidney, Renal pelvis, Ureter	29	15	22	7
Pancreatic	26	31	10	14
Colorectal	7	10	11	8
Cervical	-	7	-	22
Ovarian	-	3		
All cancers	**23**	**16**	**34**	**24**

[a] includes secondhand smoke

The PAF in a population varies according to the prevalence of the exposure to the risk factor in that population (see Figure 9). Hence the listed estimates are only valid in populations with similar historical smoking patterns. Eventually, 19% of all new cancer cases were attributable to smoking in the UK in 2010,[17] 13% in Australia the same year,[34] 12% in Korea in 2009.[35] Smoking caused 23% of all cancer deaths in Korea in 2009,[35] 31% in France in 2010,[36] 29% in the US in 2011,[23] and 31% in Indonesia in 2013.[37]

Although progress in early detection and implementation of screening in high risk groups are under way,[38,39] as well as better staging and new therapies,[40,41] lung cancer still has a high fatality rate.[28] Further, improvement in survival over the last four decades has been only marginal (the 5-year relative survival increased from 12% in 1989–1991 to 15% in 2007–2009 in Dutch men[42] and from 12% in 1975–1977 to 18% in 2005–2011 in the US).[43] Survival rates for some of the other smoking-related cancer are also very low: <10% for pancreatic cancer,[44] <20% for liver[28] and esophageal cancers.[44] Survival rates are intermediate in stomach (20–30%),[28] in colon and

rectum (>40%),[28] oral cavity and laryngeal cancers (each around 60%),[44] and high in for bladder cancer (around 75%).[44]

Primary prevention targeted at curbing smoking remains the best method to combat major cancers including lung, esophageal, oral cavity and pharyngeal, laryngeal, and bladder cancer, and also other smoking-related cancer. Smoking is a leading cause of cancer worldwide and the largest preventable cause of cancer in the European Union.[45] In practice, Stoeldraijer et al. recommend to make tobacco dependence treatment a standard of clinical care.[46] Moreover, people often combine the tobacco smoking with other poor – modifiable – lifestyle choices such as alcohol abuse,[47] unhealthy diet, and lack of physical activity, all of which make them more prone to cancer.

The burden of chronic obstructive pulmonary disease

The definition of COPD has been changing over time since the first classification of obstructive airway diseases in 1959. Today, COPD is composed as a diverse syndrome with no single disease entity. It encompasses emphysema and the obstructive form of chronic bronchitis.[48]

The list of risk factors for COPD is very long, but the key cause of COPD is tobacco smoking (including passive exposure in-utero and during childhood) (Table 4).[49] Smokers are 25 times more likely to die from COPD than never smokers (Table 2).[19]

Table 4. Risk factors of COPD that have a role during different stages of life

Stage of life	Risk factor
Host factors	• Family history of chronic obstructive pulmonary disease • Family history of asthma/atopy • Genetic constitution • Bronchial hyper-responsiveness • Atopy • Low lung function
Perinatal factors	• Maternal smoking • Maternal exposure to air pollution • Antibiotic use • Mode of delivery • Preterm birth
Childhood exposures	• Respiratory tract infections • Maternal smoking • Indoor and outdoor air pollution • Obesity/nutritional development • Childhood asthma • Airway failure to thrive
Adult exposures	• Occupational exposures • Indoor biomass exposure • Cigarette smoking • Outdoor air pollution • Indoor air pollution

Source: Postma et al.[49]

About 40–50% of lifelong smokers will develop COPD, compared with only 10% of never smokers.[50]
The condition becomes clinically apparent around the age of 40–50 years, and in many instances, at least in High-income countries, COPD patients will die from another cause.[51] COPD is commonly under-diagnosed not only in its early stages, but also when lung function is severely impaired, and hence is generally under-treated.[52] As COPD takes years to develop, prevalence is preferred to incidence to measure the burden of the condition. Prevalence of COPD is estimated to be around 10% in adults aged 40+,[53] with large differences between populations ranging from 13% in Guangzhou, China and Hannover, Germany to 14% in Manila, Philippines, 24% in Cape Town, South Africa,[54] and 24% in Maastricht, Netherlands,[55] and increases with age.[52] Despite being underestimated (73% undiagnosed in Spain, 88% in Latin America),[56] COPD imposes a significant burden in terms of impaired quality of life, ranking the 8th leading cause of Years of Lived with Disabilities worldwide in 2013.[57]

Historically, COPD has been far more frequent in men than in women, due to industrial occupational exposures and higher smoking prevalence in men. However, COPD prevalence seems to become more equally observed in men and women in high-income countries, where smoking is now similar between sexes. Today, the number of women dying from COPD in the US surpasses the number of men,[13] and the gap is closing in the Netherlands (37% of COPD deaths in women in 2000 vs. 47% in 2014).[58] Whether women are more susceptible to development of COPD than men, given equal exposures, continues to be investigated, but some evidence lends support to this hypothesis. Women may have more symptoms than men for the same number of pack-years (a measure of duration and intensity of smoking) smoked.[50] This question is important as women in low- and middle-income countries with historically a low prevalence of smoking are increasingly targeted by tobacco marketing to increase their cigarettes consumption.[59] Another possible reason for the gender differences observed is that men and women smoked different cigarettes.

COPD male death rates were estimated[60] to be the highest in Bulgaria, Georgia, Argentina and China (Figure 5A), in 2013. This is likely due to high past smoking prevalence.[61] Female death rates were estimated to be highest in North Korea, Denmark, Greece, China and India, as well as in the USA and Argentina (Figure 5B). Smoking prevalence in Denmark and Greece is indeed high among women (30%[62] and 26%, respectively), but low in India and China (3% and 2%, respectively).[61] In those Asian countries, other risk factors may play a more important role, such as indoor air pollution.[63] Conversely, death rates were lowest in Africa and the Middle-East, in both males and females.

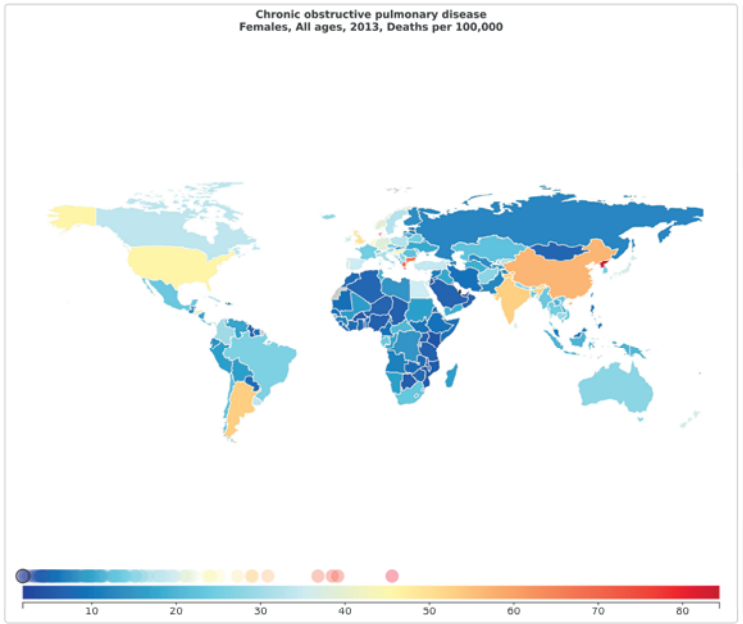

Figure 5A. Mortality from Chronic Obstructive Pulmonary Disease (age standardized rate per 100,000) for all ages in males, in 2013.
Source: Institute for Health Metrics and Evaluation[60]

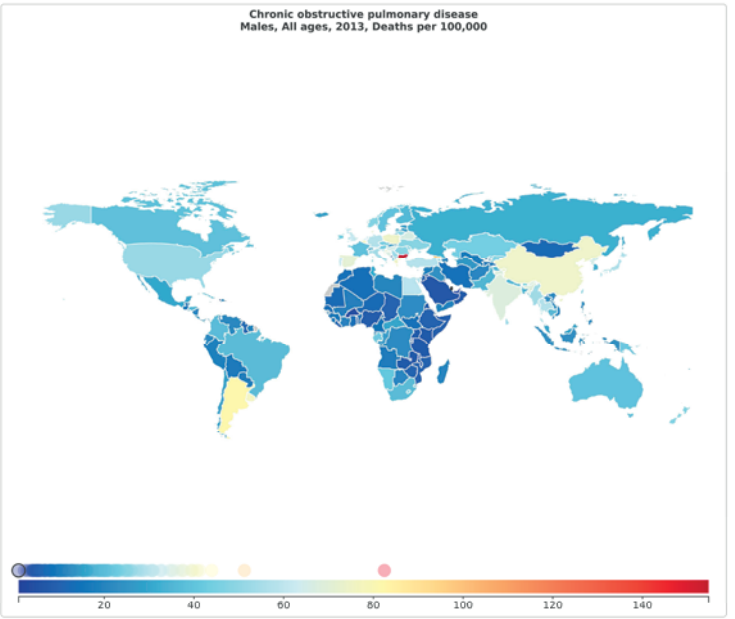

Figure 5B. Mortality from Chronic Obstructive Pulmonary Disease (age standardized rate per 100,000) for all ages in females, in 2013.
Source: Institute for Health Metrics and Evaluation[60]

According to the WHO, in 2015, COPD was the 4th leading cause of death worldwide with 3.2 million deaths (5.6% of all deaths), and is predicted to reach the 3rd place by 2030, representing 6.5% of deaths.[64] COPD deaths are expected to further increase due to increased exposition to risk factors (such as tobacco smoking in women in low- and middle-income countries, and outdoor air pollution) and to population aging and growth. As people live longer, they are more likely to experience the consequences of long-term exposure to COPD risk factors.[50] Today, more than 100,000 people die from COPD each year in the US,[13] 9,000 in the Netherlands, and 35,000 in the UK.[60]

Although COPD can now be managed,[65] it can hardly be considered as curable. The natural history and duration of COPD makes that burden of disease very high because for many years, it may go undiagnosed and untreated.
Both lung cancer and COPD are managed by pulmonologists and patients often have both conditions. For example, Dutch studies reported that COPD was the second most frequent comorbidity in lung cancer patients (found in 22% of patients), after cardiovascular disease (23% of patients) in 1993–1995,[66] and was present in 30% of lung cancer patients in 1995–2004.[67] As a result, it has been proposed to offer lung cancer screening to both smokers[68] and never smokers[69] who suffer from COPD.

In 2000, in the US, lung cancer represented 1% of all smoking-related conditions, while chronic bronchitis and emphysema represented 35% and 24% of them, respectively.[13] COPD is a major burden to many individuals, societies and healthcare budgets[52,70] throughout the world. No other disease responsible for comparable morbidity, mortality and cost is neglected by healthcare providers as much as COPD.

Recent trends in smoking-related disease burden and predictions

The global burden of disease attributable to tobacco smoking including secondhand smoke appears to be quite stable (from 6.1% to 6.3% of Disability-Adjusted Life Years [DALY] [see paragraph page 28] between 1990 and 2010).[71] However, the burden has now shifted to different world regions cancelling out when DALYs are assessed at global level. The decreases in high-income regions were offset by increases in regions such as Asia. As cigarettes are made available to a larger number of people by the tobacco industry, particularly in low- and middle-income countries (Figure 6), the burden of smoking-related diseases is bound to increase.[62]

Even in high-income countries, where the burden of smoking-related diseases is large but decreasing in men, the burden will continue to increase for some time in women,

as they massively picked-up smoking later than men. Also, the risk of lung cancer and COPD has increased over time due to changes in cigarettes.[13] For instance, a recent study in northern Europe predicts that smoking-attributable mortality will remain important for the future, especially for women.[46] In the Netherlands, the smoking-attributable mortality in men is estimated to decline from 25% in 2009 to 14% in 2050 (Figure 7). In contrast, in women, the smoking-attributable mortality is estimated to increase from 12% in 2009 to 23% in 2033 and then decline to 19% in 2050. Smoking also has an impact on the national life expectancy,[74-76] and on the mortality gender gap.[77]

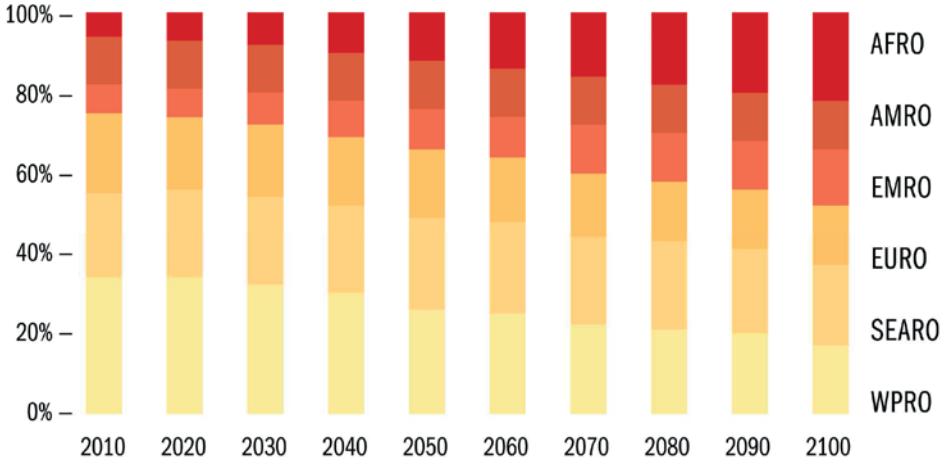

Figure 6. Estimated proportion of the world's adult smokers (men and women combined) living in each WHO region, with current tobacco control policies, over 2010-2100. AFRO (Africa), AMRO (the Americas), EMRO (the Eastern Mediterranean), EURO (Europe), SEARO (South-East Asia) and WPRO (the Western Pacific).
Source: extrapolated from Mendez et al.,[72] presented in the Tobacco Atlas[73]

As the diagnosis and death of smoking-related cancers and COPD occur after a couple of decades of exposure to tobacco smoking, even if smoking prevalence continues to decline worldwide, those diseases are likely to remain a major burden for the decades to come. The WHO predicts that the worldwide proportion of COPD deaths among all causes of deaths will increase from 6.6% in 2015 to 8.6% in 2030, and from 2.8% to 3.4% for lung cancer, respectively (as reported in The European lung white book).[50] It takes time to see the benefits of policies —such as tobacco-control policies— to prevent non-communicable diseases such as cancer[78] and COPD.[79]

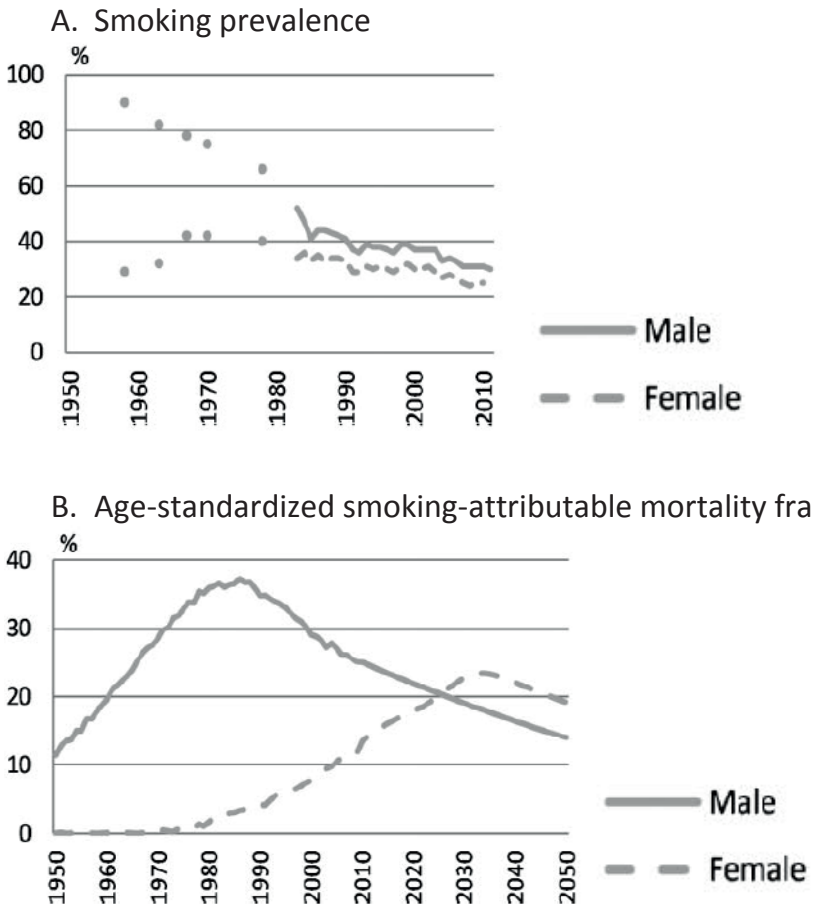

Figure 7. A. Smoking prevalence (%); B. Age-standardized smoking-attributable mortality fraction (%) in the Netherlands for 1950–2009 (observations) and 2010–2050 (projections), by sex.
Source: Stoeldraijer et al.[46]

1.2 DATA SOURCES

To investigate the burden of COPD and cancer, I have benefited from preferred access to some databases thanks to the organizations I worked for: first at IARC, in France, then at the American Cancer Society (ACS), in the USA. While working at IARC, I had prime access to Cancer Incidence in Five Continents and GLOBOCAN data. I further took advantage of the EUROCOURSE project, which aims at improving the use of cancer registries in European countries, by using data (EUREG) from the European Network of Cancer Registries. The ACS closely works with the North American Association of Central Cancer Registries (NAACCR), which allowed me to access restricted data.

Those data sources have limitations, as population coverage may be limited, the data may be of insufficient quality, not available for over long periods, or not recent. Data quality covers completeness of data, which depends not only on the completeness of the registries, but also on the degree of ascertainment (requiring access to specialized care and the availability and quality of death certificates).

Incidence

Incidence informs on the number of new cases over a defined period in a defined population. It can be expressed as an absolute number of new cases per year or as a rate per 100,000 persons per year. Incidence data were extracted from population-based cancer registries, which collect, register and analyze information on all new cancer cases in a defined population. The following international datasets were exploited: Cancer Incidence in Five Continents (CI5) series[80-83] and EUREG.[84] Both of these datasets have passed through a high level of quality standards looking at comparability, completeness and validity of the data.[80] Comparability is the extent to which a registry's coding and classification procedures and definitions adhere to established international standards and guidelines. Completeness is the degree to which all diagnosed cancer within a registry's catchment population are included in the registry database. Validity (or accuracy) is the proportion of cases recorded as having a given characteristic that truly do have that attribute.
There are fewer long-standing high-quality cancer registries in low- and middle-income countries. In particular, population coverage in Africa is still very low (Figure 8).

In addition, for United States, data were obtained from the NAACCR[85] and the Surveillance, Epidemiology and End Results (SEER) program from the National Cancer Institute.[86] NAACCR data provide quasi national coverage, while SEER offers information from population-based cancer registries in 17 geographic areas that encompass nearly 26% of the US population for longer periods of time (nine registries started in 1973).

Global incidence estimates at national level in 2012 were derived from GLOBOCAN.[21]

Mortality

Mortality is the number of deaths occurring in a given period in a specified population. It can be expressed as an absolute number of deaths per year or as a rate per 100,000 persons per year. International data for cancer and COPD deaths were obtained from the WHO mortality database,[87] which compiles the cause of death data from national offices. For the US, I used data from the Centers for Diseases Control and Prevention (CDC).[88]
All mortality datasets are at national level. Yet, mortality data are available for only for part of the national population (e.g. cause of death is registered in 4% of deaths in

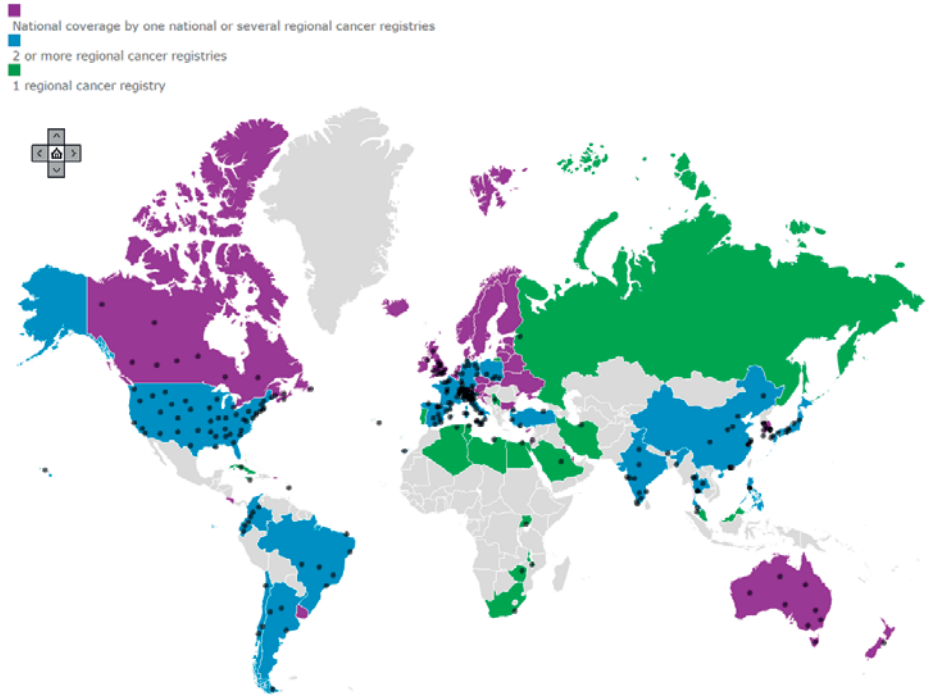

Figure 8. Location of the 290 cancer registries (black points) in 68 countries selected for data publication in Cancer Incidence in Five Continents Volume X (2003 to 2007).
Source: http://ci5.iarc.fr/CI5-X/Pages/registry-map.aspx

China, 93% in Brazil, and 100% in the Netherlands). For my studies, only high-quality data were used for greater international comparisons (high population coverage, low frequency of ill-defined causes of death, and few missing age at death).

Survival

The standard survival index is relative survival. It measures the excess mortality experienced by cancer patients compared with the general population. It is calculated by dividing the observed survival from all causes of death for the patient cohort by the expected survival in a comparable group not diagnosed with cancer as estimated by life tables. Relative survival is a theoretical population-based measure representing cancer survival in the absence of other causes of death. However, to estimate the US burden of cancer (chapter 3.1), I was interested in cancer survival in Hispanics and in minorities in the US (i.e. Asians), for whom there are no life tables available. Therefore, cause-specific survival was used, as recommended by Howlader et al.[89] Cause-specific survival is a net survival measure representing cancer survival in the absence of other causes of death. It estimates the probability of surviving a specific

cause of death (e.g. lung cancer). Estimates are calculated using a standard life table approach where individuals who die of causes other than the one specified are considered to be censored. Cause-specific survival data were provided by SEER.[86] They were used to compute the cure fraction in the US. This fraction is a statistical measure of the proportion of the patients who will have the same probability of dying than the general population. The cure fraction was used to determine the proportion of patients who will survive after a cancer diagnosis and the proportion of patients who will eventually die from their cancer.

Population

Population data were obtained from the corresponding sources where available (CI5,[80] SEER),[86] or completed with UN estimates.[90]

Population data originate from national census and are interpolated for the years between the census. Depending on the census frequency and its quality, population estimates may or may accurately reflect the actual population.

Health surveys – tobacco prevalence

Smoking is measured by prevalence (the proportion of persons in a defined population who smoke in a given year). Smoking prevalence in the US came from two surveys. The first one, BRFSS (Behavioral and Risk Factor Survey System),[91] is a health-related telephone survey that collects data about US residents regarding their health-related risk behaviors, chronic health conditions, and use of preventive services, in 50 states, Washington DC, and three U.S. territories. The BRFSS completes more than 400,000 adult interviews each year. The second one, NHIS (National Health Interview Survey),[92] has been collecting a broad range of health topics through personal household interviews, for over 50 years. The data are collected by the US Census Bureau in around 35,000 households containing about 87,500 persons, every year.

While those surveys are designed to be overall representative at state (BRFSS) or national (NHIS) level, the number of analyses by sub-group (sex, race/ethnicity, age) may be limited by sample size in some categories. Data from the 2 surveys on 14 domains were compared, including smoking. It was concluded that BRFSS and NHIS provided comparable national estimates.[93]

1.3 METHODS

To assess the burden of cancer and COPD and differences over time, between countries, sexes and sub-populations (within the US), classic descriptive epidemiological methods (age-standardized rates, trend analysis), advanced methods involving mod-

eling (age-period-cohort analysis), and complex indicators (Disability-Adjusted Life Years and population attributable fraction) were used.

Time trend analyses

To compare disease incidence or mortality between populations and over time, the event rate is standardized over a theoretical population, to obtain age-standardized rates (ASR). The world standard[94] was employed for international studies and the US 2000 population[95] for US-only studies. This process of age-standardization of the rates further allows to overcome the effect of age, which is key factor in both cancer and COPD incidence and mortality. To assess the changes in the rates, Joinpoint regressions[96] were used. It involved fitting a series of joined straight lines to ASR trends and measuring the slope of the fitted lines.[97] The monitoring of secular trends plays a direct role in determining possible causes of diseases, assessing the need for disease control measures, and in continually evaluating implemented disease-control programs.

Age-Period-Cohort analysis

Analyses encompassing the three underlying time components of age, period of event (diagnosis or death) and birth cohort offers additional insights to temporal studies of a disease. Time happens to be key in diseases such as cancer and COPD. The odds of diagnosis and mortality increase with age, due to the accumulation of genetic mutations necessary for the normal cell to become abnormal, as a result of the exposure to risk factors or stochastic events. The introduction of new detection technics (e.g. prostate-specific antigen blood concentration for prostate cancer, spirometry for COPD) in a population can increase the number of diagnoses, while the introduction of technics to remove pre-cancerous lesions (e.g. colonoscopy for colon cancer, PAP smear followed by treatment for cervical cancer) can decrease the number of diagnoses in a short period, in the entire population. Finally, successive cohorts can be increasingly exposed to carcinogens or agents which cause COPD. For example, smoking prevalence can increase or decrease in successive generations, starting around age 15-20. As such, age-period-cohort analyses provide clues as to the factors that drive a disease, informing the debate on prevention strategies.[98]

Disability-Adjusted Life Years

A composite index, called Disability-Adjusted Life Years (DALY) was developed in the 1990s to assess the burden of diseases and injuries.[99] One DALY can be thought of as the loss of one year of "healthy" life. The sum of these DALYs across the population, or the burden of disease, can be thought of as a measurement of the gap between current health status and an ideal health situation where the entire population lives to an advanced age, free of disease and disability.

DALY for a disease or health condition are calculated as the sum of the Years of Life Lost (YLL) due to premature mortality in the population, and the Years Lost due to Disability (YLD) for people living with a decreased quality of life due to a health condition or its consequences.[100]

Population attributable fraction

Relative risk (RR) is the ratio of the probability of an event occurring (for example, developing a disease) in an exposed group, to the probability of the event occurring in a control, non-exposed group. The Population Attributable Fraction (PAF) estimates the contribution of a risk factor to the disease burden in a defined population. The PAF accounts for both an estimate of relative risk as well as prevalence of the risk factor in the population (Figure 9). The PAF describes the proportional reduction in disease that would occur if exposure to a risk factor were to be eliminated.

For estimating the smoking-attributable burden of cancer, the formula for multi-category exposure[101] was used

$$PAF_s = \frac{\left(p_{0,s} + p_{1,s}\left(RR_{1,s}\right) + p_{2,s}\left(RR_{2,s}\right)\right) - 1}{p_{0,s} + p_{1,s}\left(RR_{1,s}\right) + p_{2,s}\left(RR_{2,s}\right)}$$

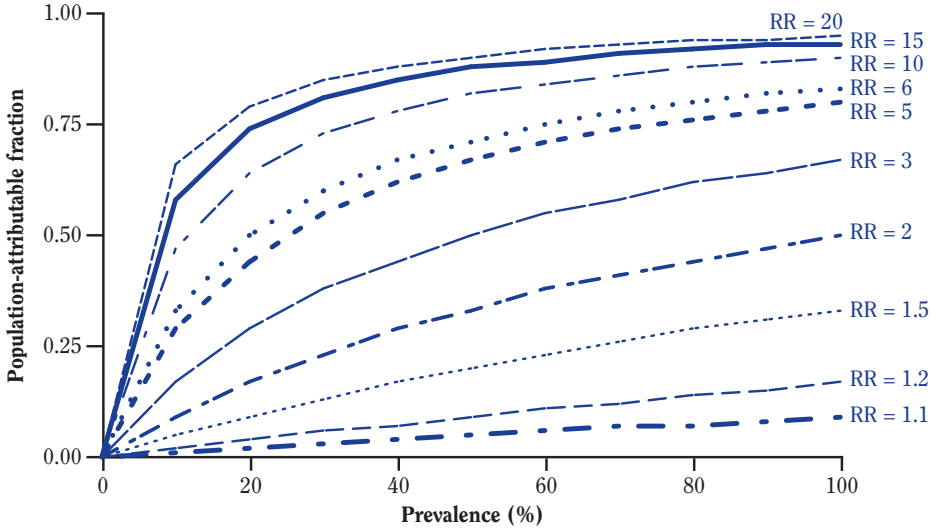

Figure 9. The relationship of relative risk (RR) to the population attributable fraction at different prevalence levels.[13]

p_0 is the proportion of never smokers, p_1 of former smokers and p_2 of current smokers. RR_1 is the relative risk for former smokers compared with never smokers, and RR_2 for current smokers compared with never smokers.

1.4 THIS THESIS

Rational

The tobacco epidemic impacts numerous diseases (Figure 3). My research aims to assess the burden of two major non-communicable diseases related to smoking, namely cancer and COPD.

Despite the decline in smoking prevalence in some industrialized countries thanks to tobacco control and awareness of the deleterious effects of smoking on health, a substantial number of the population still smokes (e.g. 40 million in the US,[102] 172 million in Europe).[103] Declines in smoking prevalence are already reflected in declines in smoking-related diseases in some countries, including in smoking-related cancers and COPD. Nevertheless, the burden of these two diseases is considerable. Smoking caused 6.1 million deaths in 2013 globally, and was the second leading risk factor for DALYs.[104] Furthermore, smoking prevalence is increasing in developing countries due to the investment of the tobacco industry into those untapped markets, where tobacco control is still weak. Smoking-related morbidity and mortality need to be prevented in those countries as well.

While it is known that smoking causes cancer and COPD, to what extent does it explain diseases occurrence today? And which populations are most impacted by smoking-related cancers and COPD? Where is the burden of these diseases increasing and decreasing?

In this thesis, I will specifically address these questions:

What is happening in the gender gap in smoking-related cancers?

- In which populations is the gender-specific incidence of smoking-related cancer still increasing in Europe?
- How does cigarette type influence lung cancer histology in men and in women?

What is the burden of smoking-related cancers in the US?

- Do non-Hispanic Blacks have a higher cancer burden and smoking-related cancer burden than other racial/ethnic groups in the US?
- Do people living in tobacco-growing states of the US have a higher burden of cancer mortality attributable to cigarette smoking?

What is the impact of smoking on another important non-communicable disease: COPD?

My contribution in assessing the burden of those two diseases is the highlight of the areas of progress —where the burden is decreasing— and areas of concern. My work provides the tools needed to continue the advocacy for tobacco control, and also for planning for health care resources —both of which are integral components of disease control programs. My strategy is to decipher the present smoking-related disease burden by getting clues from the past (smoking history and recent diseases trends), and to instruct evidence-based decisions today to improve the future burden of diseases. The ultimate objectives of this thesis are to stress the continuing need for tobacco control and to identify priority populations for tobacco control.

This research is performed at international-level, and at country-level in the US.

The international-level perspective reports smoking-related cancers and COPD burdens and trends. Countries in different regions of the world are at different stages of the tobacco epidemic, as updated by Thun *et al*.[105] In the first of the four stages, smoking prevalence is very low but increasing, while smoking-related deaths (including cancers) in the middle-ages are very rare (e.g. in women in sub-Saharan Africa).[106] During the second stage, smoking prevalence is still increasing and smoking-related deaths are increasing too. During the next stage, smoking prevalence are leveling off then decreasing, while smoking-related deaths are still on the increase (e.g. in Dutch women). Finally, in the fourth stage, both smoking prevalence and smoking-related deaths are declining (e.g. in both sexes in the US and the UK, and in Dutch men).[105]

The national-level perspective allows the examination of the influence of social norms and tobacco control on the epidemic of smoking and the subsequent rise (and fall) of smoking-related diseases at a finer level. The US are a key country in the history of smoking epidemic for at least three reasons. First, tobacco is native to the Americas. It was used as a medicine and as a hallucinogen by native American, and brought back to Europe by Spanish explorers in the sixteenth century. Second, it is in the US that the shift from roll-your-own cigarettes and pipes to manufactured cigarettes operated, thanks to the invention of the automated cigarette machine in the 1880s. Thirdly, the US played a pivotal role in the ascertainment of the crucial role of tobacco in the upsurge of several diseases, building on what had been initiated by European scientists. The natural progression of this discovery was the implementation of tobacco control

measures and the tentative to eliminate —or at least weaken— the tobacco industry, which key steps also involved the US. Moreover, the US has a large and diverse population which permits to investigate diseases at various levels such as state and race/ethnicity. Finally, the late stage of the smoking epidemic in the US is illustrative of the situation of other high-income countries, and can forecast the situation in countries where the smoking epidemic is at an earlier stage.

Finally, I acknowledge that the approach to answer the overarching study question "what is the impact of smoking on two non-communicable diseases?" has been largely influenced by the two organizations I worked for while pursuing my PhD. I started my thesis while working at IARC, for the Cancer Surveillance Section under the supervision of Dr. Freddie Bray. The key focus of the Section is the "systematic and ongoing pursuit of global cancer data and statistics for cancer control action, in keeping with one of the primary aims of IARC —to describe and elucidate cancer occurrence worldwide." The Section has a keen interest on cancer registry support and development, in global cancer indicators, and in advancing descriptive epidemiology of cancer. As a WHO agency, the mission of IARC is at global level. Hence, the first two articles of this corpus, written at IARC, have a strong international outlook. In particular, the study on trends in new cancer cases in European aimed at demonstrating the value of a new European incidence database (EUREG). Meanwhile, the goal of the Surveillance and Health Services Research program I worked for at the American Cancer Society (ACS) under the supervision of Dr. Ahmedin Jemal is to analyze population-based information on cancer occurrence, its causes, prevention, and treatment to "strengthen the scientific basis for cancer prevention and control nationally and globally". In particular, this group has a strong interest in racial/ethnic disparities in the US, which motivated the studies of the burden of cancer and of the smoking-related cancer by race and ethnicity. Results from the group, and other groups in the Intramural Research Department, are directly used by the ACS lobby at national, and at state-level, to advocate for laws preventing cancer (such as tobacco control laws and the Affordable Care Act), and in favor of cancer patients and survivors. Advancing the agenda of state-level tobacco control policy was the rationale behind the study comparing state-level smoking-attributable cancer mortality fractions. Finally, ACS also reaches to other academic and non-governmental organizations working on other non-communicable diseases to fight common risk factors (such as smoking). This is how the last piece of work on COPD was made possible in a cancer-focused organization. Regardless of the differences in tactics, both IARC and ACS endeavor at reducing the burden of cancer.

Contents

Smoking causes at least 12 cancers and I examine the incidence trends in Europe of the four cancers that are the most associated with smoking (laryngeal, lung, esophageal and oral cavity and pharyngeal cancers) (**Chapter 2.1**). I detect the convergence of male and female incidence rates. Cigarette is a product that has evolved over time, to meet the needs of consumers anxious about their health. Cigarettes gained a filter, and became low-tar –making them supposedly less deleterious. Those changes have shifted the type (histology) of the most frequent cancer caused by smoking: lung cancer. This shift is reported in Europe, Northern America and Australia in **Chapter 2.2** and gender differences are stressed.

As a preliminary step to the evaluation of the smoking-related burden of cancer in the US by race/ethnicity, I assess the burden of all cancers in the country, using DALY. With the DALY index, I compare the healthy life years loss due to each cancer and highlight cancer control priorities (**Chapter 3.1**). Then, I assess the tobacco-attributable fraction of the burden of cancer by race/ethnicity, as it turns out that each group has a different smoking prevalence based on social norms — fueled by targeted tobacco industry marketing — and level of acculturation (Hispanics, Asians) (**Chapter 3.2**). Subsequently, I study geographic (state) disparities in the US smoking-related cancer mortality, as most of tobacco control policies in the US are decided at state level (**Chapter 3.3**).

Finally, I contrast international trends of COPD and lung cancer mortality rates in an effort to tease out the influence of smoking on COPD mortality (**Chapter 4.1**).

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2

Gender differences in international incidence of smoking-related cancers

2.1

Convergence of male and female incidence rates in major tobacco-related cancers in Europe in 1988–2010

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ABSTRACT

Introduction: Smoking prevalence has been declining in men all over Europe, while the trend varies by European region among women. To study the impact of past smoking prevalence, we present a comprehensive overview of the most recent trends in incidence, during 1988–2010, in 26 countries, of four of the major cancers in the respiratory and upper gastro-intestinal tract associated with tobacco smoking.

Methods: Data from 47 population-based cancer registries for lung, laryngeal, oral cavity and pharyngeal, and oesophageal cancer cases were obtained from the newly developed data repository within the European Cancer Observatory (http://eco.iarc.fr/). Truncated age-standardised incidence rates (35–74 years) by calendar year, average annual percentage change in incidence over 1998–2007 were calculated. Smoking prevalence in selected countries was extracted from the Organisation for Economic Co-operation and Development and the World Health Organization databases.

Results: There remained great but changing variation in the incidence rates of tobacco-related cancers by European region. Generally, the high rates among men have been declining, while the lower rates among women are increasing, resulting in convergence of the rates. Female lung cancer rates were above male rates in Denmark, Iceland and Sweden (35–74 years). In lung and laryngeal cancers, where smoking is the main risk factor, rates were highest in central and eastern Europe, southern Europe and the Baltic countries. Despite a lowering of female smoking prevalence, female incidence rates of lung, laryngeal and oral cavity cancers increased in most parts of Europe, but were stable in the Baltic countries. Mixed trends emerged in oesophageal cancer, probably explained by differing risk factors for the two main histological subtypes.

Conclusions: This data repository offers the opportunity to show the variety of incidence trends by sex among European countries. The diverse patterns of trends reflect varied exposure to risk factors. Given the heavy cancer burden attributed to tobacco and the fact that tobacco use is entirely preventable, tobacco control remains a top priority in Europe. Prevention efforts should be intensified in central and eastern Europe, southern Europe and the Baltic countries.

INTRODUCTION

Tobacco was introduced into Europe by Spanish explorers returning from the Americas in the late fifteenth century. By the late nineteenth century, tobacco was being widely used by men in Europe (1), first in the forms of pipe-, cigar-smoking and snuff-taking. Then, after mass production became possible at the end of the nineteenth century, cigarettes, strongly promoted by advertising and marketing efforts, became the norm for tobacco consumption. From the 1930s, together with the forces of emancipation, women began adopting the habit on a large scale, first in North America and in northern and western Europe, until the 1970s. By the 1960s, the smoking prevalence in men was at least 70% in Denmark, the UK and Belgium, and 90% in the Netherlands, and around 30% in women (2). Thereafter, the proportion of smokers rapidly decreased in men in these parts of Europe, falling to around 40–50% by 1988. In contrast, in women, the prevalence rose gradually over time, but remained lower than in men. In southern Europe, the tobacco epidemic lagged behind that in northern and western Europe, especially in women. In Russia, a small but significant rise in the prevalence of tobacco smoking among men was reported, from 57% in 1992 to 63% in 2003, whereas rates among women more than doubled from 7% to 15% in the same period (3). From the mid-1990s until 2002, the prevalence of smoking among men in Estonia, Latvia and Lithuania was around 50% (compared to 29% in Finland), and ranged between 10% and 20% among women. Smoking increased among Lithuanian women from 6% in 1994 to 13% in 2002, but decreased among Estonian men and women (4). Mass cigarette use followed the economic development in Europe: firstly in northern and western Europe, secondly in southern Europe, thirdly in central and eastern Europe.

Cigarette smoking is a causal agent for cancers of the oral cavity, oropharynx, nasopharynx, hypopharynx, oesophagus, stomach, colorectum, liver, pancreas, nasal cavity, paranasal sinuses, larynx, lung, uterine cervix, ovary, urinary bladder, kidney, ureter and bone marrow (myeloid leukaemia). Second-hand tobacco smoke and smokeless tobacco also induce cancer (5). The European Prospective Investigation into Cancer and Nutrition Study (EPIC) calculated that among the 19 above-mentioned tobacco-related cancer cases, 35% of them were attributable to cigarette smoking (42% in men and 23% in women) (6). In 2012 in Europe (40 countries), there were an estimated almost 600,000 new cases of: lung (410,000), oral cavity and pharyngeal (100,000), oesophageal (46,000) and laryngeal cancer (40,000) (7), the cancers for which the fraction attributable to smoking is highest (with lower urinary tract). For each of these sites, men represented 71% to 90% of the patients.

Using high-quality population-based cancer registration data, this study aims to identify patterns in the incidence of major tobacco-related cancers (lung, laryngeal, oral cavity and oesophageal cancer), between 1988 and 2010, especially contrasting trends in men and women. We analysed data from 47 cancer registries covering 328 million inhabitants, representing 26 European countries, using age-standardised rates and average annual percentage change and compared smoking prevalence to lung cancer incidence.

METHODS

Incidence data by year, 5-year age group, cancer and sex and corresponding population figures were obtained from the EUREG database, part of the European Cancer Observatory (ECO) website (http://eco.iarc.fr) (8) hosted by the International Agency for Research on Cancer (IARC). The ECO website was developed within the framework of the EUROCOURSE project to enable the rapid exploration of geographical patterns and temporal trends of incidence, mortality and survival observed in European population-based cancer registries. The cancer registries were invited to submit their data, in 2010, through a web portal. As of mid-2013, 130 of the 200 European registries had contributed.

To ensure a high level of data quality and data comparability for this study, cancer registries from the EUREG database were only included in this study if they had been published in Volume IX of *Cancer Incidence in Five Continents* (CI5) (9) and had available annual incidence data for at least ten consecutive years from 1998 onwards. The rigorous process of data quality assurance in CI5 is described elsewhere (9).
To assess recent trends, the period of analysis was restricted to 1988 and thereafter. The Malta National Cancer Registry submitted data to the EUREG database for 1994-2009. To expand the length of the study period additional data for 1992–1993 were extracted from CI5plus (10), which contains annual incidence for selected cancer registries published in CI5 for the longest possible period. Additional Norwegian (2008–2009), Danish and Finnish (2008–2010) data were extracted from NORDCAN (11), a database maintained by the Association of the Nordic Cancer Registries. Lastly, Russian data were available through the Ministry of Health and Social Development (12), as data from the St Petersburg registry published in CI5 were only available for 1992–1997. Russia is a populous European country whose cancer trends serve as references for the other central and eastern European countries. Russian national data presented a high percentage of microscopically verified records (>85%), acceptable for CI5 selection standards.

Finally, population-based registries from 26 European countries (Table 1) were included in this study and grouped into four regions, according to the United Nations classification (13). Of the 26 countries, 19 had national data. For the remaining seven countries, data from regional registries were aggregated to obtain an estimate of the (unknown) national incidence (see footnote of Table 1 for the list of the regional registries). When combining regional registries, we aimed to maximize the population coverage of the country by selecting as many registries as possible that had a common registration

Table 1. Populations studied by country (N=26), study period, population covered by the registration area and proportion of the national population covered by the 47 national or regional studied registries

Region	Countries	Years	2007 population in the studied registries (thousands)	Proportion of the national population covered (%)
Central & eastern Europe				
	Belarus	1988–2007	9,702	100
	Bulgaria	1993–2008	7,660	100
	Czech Republic	1988–2008	10,323	100
	Poland§	1988–2008	2,042	5.2
	Russian Federation	1993–2008	142,115	100
	Slovakia	1988–2007	5,398	100
Northern Europe				
	Denmark	1988–2010	5,461	100
	Estonia	1988–2007	1,341	100
	Finland	1988–2010	5,289	100
	Iceland	1988–2010	311	100
	Ireland	1994–2007	4,339	100
	Latvia	1988–2007	2,276	100
	Lithuania	1988–2007	3,376	100
	Norway	1988–2009	4,708	100
	Sweden	1988–2009	9,148	100
	United Kingdom§	1988–2007	56,236	88.3
Southern Europe				
	Croatia	1988–2007	4,436	100
	Italy§	1988–2007	4,359	6.9
	Malta	1992–2009	409	100
	Slovenia	1988–2007	2,019	100
	Spain§	1988–2005	3,502[a]	7.7
Western Europe				
	Austria	1990–2009	8,301	100
	France§	1988–2009	4,388	6.8
	Germany§	1998–2007	13,888	16.1
	Switzerland§	1988–2008	968	12.3
	The Netherlands	1989–2008	16,382	100
Total			**328,376**	

§Regional registries: France (Doubs, Herault, Isere, Haut-Rhin, Somme, Tarn); Germany (Brandenburg, Hamburg, Saxony, Mecklenburg, North Rhine-Westphalia, Saarland); Poland (Kielce, Cracow); Italy (Modena, Parma, Ragusa, Romagna, Torino, Varese); Spain (Granada, Murcia, Navarra, Tarragona); Switzerland (Geneva, St Gall-Appenzell), United Kingdom (England and Scotland)

[a]Population data from 2005.

period and which met the inclusion criteria. Unfortunately, in Italy, due to the selection process, only registries from the northern part of the country were eligible.
Of the 19 cancer sites associated with tobacco, lung and larynx were estimated to have the highest population attributable fraction (AF_p) due to cigarette smoking, 82% and 84% respectively, in the EPIC study (6). Therefore, trends in both lung and laryngeal cancers may be largely explained by historical trends in tobacco use. For other cancers however, the AF_p is smaller, and other factors such as alcohol (14), infections (15) and diet (16) may also be important in determining trends in incidence. Although smoking would undoubtedly contribute to additional new cases, it would not be wise to ascribe changes in incidence of these cancers primarily to changes in tobacco use. This study is hence confined to cancer sites where at least 30% of the new cases are due to cigarette smoking (AF_p > 30%) based on the findings of the EPIC study (6). The eligible cancer sites (and corresponding ICD-10 codes) are: Oral cavity and Pharynx (C00-14), Oesophagus (C15), Larynx (C32) and Lung, bronchus, trachea (C33-34). An exception was made for cancer of the lower urinary tract (C65-C68); while up to half of the cases are attributed to smoking, we excluded this site because different and changing classification/coding practices (17) during the study period render international comparisons difficult. Stomach and colorectal cancer incidence are examined by Arnold *et al* (18).

We restricted this study to age group 35 to 74 to analyse larger, more stable rates. Annual truncated age-standardised incidence rates (ASR) were calculated for each country by sex, using the European standard population (19). To graphically summarize the trends, locally weighted regression (Lowess) curves were fitted to provide smoothed lines through the scatterplot of ASRs by calendar period. A bandwidth of 0.3 was used, i.e. 30% of the data were used in smoothing each point, except for female oesophageal and laryngeal trends, where 50% of the data were used because of the random fluctuations inherent in the small numbers involved. Rates are plotted on a log scale. Of note, for each cancer, the incidence scale is adapted to the range in incidence across the continent and varies by sex.

Changes in incidence rates were quantified for age groups 35 to 64, 65 to 74 and 35 to 74, for the 1998–2007 period (except Spain, for which 1996–2005 was used) through average annual percentage change (AAPC) and corresponding 95% confidence intervals [C.I.] based on the model from Clegg *et al*. (20). AAPCs were estimated using the Joinpoint Regression Program (version 3.5.3) from the Surveillance Research Program of the US National Cancer Institute (21), and we used the number of cases as the dependent variable, calendar year as the independent variable, and the Poisson variance of the person-years at risk.

The proportions of adenocarcinomas (AdC) and squamous cell carcinomas (SCC) among oesophageal cancers for 1998–2002 were extracted from CI5 volume IX (9).

To illustrate the association between smoking and lung cancer incidence, and to further clarify the stage of the smoking epidemic (22), we plotted the national prevalence of daily smokers aged 15 and above and the national or regional lung cancer incidence rates for ages 35 and above, for the maximum time period available in EUREG and CI5plus databases (since 1955 for Denmark). The percentage of adult daily smokers was extracted from the Organisation for Economic Co-operation and Development (23) and the World Health Organization (WHO) (24) databases. In each of the four regions, for illustrative purposes, we selected one country with a long series of smoking prevalence and lung cancer incidence data.

RESULTS

Lung cancer

Lung cancer incidence for men aged 35–74 differed markedly between countries, being highest in Belarus (161 cases per 100,000 in 2007) and lowest in Sweden (40 cases per 100,000 in 2009), in the most recent period (Figure 1). In most European countries, rates for men have decreased since the early 1990s, with the exception of Norway, Finland, Spain and France, where rates have remained broadly stable (Figure 1). Over the 1998–2007 period, a significant decline in lung cancer incidence rates in men was observed in 14 of the 26 countries in middle ages (35–64 years old) and 15 countries in older ages (65–74 years old) (Figures 2a and 2b and Appendix Table 1). The declines were stronger in older men. In the figure presenting the recent incidence rate versus the 1998-2007 AAPC in middle-aged men (Figure 2a), the countries were clustered by region: in northern European countries (but Baltic countries), lung cancer incidence rates were low and stable. Rates were intermediate and declining in western European countries, and high and declining in central and eastern European and Baltic countries. Rates in southern European countries did not have a uniform behaviour.

Among women, in the most recent period, the highest incidence rates were observed in Iceland and Denmark, with rates of 95 and 93 per 100,000 in 2010, respectively, as well as in the Netherlands (71 cases per 100,000 in 2007). Denmark appears as having a higher rate than Iceland in the graph (Figure 3) due to smoothing. In the same period, the lowest female rates were in Belarus and Lithuania (13 cases per 100,000 in 2007). In contrast to the decreasing trends observed in men, among women rates of lung cancer by age group have increased over time (Figures 4a and 4b and Appendix

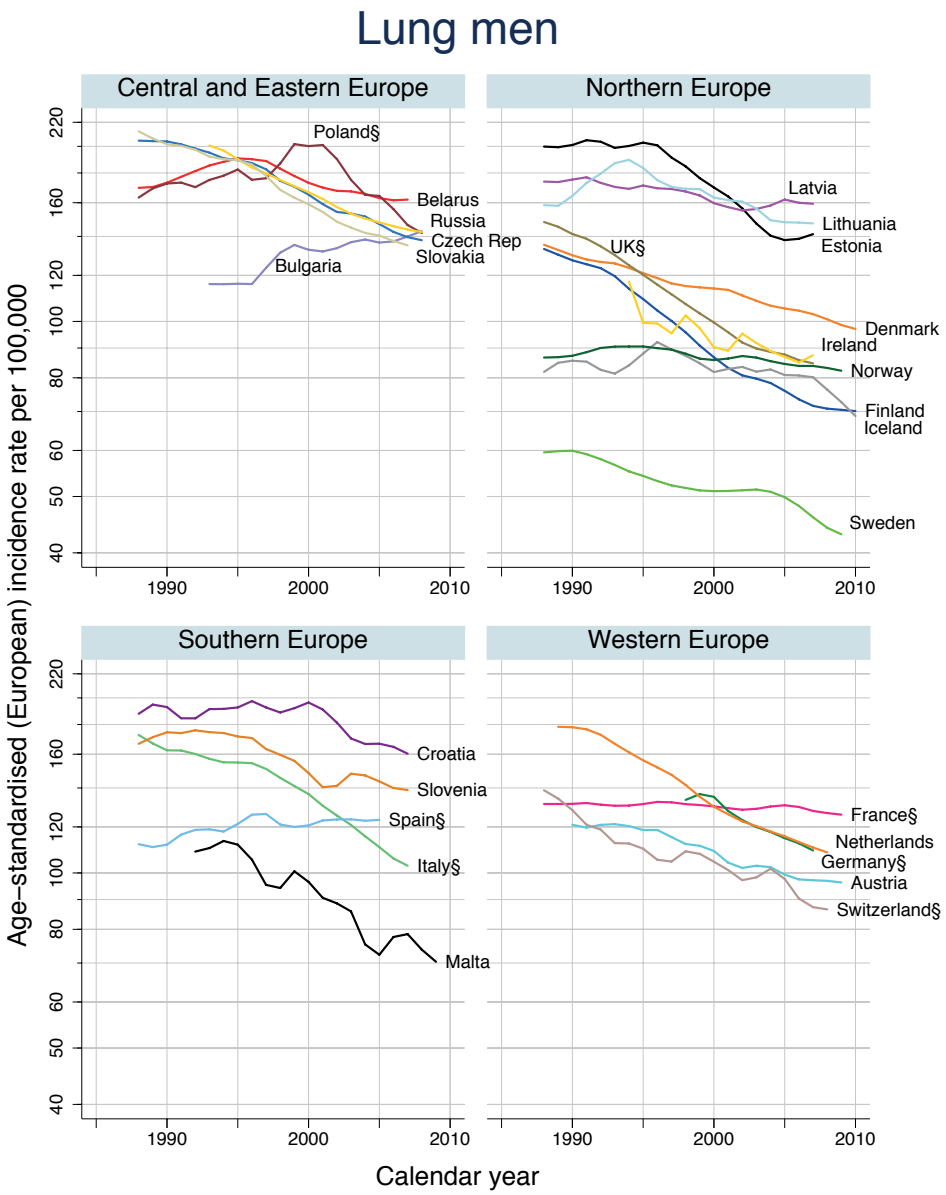

Figure 1. Trends in lung cancer age-standardised (European) incidence in men aged 35–74 by country and region, from 1988 to the most recent year available (2005 to 2010).
§ regional registries

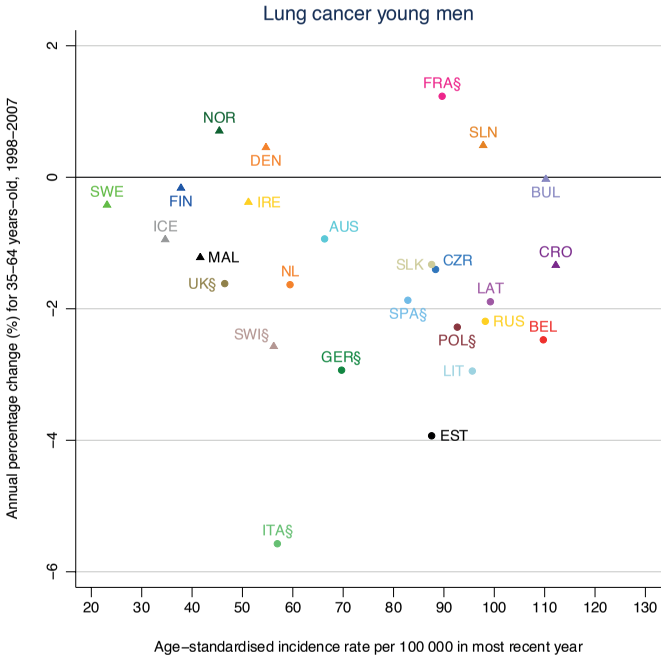

Figure 2a. Average annual percentage change (AAPC) between 1998–2007 (except 1996–2005 for Spain) and age-standardised (European) incidence rates (ASR) of the most recent year (2005 to 2010) of lung cancer in men aged 35 to 64.

Dots indicate statistically significant AAPC (p≤0.05); triangles indicate non-significant AAPC
AUS – Austria; BEL – Belarus; BUL – Bulgaria; CRO – Croatia; CZR – Czech Republic; DEN – Denmark; EST – Estonia; FIN – Finland; FRA§ – France (regional registries); GER§ – Germany (regional registries); ICE – Iceland; IRE – Ireland; ITA§ – Italy (regional registries); LAT – Latvia; LIT – Lithuania; MAL – Malta; NOR – Norway; POL§ - Poland (regional registries); RUS – Russian Federation; SLK – Slovakia; SLN – Slovenia; SPA§ – Spain (regional registries); SWE – Sweden; SWI§ – Switzerland (regional registries); NL – The Netherlands; UK§ – United Kingdom (regional registries)

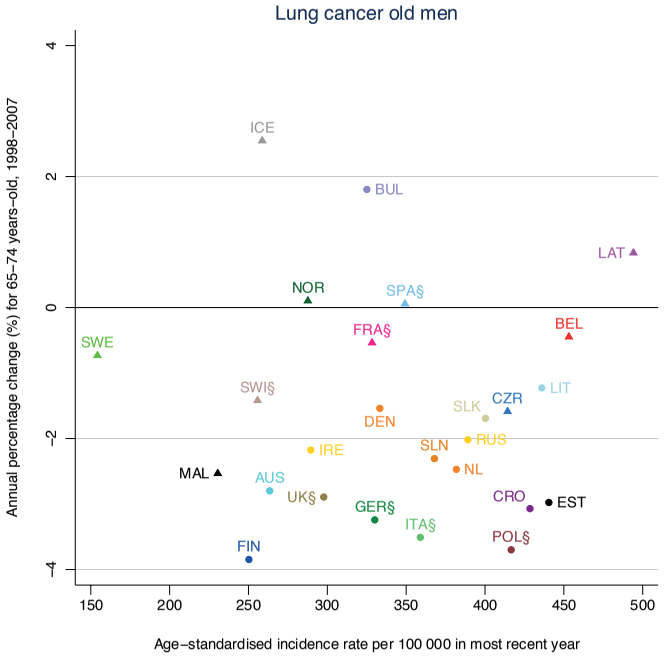

Figure 2b. Average annual percentage change (AAPC) between 1998–2007 (except 1996–2005 for Spain) and age-standardised (European) incidence rates (ASR) of the most recent year of lung cancer in men aged 65 to 74.

Dots indicate statistically significant AAPC (p≤0.05); triangles indicate non-significant AAPC.
§ regional registries

Table 1), with the notable exceptions of the declines in older Russian and Lithuanian women in 1998–2007. Very recently (after 2005), early signs of stabilisation could be detected in women aged 35–74 in central and eastern Europe, northern Europe, Switzerland and Malta (Figure 3). Figure 4a (incidence rate vs. AAPC in middle-aged

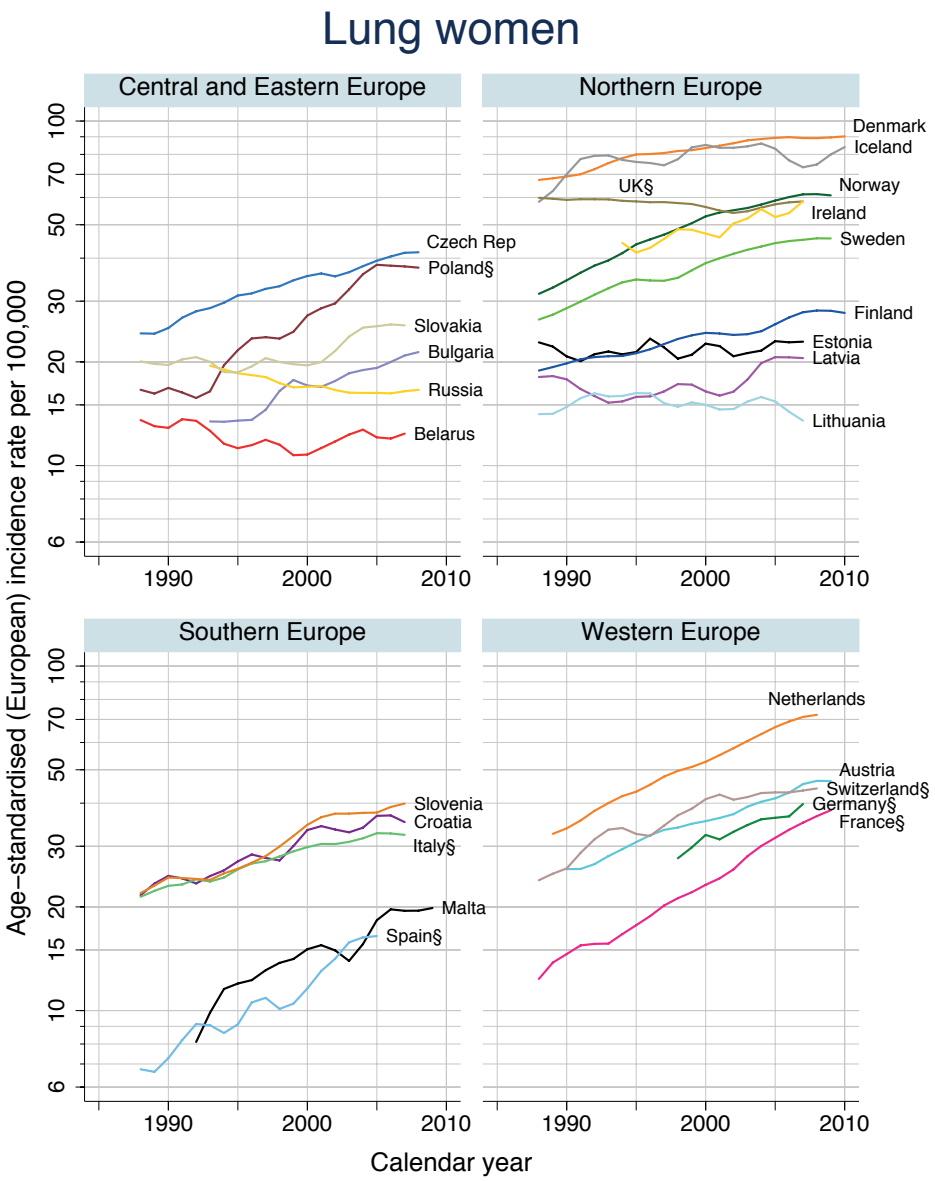

Figure 3. Trends in lung cancer age-standardised (European) incidence in women aged 35–74 by country and region, from 1988 to the most recent year available (2005 to 2010).

§ regional registries

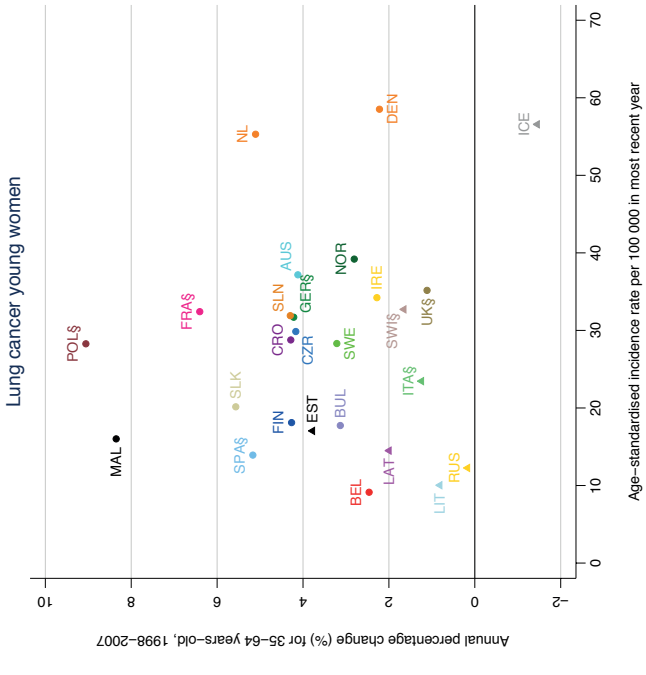

Figure 4a. Average annual percentage change (AAPC) between 1998–2007 (except 1996–2005 for Spain) and age-standardised (European) incidence rates (ASR) of the most recent year of lung cancer in women aged 35 to 64.
Dots indicate statistically significant AAPC (p≤0.05); triangles indicate non-significant AAPC. Colours indicate European regions: Central and eastern (blue), northern (green), southern (red) and western (brown).
§ regional registries

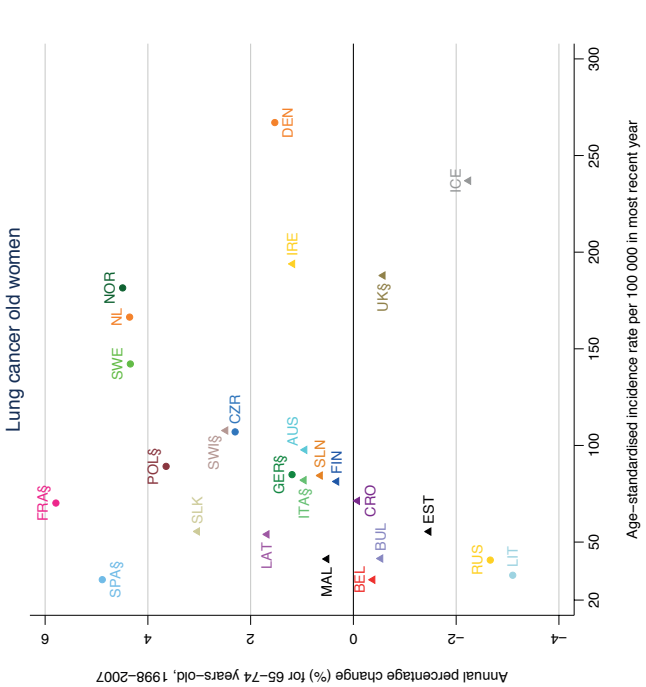

Figure 4b. Average annual percentage change (AAPC) between 1998–2007 (except 1996–2005 for Spain) and age-standardised (European) incidence rates (ASR) of the most recent year of lung cancer in women aged 65 to 74.
Dots indicate statistically significant AAPC (p≤0.05); triangles indicate non-significant AAPC. Colours indicate European regions: Central and eastern (blue), northern (green), southern (red) and western (brown).
§ regional registries

women) showed regional clusters of countries: moderate increases in lung cancer

incidence in northern countries (but stable in Baltic countries and Iceland), upper high and increasing incidence rates in western countries, low to intermediate rates with strong increases in southern Europe (but in Italy) and finally low to intermediate rates in central and eastern Europe.

Due to the convergence of the trends by sex, the male-to-female ratio has decreased during the last 20 years. Noticeably, in the most recent years (2006–2008), the highest male (aged 35–64) rates were found where the lowest female rates were: in central and eastern Europe, the Baltic countries and some southern European countries. Conversely, the lowest male rates and the highest female rates are found in northern Europe (excepting the Baltic countries) (Figure 5). The sex ratio was closest to 1 in northern countries, with incidence even higher in women than in men in Denmark, Sweden and Iceland, among people aged 35–64 (Figure 5).

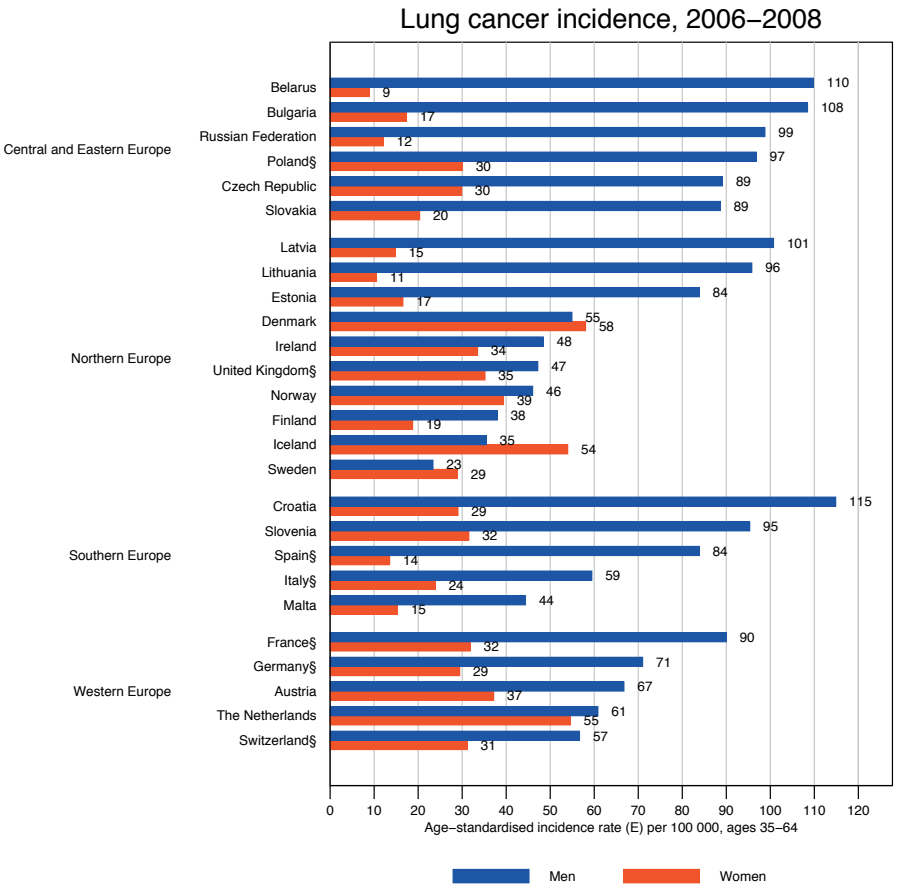

Figure 5. Age-standardised (European) lung cancer incidence rates per 100,000 in men and women aged 35–74, in European countries, by region (2006–2008).

Oral cavity and pharyngeal cancer

Within Europe, incidence of cancers of the oral cavity and pharynx among men in the most recent period varied almost 6-fold, from 12 (in Iceland in 2010) to 64 (in Slovakia 2007) per 100,000 (Figure 6). During the 1998–2007 decade, rates among men were

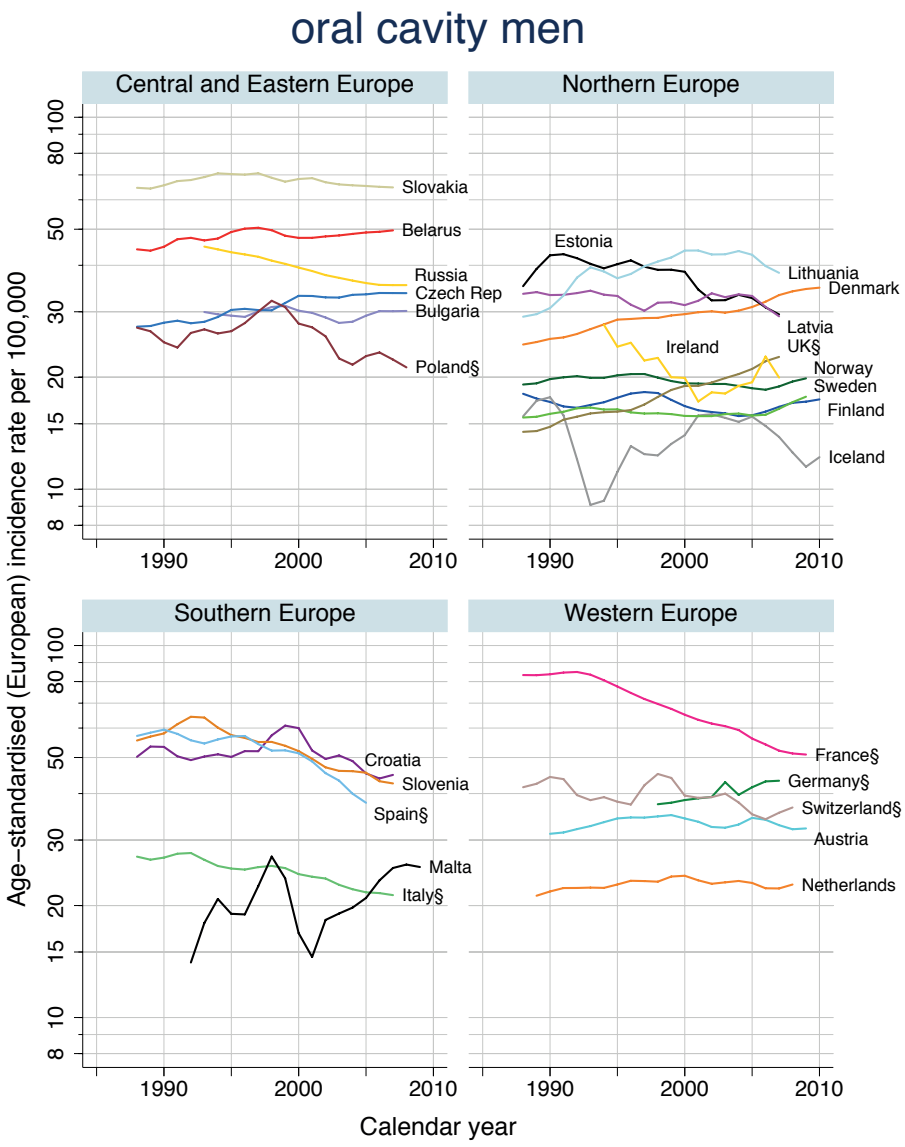

Figure 6. Trends in age-standardised (European) oral cavity and pharyngeal cancer incidence in men aged 35–74 by country and region, from 1988 to the most recent year available (2005 to 2010).

§ regional registries

stable in most countries in northern, western and central and eastern Europe (Figure 7 and Appendix Table 2). In southern European countries (Croatia, Italy, Slovenia, Spain), as well as in other countries (Russia, France, Estonia, Switzerland and Poland), declines were consistently observed. In the same period, rates in women were very low in the former Soviet countries, e.g. in Belarus and Lithuania (4 and 5 per 100,000 respectively, in 2007), and were highest in western Europe, e.g. in Switzerland (17 per 100,000 in 2008) (Figure 8). In women, rates stabilized or increased over the 1988–2007 period, with the highest increase in the Czech Republic (average increase of 6.4% per year, [95% C.I. 4.0; 8.9]) (Figure 9 and by age group in Appendix Table 2). While incidence rates were higher in men compared to women throughout the study period, as a consequence of the converging male and female incidence trends, the male-to-female ratio has decreased during the last 20 years. In 2006–2008, this ratio ranged from 12.6 in Belarus to 1.3 in Iceland.

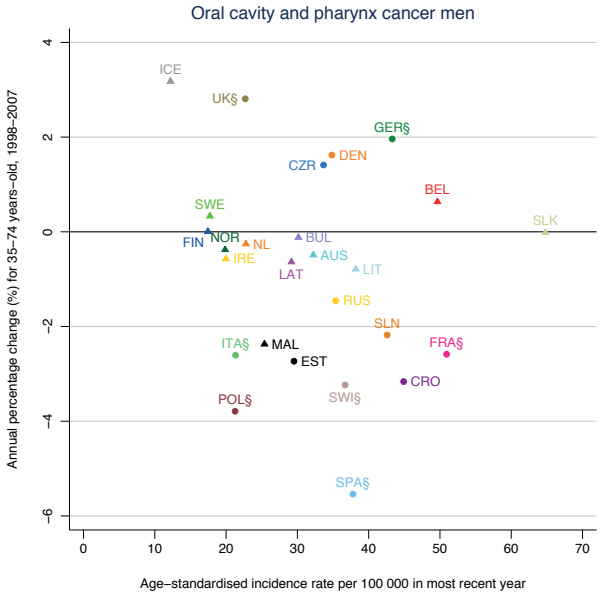

Figure 7. Average annual percentage change (AAPC) between 1998–2007 (except 1996–2005 for Spain) and age-standardised (European) incidence rates (ASR) of the most recent year of oral cavity and pharyngeal cancer in men aged 35–74.

Dots indicate statistically significant AAPC ($p \leq 0.05$); triangles indicate non-significant AAPC. Colours indicate European regions: Central and eastern (blue), northern (green), southern (red) and western (brown).
§ regional registries

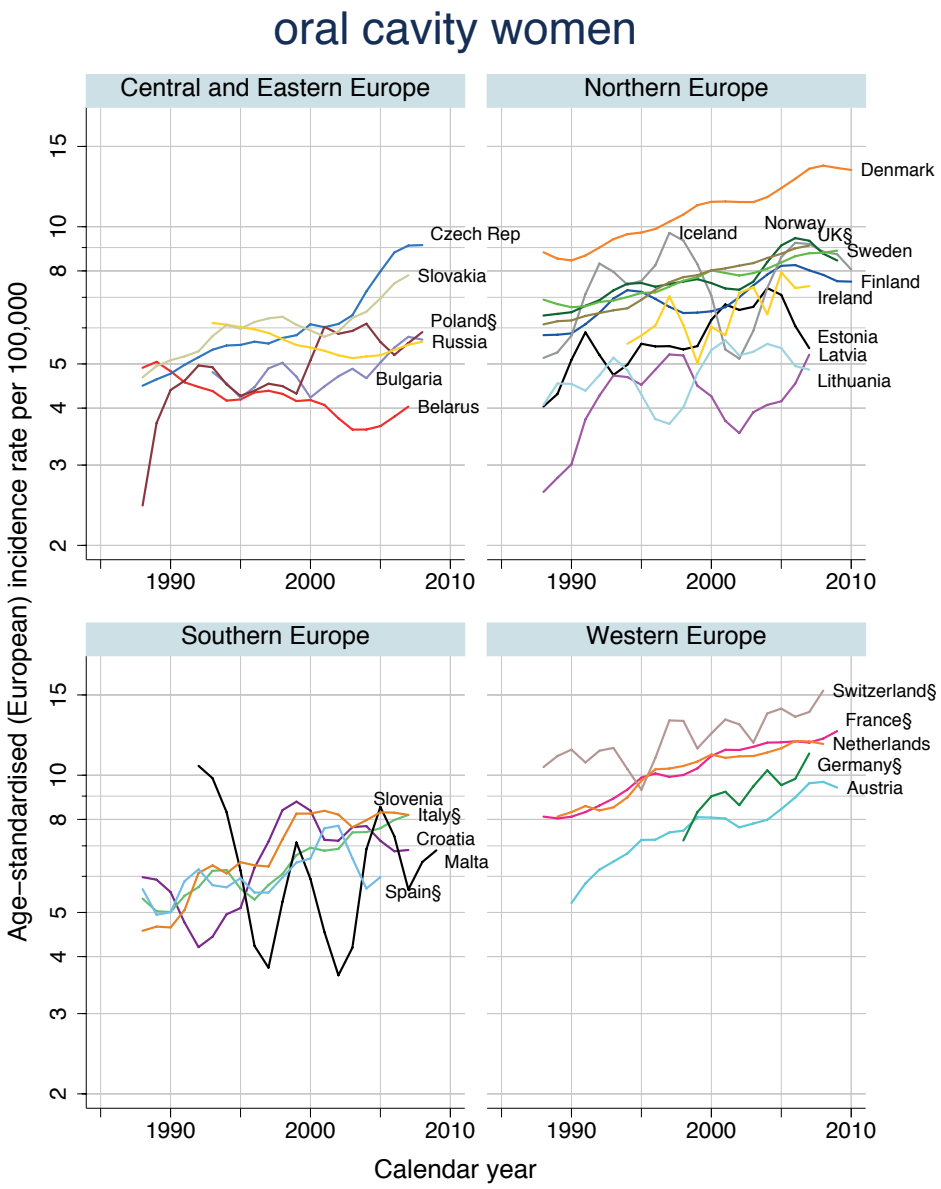

Figure 8. Trends in age-standardised (European) oral cavity and pharyngeal cancer incidence in women aged 35–74 by country and region, from 1988 to the most recent year available (2005 to 2010).

§ regional registries

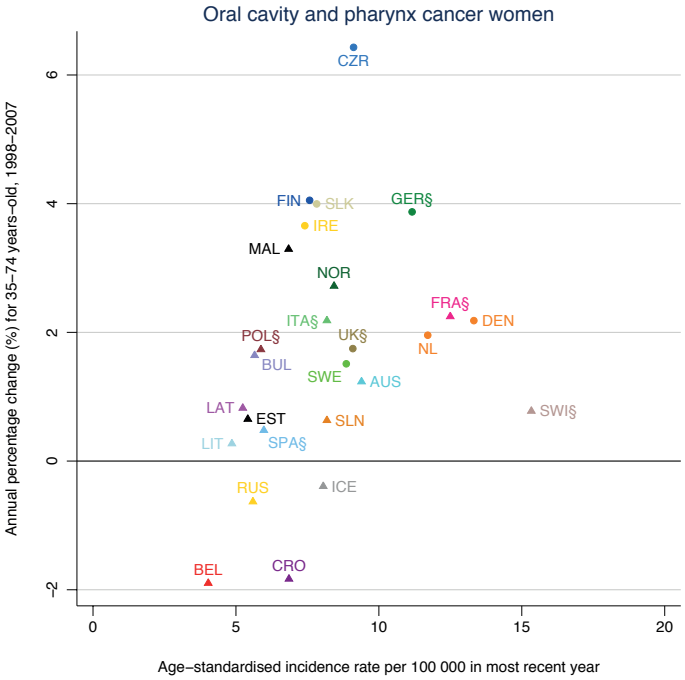

Figure 9. Average annual percentage change (AAPC) between 1998–2007 (except 1996–2005 for Spain) and age-standardised (European) incidence rates (ASR) of the most recent year of oral cavity and pharyngeal cancer in women aged 35–74.

Dots indicate statistically significant AAPC ($p \leq 0.05$); triangles indicate non-significant AAPC. Colours indicate European regions: Central and eastern (blue), northern (green), southern (red) and western (brown).
§ regional registries

Laryngeal cancer

In the most recent period, incidence of cancer of the larynx among men 35–74 was lowest in northern European countries (excluding the Baltic countries) and highest in central and eastern Europe, Baltic countries, Spain and Croatia: rates ranged from 4 per 100,000 in Sweden in 2009 to 30 per 100,000 in Bulgaria in 2008 (Figure 10). Rates tended to decline in most countries (Figures 10 and 11, and by age group in Appendix Table 3), with the greatest declines observed among men in Iceland and Poland (Average Annual Percentage Change (AAPC) of -13.7 [95% C.I. -23.3; -2.9] and -6.7 [-8.8; -9.4], respectively). In women, the incidence rates of laryngeal cancer were rather low, ranging from 0.5 to 2 per 100,000 in Belarus in 2007 and the Netherlands in 2008, respectively (Figure 12). Although the patterns were somewhat erratic due to the low number of cases, there was a suggestion of an increase over the 1998–2007 decade in middle-aged women and a decrease at older ages (Appendix Table 3). The figures presenting the recent incidence versus AAPC (Figures 11 and Appendix Figure

1) revealed regional clusters of countries (with Baltic countries included in the central and eastern European countries' cluster, in men).

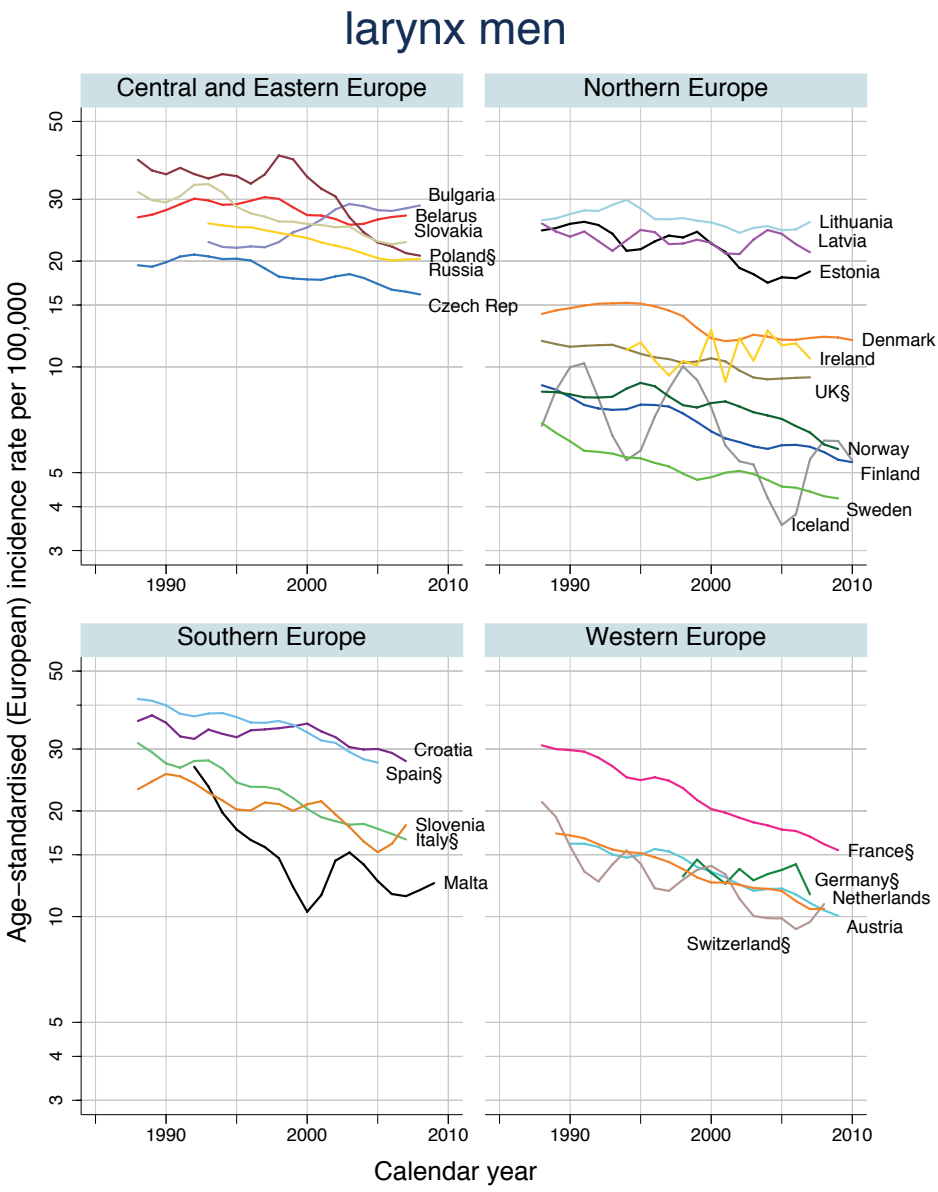

Figure 10. Trends in age-standardised (European) laryngeal cancer incidence in men aged 35–74 by country and region, from 1988 to the most recent year available (2005 to 2010).

§ regional registries

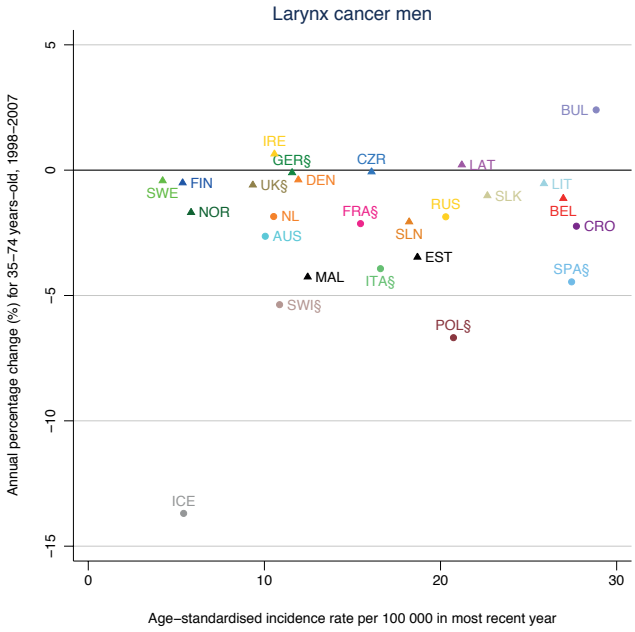

Figure 11. Average annual percentage change (AAPC) between 1998–2007 (except 1996–2005 for Spain) and age-standardised (European) incidence rates (ASR) of the most recent year of laryngeal cancer in men aged 35–74.

Dots indicate statistically significant AAPC (p≤0.05); triangles indicate non-significant AAPC. Colours indicate European regions: Central and eastern (blue), northern (green), southern (red) and western (brown).
§ regional registries

Oesophageal cancer

The variation in recent incidence of oesophageal cancer among men was 5-fold, with incidence highest in the Netherlands (24 per 100,000 in 2008) and lowest in Malta (5 per 100,000 in 2009) (Figure 13). Over the 1998–2007 period, in men aged 35–74, in general, countries in the northern half of Europe have seen increases in oesophageal cancer incidence (with the highest increase in the Netherlands: AAPC of 3.5 [95% C.I. 2.8; 4.3]), while countries in the southern half saw declines in incidence (AAPC greater than -3.0 in France, Spain and Italy) (Figure Appendix Figure 2). The increases were most pronounced in middle-aged men (AAPCs of 4.4 in the Netherlands [95% C.I. 3.1; 5.7], 4.2 in Norway [95% C.I. 0.7; 7.8], and 4.1 in Finland [95% C.I. 0.6; 7.8] in men aged 35–64 years) (Appendix Table 4). The male-to-female ratio was higher for oesophageal cancer relative to other smoking-related cancers in this study, ranging from 2.7 in Ireland to 20.8 in Belarus in 2006–2008. Because of the random fluctuations inherent in the small numbers involved, it is difficult to discern trends in women. However, incidence rates appeared to have increased over the whole study period in

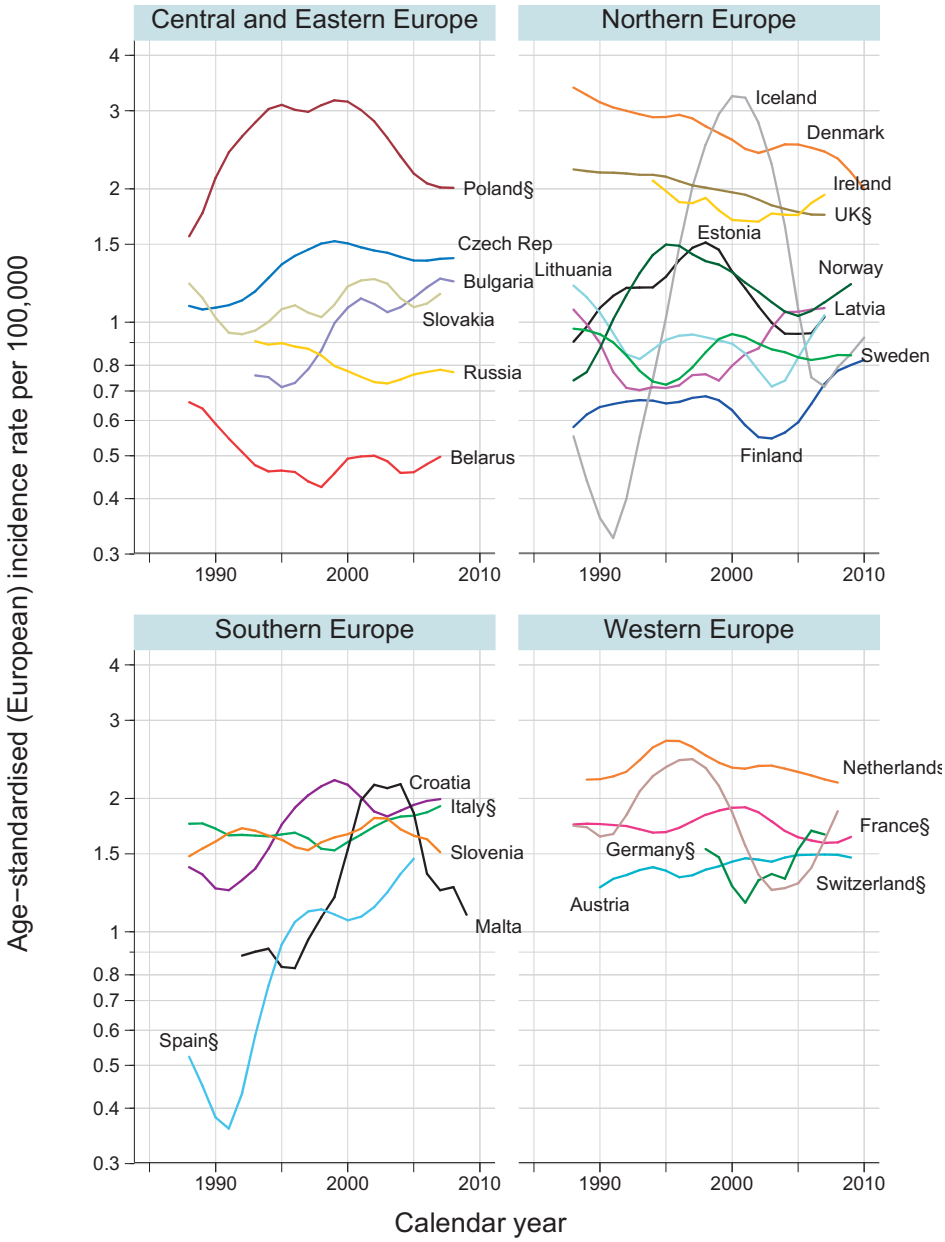

Figure 12. Trends in age-standardised (European) laryngeal cancer incidence in women aged 35–74 by country and region, from 1988 to the most recent year available (2005 to 2010).

§ regional registries

most countries in western, central and eastern Europe in women aged 35–74 (Figure 14), with the exception of a decline in Russia. Over the 1998–2007 period, in women, increases were significant only in Iceland, Germany, Denmark and the Netherlands (Appendix Figure 3).

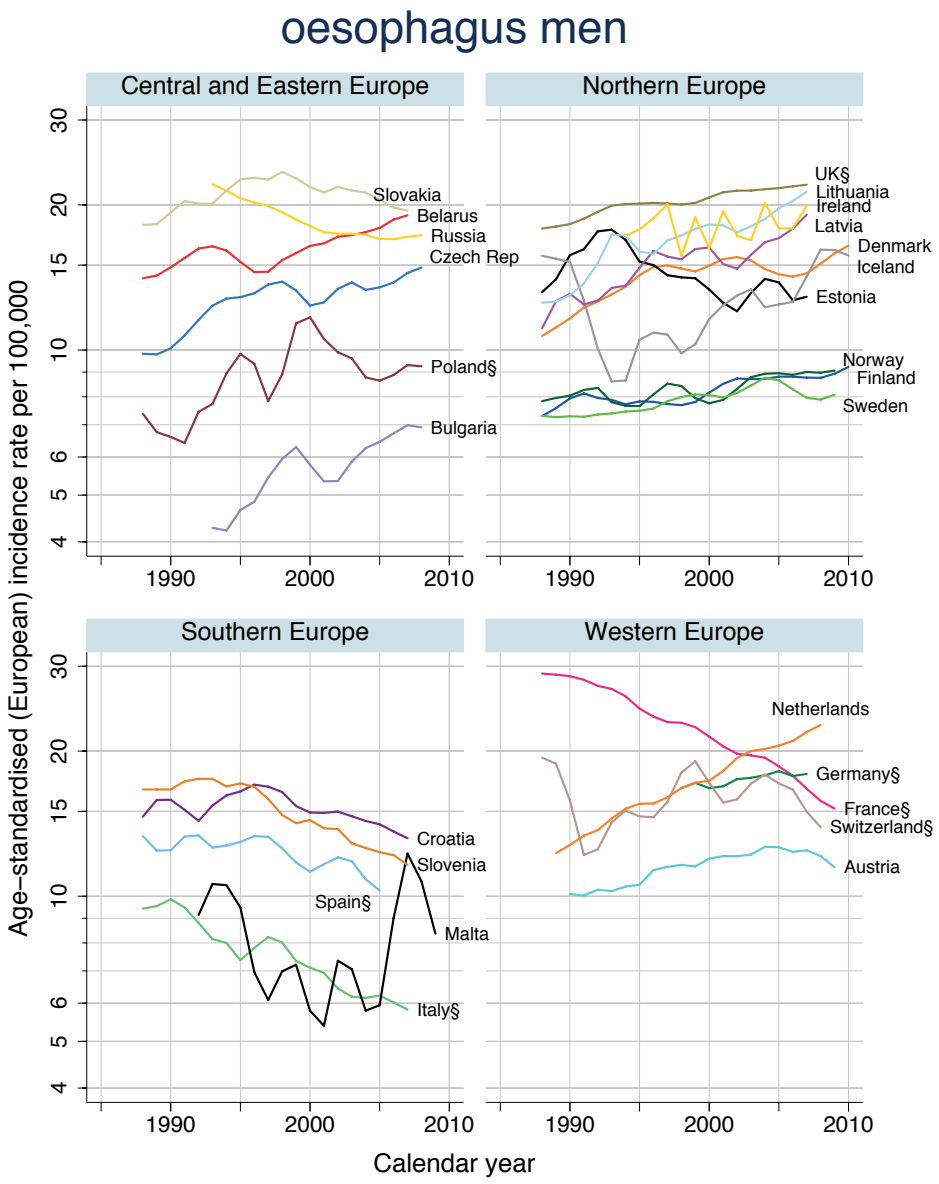

Figure 13. Trends in age-standardised (European) oesophageal cancer incidence in men aged 35–74 by country and region, from 1988 to the most recent year available (2005 to 2010).

§ regional registries

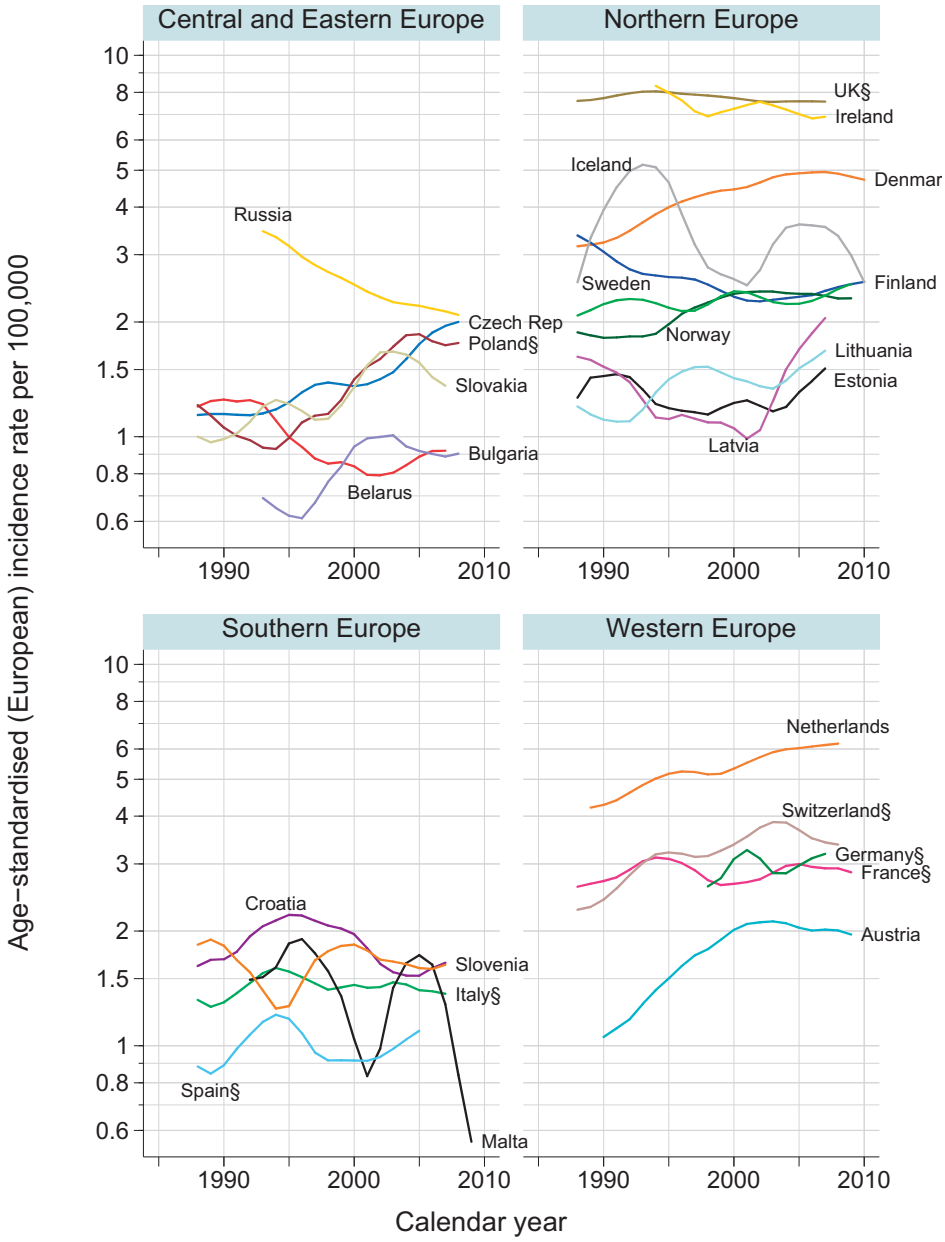

Figure 14. Trends in age-standardised (European) oesophageal cancer incidence in women aged 35–74 by country and region, from 1988 to the most recent year available (2005 to 2010).

§ regional registries

Table 2 presents the proportion of the two main histological subtypes of oesophageal cancer, SCC and AdC, by country and by sex, in 1998–2002. In men, the majority of the cases were SCC. Less than 10% of the cases were AdC in central and eastern

Table 2 Proportion of oesophageal cancer by main histological sub-type, by sex, in 1998–2002, ages 35–74. Source: Cancer Incidence in Five Continents Volume IX (9).

		Men		Women	
Region	**Country**	**Squamous Cell Carcinoma (%)**	**Adenocarcinoma (%)**	**Squamous Cell Carcinoma (%)**	**Adenocarcinoma (%)**
Central & eastern Europe					
	Belarus	66	9	43	18
	Bulgaria	-	-	-	-
	Czech Republic	56	23	55	18
	Poland§	-	-	-	-
	Russian Federation	55	8	51	9
	Slovakia	70	9	55	26
Northern Europe					
	Denmark	43	44	65	25
	Estonia	82	5	82	0
	Finland	52	37	75	19
	Iceland	34	63	22	44
	Ireland	34	54	64	24
	Latvia	63	9	31	17
	Lithuania	63	8	63	12
	Norway	50	42	66	26
	Sweden	46	47	73	23
	United Kingdom§	25	59	55	27
Southern Europe					
	Croatia	56	6	50	12
	Italy§	66	18	68	13
	Malta	36	43	60	20
	Slovenia	77	9	63	22
	Spain§	74	17	63	18
Western Europe					
	Austria	54	25	50	18
	France§	77	17	81	11
	Germany§	61	17	64	14
	Switzerland§	62	31	74	17
	The Netherlands	36	56	58	33

§Regional registries: France (Doubs, Herault, Isere, Haut-Rhin, Somme, Tarn); Germany (Brandenburg, Hamburg, Saxony, Mecklenburg, North Rhine-Westphalia, Saarland); Poland (Kielce, Cracow); Italy (Modena, Parma, Ragusa, Romagna, Torino, Varese); Spain (Granada, Murcia, Navarra, Tarragona); Switzerland (Geneva, St Gall-Appenzell), United Kingdom (England and Scotland)

Proportions in Bulgaria and Poland are not displayed due to the low proportion of microscopically verified cases (35% in men and 27% in women in Bulgaria, 57% and 43% in Poland Cracow and 77% and 74% in Kielce respectively). The other histological subtypes not displayed are: Other specified carcinoma, Unspecified carcinoma, Sarcoma, Other specified morphology and Unspecified morphology.

Europe (except in Czech Republic), the Baltic countries, Croatia and Slovenia. In the other countries of northern Europe, and in the Netherlands and Malta, AdC cases were more frequent than SCC. In women, SCC always represented the majority of the cases, except in Iceland and Latvia. The highest proportions of SCC were found in Sweden, Switzerland, Finland, France and Estonia, ranging from 73% to 82%.

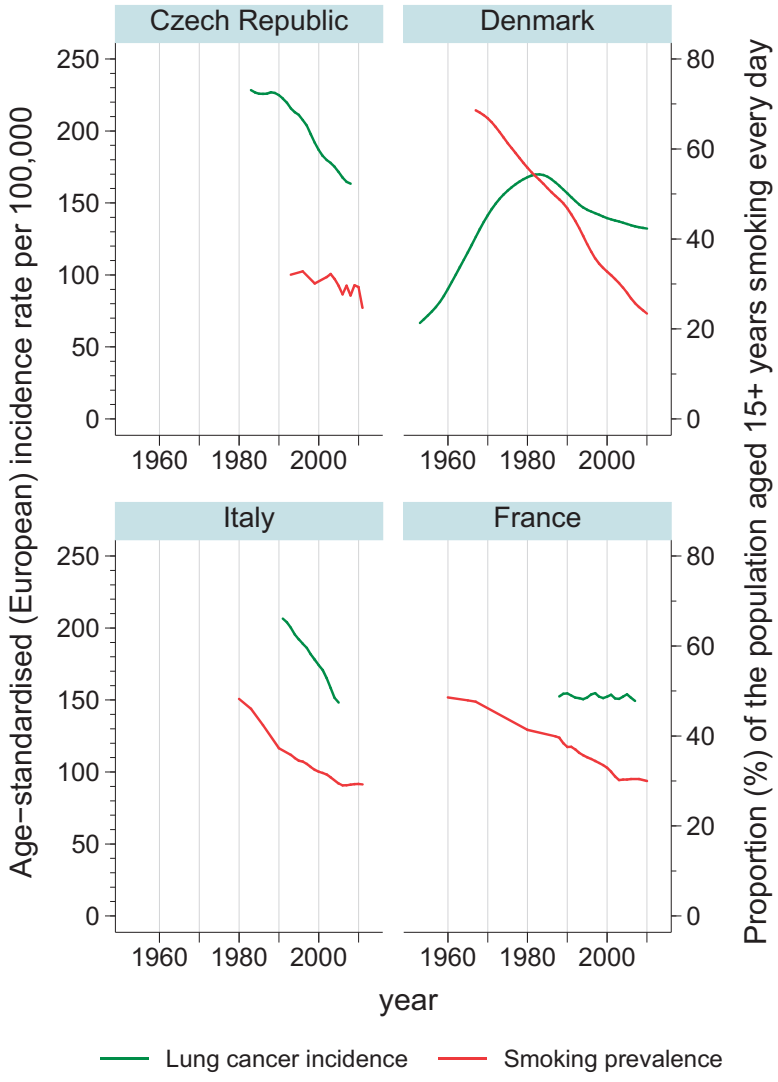

Figure 15 a. Age-standardised (European) lung cancer incidence rates per 100,000 in men aged 35 and above and prevalence of daily smokers in men aged 15 and above in Czech Republic, Denmark, Italy and France

Temporal trend of cigarette smoking and lung cancer incidence

National smoking prevalence (daily smokers aged 15 and above) and age-standardised lung cancer incidence in adults (aged 35 and above) are plotted by sex in Figures 15a and 15b, for four selected countries, one in each European region: Czech Republic (central and eastern Europe), Denmark (northern Europe), Italy (southern Europe) and France (western Europe). Although historically in those four countries the highest reported prevalence in Europe was as high as 70% (e.g. in Danish men circa 1967), the

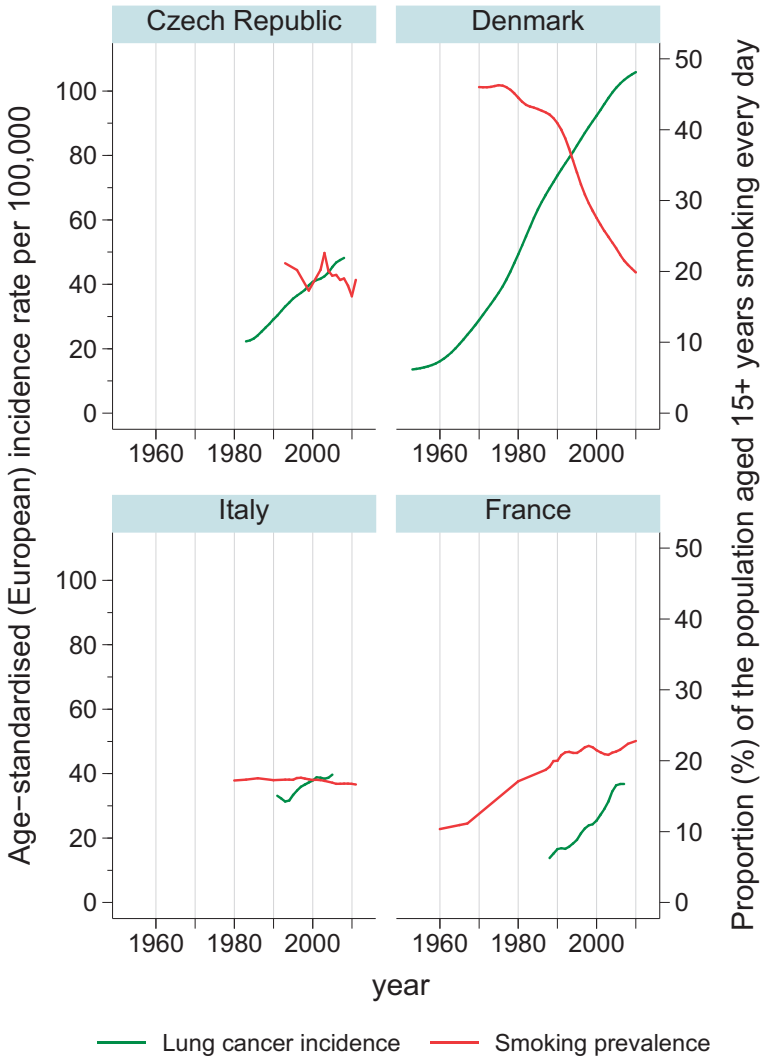

Figure 15 b. Age-standardised (European) lung cancer incidence rates per 100,000 in women aged 35 and above and prevalence of daily smokers in women aged 15 and above in Czech Republic, Denmark, Italy and France

highest current smoking prevalence was 29%, in French men. In men, the decline in smoking prevalence was reflected in a later decline or stabilization (Denmark, France) in the lung cancer incidence, with a two- to three-decade lag time. In women, smoking prevalence has been increasing in France since the 1960s, but remained stable in the Czech Republic since the mid-1980s and in Italy since the 1980s. Conversely, prevalence has markedly declined over time in Denmark, especially since the late 1990s, with current prevalence of smokers at 20% among Danish women. In contrast to the temporal trend in men, lung cancer incidence continued to increase in women in the Czech Republic, Italy and France. The high incidence in Denmark (110 cases per 100,000 in 2010) has stabilised very recently, four decades after the peak of smoking prevalence.

DISCUSSION

There remained large but changing variation in the incidence rates of tobacco-related cancers. Generally, male rates have been declining in lung, oral cavity and pharyngeal and laryngeal cancers, while female rates have been increasing in lung, oral cavity and pharyngeal cancers. In lung and laryngeal cancers, rates were highest in central and eastern Europe, southern Europe and the Baltic countries (in men). With respect to oesophageal cancer, mixed trends emerged.

Lung cancer

These analyses reveal that the gap between male and female lung cancer incidence is narrowing, particularly in northern and western Europe, with lung cancer rates in women aged 35–64 in 2006–2008 even higher than rates in men in Denmark, Iceland and Sweden. This phenomenon has also been observed in the Netherlands since the mid-1990s in women <50 years old (25). In southern Europe, declines in male incidence were also reported by Znaor *et al.* in central Serbia over the 1999-2008 period (26). While the peak of lung cancer cases seems to have been reached in men, as already reported by Malvezzi *et al*.(27), our analyses indicate that it has not yet been reached in women. It was estimated that, in Europe, in 2012, lung cancer—the majority of cases of which are attributable to smoking—was the most commonly diagnosed cancer in 15 countries and the second most common cancer in 13 further countries in men, and ranked second in three countries among women (Albania, Iceland and the UK). This neoplasm was estimated to be the most frequent cause of death by cancer in men in all European countries, with the exception of Sweden. In women, lung cancer surpassed breast cancer mortality in 12 of the 40 countries of the European region (7). Consequently, the pattern of the cancer burden in women in Europe is approaching

the cancer burden in men. Tobacco certainly plays a major role (AF_p of 82%), but occupational exposure (such as asbestos (28)) and environmental exposures also account for a small proportion of the lung cancer cases, possibly explaining some of the observed between-country differences in rates.

Oral cavity and pharyngeal cancers

Although oral cavity and pharyngeal cancers are strongly related to smoking -- with a cumulative risk among lifelong male smokers around 16 times higher than in never smokers -- (29) the trends in oral cavity and pharyngeal cancers differ noticeably from those of lung cancer. In particular, male rates have been increasing or remained stable in some countries while lung cancer incidence rates have declined (e.g., Czech Republic, Denmark, the UK and the Netherlands). This suggests that other detrimental risk factors, such as alcohol (14) and human papillomavirus (HPV) (15) may substantially modify the trends. Conversely, diets rich in fruit and vegetables may prevent upper aerodigestive tract cancers (30). For oral cavity cancer, the population attributable risk is 22% for tobacco alone and 40% for tobacco in combination with alcohol (14). According to the WHO, alcohol consumption has been increasing in Czech Republic and Denmark from around 9 litres of pure alcohol per year per person aged 15+ to 15 litres and from 7 litres to 11, respectively, over the 1960-2010 period (24). This may partly explain the increase in the number of new oral and pharyngeal cancer patients. Conversely, the highest levels of consumption in Europe used to be around 25 litres in France, 18 litres in Italy, 14 litres in Spain at the beginning of the 1960's, but 12, 6 and 10 litres respectively in 2010 (24). As heavy alcohol consumption (i.e., ≥4 drinks/day) is associated with an increased risk of about 5-fold for oral and pharyngeal cancer (31), the decrease in average consumption may partly explain the decline in the number of new cases in those countries among men -- who, on average, drink more than women. However, even low doses of alcohol consumption (i.e., ≤1 drink/day) increase the risk of cancer by about 20% (31). In Europe, around year 2000, the proportion of people abstaining from drinking alcohol for the past 12 months was, on average in each country, 18% among men and 32% among women (24), putting the rest of the population at increased risk of cancer due to alcohol consumption.

The AF_p for HPV varies by sub-site and also by European region. In the oropharynx, including tonsil and base of tongue, it has been estimated to range from 17% in southern Europe to 38–39% in northern, western and eastern Europe (15). Oropharyngeal cancer incidence significantly increased among men, and at younger ages, over the 1983-2002 period, in the Netherlands, Slovakia, Denmark and the UK, thereby increasing the total number of new oral cavity and pharyngeal cancer cases. On the contrary, oropharyngeal cancer incidence declined in France and Italy (32).

Laryngeal cancer

Tobacco and alcohol are the main drivers behind the trends of laryngeal cancer incidence. They have a synergistic effect on this cancer (33). In the ARCAGE multicentre case–control study in Europe of upper aerodigestive tract cancers, the risk estimate of hypopharyngeal/laryngeal cancer for tobacco alone was 6.7 and 1.0 for alcohol alone. However, joint exposure to tobacco and alcohol triggered an odd of 14.5 (14). The effect of alcohol on laryngeal cancer also differs by sub-site, i.e. cancer of the supraglottis is more strongly related to alcohol consumption compared to the glottis/subglottis (34). Finally, occupational exposures (35) may also have an impact on the incidence, and explain country-level differences.

Oesophageal cancer

In men, while lung cancer incidence is declining, oesophageal cancer incidence is increasing in a number of countries, particularly in the Netherlands, Finland, Belarus, Germany and the UK (ages 35–74). The difference in the observed trends for lung cancer (a proxy for past smoking behaviours) and oesophageal cancer is probably explained in part by differing risk factors for the two main subtypes of oesophageal cancer: more distantly located adenocarcinomas (AdC) and more proximal squamous cell carcinomas (SCC). They have different aetiologies. Tobacco has a stronger association with SCC, whereas gastro-oesophageal reflux disease, presence of abdominal fat and Barrett oesophagus markedly increase the risk of AdC of the oesophagus (36). In our study, the proportion of AdC in men (35–74 years old) was highest in the Netherlands, Ireland, the UK and Nordic countries (Table 2). Hence, in those countries, the observed increasing oesophageal cancer trends are likely to be mainly driven by risk factors other than smoking. A global assessment by Edgren of the oesophageal AdC epidemic showed that it started between the 1960s (the UK) and the 1990s (Scandinavia), with considerable magnitude in variation between cancer registries (37). Other local factors such as consumption of hot tea may also explain the marked differences for the high UK rates in both sexes (38). As for SCC, alcohol further modifies the risk related to tobacco smoking (14). Heavy alcohol consumption (i.e., ≥4 drinks/day) increases the risk of oesophageal SCC about 5-fold and low doses of alcohol consumption by about 30% (31). As in oral cavity and pharyngeal cancers, the important decline in the average alcohol consumption in some countries (e.g., France, Spain and Italy) may already have had a positive impact and could partly explain the marked decrease in incidence of oesophageal cancers in men in these countries.

Temporal trends in cigarette smoking and lung cancer

Recently, Thun *et al.* have modified the four stages of the "tobacco epidemic" (22) to accommodate gender differences (39). Some of the variations in smoking prevalence

between countries can be explained by differences in economic development. Today, on the one hand, in most European countries, men have reached the final stage, which involves falling smoking rates (40) and widening socioeconomic differences in smoking (41). On the other hand, women are at contrasting stages within the epidemic continuum. In most of northern Europe, the tobacco epidemic in women seems to have reached the fourth stage, whereas France still lags behind and is only at the second stage, characterized by an increase in both smoking prevalence (2) and lung cancer. We also observed longer lag times between the peak of smoking prevalence and lung cancer incidence than previously reported in the USA and Japan (40 vs. 15–30 years) (42). This could be due to differences in smoking behaviour and pattern, cigarette type, other carcinogenic exposures and susceptibility to lung cancer between countries.

The figures presenting the recent incidence rates versus the AAPC during 1998—2007 revealed regional clustering, most notably for lung and laryngeal cancers. We observed closer relationship within regions with the current burden (recent incidence rate) than with the trend (AAPC). We can infer that the today's burden in those cancer sites is the result of past regional influence, while what will happen in the future (estimated by the recent AAPC) is determined at the country level.

Some limitations of this study are worth mentioning. Firstly, seven countries had no national registration coverage. We therefore combined several regional registries to obtain a proxy of the national incidence. Still, for four countries (France, Italy, Spain and Poland) the population coverage was still less than 10%. In our analyses, we hence assumed that the cancer incidence in the rest of the population was equivalent to that in the areas covered by the regional registries. This may (or may not) be a reasonable assumption depending on whether the populations covered by the regional registries are representative of the national population, particularly in terms of smoking patterns. Secondly, although we chose cancer registries that had passed the most rigorous selection process of CI5 publication, data quality may have changed over time. In particular, there may have been improvements in completeness in some registries (43). Thirdly, in an effort to standardise our analysis across countries, we assessed the changes in rates over the 1998–2007 period. As such, this method fails to capture very recent changes (after 2005), e.g., in lung cancer in women. Finally, we grouped countries by geographical region according to the UN classification, yet heterogeneity exists within region. For example, the rates and trends in Baltic countries (Latvia, Estonia and Lithuania) resemble more closely those of the former communist states of central and eastern Europe (including Poland, Slovakia, Russian Federation, Bulgaria, Belarus and Czech Republic) than those of the other countries of northwestern Europe, possibly because of shared history and lifestyles. Likewise, incidence trends in the

Netherlands, classified as being in western Europe, more closely resemble those of the UK, Ireland and Denmark.

CONCLUSIONS

Our study illustrates the impact of the economic conditions as well as successes and failures of tobacco control policies in Europe. These policies have contributed to decreasing smoking prevalence in men, but have failed thus far to prevent smoking initiation in women or to support them in quitting smoking. Implementation was far too late in central and eastern Europe and the Baltic countries. Tobacco control remains a top priority for cancer control in Europe (44); advances in cancer therapy have not had much success in improving survival for the cancers in this study (45, 46). Key targets for prevention efforts should include men in central and eastern Europe (27), southern Europe and Baltic countries and young women across Europe (7). In recognition of the heterogeneity and diversity between populations, targeted and adaptable approaches to cancer prevention are essential (47). As the EUREG database is continuously updated with new incidence, mortality and survival data and new population-based cancer registries, it offers enormous opportunities to increase the knowledge on cancer and its control in the years to come.

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Conflict of interest statement
None declared.

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APPENDIX

Appendix Table 1. Average annual percentage change (AAPC) in the incidence of lung cancer in Europe for the 1998–2007 period, with 95% confidence intervals, in lung cancer incidence by age group and sex

		Men		Women	
Region	**Country**	**35–64 yrs**	**65–74 yrs**	**35–64 yrs**	**65–74 yrs**
Central and eastern Europe					
	Belarus	-2.5* (-3.1; -1.9)	-0.4 (-1.3; 0.4)	2.5* (0.1; 4.8)	-0.4 (-2.7; 2.0)
	Bulgaria	-0.0 (-1.0; 0.9)	1.8* (0.6; 3.1)	3.1* (1.2; 5.1)	-0.5 (-2.0; 1.0)
	Czech Republic	-1.4* (-2.1; -0.7)	-1.6 (-3.7; 0.6)	4.2* (3.1; 5.3)	2.3* (0.8; 3.8)
	Poland§	-2.3* (-3.7; -0.8)	-3.7* (-5.3; -2.1)	9.1* (5.6; 12.6)	3.6* (1.0; 6.4)
	Russian Federation	-2.2* (-2.8; -1.6)	-2.0* (-2.5; -1.5)	0.2 (-0.7; 1.1)	-2.7* (-3.3; -2.0)
	Slovakia	-1.3* (-1.9; -0.7)	-1.7* (-2.3; -1.1)	5.6* (3.3; 7.9)	3.0 (-0.2; 6.4)
Northern Europe					
	Denmark	0.5 (-0.6; 1.5)	-1.5* (-2.7; -0.4)	2.2* (1.1; 3.3)	1.5* (0.1; 3.0)
	Estonia	-3.9* (-5.5; -2.3)	-3.0* (-4.5; -1.5)	3.8 (-0.3; 8.0)	-1.5 (-4.4; 1.6)
	Finland	-0.2 (-1.3; 1.0)	-3.8* (-4.8; -2.9)	4.3* (2.3; 6.2)	0.3 (-1.9; 2.6)
	Iceland	-0.9 (-6.1; 4.5)	2.5 (-2.7; 8.1)	-1.5 (-5.3; 2.6)	-2.2 (-8.7; 4.7)
	Ireland	-0.4 (-2.0; 1.3)	-2.2* (-3.2; -1.2)	2.3* (0.4; 4.2)	1.2 (-0.2; 2.6)
	Latvia	-1.9* (-2.6; -1.2)	0.8 (-1.1; 2.8)	2.0 (-0.6; 4.6)	1.7 (-0.5; 3.9)
	Lithuania	-2.9* (-4.1; -1.8)	-1.2* (-1.9; -0.5)	0.8 (-1.4; 3.1)	-3.1* (-5.4; -0.7)
	Norway	0.7 (-0.3; 1.8)	0.1 (-1.5; 1.8)	2.8* (1.3; 4.3)	4.5* (2.3; 6.7)
	Sweden	-0.4 (-1.9; 1.1)	-0.7 (-1.6; 0.1)	3.2* (2.2; 4.2)	4.3* (3.6; 5.1)
	United Kingdom§	-1.6* (-2.1; -1.1)	-2.9* (-3.2; -2.6)	1.1* (0.3; 1.9)	-0.6 (-1.4; 0.2)
Southern Europe					
	Croatia	-1.3 (-2.9; 0.3)	-3.1* (-4.3; -1.8)	4.3* (1.6; 7.0)	-0.1 (-3.1; 3.1)
	Italy§	-5.6* (-6.7; -4.4)	-3.5* (-4.4; -2.6)	1.2 (-0.2; 2.7)	1.0 (-0.9; 2.8)
	Malta	-1.2 (-6.2; 4.0)	-2.5 (-5.7; 0.7)	8.4* (1.2; 16.0)	0.5 (-5.3; 6.7)
	Slovenia	0.5 (-1.5; 2.5)	-2.3* (-3.7; -0.9)	4.3* (2.8; 5.9)	0.6 (-2.0; 3.4)
	Spain§	-1.9* (-3.3; -0.4)	0.1 (-0.9; 1.1)	5.2* (0.8; 9.8)	4.9* (2.5; 7.4)
Western Europe					
	Austria	-0.9* (-1.9; -0.0)	-2.8* (-3.6; -2.0)	4.1* (3.1; 5.1)	0.9 (-0.5; 2.4)
	France§	1.2* (0.5; 2.0)	-0.5 (-2.1; 1.0)	6.4* (4.1; 8.7)	5.8* (3.3; 8.4)
	Germany§	-2.9* (-3.5; -2.3)	-3.2* (-3.8; -2.7)	4.2* (3.4; 5.1)	1.2* (0.5; 1.9)
	Switzerland§	-2.6 (-5.2; 0.1)	-1.4 (-4.1; 1.3)	1.7 (-1.4; 4.8)	2.5 (-0.5; 5.5)
	The Netherlands	-1.6* (-3.1; -0.1)	-2.5* (-2.8; -2.2)	5.1* (4.5; 5.7)	4.4* (3.5; 5.2)

§Regional registries: France (Doubs, Herault, Isere, Haut-Rhin, Somme, Tarn); Germany (Brandenburg, Hamburg, Saxony, Mecklenburg, North Rhine-Westphalia, Saarland); Poland (Kielce, Cracow); Italy (Modena, Parma, Ragusa, Romagna, Torino, Varese); Spain (Granada, Murcia, Navarra, Tarragona); Switzerland (Geneva, St Gall-Appenzell), United Kingdom (England and Scotland)

*p-value<0.05

Period for Spain is 1996–2005

Appendix Table 2. Average annual percentage change (AAPC) for the 1998–2007 period, with 95% confidence intervals in oral cavity and pharyngeal cancer incidence by age and sex

		Men		Women	
Region	**Country**	**35–64 yrs**	**65–74 yrs**	**35–64 yrs**	**65–74 yrs**
Central and eastern Europe					
	Belarus	0.6 (-0.6; 1.8)	1.1 (-1.1; 3.2)	1.2 (-1.0; 3.5)	-4.6* (-7.7; -1.5)
	Bulgaria	-1.0 (-2.4; 0.5)	1.8 (-0.4; 4.0)	4.5 (-0.4; 9.7)	-1.8 (-6.7; 3.4)
	Czech Republic	1.5* (0.1; 2.9)	1.4 (-0.9; 3.8)	7.9* (5.4; 10.3)	4.4* (0.1; 8.8)
	Poland§	-2.4 (-6.3; 1.6)	-6.2* (-10.4; -1.8)	3.3 (-2.7; 9.6)	-0.7 (-8.0; 7.1)
	Russian Federation	-1.5* (-2.0; -1.1)	-1.7* (-2.2; -1.2)	0.6 (-0.8; 2.1)	-2.2* (-3.0; -1.3)
	Slovakia	-0.4 (-1.2; 0.4)	2.2* (0.7; 3.6)	5.7* (2.6; 8.9)	0.1 (-4.0; 4.4)
Northern Europe					
	Denmark	1.8* (0.4; 3.2)	0.9 (-2.2; 4.1)	3.7* (1.7; 5.8)	-1.0 (-4.7; 2.9)
	Estonia	-3.6* (-6.4; -0.8)	-1.3 (-3.9; 1.4)	1.7 (-2.1; 5.7)	-1.7 (-12.1; 10.0)
	Finland	1.0 (-1.3; 3.3)	-2.3 (-5.0; 0.5)	4.5* (2.4; 6.7)	3.4 (-0.4; 7.5)
	Iceland	1.3 (-11.8; 16.4)	4.7 (-10.4; 22.4)	-1.1 (-12.3; 11.6)	2.0 (-8.6; 13.9)
	Ireland	1.1 (-1.3; 3.6)	-3.1 (-8.2; 2.3)	2.6 (-1.5; 6.8)	6.3* (3.8; 8.9)
	Latvia	-1.0 (-4.1; 2.2)	-2.9 (-8.4; 3.1)	4.6 (-1.8; 11.3)	-4.3 (-8.9; 0.6)
	Lithuania	-0.9 (-2.8; 1.0)	-0.3 (-3.0; 2.5)	0.7 (-4.6; 6.4)	-0.1 (-3.8; 3.6)
	Norway	-0.4 (-2.1; 1.4)	0.7 (-1.0; 2.5)	1.8 (-2.9; 6.7)	5.8* (0.3; 11.7)
	Sweden	0.9 (-0.2; 2.1)	-0.7 (-3.3; 1.9)	1.3 (-2.1; 4.9)	2.3 (-0.2; 5.0)
	United Kingdom§	3.5* (2.8; 4.1)	1.4* (0.1; 2.8)	2.4* (1.4; 3.4)	1.1* (0.2; 2.0)
Southern Europe					
	Croatia	-3.1* (-5.9; -0.3)	-3.9 (-7.8; 0.2)	-3.1 (-7.2; 1.1)	0.1 (-2.3; 2.6)
	Italy§	-3.6* (-4.3; -2.9)	-0.7 (-3.1; 1.8)	2.3 (-1.6; 6.2)	2.2 (-1.0; 5.5)
	Malta	2.5 (-5.5; 11.1)	-4.4 (-13.1; 5.1)	2.4 (-5.2; 10.6)	11.8 (-13.5; 44.7)
	Slovenia	-1.6 (-3.6; 0.5)	-4.3* (-6.3; -2.2)	0.3 (-2.9; 3.6)	2.0 (-6.3; 10.9)
	Spain§	-5.4* (-6.9; -3.9)	-4.6* (-6.9; -2.3)	0.9 (-6.1; 8.3)	1.1 (-4.4; 6.9)
Western Europe					
	Austria	-0.6 (-1.8; 0.6)	-0.3 (-2.3; 1.6)	1.6 (-0.8; 4.0)	0.7 (-3.9; 5.5)
	France§	-2.7* (-4.2; -1.2)	-1.8 (-4.6; 1.1)	1.8 (-2.2; 6.0)	4.2 (-1.2; 9.9)
	Germany§	1.7* (0.9; 2.4)	1.8* (0.1; 3.6)	3.7* (2.0; 5.5)	3.3* (0.8; 5.7)
	Switzerland§	-3.7 (-7.5; 0.3)	-2.3 (-7.2; 2.9)	1.9 (-4.6; 8.8)	-1.4 (-11.5; 9.8)
	The Netherlands	0.0 (-1.3; 1.4)	-1.1 (-3.0; 0.9)	2.0* (0.8; 3.2)	2.2 (-0.2; 4.7)

§Regional registries: France (Doubs, Herault, Isere, Haut-Rhin, Somme, Tarn); Germany (Brandenburg, Hamburg, Saxony, Mecklenburg, North Rhine-Westphalia, Saarland); Poland (Kielce, Cracow); Italy (Modena, Parma, Ragusa, Romagna, Torino, Varese); Spain (Granada, Murcia, Navarra, Tarragona); Switzerland (Geneva, St Gall-Appenzell), United Kingdom (England and Scotland)

*p-value<0.05

Period for Spain is 1996–2005

Appendix Table 3. Average annual percentage change (AAPC) for the 1998–2007 period, with 95% confidence intervals in laryngeal cancer incidence by age and sex

		Men		Women	
Region	**Country**	**35–64 yrs**	**65–74 yrs**	**35–64 yrs**	**65–74 yrs**
Central and eastern Europe					
	Belarus	-1.4 (-3.4; 0.6)	0.0 (-2.0; 2.1)	0.1 (-8.2; 9.2)	7.7 (-9.2; 27.7)
	Bulgaria	1.8* (0.6; 2.9)	5.7* (2.4; 9.1)	3.9 (-1.4; 9.5)	0.9 (-7.3; 9.9)
	Czech Republic	-0.4 (-1.6; 0.9)	1.4 (-0.6; 3.4)	-1.5 (-5.6; 2.8)	0.2 (-7.9; 8.9)
	Poland§	-6.0* (-8.3; -3.7)	-7.4* (-11.4; -3.3)	-6.3 (-15.4; 3.9)	-3.0 (-14.4; 9.9)
	Russian Federation	-2.0* (-2.5; -1.5)	-1.9* (-2.6; -1.2)	0.7 (-1.1; 2.5)	-2.6* (-4.7; -0.4)
	Slovakia	-1.6 (-3.5; 0.3)	1.7 (-1.9; 5.4)	0.9 (-8.5; 11.3)	3.3 (-7.6; 15.5)
Northern Europe					
	Denmark	0.4 (-2.7; 3.6)	-1.9 (-4.9; 1.2)	0.1 (-8.0; 8.9)	0.6 (-6.0; 7.6)
	Estonia	-5.4* (-9.1; -1.7)	-0.1 (-5.7; 5.9)	-2.0 (-13.8; 11.6)	-4.4 (-16.6; 9.6)
	Finland	-0.7 (-4.2; 3.0)	-0.8 (-5.3; 4.0)	8.1 (-0.2; 17.0)	-11.8* (-18.7; -4.4)
	Iceland	-13.7* (-25.0; -0.6)	-6.6 (-18.5; 7.1)	-11.1 (-21.3; 0.4)	-0.1 (-15.2; 17.6)
	Ireland	-0.1 (-2.2; 2.1)	2.3 (-3.0; 7.9)	-2.1 (-9.9; 6.4)	2.1 (-8.9; 14.4)
	Latvia	0.7 (-1.9; 3.3)	-1.2 (-6.5; 4.3)	7.2 (-4.7; 20.6)	-2.1 (-17.5; 16.1)
	Lithuania	-0.7 (-2.6; 1.3)	0.0 (-4.4; 4.6)	3.6 (-5.4; 13.5)	5.7 (-10.6; 24.9)
	Norway	-0.6 (-5.1; 4.0)	-1.8 (-5.9; 2.4)	0.1 (-7.0; 7.7)	-8.1 (-18.8; 4.0)
	Sweden	0.9 (-3.1; 5.1)	-2.3* (-4.2; -0.3)	0.6 (-6.6; 8.4)	-0.9 (-8.2; 7.0)
	United Kingdom§	-0.2 (-3.4; 3.1)	-1.5* (-2.9; -0.2)	-1.0 (-3.1; 1.2)	-3.1* (-4.4; -1.8)
Southern Europe					
	Croatia	-1.6 (-3.3; 0.2)	-4.2* (-7.8; -0.5)	0.1 (-7.2; 8.0)	-6.2 (-13.4; 1.7)
	Italy§	-4.0* (-5.6; -2.4)	-3.9* (-6.5; -1.2)	4.2 (-0.7; 9.2)	0.7 (-8.0; 10.2)
	Malta	-3.7 (-10.4; 3.6)	1.6 (-11.0; 15.9)	4.6 (-12.4; 24.8)	6.6 (-7.5; 22.9)
	Slovenia	-2.1 (-5.7; 1.7)	-2.4 (-6.6; 2.1)	1.8 (-7.7; 12.3)	-13.8* (-22.2; -4.5)
	Spain§	-4.4* (-5.5; -3.4)	-3.4 (-7.0; 0.4)	6.3 (-3.8; 17.4)	-0.8 (-16.0; 17.2)
Western Europe					
	Austria	-2.0* (-3.6; -0.4)	-4.2* (-6.9; -1.3)	2.5 (-2.4; 7.7)	-4.4 (-12.6; 4.5)
	France§	-1.9 (-3.9; 0.1)	-2.0 (-5.1; 1.1)	-0.9 (-6.3; 4.8)	-5.3 (-18.2; 9.7)
	Germany§	-1.3 (-3.0; 0.4)	-0.0 (-2.2; 2.1)	2.7 (-2.8; 8.4)	-0.9 (-7.3; 6.0)
	Switzerland§	-7.6* (-12.8; -2.0)	-1.5 (-7.9; 5.4)	0.8 (-13.0; 16.7)	14.8 (-2.4; 35.1)
	The Netherlands	-1.0 (-2.4; 0.5)	-3.3* (-5.0; -1.5)	0.3 (-2.5; 3.2)	-2.8 (-9.3; 4.1)

§Regional registries: France (Doubs, Herault, Isere, Haut-Rhin, Somme, Tarn); Germany (Brandenburg, Hamburg, Saxony, Mecklenburg, North Rhine-Westphalia, Saarland); Poland (Kielce, Cracow); Italy (Modena, Parma, Ragusa, Romagna, Torino, Varese); Spain (Granada, Murcia, Navarra, Tarragona); Switzerland (Geneva, St Gall-Appenzell), United Kingdom (England and Scotland)

*p-value<0.05

Period for Spain is 1996–2005

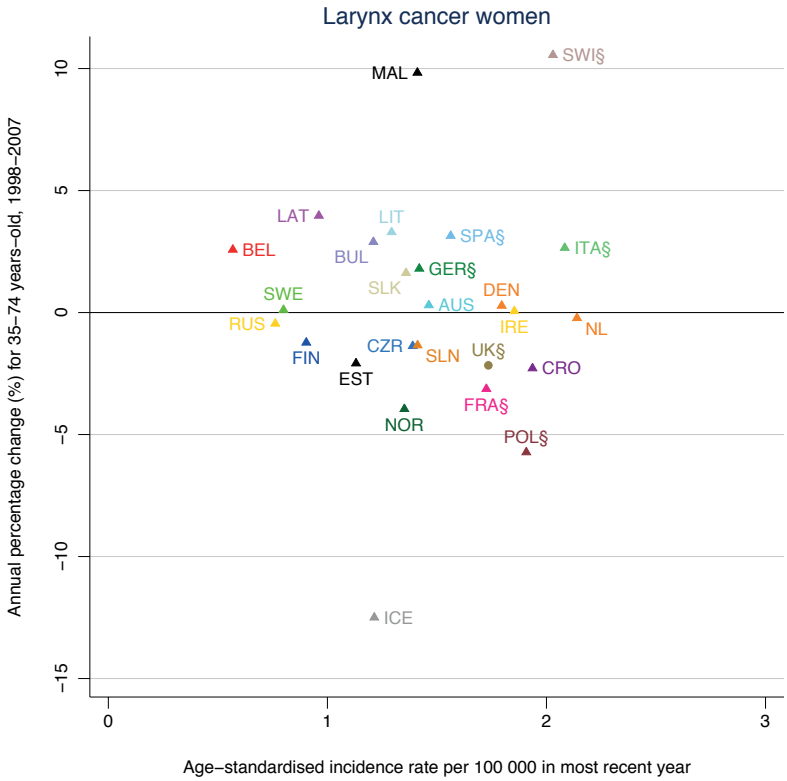
Appendix Table 4. Average annual percentage change (AAPC) for the 1998–2007 period, with 95% confidence intervals in oesophageal cancer incidence by age and sex

		Men		Women	
Region	**Country**	**35–64 yrs**	**65–74 yrs**	**35–64 yrs**	**65–74 yrs**
Central and eastern Europe					
	Belarus	2.0* (0.6; 3.5)	2.1 (-1.0; 5.3)	-0.0 (-7.2; 7.7)	-0.4 (-7.3; 7.1)
	Bulgaria	0.3 (-6.6; 7.7)	0.1 (-3.4; 3.7)	1.9 (-5.3; 9.7)	-1.3 (-7.4; 5.3)
	Czech Republic	1.0 (-1.6; 3.7)	3.1* (0.8; 5.6)	6.5 (-0.5; 13.9)	1.4 (-3.6; 6.6)
	Poland§	-1.3 (-7.0; 4.9)	-1.4 (-5.9; 3.4)	9.7 (-2.8; 23.8)	-4.5 (-14.3; 6.3)
	Russian Federation	-0.9 (-1.9; 0.1)	-2.2* (-3.3; -1.0)	-2.5* (-4.8; -0.1)	-4.9* (-5.9; -4.0)
	Slovakia	-1.5 (-4.2; 1.2)	0.2 (-4.1; 4.7)	2.1 (-9.9; 15.9)	2.0 (-6.5; 11.3)
Northern Europe					
	Denmark	0.7 (-1.8; 3.3)	-0.9 (-4.4; 2.7)	3.8* (0.6; 7.2)	2.2 (-2.9; 7.6)
	Estonia	0.7 (-4.9; 6.6)	-4.0 (-10.9; 3.4)	8.7 (-5.2; 24.8)	-1.9 (-15.1; 13.3)
	Finland	4.1* (0.6; 7.8)	0.2 (-4.4; 5.0)	3.8 (-3.6; 11.7)	-0.6 (-5.2; 4.2)
	Iceland	-2.8 (-15.2; 11.5)	10.7* (2.5; 19.5)	6.6 (-1.9; 15.9)	8.2 (-3.8; 21.7)
	Ireland	2.6 (-1.0; 6.4)	0.4 (-2.6; 3.4)	-0.1 (-3.4; 3.3)	-0.6 (-5.3; 4.3)
	Latvia	1.9 (-1.8; 5.8)	3.4 (-2.3; 9.5)	2.0 (-9.4; 14.8)	13.7* (1.9; 26.8)
	Lithuania	2.7* (0.8; 4.6)	-0.1 (-3.8; 3.6)	2.1 (-3.3; 7.8)	0.2 (-10.1; 11.7)
	Norway	4.2* (0.7; 7.8)	-0.4 (-4.6; 3.9)	-2.4 (-7.7; 3.2)	0.1 (-6.4; 7.1)
	Sweden	1.3 (-1.9; 4.7)	-0.0 (-2.7; 2.7)	2.3 (-9.8; 15.9)	-1.0 (-5.2; 3.3)
	United Kingdom§	1.9* (1.3; 2.5)	0.8* (0.4; 1.2)	0.8 (-0.4; 2.0)	-1.5* (-2.8; -0.2)
Southern Europe					
	Croatia	-1.4 (-2.8; 0.1)	-1.8 (-4.6; 1.1)	-5.1 (-12.7; 3.2)	-0.8 (-13.9; 14.1)
	Italy§	-2.5 (-6.2; 1.5)	-4.6 (-9.6; 0.6)	-3.4 (-9.5; 3.2)	0.3 (-6.7; 7.9)
	Malta	4.1 (-4.7; 13.8)	3.3 (-9.9; 18.3)	6.9 (-10.0; 27.1)	11.2 (-1.3; 25.2)
	Slovenia	0.1 (-3.0; 3.2)	-5.3 (-10.9; 0.6)	2.8 (-6.8; 13.5)	-9.0* (-16.4; -1.0)
	Spain§	-4.2* (-6.9; -1.3)	0.1 (-3.4; 3.8)	4.4 (-6.6; 16.6)	0.2 (-11.5; 13.5)
Western Europe					
	Austria	2.3* (0.5; 4.2)	-1.8 (-3.6; 0.1)	1.8 (-3.2; 6.9)	0.6 (-3.1; 4.5)
	France§	-2.1* (-4.0; -0.1)	-3.8* (-5.9; -1.7)	4.7 (-0.4; 10.0)	1.3 (-6.1; 9.2)
	Germany§	0.1 (-0.9; 0.7)	1.6* (0.3; 2.9)	0.9 (-2.9; 4.7)	0.8 (-1.8; 3.6)
	Switzerland§	-1.0 (-5.6; 3.9)	-0.4 (-5.1; 4.4)	3.2 (-0.9; 7.4)	1.7 (-18.6; 27.1)
	The Netherlands	4.4* (3.1; 5.7)	2.1* (0.6; 3.7)	2.9* (1.2; 4.7)	2.6* (0.5; 4.9)

§Regional registries: France (Doubs, Herault, Isere, Haut-Rhin, Somme, Tarn); Germany (Brandenburg, Hamburg, Saxony, Mecklenburg, North Rhine-Westphalia, Saarland); Poland (Kielce, Cracow); Italy (Modena, Parma, Ragusa, Romagna, Torino, Varese); Spain (Granada, Murcia, Navarra, Tarragona); Switzerland (Geneva, St Gall-Appenzell), United Kingdom (England and Scotland)

*p-value<0.05

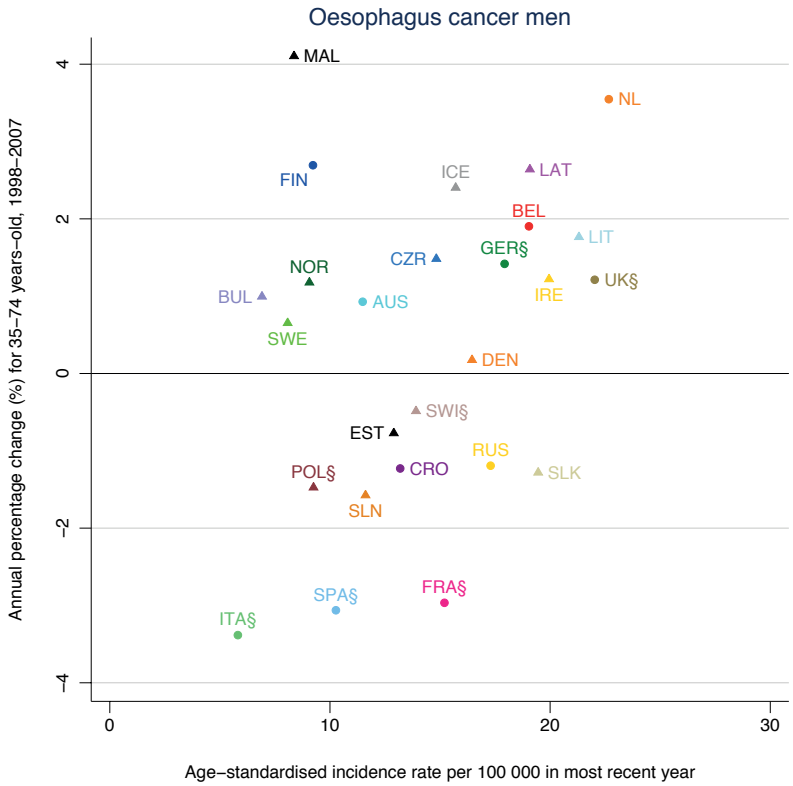
Period for Spain is 1996–2005



Appendix Figure 1. Average annual percentage change (AAPC) between 1998–2007 (except 1996–2005 for Spain) and age-standardised (European) incidence rates (ASR) of the most recent year of laryngeal cancer in women aged 35–74.

Dots indicate statistically significant AAPC ($p \leq 0.05$); triangles indicate non-significant AAPC. Colours indicate European regions: Central and eastern (blue), northern (green), southern (red) and western (brown).

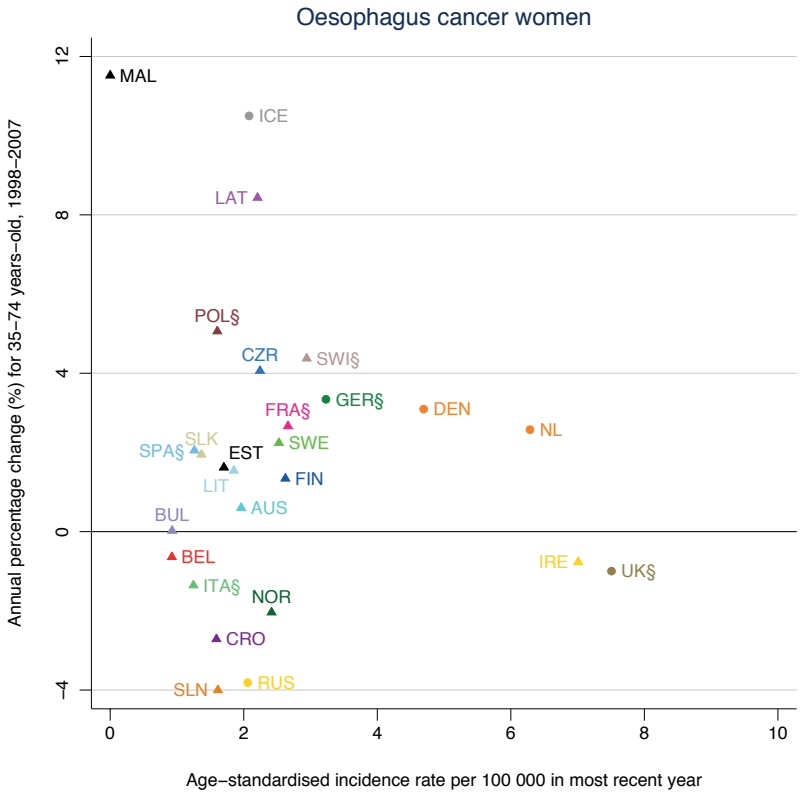
§ regional registries



Appendix Figure 2. Average annual percentage change (AAPC) between 1998–2007 (except 1996–2005 for Spain) and age-standardised (European) incidence rates (ASR) of the most recent year of oesophageal cancer in men aged 35–74.

Dots indicate statistically significant AAPC ($p \leq 0.05$); triangles indicate non-significant AAPC. Colours indicate European regions: Central and eastern (blue), northern (green), southern (red) and western (brown).

§ regional registries



Appendix Figure 3. Average annual percentage change (AAPC) between 1998–2007 (except 1996–2005 for Spain) and age-standardised (European) incidence rates (ASR) of the most recent year of oesophageal cancer in women aged 35–74.

Dots indicate statistically significant AAPC ($p \leq 0.05$); triangles indicate non-significant AAPC. Colours indicate European regions: Central and eastern (blue), northern (green), southern (red) and western (brown).

§ regional registries

2.2

International trends in lung cancer incidence by histological subtype: Adenocarcinoma stabilizing in men but still increasing in women

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ABSTRACT

Objectives: Trends in overall lung cancer incidence in different countries reflect the maturity of the smoking epidemic. Further understanding of the underlying causes for trends over time can be gained by assessing the trends by sex and histological subtype. We provide a temporal analysis of lung cancer incidence in 12 populations (11 countries), with a focus on cohort-specific trends for the main histological subtypes (squamous cell carcinomas (SCC), adenocarcinomas (AdC), and small cell carcinoma).

Material and Methods: We restrict the analysis to population-based registry data of sufficient quality to provide meaningful interpretation, using data in Europe, North America and Oceania, extracted from successive *Cancer Incidence in Five Continents* Volumes. Poorly specified morphologies were reallocated to a specified grouping on a population, 5-year period and age group basis.

Results: In men, lung cancer rates have been declining overall and by subtype, since the beginning of the study period, except for AdC. AdC incidence rates have risen and surpassed those of SCC (historically the most frequent subtype) in the majority of these populations, but started to stabilize during the mid-1980s in North America, Australia and Iceland. In women, AdC has been historically the most frequent subtype and rates continue to increase in most populations studied. Early signs of a decline in AdC can however be observed in Canada, Denmark and Australia among very recent female cohorts, born after 1950.

Conclusions: The continuing rise in lung cancer among women in many countries reinforces the need for targeted smoking cessation efforts alongside preventive actions.

INTRODUCTION

With 1.6 million new cases and 1.4 million deaths in 2008, lung cancer remains the most frequent cause of cancer worldwide and the leading cause of cancer death in men and women in 91 and 17 countries respectively, with the lifetime cumulative risk (ages<75) over 7% in men in several Eastern European countries [1]. Lung cancer patterns are largely determined by past exposure to tobacco smoking; pooled estimates indicate over 90% of cases are due to smoking among men and over 80% among women [2], although there is considerable variation by world region.

By 1930, decades after smoking had become common among men, the tobacco industry began to capitalize on changing social attitudes, promoting smoking as a symbol of women empowerment [3]. As a consequence of uptake of the habit, the incidence of female lung cancer began increasing in the 1970's in Western countries such as in the U.S. [4] and in Europe [5]. Declines in lung cancer incidence among men tended to follow the earlier uptake and cessation in those U.S. and European populations and for which rates have historically been highest [4] [5].

Lung cancer trends are more complex on stratification by histological subtype, and insight may be gained by assessing trends according to the well-established etiology by histology [2;6]. Smoking increases risk of all subtypes of lung cancer, with the risk greater for squamous cell and small cell carcinomas than for adenocarcinomas. Adenocarcinoma is consistently more frequent in women than men (in both smokers and non-smokers), with increasing rates of this subtype observed in both sexes in many high income settings [7;8].

We provide a temporal analysis of lung cancer incidence in 11 countries across three continents, with a focus on cohort-specific trends by histological subtype and sex. The results are discussed according to current etiological evidence regarding smoking and risk by subtype, alongside differences reported in tobacco consumption in these populations.

MATERIALS AND METHODS

Data Sources

New cases of lung cancer (ICD-10 C33-34) were extracted by histology, year of diagnosis, sex and age from population-based cancer registries for the period 1973-2002 contained within *CI5Plus Detailed* [9], a database of successive volumes of the *Cancer*

incidence in Five Continents (CI5) series. The specific inclusion requirement was at least 15 consecutive years of data and compilation in the last volume of the CI5 series (volume IX, covering the period 1998-2002), a criterion indicative of each registry's data quality over time.

We further restricted analysis to registries that met *all* of the following criteria (based on the mean percentages across each CI5 volume for each registry): ≥80% of microscopically-verified cases, ≤5% of cases reported by death certificates only and ≤25% of cases recorded with morphology poorly specified (as defined as either unspecified lung cancers or unspecified lung carcinomas). Registry datasets in 11 countries (two populations in the USA: Blacks and Whites) met all of the above conditions; with national registry data available for two countries (Denmark and Iceland). For the remaining countries, regional registries were aggregated to obtain a proxy of national incidence (36 regional registries in total, see Table 1, footnote). The varying start-up and final years available for each registry by country led to a pragmatic selection of registries that sought to maximise both the number of included registries and the length of period of study. The time span of observations by country varied from 15 to 30 years (Table 1). Corresponding population data were obtained from the same sources as incidence.

Reallocation of unspecified morphologies over specified subtypes

The data were extracted based on the ICD-O-2 groupings [10] [11] [12]: (1) Carcinoma partitioned into the following sub-groups: (1.1) Squamous-cell carcinoma, (1.2) Adenocarcinoma, (1.3) Small cell carcinoma, (1.4) Large cell carcinoma, (1.5) Other specified carcinoma, (1.6) Unspecified carcinoma; (2) Sarcoma; (3) Other specified cancer; (4) Unspecified cancer.

To enable comparisons of rates by subtype, we first reallocated those lung cancer cases with unspecified morphologies. Lung cancer cases were partitioned into three age groups (35-54, 55-64 and 65-74 years) and the proportion of each histological group on a registry, 5-year period and age group basis calculated and used to and then proportionally reallocate cases with unspecified cancer (4) to the three specified groups (1), (2) and (3). Secondly, we reallocated unspecified carcinoma cases (1.6) to specified carcinoma cases (1.1), (1.2), (1.3), (1.4) and (1.5). The results are presented for lung cancer and for the four major histologies: squamous-cell carcinoma (SCC), adenocarcinoma (AdC), small cell carcinoma and large cell carcinoma.

Table 1. Mean person-years, mean annual incidence, mean age-standardized (World) incidence rate, and proportion of each subtype by country (national registry or combination of regional registries), for the 1998-2002 period, for ages 35-74, by sex.

Population	Period (span)	Sex	Annual person-years [1]	Annual incidence [1]	Age-standardized incidence rate [1]	Mean proportions [1]					
						Squamous cell	Adeno-carcinoma	Small cell	Large cell	Other carcinoma	Other morpho-logies
Australia*	1983-2002 (20)	Male	3,389,713	2,754	78.7	27.5	32.7	15.4	20.9	3.1	0.3
		Female	3,430,776	1,417	39.3	17.4	40.2	17.5	20.0	4.7	0.2
Austria*	1988-2002 (15)	Male	151,775	160	103.1	31.4	42.4	17.9	5.0	3.2	0.1
		Female	158,522	60	36.1	17.3	53.8	18.4	2.7	7.5	0.3
Canada*	1978-2002 (25)	Male	5,365,600	5,330	103.8	31.7	39.5	17.0	10.1	1.4	0.2
		Female	5,477,536	3,994	73.5	21.2	47.8	18.6	9.9	2.3	0.1
Denmark	1978-2002 (25)	Male	1,280,096	1,398	102.4	33.9	37.6	21.0	5.9	1.3	0.2
		Female	1,290,477	1,111	76.6	21.9	47.6	22.3	6.0	1.9	0.3
France*	1978-2002 (25)	Male	1,313,860	1,741	124.8	42.2	30.4	14.1	9.4	3.6	0.3
		Female	1,382,935	336	22.7	20.8	46.0	15.9	10.5	6.3	0.5
Iceland	1973-2002 (30)	Male	58,773	42	73.6	26.6	39.7	18.9	11.8	2.6	0.5
		Female	58,489	45	76.0	19.6	46.1	17.9	9.0	7.4	0.0
Italy*	1988-2002 (15)	Male	255,429	415	129.6	39.3	35.4	15.9	6.6	2.6	0.1
		Female	266,597	107	32.9	23.9	48.5	14.9	7.3	5.3	0.0
Spain*	1978-2002 (25)	Male	132,820	179	120.6	43.7	20.4	15.7	17.3	2.7	0.2
		Female	132,284	24	17.0	20.5	51.6	7.7	14.7	5.6	0.0
Switzerland*	1983-2002 (20)	Male	217,747	213	96.7	33.9	33.9	17.6	12.0	2.2	0.4
		Female	227,754	91	37.3	20.4	44.2	21.2	10.1	3.5	0.5
The Netherlands*	1973-2002 (30)	Male	251,157	335	131.8	38.8	20.9	17.4	21.2	1.2	0.4
		Female	245,659	123	47.3	21.6	27.0	23.4	26.2	1.7	0.0
USA Blacks*	1978-2002 (25)	Male	568,235	760	176.9	32.2	43.5	12.7	9.6	1.8	0.3
		Female	671,819	510	91.7	25.3	48.5	14.3	9.1	2.5	0.3
USA Whites*	1978-2002 (25)	Male	4,651,855	4,688	110.3	28.8	43.3	17.7	7.6	2.4	0.2
		Female	4,767,260	3,833	81.3	20.3	48.5	20.4	7.1	3.5	0.2

* combined regional registries

Regional registries: Australia (New South Wales, South, Tasmania, Victoria and Western), Austria (Tyrol), Canada (Alberta, British Columbia, Manitoba, New Brunswick, Newfoundland, Nova Scotia, Ontario and Saskatchewan), France (Haut-Rhin, Herault, Bas-Rhin, Calvados, Doubs, Isere, Somme and Tarn), Italy (Romagna), Spain (Navarra), Switzerland (Geneva and St Gall-Appenzell), The Netherlands (Eindhoven), USA (Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco, Seattle and Utah).

Statistical methods

Cases were stratified by sex and 5-year age group and analyses restricted to the ages 35-74. Truncated age-standardized incidence rates (ASR) per 100,000 were estimated using the world standard [13]. Ten-year cohorts were obtained on subtracting the midpoints of 5-year age groups and 5-year calendar periods. The trends are presented as rates versus birth cohort by age for each sex and subtype. We selected eight populations with sufficiently large numbers of cases and at least a 20-year data span, to ensure meaningful analyses and interpretation.

Assuming incidence rates were constant within 5-year age and periods, an age-period-cohort (APC) model was fitted on assuming the number of cases followed a Poisson random variable with the logarithm of the person-years at risk specified as an offset:

$$\log(\lambda(a, p)) = \alpha_a + \beta_p + \gamma_c$$

where λ refers to the rate, α_a, β_p and γ_c are functions of age a, period p and birth cohort c. Birth cohorts c are computed as $c = p - a$. The effects were estimated and presented using the full APC model. The relative simplicity of fitting APC models belies difficulties in providing an informed presentation of the model parameters, given the irresolvable issue of non-identifiability. In order to provide a unique, non-arbitrary solution, we constrained the linear component of the period effect to have zero slope, and therefore assumed that the linear changes in trends were cohort-related. This was considered reasonable given the overwhelming evidence that exposure to tobacco and changes in its prevalence are influenced by societal and peer-related factors, placing successive generations of men and women at higher (or lower) risk of lung cancer. As the solution presented is entirely dependent on choice of allocation of the trend (drift) [14], caution is needed when interpreting the results. The model analysis and presentation was performed using *APCfit* [15] in Stata [16]. We used the default number of internal knots for each of the spline bases for the three variables (a, p and c), i.e. 4, and hence the knots were placed at each quintile (except for Australia, where we used 3 knots over the period). The vertical lines indicate the specific cohorts for which the male and female cohorts reach their maximum risk, by subtype.

RESULTS

Trends in overall lung cancer incidence: age-adjusted rates in 1973-2002 by sex

The ASR of lung cancer incidence (ages 35-74) have changed markedly from the 1970s in all studied countries, with major variations in the sex-specific scale of the

burden and the direction and magnitude of trends (Figure 1). Rates are higher in men than women, with incidence trends among men declining at variable periods, except in Spain, where increases continue to be observed. In contrast, female rates steadily increased over the study period, and only in those countries where burden is now relatively high (the U.S., possibly Australia, Canada, Denmark), have rates showed signs of a plateau. The most recent rates among men vary 2.5-fold, from 176.9 (per 100 000), among U.S. Blacks, to 73.6 in Iceland (Table 1). The U.S. black population have the highest female rates (91.7) compared with low-risk Spain (17.0).

Trends in lung cancer incidence by histological type: age-adjusted rates in 1973-2002 by sex

Among men, SCC has been the most frequent subtype in all studied countries, with incidence rates decreasing over the study period (Figure 1). Adenocarcinoma (AdC) rates started to stabilize during the mid-1980s in North America, Australia and Iceland, yet was the most common subtype in recent years in all countries except France, Spain and The Netherlands. Small cell carcinoma rates are also in decline, largely in parallel with SCC. Large cell carcinoma is the least frequent subtype in both sexes.

Two notable facts emerge when examining female lung cancer trends by subtype. AdC has been rising steadily in all countries, irrespective of trends of the other subtypes. The subtype has predominated in every population in the last decade (with the exception of The Netherlands) with the rate of change in AdC often greater than those observed for the other subtypes with calendar time.

Trends in lung cancer incidence by histological type: rates vs. birth cohort

Figures 2a and 2b illustrate the SCC and AdC trends versus birth cohort by age in eight countries by sex. The parallelism of the curves indicates the influence of generation on risk of both SCC and AdC. The peak incidence of SCC among men has occurred in all eight populations, with rates uniformly decreasing in generations born after 1930, or even earlier (circa 1915) in Australia. The generational declines in AdC cases started later than SCC, among men born during WWII in North America, Denmark and Australia. Conversely, the male rates are uniformly rising in successive generations born up to and including the 1960s cohorts in France and Spain.

In women, the marked cohort-specific declines in SCC in North America, Denmark and Australia began in cohorts born around WWII, the same generation for which a decrease in AdC was observed in men. The trends elsewhere are less easy to interpret given the random variation inherent due to small numbers. AdC rates among women rose in successive generations in each population, with an stabilization of incidence

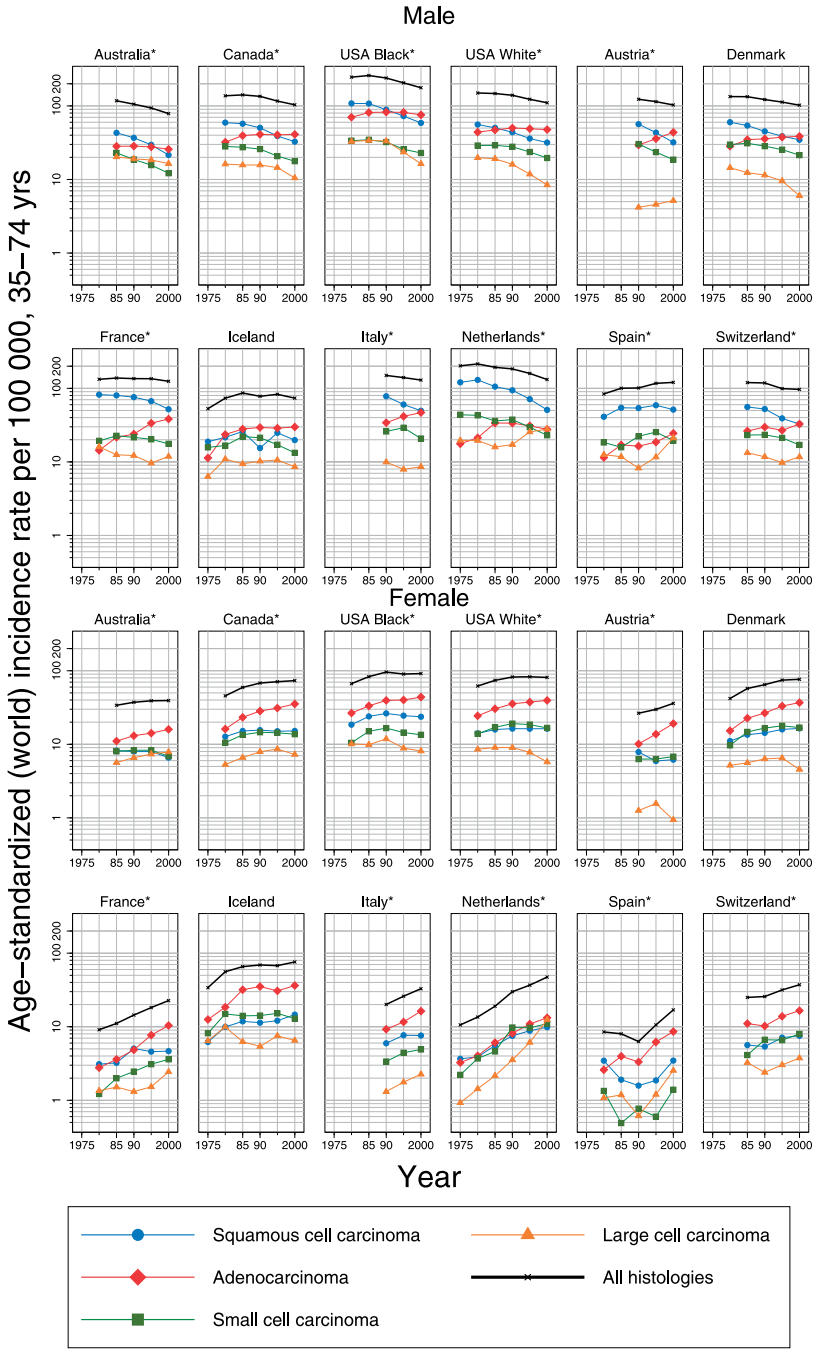

Figure 1.Lung cancer age-adjusted (World standard) incidence rates over time, by population and sex, by morphological subtype, for ages 35-74.
The black line represents all morphologies combined.

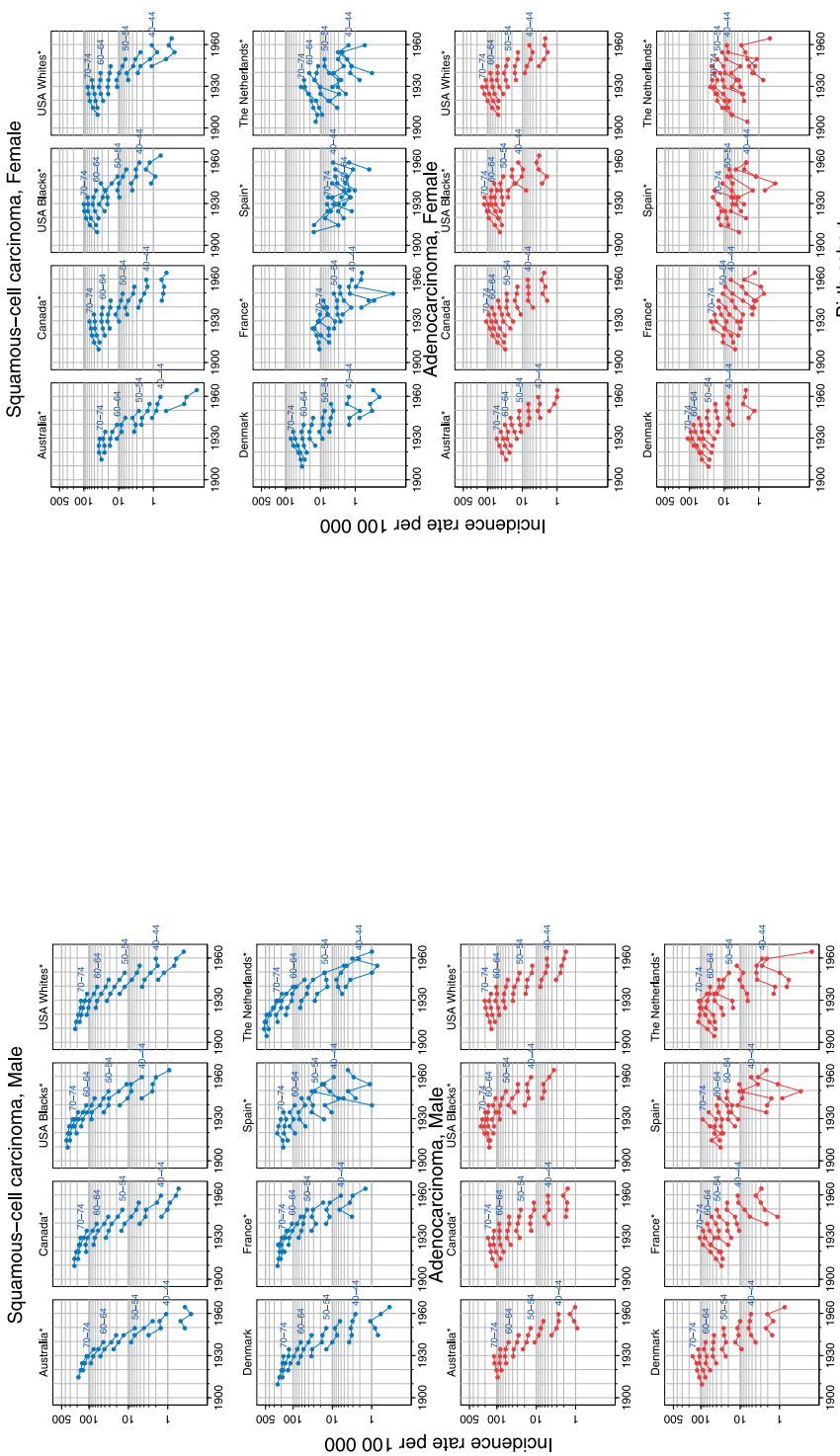

Figure 2. Lung cancer age-adjusted (World standard) incidence rates versus birth cohort by population, age (ages 35-74), for Adenocarcinoma and Squamous cell carcinoma, for a) males and b) females.

trends in Canada, Denmark and Australia among recent cohorts, born in the 1950s or thereafter.

Age-period-cohort analyses: comparisons of cohort trends in SCC and AdC by sex

Figure 3 summarizes the observed histological subtype- and sex-specific trends by population. The peak in risk of SCC consistently precedes that of AdC (except in Spain), in both sexes. The highest risk of SCC in men occurs during the beginning of the observation period, among cohorts born early in the 20th century, while the corresponding peak in women is found in cohorts born 20 to 55 years later. The time lag between maximum rate ratios of the two subtypes varies greatly across countries, from zero to 60 years. The maximum risk of AdC among women is observed in the most recent cohorts – in all populations except US Whites and Australia – affecting generations born after 1960, and in selected populations in men (France, The Netherlands). Of note are the uniformly increasing rates among female birth cohorts in France and Spain, with few signs of recent stabilization, irrespective of subtype.

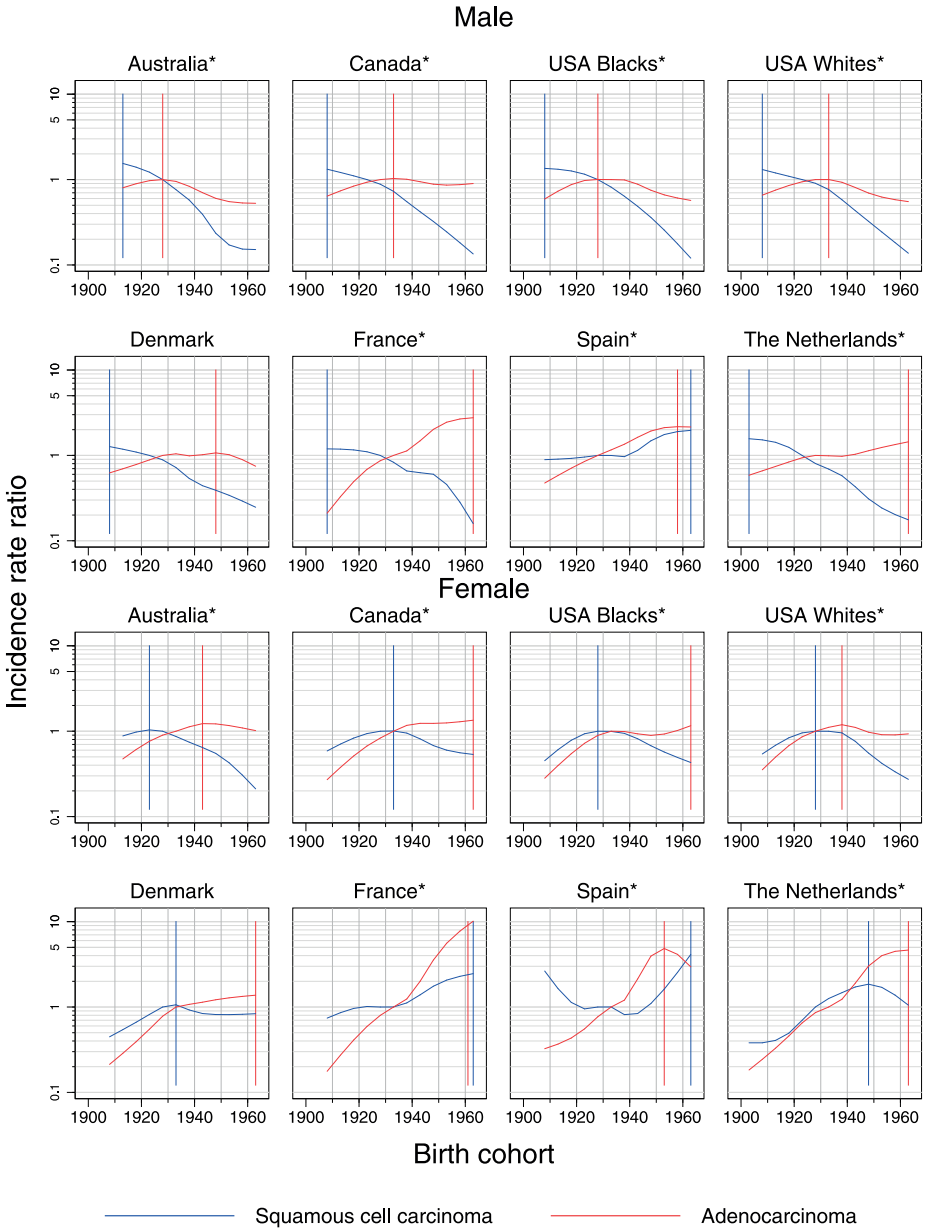

Figure 3. Cohort parameters form the APC model based on the assumption of a zero slope (drift taken up entirely by cohort) by population, subtype and sex.

The vertical lines indicate the specific cohorts for which the male and female cohorts reach their maximum risk, by subtype.

DISCUSSION

This study reports the variation in lung cancer patterns and trends across subtypes by sex in 11 countries worldwide and serves to illustrate the varying phases of the tobacco epidemic and subsequent temporal development and impact of the lung cancer epidemic by histology in each population[17]. The overall lung cancer trends are largely the product of changing prevalence in smoking (the proportion of the population who smoke regularly) and patterns of tobacco consumption (e.g. the amount smoked and composition of the cigarette). In North America, Australia and Denmark, where rates have been elevated, decreasing lung cancer trends in men have been observed for a number of decades, while rates have now begun to level off among women. In a second group of countries (Austria, France, Iceland, Italy, the Netherlands and Switzerland), male rates have been declining in contrast to the rising rates in women. Spain is perhaps the exception in that increasing rates are observed in both men and women.

The trends by subtype present a somewhat different picture. Among men, in most countries that we studied, AdC was the most predominant subtype of lung cancer in 1998-2002, as compared to 20 years before when SCC represented the most frequent of all subtypes (except in Iceland). This shift from SCC to AdC had already been observed in previously published studies at national level (in the US [18], Japan [19], Lithuanian men [20] and international level [2;7;8]. Not only did women start smoking cigarettes later, they also smoked lower-tar brands [21] and consequently developed a somewhat different profile of histological subtypes compared with men. In women, AdC was the most frequent subtype of lung cancer throughout the study period, with few exceptions (before the 1990s in France, in 1980 in Spain and in 1975 in The Netherlands). In our study, a stabilization or decline in AdC rates are seen among younger women and recent cohorts, among US Whites, and in Canada, Denmark and Australia.

The emerging predominance of AdC can be related to three factors. Firstly, the change in cigarette manufacturing; the rise of filtered, lower tar- and nicotine-containing cigarettes, smokers have tended to satiate nicotine needs by inhaling deeper [21], leading to a more peripheral distribution of tobacco smoke in the lung. This promotes a shift from central tumors (SCC and small cell carcinomas) to peripheral tumors (AdC and large cell carcinomas). Other changes in cigarette composition and design could partially explain the surge in AdC. including the decrease in polycyclic aromatic hydrocarbons in manufactured cigarettes which are SCC inducers, alongside the increase in tobacco-specific N-nitrosamines, which are AdC inducers [4]. Tobacco companies have introduced products marketed in a manner that implies they are "safer", yet research

indicates that there is no completely safe form of tobacco [22]. The results presented here show that the shift to filtered/low-tar cigarettes has merely altered the type of lung cancer.

Secondly, the risk of SCC and small cell carcinoma lung cancers increases more rapidly with increasing smoking duration than AdC [23]. Hence SCC is the first subtype to develop, and then AdC appears later. Thirdly, while the relative risk of all types of lung cancer decreases after quitting smoking, the risk of small cell carcinoma and SCC decrease more rapidly after cessation than for AdC [23]. The high risk of AdC for a longer period after quitting is in line with the higher exposure required for inducing AdC compared with SCC (deeper inhalation and longer exposure). SCC is more strongly related to smoking, while AdC is seen both in smokers and non-smokers, and is the most common type in never-smokers [2;4;23]. Since the risk of AdC decreases less rapidly after smoking cessation than for small cell carcinoma and SCC, the reduction in AdC (commonly the predominant subtype presently) will likely be seen later than for SCC where tobacco cessation is observed generationally.

Additional explanations for the distinct SCC and AdC trends could include the impact of the atmospheric pollution, as it has been estimated that 3% of lung cancer deaths are due to urban air pollution in high-income countries [24]. Air pollution, particularly oxides of nitrogen, had been suggested to increase AdC, but the absence of change in AdC rates among never smokers makes this hypothesis less tangible [25]. While indoor smoke from solid fuel use and limited ventilation is a known risk factor for lung cancer [24], it would have a limited impact in our study, given this study excluded all but high-income countries where such household use is very infrequent. Few studies have investigated occupational risk in relation to specific histological subtypes [26;27]. Given a maximum of 10% of lung cancer deaths among men and 5% among women worldwide have been estimated to be attributable to exposure of eight occupational lung carcinogens [4], such changes alone are unlikely to explain the shift in subtypes that we observe. In a large Nordic study [28] occupational risk patterns were quite similar in all main histological subtypes of lung cancer, although earlier case-control studies in British Columbia and Turkey had reported histology-specific associations [26;27]. Change in classification and coding, including improved diagnostic methods for peripheral tumors may partially explain such changes, although as Burns [25] has stated for the U.S., while changes in histological classification and diagnostic techniques may have contributed to the increase in adenocarcinoma of the lung, they are unlikely to explain the magnitude of the observed change.

Several limitations warrant mention. First, the data are somewhat limited as they capture trends only to 2002, although such availability is in line with studies to comparing incidence trends by histological subtype in several countries ([7] [8] [29]).
Only two registries had national coverage (Iceland and Denmark). For the other countries, we used regional data and assumed the regional registry datatset(s) were nationally representative.

The extent to which poorly-specified histology (morphology unspecified or specified only as carcinoma) impacts on the interpretation of the trends is an obvious concern. The reallocation procedure has been shown to perform robustly in previous analyses [7], and as in that study, we restricted analysis to populations with 25% or fewer cases with poorly-specified morphologies. Further, in the Appendix, we noted that temporal trends based on the original and the reallocated rates were very similar, and in terms of the relative frequency and ranking of subtypes across calendar periods. The strict inclusion criteria narrowed our study to 12 long-term high-quality registry populations, all of them representing highly developed countries.
In APC modeling, it is not possible to identify the linear trends attributable to period or birth cohort. As tobacco uptake and cessation is largely a cohort-related behavior – most users begin as young adults and carry the habit through adulthood – the incidence rate ratios are presented assuming that the linear trend is entirely due to birth cohort. We cannot however exclude the possibility of some underlying period-based linear trends, driven, for example, by a gradual increasing awareness of health hazards of smoking supported by emerging tobacco control laws.

The continuing increases in lung cancer and the concomitant increase in AdC, particularly among women, are of concern. Recent tobacco control policies may further reduce the burden in the longer term given laws that prohibit smoking in public places (e.g. Ireland in 2004 and Italy in 2005), or prohibit sales to minors (e.g. France in 2011, Hungary in 2013) are quite new. Smoking cessation and prevention actions against smoking initiation are evidently still needed, and careful monitoring of trends in tobacco and tobacco-related diseases is one of the key requirements in planning and evaluating tobacco control [30]. Therefore, this dissemination of detailed trends in lung cancer should provide key information on priorities for targeting the primary prevention of many tobacco-related cancers and other noncommunicable diseases.

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Conflict of interest
None declared

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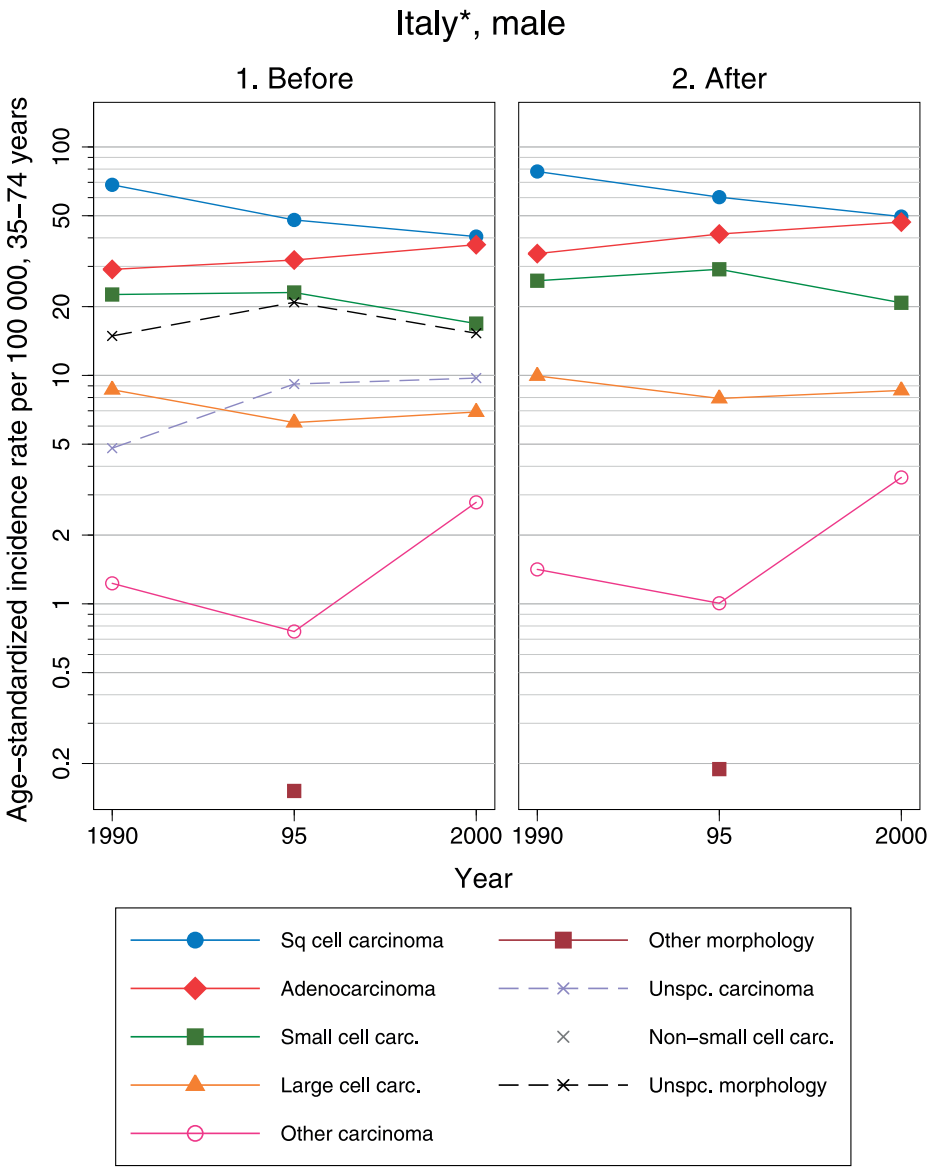
APPENDIX

Comparison of the incidence rates in each histological subtype before and after reallocation of the unspecified morphology cases, the unspecified carcinoma cases and the non-small cell carcinoma cases. Men in Italy had the most important proportion of poorly specified morphologies (i.e. the sum of the unspecified lung cancers and unspecified lung cancer carcinomas). No cases of non-small cell carcinomas were diagnosed in this population.

It was noted that following the introduction of the ICD-O-3 classification in 2000 [12], a new code had been introduced for non-small cell carcinoma (8046M), while minor changes had also been implemented in grouping histological codes. Because the ICD-O-3 classification had been used by some registries for the last period studied (1998-2002), we extracted the data directly from the last volume of CI5 (volume IX). We then made the back-conversion from ICD-O-3 to ICD-O-2 using the SEER conversion program (http://seer.cancer.gov/tools/conversion). Thus, after having performed the reallocation of unspecified morphologies over specified subtypes, we also proportionally reallocated non-small cell carcinoma (8046M, affecting data from volume IX only) to the lung carcinoma sub-groups: (1.1), (1.2) and (1.4). The temporal trends based on the original and the reallocated rates were very similar (see Appendix Figure). The relative frequency of each subtype remained unchanged across calendar periods (the ranking in the subtypes was preserved).



Appendix Figure 1

Lung cancer age-adjusted (World standard) incidence rates over time, in Italian registries, in men, by morphological subtype, for ages 35-74, before and after the reallocation of ill-defined morphological subtypes.

3

The smoking share of the cancer burden in the United States

3.1

The 2011 U.S. burden of cancer by race and ethnicity

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ABSTRACT

Introduction: In the U.S., people of different races/ethnicities have differences in cancer incidence, mortality, survival, stage at diagnosis, and receipt of treatment, resulting in variances in cancer burden. The burden of cancer in 2011 was assessed by race/ethnicity for 24 cancers using disability-adjusted life years (DALYs).

Methods: In 2014–2015, DALYs and their two components were estimated (years of life lost [YLLs] and years lived with disability) by race/ethnicity using population-based cancer registry data collected in 2013, vital statistics, and literature reviews.

Results: A total of 9.8 million DALYs (91% YLLs) were lost to cancer. Half of DALYs were due to lung (24%), breast (10%), colorectal (9%), and pancreatic (6%) cancers. Age-standardized DALY rate (ASR) ratios of non-Hispanic blacks (NHBs) over non-Hispanic whites (NHWs) for "all cancers" were 1.3 (95% CI:1.2, 1.4) times higher in men and 1.2 (95% CI:1.2, 1.3) times higher in women (ASR in NHBs 4,003 per 100,000 in men and 3,329 in women vs 3,088 and 2,758 in NHWs, respectively); ASRs were also higher in NHB for 15 cancers. Compared with NHWs, Hispanics and non-Hispanic Asians exhibited lower ASR for "all cancers" and common cancers, contrasting with a higher ASR for infection-related cancers (stomach, liver, cervix).

Conclusions: The cancer burden was highest in NHBs, followed by NHWs, Hispanics, and non- Hispanic Asians. In all races/ethnicities, the cancer burden was largely driven by YLLs, highlighting the need to prevent death at middle age through broad implementation of structural and behavioral measures of primary prevention, early detection, and treatment.

INTRODUCTION

Mortality is considered the best measure for monitoring progress against cancer, for ranking burden of disease, and for assessing racial/socioeconomic disparities between populations.[1] However, this measure is limited by its inability to consider life years lost due to premature death or decreased quality of life associated with the disease. Disability-Adjusted Life Years (DALYs) overcome these limitations by combining mortality, incidence, survival and quality of life into a summary indicator.[2] It allows easy comparison of burdens across diseases and populations. DALYs have two components: Years of Life Lost (YLLs) due to premature death and Years Lived with Disability (YLDs), i.e. diminished health due to the disease or its treatment. One DALY is equivalent to the loss of one healthy year. DALYs represent a health gap, measuring the state of a population's health compared to a normative goal of living the life expectancy in full health. They have been commonly used for assessing the burden of several diseases[3,4] across the world[5,6] since the early 1990s.[2]

Recent cancer DALY estimates for the US include 12.4 million healthy years lost in 2010 (Global Burden of Disease (GBD) 2010),[7] 14.9 million in 2012 (WHO)[8] and 13.0 million in 2013 (GBD2013).[9] Only one previous study,[10] in 1996, provided estimates by race for select cancers. However, DALYs for the US from this study and all following studies were based on modeled data, rather than observed data. Herein are provided DALYs in the US in 2011 for all cancers combined and for the 24 most common cancers by race/ethnicity and sex, using observed nationwide cancer incidence, survival, mortality and treatment data.

METHODS

Data sources and computation methods are described below and in the Supplement. Incidence data of tumors with a malignant behavior were extracted by sex and race/ethnicity for the 24 most common cancers (with an age-standardized incidence rate >1 per 100,000 in 2011),[11] and for "all other cancers" (Table S1) collected in 2013. Race/ethnicity was grouped as: Non-Hispanic White (NHW), Non-Hispanic Black (NHB), Hispanic, and Non-Hispanic Asian (NHA) (Asian or Pacific Islander). Other races (American Indian/Alaska Native and unknown race) were not presented separately (2.0% of cases) but were included in "all races/ethnicities". "Unknown ethnicity" (992 or 0.06% of cases) was excluded. Age was stratified into nineteen groups (0-1, 1-4, 5-9, . . . 80–84, ≥85).[12]

Data Sources and Statistical analysis

DALYs, the sum of YLLs and YLDs, were calculated by cancer, race/ethnicity and sex. YLLs were estimated by multiplying the number of deaths at each age group by the life expectancy at the mid-point for each age group, using the 2011 mortality data from the National Center for Health Statistics (NCHS)[13] extracted via SEER*Stat version 8.2.1, and the 2011 US life table[14] (life expectancy [LE] of 76.3 years for males and 81.1 for females). YLDs were estimated as the incidence of disease phase or disease sequela by age group, multiplied by the disability weight for that phase or sequela, multiplied by the phase duration[15] (Figure S1). The computational details are presented in Supplement 2, and the list of the disease phases and sequelae with disability weights in Table S2. For the YLDs, data from the North American Association of Central Cancer Registries (NAACCR) database were extracted for incidence; the Surveillance, Epidemiology and End Results (SEER)[12] database for proportion cured, proportion of people treated (vs. proportion not treated, Table S3), and median time to death (Table S4); and SEER and a literature review for proportion of sequelae among patients. Disability weights issued by the GBD 2013 study were used,[16] which establish the loss of health associated with disability related to various health states including cancer. These weights were based on household surveys in nine countries and a worldwide online survey. In total, about 17% of the participants lived in the US. A prior GBD study had reported high consistency in the disability weight of a health outcome between countries, highlighting a broad social understanding of the relative importance of aspects of health.[17]

The burden of cancer was also assessed with age-standardized DALY rates (ASR) per 100,000 persons, based on the 2000 US standard population,[18] for all cancers combined, 24 selected cancers, and all other cancers. All analyses were performed in 2014-2015, using SAS 9.4 and Stata 13 software. ASR ratios were calculated as the ratios of ASR in NHB, Hispanics or NHA versus ASR in NHW. Age-specific rates were calculated as the number of DALYs in an age group divided by the population size, multiplied by 100,000.

All 95% confidence intervals (CI) were estimated via simulation (Supplement 3).[19] This study used previously collected data without patient identifiers, and was determined to be exempt from full review of the NAACCR Institutional Review Board.

RESULTS

The US burden of cancer in 2011 was estimated to be over 9.8 million DALYs (Figure 1) in both sexes combined, equally shared among men (4.9 million DALYs) and women (4.9 million DALYs) (Table S5). Lung cancer was by far the largest contributor to loss

of health due to cancer, with 24% of all DALYs (2.4 million DALYs). Four cancers caused about half of all DALYs: lung, breast (10%), colorectum (9%) and pancreas (6%). Notably, 91% of the overall DALYs were due to YLLs alone.

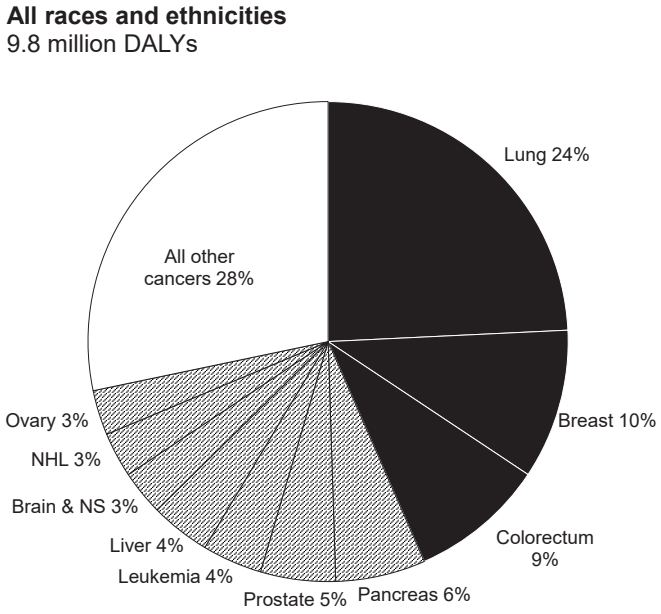
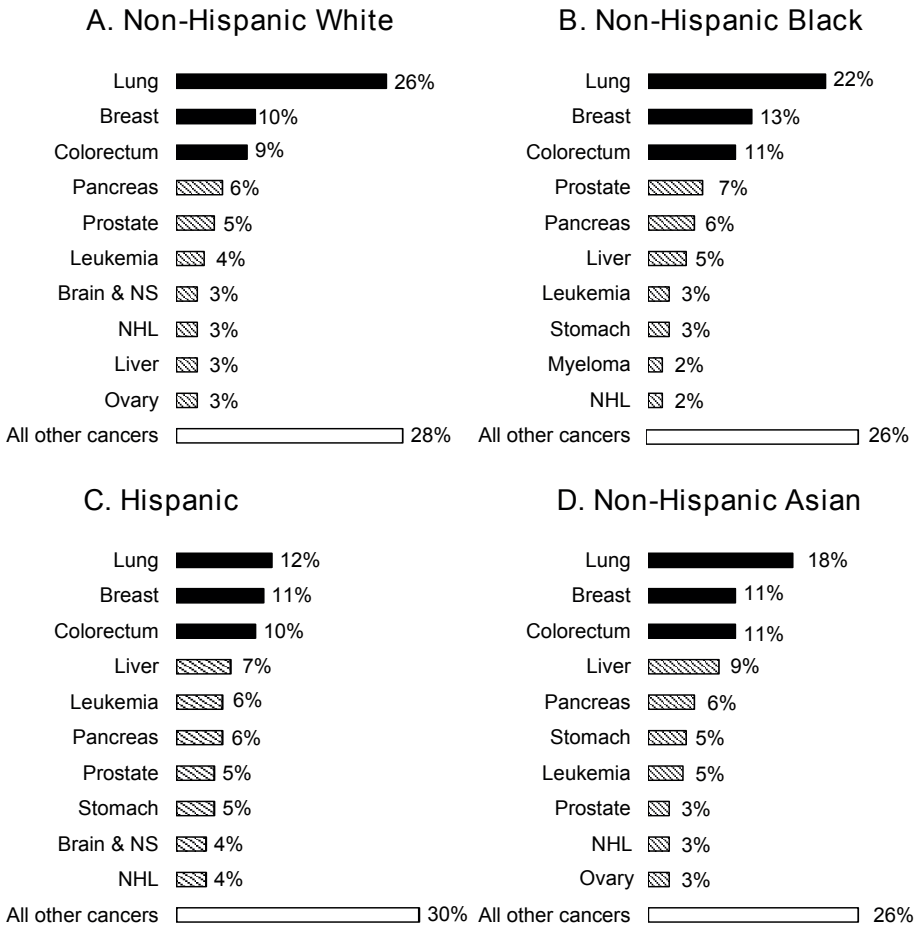


Figure 1. Proportion of Disability-Adjusted Life Years (DALYs) from each cancer over all DALYs (detailed for top 10 cancers), all races/ethnicities, in 2011
NHL: Non-Hodgkin Lymphoma; NS: nervous system
Black: Top 3 cancers for DALYs, Gray: Top 4-10 cancers, White: all other

The ASRs for all cancers were 3,046 per 100,000 persons for men and 2,694 for women (Table S6). ASRs were higher in men than in women for most of the cancers, except for breast, thyroid and gallbladder. The highest ASRs were found for lung cancer, both in men (780) and women (600). In men, prostate ranked second (325), followed by colorectum (293), pancreas (174) and liver cancer (152). In women, breast cancer had the second highest ASR (554), followed by colorectum (234), pancreas (144) and ovary (139).

For both sexes combined, in each race/ethnicity group, lung, breast and colorectal cancers were the top three cancers for DALYs, although lung cancer contributed fewer DALYs among Hispanics (12%) and NHA (18%) than among NHW (26%) and NHB (22%) (Figure 2). Breast and colorectal cancers each accounted for around 10% of all DALYs in each race/ethnic group. Liver cancer represented 7% of DALYs in Hispanics and 9% in NHA, ranking fourth in both races/ethnicities (Table S5). The share of

leukemia and stomach cancer (5-6%) in the burden of cancer was also higher among Hispanics and NHA.



NHL: Non-Hodgkin Lymphoma; NS: nervous system

Figure 2. Proportion of Disability-Adjusted Life Years (DALYs) from each cancer over all DALYs (detailed for top 10 cancers), by race/ethnicity in 2011.
Black: Top 3 cancers for DALYs, Gray: Top 4-10 cancers, White: all other cancers

Figure 3 shows ASRs for both sexes combined, by cancer, and race/ethnicity separated into YLL and YLD components. Only for a few cancers did YLDs make up over 20% of DALYs: melanoma of the skin and breast, and especially for men with prostate cancer (45%) and women with thyroid cancer (49%) (Table S6).

Compared to NHW, NHB had significantly higher ASRs for all cancers combined (1.3 [95% CI: 1.2-1.4]) times higher in men and 1.2 [95% CI: 1.2-1.3] times higher in

women), and for 15 of the 24 cancers (Figures 4), including common cancers (prostate, female breast and colorectal cancers) and infection-related cancers (stomach, liver and cervix uteri). In both sexes, compared to NHW, the excess burden among

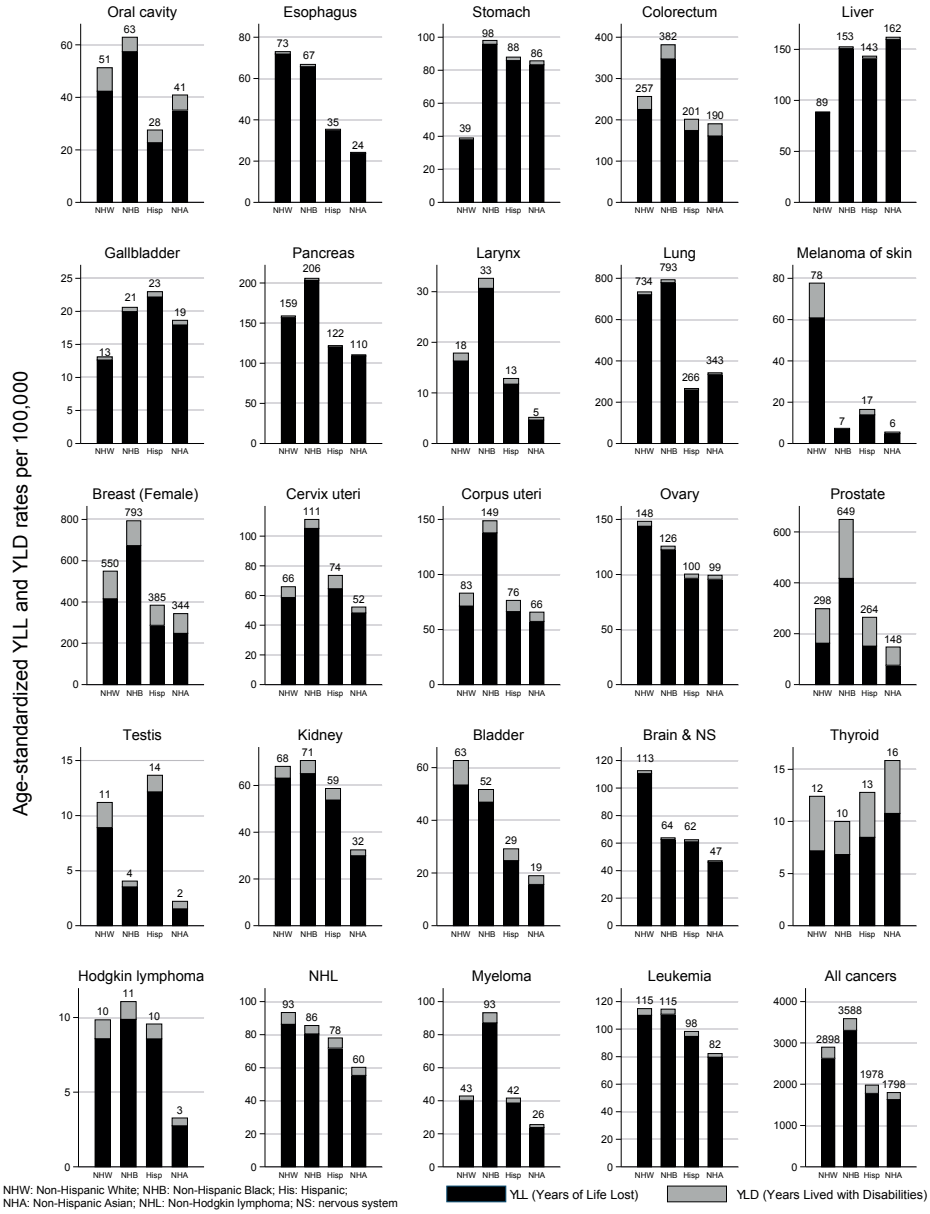


Figure 3. Age-standardized (US 2000 standard population) Disability-Adjusted Life Years (DALYs), partitioned into Years of Life Lost (YLLs) and Years Lived with Disabilities (YLDs) rates per 100,000, for 24 cancers and all cancers, by race and ethnicity, in 2011.

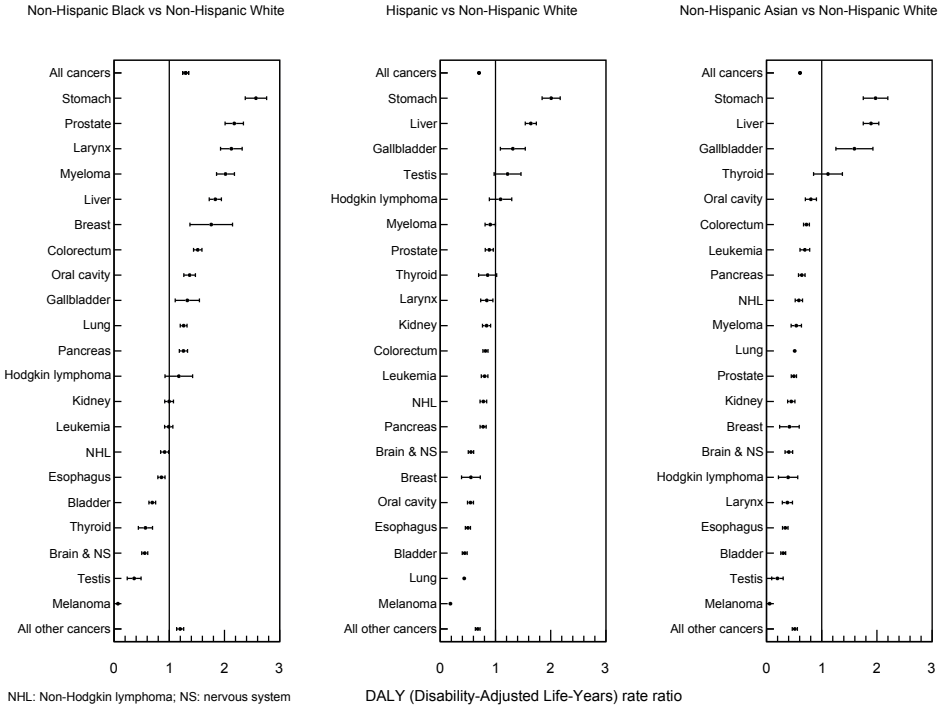


Figure 4A. Age-standardized (US 2000 standard population) Disability-Adjusted Life Years (DALYs) rate ratio for 24 cancers and for all cancers combined, in 2011, for men.

Hispanics and NHA was largely confined to liver, stomach and cervical cancers. Compared to NHW men, ASRs in stomach cancer were 2.6 (95% CI: 2.4-2.8) times higher in NHB, 2.0 (95% CI:1.8-2.2) times higher in Hispanics and 2.0 (95% CI: 1.8-2.2) times higher in NHA. The male ASRs in liver cancer were 1.8 (95% CI: 1.7-2.0) times higher in NHB, 1.6 (95% CI: 1.5-1.8) times higher in Hispanics, and 1.9 (95% CI: 1.8-2.1) times higher in NHA compared with NHW.

ASRs in cervical cancer in NHB women were about twice as high (111) as in any other race/ethnicity (66 in NHW, 74 in Hispanics and 52 in NHA) (Table S7). Notwithstanding the higher ASRs for infection-related cancers and a few other cancers, Hispanics and NHA had lower ASRs for all cancers combined (2,165 and 1,873 in men and 1,851 and 1,751 in women, in Hispanics and NHA, respectively) than did NHW (3,088 in men and 2,758 in women), for commonly diagnosed cancers (breast, colorectum, pancreas), and smoking-related cancers such as lung, laryngeal, bladder, esophageal and oral cavity cancer.[20] NHW had the highest ASR for ovarian cancer (148), melanoma (100 in men and 59 in women), brain and nervous system (129 in men and 97 in women) and bladder (men) (100) cancers.

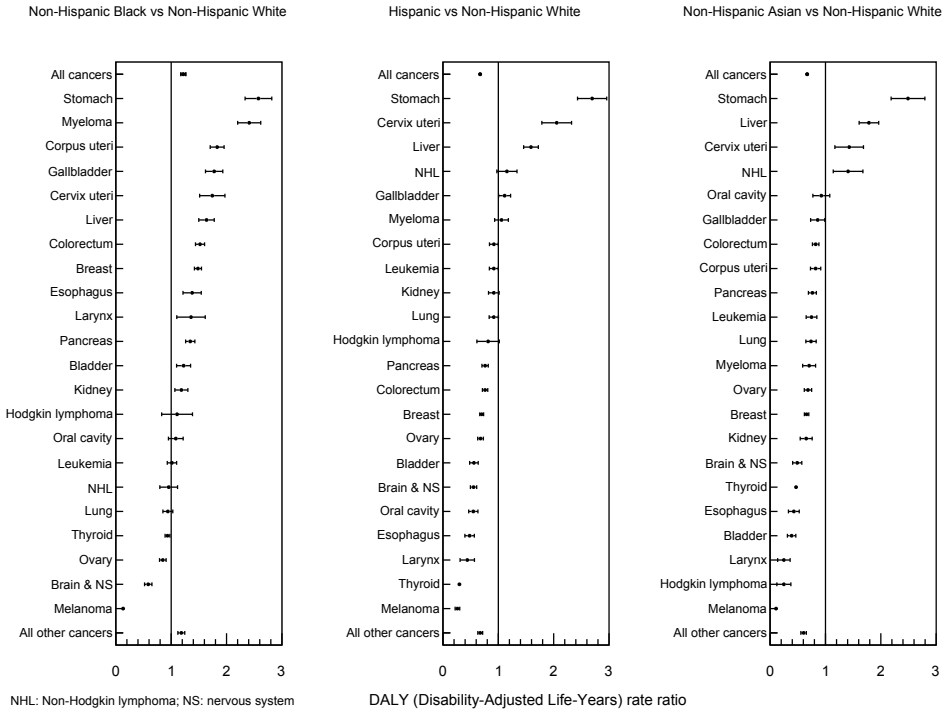


Figure 4B. Age-standardized (US 2000 standard population) Disability-Adjusted Life Years (DALYs) rate ratio for 24 cancers and for all cancers combined, in 2011, for women.
Supplementary Figures

Age-specific DALY rates were higher in the oldest age groups, starting at 50-54 years (Figure S2). In each sex, at each age group, NHB had the highest all cancers age-specific rates (prostate cancers in men, and breast and corpus uteri in women contributed most to those differences), followed by NHW, Hispanics and Asians.

Figure S3 presents the number of years lost due to premature death per person dying from cancer (YLLs per person). Each person dying from any cancer lost, on average, 16 years (95% CI: 15-16), with estimates markedly varying across races/ethnicities: from 15 years (95% CI: 14-15) for NHW to 19 years (95% CI:18-19) in Hispanics (Figure S4). The differences in YLLs per person by race/ethnicity were even greater for female breast cancer (NHW: 18 years [95% CI: 17-18]; NHB: 23 [95% CI: 22-23]; Hispanics: 23 [95% CI: 22-24]; NHA: 23 [95% CI: 22-25]). Of note, the average YLLs per person in all races/ethnicities contributed by testicular cancer in men (35 years [95% CI: 31-39]) and cervical cancer in women (26 years [95% CI: 25-27]) were the highest of any of these 24 causes of cancer death, though each represented at most 1% of all YLLs.

DISCUSSION

These results estimate that 9.8 million DALYs were lost in 2011 due to cancer— equivalent to losing 3.1% of a healthy life year, or about 2 healthy weeks (11 days) per US resident—representing 11% of the 89 million[9] DALYs from all causes in the country. YLLs represented >90% of the total DALYs, underscoring the importance of preventing premature mortality. However, YLDs accounted for a substantial proportion of the DALYs, particularly for thyroid and prostate cancers, due to their high survival rates. ASRs varied greatly across race/ethnicities; NHB had the highest ASRs of all races/ethnicities for all cancers combined and for most common cancers, whereas Hispanics and NHA had the lowest ASRs for all cancers and common cancers, but high ASRs for liver, stomach, cervix uteri and gallbladder.

Health disparities usually arise from a complex combination of several factors, including socioeconomic aspects, behavior, biology[21] and structural barriers. Compared to NHW, NHB and Hispanics are disproportionately represented in the poor[22] and uninsured[23] segments of the US population. Low- Socioeconomic Status (SES) groups are more likely to engage or persist in unhealthy behaviors;[24] to be without a usual source of care (22% in NHB versus 16% in NHW)[22] for primary prevention, early detection, timely treatment; and to have a higher number of comorbidities.[25] They also more often reside in neighborhoods unsafe for physical activity,[26] with poor access to supermarkets and healthful food.[27] While differences in smoking rates could (partly) explain the higher lung cancer rates in black men compared with white men,[28] differences in receipt of screening and lower survival rates might account for over half of the black-white disparities in mortality from colorectal cancer.[29] In contrast, the higher breast cancer mortality rates among black women compared with white women, despite their lower incidence rates, largely reflect differences in stage at diagnosis and disease biology.[30]

Previous studies[31,32] reported that Hispanics had lower incidence rates for all cancers combined and common cancers, but higher rates for infection-related cancers (i.e. liver and stomach cancers), compared to NHW. These patterns are largely thought to reflect the burden in their countries of origin,[33] since over 35% of Hispanics in the US are foreign-born.[34] Similar to their countries of origin, Hispanics in the US have higher prevalence of cancer-related infections (e.g., Hepatitis B virus,[35] *Helicobacter pylori)*[36] and lower prevalence of smoking[37] than the US population. Furthermore, they consume more plant-based food,[38] which is associated with lower risk of several cancers.[39] However, cancer rates for Hispanics as a group mask substantial variation by country of origin because of differences in length of stay and degree of acculturation. A study in Florida[40] reported that the low cancer rates in Hispanics compared to NHW were limited to Mexicans, who immigrated more recently. Cubans —who immigrated

earlier and achieved higher SES— and Puerto Ricans (US citizens) showed rates similar to those of NHW. Likewise, cancer rates among Asians in the US substantially vary by country of origin. For example, cervical cancer incidence rate in Vietnamese women (recent migrants) is about twice as high as in Japanese women, who have been in the US for generations and have similar rate as NHW.[41] Notably, colorectal cancer rates in Japanese have exceeded the rates in NHW in part because of increased adoption of US lifestyle in subsequent generations of immigrants.[41,42]

Although ASRs for all cancers combined are substantially lower in women, total DALYs are comparable between women and men. This is due to the higher life expectancy of women compared to men[43] and higher cancer mortality rates in middle-aged women (30-54).[11] Female breast cancer is the largest contributor to YLLs in middle ages. Cervical, ovarian, and corpus uteri cancers (only in ages 45-54 for the latter) also contribute to higher YLLs in middle-aged women. The higher ASRs in men reflects differences in prevalence of known risk factors — such as smoking[20]— as well as biological differences.[44,45]

These findings of 9.8 million DALYs are lower than those of the GBD 2013 (13.0 million),[9] possibly due to differences in age at death and a rising number of deaths between 2011 counts and 2013 projections, and the fact that GBD modeled prevalence of disabilities while this study used observed incidence. The YLLs computed by SEER in 2011 (9.1 million years)[11] were slightly higher than in the present study (8.9 million years) because SEER used 1-year age groups. However, none of these studies presented estimates by race/ethnicity.

YLLs constitute 91% of the cancer burden, stressing the need to direct efforts to prevent premature death from cancer, particularly at middle ages. A substantial proportion of DALYs due to cancer could be avoided with primary prevention, screening and early detection. Eleven of the top 15 cancers for DALYs are related to two preventable risk factors: smoking and alcohol.[36] The majority of colorectal and cervical cancers (9% and 1% of cancer DALYs, respectively) can be prevented through screening, as can most future cervical cancer through vaccination. Furthermore, breast (10% of cancer DALYs), colorectal and cervical cancers can be detected early, through screening and clinical manifestation, when treatment is more effective. Screening for lung cancer among high-risk individuals could potentially avert approximately 12,000 deaths per year[46] (80,400 YLLs based on a median age at death of 72 years).[11]

The GBD2010 study showed that, in the US, cancer had the highest YLL fraction of DALY (94%) compared with other major diseases with high burden, including ischemic heart disease (91%), cerebrovascular disease (75%) and COPD (47%).[7]

Although the overall YLDs accounts for only 9% of ASRs for all cancers combined, it represents a substantial proportion of the burden in several cancers. Moreover, the YLD share is expected to increase in the future as survival improves because of advances

in early detection and treatment for many cancers. Cured patients contributed most to the total YLDs (76%); those who died from cancer despite of (curative) treatment contributed 20% of YLDs; those offered palliative treatment or diagnosed upon death contributed the least (4%). This highlights the need to:

- prevent or manage treatment side effects (incontinence, impotence, dyspareunia, etc.)[47-50]
- improve quality of life[51] among the ever-growing number of cancer survivors.[52]

The strength of this study, besides as a contemporary burden of cancer study according to DALYs by race is, for the first time, its report of outcomes by ethnicity; secondarily, the frequency of the disabilities – necessary for YLD estimation – is largely based on observed data from population-based registries.

Limitations

The limitations of this study are mainly related to the availability and quality of data. These may have prevented full capture of the total spectrum of disabilities associated with cancer, hereby underestimating the YLDs in several ways. First, data on the prevalence of disabilities among cancer patients, particularly late effects, and in the community remain rare. Furthermore, they vary widely due to discrepancies in studied populations, definitions, outcome measures, and overall study design. All too often, the prevalence of a disability is estimated in a small and restricted population (specific stage, mode of treatment or age group). In addition, not all cancer-related disabilities can be accounted for due to the lack of information on prevalence of disabilities (although common, major depression in cancer patients is not systematically diagnosed).[53] The second limitation is the lack of corresponding disability weight. For instance, there are no disability weights for fecal incontinence –affecting almost 40% of rectal cancer patients treated with total mesorectal excision[54] and >10% of women with hysterectomy for cervical cancer–[49] nor for bone-health issues, cognitive function decrements, peripheral neuropathy, or fatigue, which affect cancer survivors at different levels.[55] Finally, only one disability weight exists for "Diagnosis and primary therapy" for all cancers, while treatment varies by cancer type and stage. However, the loss of health was differentiated during this disease phase by using cancer-specific durations (from 1 month for melanoma to >1 year for colorectal cancer). The overall underestimation of YLDs may contribute to the high proportion of YLLs in DALYs.

CONCLUSIONS

For all cancers, YLLs constituted the majority of the cancer burden, irrespective of race/ethnicity. This stresses the need to direct efforts to prevent premature death,

particularly at middle ages, through broad implementation of known effective interventions from primary prevention, to early detection and treatment.

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JLT, AJ and IS made substantial contributions to conception and design of the work. JLT and CCL acquired the data. JLT performed the analysis. All authors participated in the interpretation of data for the work; JLT, AJ and IS also participated in the drafting of the work. All authors revised it critically for important intellectual content. All authors gave final approval of the version to be published.

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SUPPLEMENTARY MATERIAL

Supplement 1 Cancers selected

Data for 24 cancers with age-standardized incidence >1 per 100,000 in 2011 were extracted, "All other cancers" and "All cancers". "All other cancers" were deducted based on "All cancers" and the sum of each specified cancer. Only cases with malignant behavior were extracted (see Table S1 for ICD-9 codes).

Table S1. Cancers selected and corresponding International Classification of Diseases-9 codes (ICD-9)

Cancer	ICD-9
All cancers	140-208, 238.6
Oral cavity and pharynx	140-149
Esophagus	150
Stomach	151
Colorectum and anus	153-154.8, 159.0
Liver and intrahepatic bile ducts	155.0-155.2
Gallbladder and other biliary	156.0-156.9
Pancreas	157
Larynx	161
Trachea, mediastinum and other respiratory organs, bronchus and lung	162, 164, 165
Melanoma of skin	172
Breast	174-175
Cervix uteri	180
Corpus and uterus, not otherwise specified	179, 182
Ovary	183.0
Prostate	185
Testis	186
Kidney, renal pelvis and ureter	189.0-189.2
Bladder	188
Brain and other nervous system	191, 192
Thyroid	193
Hodgkin lymphoma	201
Non-Hodgkin lymphoma	200, 202.0-202.2, 202.8-202.9
Myeloma	203.0, 238.6
Leukemia	204-208
All other cancers	those not abovementioned but included in 140-208, 238.6

Source:[44]

Supplement 2 Computation of Years of Life Lived with Disabilities (YLDs)

Years of Life Lived with Disabilities (YLDs) were computed as the incidence *i* of disease phase or disease sequelae *y* at age group *x*, multiplied by the disability weight *dw* for that phase or sequela, multiplied by the phase duration *d*.

$$YLD = \sum_{x,y} i_{x,y}\, dw_y\, d_y$$

A four-stage natural disease history for cancer was followed, as presented in Figure S1, to determine the number of patients in each disease phase. Figure S1 only presents the disease phases that trigger disabilities and does not aim to represent the whole the cancer continuum. The details of the method that was adapted and its validation were described by Soerjomataram et al.[1] and Global Burden of Disease Study 2013 Collaborators.[2,3] A summary of the sources of data[4-28] are presented in context, in Table S2. In this study, four possible pathways for newly-diagnosed patients were assumed, based on the cancer history:

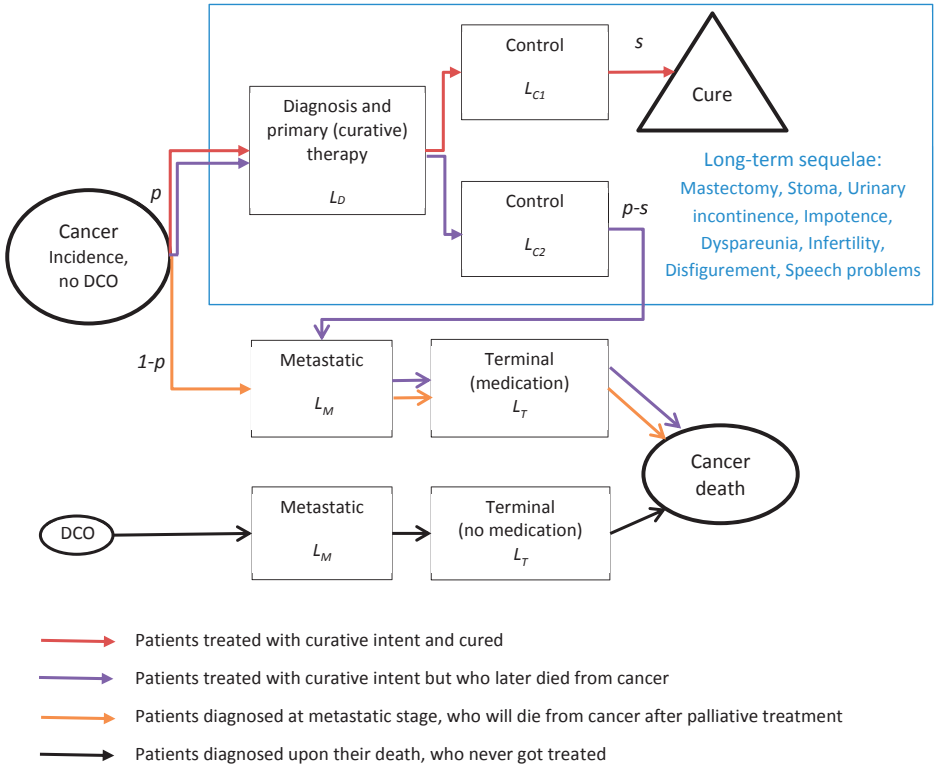


Figure S1. Disabilities in a four-stage natural disease history for cancer

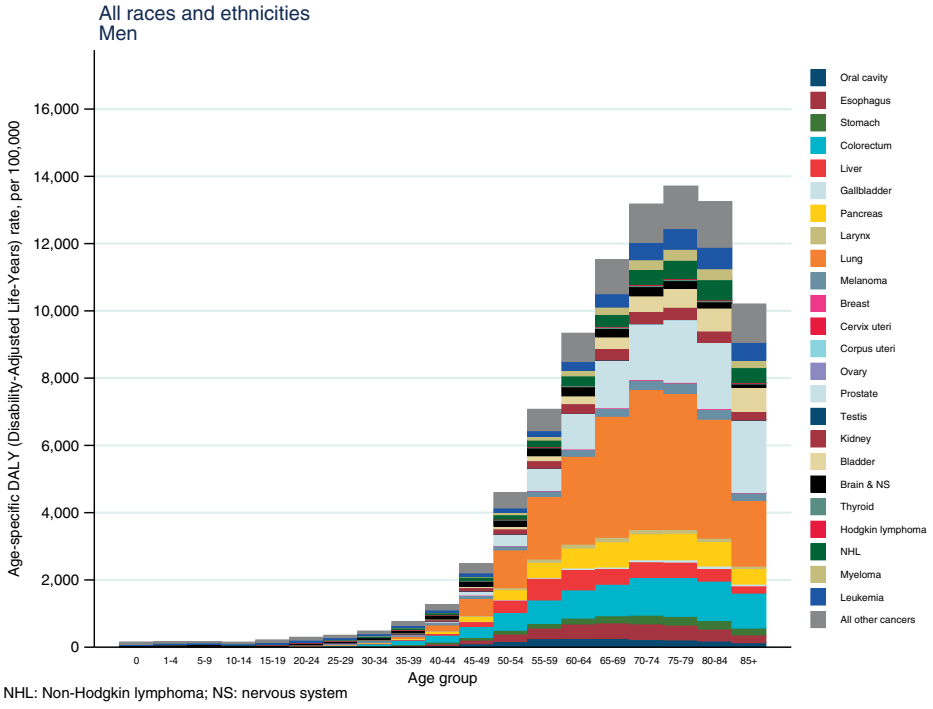
Table S2. Incidence and duration of cancer phase or disability, mean proportion of patients with disability and disability weights

Cancer phase or disability	Cancer	Incidence and duration of phase	Proportion with disability	Disability weight[41]
Diagnosis and primary therapy	All	Patients diagnosed in 2011[4] and treated with curative intent (excluding DCO and autopsy only diagnoses). Duration = Cancer-specific[7]		0.288
Control phase	All	Patients diagnosed in 2011[4] and treated with curative intent (excluding DCO and autopsy only diagnoses). Duration = 5 years (10 years for prostate and breast cancer)[6] - Diagnosis and primary therapy phase (or less when patient dies earlier)		0.049
Metastatic phase	All	Patients diagnosed in 2011[4] and died after curative, palliative or no treatment. Duration = 3 months[8]		0.451
Terminal phase, with medication	All	Patients diagnosed in 2011[4], and either died after curative treatment or had only palliative treatment (excluding DCO and autopsy only diagnoses). Duration = 1 month[8]		0.540
Terminal phase, without medication	All	2011 DCO and autopsy only diagnoses.[4] Duration = 1 month[8]		0.569
Mastectomy	Breast (women and men)	Patients with mastectomy	0.40	0.036
Stoma	Bladder	91% after radical cystectomy[9]	0.06	0.095
	Rectum	40% (from 26% to 49% depending on the study reviewed)[10]	0.40	
Urinary incontinence	Bladder	Men: 10% after radical cystectomy including prostate removal and orthotopic neobladder reconstruction[11] 10% after radical cystectomy and orthotopic neobladder (8%[12] – 11%[13]) 7% after radical cystectomy and ileal conduit reconstruction[14] Women: 36% after complete cystectomy with reconstruction, excluding abdominal pouch and pouch NOS (30% after ileal neobladder, 43% with orthotopic bladder replacement)[15,16]	0.01	0.139
	Cervix uteri	83% after radical hysterectomy[17]	0.15	
	Prostate	20% (between 14% and 24% 1 year after treatment, depending on treatment)[18]	0.20	
Impotence (in men aged 15-74)	Prostate	52%[19]	0.52	0.017
	Rectum	32%[20]	0.32	

Dyspareunia (in women aged 15-74)	Bladder	Bladder cancer patients with radical cystectomy with pelvic exenteration (comprises total hysterectomy) => 18% with radical hysterectomy have dyspareunia[21]	0.01	as Impotence
	Breast	40% (24% to 57% depending on treatment type and patient age)[22-24]	0.40	
	Cervix uteri	25% (5% to 55% depending on the study reviewed)[45]	0.25	
	Corpus and Uterus NOS	30% (17% to 46% depending on treatment)[21,25-27]	0.30	
	Rectum	46%[20]	0.46	
Infertility, primary (in women 20-39 and men 20-59)	Bladder	Patients with radical cystectomy with pelvic exenteration (comprises prostatectomy and hysterectomy)	0.05	0.008
	Cervix uteri	Patients with total hysterectomy	0.50	
	Corpus and Uterus NOS	Patients with total hysterectomy or bilateral oophorectomy	0.75	
	Ovary	Patients with hysterectomy or bilateral oophorectomy	0.32	
	Prostate	Patients with total prostatectomy	0.56	
Disfigurement, level 1	Melanoma of the skin	All cases *not* located on the face (ICD-O-3 C44.5-C44.7), and NOS (C44.9)[4]	0.79	0.011
Disfigurement, level 2	Melanoma of the skin	All cases located on the face (C44.0-C44.4) and overlapping (C44.8)[4]	0.21	0.067
	Oral cavity and pharynx	24%[28]	0.24	
Speech problems	Larynx	Patients with laryngectomy	0.14	0.051
	Oral cavity and pharynx	26%[28]	0.26	

Note: DCO: Death Certificate Only; NOS: not otherwise specified

1) Those diagnosed, treated with curative intent (p) and cured (s) from cancer (red path on Figure S1). They underwent a period of disability during the diagnosis and primary therapy phase (L_D), and the control phase (L_{C1}) during which patients underwent intensive follow-up and, for some of them, light treatment. Those patients, considered as cured, will live on their life expectancy. A fraction of those patients suffer from sequelae, either from the disease or from its treatment. The sequelae were accounted for since time of "diagnosis and primary therapy";
2) Those who died after treatment and a (shorter) control phase (p-s) (purple path). They underwent a period of disability during the diagnosis and primary therapy phase (L_D), the control phase (L_{C2}), then the metastatic (L_{M1}) and terminal (L_T) phases. A fraction of those patients suffer from sequelae, either from the disease or from its treatment, starting at the time of "diagnosis and primary therapy";
3) Those who did not receive curative treatment (1-p) and underwent a period of disability during metastatic phase (with medication) (L_{M1}) and terminal phase (L_T) (orange path). Those patients can receive some palliative treatment;
4) Those diagnosed upon their death ("death certificate only" and autopsy) underwent a metastatic phase (without medication) (L_{M2}) and a terminal phase (L_T) (black path).



NHL: Non-Hodgkin lymphoma; NS: nervous system

Figure S2. Age-specific DALY rate, by race/ethnicity and sex

How to determine the number of cancer patients?

Cancer incidence

To estimate the number of patients diagnosed in 2011, access to incidence data from the North American Association of Central Cancer Registries (NAACCR)[4] covering 95.4% of the total population for 2011 was obtained. Data was extracted using SEER*Stat version 8.2.1. Incidence was corrected for partial population coverage, and adjusted for delayed reporting using SEER cancer-, gender-, race- (All/White/Black) and age- (<50/50-64/65+) ratios provided by Surveillance, Epidemiology and End Results (SEER) at http://surveillance.cancer.gov/delay/canques.html. The "All cancers" delay ratio was applied to "Gallbladder cancer" and "All races" to Hispanic and NHA data because no delay ratios were provided for Gallbladder nor Hispanics and NHA. Adjusting for delayed reporting augmented the number of new cases by 2.1%.
The number of patients who are diagnosed with cancer upon their death (black path), also known as DCO (death certificates only) is indicated in the NAACCR file.

How to determine the number of patients treated (red and purple paths) and the number not treated with curative intent (orange path)?

Proportion treated (p) and proportion not treated (1-p)

To compute the proportion of patients treated with curative intent (p), the first step was to estimate the proportion of patients not treated with curative intent ($1-p$) (those patients will have some palliative treatment). For almost all cancers, those patients were assumed to be the average annual number of patients diagnosed in 2010-2011 at stage IV and who did not receive curative surgery nor curative radiotherapy, in SEER18.[29]
For a few cancers (myeloma, leukemia, lymphoma), patients are primarily treated with chemotherapy (not available in the SEER database). To estimate the number of those patients not treated, a literature review (details in Table S3) was conducted.[30,31]
To obtain the number of patients treated and the number not treated, the number of patients diagnosed with cancer (excluding DCO) was then multiplied by the proportion treated and the proportion not treated.

How to determine the number of patients cured from cancer (red path on Figure S1) and the number not cured (purple path)?

Proportion cured (s)

To determine the number of patients cured, among the patients treated, the cure fraction was used. Proportion cured (s), or cure fraction, is defined as the proportion of patients who survived the disease and no longer experience excess mortality

Table S3. Estimated proportion of cancer patients without curative treatment or treatment to significantly prolong life

Cancer	Patients receiving no curative treatment
All cancers (excluding basal and squamous skin cancer), Oral cavity and pharynx, Esophagus, Stomach, Colorectum and anus, Liver and intrahepatic bile ducts, Gallbladder and other biliary, Pancreas, Larynx, Trachea, mediastinum and other respiratory organs, bronchus and lung, Melanoma of skin, Breast, Cervix uteri, Corpus and Uterus Not Otherwise Specified, Ovary, Prostate, Testis, Kidney, renal pelvis and ureter, Bladder, Brain and other nervous system, Thyroid	Stage IV and no radiotherapy or surgery in SEER18[32]
Hodgkin lymphoma	19%[30]
Non-Hodgkin lymphoma	16%[30]
Myeloma	0%[31]
Leukemia	50% of patients 70+ years[30]

Note: All patients with Myeloma are treated with the intent to significantly prolong life, yet for now the disease is not considered as curable.[31]

rate. Survival time of patients diagnosed in 1992-2007 and followed through end of 2012, was used, as reported in SEER13[32], excluding DCO (death certificate only) and autopsy and patients with unknown survival time. Patients with multiple primaries were included. Data by cancer were extracted, by race/ethnicity, and by large age group (0-39, 40-64 and 65+ years), for both sexes combined. As the study includes racial minorities and ethnicity, for which life tables were available only recently, cause-specific survival was used, as recommended by Howlader.[33] CanSurv (http://srab.cancer.gov/cansurv) version 1.3, a Windows program was used to obtain the cure fraction, with a lognormal distribution to model survival time in a mixture cure model. A mixture model assumes that a fraction of patients will die from their cancer, while another fraction will eventually be considered as cured. The mixture cure model assumes that the survival function $S(t)=c+(1-c)\ G(t;\mu,\sigma)$, and the cure fraction c is the value of the survival function when the time t goes to infinity. Screen shots of the model specification in CanSurv and software output are presented in Figure S5.

For five cancers (esophageal, pancreas, liver, gallbladder in most racial/ethnic groups and lung), the cure fraction was determined to be <1%. In those instances, the 10-year relative survival rates were used (patients diagnosed in 2002, followed-up through end of 2012), all races combined, both sexes combined, all ages combined, in SEER9.[34] Cause-specific survival estimates are not available in SEER Statistics for gallbladder for "American Indians and Unknown race". Also, the numbers for the cure fraction for NHW for gallbladder were too small for the model to converge. So the cure fraction of all races/ethnicities combined, by large age group, was used for gallbladder for NHW and for "American Indians and Unknown race".

To obtain the number of patients cured, the number of patients treated was then multiplied by the proportion cured (*s*) (red path). To determine the number of patient

not cured, the number of patients treated was multiplied by the proportion not cured (1-*s*) (purple path).

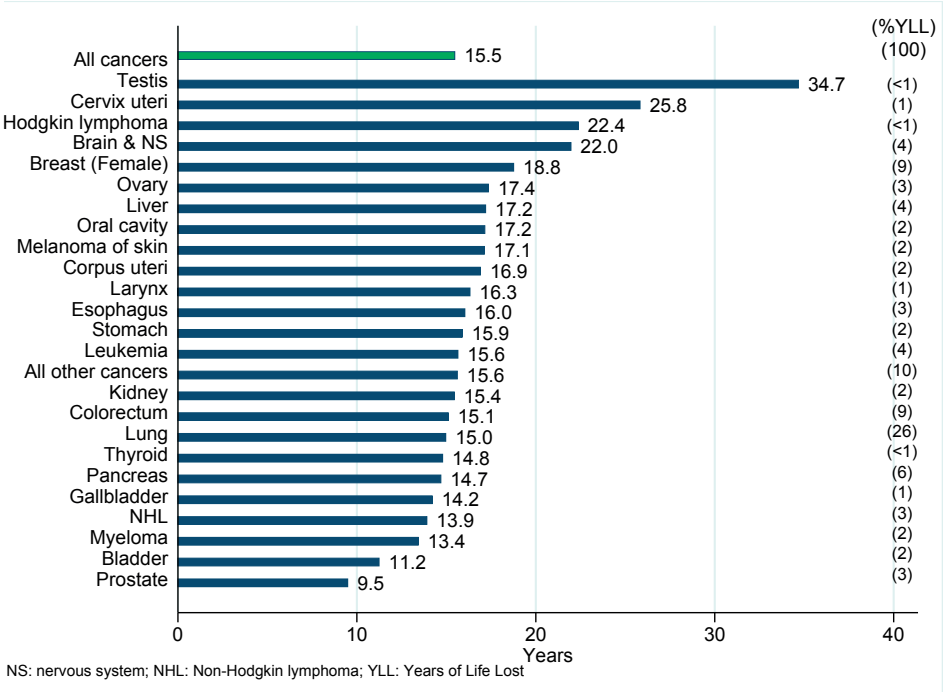


Figure S3. Average Years of Life Lost (YLLs) per person dying of cancer, all races/ethnicities, both sexes, and contribution (%) of the YLLs of each cancer in total YLLs

How to determine the number of patients who have sequelae due to cancer or its treatment (red path and purple path)?

Proportion of survivors with sequelae (s)

The proportion of survivors with sequelae was either derived from the surgical procedure (e.g., 100% of cervical cancer patients are infertile after radical hysterectomy) or determined through a literature review in PubMed (e.g. 46% of female rectal cancer patients suffer from dyspareunia),[20] or a combination of the two (91% of bladder cancer patients have a stoma after radical cystectomy). [9] The review was conducted using the combination of the following MESH terms: disability, sequela, complication, sexual health or function, side-effects, the list of disabilities and of cancers. The average annual number of surgical procedures over the 2010-2011 period was obtained from SEER18[29] and later divided by the number of patients over the same period, on a sex-, age group-, cancer- and race/ethnicity-basis (excluding death certificates only

and autopsies) to find the proportion of patients with some sequelae. The average proportions by cancer are listed in Table S2.

Some disabling conditions are also found in the cancer-free population; the proportion of some disabilities in some cancer patients was therefore reduced. The risk of some disabilities, such as impotence, increases with age.[35] Among young patients, any disability would be due to the treatment. Conversely, the frequency of some disabilities in the older general population would be equivalent or higher to the frequency of the disability due to cancer or its treatment. Hence, firstly the impact of some disabilities was restricted to some age groups (e.g. 20-39 for female infertility), and secondly a small discount was applied to the youngest age group (i.e. considering the majority of the disability in these age groups is due to cancer), up to a large discount to the eldest age group (i.e. a smaller fraction of the disability in those age groups is actually due to cancer). On average, a mean discount of 22% (from 11% for ages 15-19 to 51% for ages 70-74, based on the distribution of impotence in the MALES study)[35] was applied on the proportion of men affected by cancer-related impotence, 5% from dyspareunia[36] (2% to 8% for ages classes 15-19 to 70-74, respectively), 6% (3% to 9%) from male and 10% (6% to 14%) in female urinary incontinence,[37] and discounted 15%[38] (10% for ages 20-24 up to 20% for the last age-group) from the surgical procedures causing infertility. The discounts are presented by age group and disability in Table S8.

For the sequelae of melanoma, two levels of disfigurement were used, depending on the location of the lesion, based melanoma incidence in 2011 at national level (NAACCR file).[4] The average frequency of melanoma location ("on the face or overlapping lesion" for disfigurement level 2, and "not on the face nor overlapping" for disfigurement level 1) over 2010-2011[4] was computed on an age-, race-, ethnicity- and sex-basis, and applied the distribution of lesion location to the 2011 new cases.

To obtain the number of patients with sequelea, the number of patients cured was multiplied by the proportion of patients with sequelea, for each sequela (red path). To determine the number of patients who are treated with curative intent but eventually die from their cancer who also experience sequelae, the number of those patients was multiplied by the proportion of patients with sequelae (purple path).

How long does each patient live in each disease phase or sequela phase?

DURATION OF DISEASE PHASES

Diagnosis and primary therapy L_D

The duration of the diagnosis and primary therapy phase L_D was obtained from a prior cancer study.[7]

Control phase L_{C1} in patients who were cured

The control phase was assumed to end 5 years (10 years for breast and prostate cancer patients)[6] after the diagnosis. The cancer-specific "Diagnosis and primary treatment" duration L_D was deducted from 5 years (or 10 years) to obtain the Control phase duration L_{C1}.

Metastatic L_M and Terminal phases L_T

The Metastatic phase L_M was set to last for 3 months[8] and the Terminal phase L_T, where patients are at the final stage of living, was uniformly set to 1 month.[8] Those metastatic and terminal phases are used only for patients who will die from cancer and do not apply to all patients diagnosed at metastatic phase.

Control phase L_{C2} in patients who are treated with curative intent, then die

The median survival time was first obtained, by cancer, from patients who died from their cancer (cause of death is "attributable to this cancer diagnosis"), diagnosed over the 1992-2006 period, followed-up through December 2011, from SEER13[29] (Table S4), extracted through the SEER*Stat "Case list session" module. DCO patients and autopsies were excluded as they were counted in the fourth possible pathway for patients. The Metastatic L_{M1} and Terminal phases L_T (4 months in total), and the (cancer-specific) Diagnosis and primary therapy phase L_D were deducted from the median survival time, to obtain the duration of the Control phase L_{C2}. When the survival time was shorter than the sum $L_D + L_{M1} + L_{T,}$ the time in Diagnosis and primary treatment phase L_D were reduced accordingly. Since the people who were treated for liver or pancreas cancer and died from the cancer had a median survival time of 3 months, the duration of the Metastatic phase L_{M1} was also reduced to 2 months.

Sequelae phase

Sequelae were assumed to start with the Diagnosis and primary therapy phase and lasted until the end of life (corresponding to the life expectancy at age at diagnosis), or until the end of the disability period (infertility was counted until age 39 for women and age 59 for men, dyspareunia and impotence until the age of 74), or the end of life for those who died of cancer.

When the same patients had several possible sequelae (e.g. urinary incontinence, impotence and infertility for prostate cancer patients), each disability was counted separately and then added.

The case of active surveillance prostate cancer patients

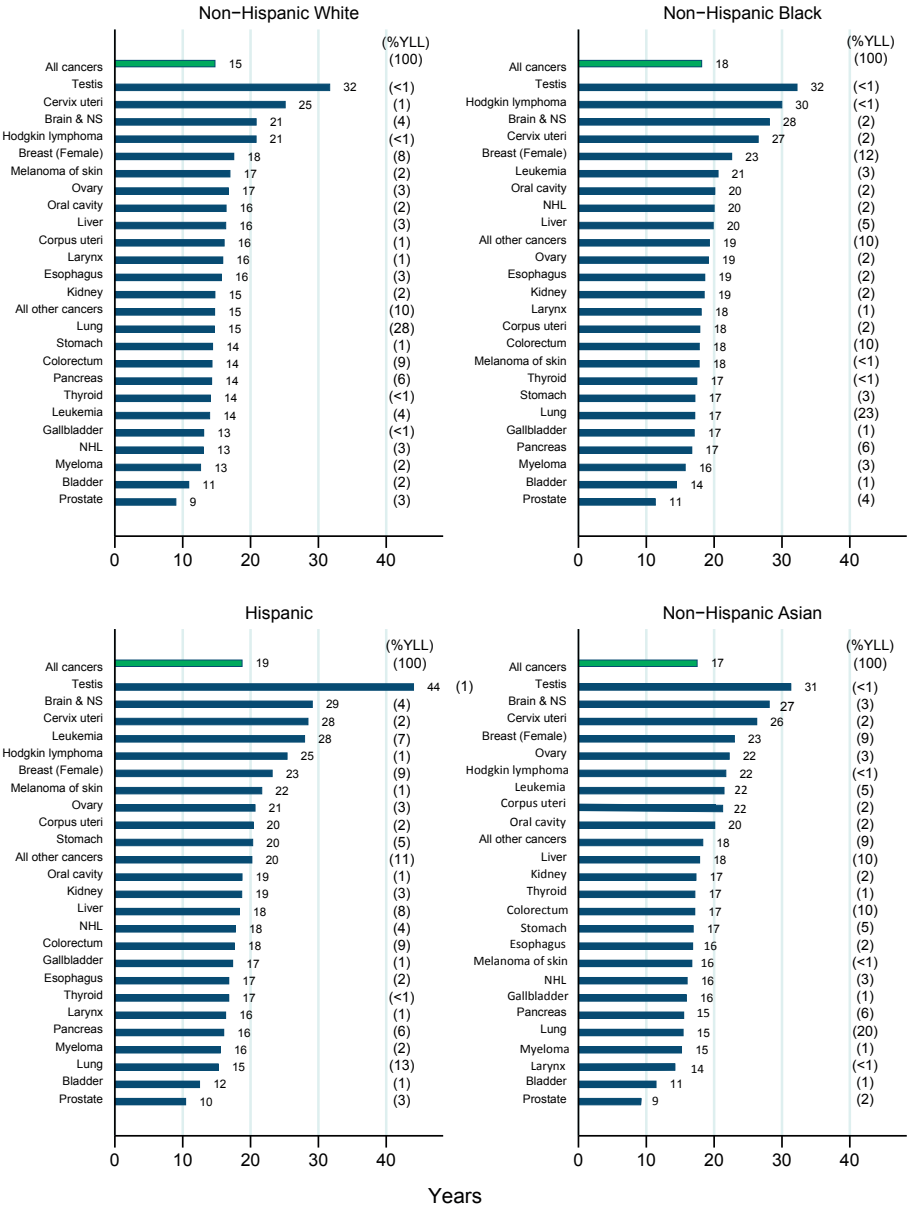
A fraction of prostate cancer patients will not undergo an intensive curative therapy; rather, they will get "active surveillance". According to the National Comprehensive

Cancer Network (NCCN) guidelines,[39] this is the management of choice for low-risk prostate cancer patients with life expectancy of ≥20 years. It involves biopsies and PSA testing at least every 6 months. The NCCN defines the low-risk group as patients with tumors stage T1 to T2a, low Gleason score and PSA levels. In a retrospective study from Hoffman, 20% of patients age 66 years and older were not treated with up-front treatment.[40] The proportion of patients diagnosed at T1-T2a stage, in 2010-2011, in SEER18 was computed; and applied 20% of it to all prostate cancer patients age 65+ in the NAACCR dataset to estimate the number of low-risk patients at national level who would go through active surveillance. The disability weights for "Control phase" was used in lieu of the "Diagnosis and Primary therapy phase" for those patients throughout their life expectancy.

Disability weights issued by the GBD 2013 study[41] which establish the loss of health associated with disability related to various health states including cancer (Table S2) were used. Due to unavailability of disability weight for dyspareunia in women with bladder, breast, cervical, corpus uteri and rectal cancers, the disability weight of impotence in men was applied. Also, because the definition of "mastectomy" in the GBD 2013 focuses on lymphedema, which is as frequently experienced by men as by women,[42] this disability weight was applied to both women and men.

Supplement 3 Calculation of the confidence intervals on DALYs

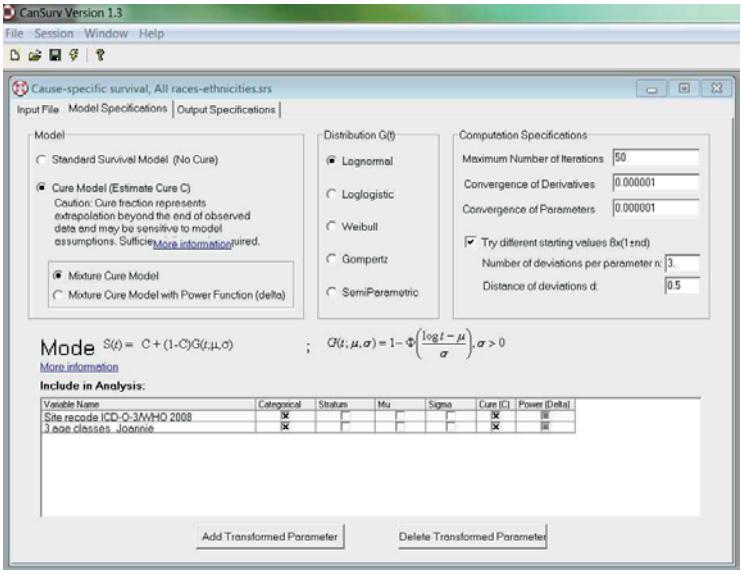
The 95% confidence intervals for the estimates of DALYs, YLLs, YLDs and rate ratios were determined using a simulation method in which random numbers were generated for all the parameters.[43] In detail, random numbers were generated within each sex, race/ethnicity, cancer and age group for: the number of cases, the proportion of patients treated, the proportion of prostate cancer patients diagnosed at early stage, the cure fraction, life expectancy, each disability weight, the proportion of patients in each disease phase or with a disability, and the duration of each disease phase or disability. Case counts and duration of disease phase or disability were assumed to follow a Poisson distribution. For each Poisson distribution, the mean of the parameter was specified. The Normal distribution was used for the cure fraction, life expectancy, frequency of early stage at diagnosis in prostate cancer patients and frequency of disabilities. The means and the standard deviations of the Normal distributions were specified. Confidence intervals for disability weights were available at their source.[41] The few values randomly generated for proportions and disability weights that were outside [0;1] were replaced by 0 when negative and replaced by 1 when greater than 1. The few negative values generated for life expectancies were replaced by 0. The simulation process was replicated 1,000 times, a large enough number of replications that allowed the confidence intervals to be stable when the whole simulation process was repeated.



NS: nervous system; NHL: Non-Hodgkin lymphoma; YLL: Years of Life Lost

Figure S4. Average Years of Life Lost (YLLs) per person dying of cancer, by race/ethnicity, both sexes, and contribution (%) of the YLLs of each cancer in total YLLs

A. Model specification in CanSurv to compute cure fractions



B. Cure fraction plots for colon and rectum, for ages 65 years and above, all races/ethnicities, both sexes

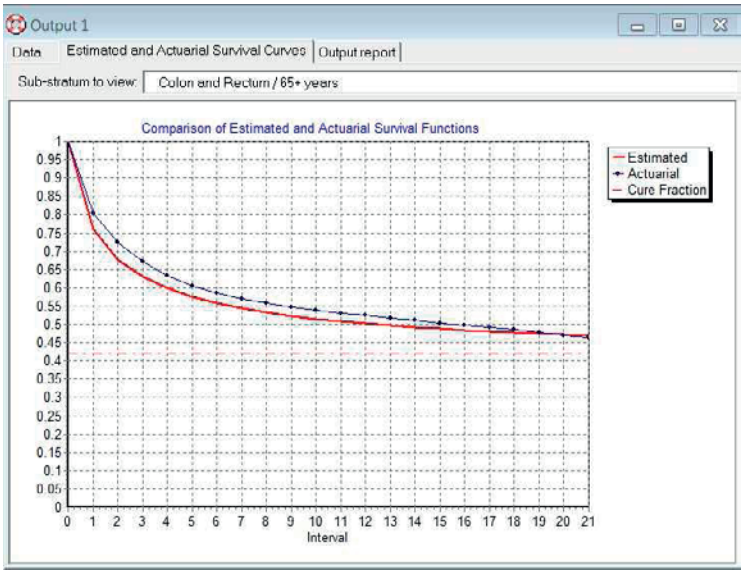


Figure S5. Model specification and cure fraction output in CanSurv software, with the example of colon and rectum cancer, ages 65 years and above in all races/ethnicities.

Table S4. Median time to death for those who die of cancer, by cancer

Cancer	Time to death (months)
Liver	3
Pancreas	3
Gallbladder	5
Stomach	6
Lung	6
Esophagus	7
All Other cancers	7
Brain, nervous system	8
Leukemia	9
Kidney, renal pelvis and ureter	11
Non-Hodgkin lymphoma	11
Testis	14
Oral cavity and pharynx	16
Cervix uteri	17
Corpus and uterus not otherwise specified	18
Bladder	18
Ovary	19
Colorectum and anus	19
Hodgkin lymphoma	20
Thyroid	21
Larynx	22
Myeloma	22
Melanoma of skin	30
Breast	42
Prostate	53

Source: SEER13 1992-2011[29]

Table S5A. Number of Disability-Adjusted Life Years (DALYs), with 95% confidence interval, rank of cancer, and proportion of Years of Life Lost (YLLs) in DALYs, in All races/ethnicities and Non-Hispanic Asians, in 2011

MEN						
Cancer	All races/ethnicities			Non-Hispanic Asians		
	DALYs	Rank	% YLLs	DALYs	Rank	%YLLs
All cancers [a]	4905310 (4779980;5036390)		90	128530 (124250;132920)		91
Lung	1268410 (1230110;1307090)	(1)	98	27280 (25690;28880)	(1)	98
Prostate	514980 (490630;541860)	(2)	51	9100 (8310;9860)	(4)	46
Colorectum	469520 (456320;483220)	(3)	88	14540 (13480;15720)	(3)	84
Pancreas	284460 (274960;294640)	(4)	99	7480 (6740;8240)	(5)	99
Liver	262430 (253870;270960)	(5)	99	17870 (16560;19240)	(2)	99
Leukemia	210460 (203640;217640)	(6)	96	6960 (6010;7970)	(6)	97
Esophagus	188360 (182070;195190)	(7)	98	3080 (2590;3560)	(11)	98
Brain & NS	179570 (174320;185460)	(8)	98	4060 (3310;4830)	(10)	98
NHL	173320 (167290;179350)	(9)	93	4520 (3970;5150)	(9)	92
Kidney	147860 (142480;153060)	(10)	93	3000 (2520;3520)	(12)	92
Bladder	138250 (132610;144490)	(11)	85	1760 (1500;2090)	(13)	81
Oral cavity	126940 (122770;131580)	(12)	84	4610 (3980;5230)	(8)	87
Melanoma of skin	122390 (118160;127060)	(13)	79	360 (210;540)	(18)	86
Stomach	105510 (101510;109510)	(14)	97	6860 (6110;7680)	(7)	97
Myeloma	86400 (82640;89940)	(15)	93	1760 (1440;2130)	(14)	92
Larynx	51260 (48960;53620)	(16)	92	720 (520;960)	(17)	91
Gallbladder	20690 (19370;22010)	(17)	96	1270 (960;1610)	(15)	96
Hodgkin lymphoma	17420 (15990;18930)	(18)	88	340 (170;590)	(19)	86
Testis	15960 (14410;17520)	(19)	83	190 (70;360)	(20)	67
Thyroid	15820 (14730;16970)	(20)	76	800 (590;1040)	(16)	77
Breast	8750 (8030;9600)	(21)	76	150 (80;240)	(21)	72
All Other cancers	495040 (481220;509890)	—	98	11630 (10560;12840)	—	98

Table S5A. Number of Disability-Adjusted Life Years (DALYs), with 95% confidence interval, rank of cancer, and proportion of Years of Life Lost (YLLs) in DALYs, in All races/ethnicities and Non-Hispanic Asians, in 2011 (continued)

	WOMEN					
Cancer	All races/ethnicities			Non-Hispanic Asians		
	DALYs	Rank	% YLLs	DALYs	Rank	%YLLs
All cancers [a]	4924790 (4799120;5061220)		91	149640 (144570;154690)		90
Lung	1125180 (1090890;1161010)	(1)	98	23510 (22020;25060)	(2)	98
Breast	992330 (963990;1019620)	(2)	77	30960 (28990;32910)	(1)	72
Colorectum	431760 (418280;446460)	(3)	88	14960 (13870;16130)	(3)	86
Pancreas	271080 (260880;280570)	(4)	99	8890 (8010;9720)	(4)	99
Ovary	256500 (248860;264850)	(5)	97	8860 (7920;9960)	(5)	96
Leukemia	167830 (161600;174350)	(6)	96	5850 (5040;6740)	(9)	97
Corpus uteri	167610 (161890;173230)	(7)	87	5990 (5300;6800)	(8)	87
Brain & NS	144810 (139850;150020)	(8)	98	3730 (3050;4510)	(12)	98
NHL	132740 (127500;138070)	(9)	92	4350 (3780;5000)	(11)	92
Cervix uteri	116580 (112630;121150)	(10)	91	4670 (3970;5470)	(10)	92
Liver	113380 (108780;117980)	(11)	99	7720 (6870;8570)	(6)	99
Kidney	83880 (80160;87340)	(12)	92	2050 (1630;2540)	(13)	93
Melanoma of skin	77160 (73860;80590)	(13)	76	470 (310;700)	(20)	85
Myeloma	77090 (73740;80770)	(14)	94	1890 (1520;2300)	(15)	94
Stomach	74500 (71390;78220)	(15)	98	6340 (5540;7130)	(7)	98
Bladder	58710 (55450;61780)	(16)	88	800 (600;1020)	(18)	83
Oral cavity	49590 (47230;52010)	(17)	83	2040 (1660;2500)	(14)	84
Esophagus	47150 (44680;49530)	(18)	98	780 (560;1040)	(19)	98
Gallbladder	32400 (30450;34370)	(19)	97	1500 (1150;1860)	(17)	96
Thyroid	25670 (24070;27320)	(20)	54	1720 (1390;2060)	(16)	61
Larynx	15020 (13940;16170)	(21)	93	60 (10;140)	(22)	82
Hodgkin lymphoma	12360 (11170;13560)	(22)	87	180 (60;350)	(21)	79
All Other cancers	452400 (438400;468150)	—	97	12110 (10970;13300)	—	97

[a] Excludes basal and squamous skin cancers

Note: NS: nervous system; NHL: Non-Hodgkin lymphoma

Table S5B. Number of Disability-Adjusted Life Years (DALYs), with 95% confidence interval, rank of cancer, and proportion of Years of Life Lost (YLLs) in DALYs, in Non-Hispanic Whites, Non-Hispanic Blacks and Hispanics, in 2011

	MEN								
Cancer	Non-Hispanic White			Non-Hispanic Black			Hispanic		
	DALYs	Rank	% YLLs	DALYs	Rank	% YLLs	DALYs	Rank	% YLLs
All cancers [a]	3760310 (3656360;3877550)		90	630570 (611150;646130)		91	335590 (326990;344700)		91
Lung	1024650 (992630;1059420)	(1)	98	161160 (155550;166940)	(1)	98	47560 (45390;49960)	(1)	98
Prostate	369340 (347280;394290)	(2)	52	91120 (86340;96220)	(2)	57	32560 (30590;34740)	(4)	50
Colorectum	345430 (334490;356330)	(3)	88	68460 (65510;71350)	(3)	91	36070 (34200;38030)	(2)	86
Pancreas	220020 (212610;227600)	(4)	99	35130 (33140;36890)	(5)	99	19810 (18520;21210)	(6)	99
Liver	165420 (159610;171050)	(5)	99	42350 (40000;44520)	(4)	99	33930 (32100;35840)	(3)	99
Esophagus	157250 (152020;162680)	(6)	98	17830 (16610;19230)	(9)	98	9350 (8480;10360)	(11)	98
Leukemia	156360 (150150;162310)	(7)	96	22270 (20700;24000)	(6)	97	23420 (21620;25430)	(5)	96
Brain & NS	145130 (139610;150130)	(8)	98	13300 (11990;14720)	(13)	98	15530 (13990;17110)	(8)	98
NHL	136120 (130340;141100)	(9)	93	17260 (15970;18650)	(10)	94	14190 (13100;15360)	(9)	92
Bladder	120130 (114870;125410)	(10)	85	9870 (9040;10770)	(15)	90	5340 (4760;5900)	(14)	84
Melanoma of skin	116140 (112060;120900)	(11)	80	1090 (800;1390)	(19)	92	3120 (2620;3680)	(17)	87
Kidney	115850 (111430;120300)	(12)	93	15100 (13950;16380)	(12)	92	12560 (11470;13760)	(10)	92
Oral cavity	96050 (92570;99940)	(13)	83	18090 (16790;19490)	(8)	92	6750 (6040;7500)	(12)	83
Myeloma	62300 (59640;65250)	(14)	93	15370 (14160;16490)	(11)	94	6260 (5600;6960)	(13)	93
Stomach	60990 (58170;63930)	(15)	97	20090 (18790;21420)	(7)	98	16530 (15220;17870)	(7)	98
Larynx	36610 (34700;38560)	(16)	91	10070 (9130;11000)	(14)	94	3450 (2970;3990)	(16)	92
Gallbladder	14510 (13540;15590)	(17)	96	2270 (1840;2690)	(17)	97	2300 (1890;2790)	(19)	96
Thyroid	12380 (11460;13360)	(18)	76	950 (720;1230)	(20)	79	1490 (1190;1840)	(20)	77
Hodgkin lymphoma	11930 (10810;13090)	(19)	88	2410 (1900;2980)	(16)	90	2640 (2090;3180)	(18)	90
Testis	10710 (9630;12010)	(20)	80	740 (460;1090)	(21)	87	4090 (3340;5040)	(15)	89
Breast	6600 (5940;7310)	(21)	75	1470 (1130;1820)	(18)	84	480 (310;690)	(21)	72
All Other cancers	378960 (366880;392580)	—	98	63330 (60570;66190)	—	98	37690 (35370;39950)	—	98

Table S5B. Number of Disability-Adjusted Life Years (DALYs), with 95% confidence interval, rank of cancer, and proportion of Years of Life Lost (YLLs) in DALYs, in Non-Hispanic Whites, Non-Hispanic Blacks and Hispanics, in 2011 (continued)

	WOMEN								
Cancer	Non-Hispanic White			Non-Hispanic Black			Hispanic		
	DALYs	Rank	% YLLs	DALYs	Rank	% YLLs	DALYs	Rank	% YLLs
All cancers [a]	3719660 (3615390;3831560)		91	675370 (658950;692080)		93	339360 (330390;349090)		89
Lung	936960 (907780;966210)	(1)	98	126050 (121260;130950)	(2)	98	32070 (30290;33880)	(2)	97
Breast	716370 (690900;740460)	(2)	76	162820 (157210;168290)	(1)	85	73670 (70230;77060)	(1)	75
Colorectum	312970 (301900;323460)	(3)	88	69410 (66430;72480)	(3)	91	30310 (28540;32040)	(3)	87
Pancreas	204580 (196840;212940)	(4)	99	38180 (35910;40180)	(4)	99	17680 (16470;19060)	(6)	99
Ovary	202350 (195250;209070)	(5)	97	25330 (23710;26960)	(6)	97	18330 (16970;19690)	(5)	96
Leukemia	121660 (116920;126720)	(6)	96	19250 (17740;20840)	(8)	97	19720 (17960;21660)	(4)	97
Brain & NS	116350 (111970;120710)	(7)	98	11770 (10470;13230)	(13)	98	11850 (10410;13410)	(11)	98
Corpus uteri	116160 (112030;120790)	(8)	86	30200 (28420;32070)	(5)	93	13850 (12730;14980)	(9)	86
NHL	102130 (97160;106810)	(9)	92	13720 (12510;14940)	(12)	94	11570 (10490;12790)	(12)	92
Cervix uteri	72720 (69590;76120)	(10)	90	22420 (20760;24220)	(7)	95	15420 (14080;16830)	(7)	87
Liver	72600 (69500;76260)	(11)	99	17880 (16400;19300)	(9)	99	13820 (12730;15050)	(10)	99
Melanoma of skin	70880 (67720;73970)	(12)	77	1450 (1110;1840)	(22)	92	2980 (2450;3520)	(17)	80
Kidney	62810 (59790;65810)	(13)	92	10720 (9700;11800)	(14)	92	7330 (6500;8220)	(13)	91
Myeloma	51560 (48860;54310)	(14)	94	17010 (15740;18320)	(10)	94	6100 (5400;6830)	(14)	93
Bladder	46980 (44170;49700)	(15)	87	7600 (6860;8380)	(15)	92	2830 (2380;3300)	(18)	88
Stomach	38570 (36510;40740)	(16)	97	14290 (13140;15500)	(11)	98	14540 (13320;15850)	(8)	98
Oral cavity	37780 (35730;39870)	(17)	83	6260 (5510;7040)	(17)	89	2790 (2320;3320)	(19)	81
Esophagus	36270 (34450;38390)	(18)	98	7530 (6710;8380)	(16)	98	2130 (1720;2570)	(20)	98
Gallbladder	20450 (19170;21930)	(19)	97	5050 (4420;5700)	(18)	98	4920 (4250;5570)	(15)	97
Thyroid	17960 (16580;19470)	(20)	52	2730 (2320;3130)	(19)	63	2990 (2600;3410)	(16)	51
Larynx	11700 (10700;12740)	(21)	92	2380 (1920;2880)	(20)	93	650 (420;930)	(22)	91
Hodgkin lymphoma	8810 (7900;9830)	(22)	87	1870 (1380;2390)	(21)	89	1360 (1000;1820)	(21)	86
All Other cancers	342350 (330400;354580)	—	97	61580 (59030;64440)	—	98	32550 (30450;34390)	—	97

[a] Excludes basal and squamous skin cancers

Notes: NS: nervous system; NHL: Non-Hodgkin lymphoma

Table S6. Disability-Adjusted Life Years (DALYs) age-standardized rates (ASR) per 100,000, with 95% confidence intervals, rank of cancer, and proportion of Years of Life Lost (YLLs) rate in ASR, in All races/ethnicities, in 2011

Cancer	MEN			WOMEN			BOTH SEXES		
	ASR	Rank	%YLLs	ASR	Rank	%YLLs	ASR	Rank	%YLLs
All cancers [a]	3046 (2962;3130)		90	2694 (2632;2763)		91	2842 (2791;2894)		91
Lung	780 (755;805)	(1)	98	600 (582;619)	(1)	98	682 (666;696)	(1)	98
Breast	5 (5;6)	(21)	76	554 (539;568)	(2)	77	294 (286;302)	(2)	77
Colorectum	293 (284;302)	(3)	88	234 (227;241)	(3)	88	262 (256;267)	(3)	88
Pancreas	174 (168;180)	(4)	99	144 (138;149)	(4)	99	158 (154;162)	(4)	99
Prostate	325 (310;342)	(2)	55	—	—	—	145 (139;153)	(5)	53
Leukemia	137 (132;142)	(6)	96	96 (93;100)	(6)	96	115 (112;118)	(6)	96
Liver	152 (147;157)	(5)	99	61 (59;63)	(11)	99	104 (102;107)	(7)	99
Brain & NS	112 (109;116)	(8)	98	84 (81;87)	(8)	98	97 (95;100)	(8)	98
NHL	111 (107;116)	(9)	93	72 (69;75)	(9)	92	90 (88;93)	(9)	92
Ovary	—	—	—	139 (135;143)	(5)	97	74 (72;76)	(10)	97
Kidney	91 (87;94)	(10)	93	45 (43;47)	(12)	92	66 (64;68)	(11)	92
Esophagus	113 (109;117)	(7)	98	25 (24;26)	(18)	98	66 (64;68)	(12)	98
Melanoma of skin	77 (74;80)	(12)	79	44 (42;46)	(13)	76	59 (58;61)	(13)	78
Bladder	91 (86;95)	(11)	85	31 (30;33)	(16)	88	57 (55;59)	(14)	86
Stomach	67 (64;69)	(14)	97	42 (40;44)	(14)	98	53 (52;55)	(15)	97
Oral cavity	75 (73;78)	(13)	84	27 (26;28)	(17)	83	50 (49;51)	(16)	84
Corpus uteri	—	—	—	89 (86;92)	(7)	87	47 (46;49)	(17)	87
Myeloma	55 (53;57)	(15)	93	41 (39;43)	(15)	94	47 (46;49)	(18)	94
Cervix uteri	—	—	—	71 (69;74)	(10)	90	37 (35;38)	(19)	90
Larynx	30 (29;32)	(16)	91	8 (7;9)	(21)	93	18 (18;19)	(20)	92
Gallbladder	13 (12;14)	(17)	96	17 (16;18)	(19)	97	15 (15;16)	(21)	97
Thyroid	10 (9;10)	(20)	75	15 (14;16)	(20)	51	12 (12;13)	(22)	60
Hodgkin lymphoma	11 (10;12)	(18)	88	8 (7;8)	(22)	87	9 (9;10)	(23)	88
Testis	10 (9;11)	(19)	82	—	—	—	5 (5;6)	(24)	82
All Other cancers	311 (302;321)	—	98	249 (242;257)	—	97	278 (271;284)	—	98

[a] Excludes basal and squamous skin cancers

Notes: NS: nervous system; NHL: Non-Hodgkin lymphoma

Table S7A. Disability-Adjusted Life Years (DALYs) age-standardized rates (ASR) per 100,000, with 95% confidence intervals, rank of cancer, and proportion of Years of Life Lost (YLLs) rate in ASR, in Non-Hispanic Whites and Non-Hispanic Blacks, in 2011

	MEN					
Cancer	Non-Hispanic White			Non-Hispanic Black		
	ASR	**Rank**	**%YLLs**	**ASR**	**Rank**	**%YLLs**
All cancers [a]	3088 (3000;3183)		91	4003 (3868;4114)		91
Lung	817 (790;847)	(1)	98	1031 (994;1069)	(1)	98
Prostate	298 (281;316)	(2)	55	650 (616;688)	(2)	64
Colorectum	288 (278;297)	(3)	88	436 (417;454)	(3)	91
Pancreas	176 (169;182)	(4)	99	221 (209;232)	(5)	99
Leukemia	138 (132;144)	(5)	96	137 (127;146)	(6)	97
Brain & NS	129 (124;134)	(6)	98	72 (65;79)	(13)	98
Liver	128 (123;132)	(7)	99	234 (222;247)	(4)	99
Esophagus	125 (121;129)	(8)	98	107 (100;115)	(8)	98
NHL	116 (111;120)	(9)	93	106 (99;114)	(9)	94
Bladder	100 (95;104)	(10)	85	69 (64;75)	(14)	89
Melanoma of skin	100 (96;104)	(11)	80	7 (5;9)	(19)	92
Kidney	94 (90;98)	(12)	93	94 (87;101)	(12)	92
Oral cavity	76 (74;79)	(13)	83	105 (97;112)	(10)	92
Myeloma	51 (49;54)	(14)	93	104 (96;111)	(11)	93
Stomach	51 (48;53)	(15)	97	131 (123;139)	(7)	98
Larynx	29 (27;30)	(16)	91	61 (56;66)	(15)	94
Gallbladder	12 (11;13)	(17)	96	16 (13;18)	(16)	96
Hodgkin lymphoma	12 (10;13)	(18)	88	14 (11;17)	(17)	90
Testis	11 (10;13)	(19)	80	4 (3;6)	(21)	87
Thyroid	10 (9;11)	(20)	74	6 (5;7)	(20)	79
Breast	5 (5;6)	(21)	75	10 (7;12)	(18)	82
All Other cancers	322 (311;333)	—	98	385 (369;403)	—	98

Table S7A. Disability-Adjusted Life Years (DALYs) age-standardized rates (ASR) per 100,000, with 95% confidence intervals, rank of cancer, and proportion of Years of Life Lost (YLLs) rate in ASR, in Non-Hispanic Whites and Non-Hispanic Blacks, in 2011 (continued)

	WOMEN					
Cancer	Non-Hispanic White			Non-Hispanic Black		
	ASR	**Rank**	**% YLLs**	**ASR**	**Rank**	**%YLLs**
All cancers [a]	2758 (2686;2829)		91	3329 (3248;3415)		93
Lung	665 (644;686)	(1)	98	620 (597;645)	(2)	98
Breast	550 (530;569)	(2)	76	793 (766;821)	(1)	85
Colorectum	228 (222;236)	(3)	88	342 (327;356)	(3)	91
Ovary	148 (143;153)	(4)	97	126 (118;134)	(6)	97
Pancreas	143 (138;149)	(5)	99	193 (182;203)	(4)	99
Brain & NS	97 (93;100)	(6)	98	57 (51;64)	(13)	98
Leukemia	96 (92;100)	(7)	96	97 (90;105)	(8)	97
Corpus uteri	83 (80;86)	(8)	86	149 (140;158)	(5)	93
NHL	73 (70;77)	(9)	92	69 (63;75)	(12)	94
Cervix uteri	66 (63;69)	(10)	89	111 (103;120)	(7)	95
Melanoma of skin	59 (56;61)	(11)	76	8 (6;10)	(22)	92
Liver	53 (50;55)	(12)	99	86 (79;93)	(9)	99
Kidney	45 (43;47)	(13)	92	53 (48;58)	(14)	92
Myeloma	36 (34;38)	(14)	94	86 (80;93)	(10)	94
Bladder	32 (31;34)	(15)	87	39 (36;43)	(15)	92
Stomach	28 (27;30)	(16)	98	73 (68;80)	(11)	97
Oral cavity	28 (27;30)	(17)	82	30 (26;33)	(17)	89
Esophagus	26 (25;28)	(18)	98	36 (32;40)	(16)	98
Thyroid	15 (13;16)	(19)	47	13 (11;15)	(19)	63
Gallbladder	14 (13;15)	(20)	97	25 (22;28)	(18)	97
Larynx	8 (8;9)	(21)	92	11 (9;14)	(20)	93
Hodgkin lymphoma	8 (7;9)	(22)	86	9 (7;11)	(21)	89
All Other cancers	258 (250;267)	—	97	304 (291;319)	—	98

[a] Excludes basal and squamous skin cancers

Note: NS: nervous system; NHL: Non-Hodgkin lymphoma

Table S7B. Disability-Adjusted Life Years (DALYs) age-standardized rates (ASR) per 100,000, with 95% confidence intervals, rank of cancer, and proportion of Years of Life Lost (YLLs) rate in ASR, in Hispanics and Non-Hispanic Asians, in 2011

	MEN					
Cancer	Hispanic			Non-Hispanic Asian		
	ASR	**Rank**	**%YLLs**	**ASR**	**Rank**	**%YLLs**
All cancers [a]	2165 (2096;2235)		90	1873 (1804;1939)		91
Lung	355 (338;373)	(1)	97	417 (392;441)	(1)	98
Prostate	264 (248;281)	(2)	57	148 (135;160)	(4)	52
Colorectum	235 (224;247)	(3)	86	208 (194;224)	(3)	83
Liver	209 (199;221)	(4)	99	242 (225;259)	(2)	99
Pancreas	136 (127;146)	(5)	99	112 (102;123)	(5)	99
Leukemia	111 (104;118)	(6)	96	96 (83;109)	(7)	97
Stomach	102 (95;110)	(7)	97	100 (90;112)	(6)	97
NHL	91 (84;97)	(8)	92	68 (61;76)	(8)	92
Kidney	79 (72;85)	(9)	92	42 (36;49)	(12)	91
Brain & NS	72 (66;78)	(10)	98	52 (43;62)	(10)	98
Esophagus	63 (57;69)	(11)	98	42 (36;49)	(11)	98
Myeloma	47 (42;51)	(12)	92	28 (23;33)	(14)	92
Bladder	44 (40;49)	(13)	83	30 (26;35)	(13)	82
Oral cavity	42 (38;46)	(14)	83	61 (53;70)	(9)	87
Larynx	24 (21;28)	(15)	91	11 (8;14)	(17)	90
Melanoma of skin	18 (16;21)	(16)	86	6 (3;8)	(18)	87
Gallbladder	16 (13;18)	(17)	95	19 (15;23)	(15)	96
Testis	14 (11;17)	(18)	89	2 (1;4)	(21)	69
Hodgkin lymphoma	13 (11;15)	(19)	91	5 (2;8)	(19)	86
Thyroid	9 (7;11)	(20)	79	11 (9;15)	(16)	78
Breast	3 (2;4)	(21)	73	2 (1;4)	(20)	73
All Other cancers	218 (206;231)	—	97	165 (150;181)	—	98

Table S7B. Disability-Adjusted Life Years (DALYs) age-standardized rates (ASR) per 100,000, with 95% confidence intervals, rank of cancer, and proportion of Years of Life Lost (YLLs) rate in ASR, in Hispanics and Non-Hispanic Asians, in 2011 (continued)

WOMEN						
Cancer	Hispanic			Non-Hispanic Asian		
	ASR	**Rank**	**% YLLs**	**ASR**	**Rank**	**%YLLs**
All cancers [a]	1851 (1798;1911)		90	1751 (1692;1812)		90
Breast	385 (368;402)	(1)	75	344 (323;365)	(1)	72
Lung	197 (187;208)	(2)	97	284 (267;303)	(2)	98
Colorectum	173 (164;183)	(3)	87	176 (164;189)	(3)	86
Pancreas	109 (102;117)	(4)	99	109 (99;119)	(4)	99
Ovary	100 (93;108)	(5)	96	99 (89;111)	(5)	96
Leukemia	88 (81;95)	(6)	97	70 (61;81)	(8)	97
Liver	84 (77;91)	(7)	99	94 (84;104)	(6)	99
Stomach	77 (71;83)	(8)	98	74 (65;83)	(7)	98
Corpus uteri	77 (71;82)	(9)	87	66 (59;74)	(9)	87
Cervix uteri	74 (67;80)	(10)	88	52 (45;61)	(11)	92
NHL	67 (61;73)	(11)	92	54 (47;61)	(10)	92
Brain & NS	53 (47;59)	(12)	98	43 (34;52)	(12)	98
Kidney	41 (37;46)	(13)	91	24 (20;30)	(13)	93
Myeloma	38 (34;42)	(14)	93	24 (19;29)	(14)	94
Gallbladder	29 (25;33)	(15)	97	18 (14;23)	(17)	97
Bladder	18 (15;21)	(16)	88	11 (8;13)	(18)	84
Thyroid	16 (14;19)	(17)	58	20 (16;23)	(16)	63
Melanoma of skin	15 (13;18)	(18)	81	6 (4;8)	(20)	86
Oral cavity	15 (13;18)	(19)	82	24 (19;29)	(15)	84
Esophagus	13 (10;15)	(20)	98	9 (7;12)	(19)	98
Hodgkin lymphoma	7 (5;9)	(21)	87	2 (1;4)	(21)	79
Larynx	4 (3;5)	(22)	91	1 (0;2)	(22)	81
All Other cancers	174 (163;183)	—	97	144 (131;158)	—	97

[a] Excludes basal and squamous skin cancers
Note: NS: nervous system; NHL: Non-Hodgkin lymphoma

Table S8. Discounts applied to the frequency of disabilities to account for prevalence in the general population

Age (years)	Impotence men (%)	Dyspareunia women (%)	Incontinence men (%)	Incontinence women (%)	Infertility men (%)	Infertility women (%)
0			3	6		
1-4			3	6		
5-9			3	6		
10-14			3	6		
15-19	11	2	3	6		
20-24	11	2	3	6	10	10
25-29	11	2	3	6	10	15
30-34	15	3.5	3	6	10	15
35-39	15	3.5	3	6	15	20
40-44	21	4.5	6	10	15	
45-49	21	4.5	6	10	20	
50-54	30	5.5	6	10	20	
55-59	30	5.5	6	10	20	
60-64	41	6.5	6	10		
65-69	41	6.5	9	14		
70-74	51	8	9	14		
75-79			9	14		
80-84			9	14		
85+			9	14		

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3.2

Cigarette smoking-attributable burden of cancer by race and ethnicity in the United States

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(Submitted)

ABSTRACT

Cigarette smoking is a leading preventable cause of death and disability from cancer in the US. We estimated smoking-attributable Disability-Adjusted Life Years (DALYs) lost, overall and within racial/ethnic groups, using published DALY estimates, smoking prevalence from survey data, and relative risks from large cohort studies. In 2011, 2.6 million DALYs were lost to cancer due to cigarette smoking (27% of all DALYs lost to cancer). Smoking-attributable DALY rates were higher in men (968 per 100,000 people [95% confidence interval: 943–992]) than women (557 [540–574]). In combined sex analyses, DALY rates were higher in non-Hispanic Blacks (960 [934–983]) and non-Hispanic Whites (786 [768–802]) than in Hispanics (409 [399–421]) and non-Hispanic Asians (335 [320–350]). However, smoking-attributable cancer burden is substantial in all racial and ethnic groups, underscoring the need for intensified tobacco cessation in all populations.

BRIEF COMMUNICATION

Cigarette smoking remains a leading preventable cause of cancer death [1] and the second leading cause of overall Disability-Adjusted Life Years (DALYs) lost in the US.[2] Previous study estimated that smoking causes over 160,000 cancer deaths each year nationwide [3-5] and accounts for 21% of cancer deaths in Hispanics, 26% in non-Hispanic Whites (NHW), and 27% in non-Hispanic Blacks (NHB).[5] However, these estimates did not consider life years lost due to premature death and disability, measured by DALYs. We report estimates of cigarette smoking-attributable DALYs for the US overall and by race/ethnicity, to document smoking-related racial/ethnic health disparities.

The number of smoking-attributable DALYs lost to cancer was calculated as the sum of smoking-attributable Years of Life Lost (YLL) and smoking-attributable Years Lived with Disabilities (YLD). The smoking-attributable YLL and YLD were computed by multiplying the overall YLL and YLD for cancer previously calculated [6] for 2011, for adults 35 and older, by the population attributable fraction (PAF) for cigarette smoking, computed with the standard formula [7] for multi-category exposure. This formula incorporated smoking prevalence (never, former, current) and relative risks (RRs) for cancer death and occurrence. Smoking prevalence in 2009-2011, by race/ethnicity, sex, and age group was obtained from the National Health Interview Survey.[8] Race/ethnicity was grouped as: NHW, NHB, Hispanic, and non-Hispanic Asian (NHA). Other races (American Indian/Alaska Native and unknown race) are not presented but are included in "All races/ethnicities". We used RRs from large US prospective studies for death from, or occurrence of, 12 cancers caused by smoking according to the US Surgeon General:[9] cancers of the lip, oral cavity, and pharynx; esophagus; stomach; colon and rectum; liver; pancreas; larynx; trachea, lung and bronchus; cervix uteri; kidney and renal pelvis; urinary bladder; and acute myeloid leukemia. Specifically, we used RRs for cancer death by age group and sex for the 12 cancers combined, [4] and RRs for cancer occurrence by specific cancer and sex.[10]

The proportion of all DALYs lost to cancer that was attributable to smoking was calculated by dividing the number of smoking-attributable DALYs lost from cancer in people ages 35 and over, by the total number of DALYs lost to cancer for all ages. Age-standardized rates (ASRs) of DALYs were calculated using the US 2000 standard population. The 95% confidence intervals (CI) were estimated via a bootstrap method. [11]

Overall, 2.6 million DALYs (95% confidence interval 2.6–2.7 million) lost to cancer were lost to cigarette smoking in 2011 in the US, representing 27% of DALYs (26%–27%) lost to cancer (Figure 1). The smoking-attributable cancer burden was higher in men (1.6 million DALYs [1.5–1.6 million]) than in women (1.0 million DALYs [1.0–1.1 million]), and varied substantially by race/ethnicity, ranging from 10-12% in NHA and Hispanic women to 33-34% in NHW and NHB men.

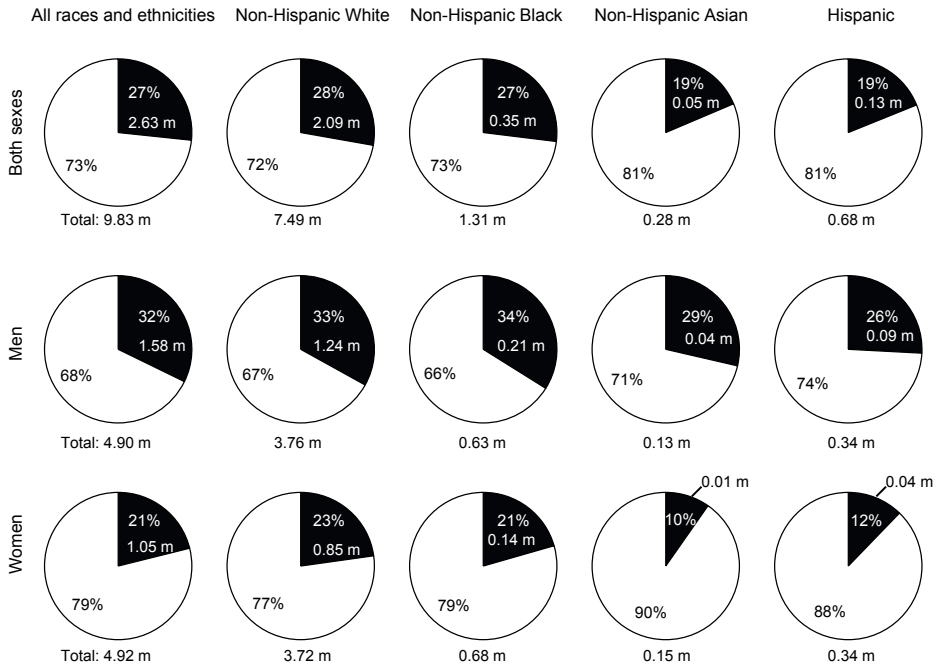

Figure 1 Proportion and number (in millions) of Disablity-Adjusted Life Years (DALYs) due to cancer attributable to cigarette smoking by sex and race/ethnicity
Black: smoking-attributable DALYs. White: not smoking-attributable DALYs

The smoking-attributable cancer burden, measured by DALY ASRs, was highest in NHB and NHW men (1,331 [1286–1372] and 994 [965–1021] DALYs per 100,000 people, respectively) (Figure 2). ASRs were about 40% lower in NHA and Hispanic men than in NHW men. Similarly, in women, the smoking-attributable ASRs were highest in NHB and NHW (679 [654–703] and 604 [584–624], respectively), and about two-thirds lower in NHA and Hispanics.

The large variations in smoking-attributable cancer burden by sex and race/ethnicity reflect differences in current and past cigarette smoking prevalence. Smoking prevalence has traditionally been higher in men than in women in every racial and ethnic

group, and in Blacks and Whites than in Hispanics or Asians. Among men, NHB used to have the highest smoking prevalence of all racial/ethnic groups [12] but have now almost matched the smoking prevalence of NHW (22% in NHB vs. 19% in NHW).[13] Reasons for high smoking prevalence among NHB include targeted marketing from the tobacco industry [14] and higher proportion of people with low socioeconomic status (SES), [15, 16] a characteristic strongly associated with smoking.[13] In contrast, smoking prevalence in Asians (10%) and Hispanics (11%) [13] is lower, despite a high frequency of low SES among Hispanics. This may in part reflect the high proportion of Asian and Hispanic migrants and the lower smoking prevalence in their countries of origin.[17, 18]

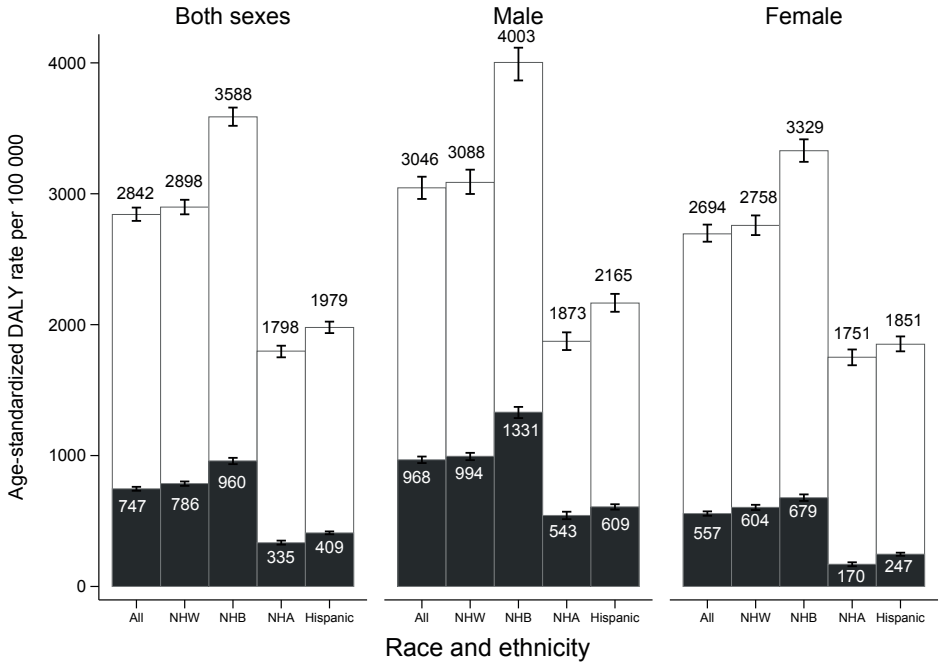

Figure 2 Age-standardized Disablity-Adjusted Life Years (DALYs) rates due to cancer attributable to cigarette smoking by sex and race/ethnicity

Black: smoking-attributable age-standardized DALY rate. White: not smoking-attributable age-standardized DALY rate

All: All races and ethnicities. NHW: non-Hispanic White. NHB: non-Hispanic Black. NHA: non-Hispanic Asian.

This is the first study to detail the cancer burden attributable to smoking in the US using DALYs, both overall and within racial/ethnic groups. These estimates are valuable for tobacco control program to document and evaluate changes in smoking-related racial/ethnic health disparities. However, the limitations of the study must be borne in mind. RRs for both cancer occurrence and death were derived from large cohort

studies including predominantly white participants, as sufficiently precise RRs from prospective studies for specific racial/ethnic groups in the US are not available. These RRs may not accurately reflect the risk in Hispanics and Asians, who have lower smoking duration and intensity.[17] In addition, we estimated only the cancer burden attributable to cigarette smoking; our estimate does not include cancer burden from secondhand smoke, or use of pipes, cigars or smokeless tobacco.

In conclusion, despite substantial declines in smoking prevalence over the past five decades, cigarette smoking accounted for close to 3 out of the 10 million healthy life years lost to cancer per year in the US. Although the share of the smoking-attributable cancer burden is largest in NHB and NHW, the burden is substantial in Hispanics and Asians as well, underscoring the need for intensified tobacco cessation in all populations to reduce the burden of smoking-related cancer and other smoking-related diseases.

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3.3

State-level cancer mortality attributable to cigarette smoking in the United States

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ABSTRACT

Importance: State-specific information about the health burden of smoking is valuable because state-level initiatives are at the forefront of tobacco control. Smoking-attributable cancer mortality estimates are currently available nationally and by cancer, but not by state.

Objective: To calculate the proportion of cancer deaths among adults 35 years and older that were attributable to cigarette smoking in 2014 in each state and the District of Columbia.

Design: The population attributable fraction (PAF) of cancer deaths due to cigarette smoking was computed using relative risks for twelve smoking-related cancers from large US prospective studies and state-specific smoking prevalence data from the Behavioral Risk Factor Surveillance System.

Results: We estimate at least 167,133 cancer deaths in 2014 (28.6% of all cancer deaths, 95% confidence interval 28.2%–28.8%) were attributable to cigarette smoking. Among men, the proportion of cancer deaths attributable to smoking ranged from a low of 21.8% in Utah (19.9%–23.5%) to a high of 39.5% in Arkansas (36.9%–41.7%), but was ≥30% in every state except Utah. Among women, the proportion ranged from 11.1% in Utah (9.6%–12.3%) to 29.0% in Kentucky (27.2%–30.7%) and was ≥20% in all states except Utah, California, and Hawaii. Nine of the top ten ranked states for men and six of the top ten states for women were located in the South. In men, smoking explained nearly 40% of cancer deaths in the top five ranked states (Arkansas, Louisiana, Tennessee, West Virginia, and Kentucky). In women, smoking explained more than 26% of all cancer deaths in the top five ranked states, which included three Southern states (Kentucky, Arkansas and Tennessee), and two Western states (Alaska and Nevada).

Conclusions and relevance: The proportion of cancer deaths attributable to cigarette smoking varies substantially across states and is highest in the South, where up to 40% of cancer deaths in men are caused by smoking. Increasing tobacco control funding, implementing innovative new strategies, and strengthening tobacco control policies and programs, federally and in all states and localities would further increase smoking cessation, decrease initiation, and reduce the future burden of morbidity and mortality associated with smoking-related cancers.

INTRODUCTION

Smoking prevalence in the US has been more than halved since the release of the first Surgeon General's Report on the health hazards of cigarette smoking in 1964, as a result of increased awareness and implementation of public health policies against smoking.[1] Nevertheless, there are still 40 million current adult cigarette smokers, and smoking remains the largest preventable cause of death from cancer and other diseases.[2] Cigarette smoking accounted for an estimated 28.7% of all cancer deaths in US adults 35 years and older in 2010.[3] However, there are no such estimates by state, despite substantial geographic variation in smoking prevalence.[4] State-specific smoking-attributable mortality is particularly valuable for public health advocates and policy-makers because state-level initiatives are at the forefront of tobacco control efforts. Herein, we estimate the proportion of all cancer deaths explained by cigarette smoking in adults aged ≥35 years in each of the 50 states and the District of Columbia (DC). For convenience, we refer to DC as a state hereafter.

METHODS

We estimated the state-specific proportion of cigarette smoking-attributable cancer mortality (SACM) using methods similar to those of the 2014 Surgeon General's Report,[1] based on 12 cancers caused by cigarette smoking (acute myeloid leukemia and cancers of the oral cavity and pharynx; esophagus; stomach; colorectum; liver; pancreas; larynx; trachea, lung, and bronchus; cervix uteri; kidney and renal pelvis; and urinary bladder). To avoid potential bias, we calculated the overall population attributable fraction (PAF) for cancer deaths in each state using the weighted sums method.[5] Specifically, we first calculated the PAF for each sex and age group (35-49, 50-54, 55-59, … 85+) in each state, using the standard formula for multi-category exposure:[6]

$$PAF_s = \frac{\left(p_{0,s} + p_{1,s}\left(RR_{1,s}\right) + p_{2,s}\left(RR_{2,s}\right)\right) - 1}{p_{0,s} + p_{1,s}\left(RR_{1,s}\right) + p_{2,s}\left(RR_{2,s}\right)}$$

where s = age; p_0, p_1, p_2 = proportion of never, former, and current smokers, respectively; and RR_1, RR_2 = relative risk for former and current smokers, respectively, compared with never smokers.

Age-, sex- and state-specific smoking prevalence (never, former, or current) were calculated based on data from the 2014 Behavioral Risk Factor Surveillance System

survey (BRFSS), which is the only national survey designed to provide reliable state-level estimates of health behaviors.[4] Smoking prevalence estimates were based on 372,759 survey participants 35 years and older who provided information on smoking status. These smoking prevalence estimates were generated from the weighted public data provided by the Centers for Disease Control and Prevention (CDC). Weighting was based on characteristics such as sex, age, race and ethnicity, education, and marital status to adjust for nonresponse bias and ensure that the sample was representative.[7]
Age- and sex-specific (but not state-specific) relative risks for death for current and former smoking status were those for a composite outcome of any of the 12 smoking-related cancers as reported from analyses of the Cancer Prevention Study-II (442,960 participants) and Pooled Contemporary Cohort (954,029 participants).[3]
For each state, the number of smoking-attributable cancer deaths in each age and sex group was calculated by multiplying the age- and sex-specific PAFs by the corresponding observed 2014 cancer death counts obtained from the National Center for Health Statistics.[8] The total number of smoking-attributable cancer deaths in each state was then calculated by summing across all age and sex groups. Finally, the overall SACM in each state was calculated by dividing the number of estimated smoking-attributable cancer deaths by the total number of cancer deaths among persons 35 year and older in each state. The 95% confidence intervals on the SACM were estimated via a bootstrap method,[9] with 5,000 simulations.
To illustrate the geographic variation in SACM, we mapped the results grouping states by number rank (1 being the highest SACM).
Differences in SACM between states may be partly due to differences between states in racial and ethnic composition because smoking prevalence substantially varies by race/ethnicity.[2] To compare a measure of SACM between states that was not influenced by racial and ethnic composition, we calculated SACM by state for non-Hispanic White (NHW) men. We then assessed whether variation in SACM across states in NHW men was similar to that for all races/ethnicities combined using Spearman's correlation. Sparse data precluded similar comparison for other racial/ethnic and sex groups. However, we also calculated national SACM estimates for NHW, non-Hispanic blacks (NHB), and Hispanics using smoking prevalence from in the National Health Interview Survey (NHIS, 51,637 participants 35 years and older) during 2013–2014[10] and relative risks of cancer death as described above.
Finally, as a sensitivity analysis, we compared the SACM in four regions (South, Midwest, West, and Northeast according to the Bureau of Census classification)[11] using smoking prevalence from the NHIS with that estimated using smoking prevalence from the BRFSS.

RESULTS

In 2014, at least 167,133 cancer deaths (28.6% of all cancer deaths) in persons aged ≥35 years in the US were attributable to cigarette smoking, with 103,609 of these deaths occurring in men (62.0%) and 63,524 in women (38.0%) (Table 1). The proportion of SACM ranged from 21.8% in Utah to 39.5% in Arkansas among men, and from 11.1% in Utah to 29.0% in Kentucky among women. Many of the states with the highest proportions of SACM were located in the South, including nine of the top ten states for men (Arkansas, Louisiana, Tennessee, West Virginia, Kentucky, Alabama, Mississippi, North Carolina and Oklahoma) (Figure 1). Notably, smoking explained nearly 40% of adult male cancer deaths in five of these states. Southern states dominated the top ten SACM states among women as well, but the second and third ranked states were Alaska (27.5%) and Nevada (27.1%) — which ranked 18th and 20th, respectively, in men. For both sexes combined, seven of the top ten states were located in the South, two in the West (Alaska and Nevada) and one in the Midwest (Missouri). While California had the lowest SACM after Utah, it had the highest number of deaths explained by smoking, because of its large population.

A. Men

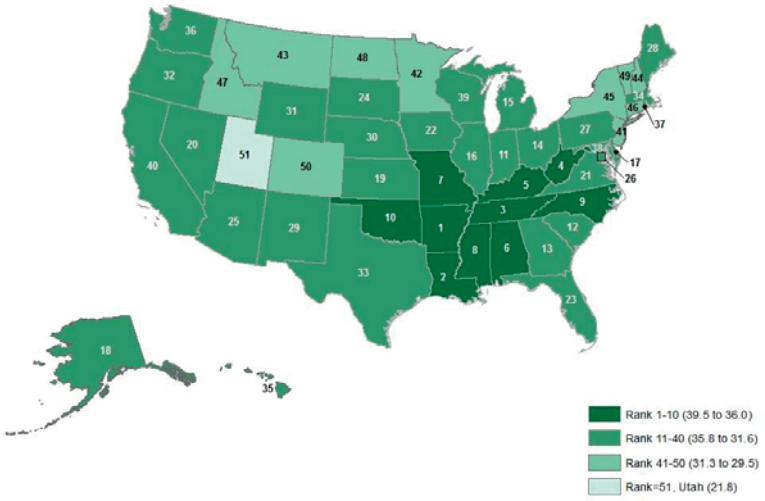

Figure 1A. Rank and proportion of cancer mortality attributable to cigarette smoking, for men (A), women (B), and both sexes (C) in 2014

Footnote: States are ranked by the proportion of cancer deaths attributable to cigarette smoking, from highest (1) to lowest (51). States were categorized into four groups (group 1, states ranked 1-10; group 2, those ranked 11-40; group 3, those ranked 41-50; and group 4, Utah alone as the proportion was substantially lower than in any other state). The color of the state indicates the proportion of cancer deaths attributable to cigarette smoking.

B. Women

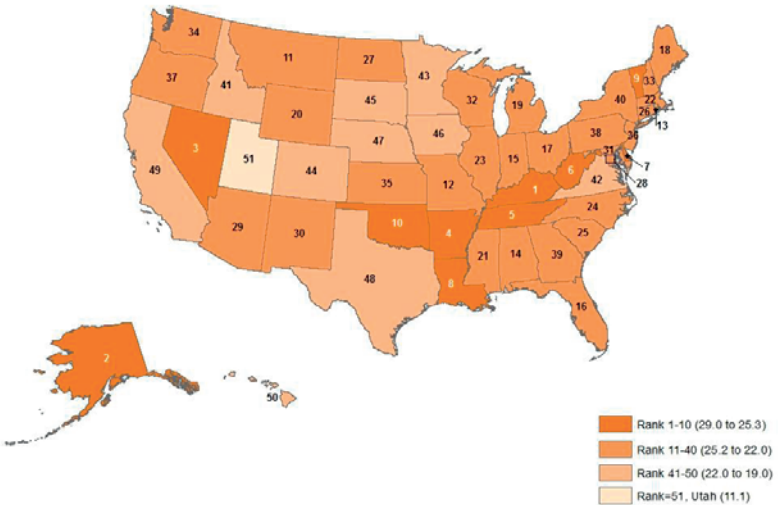

Figure 1B. Rank and proportion of cancer mortality attributable to cigarette smoking, for men (A), women (B), and both sexes (C) in 2014

Footnote: States are ranked by the proportion of cancer deaths attributable to cigarette smoking, from highest (1) to lowest (51). States were categorized into four groups (group 1, states ranked 1-10; group 2, those ranked 11-40; group 3, those ranked 41-50; and group 4, Utah alone as the proportion was substantially lower than in any other state). The color of the state indicates the proportion of cancer deaths attributable to cigarette smoking.

C. Both sexes

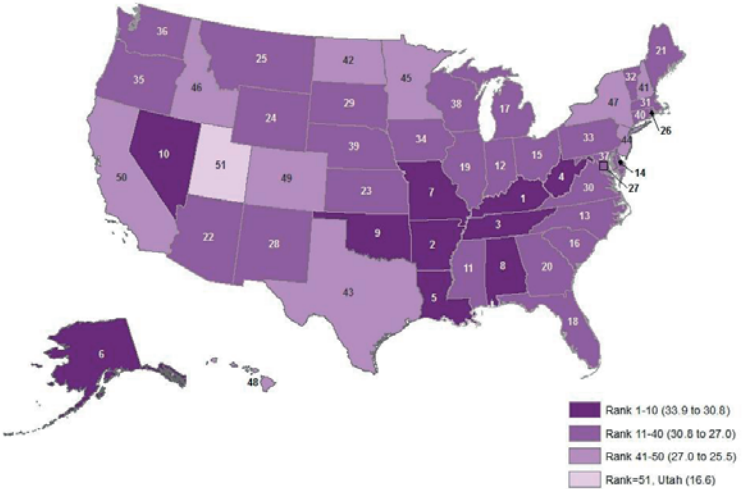

Figure 1C. Rank and proportion of cancer mortality attributable to cigarette smoking, for men (A), women (B), and both sexes (C) in 2014

Footnote: States are ranked by the proportion of cancer deaths attributable to cigarette smoking, from highest (1) to lowest (51). States were categorized into four groups (group 1, states ranked 1-10; group 2, those ranked 11-40; group 3, those ranked 41-50; and group 4, Utah alone as the proportion was substantially lower than in any other state). The color of the state indicates the proportion of cancer deaths attributable to cigarette smoking.

Table 1. Number and proportion of cancer deaths attributable to cigarette smoking in 2014 in adults 35 years and older

	Men and Women				Men				Women			
State	Rank	Smoking-attributable cancer deaths	Cancer deaths	Smoking-attributable proportion of cancer deaths (%) (95% confidence interval)	Rank	Smoking-attributable cancer deaths	Cancer deaths	Smoking-attributable proportion of cancer deaths (%) (95% confidence interval)	Rank	Smoking-attributable cancer deaths	Cancer deaths	Smoking-attributable proportion of cancer deaths (%) (95% confidence interval)
Kentucky	1	3452	10165	34.0 (32.4;35.3)	5	2104	5514	38.2 (35.9;40.3)	1	1347	4651	29.0 (27.2;30.7)
Arkansas	2	2175	6490	33.5 (31.9;35.0)	1	1404	3556	39.5 (36.9;41.7)	4	771	2934	26.3 (24.4;28.1)
Tennessee	3	4613	14031	32.9 (31.2;34.3)	3	2919	7579	38.5 (36.0;40.7)	5	1694	6452	26.3 (24.2;28.2)
West Virginia	4	1581	4845	32.6 (31.2;33.9)	4	1003	2628	38.2 (36.0;40.2)	6	578	2217	26.1 (24.2;27.8)
Louisiana	5	3044	9350	32.6 (31.0;34.0)	2	1943	5042	38.5 (36.0;40.7)	8	1101	4308	25.5 (23.7;27.2)
Alaska	6	296	943	31.4 (29.2;33.3)	18	184	536	34.3 (31.2;37.0)	2	112	407	27.5 (24.3;30.1)
Missouri	7	4047	12932	31.3 (29.8;32.8)	7	2519	6816	37.0 (34.6;39.2)	12	1528	6116	25.0 (23.0;26.7)
Alabama	8	3183	10180	31.3 (29.8;32.6)	6	2025	5478	37.0 (34.7;38.9)	14	1159	4702	24.6 (22.9;26.2)
Oklahoma	9	2441	7852	31.1 (29.8;32.3)	10	1529	4245	36.0 (34.0;37.8)	10	912	3607	25.3 (23.7;26.8)
Nevada	10	1535	4968	30.9 (28.7;32.8)	20	921	2703	34.1 (30.7;36.8)	3	614	2265	27.1 (24.0;29.6)
Mississippi	11	1992	6462	30.8 (28.8;32.6)	8	1290	3545	36.4 (33.5;38.9)	21	702	2917	24.1 (21.8;26.1)
Indiana	12	4099	13407	30.6 (29.3;31.7)	11	2560	7155	35.8 (33.8;37.5)	15	1539	6252	24.6 (23.1;26.0)
North Carolina	13	5844	19133	30.5 (29.1;31.8)	9	3723	10241	36.4 (34.2;38.2)	24	2121	8892	23.9 (22.1;25.4)
Delaware	14	591	1949	30.3 (28.4;32.0)	17	344	999	34.4 (31.7;36.9)	7	247	950	26.0 (23.5;28.2)
Ohio	15	7598	25211	30.1 (28.7;31.5)	14	4679	13258	35.3 (33.1;37.2)	17	2919	11953	24.4 (22.5;26.2)
South Carolina	16	2962	9842	30.1 (28.9;31.2)	12	1907	5349	35.7 (33.9;37.2)	25	1055	4493	23.5 (22.0;24.9)
Michigan	17	6232	20936	29.8 (28.4;31.0)	15	3803	10870	35.0 (32.8;36.8)	19	2429	10066	24.1 (22.4;25.7)
Florida	18	12596	42818	29.4 (28.2;30.6)	23	7773	23109	33.6 (31.9;35.3)	16	4823	19709	24.5 (22.9;25.9)
Illinois	19	7114	24273	29.3 (27.6;30.8)	16	4282	12423	34.5 (31.8;36.8)	23	2832	11850	23.9 (21.8;25.8)
Georgia	20	4816	16465	29.2 (27.6;30.7)	13	3120	8766	35.6 (33.0;37.8)	39	1696	7699	22.0 (20.1;23.7)
Maine	21	927	3195	29.0 (27.6;30.2)	28	567	1715	33.1 (31.0;34.9)	18	359	1480	24.3 (22.7;25.8)
Arizona	22	3246	11311	28.7 (27.6;29.7)	25	2031	6094	33.3 (31.6;34.9)	29	1215	5217	23.3 (22.0;24.5)
Kansas	23	1587	5540	28.6 (27.5;29.7)	19	1006	2943	34.2 (32.4;35.7)	35	581	2597	22.4 (20.9;23.7)
Wyoming	24	251	880	28.5 (27.2;29.9)	31	154	477	32.3 (30.2;34.3)	20	97	403	24.1 (22.3;25.7)
Montana	25	581	2049	28.4 (26.9;29.7)	43	335	1074	31.2 (29.2;33.0)	11	246	975	25.2 (23.1;27.2)
Rhode Island	26	631	2226	28.3 (26.9;29.7)	37	361	1134	31.9 (29.6;33.8)	13	269	1092	24.7 (22.5;26.6)

Table 1. Number and proportion of cancer deaths attributable to cigarette smoking in 2014 in adults 35 years and older (continued)

	Men and Women				Men				Women			
State	Rank	Smoking-attributable cancer deaths	Cancer deaths	Smoking-attributable proportion of cancer deaths (%) (95% confidence interval)	Rank	Smoking-attributable cancer deaths	Cancer deaths	Smoking-attributable proportion of cancer deaths (%) (95% confidence interval)	Rank	Smoking-attributable cancer deaths	Cancer deaths	Smoking-attributable proportion of cancer deaths (%) (95% confidence interval)
District of Columbia	27	310	1100	28.2 (26.1;30.0)	26	179	538	33.3 (29.6;36.3)	28	131	562	23.3 (21.1;25.2)
New Mexico	28	964	3420	28.2 (26.7;29.5)	29	601	1843	32.6 (30.4;34.6)	30	362	1577	23.0 (21.0;24.7)
South Dakota	29	476	1688	28.2 (26.2;30.0)	24	316	944	33.5 (30.7;36.0)	45	159	744	21.4 (18.7;23.9)
Virginia	30	4110	14611	28.1 (26.7;29.4)	21	2578	7637	33.8 (31.6;35.7)	42	1532	6974	22.0 (20.2;23.5)
Massachusetts	31	3565	12677	28.1 (26.8;29.3)	34	2085	6520	32.0 (30.1;33.7)	22	1480	6157	24.0 (22.3;25.6)
Vermont	32	382	1359	28.1 (26.6;29.4)	49	227	750	30.2 (28.1;32.2)	9	155	609	25.5 (23.3;27.4)
Pennsylvania	33	7931	28437	27.9 (26.6;29.1)	27	4917	14775	33.3 (31.3;35.1)	38	3014	13662	22.1 (20.5;23.6)
Iowa	34	1793	6443	27.8 (26.5;29.0)	22	1146	3406	33.7 (31.7;35.4)	46	647	3037	21.3 (19.5;22.9)
Oregon	35	2143	7784	27.5 (26.0;28.9)	32	1315	4072	32.3 (30.0;34.4)	37	828	3712	22.3 (20.5;24.0)
Washington	36	3298	12042	27.4 (26.1;28.6)	36	2024	6349	31.9 (30.0;33.6)	34	1275	5693	22.4 (20.7;23.9)
Maryland	37	2900	10629	27.3 (25.8;28.5)	38	1701	5370	31.7 (29.3;33.7)	31	1199	5259	22.8 (21.1;24.3)
Wisconsin	38	3081	11295	27.3 (25.7;28.7)	39	1884	5969	31.6 (29.1;33.8)	32	1197	5326	22.5 (20.4;24.4)
Nebraska	39	927	3422	27.1 (26.0;28.1)	30	598	1845	32.4 (30.7;33.9)	47	329	1577	20.8 (19.5;22.1)
Connecticut	40	1774	6565	27.0 (25.6;28.3)	46	1017	3325	30.6 (28.4;32.6)	26	758	3240	23.4 (21.4;25.1)
New Hampshire	41	723	2680	27.0 (25.5;28.3)	44	432	1387	31.2 (28.9;33.1)	33	290	1293	22.5 (20.5;24.2)
North Dakota	42	341	1266	27.0 (25.4;28.3)	48	200	659	30.3 (28.0;32.2)	27	142	607	23.3 (21.3;25.2)
Texas	43	10310	38269	26.9 (25.4;28.3)	33	6616	20542	32.2 (29.7;34.3)	48	3695	17727	20.8 (19.1;22.5)
New Jersey	44	4388	16411	26.7 (25.4;28.0)	41	2520	8051	31.3 (29.1;33.3)	36	1867	8360	22.3 (20.5;24.0)
Minnesota	45	2552	9549	26.7 (25.6;27.8)	42	1561	4990	31.3 (29.5;33.0)	43	991	4559	21.7 (20.3;23.0)
Idaho	46	731	2752	26.6 (24.9;28.0)	47	455	1494	30.4 (28.0;32.6)	41	277	1258	22.0 (19.9;23.9)
New York	47	9296	35024	26.5 (25.0;28.0)	45	5467	17616	31.0 (28.5;33.3)	40	3830	17408	22.0 (20.0;23.8)
Hawaii	48	642	2466	26.0 (24.2;27.7)	35	427	1340	31.9 (29.2;34.2)	50	214	1126	19.0 (16.5;21.2)
Colorado	49	1876	7310	25.7 (24.5;26.8)	50	1130	3826	29.5 (27.8;31.1)	44	746	3484	21.4 (19.8;23.0)
California	50	14689	57547	25.5 (24.0;26.9)	40	9388	29755	31.6 (29.2;33.7)	49	5302	27792	19.1 (17.0;20.9)
Utah	51	495	2979	16.6 (15.4;17.7)	51	337	1547	21.8 (19.9;23.5)	51	158	1432	11.1 (9.6;12.3)
Total		167133	585178	28.6 (28.2;28.8)		103609	307799	33.7 (33.2;34.0)		63524	277379	22.9 (22.5;23.2)

State-specific rankings for NHW men were generally similar to those for all raceraces/ethnicities combined (Spearman's correlation coefficient = 0.91, p<0.001), with the notable exception of DC (SACM of 18.5% in NHW men vs. 33.3% in men overall) (eFigure 1). Nationally, NHBs had the highest SACM (26.9%), followed by NHWs (25.5%) and Hispanics (20.5%) (Figure 2). Finally, estimates of SACM at the regional level using smoking prevalence from the NHIS were equivalent to those estimated using smoking prevalence from BRFSS (eTable 1).

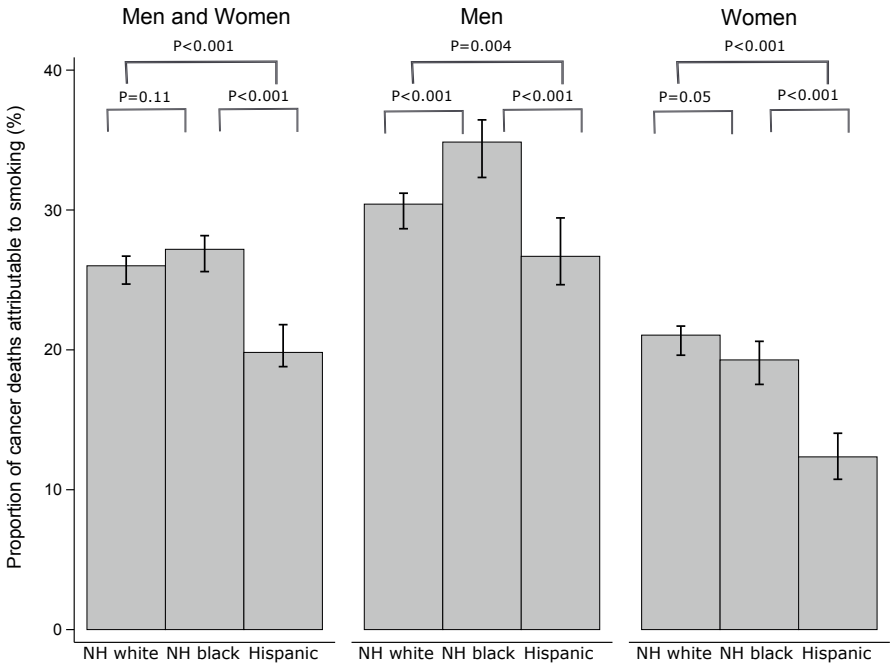

Figure 2. National proportion of cancer deaths attributable to cigarette smoking, by race and ethnicity, with 95% confidence intervals, in 2014

DISCUSSION

In most states, about a third of cancer deaths in men and a quarter in women are explained by cigarette smoking. However, consistent with smoking-attributable all-cause mortality,[12] cancer deaths are associated with cigarette smoking less often in Western states and more often in the South, particularly among men. For example, smoking accounted for nearly 40% of cancer deaths among men in five Southern states. The larger burden of SACM in men than in women likely reflects a lower prevalence of smoking among women than men in the older birth cohorts.[13,14] However, gender differences in SACM may diminish in the future because smoking histories and risk of

mortality from smoking-related diseases are comparable for men and women in more recent birth cohorts.[15] In fact, female smoking prevalence recently surpassed male smoking prevalence in South Dakota, Montana, and Arkansas.[16]

Higher SACM in the South is driven by higher historic smoking prevalence, which has prevailed in large part due to weaker tobacco control policies and programs. Policy initiatives are heavily influenced by the tobacco industry in all states,[17,18] especially those in the South,[19] where 95% of the US tobacco crop is grown.[20] Although spending on tobacco control is inversely associated with smoking prevalence,[21,22] only five states spent at least 50% of the amount recommended by the Centers of Disease Control and Prevention (CDC) in 2016.[23] In particular, eight of the 21 states that spend less than 10% of the CDC recommended amount are located in the South (Alabama, Georgia, Kentucky, North Carolina, South Carolina, Tennessee, Texas, and Virginia). Tobacco control spending by all states combined was under $500 million in 2016, far less than the $10 billion spent annually by the tobacco industry on marketing.[24]

Public smoking restrictions and high cigarette prices (through excise taxes, price promotion restrictions, and minimum price laws)[25] are among the most effective tobacco control policies,[26,27] and both are primarily legislated by states. Again, the least restrictive public smoking policies and most affordable cigarettes are in the South. Nine of fourteen states with the least comprehensive smoke-free indoor air laws are in this region[28] and the average cigarette excise tax is $0.49 in major tobacco states, compared with $1.80 in other states (and as high as $4.35 in New York).[29] However, there are signs that the tobacco industry's influence has waned somewhat in Southern tobacco-growing states in recent years, facilitating improvement in tobacco control policies[30] and highlighting the opportunity for more rapid progress in the future.

The higher SACM in Southern states may also be due in part to disproportionately high levels of low socioeconomic status, which is associated with higher smoking prevalence[2] and lower smoking cessation rates.[31] Smoking prevalence among adults with a high school education or less are two to four times those among college graduates[2] and people with a lower educational attainment have a lower awareness of the health hazards of smoking.[32] Only half (50%) of adults in Kentucky have more than a high school education, compared with 68% in Colorado.[31] In addition, racial differences in smoking prevalence and population distribution may account for some variation in the SACM by state. For example, black men have a higher SACM and a higher proportion of smoking-attributable all-cause mortality,[33] reflecting historically higher smoking prevalence compared with white men.[34] In some Southern states (e.g. Louisiana, Mississippi), blacks account for more than 30% of the population compared with less than 5% in many Western and Northern states (e.g. Utah, Connecticut).[35] Conversely, some states, such as California and Texas, are disproportionately populated by Hispanics,[35] among whom SACM is lower. Nevertheless, the SACM by state for NHW men is gener-

ally similar to that of all men, indicating that variation in racial composition is unlikely to be the driving factor for state differences in SACM. Of note, DC showed the lowest SACM for NHW men, reflecting the large proportion of highly educated men (85% with a Bachelor's degree or more)[31] in whom awareness about the health hazards of smoking is highest.[32] The comparatively low SACM in Utah reflects the religious prohibition of smoking among Mormons.[36]

In addition to Southern states, Alaska and Nevada had particularly high SACM, especially among women. In Alaska, which had the second highest SACM in women, smoking prevalence was the same in men and women in 2009, in contrast to most states where it was 10% to 60% higher in men.[16] Nevada is one of a handful of non-Southern states that still allows smoking in bars and casinos.[37] A previous study of smoking-attributable all-cause mortality found that Nevada had the highest fraction of deaths explained by smoking of any state.[38] Missouri is another non-Southern state with high SACM, ranking seventh for both sexes combined. It has the lowest cigarette excise tax ($0.17) of any state, 90% lower than the national average of $1.65.[29]

Tobacco control has been credited with preventing about 8 million premature deaths in the US over the past five decades, equivalent to 157 million years of life saved.[39] Our data shows that there remains the potential to avert many more premature deaths in light of suboptimal funding for tobacco control programs, not only in the South, but in all states. As of 2016, two-thirds of states lack 100% smoke-free laws in public places to protect the general public from second hand smoke;[40] no state[41] has a cigarette excise tax that accounts for at least for 70% of the retail price, as recommended by the WHO;[42] and only one state (North Dakota) funds its tobacco control programs at the level recommended by the CDC.[23] The Affordable Care Act includes coverage of cessation treatments without cost-sharing for the privately and Medicare-insured. However, for Medicaid enrollees – who are twice as likely to smoke[2] – coverage is state-governed, and only seven states provide comprehensive coverage (Connecticut, Indiana, Massachusetts, Minnesota, Nevada, Pennsylvania, Vermont).[43] Although there has generally been a stagnation in the adoption of traditional comprehensive tobacco control,[44] some states and localities have implemented innovative approaches to fight the tobacco epidemic. For instance, California, Hawaii, and 145 smaller localities have raised the tobacco sales age to 21[45] —a measure supported by the Institute of Medicine.[46] Likewise, communities across the US have passed laws that limit or prohibit smoking in multi-family housing.[47] The federal government can do much more to accelerate cessation and discourage initiation, including requiring manufacturers of tobacco products to reduce nicotine content to nonaddictive levels,[48] raising federal tobacco taxes, and maintaining funding of anti-smoking campaigns.[49] With fully one-third of tobacco-related cancer deaths in men and one-quarter in women preventable with current knowledge, tobacco control should spearhead the Cancer Moonshot initia-

tive to accelerate progress against cancer. However, it is important to realize that given the lag time between tobacco use and cancer diagnosis,[50] the impact of today's policies will be most evident on the future cancer burden.

Our study likely underestimated deaths caused by tobacco use for several reasons. First, only 12 cancers were included for consistency with the Surgeon General's report;[1] however, cigarette smoking is associated with excess mortality for additional cancers.[3,51] Second, self-reported data are known to underestimate smoking prevalence.[52] Third, deaths caused by tobacco exposures other than active cigarette smoking, including second hand smoke, pipes, hookahs, cigars, smokeless tobacco, and electronic nicotine delivery systems, were not included in our analysis. Due to changing patterns of tobacco use,[53] products other than cigarettes may account for a greater proportion of all tobacco-related cancer deaths in the future. Finally, confidence intervals for SACM in some states were relatively wide due to limited precision of smoking prevalence estimates available from BRFSS in some age groups. However, the BRFSS is the only national survey designed to provide estimates of state-level smoking status. Although the response rate for the BRFSS is lower (47%) than that for the NHIS (61%),[10] the surveys report generally comparable smoking prevalence estimates[54] which generate remarkably similar SACM when compared at the regional level. Notably, higher SACM was less apparent in the Census Bureau-defined Southern region because it includes states such as Maryland, which has exceptionally low smoking prevalence (16.4% in 2013),[55] and Texas, which has a large lower-smoking Hispanic population.[56] This illustrates the high variability of smoking-attributable disease within regions and supports the value of state-specific analyses.

CONCLUSION

The proportion of cancer deaths attributable to cigarette smoking varies substantially across states and is highest in the South, where up to 40% of cancer deaths in men are caused by smoking. However, the human costs of cigarette smoking are staggering in all states, regardless of ranking. Increasing tobacco control funding, implementing innovative new strategies, and strengthening tobacco control policies and programs, federally and in all states and localities would further increase smoking cessation, decrease initiation, and reduce the future burden of smoking-related cancers.

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All authors declare no conflict of interest.

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eTable 1. Number and proportion of cancer deaths attributable by US region to smoking using smoking prevalence from the Behavioral Risk Factor Surveillance System (BRFSS) and the National Health Interview Survey (NHIS)

	Cancer deaths attributable to smoking and 95% confidence interval		Proportion of cancer deaths attributable to smoking (%) and 95% confidence interval	
	BRFSS	**NHIS**	**BRFSS**	**NHIS**
Northeast	29698	32312	27.3 (25.9;28.6)	28.2 (26.4;29.8)
Midwest	40164	40235	29.3 (27.9;30.6)	29.5 (27.9;30.9)
South	66069	65375	29.8 (28.4;31.1)	30.3 (29.0;31.5)
West	32037	30543	26.4 (25.0;27.8)	27.3 (25.7;28.7)
US	167968	168465	28.7 (27.8;29.2)	28.8 (28.2;30.2)

4

Impact of smoking on chronic obstructive pulmonary disease mortality

4.1

Comparative international trends in chronic obstructive pulmonary disease and lung cancer mortality, 1994–2013

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(submitted)

ABSTRACT

Background: Chronic obstructive pulmonary disease (COPD) and lung cancer are common among smokers, often overlapping in the same patients. Our objectives were to present international patterns and trends of COPD mortality —in some countries for the first time— and to tease out the contribution of smoking in COPD mortality, using lung cancer as indirect indicator of the accumulated hazards of smoking.

Methods: Death counts in adults 35 years and older for each condition, for 1994–2013, were extracted from the WHO mortality database, for 46 countries with data span ≥11 years, and 13 countries for shorter periods. Age-standardized mortality rates, average annual percentage change in rates, mean age at death, and future death counts, by sex, cause of death, and country were reported.

Findings: Since around 2003, mortality rates declined or were stable in men in both COPD and lung cancer in 45 out of 46 countries, and in 40 countries in women in COPD. In contrast, female lung cancer increased in half of the countries. The declines were greater in COPD than lung cancer. Meanwhile, the number of deaths increased in both conditions, largely for demographic reasons. Around 2011–2013, rates for both men and women in high-income countries were up to ten times higher in lung cancer than COPD. In contrast, in most middle-income countries in Latin America and Asia, COPD rates were up to five times higher than lung cancer rates. Despite favorable declining trends, future deaths counts will not drop because of population growth and ageing.

Interpretation: The higher COPD than lung cancer rates in middle-income Latin American and Asian countries highlight the role of risk factors beyond smoking in COPD death, including poverty, air pollution, respiratory infections, and asthma in those countries.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) and lung cancer (lung cancer) are major causes of mortality worldwide. In 2015, COPD was the fourth-leading cause of death (5·6% of deaths) and lung cancer the seventh (2·9% of deaths), with large regional variations.[1] Since the beginning of their rise at the turn of the twentieth century, international trends in lung cancer mortality have been extensively reported in industrialized countries.[2-4] Lung cancer etiology is well-studied and largely follows the trend and pattern of tobacco smoking prevalence with a 20–30-year lag time. However, lung cancer is also frequent in never-smoking women in Asia, in part due to genetic susceptibility and indoor air pollution.

Contrary to lung cancer, the research on COPD is more recent. Lung cancer and COPD share several etiological factors, and in particular tobacco smoking.[5] Accordingly, patients are often affected by both diseases (e.g. 20% of lung cancer patients in Europe[6, 7] and 50% of lung cancer patients in New Zealand).[8] It has been postulated that the epidemiology of lung cancer and COPD mirror each other,[9] but with different courses. On the one hand, lung cancer is mostly diagnosed after prolonged exposure to tobacco smoke. On the other hand, and although the condition becomes clinically apparent around the age of 40–50 years, the causes of COPD –other than smoking– can be traced back early in life, through insults to the lung (e.g. respiratory tract infections, exposure to maternal smoking, and air pollution) or sub-optimal lung development (due to undernourishment).[10] The proportion of smoking-attributable deaths in each condition varies by country and by sex. In 2000, around 90% of lung cancer and 85% of COPD deaths in men in high-income countries (HICs) were attributed to smoking, and 80% and 60% in low- and middle-income countries (LMICs), respectively.[11] The proportions were lower in women in HICs (around 78% of lung cancer and 70% of COPD deaths attributable to smoking) and in LMICs (50% and 34%, respectively).

Observed data from HICs[5, 9, 12-17] and modeled data in a global study[18] have reported declines in COPD mortality rates since the 1990s or the 2000s, depending on the country. Yet, little is known about trends in COPD mortality in LMICs, in Latin America, and more recently in Asia. Our first objective was to describe the most up-to-date trends in COPD mortality, including in Latin America and Asia, and by income group. Our second objective was to tease out the contribution of smoking in COPD mortality. As long-term annual smoking prevalence is not available for all countries, lung cancer mortality was used as an indirect indicator of the accumulated hazards of smoking.[19] Our hypothesis was that if smoking had the same impact on COPD and lung cancer mortality, then trends and patterns in lung cancer and COPD mortality rates would fairly match within one country and one sex. Finally, we reported the change in death

counts of these two conditions in high-income and middle-income countries over the last ten years and provided insight on their future burdens based on historical trends.

METHODS

Death counts for ages 35 and older –to focus on the effects of smoking– were extracted from the World Health Organization (WHO) mortality database[20] by sex and 5-year age group. Underlying cause of death ICD-10 codes J40-44 for COPD (chronic bronchitis [J40-J42], emphysema [J43], and other COPD [J44]),[17] and C33-C34 for trachea, bronchus and lung cancer were extracted for 1994–2013 (varying by country). No imputation of ill-defined codes was performed. Data from countries with at least 70% of national population coverage and less than 20% of ill-defined cause of death since 1995, with the most recent year available after 2005 and a national population ≥300 000 inhabitants in 2010 were selected. Sixty-one countries met the criteria, with 46 of them providing ≥11 years of continuous data —the minimum number of years required for trend analysis. Only years with less than 10% of deaths from COPD at unknown age were analyzed. Corresponding population data were obtained from the same database, and completed with United Nations (UN) population 2015 revision estimates. Countries were grouped into regions according to the UN classification, and into income group (41 HICs and 20 middle-income countries [MICs]) according to the World Bank classification. Notably, no low-income country passed the selection process. Specifically, there were no representative data from sub-Saharan Africa, India and China.

Age-standardized mortality rates were computed using the world standard population. COPD and lung cancer rates for the last two years (around 2011–2013) were compared to depict the most recent mortality burden. To assess changes in trends, the annual percent change (APC) and the average annual percentage change (AAPC) for the last ten available years of data were computed, using a Joinpoint regression analysis (details in Supplement). Details of the mean age at death computation are in the Supplement.

Relatively simple models were used to predict 2016 and 2030 premature (ages 35–69) mortality burdens, by sex, condition, and country income group. National mortality trends over the last 10 years were assumed to continue until 2030, and future rates were applied to UN forecasted national populations.

Role of the funding source

The study sponsor had no role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

RESULTS

Over the whole study period, in most of the countries selected for trend analysis, rates have been declining —generally steadily— or remained stable, in both sexes in COPD, and in male lung cancer (Figure 1 and Supplement Tables 2 and 3A). In contrast, female lung cancer rates have been increasing in half of the countries (Supplement Table 3B). For instance, in the Netherlands, over 1996–2013, COPD rates remained stable in women but were halved in men. Meanwhile, female lung cancer rates doubled and male rates declined by a third.

Over the last ten years (since around 2003), male rates declined or were stable in both conditions in all countries and across income levels except for three populations (COPD rates increased in Paraguay and Czech Republic, as well as lung cancer rates in Paraguay and Romania) (Figure 2A). The declines were greater in COPD than lung cancer rates, and very large in some countries (≥6% annual decline in The Republic of Moldova, Kyrgyzstan, Slovenia, and Malta). Female COPD rates also declined or levelled off in all countries except six HICs European countries (Luxembourg, Czech Republic, Hungary, Norway, Croatia, and Germany). In contrast, female lung cancer rates were modestly declining or stable in about half of the countries (in America, Asia, Northern Europe, Republic of Moldova, Luxembourg, Malta and New Zealand) while they were increasing in five South American countries, Israel, 15 European countries, and Australia (Figure 2B). Declines in lung cancer rates were greater in men than in women. As a result, male and female trends have been converging in 25 of 46 countries in COPD (in Northern, Central and South America, Northern, Southern and Western Europe, and Oceania) and 40 of 46 countries in lung cancer.

Recent mortality rates (around 2011–2013) varied around 18-fold between the countries with the lowest and the highest rates in men in both COPD and lung cancer, and 25- and ten-fold in women, respectively (Figure 3 and Supplement Tables 1A and 1B). The lowest COPD mortality rates were observed in Kuwait and Japan, in both men and women (around ten and two deaths per 100 000 person-years, respectively). The highest COPD rates were observed in Kyrgyzstan and the Philippines in men (around 120), and in Kyrgyzstan and Denmark in women (around 50). Female COPD rates were usually lower than male rates, but nearly matched in Sweden, Iceland, Denmark and the USA. The lowest lung cancer mortality rates (≤30 in men and ≤15 in women) were observed in MICs in Latin America, the Caribbean and Asia; the highest rates were observed in HICs, all over Europe in men (≥100) and Northern and Western Europe, and Canada in women (≥60). Hungary exhibited the highest lung cancer rates in both men and women (178 and 73, respectively). In both sexes, mortality COPD rates were generally higher than lung cancer rates in MICs, and always lower than lung cancer rates in HICs (except in Venezuelan women).

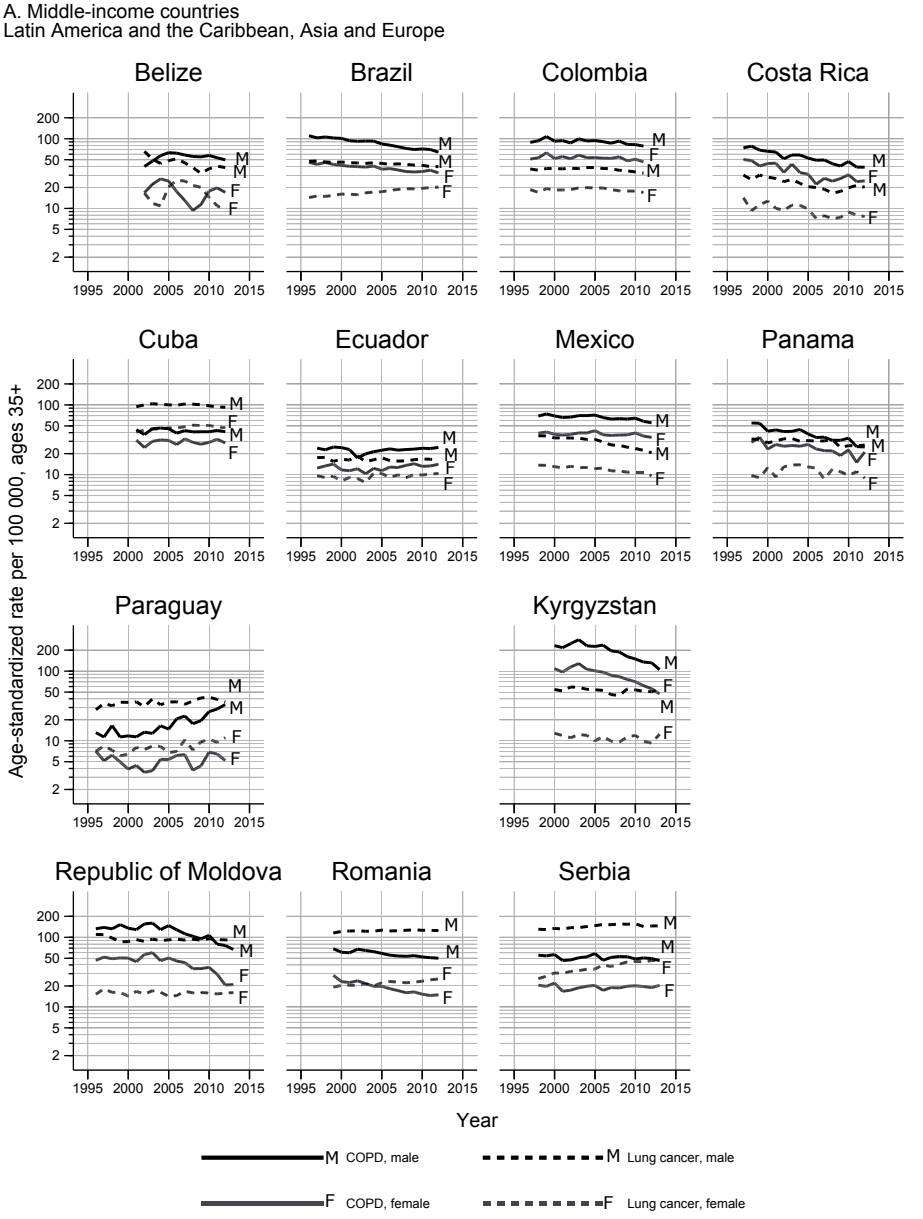

Figure 1A Trends in age-standardized mortality rates in chronic obstructive pulmonary disease (COPD) and lung cancer, for ages 35 and older

Portugal had no data for 2004–2006, Trinidad and Tobago had no data for 2003. Age-standardized rates from countries with fewer than 1 million inhabitants (Bahamas, Belize, Iceland, and Malta) were smoothed with a moving average of 50% of the annual values.

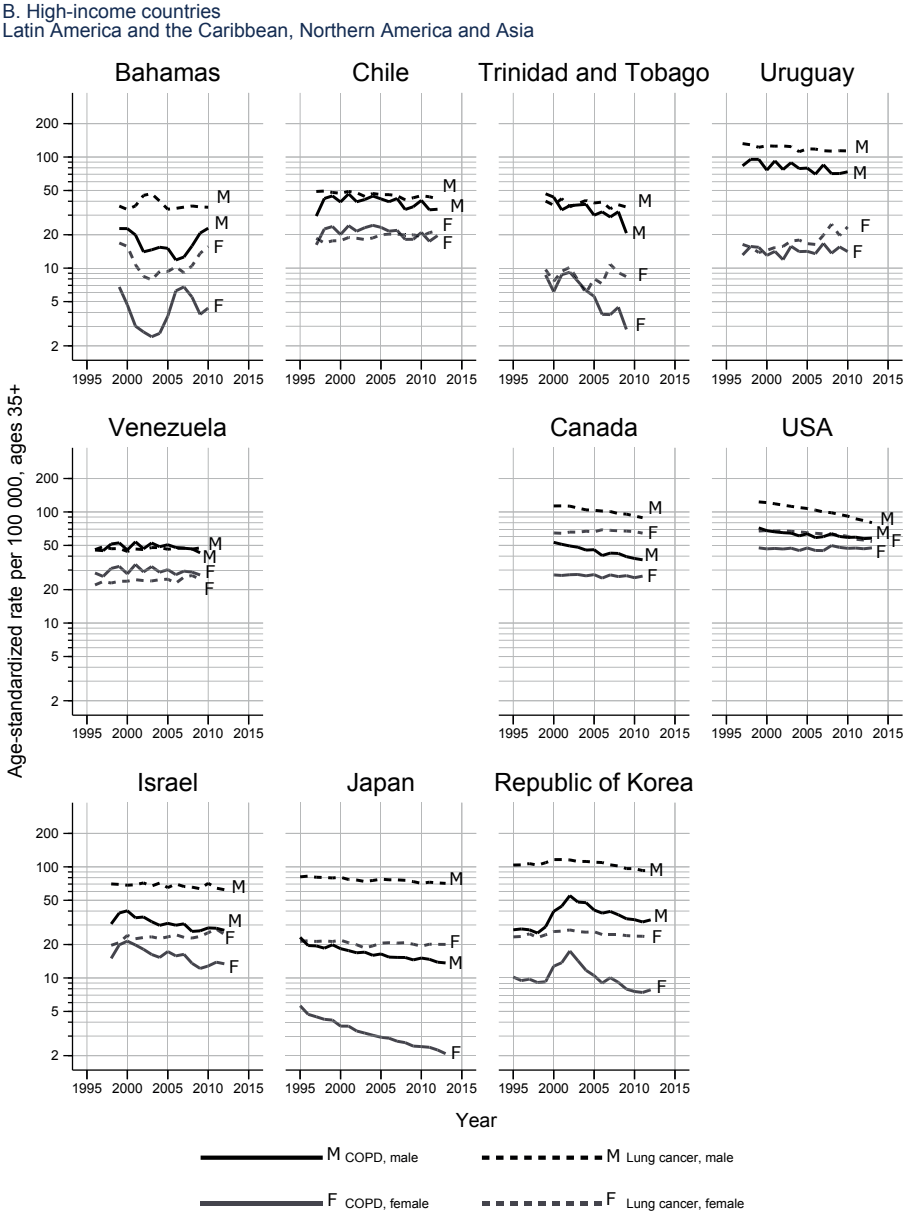

Figure 1B Trends in age-standardized mortality rates in chronic obstructive pulmonary disease (COPD) and lung cancer, for ages 35 and older

Portugal had no data for 2004–2006, Trinidad and Tobago had no data for 2003. Age-standardized rates from countries with fewer than 1 million inhabitants (Bahamas, Belize, Iceland, and Malta) were smoothed with a moving average of 50% of the annual values.

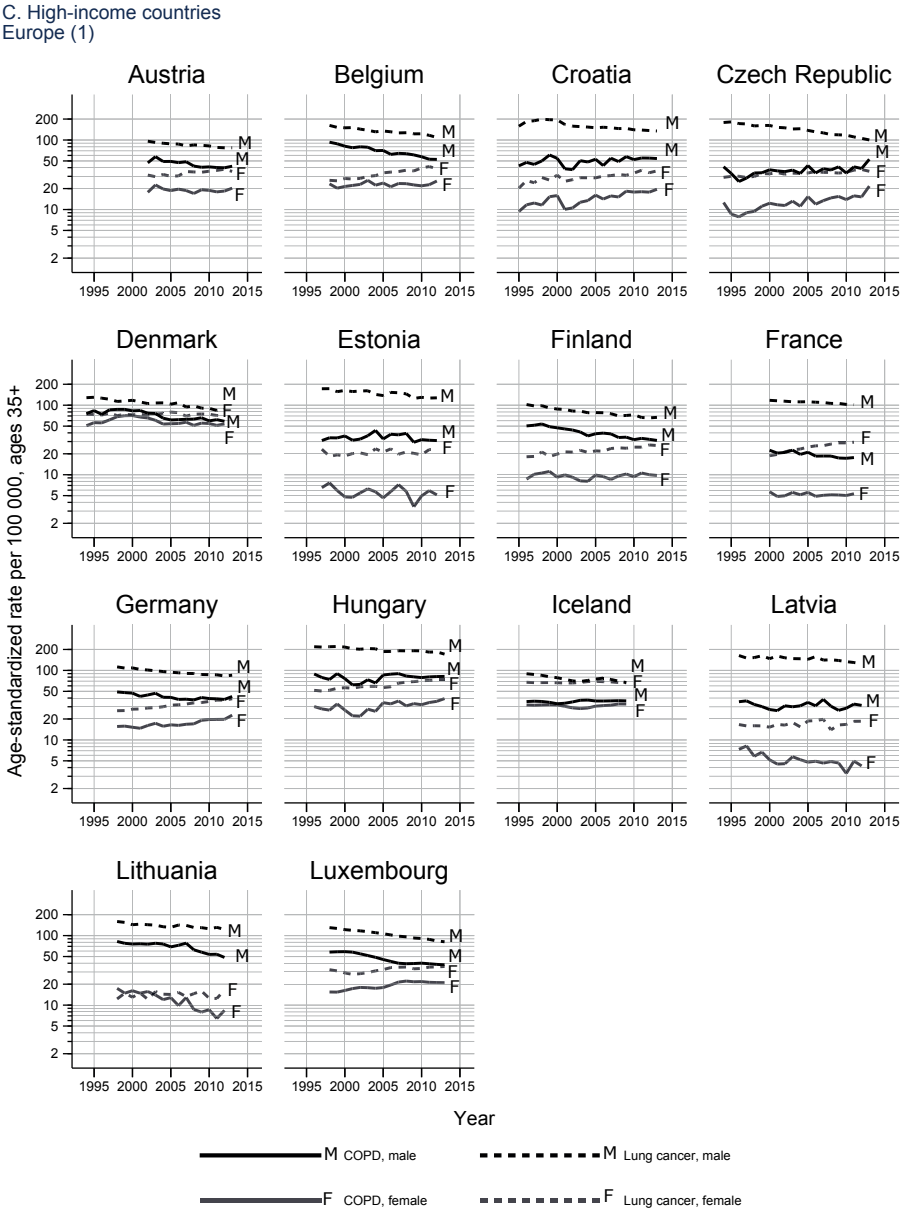

Figure 1C Trends in age-standardized mortality rates in chronic obstructive pulmonary disease (COPD) and lung cancer, for ages 35 and older

Portugal had no data for 2004–2006, Trinidad and Tobago had no data for 2003. Age-standardized rates from countries with fewer than 1 million inhabitants (Bahamas, Belize, Iceland, and Malta) were smoothed with a moving average of 50% of the annual values.

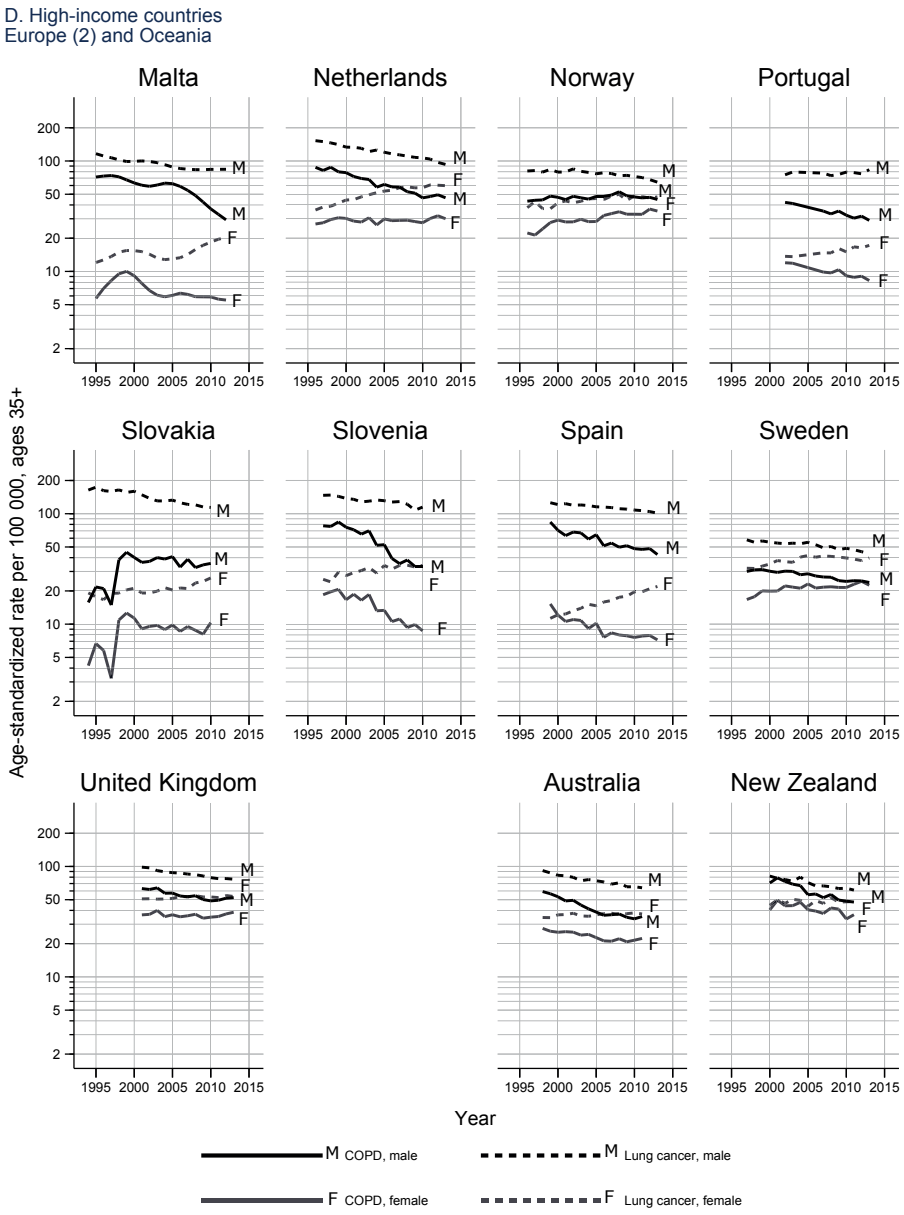

Figure 1D Trends in age-standardized mortality rates in chronic obstructive pulmonary disease (COPD) and lung cancer, for ages 35 and older

Portugal had no data for 2004–2006, Trinidad and Tobago had no data for 2003. Age-standardized rates from countries with fewer than 1 million inhabitants (Bahamas, Belize, Iceland, and Malta) were smoothed with a moving average of 50% of the annual values.

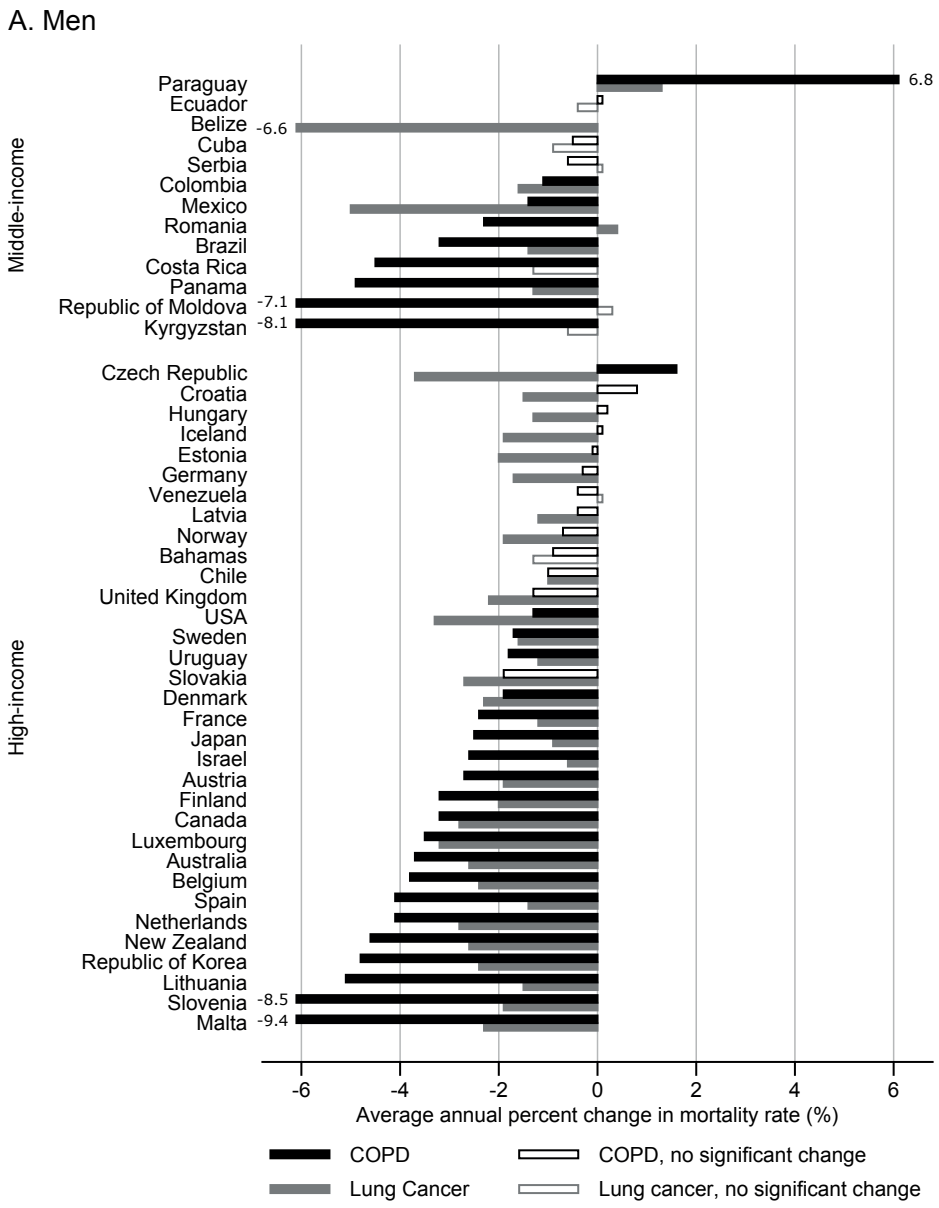

Figure 2A Average annual percent change over the last ten years (since around 2003) in chronic obstructive pulmonary disease (COPD) and lung cancer mortality rates, for ages 35 and older, in men

Values are sorted by decreasing average annual percent (AAPC) change in COPD mortality rate, within income group.

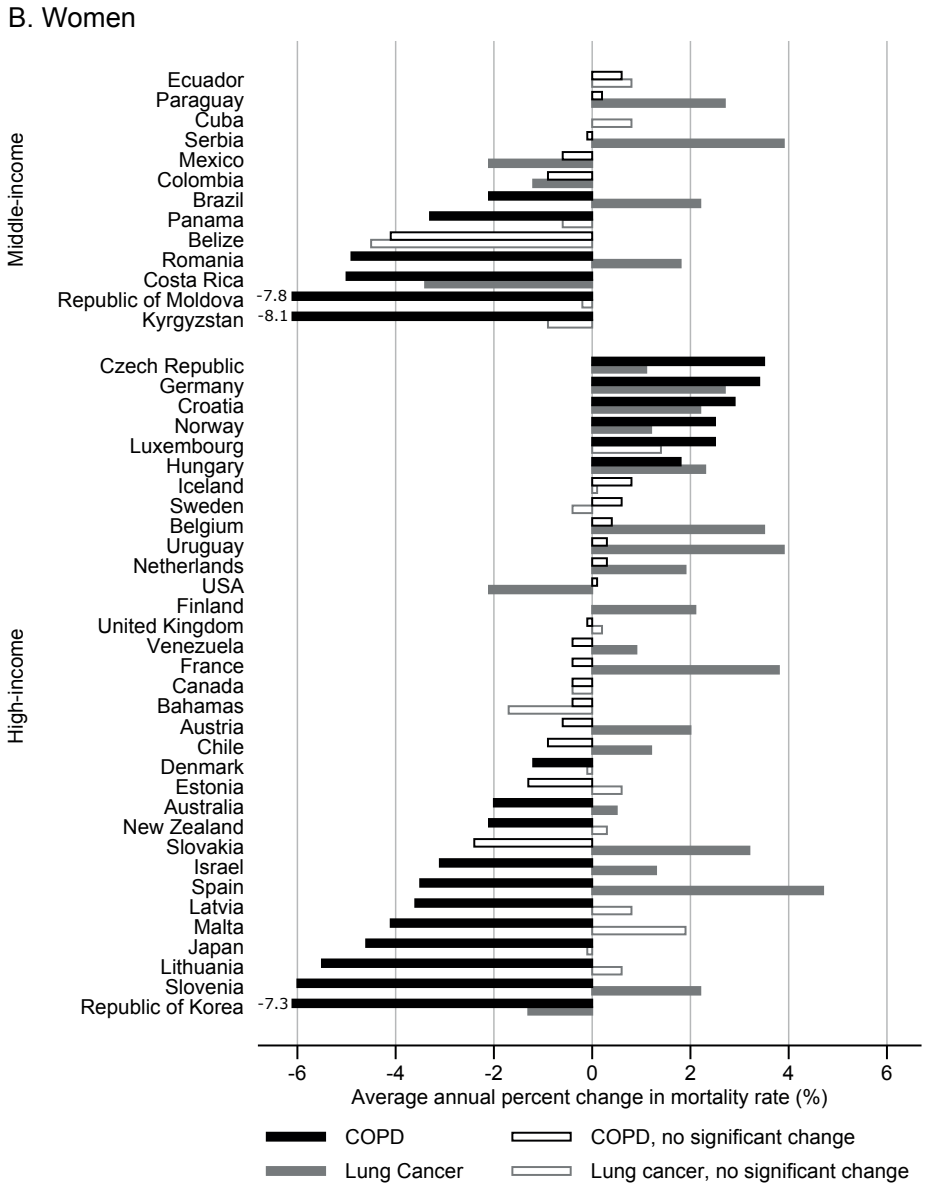

Figure 2B Average annual percent change over the last ten years (since around 2003) in chronic obstructive pulmonary disease (COPD) and lung cancer mortality rates, for ages 35 and older, in women

Values are sorted by decreasing average annual percent (AAPC) change in COPD mortality rate, within income group.

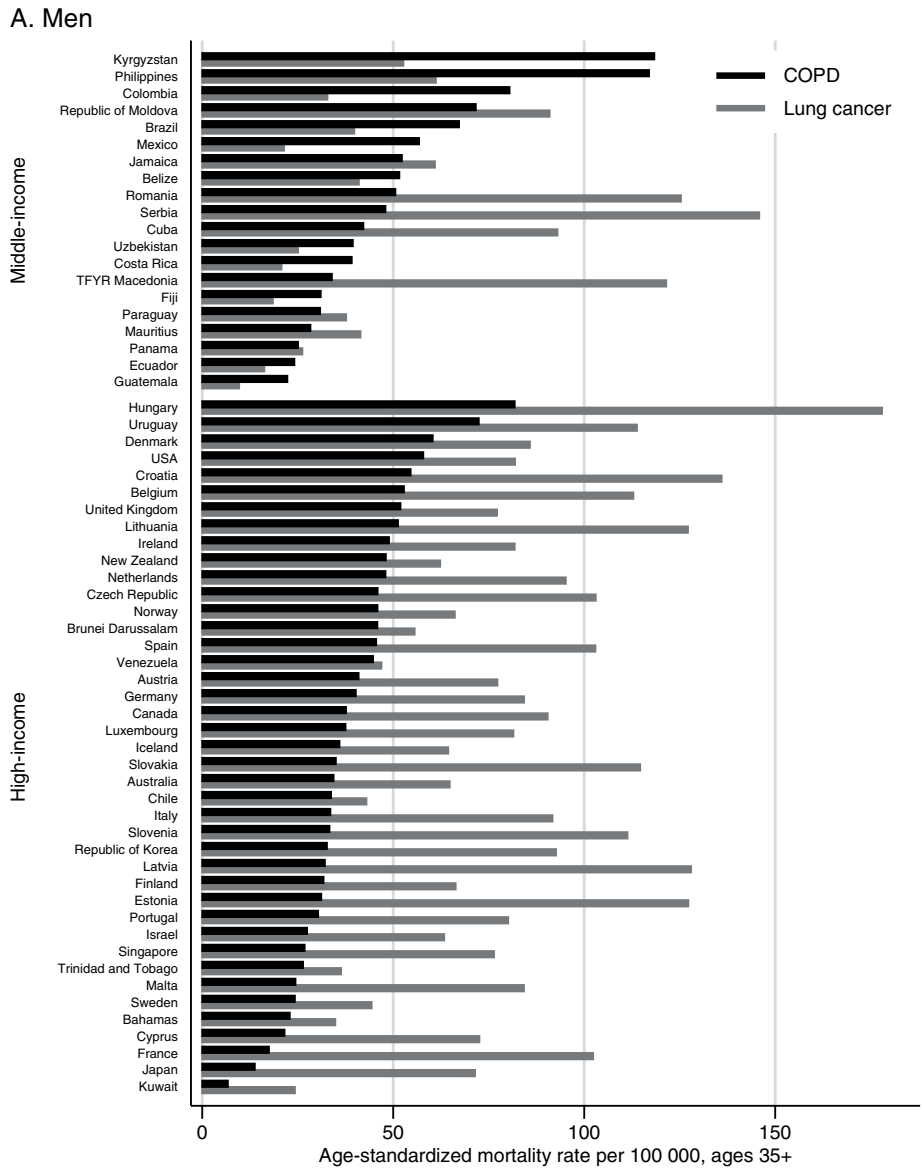

Figure 3A Mean age-standardized mortality rate in chronic obstructive pulmonary disease (COPD) and lung cancer, for ages 35 and older, over the last two years of data (around 2011–2013), in men

Values are sorted by decreasing age-standardized mortality rate in COPD, within income group.

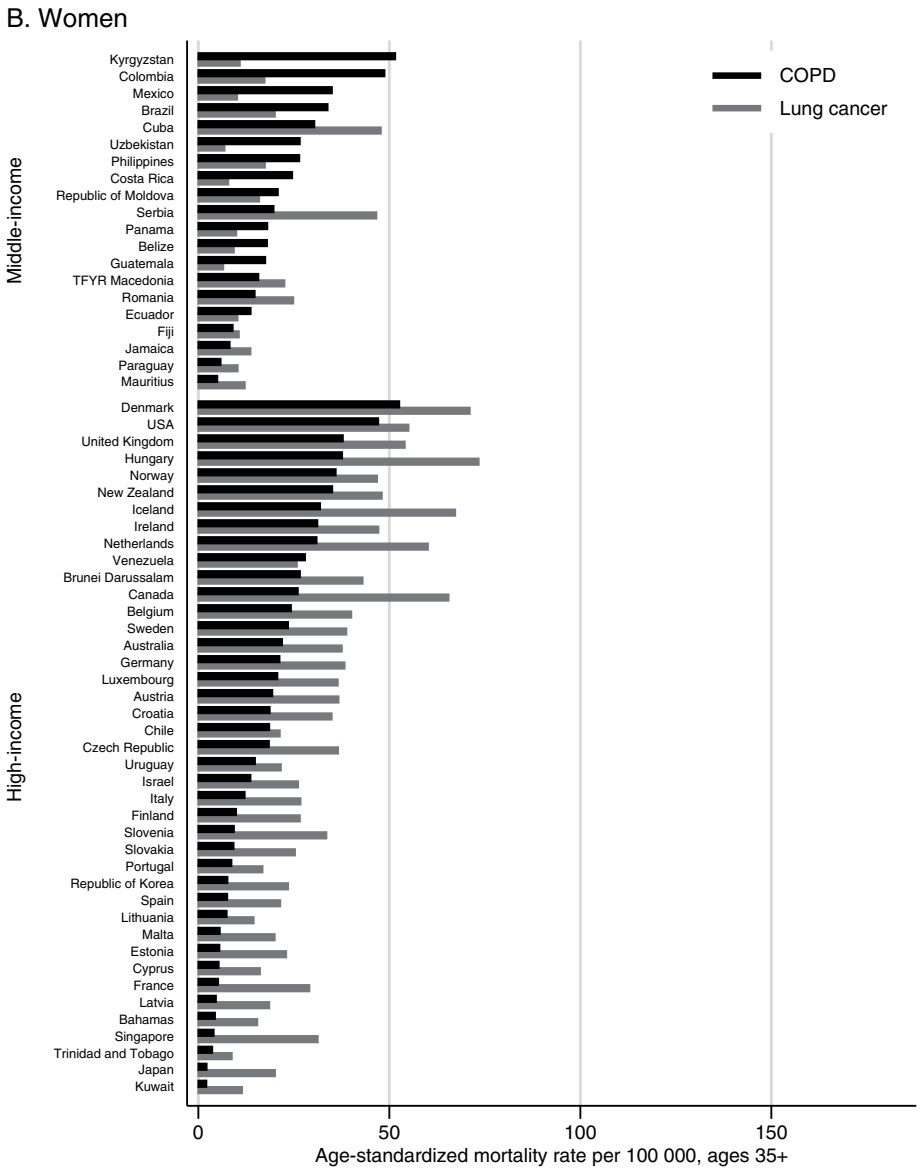

Figure 3B Mean age-standardized mortality rate in chronic obstructive pulmonary disease (COPD) and lung cancer, for ages 35 and older, over the last two years of data (around 2011–2013), in women

Values are sorted by decreasing age-standardized mortality rate in COPD, within income group.

The number of COPD and lung cancer deaths increased over the last ten years in most of the countries (Table 1). This increase was greater in women than in men (21% increase in deaths in COPD and 24% lung cancer in women, vs. 13% and 6% in men, respectively) and greater in MICs than in HICs. During the last two years of data, almost 438 000 people (44% women), aged 35 years and older, died from COPD annually, in the 61 countries studied (Table 1). Meanwhile, 577 000 died from lung cancer (36% women). However, COPD deaths exceeded lung cancer deaths, in the majority of countries (all MICs) in Latin America (such as Brazil, Colombia, and Mexico) and some Asian countries (Kyrgyzstan, Uzbekistan, and the Philippines). Additionally, more women died from COPD than lung cancer in seven HICs: Chile, Denmark, Norway, Portugal, USA, Uruguay and Venezuela. Of note, the number of COPD deaths among women surpassed that of men in Northern Europe (Denmark, Iceland, and Sweden) and in the USA, and was identical in Norway.

Table 1A. Chronic obstructive pulmonary disease (COPD) and lung cancer (LC) deaths, during the last two years of available data, proportional change in death counts, mean age at death, in middle-income countries

			Men						Women					
			Mean annual deaths		Change in deaths over the last 10 years (%)		Mean age at death (years)		Mean annual deaths		Change in deaths over the last 10 years (%)		Mean age at death (years)	
Region	**Country**	**Study period**	**COPD**	***LC***	**COPD**	***LC***	**COPD**	***LC***	**COPD**	***LC***	**COPD**	***LC***	**COPD**	***LC***
Africa														
	Mauritius	2005–2013	70	*107*	*	*	76	*68*	20	*42*	*	*	82	*69*
Latin America and the Caribbean														
	Belize	2002–2012	19	*15*	†	†	72	*66*	8	*4*	†	†	73	*66*
	Brazil	1996–2012	22719	*13861*	13%	*29%*	76	*68*	16456	*8880*	31%	*75%*	76	*67*
	Colombia	1997–2011	5824	*2341*	29%	*25%*	79	*70*	5017	*1577*	39%	*37%*	81	*70*
	Costa Rica	1997–2012	416	*197*	12%	*22%*	82	*71*	341	*88*	3%	*12%*	84	*72*
	Cuba	2001–2012	1721	*3235*	29%	*14%*	77	*70*	1309	*1812*	40%	*38%*	75	*70*
	Ecuador	1997–2012	707	*424*	83%	*35%*	83	*73*	510	*303*	78%	*76%*	84	*71*
	Guatemala	2005–2012	414	*176*	*	*	78	*70*	410	*141*	*	*	78	*69*
	Jamaica	2000–2006	303	*286*	*	*	75	*66*	59	*78*	*	*	79	*70*
	Mexico	1998–2012	11986	*4072*	22%	*-9%*	79	*71*	9769	*2252*	31%	*8%*	81	*70*
	Panama	1998–2012	206	*178*	-10%	*15%*	81	*71*	178	*78*	9%	*10%*	83	*70*
	Paraguay	1996–2012	297	*355*	236%	*47%*	75	*69*	71	*102*	131%	*69%*	80	*68*
Asia														
	Kyrgyzstan	2000–2013	769	*335*	-48%	*1%*	73	*64*	545	*98*	-49%	*3%*	79	*65*
	Philippines	1999–2008	9467	*5686*	68%	*35%*	71	*64*	2803	*2051*	27%	*44%*	74	*65*
	Uzbekistan	2004–2005	1052	*691*	*	*	69	*62*	953	*227*	*	*	72	*61*

Table 1A. Chronic obstructive pulmonary disease (COPD) and lung cancer (LC) deaths, during the last two years of available data, proportional change in death counts, mean age at death, in middle-income countries (continued)

			Men						Women					
			Mean annual deaths		Change in deaths over the last 10 years (%)		Mean age at death (years)		Mean annual deaths		Change in deaths over the last 10 years (%)		Mean age at death (years)	
Region	**Country**	**Study period**	**COPD**	***LC***	**COPD**	***LC***	**COPD**	***LC***	**COPD**	***LC***	**COPD**	***LC***	**COPD**	***LC***
Europe														
	Republic of Moldova	1996–2013	594	*743*	-39%	*15%*	73	*63*	314	*190*	-51%	*15%*	79	*67*
	Romania	1999–2012	3691	*7752*	-10%	*11%*	75	*66*	1782	*2057*	-19	*32*	80	*68*
	Serbia	1998–2013	1494	*3767*	6	*12*	75	*66*	865	*1386*	23	*43*	77	*66*
	TFYR Macedonia	2006–2010	196	*662*	*	*	74	*65*	116	*135*	*	*	75	*64*
Oceania														
	Fiji	2006–2012	36	*23*	†	†	69	*66*	11	*16*	†	†	69	*63*
Middle-income			61975	*44901*	23%	*23%*	76	*67*	41531	*21512*	29%	*51%*	78	*68*

Mean annual deaths were calculated by averaging the reported two last years of data. The proportional change in death counts over the last ten years is the difference between average death count for the most recent two years and average death count nine and ten years prior, divided by the average death count nine and ten years prior.
* Percentages not presented due to less than ten years of data
† Percentages not presented due to fewer than 50 mean deaths per year in the most recent two years, separately for each sex.
Totals may not sum up due to rounding. Data from countries with less than 50 deaths in one sex are included in the percentage change in death counts for Middle-income countries, High-income countries and grand total.

Premature COPD deaths (ages 35–69) were estimated to decrease by 10% in the 13 MICs, and to increase by 2% in the 33 HICs with trend analyses, between 2016 and 2030. Contrariwise, lung cancer premature deaths were projected to increase by 12% in MICs while decreasing by 14% in HICs (Supplemental Figure 1).

In the studied countries, over the most recent two years, among people 35 years and older, the mean age at death due to COPD was 78 years in men, and 79 in women (two to three years lower in MICs than in HICs) (Table 1). This was seven years older than the mean age at death from lung cancer (five years lower in MICs than in HICs). Supplemental Figure 2 displays the frequency of each of the ICD-10 codes used to report COPD deaths, in the last two years. "Other COPD" was the most frequently reported condition, causing 84% of COPD deaths. However, emphysema was reported to be responsible for more than a third of deaths in Austrian, Japanese, Latvian, and Paraguayan men, and Uzbek women.

Table 1B. Chronic obstructive pulmonary disease (COPD) and lung cancer (LC) deaths, during the last two years of available data, proportional change in death counts, mean age at death, in high-income countries

			Men						Women					
			Mean annual deaths		Change in deaths over the last 10 years (%)		Mean age at death (years)		Mean annual deaths		Change in deaths over the last 10 years (%)		Mean age at death (years)	
Region	Country	Study period	COPD	LC	COPD	LC	COPD	LC	COPD	LC	COPD	LC	COPD	LC
Latin America and the Caribbean														
	Bahamas	1999–2010	14	22	†	†	70	64	4	12	†	†	79	69
	Chile	1997–2012	1591	1694	21%	28%	80	70	1392	1109	27%	58%	82	71
	Trinidad and Tobago	1999–2009	67	95	-26%	18%	73	65	14	31	†	†	76	71
	Uruguay	1997–2010	769	992	-7%	-2%	77	69	265	244	24%	50%	79	69
	Venezuela	1996–2009	1705	1838	30%	42%	75	66	1473	1191	42%	55%	78	66
Northern America														
	Canada	2000–2011	5389	10515	2%	5%	79	72	5164	8737	26%	28%	80	72
	USA	1999–2013	67294	86124	16%	-4%	77	71	74395	70571	21%	3%	78	72
Asia														
	Brunei Darussalam	2011–2012	22	26	†	†	78	69	13	21	†	†	79	68
	Cyprus	2004–2012	70	191	*	*	81	70	24	48	*	*	83	69
	Israel	1998–2012	636	1180	11%	23%	79	71	490	616	9%	44%	82	72
	Japan	1995–2013	13137	51680	24%	21%	83	76	3739	20394	0%	32%	86	78
	Kuwait	2012–2013	13	71	*	*	76	68	5	25	*	*	64	74
	Republic of Korea	1995–2012	3823	11821	5%	28%	79	71	1746	4409	-20%	33%	83	73
	Singapore	2012–2013	273	788	*	*	77	71	65	404	*	*	83	72
Europe														
	Austria	2002–2013	1514	2370	-2%	2%	77	70	1131	1320	-6%	28%	81	70
	Belgium	1998–2012	2674	4721	-18%	-6%	78	72	1733	1784	5%	51%	80	69
	Croatia	1995–2013	989	2097	37%	-1%	77	69	626	697	80%	34%	81	70
	Czech Republic	1994–2013	1802	3789	67%	-11%	74	69	1161	1715	82%	28%	78	70
	Denmark	1994–2012	1528	1890	-5%	0%	78	72	1809	1763	5%	19%	79	72
	Estonia	1997–2012	137	506	7%	-11%	75	70	50	163	15%	28%	77	73
	Finland	1996–2013	803	1468	13%	5%	77	72	342	726	39%	43%	77	73
	France	2000–2011	5265	22279	10%	7%	80	69	2722	7510	23%	61%	84	69
	Germany	1998–2013	16962	29682	20%	3%	77	71	13269	14924	40%	38%	80	71
	Hungary	1996–2013	2844	5583	34%	-4%	74	66	2218	3149	58%	33%	77	68
	Iceland	1996–2009	42	63	†	11%	80	72	47	71	†	33%	81	73
	Ireland	2007–2010	684	1012	*	*	79	71	640	690	*	*	81	73
	Italy	2003–2012	12688	25043	-10%	-3%	83	74	8155	8601	-1%	34%	86	73
	Latvia	1996–2012	207	785	11%	-10%	72	69	55	198	-20%	8%	74	71
	Lithuania	1998–2012	532	1133	-24%	-7%	75	69	168	238	-41%	13%	79	73

Table 1B. Chronic obstructive pulmonary disease (COPD) and lung cancer (LC) deaths, during the last two years of available data, proportional change in death counts, mean age at death, in high-income countries (continued)

			Men						Women					
			Mean annual deaths		Change in deaths over the last 10 years (%)		Mean age at death (years)		Mean annual deaths		Change in deaths over the last 10 years (%)		Mean age at death (years)	
Region	**Country**	**Study period**	**COPD**	**LC**	**COPD**	**LC**	**COPD**	**LC**	**COPD**	**LC**	**COPD**	**LC**	**COPD**	**LC**
	Luxembourg	1998–2013	77	143	11%	-4%	79	72	66	71	78%	39%	82	69
	Malta	1995–2012	44	135	†	17%	79	73	12	35	†	†	72	71
	Netherlands	1996–2013	3660	6265	2%	-1%	80	72	3054	4026	26%	45%	79	69
	Norway	1996–2013	1026	1224	19%	3%	79	73	1026	947	41%	31%	79	72
	Portugal	2002–2013	1719	3002	0%	17%	80	69	912	833	8%	46%	83	71
	Slovakia	1994–2010	518	1588	6%	-13%	74	67	223	495	0%	41%	75	68
	Slovenia	1997–2010	262	768	-34%	4%	78	69	141	306	-29%	50%	81	70
	Spain	1999–2013	11525	17607	-2%	6%	82	71	3177	3957	-4%	69%	85	69
	Sweden	1997–2013	1289	1856	-1%	2%	80	73	1550	1746	29%	23%	80	73
	United Kingdom	2001–2013	15534	19409	4%	-1%	79	74	14924	16028	14%	18%	80	74
Oceania														
	Australia	1998–2011	3125	4940	-4%	6%	79	73	2521	3158	15%	29%	80	72
	New Zealand	2000–2011	823	901	-11%	6%	80	72	736	765	-4%	28%	80	72
High-income			183066	327286	10%	4%	79	72	151247	183714	19%	21%	80	73
Middle- and high-income			*245041*	*372187*	*13%*	*6%*	*78*	*71*	*192778*	*205226*	*21%*	*24%*	*79*	*72*

Mean annual deaths were calculated by averaging the reported two last years of data. The proportional change in death counts over the last ten years is the difference between average death count for the most recent two years and average death count nine and ten years prior, divided by the average death count nine and ten years prior.
* Percentages not presented due to less than ten years of data
† Percentages not presented due to fewer than 50 mean deaths per year in the most recent two years, separately for each sex.
Totals may not sum up due to rounding. Data from countries with less than 50 deaths in one sex are included in the percentage change in death counts for Middle-income countries, High-income countries and grand total.

DISCUSSION

This is the first study contrasting worldwide COPD and lung cancer mortality in magnitude and over time. Sharp differences in COPD and lung cancer mortality existed between country, income level, and gender. Since around 2003, COPD mortality has declined in many countries –sometimes drastically– in HICs and as well as in MICs, both in men and in women. For instance, COPD rates were halved in only ten years in Slovenia and Kyrgyzstan. Meanwhile, lung cancer mortality has more uniformly declined, but to a lesser extent than COPD, with the notable exception of the increase in female rates in half of the countries (mostly HICs). Around 2011–2013, in HICs, COPD mortality rates were lower than lung cancer, while COPD rates were up to five times higher than lung cancer rates in MICs in Latin America and Asia.

We report for the first time the inverse relationship between COPD and lung cancer mortality in MICs in Latin America and Asia. This suggests a distinct role of other risk factors for COPD, and probably also for lung cancer, in less wealthy nations as compared to wealthier ones. We had hypothesized that lung cancer mortality trends and patterns would, to some extent, be similar to the ones for COPD within one population (country/sex). It turned out that, even in countries with low smoking prevalence (substantiated by low lung cancer rates), COPD mortality could be high. For example, circa 2012, female COPD rate in Kyrgyzstan was around 53 per 100 000, similar to that in Denmark. Yet, the female smoking prevalence in Kyrgyzstan was less than 5%[21] contrasting that observed in Denmark (39% in 1980 and 18% in 2012).[22] Several reasons could explain this finding. First, in populations with low smoking prevalence (e.g. in women in some MICs), high COPD mortality might be driven by other risk factors such as asthma in childhood (e.g. prevalence around 23% in Brazilian teenagers),[23] bronchial hyper-reactivity,[6] and most importantly the harming role of poverty on lungs.[24, 25] Poverty acts through poor nutritional status, crowding, exposure to pollutants, second-hand exposure to smoking, early respiratory infections and poor access to health care.[26] Contrariwise, the impact of high smoking prevalence in other populations (e.g. in women in some HICs) would surpass the impact of other risk factors, and, combined with genetic factors, lead to both high COPD and lung cancer mortality. Second, the magnitude of the two diseases could substantially differ by country and sex depending on differences in exposure to risk factors: occupational exposures (such as working in coal mines),[27] indoor air pollution (solid fuel for cooking is commonplace in Guatemala and the Philippines),[28] outdoor air pollution, and respiratory infections (such as tuberculosis).[29] Lastly, under-reporting —frequent in COPD—[30] and differences in coding practices may partly explain this finding.

The declines in the COPD rates in both sexes and male lung cancer rates in the highest income nations likely reflect declines in smoking prevalence. In addition, for COPD, recent progress in the diagnosis and management[31] —most COPD patients die from another cause—[32] in combination with declines in poverty[24] in fast growing economies, such as in Latin America,[18] probably also contribute. This is consistent with the result from a global study of modeled COPD mortality trends[18] that age-specific COPD mortality rates fall as country income rises.

The narrowing of the gender gap in COPD rates in half of the countries (most HICs) was previously reported in the most comprehensive population-based observational study in Europe.[16] Equally, converging male and female lung cancer rates have been described before.[4] In countries where women have been smoking as much and as long as men (e.g. USA, Denmark, and Sweden),[22] female mortality from COPD and lung cancer were very similar to male mortality. If more women pick up the habit, in particular in LMICs, the gender gap will eventually close in other countries.

While favorable declines in rates were observed in the majority of the countries under study, these two conditions still translated into a substantial number of adult deaths. Over the last ten-year period, the number of COPD and lung cancer deaths increased by 13% in men and 21% in women, and 6% and 24%, respectively —with greater increases in MICs than in HICs— as more people reached older ages. Even if those advantageous trends were to continue, the studied countries would not meet the Sustainable Development Goals (SDG) of the UN "to reduce by one third premature mortality from non-communicable diseases by 2030", for COPD and lung cancer deaths. Population growth and ageing effects would overcome the declines in mortality rates. Further, we may see extra increases in deaths because of greater exposure to risk factors such as outdoor air pollution in the growing urban populations,[26, 33] and consequences of additional declines in mortality from cardio-vascular disease and acute infection.

So what steps can be taken to curtail this future burden? First, stopping smoking remains the most important intervention affecting the development and the prognosis of COPD[6, 34] and lung cancer,[35] as well as avoiding any smoking uptake —particularly in countries in economic transition. Hence, expanding the implementation of the MPOWER measures from the WHO is essential. Second, poverty is a major risk factor for COPD in LMICs. The recent call to reduce the proportion of the population living in poverty by half by 2030 in the SDG will strengthen poverty eradication actions. Finally, COPD can be managed,[36] and the observed success in the reduction of COPD death in many countries is partly due to management improvements. Therefore, access to diagnosis and treatment must be expanded to the remaining populations.

The strengths of this study include the extensive international coverage of COPD and lung cancer mortality, using up-to-date high-quality observed data. Nevertheless, several limitations of this study should be kept in mind. Firstly, under-diagnosis and underreporting of COPD are universal,[30, 37, 38] probably more so in MICs and older people. However, the distribution of COPD ICD-10 codes in MICs is similar to that in HICs, and restricting the analysis to ages 35–69 revealed results (not shown) similar to the ones for ages 35 and older, supporting the robustness of our analysis on ages 35 and older. Secondly, expanding the analysis to the contributing causes of death mentioned on the death certificates would give a better picture of the mortality attributable to COPD and lung cancer,[39] and should be pursued. For those reasons, this study most likely underestimates the true mortality burden of both conditions, particularly in COPD. Given the country selection process, the results may not be fully extrapolated to all HICs and MICs, and the lack of data from low-income countries hinders conclusions for those countries. Additional studies on the prevalence of COPD risk factors, in Latin America, Asia, and Africa could help interpret these results, and

further studies on COPD prevalence and lung cancer incidence in LMICs could discriminate the hypotheses for the high COPD rates in some countries.

In most of the countries studied, declines in COPD and lung cancer rates were observed, except for lung cancer in females. While past smoking likely drove recent COPD mortality trends in HICs, other risk factors such as poverty, air pollution, respiratory infections, and asthma likely played an added role causing high COPD mortality in MICs in Latin America and Asia. As such, regionally tailored strategies are needed to successfully further decrease COPD mortality. COPD and lung cancer deaths can be largely reduced through the reduction of exposure to risk factors, particularly smoking, air pollution, harmful occupational exposure, respiratory infections, and through the reduction of poverty.

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JLT acquired the data, did the statistical analysis, and drafted the manuscript, with input from JS and IS. JLC, JA, JWC, and IS critically reviewed the manuscript for important intellectual content. JWC and JLT designed the study. All authors contributed to the literature review. JLT had full access to all the data in the study, and had final responsibility for the decision to submit for publication.

The authors declare no competing interests.

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SUPPLEMENTAL MATERIAL

Average Annual Percent Change

Average Annual Percent Change (AAPC) is a geometrically weighted average of the different annual percentage changes from the Joinpoint trend analysis, for which weights are equal to the length of each segment during the specified time interval.[1] Logarithmic transformation of the rates and calculation of standard errors using the binomial approximation were chosen for the Joinpoint analysis. We depicted the relationship between COPD and lung cancer rates in Europe and Latin America (for which there were sufficient countries), by sex, with a weighted linear regression and weighted pairwise correlation coefficients.

Fifty countries had a data span of at least 11 years and were included in the trend analysis. However, Portugal had no data for 2004–2006, and Trinidad and Tobago had no data for 2003. Hence logarithmic transformation of null rates could not be performed. AAPC were not computed (figures 3A and 3B), however trends for those countries were presented on figure 2.

Joinpoint regression Program version 4.2.0.2 was used.

Mean age at death

Mean age at death was obtained by multiplying the number of deaths, after age 34, in each age group, by the age at the middle of the age group (e.g. 47.5 years for age group 45–49), and by 90 for age group 85+. The sum of the products was then divided by the total number of deaths.

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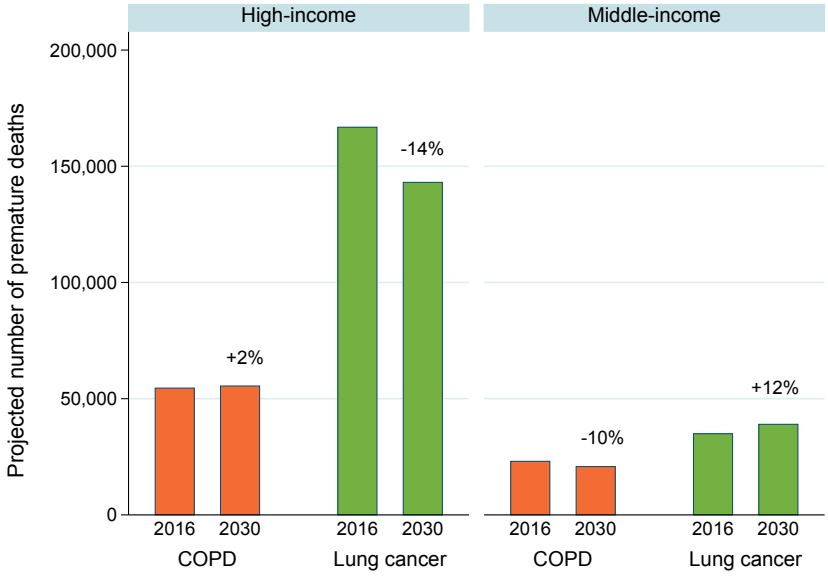
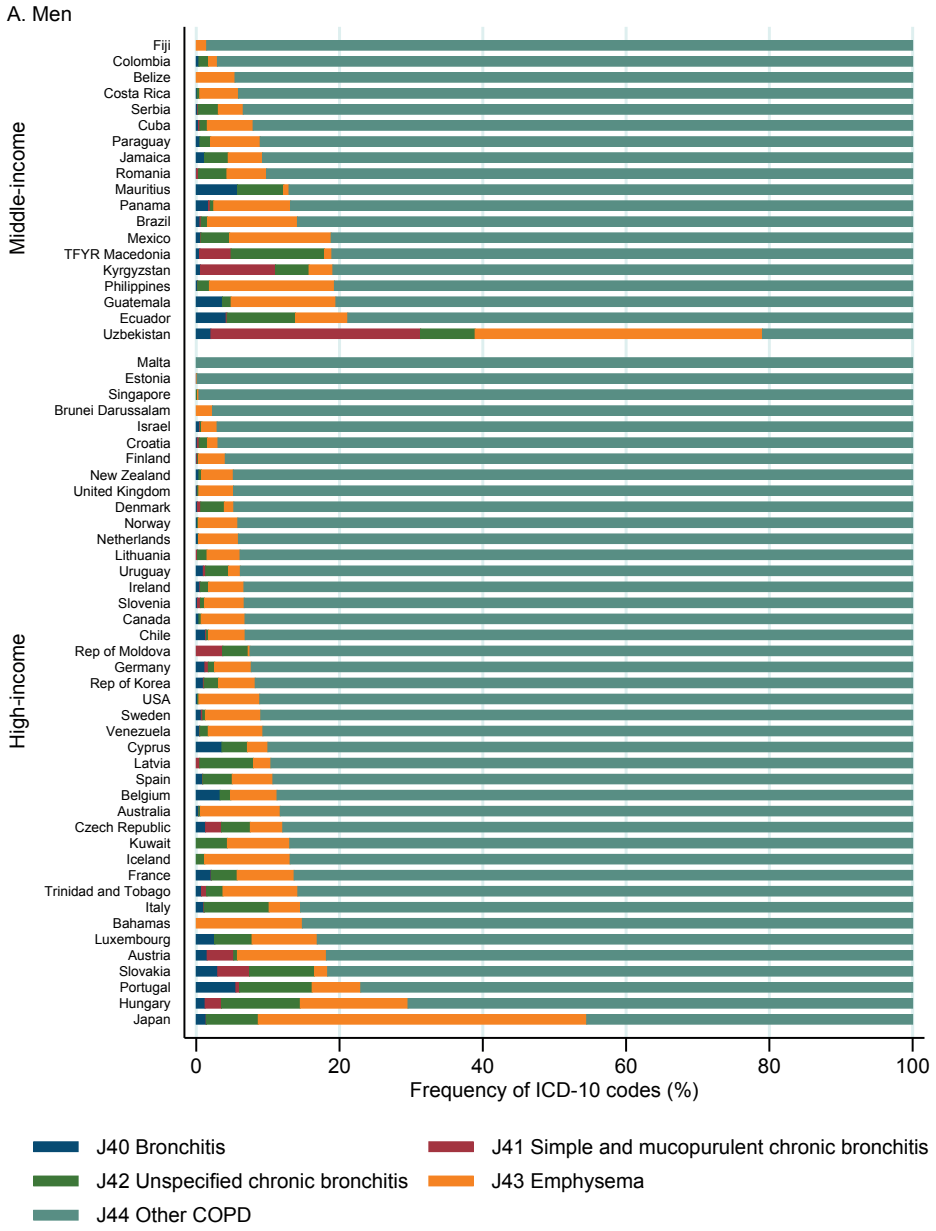
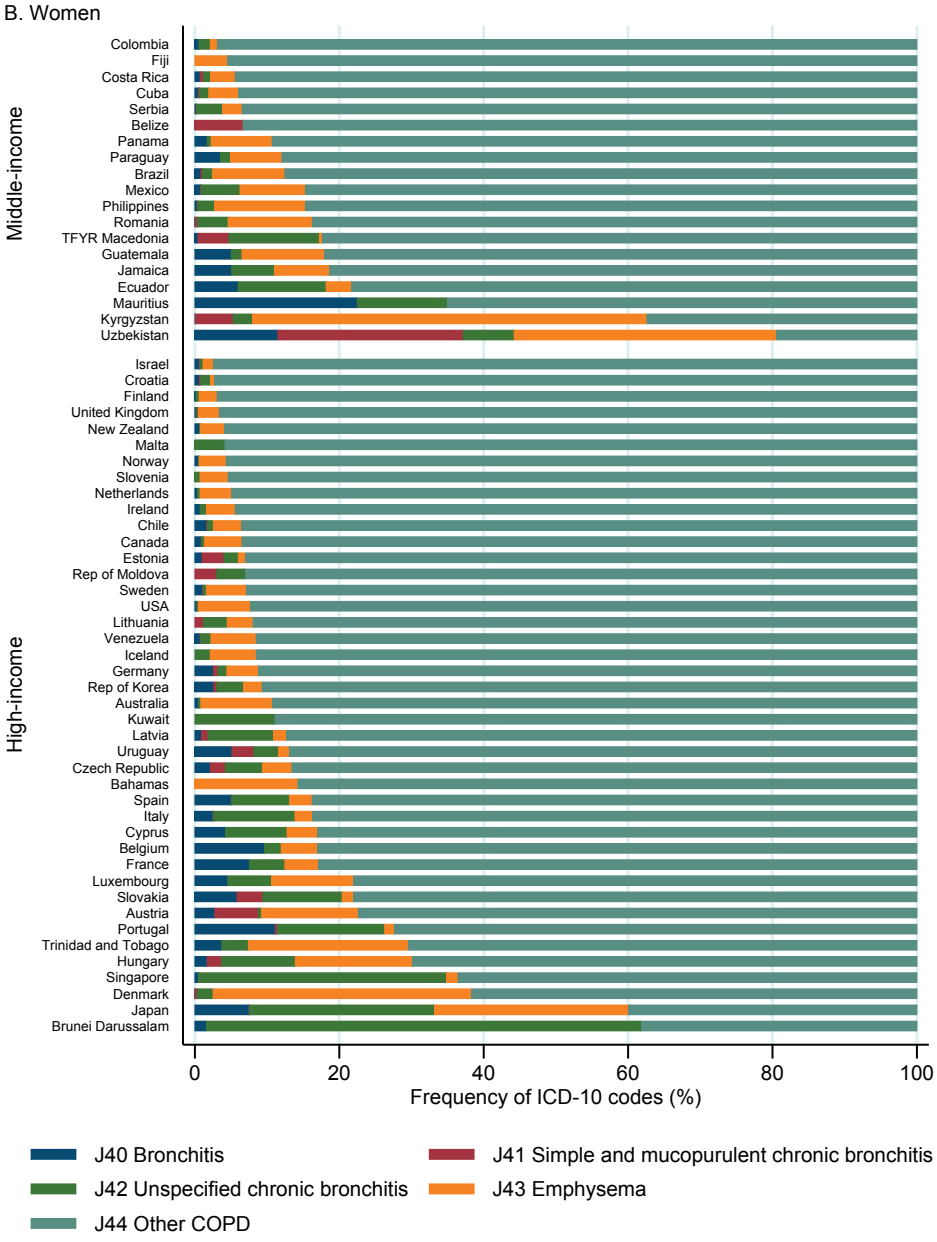


Supplemental figure 1. Number of projected chronic obstructive pulmonary disease (COPD) and lung cancer premature (ages 35–69) deaths



Supplemental figure 2A. Mean proportion of each condition within chronic obstructive pulmonary disease (COPD), over the last two years (around 2011–2013), for ages 35 and older, in men



Supplemental figure 2B. Mean proportion of each condition within chronic obstructive pulmonary disease (COPD), over the last two years (around 2011–2013), for ages 35 and older, in women

Supplement table 1A Mean age at death due to chronic obstructive pulmonary disease (COPD) and lung cancer (LC), over the last two years, in middle-income countries

		Men				Women			
		Ages 35 and above		Ages 35–69		Ages 35 and above		Ages 35–69	
Region	**Country**	**COPD**	***LC***	**COPD**	***LC***	**COPD**	***LC***	**COPD**	**LC**
Africa									
	Mauritius	63	*60*	76	*68*	62	*59*	82	*69*
Latin America and the Caribbean									
	Belize	59	*56*	72	*66*	48	*57*	73	*66*
	Brazil	61	*60*	76	*68*	61	*58*	76	*67*
	Colombia	62	*60*	79	*70*	62	*59*	81	*70*
	Costa Rica	63	*61*	82	*71*	61	*60*	84	*72*
	Cuba	62	*61*	77	*70*	62	*60*	75	*70*
	Ecuador	61	*59*	83	*73*	61	*58*	84	*71*
	Guatemala	60	*59*	78	*70*	60	*57*	78	*69*
	Jamaica	61	*58*	75	*66*	63	*58*	79	*70*
	Mexico	62	*60*	79	*71*	61	*58*	81	*70*
	Panama	61	*61*	81	*71*	62	*58*	83	*70*
	Paraguay	62	*60*	75	*69*	59	*57*	80	*68*
Asia									
	Kyrgyzstan	58	*58*	73	*64*	58	*57*	79	*65*
	Philippines	61	*59*	71	*64*	60	*58*	74	*65*
	Uzbekistan	59	*57*	69	*62*	60	*55*	72	*61*
Europe									
	Republic of Moldova	60	*59*	73	*63*	61	*58*	79	*67*
	Romania	60	*60*	75	*66*	60	*59*	80	*68*
	Serbia	62	*60*	75	*66*	62	*59*	77	*66*
	TFYR Macedonia	62	*59*	74	*65*	60	*58*	75	*64*
Oceania									
	Fiji	59	*58*	69	*66*	61	*57*	69	*63*
Middle-income		61	*60*	76	*67*	61	*59*	78	*68*

Supplement table 1B Mean age at death due to chronic obstructive pulmonary disease (COPD) and lung cancer (LC), over the last two years, in high-income countries

		Men				Women			
		Ages 35 and above		Ages 35–69		Ages 35 and above		Ages 35–69	
Region	**Country**	**COPD**	***LC***	**COPD**	***LC***	**COPD**	***LC***	**COPD**	***LC***
Latin America and the Caribbean									
	Bahamas	61	*58*	70	*64*	68	*63*	79	*69*
	Chile	63	*61*	80	*70*	63	*60*	82	*71*
	Trinidad and Tobago	59	*59*	73	*65*	60	*57*	76	*71*
	Uruguay	63	*60*	77	*69*	62	*59*	79	*69*
	Venezuela	60	*59*	75	*66*	60	*58*	78	*66*
Northern America									
	Canada	63	*62*	79	*72*	63	*61*	80	*72*
	USA	62	*61*	77	*71*	62	*61*	78	*72*
Asia									
	Brunei Darussalam	58	*59*	78	*69*	56	*59*	79	*68*
	Cyprus	63	*62*	81	*70*	63	*59*	83	*69*
	Israel	62	*60*	79	*71*	62	*60*	82	*72*
	Japan	64	*63*	83	*76*	63	*62*	86	*78*
	Kuwait	58	*59*	76	*68*	38	*63*	64	*74*
	Republic of Korea	63	*61*	79	*71*	62	*59*	83	*73*
	Singapore	62	*60*	77	*71*	64	*59*	83	*72*
Europe									
	Austria	63	*61*	77	*70*	63	*61*	81	*70*
	Belgium	63	*61*	78	*72*	62	*59*	80	*69*
	Croatia	62	*61*	77	*69*	61	*60*	81	*70*
	Czech Republic	63	*63*	74	*69*	63	*62*	78	*70*
	Denmark	63	*63*	78	*72*	63	*62*	79	*72*
	Estonia	63	*61*	75	*70*	62	*61*	77	*73*
	Finland	64	*63*	77	*72*	64	*62*	77	*73*
	France	62	*60*	80	*69*	61	*58*	84	*69*
	Germany	63	*61*	77	*71*	62	*60*	80	*71*
	Hungary	61	*61*	74	*66*	61	*60*	77	*68*
	Iceland	65	*59*	80	*72*	64	*61*	81	*73*
	Ireland	64	*61*	79	*71*	64	*61*	81	*73*
	Italy	63	*62*	83	*74*	63	*60*	86	*73*
	Latvia	61	*61*	72	*69*	61	*60*	74	*71*
	Lithuania	62	*61*	75	*69*	60	*59*	79	*73*
	Luxembourg	63	*60*	79	*72*	65	*59*	82	*69*
	Malta	64	*63*	79	*73*	61	*61*	72	*71*
	Netherlands	63	*62*	80	*72*	62	*60*	79	*69*
	Norway	64	*63*	79	*73*	64	*62*	79	*72*
	Portugal	63	*60*	80	*69*	63	*58*	83	*71*
	Slovakia	61	*61*	74	*67*	60	*60*	75	*68*
	Slovenia	63	*60*	78	*69*	60	*59*	81	*70*
	Spain	63	*61*	82	*71*	62	*58*	85	*69*
	Sweden	64	*63*	80	*73*	64	*63*	80	*73*
	United Kingdom	63	*62*	79	*74*	63	*62*	80	*74*
Oceania									
	Australia	63	*61*	79	*73*	62	*61*	80	*72*
	New Zealand	63	*62*	80	*72*	63	*60*	80	*72*
High-income		63	*61*	79	*72*	62	*61*	80	*73*
Middle- and high-income		62	*61*	78	*71*	62	*60*	79	*72*

Supplement table 2A Trends in chronic obstructive pulmonary disease (COPD) mortality rates, for 1994–2013, and over the last ten years (95% confidence interval), in men

	Trend 1		Trend 2		Trend 3		Trend 4		Last 10 years	
	Period	APC	Period	APC	Period	APC	Period	APC	Period	AAPC
Middle-income										
Latin America and the Caribbean										
Belize	2002 – 2012	0·0							2003 – 2012	0·0 (-4·4 ; 4·5)
Brazil	1996 – 2012	-3·2*							2003 – 2012	-3·2* (-3·5 ; -2·8)
Colombia	1997 – 2011	-1·1*							2002 – 2011	-1·1* (-2·0 ; -0·3)
Costa Rica	1997 – 2012	-4·5*							2003 – 2012	-4·5* (-5·2 ; -3·7)
Cuba	2001 – 2012	-0·5							2003 – 2012	-0·5 (-1·7 ; 0·7)
Ecuador	1997 – 2012	0·1							2003 – 2012	0·1 (-0·8 ; 1·0)
Mexico	1998 – 2012	-1·4*							2003 – 2012	-1·4* (-2·0 ; -0·7)
Panama	1998 – 2012	-4·9*							2003 – 2012	-4·9* (-5·9 ; -3·9)
Paraguay	1996 – 2012	6·8*							2003 – 2012	6·8* (5·0 ; 8·7)
Asia										
Kyrgyzstan	2000 – 2003	7·6	2003 –2013	-8·1*					2004 – 2013	-8·1* (-9·9 ; -6·1)
Europe										
Republic of Moldova	1996 – 2003	2·4	2003 – 2013	-7·1*					2004 – 2013	-7·1* (-9·4 ; -4·8)
Romania	1999 – 2012	-2·3*							2003 – 2012	-2·3* (-2·9 ; -1·6)
Serbia	1998 – 2013	-0·6							2004 – 2013	-0·6 (-1·4 ; 0·2)
High-income										
Latin America and the Caribbean										
Bahamas	1999 – 2010	-0·9							2001 – 2010	-0·9 (-5·7 ; 4·2)
Chile	1997 – 2012	-1·0							2003 – 2012	-1·0 (-2·3 ; 0·4)
Uruguay	1997 – 2010	-1·8*							2001 – 2010	-1·8* (-3·0 ; -0·6)
Venezuela	1996 – 2009	-0·4							2000 – 2009	-0·4 (-1·4 ; 0·7)
Northern America										
Canada	2000 – 2011	-3·2*							2002 – 2011	-3·2* (-3·6 ; -2·7)
USA	1999 – 2013	-1·3*							2004 – 2013	-1·3* (-1·7 ; -0·9)

Supplement table 2A Trends in chronic obstructive pulmonary disease (COPD) mortality rates, for 1994–2013, and over the last ten years (95% confidence interval), in men (continued)

	Trend 1		Trend 2		Trend 3		Trend 4		Last 10 years	
	Period	APC	Period	APC	Period	APC	Period	APC	Period	AAPC
Asia										
Israel	1998 – 2012	-2·6*							2003 – 2012	-2·6* (-3·6 ; -1·5)
Japan	1995 – 2013	-2·5*							2004 – 2013	-2·5* (-2·9 ; -2·1)
Republic of Korea	1995 – 1998	-2·5	1998 – 2002	20·6*	2002 – 2006	-8·1*	2006 – 2012	-3·2*	2003 – 2012	-4·8* (-7·3 ; -2·3)
Europe										
Austria	2002 – 2013	-2·7*							2004 – 2013	-2·7* (-4·1 ; -1·4)
Belgium	1998 – 2012	-3·8*							2003 – 2012	-3·8* (-4·3 ; -3·4)
Croatia	1995 – 2013	0·8							2004 – 2013	0·8 (-0·2 ; 1·8)
Czech Republic	1994 – 2013	1·6*							2004 – 2013	1·6* (0·5 ; 2·6)
Denmark	1994 – 1999	3·2*	1999 – 2005	-5·3*	2005 – 2012	-0·9			2003 – 2012	-1·9* (-3·7 ; -0·1)
Estonia	1997 – 2012	-0·1							2003 – 2012	-0·1 (-1·5 ; 1·4)
Finland	1996 – 2013	-3·2*							2004 – 2013	-3·2* (-3·7 ; -2·8)
France	2000 – 2011	-2·4*							2002 – 2011	-2·4* (-3·2 ; -1·5)
Germany	1998 – 2007	-2·7*	2007 – 2013	0·8					2004 – 2013	-0·3 (-1·9 ; 1·2)
Hungary	1996 – 2013	0·2							2004 – 2013	0·2 (-0·8 ; 1·2)
Iceland	1996 – 2009	0·1							2000 – 2009	0·1 (-1·7 ; 1·9)
Latvia	1996 – 2012	-0·4							2003 – 2012	-0·4 (-1·5 ; 0·8)
Lithuania	1998 – 2007	-1·1*	2007 – 2012	-8·1*					2003 – 2012	-5·1* (-6·4 ; -3·7)
Luxembourg	1998 – 2013	-3·5*							2004 – 2013	-3·5* (-4·5 ; -2·5)
Malta	1995 – 2006	-1·6	2006 – 2012	-13·1*					2003 – 2012	-9·4* (-15·8 ; -2·5)
Netherlands	1996 – 2013	-4·1*							2004 – 2013	-4·1* (-4·5 ; -3·6)
Norway	1996 – 2008	1·1*	2008 – 2013	-2·0*					2004 – 2013	-0·7 (-1·6 ; 0·3)
Slovakia	1994 – 1999	22·0*	1999 – 2010	-1·9					2001 – 2010	-1·9 (-4·0 ; 0·3)
Slovenia	1997 – 1999	5·9	1999 – 2010	-8·5*					2001 – 2010	-8·5* (-10·5 ; -6·5)
Spain	1999 – 2013	-4·1*							2004 – 2013	-4·1* (-5·0 ; -3·3)
Sweden	1997 – 2013	-1·7*							2004 – 2013	-1·7* (-2·0 ; -1·4)
United Kingdom	2001 – 2010	-2·9*	2010 – 2013	2·0					2004 – 2013	-1·3 (-2·9 ; 0·3)
Oceania										
Australia	1998 – 2006	-5·8*	2006 – 2011	-1·6					2001 – 2011	-3·7* (-4·8 ; -2·6)
New Zealand	2000 – 2011	-4·6*							2002 – 2011	-4·6* (-5·8 ; -3·5)

APC: Annual percent change. AAPC: Average annual percent change. * indicates the APC or AAPC is statistically different from zero.

Supplement table 2B Trends in chronic obstructive pulmonary disease (COPD) mortality rates, for 1994–2013, and over the last ten years (95% confidence interval), in women

	Trend 1		Trend 2		Trend 3		Trend 4		Last 10 years	
	Period	APC	Period	APC	Period	APC	Period	APC	Period	AAPC
Middle-income										
Latin America and the Caribbean										
Belize	2002 – 2012	-4·1							2003 – 2012	-4·1 (-12·2 ; 4·8)
Brazil	1996 – 2012	-2·1*							2003 – 2012	-2·1* (-2·4 ; -1·8)
Colombia	1997 – 2011	-0·9							2002 – 2011	-0·9 (-1·8 ; 0·0)
Costa Rica	1997 – 2012	-5·0*							2003 – 2012	-5·0* (-6·3 ; -3·7)
Cuba	2001 – 2012	0·0							2003 – 2012	0·0 (-1·5 ; 1·6)
Ecuador	1997 – 2012	0·6							2003 – 2012	0·6 (-0·3 ; 1·6)
Mexico	1998 – 2012	-0·6							2003 – 2012	-0·6 (-1·3 ; 0·1)
Panama	1998 – 2012	-3·3*							2003 – 2012	-3·3* (-4·7 ; -1·9)
Paraguay	1996 – 2012	0·2							2003 – 2012	0·2 (-1·9 ; 2·2)
Asia										
Kyrgyzstan	2000 – 2003	6·2	2003 – 2013	-8·1*					2004 – 2013	-8·1* (-9·7 ; -6·5)
Europe										
Republic of Moldova	1996 – 2003	2·6	2003 – 2013	-7·8*					2004 – 2013	-7·8* (-10·4 ; -5·2)
Romania	1999 – 2012	-4·9*							2003 – 2012	-4·9* (-5·6 ; -4·1)
Serbia	1998 – 2013	-0·1							2004 – 2013	-0·1 (-0·9 ; 0·7)
High-income										
Latin America and the Caribbean										
Bahamas	1999 – 2010	-0·4							2001 – 2010	-0·4 (-9·3 ; 9·5)
Chile	1997 – 2012	-0·9							2003 – 2012	-0·9 (-2·3 ; 0·4)
Uruguay	1997 – 2010	0·3							2001 – 2010	0·3 (-1·0 ; 1·7)
Venezuela	1996 – 2009	-0·4							2000 – 2009	-0·4 (-1·5 ; 0·8)

Supplement table 2B Trends in chronic obstructive pulmonary disease (COPD) mortality rates, for 1994–2013, and over the last ten years (95% confidence interval), in women (continued)

	Trend 1		Trend 2		Trend 3		Trend 4		Last 10 years	
	Period	APC	Period	APC	Period	APC	Period	APC	Period	AAPC
Northern America										
Canada	2000 – 2011	-0·4							2002 – 2011	-0·4 (-0·8 ; 0·0)
USA	1999 – 2013	0·1							2004 – 2013	0·1 (-0·2 ; 0·5)
Asia										
Israel	1998 – 2012	-3·1*							2003 – 2012	-3·1* (-4·6 ; -1·7)
Japan	1995 – 1997	-11·1*	1997 – 2013	-4·6*					2004 – 2013	-4·6* (-5·0 ; -4·2)
Republic of Korea	1995 – 1999	-0·7	1999 – 2002	21·8*	2002 – 2005	-16·4*	2005 – 2012	-4·5*	2003 – 2012	-7·3* (-10·3 ; -4·1)
Europe										
Austria	2002 – 2013	-0·6							2004 – 2013	-0·6 (-2·0 ; 0·9)
Belgium	1998 – 2012	0·4							2003 – 2012	0·4 (-0·5 ; 1·3)
Croatia	1995 – 2013	2·9*							2004 – 2013	2·9* (1·9 ; 4·0)
Czech Republic	1994 – 2013	3·5*							2004 – 2013	3·5* (2·3 ; 4·7)
Denmark	1994 – 2000	6·1*	2000 – 2004	-7·0*	2004 – 2012	-0·5			2003 – 2012	-1·2* (-2·2 ; -0·2)
Estonia	1997 – 2012	-1·3							2003 – 2012	-1·3 (-3·2 ; 0·6)
Finland	1996 – 2013	0·0							2004 – 2013	0·0 (-0·8 ; 0·8)
France	2000 – 2011	-0·4							2002 – 2011	-0·4 (-1·4 ; 0·6)
Germany	1998 – 2007	0·9	2007 – 2013	4·7*					2004 – 2013	3·4* (2·1 ; 4·8)
Hungary	1996 – 2013	1·8*							2004 – 2013	1·8* (0·8 ; 2·9)
Iceland	1996 – 2009	0·8							2000 – 2009	0·8 (-1·3 ; 3·0)
Latvia	1996 – 2012	-3·6*							2003 – 2012	-3·6* (-5·0 ; -2·2)
Lithuania	1998 – 2012	-5·5*							2003 – 2012	-5·5* (-7·0 ; -4·1)
Luxembourg	1998 – 2013	2·5*							2004 – 2013	2·5* (0·5 ; 4·5)
Malta	1995 – 2012	-4·1*							2003 – 2012	-4·1* (-7·3 ; -0·9)

Supplement table 2B Trends in chronic obstructive pulmonary disease (COPD) mortality rates, for 1994–2013, and over the last ten years (95% confidence interval), in women (continued)

	Trend 1		Trend 2		Trend 3		Trend 4		Last 10 years	
	Period	APC	Period	APC	Period	APC	Period	APC	Period	AAPC
Netherlands	1996 – 2013	0·3							2004 – 2013	0·3 (-0·2 ; 0·8)
Norway	1996 – 2013	2·5*							2004 – 2013	2·5* (1·9 ; 3·1)
Slovakia	1994 – 1999	18·8*	1999 – 2010	-2·4					2001 – 2010	-2·4 (-5·0 ; 0·2)
Slovenia	1997 – 2010	-6·0*							2001 – 2010	-6·0* (-7·8 ; -4·0)
Spain	1999 – 2001	-15·2*	2001 – 2013	-3·5*					2004 – 2013	-3·5* (-4·8 ; -2·1)
Sweden	1997 – 2002	4·5*	2002 – 2013	0·6					2004 – 2013	0·6 (-0·3 ; 1·4)
United Kingdom	2001 – 2013	-0·1							2004 – 2013	-0·1 (-0·9 ; 0·6)
Oceania										
Australia	1998 – 2011	-2·0*							2001 – 2011	-2·0* (-2·5 ; -1·4)
New Zealand	2000 – 2011	-2·1*							2002 – 2011	-2·1* (-3·6 ; -0·6)

APC: Annual percent change. AAPC: Average annual percent change. * indicates the APC or AAPC is statistically different from zero.

Supplement table 3A Trends in lung cancer mortality rates, for 1994–2013, and over the last ten years (95% confidence interval), in men

	Trend 1		Trend 2		Trend 3		Trend 4		Last 10 years	
	Period	APC	Period	APC	Period	APC	Period	APC	Period	AAPC
Middle-income										
Latin America and the Caribbean										
Belize	2002 – 2012	-6·6*							2003 – 2012	-6.6* (-11.9 ; -1.1)
Brazil	1996 – 2008	-0·8*	2008 – 2012	-2·0*					2003 – 2012	-1.4* (-1.9 ; -0.9)
Colombia	1997 – 2005	0·9*	2005 – 2011	-2·9*					2002 – 2011	-1.6* (-2.3 ; -1.0)
Costa Rica	1997 – 2009	-4·4*	2009 – 2012	5·3					2003 – 2012	-1.3 (-5.0 ; 2.6)
Cuba	2001 – 2008	0·7	2008 – 2012	-2·9*					2003 – 2012	-0.9 (-2.1 ; 0.2)
Ecuador	1997 – 2012	-0·4							2003 – 2012	-0.4 (-1.0 ; 0.1)
Mexico	1998 – 2005	-1·9*	2005 – 2012	-5·9*					2003 – 2012	-5.0* (-5.6 ; -4.4)
Panama	1998 – 2012	-1·3*							2003 – 2012	-1.3* (-2.3 ; -0.4)
Paraguay	1996 – 2012	1·3*							2003 – 2012	1.3* (0.5 ; 2.2)
Asia										
Kyrgyzstan	2000 – 2013	-0·6							2004 – 2013	-0.6 (-1.6 ; 0.4)
Europe										
Republic of Moldova	1996 – 1999	-7·4*	1999 – 2013	0·3					2004 – 2013	0.3 (-0.2 ; 0.7)
Romania	1999 – 2012	0·4*							2003 – 2012	0.4* (0.2 ; 0.7)
Serbia	1998 – 2008	2·0*	2008 – 2013	-1·5*					2004 – 2013	0.1 (-0.7 ; 0.8)
High-income										
Latin America and the Caribbean										
Bahamas	1999 – 2010	-1·3							2001 – 2010	-1.3 (-5.7 ; 3.3)
Chile	1997 – 2012	-1·0*							2003 – 2012	-1.0* (-1.4 ; -0.7)
Uruguay	1997 – 2010	-1·2*							2001 – 2010	-1.2* (-1.6 ; -0.8)
Venezuela	1996 – 2009	0·1							2000 – 2009	0.1 (-0.3 ; 0.4)

Supplement table 3A Trends in lung cancer mortality rates, for 1994–2013, and over the last ten years (95% confidence interval), in men (continued)

	Trend 1		Trend 2		Trend 3		Trend 4		Last 10 years	
	Period	APC	Period	APC	Period	APC	Period	APC	Period	AAPC
Northern America										
Canada	2000 – 2002	-0·7	2002 – 2011	-2·8*					2002 – 2011	-2.8* (-3.1 ; -2.5)
USA	1999 – 2005	-2·3*	2005 – 2013	-3·5*					2004 – 2013	-3.3* (-3.4 ; -3.2)
Asia										
Israel	1998 – 2012	-0·6*							2003 – 2012	-0.6* (-1.1 ; -0.1)
Japan	1995 – 2013	-0·9*							2004 – 2013	-0.9* (-1.0 ; -0.8)
Republic of Korea	1995 – 2002	1·8*	2002 – 2012	-2·4*					2003 – 2012	-2.4* (-2.9 ; -1.9)
Europe										
Austria	2002 – 2013	-1·9*							2004 – 2013	-1.9* (-2.2 ; -1.6)
Belgium	1998 – 2012	-2·4*							2003 – 2012	-2.4* (-2.7 ; -2.1)
Croatia	1995 – 1998	8·2*	1998 – 2002	-6·2*	2002 - 2013	-1.5*			2004 – 2013	-1.5* (-2.2 ; -0.8)
Czech Republic	1994 – 2004	-2·4*	2004 – 2013	-3·7*					2004 – 2013	-3.7* (-4.4 ; -3.1)
Denmark	1994 – 2012	-2·3*							2003 – 2012	-2.3* (-2.6 ; -2.0)
Estonia	1997 – 2012	-2·0*							2003 – 2012	-2.0* (-2.6 ; -1.5)
Finland	1996 – 2002	-3·7*	2002 – 2013	-2·0*					2004 – 2013	-2.0* (-2.5 ; -1.5)
France	2000 – 2011	-1·2*							2002 – 2011	-1.2* (-1.4 ; -1.0)
Germany	1998 – 2010	-2·2*	2010 – 2013	-0·5					2004 – 2013	-1.7* (-2.2 ; -1.1)
Hungary	1996 – 2013	-1·3*							2004 – 2013	-1.3* (-1.6 ; -1.1)
Iceland	1996 – 2009	-1·9*							2000 – 2009	-1.9* (-3.6 ; -0.1)
Latvia	1996 – 2012	-1·2*							2003 – 2012	-1.2* (-1.7 ; -0.8)
Lithuania	1998 – 2012	-1·5*							2003 – 2012	-1.5* (-1.9 ; -1.1)
Luxembourg	1998 – 2013	-3·2*							2004 – 2013	-3.2* (-4.0 ; -2.3)
Malta	1995 – 2012	-2·3*							2003 – 2012	-2.3* (-3.2 ; -1.4)

Supplement table 3A Trends in lung cancer mortality rates, for 1994–2013, and over the last ten years (95% confidence interval), in men (continued)

	Trend 1		Trend 2		Trend 3		Trend 4		Last 10 years	
	Period	APC	Period	APC	Period	APC	Period	APC	Period	AAPC
Netherlands	1996 – 2013	-2·8*							2004 – 2013	-2.8* (-3.0 ; -2.6)
Norway	1996 – 2003	-0·1	2003 – 2013	-1·9*					2004 – 2013	-1.9* (-2.6 ; -1.3)
Slovakia	1994 – 2010	-2·7*							2001 – 2010	-2.7* (-3.1 ; -2.3)
Slovenia	1997 – 2010	-1·9*							2001 – 2010	-1.9* (-2.3 ; -1.4)
Spain	1999 – 2013	-1·4*							2004 – 2013	-1.4* (-1.5 ; -1.2)
Sweden	1997 – 2013	-1·6*							2004 – 2013	-1.6* (-1.9 ; -1.3)
United Kingdom	2001 – 2013	-2·2*							2004 – 2013	-2.2* (-2.4 ; -2.1)
Oceania										
Australia	1998 – 2011	-2·6*							2001 – 2011	-2.6* (-3.0 ; -2.3)
New Zealand	2000 – 2011	-2·6*							2002 – 2011	-2.6* (-3.3 ; -2.0)

APC: Annual percent change. AAPC: Average annual percent change. * indicates the APC or AAPC is statistically different from zero.

Supplement table 3B Trends in lung cancer mortality rates, for 1994–2013, and over the last ten years (95% confidence interval), in women

	Trend 1		Trend 2		Trend 3		Trend 4		Last 10 years	
	Period	APC	Period	APC	Period	APC	Period	APC	Period	AAPC
Middle-income										
Latin America and the Caribbean										
Belize	2002 – 2012	-4·5							2003 – 2012	-4.5 (-15.1 ; 7.3)
Brazil	1996 – 2012	2·2*							2003 – 2012	2.2* (2.0 ; 2.4)
Colombia	1997 – 2005	1·2*	2005 – 2011	-2·4*					2002 – 2011	-1.2* (-2.3 ; -0.1)
Costa Rica	1997 – 2012	-3·4*							2003 – 2012	-3.4* (-4.9 ; -1.9)
Cuba	2001 – 2009	2·6*	2009 – 2012	-2·8*					2003 – 2012	0.8 (0.0 ; 1.6)
Ecuador	1997 – 2012	0·8							2003 – 2012	0.8 (-0.1 ; 1.7)
Mexico	1998 – 2012	-2·1*							2003 – 2012	-2.1* (-2.5 ; -1.7)
Panama	1998 – 2012	-0·6							2003 – 2012	-0.6 (-2.9 ; 1.8)
Paraguay	1996 – 2012	2·7*							2003 – 2012	2.7* (1.4 ; 4.0)
Asia										
Kyrgyzstan	2000 – 2013	-0·9							2004 – 2013	-0.9 (-2.3 ; 0.5)
Europe										
Republic of Moldova	1996 – 2013	-0·2							2004 – 2013	-0.2 (-0.8 ; 0.4)
Romania	1999 – 2012	1·8*							2003 – 2012	1.8* (1.4 ; 2.3)
Serbia	1998 – 2013	3·9*							2004 – 2013	3.9* (3.4 ; 4.4)
High-income										
Latin America and the Caribbean										
Bahamas	1999 – 2010	-1·7							2001 – 2010	-1.7 (-6.0 ; 2.7)
Chile	1997 – 2012	1·2*							2003 – 2012	1.2* (0.8 ; 1.7)
Uruguay	1997 – 2010	3·9*							2001 – 2010	3.9* (2.3 ; 5.5)
Venezuela	1996 – 2009	0·9*							2000 – 2009	0.9* (0.4 ; 1.4)

Supplement table 3B Trends in lung cancer mortality rates, for 1994–2013, and over the last ten years (95% confidence interval), in women (continued)

	Trend 1		Trend 2		Trend 3		Trend 4		Last 10 years	
	Period	APC	Period	APC	Period	APC	Period	APC	Period	AAPC
Northern America										
Canada	2000 – 2006	0·8*	2006 – 2011	-1·3*					2002 – 2011	-0.4 (-0.8 ; 0.0)
USA	1999 – 2002	0·1	2002 – 2007	-1·2*	2007 – 2013	-2·5*			2004 – 2013	-2.1* (-2.3 ; -1.9)
Asia										
Israel	1998 – 2012	1·3*							2003 – 2012	1.3* (0.6 ; 2.0)
Japan	1995 – 2000	0·0	2000 – 2003	-3·3*	2003 – 2006	1·4	2006 – 2013	-0·5*	2004 – 2013	-0.1 (-0.6 ; 0.5)
Republic of Korea	1995 – 2002	1·7*	2002 – 2012	-1·3*					2003 – 2012	-1.3* (-1.9 ; -0.8)
Europe										
Austria	2002 – 2013	2·0*							2004 – 2013	2.0* (1.2 ; 2.8)
Belgium	1998 – 2012	3·5*							2003 – 2012	3.5* (3.0 ; 4.0)
Croatia	1995 – 2013	2·2*							2004 – 2013	2.2* (1.6 ; 2.8)
Czech Republic	1994 – 2013	1·1*							2004 – 2013	1.1* (0.8 ; 1.3)
Denmark	1994 – 2012	-0·1							2003 – 2012	-0.1 (-0.4 ; 0.3)
Estonia	1997 – 2012	0·6							2003 – 2012	0.6 (-0.4 ; 1.6)
Finland	1996 – 2013	2·1*							2004 – 2013	2.1* (1.8 ; 2.5)
France	2000 – 2005	6·1*	2005 – 2011	2·7*					2002 – 2011	3.8* (3.2 ; 4.4)
Germany	1998 – 2013	2·7*							2004 – 2013	2.7* (2.5 ; 2.8)
Hungary	1996 – 2013	2·3*							2004 – 2013	2.3* (2.0 ; 2.7)
Iceland	1996 – 2009	0·1							2000 – 2009	0.1 (-0.7 ; 0.9)
Latvia	1996 – 2012	0·8							2003 – 2012	0.8 (0.0 ; 1.7)
Lithuania	1998 – 2012	0·6							2003 – 2012	0.6 (-0.7 ; 2.0)
Luxembourg	1998 – 2013	1·4							2004 – 2013	1.4 (-1.2 ; 4.1)
Malta	1995 – 2012	1·9							2003 – 2012	1.9 (-0.2 ; 4.1)

Supplement table 3B Trends in lung cancer mortality rates, for 1994–2013, and over the last ten years (95% confidence interval), in women (continued)

	Trend 1		Trend 2		Trend 3		Trend 4		Last 10 years	
	Period	APC	Period	APC	Period	APC	Period	APC	Period	AAPC
Netherlands	1996 – 2007	4·1*	2007 – 2013	0·8					2004 – 2013	1.9* (1.4 ; 2.4)
Norway	1996 – 2013	1·2*							2004 – 2013	1.2* (0.7 ; 1.8)
Slovakia	1994 – 2007	1·2*	2007 – 2010	7·2*					2001 – 2010	3.2* (1.2 ; 5.1)
Slovenia	1997 – 2010	2·2*							2001 – 2010	2.2* (1.3 ; 3.0)
Spain	1999 – 2013	4·7*							2004 – 2013	4.7* (4.5 ; 5.0)
Sweden	1997 – 2005	3·3*	2005 – 2013	-0·8					2004 – 2013	-0.4 (-1.1 ; 0.4)
United Kingdom	2001 – 2008	1·0*	2008 – 2013	-0·5					2004 – 2013	0.2 (-0.3 ; 0.6)
Oceania										
Australia	1998 – 2011	0·5*							2001 – 2011	0.5* (0.2 ; 0.9)
New Zealand	2000 – 2011	0·3							2002 – 2011	0.3 (-0.7 ; 1.2)

APC: Annual percent change. AAPC: Average annual percent change. * indicates the APC or AAPC is statistically different from zero.

5

Discussion and summary

5.1 GENERAL DISCUSSION

When looking at the current burden of smoking-related diseases, we actually see the consequences of past smoking exposure, with a particularly long lag time of several decades for smoking-related cancers and COPD. Taking up and sustaining the habit of smoking is not only a personal choice but also the result of multiple factors including influences of tobacco industry marketing, the addictive nature of tobacco, social norms, and tobacco control (or lack thereof). Therefore, smoking-related diseases, such as cancer and COPD, are now more frequent in some countries (in Bulgaria rather than in Sweden),[1] in men than in women, in regions where tobacco is grown (the South of the US) or transformed (the southeastern part of the Netherlands).[2] Of course, tobacco marketing strategies and cigarettes change over time, and so do social norms —it is now acceptable for women to smoke in industrialized countries.[3] In addition, as trade agreements opened new markets in developing countries, tobacco production and manufacturing shifted to these regions.

The previous chapters contrasted the current burden of smoking-related cancer and COPD between (sub-)populations, and its evolution over time. In this discussion, the main findings and their interpretation are presented in the first part, followed by the limitations of studies in the second part. The third part describes the public health implications of this elevated burden, followed by the fourth part, which gives recommendations on how to reduce it.

MAIN EPIDEMIOLOGIC FINDINGS

Studies performed at IARC, under the supervision of Dr. Freddie Bray

What is happening in the gender gap in smoking-related cancers?

- In which populations is the gender-specific incidence of smoking-related cancer still increasing in Europe?

Over the 1988–2007 period, in Europe, trends varied among the four major cancers related to tobacco smoking: cancer of the lung, oral cavity and pharynx, larynx, and esophagus (chapter 2.1).

In most of the countries, male lung cancer incidence rates had decreased since the early 1990s. Increases in male lung cancer incidence were only observed in middle-aged French (35–64 years old) and in older Bulgarians (65–74 years old), a sign that the

lung cancer epidemic was still on its rise in France while fading in Bulgaria. In contrast, over the same period, lung cancer incidence continued to increase among middle-aged women in 19 out of the 26 countries, and in nine countries in the older female populations (Table 1). Since 2005 however, signs of stabilization were detected in women aged 35–74 in central and eastern Europe, northern Europe, Switzerland and Malta. As for the other smoking related cancers such as oral cavity and pharyngeal cancer, incidence rate only increased in few countries among men (in the Czech Republic, Denmark [both in middle ages only], in Slovakia [among older ages only], UK, and Germany). Incidence also increased in these countries among women, as well as in Ireland, Norway (in older ages), and in the Netherlands in middle-aged populations. Bulgarian men was the only group with increasing laryngeal cancer incidence. Among women, the rates were very low, hence conclusion was difficult to draw. Finally, surges in esophageal cancer incidence in men were generally restricted to the northern half of Europe, whereas in women, increases appeared to occur in most countries in western, central and eastern Europe.

Table 1. Direction of the average annual percent change in incidence over 1998–2007, sorted by the direction of the trend in lung cancer incidence in men, then women

Country	***Lung***		***Oral cavity***		***Larynx***		***Esophagus***	
	Men	Women	Men	Women	Men	Women	Men	Women
France	↗	↗	↘	↔	↘	↔	↘	↔
Czech Republic	↘	↗	↗	↗	↔	↔	↔	↔
United Kingdom	↘	↗	↗	↗	↔	↘	↗	↘
Germany	↘	↗	↗	↗	↔	↔	↗	↗
Poland	↘	↗	↘	↔	↘	↔	↔	↔
Spain	↘	↗	↘	↔	↘	↔	↘	↔
The Netherlands	↘	↗	↔	↗	↘	↔	↗	↗
Slovakia	↘	↗	↔	↗	↔	↔	↔	↔
Austria	↘	↗	↔	↔	↘	↔	↗	↔
Belarus	↘	↗	↔	↔	↔	↔	↗	↔
Russian Federation	↘	↔	↘	↔	↘	↔	↘	↘
Italy	↘	↔	↘	↔	↘	↔	↘	↔
Estonia	↘	↔	↘	↔	↔	↔	↔	↔
Latvia	↘	↔	↔	↔	↔	↔	↔	↔
Lithuania	↘	↔	↔	↔	↔	↔	↔	↔
Denmark	↔	↗	↗	↗	↔	↔	↔	↗
Croatia	↔	↗	↘	↔	↘	↔	↘	↔
Slovenia	↔	↗	↘	↔	↔	↔	↔	↔
Finland	↔	↗	↔	↗	↔	↔	↗	↔
Ireland	↔	↗	↔	↗	↔	↔	↔	↔
Bulgaria	↔	↗	↔	↔	↗	↔	↔	↔
Norway	↔	↗	↔	↔	↔	↔	↔	↔
Sweden	↔	↗	↔	↔	↔	↔	↔	↔
Malta	↔	↗	↔	↔	↔	↔	↔	↔
Switzerland	↔	↔	↘	↔	↘	↔	↔	↔
Iceland	↔	↔	↔	↔	↘	↔	↔	↗

Note: Changes in incidence trends for lung cancer are for ages 35–64 years, and ages 35-74 for the other cancers.

Incidence generally declined among men in three cancers (lung, oral cavity and pharynx, and larynx), while increased in women in two cancers (lung and oral cavity and pharynx). As a consequence, the gender gap in these smoking-related cancers narrowed in Europe, the mark of the earlier declines in smoking prevalence among men contrasting with stable or increasing prevalence among women. The closing of the gender gap was most evident in lung cancer because of the high smoking-attributable fraction (≥80%).[4] The fraction is as high in laryngeal cancer as in lung cancer, but the very low number of new cases in women hinders tangible conclusions on the direction of the trends. Differences in the prevalence and trends of additional risk factors —in particular obesity and alcohol consumption— may explain the apparent absence of convergence of male and female cancer incidence in some countries and in esophageal cancer incidence.

- How does cigarette type influence lung cancer histology in men and in women?

Chapter 2.2 examined the lung cancer epidemic in eleven high-income countries, over the 1973–2002 period, by analyzing trends in new lung cancer cases by histological subtypes: adenocarcinoma (AdC), squamous cell carcinoma (SCC), small cell carcinoma, large cell carcinoma, and other subtypes combined. It appeared that within the overall declining trends in lung cancer incidence in male, different trends emerged at the subtype level. SCC —the most frequently diagnosed subtype among men at the beginning of the study— rates declined over time and were ultimately exceeded by AdC rates in most countries starting around the 1990s. In contrast, among women, AdC was the dominant subtype throughout the whole period, and rates of AdC increased over time. As a consequence, at the end of the study period, the distribution of the cases' subtypes in men was more similar to the distribution in women. The adoption of new cigarettes, first by women and later by men, around the 1950s (filtered cigarettes with lower nicotine and tar contents, less polycyclic aromatic hydrocarbons and more tobacco-specific N-nitrosamines) advertised as "safer cigarettes" (mild/light) probably explains the gender differences in the distribution of subtypes.[5]

In several high-income countries, the gender gap in smoking-related cancer incidence is narrowing because the younger female cohorts have smoked (age at initiation, type of cigarette smoked, quitting rates and total smoking years) more like their male counterparts than previous generations. While declines in smoking-related cancer incidence in men —as a result of tobacco control and rising awareness of the harms of tobacco— are welcome, in most of high-income countries, the number of new cases in women is still growing. This means that, in the past, tobacco control has, to a large extent, failed to prevent smoking initiation and to support smoking cessation among women.

Studies performed at the American Cancer Society, under the supervision of Dr. Ahmedin Jemal

What is the burden of smoking-related cancers in the US?

- Do non-Hispanic Blacks have a higher cancer burden and smoking-related cancer burden than other racial/ethnic groups in the US?

Chapter 3.1 described the burden of cancer in the US in 2011. DALY rates for all cancers combined were higher in non-Hispanic Blacks than in any other racial/ethnic group (30% higher than in non-Hispanic Whites, 80% higher than in Hispanics, and 100% higher than in non-Hispanic Asians). Chapter 3.2 examined the smoking-attributable fraction of the burden of 12 smoking-related cancers. The population attributable fraction (PAF) was substantial in every racial/ethnic group. It was highest in non-Hispanic Whites and non-Hispanic Blacks (27% and 28% of all DALYs due to cancer, respectively). The fraction was about two-thirds lower among non-Hispanic Asians and Hispanics (both at 19% of DALYs). Within each race/ethnicity, the burden was always higher in men than in women. Those differences in the smoking-attributable fraction of the cancer burden emerged because of differences in current and past smoking prevalence between races/ethnicities and genders. Variations in smoking prevalence reflect differences in social norms, socio-economic status —tobacco use is higher among poor, less educated people— targeted tobacco marketing, and acculturation level among immigrants (recent Hispanic and Asian immigrants smoke as little as in their country of origin). The smoking-attributable fraction shows the theoretical health gains if tobacco smoking was eliminated: from 10% of the cancer burden in non-Hispanic Asian women to 34% in non-Hispanic Black men.

- Do people living in tobacco-growing states of the US have a higher burden of cancer mortality attributable to cigarette smoking?

Nowadays, 95% of US tobacco is grown in six southern states (North Carolina, Kentucky, Tennessee, Virginia, South Carolina, and Georgia). Kentucky exhibited the highest smoking-attributable proportion of cancer deaths (34%) out of the 51 states in the US, as estimated in Chapter 3.3. Besides Kentucky, the other main tobacco-growing states were also confronted with high fractions of smoking-attributable cancer deaths (Tennessee 33%, North Carolina 31%, South Carolina 30%, and Georgia 29%). Virginia ranks the lowest (#30) of the tobacco-growing states, but still has 28% of its cancers deaths attributable to smoking. This high burden from smoking-related cancers is due to high past and current smoking prevalence, likely reflecting weaker tobacco control policies and social norms made possible by the large economic influence of the tobacco industry in those states. However, other factors also contribute.

Large poor and less educated populations —frequently smokers— can be found in those tobacco-growing states. Those large deprived populations are also common in the rest of the South, and the Appalachian region: Louisiana, Alabama, Mississippi, and West Virginia have 15%–18% of their population not graduating from high school (national average is 14%) and 16%–22% of their population living in poverty (national average is 15%).[6] In these four states, at least 31% of cancer deaths explained are by smoking. The fraction is the lowest in California (26%), where tobacco control is strong and large non-smoking Hispanic populations live, and in Utah (17%) where social norms (55% of people are Mormons) proscribe smoking.

What is the impact of smoking on another important non-communicable disease: COPD?
Using lung cancer mortality as a marker of past and current smoking exposure, we investigated in 61 high- and middle-income countries whether COPD mortality was high where lung cancer mortality was high, and vice-versa, keeping in mind possible condition-specific lag times. It turned out that while lung cancer and COPD mortality where strongly correlated in high-income countries among women, they were only moderately correlated among men in both high- and middle-income countries. No correlation was found among women in middle-income countries. In fact, around 2011–2013, lung cancer mortality rates were up to 10 times higher than COPD mortality rates in the majority of the countries, whereas in most of middle-income countries in Latin America and Asia, the reverse was true. Also, while both lung cancer and COPD were declining in men over the last 10 years (around 2002-2012), lung cancer was increasing in about half of the countries and COPD was increasing in six European countries in women. Progress in the diagnosis and treatment of COPD symptoms (as opposed to limited progress in lung cancer treatment) as well as declines in poverty —a major risk factor for COPD—further mitigated the association between smoking and COPD. In conclusion, while smoking had a major role in driving the COPD mortality rate in high-income countries, additional risk factors had to be also important (such as poverty and respiratory infections) in middle-income countries.

STUDY LIMITATIONS AND BIASES

When interpreting our results, some limitations and biases must be taken into account — beyond those specifically mentioned in the articles— related to the data or the methods.

Data

As previously mentioned in the introduction, incidence data coverage varies by region and only one in five low- and middle-income country has the data to assess the burden

of cancer. IARC has brought together international partners to launch the Global Initiative for Cancer Registry Development (GICR).[7] The GICR aims at implementing new population-based cancer registries in countries where there are none, and at improving the quality of existing ones. Likewise, only 20% of the countries worldwide have quality mortality data. Current efforts focus on improving death registration techniques, whether by developing verbal autopsy standards,[8] or improving the surveys to collect mortality information.[9] Having data for more countries would allow the surveillance of the burden of cancer, COPD and other diseases (mortality), in particular in low- and middle-income countries —for which information is now largely missing— where the smoking epidemic is at an earlier stage.

Furthermore, while cancer is most of the time accurately reported as cause of death (at least for lung cancer), COPD is underreported as cause of death for several reasons.

1) it is largely underdiagnosed (e.g. 73% of underdiagnosis in Spain);[10]
2) COPD may not be reported on death certificates in COPD patients (e.g. 42% of deaths certificates in COPD patients in TORCH trial did not mention COPD,[11] or 55% in the Copenhagen City Heart Study);[12]
3) COPD is not reported as secondary cause of death in most national mortality datasets which feed the WHO mortality database.

Even in countries with high-quality cancer registration as in the US, I was not able to study the burden of diseases of some minorities due to their under-representation in surveys and small population size. For instance, American Indians/Alaska Natives represent 1.2% of the US population.[6] The small number of cases and deaths by age group and sex forbids the calculations of DALYs and smoking population attributable fractions for this population. It is all the more important to examine the burden of diseases of American Indian/Alaska Natives than they have the highest smoking prevalence of all racial/ethnic groups (29% compared with 17% at national level).[13]

Finally, smoking status is self-reported in those surveys. Self-reported smoking status is usually slightly underestimated,[14] as are other socially undesirable behaviors. The degree of bias depends on the population examined. For example, among people in which smoking is seen as particularly undesirable, such as individuals who have smoking-related diseases, the discrepancy between measured and reported smoking rates can be high.

Methods

Disability weights

The estimation of the burden of diseases, with DALYs, involves many parameters. Among those parameters are disability weights, used for the YLD component —time spent in reduced health. The disability weights range from 0 (perfect health) to 1 (a

health equivalent to death). Having participated in two burden of cancer projects, using different sets of disability weights, I was able to witness their impact on the DALY estimates. The disability weights used in the 2008 Global burden of cancer[15] project were derived from Dutch[16] and Victorian[17] burden of disease studies, as well as earlier estimates from the global burden of disease (GBD) project from 1996.[18] The Victorian burden of disease study itself elaborated on the GBD1996 and the Dutch study. In all of these studies, the disability weights were estimated using a person trade-off method whereby a panel of experts (Dutch study) or health workers "from all regions of the world" (GBD 1996) were asked to value the severity of various conditions on a scale of 0 to 1 relative to a set of pre-determined weights of several conditions.[19] Meanwhile, the disability weights used in the 2011 US burden of cancer were published in 2012[20] and updated in 2015[21] by the Global Burden of Disease Study Collaborators. These were established by conducting 30 000 online and household surveys in Bangladesh, Indonesia, Peru, Tanzania and the US. In the surveys, participants were given examples of two persons with two disabilities and were asked to choose which person was 'the healthiest'. Consequently, some of the new cancer-related disability weights were lower than disability weights previously used[19] (Table 2).

Table 2. Comparison of cancer-related disability weights in the 2008 and the 2011 cancer burden projects

Disability	Disability weights used for 2008 Global cancer burden[19]	Disability weights used for 2011 US cancer burden[21]
Cancer: diagnosis and primary therapy	0.270 to 0.560	0.288
Cancer: follow-up	0.140 to 0.370	0.049
Cancer: metastatic	–	0.451
Terminal phase: with medication	0.900 (pre-terminal) 0.930	0.540
Terminal phase: without medication	–	0.569
Mastectomy	0.200	0.036
Stoma	0.211	0.095
Urinary incontinence	0.157	0.139
Impotence	0.195	0.017
Infertility: Primary (wants to have a child and has a fertile partner, but the couple cannot conceive)	0.180	0.008
Speech problems	0.200	0.051
Disfigurement level I (has a slight, visible physical deformity that others notice, which causes some worry and discomfort)	0.016	0.011
Disfigurement level II (has a visible physical deformity that causes others to stare and comment. As a result, the person is worried and has trouble sleeping and concentrating)	0.056	0.067

(0 is equivalent the best possible health; 1 is the worst possible health)

Several inconsistencies between disability weights published in 2012 were noticed and reported by the WHO[22] and others,[23] some of which were addressed in the 2015 update. Tackling the remaining issues for specific disability weights will largely need to await for further empirical research as it is likely that an important cause of these inconsistencies relates to the framing and wording of the lay descriptions.
In spite of differences in the methods applied to establish the disability weights used in 2008 Global burden of cancer and the 2011 US burden of cancer, the impact on the DALYs has been limited, as most of the burden ended up coming from premature mortality (YLL) (93% and 91%, respectively). Assessing the burden of a disease with high disabilities and low fatality (such as COPD) with the two sets of disability weights might have given a different picture.

Relative risk of former smokers

Two of my studies involved computing PAF using Relative Risk (RR, effect size linking smoking to cancer): the smoking-attributable cancer deaths by state study (chapter 3.3) and the smoking-attributable burden of cancer by race/ethnicity study (chapter 3.2). The RR of cancer diagnosis or death of former smokers is lower than the RR of current smokers. However, the RR should not be seen as discrete values, but as a continuously changing function of the risk of diagnosis, or death. It takes time for a smoker who quits smoking to acquire the diagnosis/mortality risk of the former smokers' group.[24] Time since tobacco quitting was not available in the datasets I used. Therefore, the results may be underestimated for recent quitters —who have a RR close to current smokers—and overestimated for long-time quitters —who have a RR close to never smokers. The RR were computed in a cohort study with a certain distribution of former smokers and given quitting durations, which might not apply well to other US populations.

Socioeconomic status

Our studies did not take into account socioeconomic status (SES), another key demographic factor for smoking besides race/ethnicity, and gender. Smoking started as a habit among higher SES. It also declined earlier in higher SES, while simultaneously rising in the lower SES groups. Smoking may be chosen by low SES people to cope with stress and deprivation,[25] and due to social norms. Disadvantage increases the likelihood of smoking, and smoking makes circumstances worse (less money for essential goods and services, greater financial stress, poorer health).[26] It is a vicious circle (Figure 1). If the current trends in smoking prevalence continue (slower declines in the lowest SES group and greater declines in high SES group), inequality in health will increase (for example in lung cancer incidence).[27] Studies have shown persisting socioeconomic disparities in mortality,[28] in race/ethnicity,[29] in smoking in high income

countries,[13,30] as well as the contribution of smoking to socioeconomic inequalities in mortality.[31] High smoking prevalence in low socioeconomic group is a marker of late phase of the smoking epidemic.[32] Patterns of potential reduction in inequality differ by country or region and sex.[33] Reducing smoking prevalence can reduce socioeconomic inequalities in health and mortality. Thus, studies on the burden of smoking-related diseases by socioeconomic should be pursued; they are critical to support the great need for tobacco control policies targeted at low SES.[34]

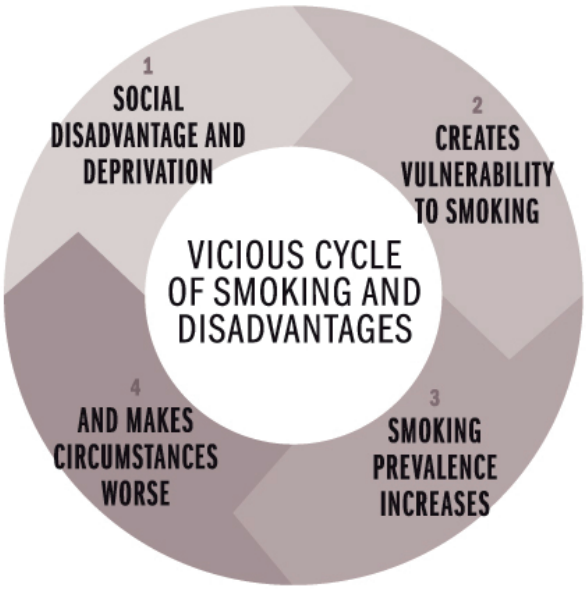


Figure 1. The vicious circle of low socioeconomic status and smoking.
Source: [26] as in The Tobacco Atlas[35]

Descriptive studies

All the studies of this corpus are based on cancer registry and mortality datasets which do not report individual lifestyle data such as smoking status. Thus, the fraction of diagnosis and deaths which are attributable to smoking can only be inferred.

IMPLICATIONS

This research shows that the burden of smoking-related cancer and of COPD is large and still increasing in some populations. Cigarette consumption seems to have peaked at about 6 trillion cigarettes annually sometime after the turn of the twenty-first century, but the deadly effects of this epidemic will still be felt for many decades even

if global use continues to decline.[36] Furthermore, because of population growth and ageing, the number of smoking-related disease cases is anticipated to grow, even in areas where the risk of smoking-related disease has been declining.
So what can be done?

Lung cancer screening

Lung cancer is the most frequent smoking-related cancer. Lung cancer patients have high fatality rate, in part because few tumors are diagnosed at local stage (16% in the US,[37] 20–30% in the Netherlands)[38] when survival rate is highest (55% 5-year survival in the US).[37] Lung cancer screening using low-dose computed tomography (LDCT) —which came on the market during the late 1990's—offered at least two advantages. First and foremost, if detected early, a tumor is easier to cure, surgically in the first place, because it is at lower stage and there are more treatment options available[39] —including some of the promising immunotherapies.[40] As a consequence, cure rate is higher and sequelae are less important. Second, earlier diagnosis means slightly younger patients, hence less likely to have co-morbidities and therefore, once again, more treatment options and better survival.

LDCT lung cancer screening is available in the US since 2013 for the current and former (who quitted less than 15 years ago) heavy-smokers (at least 30 pack years, a combined measure of the number of cigarettes smoked per day and the duration of the exposure), aged 55-80 years old. The decision made by the US Preventive Services Task Force to recommend annual lung cancer screening[41] is based on the results of the National Lung Screening Trial (NLST) showing a 20% decrease in lung cancer mortality compared with screening with chest x-ray.[42] In 2013, 8.4 million Americans met those criteria.[43] There is concern that the favorable balance between the benefits and harms of screening observed in the idealized conditions of the NLST may be difficult to replicate when lung-cancer screening is introduced in diverse clinical practice settings.[44] The US population eligible for lung cancer screening is probably less likely to benefit from early detection than NLST participants because they face a high risk of death from competing causes.[43]

In Europe, the Dutch-Belgian NELSON lung cancer screening trial is investigating whether screening with LDCT can reduce lung cancer mortality by at least 25% compared with no screening, at 10 years of follow-up.[45] The targeted population is individuals aged 50–75 years, who had a smoking history of at least 15 cigarettes per day for at least 25 years, or at least 10 cigarettes for at least 30 years, and were still smoking or had quit less than 10 years ago. The trial, which started in 2003 and includes around 16 000 participants,[46] further aspires to establish guidelines for the

optimum patient management strategies, based on characteristics of detected nodules.[47] About half of people screened have one or more pulmonary nodules, but only a small percentage of these people has lung cancer. Nodules detected by screening are followed-up for size and growth rate to determine which nodules require additional diagnostic procedures. This protocol aims at reducing the number of additional procedures for benign nodules.[48]

National screening is hard to implement, requires health services that only few countries can afford, and would have only a small impact on lung cancer mortality. A study estimated that LDCT could prevent approximately 12 000 lung cancer deaths per year in the US,[49] or approximately 8% of the estimated 158 000 lung cancer deaths in 2016.[37] In any case, current smokers should be advised to stop smoking at every screening visit,[50] as screening is not a substitute for smoking cessation.[44] Besides, smoking also increases the risk for other cancers[51] and other diseases.[52] As COPD and lung cancer share common pathogenic mechanisms,[53] it has been proposed to offer lung cancer screening to both smoker[54] and never smoker[55] COPD patients.

In conclusion, although relevant, for now there is some uncertainty whether lung cancer screening will have an impact at population level as large as the impact observed in the NLST trial. Moreover, more research is needed to decrease the frequency of false-positive tumors and to determine the optimal screening interval.[56] Therefore, recommendation of population-wide screening should be done with caution.

Improved COPD detection and treatment

COPD is universally underdiagnosed —80% of the participants in a survey in 27 countries in Europe, Asia, South America, South Africa, Nigeria, and Canada had an undiagnosed COPD—[57] even after years of multiple interventions such as population spirometry (a measure of lung function) and case finding. In the Netherlands, nearly 600,000 people are diagnosed with COPD, and 300 000 are unaware they are at high risk for COPD.[58] Apart from primary care as the central venue to screen for COPD, other options might be considered, such as voluntary testing of patients in pharmacies. In healthcare settings, given the rising number of COPD cases among women, spirometry should predominantly be performed not only among elderly male smokers but also among younger smoking women.

If COPD was more often detected, patients could benefit of improved quality of life and decreased odds of emergency department visits and hospitalization[59] owing to effective management strategies now available. Management of COPD includes both pharmacologic and non-pharmacologic treatments.[60] Still, medications for COPD have

had variable, yet limited, successes in modifying the long-term decline in lung function, depending on the type (emphysema or bronchitis) and the delay in diagnosis. Better treatments are needed. Nevertheless, at all stages of COPD, regular physical activity and exercise can aid symptom control, improve quality of life, reduce rates of hospitalization, and improve morbidity and respiratory mortality.[61] Higher numbers of cigarette pack years is associated with higher COPD mortality.[62] Because of its long preclinical course, quitting early is needed to obtain reductions in morbidity and mortality due to COPD.

Smoking cessation

Quitting smoking before the age of 40 eliminates almost all of the excess smoking-related risk of death from lung cancer and COPD compared with never smokers.[61,63] When smoking ceases, the lung cancer death rate stops increasing steeply and remains almost constant.[64] Smokers with cancer who quit smoking improve their chance of survival, and decrease their chance of secondary cancer and of cancer recurrence;[65] smokers with COPD benefit from quitting regardless of previous heavy smoking or age.[66]

Finally, decreasing the number of smokers also protects nonsmokers from secondhand smoke, which causes in adults: lung cancer, coronary heart disease, strokes, and has reproductive effects in women; and in children: sudden infant death syndrome, low birth weight, impaired lung function, lower respiratory illness, and middle ear disease.[52] Smoking cessation benefits virtually everyone, smoker and nonsmoker.

Mortality in the near future and throughout the first half of the 21st century could be substantially reduced by current smokers giving up the habit.[67] Widespread cessation of smoking in the UK has already approximately halved lung cancer mortality that would have been expected had former smokers continued to smoke.[67]

In the US, smoking prevalence was 42% in 1965 and current smokers outnumbered former smokers three to one.[68] In 2014, there were more former cigarette smokers (22%)[13] than current smokers (18% or 40 million).[52] Likewise, in the Netherlands, there were 29% of former cigarette smokers and 25% of current smokers in 2015.[30] Furthermore, in the US, two-thirds of adult smokers want to stop smoking, and 43% of smokers have made a quit attempt in the past year.[52] The vast majority of smokers regret starting smoking: around 90% in Canada, the US, the UK, Australia,[69] South Korea, and Thailand;[70] 80% in New Zealand; [71] and 'only' around 75% in Malaysia and China.[70] There's no other product with even a fraction of such customer disloyalty. Nicotine —one of tobacco's components—is addictive and therefore central in con-

tinuing smoking and in the difficulty of quitting.[52] In addition, the tobacco industry has designed its cigarettes to precisely control nicotine delivery levels and provide nicotine doses sufficient to create and sustain addiction.[72] All forms of tobacco have the potential to be addictive because they contain nicotine, but cigarettes are the most efficient for delivering nicotine into the body.[73] Several individual factors interact to determine the level of addiction, including type of tobacco use (e.g. cigarettes, smokeless tobacco), duration of tobacco use, amount of tobacco use (i.e. number of cigarettes smoked per day), and genetic predisposition.[74]

Tobacco dependence is a chronic disease that often requires repeated intervention and multiple attempts to quit.[75] Effective treatments exist, however, that can significantly increase rates of long-term abstinence from smoking.

There are two types of treatments: counseling treatments and medications.

1) Several pharmacologic treatments are available. Smokers are more frequently abstinent 6 months after stopping smoking when they used nicotine replacement therapy (NRT) (18% alone, 32% when using a combination of patches and oral medication or inhaler), varenicline (28%), bupropion (19%) compared with placebo (11%).[76] Cytisine is more effective than NRT and cheaper than other pharmacotherapies, and could offer a valid help to smokers who cannot afford pharmacotherapies, including in low- and middle-income countries. Unfortunately, so far it is only available in Eastern Europe.[77]
2) Individual, group, and telephone counseling are effective, and their effectiveness increases with treatment intensity. Two components of counseling are especially successful: practical counseling (problem solving/skills training), and social support.[75] The landscape of tobacco cessation is evolving and new technologies provide new ways to deliver smoking cessation help: social media support, texts, smartphone applications. The advantage is that every smoker can find a solution that suits his/her needs and preferences.

Combining counseling and medication is even more effective than using only one method.[75] Other types of interventions reinforce the impact of those treatments:[78] advice from physician,[79] self-help materials, mass media communications campaigns, Quit and Win challenges, and smoke-free places. Activities which activate our reward system (such as learning something new and exciting or being in a passionate love relationship)[80] can help smokers who quit remain abstinent from smoking.[81]

Promoting smoking cessation activities also translates into quit attempts even among smokers not using cessation assistance, because such messages normalize quitting and reassure smokers that help is available should they need it.[82]

I have shown (Chapters 2.1 and 4.1) that lung cancer incidence and mortality, as well as COPD mortality, are increasing among women, particularly in Europe. Women seem to be less successful at quitting smoking than men, although there are scant global data on this issue.[73] Unless effective, comprehensive and sustained initiatives are implemented to increase cessation rates among women and to prevent smoking uptake among young women, the prevalence of female smoking in developed and developing countries is likely to rise to 20% by 2025.[83] The tobacco industry has used female empowerment and beauty as their main themes to market cigarettes to women.[3] The same powerful strategy can be used in anti-smoking ads, as demonstrated by the WHO campaign targeting women (figure 2), to dismantle the tobacco industry's marketing strategy, deter women from smoking and encourage them to quit smoking.

Likewise, chapter 3.2 demonstrated that the smoking-attributable burden of cancer in the US is as large as in non-Hispanic Whites than in non-Hispanic Blacks. Therefore, anti-smoking campaigns should target, or at least include, Black people (figure 2). Of note, quitlines in the US —an evidence-based tobacco cessation service offering free counseling, accessible by calling a number— are available in Spanish, Mandarin, Cantonese, Korean, and Vietnamese to meet the needs of non-English speakers.

Tobacco control

While smoking cessation aims at decreasing the risk of smoking-related health problems among smokers and those exposed to secondhand smoke, tobacco control aims not only at making current smokers quit, but also to prevent people from taking-up the habit in the first place. Primary prevention takes time to implement and the results are delayed.[84] The greatest effect on reducing morbidity and mortality in the next 10–20 years will come from cessation by current smokers. In contrast, primary prevention will mainly reduce smoking-related diseases 20+ years from now. The two interventions are therefore complementary.

The decision to experiment with cigarettes, to become a regular smoker and to sustain the habit as many determinants, at individual, personal environment, and social and cultural environment level (figure 3). Therefore, the tobacco epidemic is being tackled in several ways. The WHO lists proven effective strategies to end this epidemic in the MPOWER measures:[86]

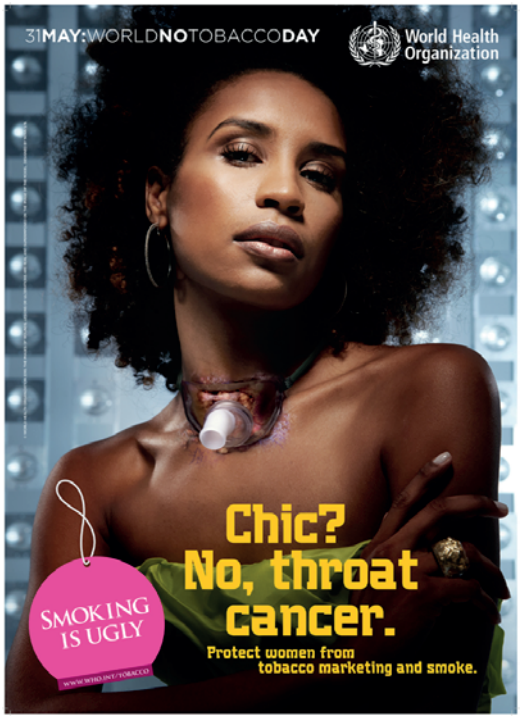


Figure 2. Poster of the 2010 WHO World No Tobacco Day focused on Gender and tobacco, with an emphasis on marketing to women.

1) **M**onitor use and prevention policies. The WHO encourages the use of standards and scientific and evidence-based protocols for tobacco surveys, as well as disseminating their results. It also promotes monitoring of tobacco control policies and reporting of tobacco-related health outcomes. In 2012, 2.8 billion people in 54 countries were covered by effective tobacco use surveillance.[87]
2) **P**rotect people from tobacco smoke. Complete prohibition of smoking in all indoor environments is the only intervention that effectively protects people from the harm of secondhand smoke. Smoke-free environments also help smokers who want to quit. It reduces smoking prevalence and tobacco consumption among workers.[86] So far, only 16% of the world population is covered by comprehensive smoke-free laws.[35]
3) **O**ffer help to quit tobacco use (see page 244)
4) **W**arn about the dangers of tobacco. The extreme addictiveness of tobacco and the full range of health dangers have not been adequately exposed to the public. Furthermore, comprehensive warnings about the dangers of tobacco are critical to changing its image, especially among adolescents and young adults.

5) **E**nforce bans on tobacco advertising, promotion and sponsorship. In spite of vehement denial from tobacco companies —which pretend to simply aiming at increasing their market share— tobacco marketing enrolls new customers. Some of the new consumers become addicted to tobacco (the younger the faster the addiction)[88] and turn into long-term smokers. Moreover, marketing normalizes tobacco use and presents it as no different from other consumer product. Finally, marketing strengthens the tobacco industry's influence over the media, as well as sporting and entertainment businesses, through billions of dollars in annual spending on advertising, promotion and sponsorship.
6) **R**aise taxes on tobacco. Significant increases in tobacco taxes (to more than 75% of the retail price) encourage current tobacco users to stop using, prevent potential users from taking up tobacco use, and reduce consumption among those that continue to use, with the greatest impact on the young and the poor.[89] Raising taxes on tobacco products is the most effective way to reduce tobacco use,[90] yet it is the least widely implemented measure.[91] Kulik[92] argues that price increases should be coupled with strong efforts to provide free access to smoking cessation services to prevent further deterioration of the financial situation of poor smokers.

MPOWER is being implemented across the world. WHO estimates that 2.8 billion people in 103 countries are now covered by at least one MPOWER measure at the highest level.[91] Overall, countries with higher levels of MPOWER measures experience greater decreases in current smoking prevalence.[93]

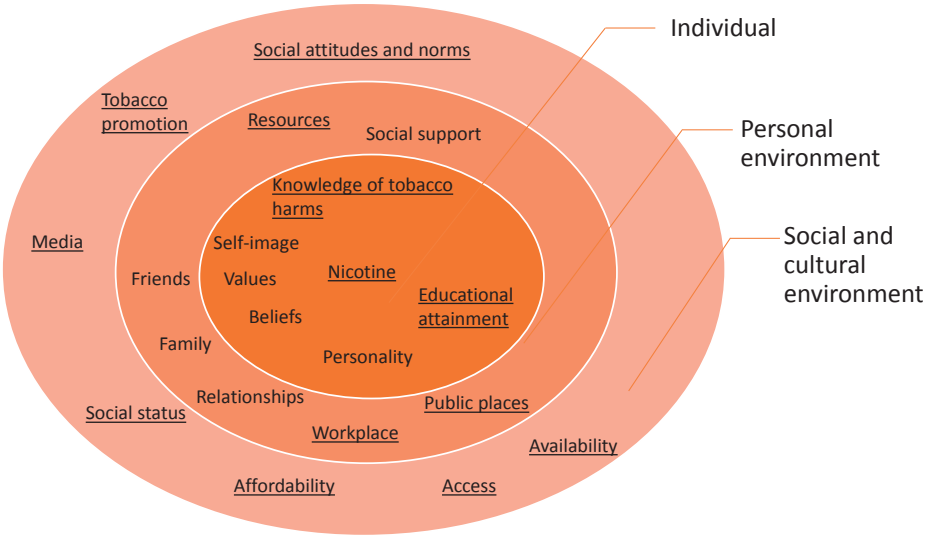


Figure 3. Factors associated with smoking
Underlined factors are amenable through policy (e.g. establish smoke-free workplaces)
Source: Adapted from "Towards a future without tobacco"[85]

The WHO also conceived the world's first treaty against tobacco, the Framework Convention on Tobacco Control (FCTC),[94] to steer global and country level action against the tobacco epidemic. It was unanimously adopted at the World Health Assembly in May 2003. The treaty, signed by 168 countries as of May 2016, provides practical policy interventions. It fosters a move from occasional surveys to surveillance systems, from information and education to changing social and cultural norms, a move from demand-side awareness to supply-side controls, and from isolated quit programs to a more integrated approach to health services.[95]

Which countries of the world are showing the way in tobacco control?

One would think that high-income countries would have stronger tobacco regulations, but as shown in Table 3, some low- and middle-income countries took the lead in some areas such as banning tobacco advertising, promotion and sponsorship. Interestingly, tobacco control level differs from one country to another within Europe, hence smoking prevalence varies greatly (from 13% in Sweden to 39% in Greece).[98] Those variations will later translate in differences in tobacco-related cancer burden.[1] In 2013, the UK, Ireland, Iceland, and Norway were the forerunners while Czech Republic, Cyprus, Germany and Austria had the weakest tobacco control.[99] The leading countries had in common high tobacco prices, comprehensive smoke-free legislation, and comprehensive tobacco ban. Through a directive, applicable in May 2016 to EU Member States,[100] the EU aims at raising the level of health protection of all its inhabitants. It is a step forward in tobacco control, and includes for instance:

- larger and mandatory health warnings on both cigarette packages and roll-your-own (RYO) —a product increasingly popular in Europe–[101] tobacco packs;
- the ban of flavored cigarettes and RYO tobacco products (such as menthol in 2020);
- the ban of packages of less than 20 cigarettes (favored by youth, with low purchasing power).
- health warning on e-cigarettes and limits the size of e-cigarette tanks and their nicotine concentration.
- combating illicit tobacco trade by increasing the traceability of cigarette packs.

Member States are free to apply stronger regulations in their countries, such as plain cigarette packages (Table 3).

There are strong antagonist forces opposing tobacco control. The goal of the tobacco industry, as any other for-profit company, is to sell tobacco with the least hindrance. It exploits multiple tactics and acts on several domains including scientific, political,[102] and economic.[103] It engages into sophisticated pathways to influence policy using lobbying, the media, public relations, industry allies, and contributions to legislators.[104]

Table 3. Leading countries for WHO MPOWER measures

MPOWER measure	Leading countries
Monitor use and prevention policies	Tobacco use is monitored in 54 countries including most European countries, Australia, New Zealand, the USA, Canada, Japan, South Korea, Chile, Argentina, Uruguay, Egypt, India, Iran, Oman, Thailand, Malaysia…[87]
Protect people from tobacco smoke	Comprehensive smoke-free law covering all indoor public places and workplaces: Chile, Jamaica, Madagascar, Russian Federation, and Suriname[91]
Offer help to quit tobacco use	Appropriate cessation services in Argentina, Belgium, Brunei Darussalam, Malta, Mexico[91] and the Netherlands[96]
Warn about the dangers of tobacco	Thailand (picture warnings on 85% of both sides of packages), Uruguay (80%), Brunei, Canada and Nepal (75%)[97] Australia has implemented standard (plain) packages. France, Ireland, and the UK are deploying them in 2016.
Enforce bans on tobacco advertising, promotion and sponsorship	Complete ban on all tobacco advertising, promotion and sponsorship: Kiribati, Nepal, Russian Federation, Suriname, United Arab Emirates, Uruguay, and Yemen[91]
Raise taxes on tobacco	Taxes raised to >75% of retail price: Bangladesh, Bosnia and Herzegovina, Croatia, Kiribati, New Zealand, Romania, and Seychelles[91]

These efforts involve campaigns to neutralize clean indoor air legislation, minimize tax increases, and preserve the industry's freedom to advertise and sell tobacco. The tobacco industry diverts attention from the health issues by focusing attention on the economic issues. For example, they use their employees to lobby against legislation with the excuse that it threatens their job security. At the same time, the tobacco industry also fuels problems as a way to fight economic constrains. For instance, it participates in smuggling as a way to counter tax hikes,[105] and weakens the impact of tax increases with product discounts.[106]

Twenty years ago, Barendregt et al.[107] came to the conclusion that, from an economic point, smoking cessation would lead to increased health care costs (as smokers die prematurely, they save health care costs of older ages, as well as pensions distribution). The study was vigorously contested, as was a study sponsored by the tobacco industry arguably presenting the financial advantage for the Czech Republic to maintain its weak tobacco control.[108] Overtime, more studies have shown that smoking is clearly an economic burden to societies: 120 billion euros were lost to tobacco smoking in France in 2010[109] —taking into account the savings on pension funds, 33 billion euros in the Netherlands,[110] 544 billion euros in 2009 in European Union,[111] and 289 billion dollars per year in the US in 2009–2012.[52]

Furthermore, growing tobacco contributes to people being undernourished by using agricultural land, water, and labor that could be used to produce food instead. Six of the top ten tobacco-producing countries had undernourishment rates between 5% and 27% in 2009.[112] In addition, tobacco production requires heavy use of fertilizers, pesticides, and wood (200 000 hectares of forest are cleared to cure tobacco each

year).[113] Farm workers, especially child laborers, are at risk of nicotine toxicity, caused by handling tobacco leaves without protection during harvest and processing.[114] Child labor is observed in all countries with family-operated tobacco farms, with children working full time or during non-school hours. In addition, more than 175 000 tons of cigarette butts —containing hazardous substances such as arsenic, lead and nicotine— are discarded annually.[115] The FCTC also addresses the environmental damage of tobacco.

Based on the existence of those opposing forces (tobacco control vs. tobacco industry), we can infer two scenarios:

1) The tobacco industry masters ways to obstruct tobacco control,[106,116] and the imprint of the culture of smoking will remain for a long time in media (books and movies).[117] The addictive component of tobacco can transform people who just want to try cigarettes into long-term users and later impede smoking cessation. So tobacco use will persist for centuries.
2) The experience of countries such as Australia, the UK, and the US, where male smoking prevalence has fallen from 70% post war to 15–20% today, provides living proof that targeted tobacco control strategies can work, albeit at a slow pace. Smoking prevalence among the population with the most acute knowledge of the health impact of smoking in the US —medical doctors— was as low as 2.5% in 2006-2007.[118] It will take time, but smoking will eventually disappear.

Resistance for change exists but is surmountable. If additional effective measures are not adopted, there could be 1 billion smoking-related deaths in this century.[119] The tobacco-related public health harms, in addition to the economic and environmental burdens, are serious enough to morally justify the end of tobacco use.

RECOMMENDATIONS

Based on the conclusions of my studies and their limitations, several actions can be recommended to improve public health.

Improve monitoring of smoking prevalence in racial minorities

As the need for tobacco control policies which target high smoking prevalence racial groups continues (e.g. American Indians and Alaska Natives in the US),[13] so does the need for monitoring their effectiveness. Clearly, more efforts are necessary to improve data collection of smoking prevalence in minorities, as well as country of birth, time since arrival in the country —as acculturation plays a role in smoking prevalence—[120]

and country of ancestors. Those efforts should comprise sample sizes large enough to allow reliable estimates.

Tobacco endgame

Tobacco is the only legal product that kills prematurely more than one out of two[121] of its users when used exactly as intended by manufacturers. The feat of the tobacco industry resides in marketing an addictive carcinogen as a lifestyle choice. '[T]he root cause of the smoking epidemic is also evident: the tobacco industry aggressively markets and promotes lethal and addictive products, and continues to recruit youth and young adults as new consumers of these products.'[52] If any other consumption product, for example spinach, had been proven to be as deadly, it would have been long banned from production, distribution, marketing and consumption.

What makes tobacco special and so challenging to eradicate is its addictive component —addiction to spinach is unheard of. Decreasing the nicotine contents of cigarettes to less-addictive (legally possible in the US since 2009 and under the control of the FDA) or non-addictive levels has been proposed.[122] The idea is that fewer young people who experiment with cigarettes would become addicted adult smokers, and previously addicted smokers would find it easier to quit smoking. The few preliminary studies led to conflicting results. A meta-analysis showed that either gradually or immediately reducing nicotine contents would lead to minimal compensatory smoking (increased intensity or rate of smoking),[123] while a randomized controlled trial showed an impact on cigarette consumption and puffing behaviour with intermediate and low levels of nicotine in cigarettes.[124] This emphasizes the importance of using multiple behavioural and biologic measures to study the effect of reduced nicotine content cigarettes.

Stronger, new actions are needed to eliminate tobacco as a health, economic and environmental burden, on the medium term. Now, serious people are discussing ending tobacco as a public health problem. New Zealand, Scotland and Finland have officially established the goal of doing so by 2025, 2034, and 2040, respectively.[125] It is called the "tobacco endgame" and aims at phasing out the use of tobacco. There are several potential strategies to achieve this goal:[125]

1) further implement measures from the FCTC
2) replace cigarettes with alternative products (harm reduction)
3) deny tobacco sales to people born after a certain year (the tobacco-free generation proposal)

More FCTC

It is the strategy chosen by New Zealand, Scotland and Finland to reach the end of tobacco use in their countries over the next 10–25 years. Although tobacco control has been successful in decreasing tobacco use of the past half century, the first strategy advocating for 'more of the same', as recommended by the FCTC and MPOWER (more populations covered by measures, stronger measures, more measures adopted), is only a preliminary phase which creates a climate that facilitates the shrinking of tobacco use. All of those measures discourage rather than prohibit adult tobacco use. Even implemented fully, those measures may be insufficient to achieve an endgame but can set a stage where other initiatives become feasible.[125]

Harm reduction

This strategy is not usually considered as an endgame strategy because the goal is to reduce rather than eliminate tobacco-related harm, by encouraging cigarette smokers to switch to less harmful nicotine products such as smokeless-tobacco and electronic cigarettes (e-cigarettes).

Over 300 million people around the world use smokeless tobacco products, the vast majority of whom live in South Asia.[35] Those products cause cancers of the oral cavity, pancreas and esophagus.[51] However, smokeless tobacco causes less pulmonary diseases than cigarettes. Therefore, if smokers immediately and permanently switched to low nitrosamine —a cancer inducing substance— smokeless tobacco, such as snus (marketed in Sweden), their risk would be reduced.[126] Yet, if smokers maintained a dual use (snus and cigarettes) —as currently promoted by the tobacco industry— there would be no health benefit at population level in a country like the US.[127]

A rapidly growing form of nicotine delivery product is e-cigarettes. E-cigarette use is anticipated to be much less harmful than smoking conventional cigarettes[128] because it avoids the inhalation of most of toxic combustion products. The extent of the harm reduction has yet to be established,[129] but what we know is that they are not harmless.[130,131] There is a heated debate whether or not officials should promote e-cigarettes.[131-133]

On the positive side, they can be seen as a means for smokers to decrease or substitute their cigarette consumption, or as temporary aid to smoking cessation. A Finnish study offered 48 participants unwilling to stop smoking cigarettes to use e-cigarettes. Six months after the end of the study, 21% of them had stopped cigarette smoking, 23% had cut their cigarette consumption at least by half, and the remaining participants smoked at least 50% more cigarettes,[134] suggesting positive effects in light smokers. Other studies have been performed, and reported positive results.[135-137] E-cigarettes rapidly evolve to offer a better experience to users, closer to smoking cigarettes. Thus,

randomized controlled trials with those new products are necessary (and under way). Most importantly, these studies have to compare the effectiveness of e-cigarettes for quitting against other measures, like NRT and counseling.

On the negative side, they have the potential to renormalize cigarette use if they are permitted in venues where cigarettes are banned, they can appeal to nonsmokers and former smokers, and they maintain nicotine addiction. Certainly, under no circumstance is nicotine a biological need —but in the 1950s, it was presumed to be an essential drug for calming and stimulating stressed people. Nicotine is a poison.[138] Encouraging the sale of nicotine products is supporting people buying a poison. In the US, a third of cigarette smokers also used e-cigarettes in 2013. More troublesome was the report of e-cigarette use among former smokers (5%) and even in never-smokers (1%). Although smokers were most likely to use these products, almost a third of current e-cigarette users were nonsmokers, suggesting that e-cigarettes contribute to primary nicotine addiction and to renormalization of tobacco use.[139] Also of concern were the results of a study among high school students in Los Angeles showing that those who had ever used e-cigarettes at baseline compared with nonusers were more likely to report initiation of combustible tobacco use over the next year.[140]

Regardless of whether or not e-cigarettes are a gateway to conventional cigarette use, there is no reasons for minors to use a product for which the presumed public health benefit is harm reduction for adult smokers.[141] Therefore, strict regulations are needed to forbid sales to minors, advertising directed to youth, flavoring, and use in smoke-free places; to tax e-cigarettes; to have them exclusively sold by licensed retailers; and to require health warning on the product to ensure that e-cigarettes do not contribute to preventable chronic diseases. Nevertheless, controlling for e-cigarette ads on the internet will prove challenging, if at all possible.

Both smokeless tobacco and e-cigarettes are still addictive and harmful, but again, much less than cigarettes. As long as cigarettes are available for purchase, there is a potential for smokeless tobacco and e-cigarettes to be gateways to cigarettes (increasing the number of cigarette smokers) and to maintain nicotine addiction (getting nicotine when cigarette smoking is not permitted). Those harm reduction solutions are thus only appealing if cigarettes are banned. Another way to see this is that smokeless tobacco and e-cigarettes make cigarettes bans possible.[142] After eliminating cigarettes, a second step can be to diminish the nicotine contents of the other tobacco products, so as to make them less addictive and attractive. Overtime,

there would be lower intake and lower dependence upon those better —but still not safe— alternatives.

Tobacco-free generation

Increasing the minimum legal sale age for tobacco products, as required by the FCTC, can be seen as an intermediate step to the proposal to the tobacco-free generation. For instance, the minimum smoking age in the Netherlands was raised from 16 to 18 years only in 2014, 57 years after the first warning in the Health Council report — which only warned of the danger in children.[143] Nearly 9 out of 10 smokers experiment cigarettes under the age of 18, and 98% of smokers started before the age of 26 in the US.[52] Furthermore, the vast majority of Americans who begin daily smoking during adolescence are addicted to nicotine by young adulthood.[144] Therefore, preventing youth initiation may be the key to ending the tobacco epidemic. Nevertheless, there are two important drawbacks to the existing 'underage' restriction.

1) It creates a rite-of-passage effect: underage people may think that by smoking they appear 18.[145] This belief has been exploited by the tobacco industry's mock tobacco control campaigns 'Kids don't smoke'. Prohibiting sales to minors does reduce cigarette consumption among them, but only to a certain extent does it reduce cigarette initiation. Banning cigarettes makes them attractive to a fraction of teen specifically because cigarettes are outlawed. Therefore, renewed anti-smoking campaigns backed by behavioral science to address smoking initiation triggers in adolescents are needed. Teens are introduced to cigarettes by same-age peers or individuals of legal age and in the same circles (at school or siblings), when they are not directly bought from careless tobacco retailers. In an effort to overcome this loophole, some localities in the US have raised the age higher. In 2015, Hawaii became the first state to enact a law increasing the tobacco sales age to 21, followed by California in 2016. More than 125 localities, including New York City, have raised the tobacco sales age to 21.[88] According to a study by the Institute of Medicine of the National Academies using two established and complementary tobacco simulation models —SimSmoke and CISNET modeling— raising the minimum age of legal access to tobacco to 21 is predicted to result in a 12% decrease in the prevalence of tobacco use among today's teenagers once they become adults —because some people will never start smoking— and later reduce smoking-related deaths by 10%.[146] There is extensive public support (71%) for this ruling in the US, including among smokers (58%) and people aged 18-20 (62%).[147]

2) But, it has an adverse signaling effect: if the government forbids access to tobacco for people under a certain age, then it implies that it is acceptable for people with legal age to buy it.[145] Thus, the tobacco industry's frequent claim is: 'It's a legal product'.

Yet this does not make tobacco a safe product. There is irony in the message sent to citizens: 'You can buy cigarettes, but don't do it'. The paradox goes on when adults are able to buy cigarettes, but are strongly encouraged to stop using them (which would not prove so challenging if cigarettes were not addictive).

The tobacco-free generation proposal, by prohibiting the sale of tobacco to individuals born after a certain year, aims at overcoming the defects of rite-of-passage and misleading messages of current youth access laws. The proposition to ban people born after 2000 from smoking has for example been discussed at the Senate of the Provinces of Tasmania and Queensland, Australia, and in Singapore, but has not been adopted. With this measure, the impact on supply is gradual and obvious, but the impact on demand is also important. It sets the stage for new types of public health messages: 'tobacco is something of the past'. Over time, the age gap between teenagers and the last cohort of smokers steadily widens, facilitating a change of norms. Hence, enforcement becomes progressively easier: 'the best law is one that so shapes social norms that it becomes self-enforcing'.[148] Tobacco use will thereby gradually disappear. If the teenagers of today became the first tobacco free generation, the positive outcome on mortality rates would chiefly take place in the middle or second half of the 21st century. Secondhand and third-hand (smoke residue left in furniture, carpets, etc.) will also decrease gradually.

The measure may seem to be drastic to some. However, the estimation of 450 million adults prematurely killed by smoking between 2000 and 2050[149] calls for drastic action, and there are precedents for the generational method. It was used to phase out opium smoking in Formosa (now known as the island of Taiwan) in 1900, and in British Ceylon in 1910. Within 35 years, opium use was eradicated.[145] Additionally, despite of the economic consequences, 60 countries have already completely banned asbestos (only partial ban in the US) because of its deleterious health effects. It is therefore possible to do the same with tobacco.
Possible endgame implementation strategies can integrate ideas from the FCTC, harm reduction and the tobacco-free generation.

Advancing tobacco control in low- and middle-income countries

Tobacco use in low- and middle-income countries (LMICs) is not new. Trade in tobacco and its products has expanded dramatically in the 1980s as result of a variety of bilateral, regional and international trade agreements that have significantly reduced trade barriers.[150] Tobacco industries invested in those countries to increase their profits.[151,152] The ingredients for a tobacco epidemic are already in place: in 2000, eight out of ten smokers lived in developing countries.[150] Over the past 15 years, smoking

prevalence only increased in LMIC (figure 4) and Croatia (a high-income country since 2008). As a consequence, cigarette smoking was very strong in 2012 in Chile (32% prevalence in men and 26% in women), in Egypt (36% in men and 1% in women), and Indonesia (57% in men and 4% in women) for instance (figure 5).[153] On average, 50% of men and 9% of women smoke in LMICs, while the gender gap narrowed in high-income countries (being 35% and 22%, respectively).[32]

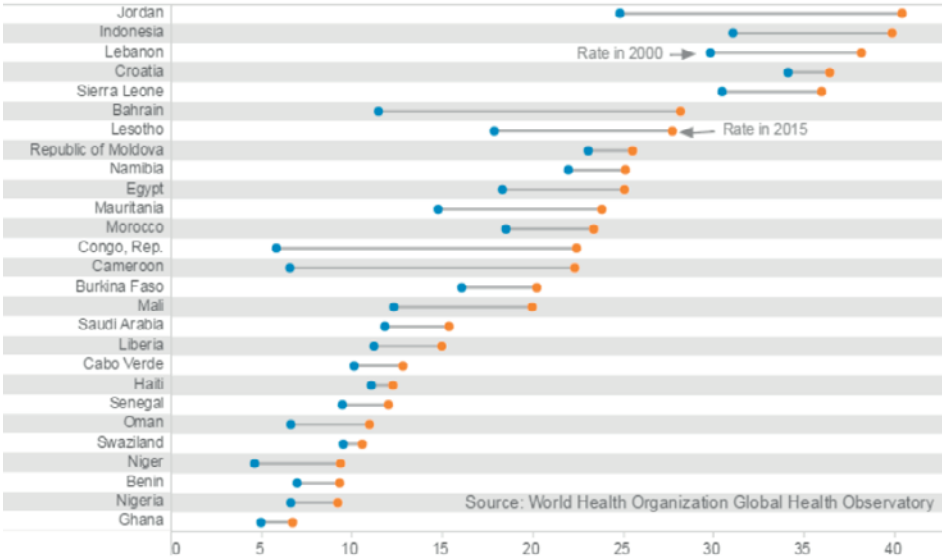


Figure 4. Where did smoking prevalence rise between 2000 (blue) and 2015 (orange)?[154]

In LMICs, greater attention is being given to the ubiquitous problem of poverty. Within the health sector, this focus translates into improving access to health services, and reducing the burden of communicable diseases. Indeed, risk factors for chronic disease, such as smoking and poor diet, are arguably seen as matters of individual lifestyle choice, and not the consequences of various circumstances that go beyond personal choice (figure 3), including lack of investment from governments. Nevertheless, there is an inextricable relationship between tobacco and poverty (figure 1). At the country-level, tobacco generates large productivity loss[155] and healthcare cost, which undermine economic development in many countries.[35] At the individual-level, tobacco spending adds directly to financial stress. The WHO estimates that as much as 10% of household income can be spent on tobacco products, leaving less money for food, education, housing, and clothing.[32] Disadvantaged populations (in countries from all income levels) sustain the habit because smoking can be seen as a means of coping with difficult circumstances, as an "affordable" recreation, and as a response to stress and exclusion.[26]

We can expect that, as economic development is achieved by low-income countries, they will transition into becoming middle-income countries. Henceforth, cigarettes will be marketed to more people and more people will be able to afford them. While smoking prevalence is still very low in low-income countries (e.g. 5% in Sudan and Niger, and 4% in Ethiopia) (figure 5) it could increase to the level of middle-income countries —although smoking prevalence in middle-income country is very diverse— (e.g. 11% in Algeria and Kenya, 25% in Bolivia, and 30% in Indonesia).[153] It is therefore critical to now establish and expand strong tobacco control where tobacco smoking is common, and educate the people on the harms of tobacco and ban tobacco marketing where tobacco smoking is rare.

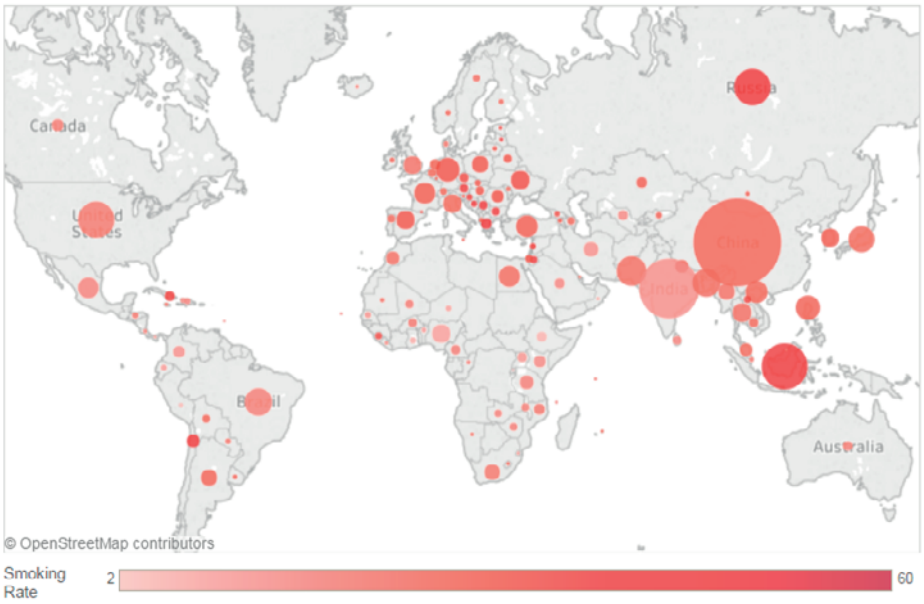


Figure 5: Over a billion people smoke worldwide
Circle size: number of smokers in 2012. Darker color: higher smoking prevalence
Source: WHO's Global Health Observatory,[159] as in[154]

The FCTC aims at implementing tobacco control in all countries, regardless of the smoking prevalence or the economic level. The FCTC has been integrated into the Sustainable Development Goals of the United Nations (17 goals directed to a sustainable development to meet by 2030 which aspire to human-rights-centered approaches to ensuring the health and wellbeing of all people). This gives an additional incentive for governments in LMICs to act on tobacco control. Several LMICs already lead the way in tobacco regulation (Table 3). Four LMICs have all MPOWER measures in place

at the highest level (Turkey, Uruguay, Panama and Iran), three more are only one step away from the highest level (Brazil, Argentina and Nepal). About 1.8 billion people —a third of all people living in LMICs— are now protected by at least one MPOWER measure at the highest level.[91] For example, smoking prevalence monitoring —the first measure of MPOWER— is achieved by the GATS (Global Adult Tobacco Survey), in more than 25 LMICs with highest burden of tobacco use, including India, Indonesia, Nigeria, Philippines, Senegal, Thailand, and Viet Nam.

Yet, signing the FCTC is not sufficient. For instance, China ratified it in 2005 and smoking prevalence has been stable (53% of men and 2% of women) for the past five years.[156] Annual tobacco-related deaths in China are projected to rise to two million by 2030, when the young adult smokers of the turn of century reach middle-age. Similarly, at current risk, India will have one million tobacco-related deaths during the 2010s, and the number will grow as population rise. At this pace, global annual tobacco-attributable deaths are predicted to reach ten million around 2030.[149] The tobacco industry is constantly working at fighting tobacco control, directly in LMICs,[157] or using LMICs to challenge global tobacco control.[158]

Advances in tobacco control in LMICs —where most of today's smokers live (figure 5)— are urgently needed. In particular, vigilance is required to ensure that women in LMICs, especially in those with rapidly growing economies,[160] do not begin to smoke in large numbers as women have done in some high-income countries.[161]

Air pollution control

Avoiding cigarette smoking and secondhand smoke is a smart way to avoid smoking-related cancers, COPD, and other smoking-related diseases. Yet it is not sufficient. Besides smoking, air pollution —both indoor and outdoor— is another common risk factor to lung cancer in many countries[162,163] and COPD.[164] Furthermore, air pollution also affects adults with respiratory symptoms in urban areas.[165]

Some of the problematic air pollution pollutants are called fine particulate matter ($PM_{2.5}$). These small particles can get past the body's normal defenses and penetrate deep into the lungs. They are most abundant in LMICs in Africa and Asia[166] (figure 6), and come from both human and natural sources (such as wind filled with mineral dust from the Arabian and Saharan deserts). More than 80% of the world's population breathe polluted air that exceeds the WHO's recommended level of 10 micrograms per cubic meter of $PM_{2.5}$.[167]

Outdoor air pollution is generated by transport, power generation, industrial activity (including farming), biomass burning, and domestic heating for example. Pollution

levels in western Europe and North America have generally declined since the late 20th century, but they are increasing in some rapidly industrializing countries, notably in Asia.

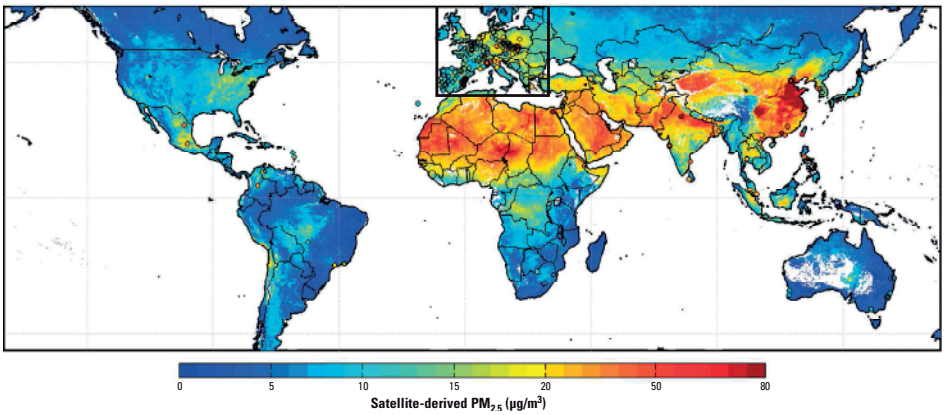


Figure 6. Global satellite-derived fine particle matter ($PM_{2.5}$) average distribution over 2001–2006
Source:[166]

Reducing the public health impacts of outdoor air pollution requires addressing the main sources of outdoor pollution. Although individuals can contribute to the reduction of outdoor air pollution, it also requires action by public authorities at the national, regional and even international levels. For instance, while the final decision to commute by bicycle is left to individuals, the creation of infrastructures for bicycles is essential for the promotion of this fossil energy-free means of transportation.

Indoor air pollution includes biomass burning for cooking and heating, as well as heating of some oils used for cooking.[168] Women and children can be at a particularly high risk of lung diseases from exposure to household air pollution.[169] A wide range of interventions are available to reduce indoor air pollution and associated health effects. Interventions can be classified according to their target:

1) interventions on the source of pollution: using alternative fuels (solar power, electricity, or biogas) and improved stoves
2) interventions to the living environment: build chimneys, cooking windows, or smoke hoods
3) interventions to user behavior: keeping young children away from smoke

Epidemiological studies are essential to monitor the impact of (indoor and outdoor) air pollution and monitor the effect of interventions. For example, for many years, Xuanwei, a farming town in western China, had one of the highest incidence rates of lung cancer in the world. Women were developing cancer at equal or higher rate than men,

although women rarely smoked. However, they used coal in open fire pits to cook, and coal again to heat their poorly ventilated houses. Lung cancer rates declined after the Chinese government offered a financial incentive to families building chimneys, and families started to use a portable stove they could carry outside.[168]

So far, too many people in LMICs continue to lack access to affordable, life-saving clean energy systems. Several decades of research, national stove programs and international initiatives have yet to lead to a significant reduction in the population depending on polluting fuels and technologies to meet their daily energy needs. Roughly the same number of people today cook with polluting energy systems as did 30 years ago. Population growth has outstripped incremental progress in increasing access to clean, modern energy systems.[169] Access to affordable, reliable, sustainable and modern energy for all is now one of the Sustainable Development Goals. This ought to spur further action on reducing pollutant emissions.

5.2 CONCLUSIONS AND FUTURE RESEARCH

Our work evaluated the smoking-related burden of cancer and COPD in several populations and subpopulations within a country, and their changes over time. We have shown that smoking-related cancer incidence rates are declining in most of studied populations —mainly high- and very high-income countries— among men, following longstanding reductions in smoking prevalence. In contrast, due to delayed declines in smoking prevalence among women, smoking-related cancer (particularly lung cancer) incidence rates were still increasing, except for some declines in few European populations. In many countries, COPD mortality rates declines, probably due to declines in smoking prevalence, as well as increasing wealth. In LMIC in Asia and Latin America, female COPD mortality rates were high and declining despite low smoking prevalence.

We also expanded our analyses on the smoking-related burden of cancer in a high-income country which was at the origin of mass production, marketing, and sales of tobacco: the US. Firstly, that the fraction of cancers deaths attributable to cigarette smoking can be large (29%), with fractions higher than 30% in Southern states and at low as 17% in Utah. Secondly, that the smoking-related burden of cancer is substantial in every racial/ethnic group (from 19% in Hispanics and non-Hispanic Asians, to around 28% in non-Hispanic Whites and non-Hispanic Blacks).

On the one hand, our findings highlight the potential health gains in every population that can be achieved with a reduction or elimination of tobacco use. On the other hand, they show the long lag time for the effects of prevention (declines in smoking prevalence) to be reflected in population health. Those results stress the continuing

need for tobacco control and identify women (particularly in LMIC, where smoking prevalence is still low), Blacks and Whites, and Southern states populations in the US, as group which would particularly benefit from tobacco control.

However, the generalization of those conclusions to the global population are limited by the fact that we could only access data for some countries, most of them being high-income countries. Our studies in the US showed large disparities between racial/ethnic groups, as well as geographic location, and we can speculate that the disparities are even larger at global level. This means that tobacco control has to be implemented at global level, as intended by the FCTC.

This work glances at what could be a tobacco-free world, from the cancer and COPD health perspectives. Despite its successes in the recent past, there is a need for a breakthrough in tobacco control. Most importantly, to put tobacco behind us, tobacco control has to be integrated at a very large scale that goes beyond public health and economic gains. It has to be addressed in a general context of human development.[95] The FTCT has been integrated in one of the health targets of the Sustainable Development Goals: "Ensure healthy lives and promote well-being for all at all ages". Tobacco control must also be considered as part of other Goals: ending poverty, achieve food security, promote sustainable economic growth, end child labor, promote safe working environments, sustainably manage forests, reduce corruption and bribery, develop accountable and transparent institutions at all levels through various pathways illustrated in Figure 7.

Future research agenda

There is substantial evidence on the negative health impact of tobacco, whether from first-hand or secondhand smoking, or smokeless tobacco use, in high-income countries. There is also a growing demonstration of the high economic cost of tobacco, at individual- and national-level. Finally, the ambivalent role of the tobacco industry (knowingly selling deadly products while pretending to be public health partners) and its constant interference in politics and economic and health policy has repeatedly been reported.[102,151,170]

Nevertheless, numerous questions related to tobacco remain —besides clinical research to find life-saving cures— calling on a wide range of experts (table 4).

Figure 7. Possible leverages for tobacco control.
Source: adapted from[35]

Table 4. A sketch of future research on tobacco-related topics

Type of studies	Subject / study question
Environmental studies	What is the environmental burden of tobacco throughout its lifecycle at national and global level (from farming, to curing, to use, and to disposal)?
Occupational studies	How can the working conditions (safety) of farmers producing and transforming tobacco leaves be improved?
Laboratory studies	Is nicotine the only addictive component in tobacco?
Behavioral studies	How can behavior related to tobacco use be changed and the change sustained? How effective are e-cigarettes compared to existing smoking cessation tool?
Epidemiological studies	What is the prevalence of emerging tobacco products use (e-cigarettes, hookah, little cigars, etc.)? What is the health impact of e-cigarettes? How do cancer incidence rates in two neighboring countries with different levels of tobacco control compare, using cancer registry data? Can tobacco control implementation be detected in period-cohort analyses of cancer incidence, using cancer registry data? What is the smoking-related cancer incidence in LMICs? What would be the smoking-related global mortality in 2030, based on several tobacco control scenarios (different levels of MPOWER measures)?
Political studies	How can the influence of lobbies be better regulated?
Business studies	What is the tax/regulatory threshold for tobacco industries to make insufficient profit and give up selling deadly products?
New technologies	Can we create a smartphone app which can make a difference in smoking initiation and smoking cessation?

In this thesis, we have used population-based cancer registry data and national vital statistics to describe the large smoking-related burden of two non-communicable diseases, demonstrating the need for a broad alliance against tobacco, to end tobacco use in the twenty-first century.

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5.3 SUMMARY

Prior to the nineteenth century, lung cancer was a rare disease. It took time, intelligence, and fortitude to prove that cigarette smoking was responsible of the rapid increase in lung cancer deaths observed in high-income countries in Northern America and Europe during the first half of the twentieth century. During the second half of that century, more diseases would be causally linked to smoking, including eleven more cancer types, chronic obstructive respiratory disease (COPD), and cardiovascular diseases. Even sixty years after irrefutable evidence of the health harms of tobacco and the implementation of tobacco control policies leading to declines in smoking prevalence, the burden of smoking-related cancers and COPD remains colossal and underrated. Therefore, the international burden of the smoking-related cancers and COPD was assessed at the turn of the twenty-first century, with a special focus on Europe and the United States of America —a country which played a pivotal role in the dissemination of cigarettes throughout the world.

In Europe, smoking-related cancer incidence remains high as there is a lag time of several decades between smoking and disease diagnosis. Mass cigarette use followed the economic development of the continent: firstly, in northern and western Europe, secondly southern Europe, and thirdly in central and eastern Europe. Adoption of smoking by women lagged behind that of men by decades, and never reached the very high male smoking prevalence. Over the 1998–2007 period, lung cancer incidence —of which more than 80% of cases are due to smoking— declined or levelled off in men all over Europe (Chapter 2.1), following sharp declines in smoking prevalence since the 1950s. In contrast, female lung cancer incidence increased in 19 countries over the same period. In other major smoking-related cancers (oral cavity and pharyngeal, laryngeal, and esophageal), the effect of past smoking prevalence trends is less evident because of lower smoking-attributable fractions, concomitant trends of risk factors specific to those sites, or low number of cases. Over the 1998–2007 period, incidence rate of oral cavity and pharyngeal cancer only increased in few countries among men in some age groups (in the Czech Republic, Denmark, in Slovakia, UK, and Germany). Incidence also increased in some age groups in these countries among women, as well as in Ireland, Norway, and in the Netherlands. Laryngeal cancer incidence just increased among Bulgarian men, while the number of cases remained very low in European women. Finally, surges in esophageal cancer incidence among men were generally restricted to the northern half of Europe, whereas among women, increases appeared to occur in most countries in western, central and eastern Europe.

Manufactured cigarettes are a product which has constantly evolved since their launch at the end of the nineteenth century, to attract and retain smokers. The changes in cigarette design and composition are reflected, with a lag time, in populations in changes in the distribution of lung cancer sub-types. While lung cancer incidence declined or remained stable over 1973–2002 among men in all of the eleven high-income countries studied —except Spain— trends varied by subtype (chapter 2.2). Squamous cell carcinoma (SCC) has been the most frequently diagnosed subtype of lung cancer among men at the beginning of the study period. However, adenocarcinoma (AdC) diagnoses surpassed SCC diagnoses among men in six countries starting around the 1990s. Contrary to the declines in SCC incidence, AdC incidence leveled off or even increased over time. In contrast, AdC was always the predominant subtype of lung cancer and continued to increase among women throughout the study period. Reasons for the shift of the lung cancer epidemic from SCC to AdC subtypes among men include: first, the rise of filtered, lower tar- and nicotine-containing cigarettes led smokers to inhale deeper into the lungs (to get the same dose of nicotine), replacing central tumors (often SCC) with peripheral tumors (often AdC); second, changes in the carcinogenic mix of cigarette smoke. Because women picked up the habit a few decades after men, when filtered/low-tar and low-nicotine cigarettes had swamped the market, and because women were targets for these new 'light cigarettes', AdC was always more frequent than SCC among them.

Each year, cancer is responsible for around 10 million disability-adjusted life years (DALYs) lost (as the combination of years lost due to premature death and years lived with decreased quality of life due to disabilities) in the US (chapter 3.1). The burden of cancer is equivalent among men and women –each losing 5 million DALYs to cancer. However, the fraction of this burden attributable to cigarette smoking is higher among men than among women (32% and 21%, respectively) (chapter 3.2). It also varies by race/ethnic group; it is higher among non-Hispanic Whites and non-Hispanic Blacks (around 28%) than among non-Hispanic Asians and Hispanics (19%). Those differences in the smoking-attributable fraction of the cancer burden emerge because of differences in current and past smoking prevalence between races/ethnicities and genders, reflecting variances in social norms, socioeconomic status, targeted tobacco marketing, and acculturation level among immigrants. The smoking-attributable fraction shows the theoretical health gains if tobacco smoking was eliminated: from 10% of the cancer burden among non-Hispanic Asian women to 34% among non-Hispanic black men.

Besides gender and racial/ethnic differences, there are also geographic differences in the smoking-related cancer mortality the US (chapter 3.3). The national smoking-

attributable fraction of cancer deaths is 29%, but is higher in Southern states: Kentucky (34%) —the highest fraction of all 51 states— Tennessee (33%), North Carolina (31%), South Carolina (30%), Georgia (29%), etc. This high mortality from smoking-related cancers is due to high smoking prevalence, likely reflecting weaker tobacco control policies and social norms made possible by the large economic influence of the tobacco industry in those tobacco-growing states. The fraction is also high in states with large poor and less educated populations, in the rest of the South (Louisiana, Alabama, and Mississippi), and in the Appalachian region (West Virginia). It is lowest in California (26%), where tobacco control is strong and large non-smoking Hispanic populations live, and in Utah (17%) where social norms (55% of people are Mormons) proscribe smoking. It is important to note that the effect of tobacco control on cancer deaths due to smoking are only visible on the long term, hence it is essential to implement it as soon as possible.

Using lung cancer mortality as a marker of past and current smoking exposure, in chapter 4.1, we investigated the effect of smoking on COPD mortality in 61 in high- and middle-income countries. It turned out that while lung cancer and COPD mortality where strongly correlated in high-income countries among women, they were only moderately correlated among men in both high- and middle-income countries. No correlation was found among women in middle-income countries. In fact, around 2011–2013, lung cancer mortality rates were up to 10 times higher than COPD mortality rates in the majority of the countries, whereas in most of middle-income countries in Latin America and Asia the reverse was true. Also, while both lung cancer and COPD mortality were declining among men over the last 10 years (around 2002-2011), lung cancer mortality was increasing in about half of the countries and COPD was increasing in six European countries among women. Progress in the diagnosis and treatment of COPD symptoms (as opposed to limited progress in lung cancer treatment), as well as declines in poverty—a major risk factor for COPD— in the studied countries further mitigated the association between smoking (tracked by lung cancer mortality) and COPD mortality. In conclusion, while smoking had a major role in driving the COPD mortality rate in high-income countries, additional risk factors had to be also important to explain COPD mortality in middle-income countries.

We showed that the international burden of smoking-related cancer and COPD is large. Despite the global declines in smoking prevalence since the 1990s, the burden will continue to be large for some time due to the considerable lag time between smoking and ensuing cancer or COPD. In fact, lung cancer incidence and mortality are still increasing among women in most European populations. Furthermore, although the

mortality rate of smoking-related cancer and COPD mostly declined over 2002–2011, the number of deaths increased because of mere population growth and ageing.

Since the definitive evidence of the link between smoking and numerous diseases starting in the mid-1950s, the very high male smoking prevalence has been halved in high-income countries. However, tobacco control and increased awareness of the harmful effects of tobacco had only limited bearing on female smoking prevalence, at least until the 1990s. Therefore, there is a continuing need for tobacco control. It should not take another sixty years to cut smoking prevalence by two in high-income countries and among men in middle-income countries, and to prevent women in middle-income countries from picking up the deadly habit. If we want to eradicate tobacco-related diseases, tobacco control policies must be strengthened, harm-reduction solutions (smokeless tobacco and electronic-cigarettes) must be investigated for addicted smokers, and tobacco-free generation measures (i.e. ending the legal provision of tobacco to the generations that have not yet commenced consumption) should be undertaken. The damaging effects of tobacco go beyond their deleterious impact on health. Tobacco production triggers deforestation, and diverts land and water from food production; tobacco use causes economic losses for consumers and societies; and tobacco disposal produces toxic waste. A multidisciplinary approach is thus needed to strike tobacco at every stage, so that the harms of tobacco are put to an end in the twenty-first century.

5.4 SAMENVATTING

Vóór de negentiende eeuw was longkanker een zeldzame ziekte. Het kostte tijd, vernuft en standvastigheid om te bewijzen dat het roken van sigaretten verantwoordelijk was voor de snelle stijging van longkanker sterfgevallen, waargenomen in de rijkere landen in Noord-Amerika en Europa in de eerste helft van de twintigste eeuw. In de tweede helft van die eeuw, bleken meer ziekten oorzakelijk verband te houden met roken, waaronder elf soorten kanker, chronische obstructieve luchtwegaandoeningen (COPD) en hart- en vaatziekten. Zelfs zestig jaar na onweerlegbaar bewijs van de gezondheidschade van tabak en steeds verdergaand tabaksbeleid leidde tot afname van het aantal rokers, blijft de last van roken gerelateerde kankers en COPD behoorlijk onderschat. Daarom is de internationale last van het roken gerelateerde kankers en COPD nog eens beoordeeld aan het begin van de 21ste eeuw, met een speciale focus op Europa en de Verenigde Staten van Amerika die zo'n cruciale rol hebben gespeeld in de verspreiding van sigaretten wereldwijd.

In Europa bleef de roken gerelateerde incidentie van kanker hoog, vanwege een decennia durend interval tussen het roken en de diagnose van de kankers. Massaal gebruik van sigaretten volgde de economische ontwikkeling van het continent: eerst in Noord- en West-Europa, vervolgens in Zuid-Europa, en gevolgd door Midden- en Oost-Europa. Het roken door vrouwen liep tientallen Jaren achter bij de mannen en bereikte nooit de hier en daar zeer hoge mannelijke rookprevalentie. In de periode 1998-2007 is de longkanker incidentie bij mannen-waarvan meer dan 80% te wijten is aan roken- gedaald of afgevlakt in heel Europa (hoofdstuk 2.1), naar aanleiding van scherpe dalingen van het aantal rokers sinds de jaren 50. Daarentegen nam de longkanker incidentie bij vrouwen sterk toe in de 19 landen in dezelfde periode. Bij andere belangrijke roken gerelateerde kankers (mond- en keelholte, strottenhoofd en slokdarm) was het effect van het vroegere rookprevalentie trends minder evident, maar de toerekenbare fractie door het roken werd ook beinvloed door min of meer gelijktijdige invloeden van andere risicofactoren die specifiek zijn voor deze sites, maar ook het kleine aantal gevallen maakt dit niet mogelijk. Gedurende 1998-2007 bleek de incidentie van kanker in de mond- en keelholte alleen maar te zijn toegenomen in Tsjechië, Denemarken, Slowakije, het Verenigd Koninkrijk en Duitsland. De incidentie was alleen toegenomen in sommige leeftijdsgroepen bij vrouwen in Ierland, Noorwegen, en in Nederland. De incidentie van strottenhoofdkanker was alleen toegenomen bij Bulgaarse mannen, terwijl het aantal gevallen zeer laag bleef bij Europese vrouwen. Forse stijgingen bij slokdarmkanker bij mannen bleven over het algemeen beperkt tot de noordelijke helft van Europa, terwijl dit bij vrouwen in de meeste landen van West-, Midden- en Oost-Europa ook het geval was.

De industrieel vervaardigde sigaretten evolueerden voortdurend sinds de lancering eind Jaren '80 van de negentiende eeuw, om steeds nieuwe rokers te bedienen en te behouden. De veranderingen in sigaretontwerp en samenstelling bleken later uit veranderingen in de frequentie van longkanker subtypes. De meest vóórkomende subtypes zijn plaveiselcelcarcinoom (SCC) en Adenocarcinoom (ADC) van de long. Terwijl de longkanker incidentie daalde of stabiel bleef in 1973-2002 bij mannen in alle elf rijke landen -behalve Spanje- varieerden de trends per subtype aanzienlijk (hoofdstuk 2.2). SCC was het meest gediagnosticeerde subtype van longkanker bij mannen in het begin van de studie. Maar ADC diagnoses overtroffen SCC diagnoses bij mannen in zes landen rond 1990. In tegenstelling tot de daling van de SCC incidentie, vlakte de ADC incidentie af of steeg zelfs. Daarentegen was ADC altijd het overheersende subtype van longkanker bij vrouwen gedurende de studieperiode. Op grond van velerlei ander onderzoek zijn de meest aannemelijke redenen voor deze verschuiving van de longkanker-epidemie van SCC naar ADC:

1. de opkomst van de gefilterde, lagere teer- en nicotine bevattende sigaretten leidde tot dieper inhaleren in de longen (om dezelfde dosis nicotine te krijgen), en tot vervanging van centrale door perifereer gelegen tumoren (vaak ADC);
2. veranderingen in de kankerverwekkende mix van sigarettenrook. Omdat vrouwen de rookgewoonte een paar decennia na de mannen overnamen, toen gefilterd / laag teergehalte en lage-nicotine sigaretten de markt overspoelden, en
3. omdat vrouwen de ideale doelgroep vormden voor deze nieuwe 'light sigaretten'. Bij hen werd ADC dus altijd vaker aangetroffen dan SCC.

Per jaar is kanker in de VS verantwoordelijk voor ongeveer 10 miljoen disability-adjusted life years (DALY's) (als de combinatie van jaren verloren door vroegtijdige sterfte en jaren geleefd met een verminderde kwaliteit van leven als gevolg van een handicap) (hoofdstuk 3.1). De last van kanker is ongeveer gelijk bij mannen en vrouwen met elk 5.000.000 DALY's. Het deel van deze last te wijten aan het roken van sigaretten is echter veel hoger bij mannen dan bij vrouwen (32% en 21%, respectievelijk) (hoofdstuk 3.2). Het verschilt ook per etnische groep: hoger bij de niet-Spaanse blanken en niet-Spaanse zwarten (ongeveer 28%) dan bij de niet-Spaanse Aziaten en Latijns-Amerikanen (19%). Deze verschillen ontstonden als gevolg van verschillen in de vroegere (en huidige) rookprevalentie tussen deze etnische groepen als gevolg van verschillende sociale normen, sociaal-economische status, maar ook gerichte tabak marketing en acculturatie niveau onder allochtonen. De aan roken toerekenbare fractie toont de theoretische gezondheidswinst als het roken van tabak werd geëlimineerd (en zonder eventuele bijwerkingen hiervan): van 10% van de kankerlast bij niet-Spaanse Aziatische vrouwen tot 34% bij niet-Spaanse zwarte mannen.

Naast verschillen per geslacht en etnische groep bleek er ook aanzienlijke geografische variatie in de aan roken gerelateerde kankersterfte de VS (hoofdstuk 3.3). Nationaal bedraagt dit aandeel ongeveer 29%, maar bleek het beduidend hoger in zuidelijke staten, waar traditioneel veel tabak werd verbouwd: Kentucky (34%), Tennessee (33%), Noord-(31%) en Zuid Carolina (30%). Deze hoge sterfte aan roken gerelateerde kankers is te wijten aan een veel hogere prevalentie van roken, waarschijnlijk als gevolg van het minder strenge tabaksgebruikbeleid en heersende sociale normen voortvloeiend uit de grote sociale en economische invloed van de tabaksindustrie in deze staten. Maar de fractie bleek ook hoog in zuidelijke staten met een relatief grote arme, laag opgeleide bevolking (Louisiana, Alabama en Mississippi), en in de Appalachen regio (West Virginia). Daarentegen was die lager in California (26%), waar de strengere bestrijding van het tabaksgebruik ook aansloeg op de aldaar sterk groeiende Spaanstalige bevolking, en het laagst in Utah (17%), waar sociale normen (55% Mormonen) traditioneel het roken verboden. Omdat het effect van tabaksgebruik op kankerdood door roken alleen op de lange termijn effect sorteert, is het essentieel zo spoedig mogelijk actie te nemen.

Met behulp van de sterfte aan longkanker als een ''marker'' van het vroegere rookgedrag en ook de huidige roken blootstelling, onderzocht ik in hoofdstuk 4.1 het effect van roken op de sterfte aan chronisch long lijden (COPD) in 61 in hoge en midden-inkomens landen met enigszins betrouwbare doodsoorzakenstatistiek. Terwijl longkanker en COPD sterfte sterk gecorreleerd waren in de rijke landen, met name bij vrouwen, bleek dit verband minder sterk bij vrouwen in de midden-inkomens landen. In 2011-13 bleken de, longkanker sterftecijfers tot 10 keer hoger dan die van COPD in het merendeel van de landen, met uitzondering van de meeste midden-inkomens landen in Latijns-Amerika en Azië die het omgekeerde lieten zien. Terwijl tussen 2002 en 2011) zowel de longkanker als de COPD sterfte daalde bij mannen, steeg de longkanker sterfte in de helft van de landen bij vrouwen, maar de COPD-sterfte alleen in zes Europese landen, waar ook grote toenames van het rookgedrag plaatsvonden. Vooruitgang in de diagnose en behandeling van COPD symptomen (in tegenstelling tot de beperkte vooruitgang in de behandeling van longkanker), evenals dalingen in armoede een belangrijke risicofactor voor COPD- in de bestudeerde landen verder beperkt het verband tussen roken (gevolgd door longkanker sterfte) en COPD sterfte. Tot slot, terwijl het roken een belangrijke invloed had op het COPD sterftecijfer in rijke landen, hadden bijkomende risicofactoren een belangrijk aandeel in de COPD sterfte in midden-inkomens landen.

Al met al lieten we zien dat de internationale last van roken gerelateerde kanker en COPD onverminderd groot is. Ondanks de globale afname van het aantal rokers sinds

de jaren 1990, zal de last nog enige tijd groot blijven als gevolg van de aanzienlijke tijdas tussen roken en de daaruit voortvloeiende kanker en/of COPD. In feite namen longkanker incidentie en sterfte zelfs nog steeds toe bij vrouwen in de meeste Europese populaties. Hoewel het sterftecijfer aan roken gerelateerde kanker en COPD meestal afnam in de periode 2002-2011, steeg het aantal doden als gevolg van louter bevolkingsgroei en vergrijzing.

Aangezien het definitieve bewijs voor het verband tussen roken en tal van ziekten al in de Jaren '50 zeer aannemelijk was, heeft de zeer hoge mannelijke prevalentie van roken van toen geleid tot de zeer ongunstige situatie in landen met hoge inkomens. Het blijft zeer verwonderlijk dat de bewustwording van de schadelijke effecten van tabak zo lang zo beperkt bleef bij vrouwen, vaak tot in de jaren '90. Het moet niet nog zestig jaar duren om de prevalentie van roken te halveren in rijke landen en bij mannen in het midden-inkomenslanden, noch om te voorkomen dat vrouwen in midden-inkomens landen de dodelijke gewoonte oppakken. Als we tabak gerelateerde ziekten willen uitroeien, moet bestrijding van het tabaksgebruik worden geintensiveerd, moet worden onderzocht of schadebeperkende oplossingen (rookloze tabak en elektronische sigaretten) waardevol zijn voor verslaafde rokers, en moet er naar tabak-vrije (jongere) generaties worden gestreefd (door beëindiging van de wettelijke erkenning van tabak aan die generaties).

De schadelijke effecten van tabak gaan overigens verder dan hun schadelijke invloed op de gezondheid. Tabaksproductie draagt ook bij aan ontbossing en onttrekt land en water aan voedselproductie. Het gebruik van tabak is al met al in economisch opzicht schadelijk voor zowel consument als samenleving; en tabak produceert ook giftig afval. Een multidimensionele, -sectorale en -disciplinaire aanpak is dus nodig om het tabaksgebruik een slag toe te brengen in elke fase, opdat er nog in de 21ste eeuw een einde komt aan de schade van tabak.

5.5 RÉSUMÉ (FRENCH SUMMARY)

Avant le XIXème siècle, le cancer du poumon était une maladie rare. Il aura fallu du temps, de la perspicacité et de la persévérance pour arriver à démontrer que le tabagisme était la cause de l'accroissement rapide du nombre de morts par cancer du poumon dans les pays à hauts revenus en Amérique du Nord et en Europe durant la première moitié du XXème siècle. Au cours de la seconde moitié du XXème siècle, on découvrira que le tabagisme est également responsable d'autres maladies, dont onze types de cancer, de la bronchopathie pulmonaire chronique obstructive (BPCO) et de certaines maladies cardiaques. Même soixante ans après la preuve irréfutable des effets délétères du tabac sur la santé et la mise en place de politiques de lutte contre le tabagisme ayant mené à une baisse de sa prévalence, le fardeau des cancers liés au tabac et de la BPCO reste colossal et sous-estimé. C'est pourquoi, j'ai souhaité évaluer le fardeau mondial des cancers liés au tabac et de la BPCO au tournant du XXème siècle, avec une attention particulière pour l'Europe et les Etats-Unis (un pays qui a joué un rôle fondamental dans la dissémination du tabagisme dans le monde).

En Europe, l'incidence des cancers liés au tabac reste élevée, car il faut plusieurs décennies après l'adoption de l'habitude de fumer pour que la maladie se développe et soit diagnostiquée. La consommation de masse des cigarettes est allée de pair avec le développement économique du continent : tout d'abord en Europe du Nord et de l'Ouest, ensuite au Sud, enfin en Europe centrale et de l'Est. Les femmes ont adopté la cigarette plusieurs décennies après les hommes, sans jamais atteindre leur niveau très élevé de consommation. Sur la période 1998-2007, l'incidence du cancer du poumon (dont 80% des cas sont attribuables à la cigarette) a décliné ou s'est stabilisée chez les hommes dans toute l'Europe (chapitre 2.1), suite à une baisse drastique du tabagisme initiée dans les années 1950. Au contraire, sur la même période, l'incidence du cancer du poumon chez les femmes augmentait dans 19 pays. L'impact du taux de tabagisme sur l'incidence des décennies plus tard d'autres cancers fréquents liés au tabac (cancers de la cavité orale et du pharynx, du larynx et de l'œsophage) est moins évident pour plusieurs raisons. Premièrement, du fait du rôle secondaire de la cigarette dans ces cancers ; deuxièmement, des changements de prévalence d'autres facteurs de risques spécifiques pour ces maladies ; ou troisièmement, du faible nombre de cas. Sur la période 1998-2007, le taux d'incidence du cancer de la cavité orale et du pharynx n'a augmenté que dans quelques populations dans certaines classes d'âge chez les hommes : en République Tchèque, au Danemark, en Slovaquie, au Royaume-Uni et en Allemagne. Le nombre de cas a également augmenté dans certaines classes d'âge chez les femmes dans ces pays, ainsi qu'en Irlande, en Norvège et aux Pays-Bas. L'incidence du cancer du larynx a uniquement augmenté parmi les hommes en

Bulgarie, alors que le nombre de cas est resté très faible chez les femmes partout en Europe. Enfin, c'est seulement dans la moitié nord de l'Europe que le nombre de cas du cancer de l'œsophage chez les hommes a cru, alors que chez les femmes les cas ont augmenté dans la plupart des pays en Europe de l'Ouest, centrale et de l'Est.

Depuis leur lancement à la fin du XIXème siècle, les cigarettes manufacturées ont constamment évolué, afin d'attirer et de retenir les fumeurs. Les changements dans le design et la composition des cigarettes se sont traduits des années plus tard par des changements dans la fréquence des sous-types de cancer du poumon dans les populations. Les principaux sous-types sont les carcinomes épidermoïdes (CE) ou à cellules squameuses et les adénocarcinomes (AdC) du poumon. Alors que l'incidence du cancer du poumon a décliné ou est restée stable sur la période 1973-2002 chez les hommes dans les onze pays étudiés à hauts revenus (sauf en Espagne), les tendances ont varié par sous-type (chapitre 2.2). Les CE étaient les cancers du poumon le plus souvent diagnostiqués chez les hommes au début de l'étude. Pourtant, aux alentours des années 1990, les AdC devinrent le sous-type le plus fréquent. Alors que le nombre de cas de CE déclinait, le nombre d'AdC restait stable ou même augmentait au cours du temps. Au contraire, chez les femmes, les cas d'AdC ont prédominé sur toute la période d'étude et ont continuellement augmenté. Il existe plusieurs raisons pour expliquer le basculement du sous-type dominant du CE vers l'AdC chez les hommes. Tout d'abord, la mise sur le marché de cigarettes avec filtre et à plus faible teneur en goudron et en nicotine a incité les fumeurs à inspirer plus profondément (pour obtenir la même dose de nicotine). Comme la fumée s'insinuait plus loin dans les bronches, les tumeurs logées au centre des poumons (souvent des CE) ont été remplacées par des tumeurs à leur périphérie (souvent des AdC). Ensuite, avec le changement de la composition des cigarettes, le mélange des carcinogènes et leurs niveaux respectifs ont également changé. Comme les femmes ont adopté massivement la cigarette des décennies après les hommes, à un moment où ces cigarettes avec filtre et à teneur plus faible en goudron et en nicotine avaient inondé le marché, et qu'en outre, elles étaient la cible de campagnes de publicité pour ces cigarettes dites « légères », les AdC ont toujours été plus fréquemment diagnostiqués chez elles que les CE.

Chaque année, aux Etats-Unis, le cancer est responsable de la perte d'environ 10 millions d'années de vie ajustées sur l'incapacité (AVAI) (chapitre 3.1). Les AVAI sont la combinaison du nombre d'années de vie perdues à cause d'une mort prématurée (c'est-à-dire avant l'espérance de vie) et du nombre d'années vécues avec une incapacité due à une pathologie ou un accident. Les AVAI mesurent le fardeau d'une maladie. Aux Etats-Unis, les hommes et les femmes perdent un nombre équivalent d'AVAI à cause du cancer — soit 5 millions d'AVAI chacun. Cependant, la fraction de

ces AVAI perdues attribuables à la cigarette est plus élevée chez les hommes (32%) que chez les femmes (21%) (chapitre 3.2). Cette fraction varie également suivant la race/l'ethnie : elle est plus élevée chez les Blancs non-hispaniques et les Noirs non-hispaniques (environ 28% du fardeau du cancer est dû à la cigarette) que chez les Asiatiques et les Hispaniques (19%). Ces écarts sont le résultat de différences dans la prévalence du tabagisme actuel et passé entre les races, les ethnies et les sexes. Les différences dans la prévalence du tabagisme sont elles-mêmes issues de variations dans les normes sociales (acceptabilité du tabagisme), du statut économique et social (il y a plus de fumeurs chez les pauvres et les personnes moins éduquées), les cibles du marketing des cigarettiers et du degré d'adoption du mode de vie américain par les migrants hispaniques. Ce calcul montre qu'on pourrait en théorie abaisser le fardeau du cancer de 10% chez les femmes asiatiques à 34% chez les hommes Noirs non-hispaniques en éliminant totalement les cigarettes.

Outre les différences entre les races, les ethnies et les sexes, il existe également des différences géographiques dans la mortalité due au tabac aux Etats-Unis (chapitre 3.3). Au niveau national, 29% des décès par cancers peuvent être attribués à la cigarette, mais cette fraction est plus élevée dans les Etats du Sud : 34% au Kentucky (la fraction la plus haute parmi les 51 Etats), 33% au Tennessee, 31% en Caroline du Nord, 30% en Caroline du Sud, 29% en Géorgie, 28% en Virginie, etc. La prévalence élevée du tabagisme dans ces Etats du Sud explique la forte proportion des décès par cancer due à la cigarette. Cette forte prévalence résulte de politiques de lutte contre le tabac plus faibles et des normes sociales quant à l'acceptabilité du tabagisme dans les Etats du Sud, elles-mêmes rendues possibles par la puissante influence économique de l'industrie du tabac. En effet, 95% du tabac produit aux Etats-Unis provient de ces six Etats. Cependant, la fraction des décès par cancer due à la cigarette est également élevée dans les Etats ayant de larges populations de personnes pauvres et peu éduquées dans le reste du Sud des Etats-Unis (Louisiane, Alabama et Mississippi) et dans la région des Appalaches (Virginie Occidentale). Au contraire, cette fraction est la plus faible en Californie (26%) où une politique vigoureuse de lutte contre le tabagisme est poursuivie depuis 25 ans et où vit une grande communauté hispanique (qui fume peu), et en Utah (17%) où des normes religieuses (55% des habitants sont Mormons) proscrivent la cigarette. Il faut souligner que les effets d'une politique de lutte du tabagisme sur la mortalité par cancer due au tabac s'observent à long terme et qu'il faut donc la mettre en place le plus rapidement possible.

En utilisant le taux de mortalité par cancer du poumon comme marqueur de l'exposition au tabac, j'ai examiné l'influence du tabagisme sur la mortalité par BPCO dans 61 pays à hauts et moyens revenus (chapitre 4.1). Il ressort de cette analyse que si

l'association entre le tabac et la mortalité par BPCO est forte dans les pays à hauts revenus chez les femmes, l'association est modérée chez les hommes dans les pays à hauts et moyens revenus. En outre, aucune corrélation n'a été trouvée chez les femmes dans les pays à revenus moyens. Pour preuve, aux alentours de 2011-2013, le taux de mortalité par cancer du poumon était jusqu'à 10 fois plus élevé que celui par BPCO dans la majorité des pays, sauf dans la plupart des pays à revenus moyens en Amérique latine et en Asie, où l'inverse était observé. Par ailleurs, alors que les taux de mortalité du cancer du poumon et de la BPCO ont baissé sur les dix dernières années (aux environs de 2002-2011) chez les hommes, le taux de mortalité du cancer du poumon a augmenté dans la moitié des pays et celui de la BPCO dans six pays européens chez les femmes. Les progrès dans le diagnostic et le traitement de la BPCO (par opposition aux progrès limités dans le traitement du cancer du poumon), ainsi que le déclin de la pauvreté — un facteur de risque majeur de la BPCO — dans les pays étudiés, ont également atténué la relation entre le tabagisme (signalé par les décès par cancer du poumon) et les décès par BPCO. En conclusion, si le tabagisme joue un rôle majeur dans la mortalité par BPCO dans les pays à hauts revenus, des facteurs de risque supplémentaires sont également importants pour expliquer la mortalité par BPCO dans les pays à revenus moyens.

J'ai montré que le fardeau international des cancers liés au tabac et de la BPCO est gigantesque. En dépit de la baisse de la prévalence du tabagisme au niveau mondial depuis les années 1990, ce fardeau continuera à être colossal pendant longtemps à cause de la longue période de latence entre l'adoption de l'habitude de fumer et les cancers et les BPCO consécutifs. Au demeurant, l'incidence et la mortalité du cancer du poumon continuent d'augmenter chez les femmes dans la plupart des pays européens. De plus, malgré la baisse du taux de mortalité des cancers liés au tabagisme et de la BPCO sur la période 2002-2011, le nombre de morts a augmenté simplement à cause de l'accroissement et du vieillissement de la population.

Depuis la preuve indiscutable du lien entre le tabagisme et de nombreuses maladies à partir du milieu des années 1950, la très forte prévalence du tabagisme chez les hommes a été divisée par deux dans les pays à hauts revenus. En revanche, la lutte contre le tabagisme et l'augmentation de la prise de conscience des effets délétères du tabac sur la santé n'ont eu qu'un impact limité sur le tabagisme des femmes, au moins jusque dans les années 1990. C'est pourquoi, il y a un besoin continu de lutte contre le tabagisme. Il ne faudrait pas mettre encore soixante ans pour diminuer de moitié la prévalence du tabagisme chez les hommes et les femmes dans les pays à hauts revenus et chez les hommes dans les pays à revenus moyens, et pour empêcher les femmes habitant les pays à revenus moyens d'adopter la cigarette. Si nous voulons

éradiquer les maladies liées au tabac, les politiques de lutte contre le tabac doivent être renforcées, les solutions de substitution comportant moins de risque pour la santé (tabac sans combustion et cigarette électronique) doivent être examinées pour les fumeurs dépendants et, enfin, des mesures pour une génération sans tabac (c'est-à-dire l'interdiction de la vente du tabac aux générations qui n'ont pas commencé à fumer) doivent être adoptées. Les effets dévastateurs du tabac vont au-delà des risques pour la santé. La production de tabac engendre des déforestations et détourne les terres arables et l'eau de la production de nourriture ; le tabac génère des pertes économiques pour ses consommateurs et la société ; et les déchets des cigarettes sont toxiques. Une approche multidisciplinaire est donc nécessaire pour combattre le tabac à chaque étape de la vie du produit, afin que les méfaits du tabac cessent au cours du XXIème siècle.

6

About the author

6.1 LIST OF PUBLICATIONS

ARTICLES

This thesis

1. **Lortet-Tieulent J**, Renteria E, Sharp L, et al. Convergence of decreasing male and increasing female incidence rates in major tobacco-related cancers in Europe in 1988–2010. Eur J Cancer. 2015;51(9):1144-1163.
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3. **Lortet-Tieulent J**, Soerjomataram I, Lin CC, Coebergh JW, Jemal A. US burden of cancer by race and ethnicity according to Disability-Adjusted Life Years (DALYs). Am J of Prev Med. 2016 (in press for November 2016 issue).
4. **Lortet-Tieulent J**, Kulhánová I, Jacobs EJ, Coebergh JW, Soerjomataram I, Jemal A. Cigarette smoking-attributable cancer burden by race and ethnicity in the United States. (submitted)
5. **Lortet-Tieulent J**, Goding Sauer A, Siegel R, et al. State-level cancer mortality attributable to cigarette smoking in the United States. JAMA Int Med (accepted)
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countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015;386(10010):2287-2323.
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1. Cancer by organs. Bray F, Forman D. In World Cancer Report 2014. Stewart B and Wild CP. WHO. 2013
2. Cancer in Women: Global Burden and Insights from Gender Comparisons. McCormack V, **Lortet-Tieulent J**, Shin HR, Bray F. Women and health, 2nd edition. Goldman MB and Hatch MC. Elsevier. 2013

6.2 CV

Joannie Lortet-Tieulent was born on the 22nd of June 1975, in Chambery, in the Alps, in France. In 1993, she completed her secondary education in Lycée Vaugelas in Chambery. Curious and high-spirited, she went on for a 2-year Bachelor's degree in biology at the Université de Savoie, by the Bourget Lake, close to Chambery. Starting in 1995, she would go each year further away from her place of birth. In 1996, she completed a License in population biology in Université Joseph Fourier in Grenoble (still in the Alps). Then she enrolled into an exchange program for a year, at the University of Waterloo, in Ontario, Canada, for the first year of her Master's degree, in organisms and population biology. Her thesis analyzed dead log utilization by wildlife in Algonquin Provincial Park in Ontario. Back to France, thrilled by the power of statistics, she switched her major to biostatistics for her second year of the Master's degree at Université Claude Bernard, in Lyon. That year's master thesis would be on tropical tree growth modeling, sending her to India, at the French Institute in Pondicherry and into the jungle in Karnataka.

After she got her diploma, in 1998, she was hired as a park ranger for a year, in Newport News, Virginia, USA, to lead a tick population study and rescue orphaned and injured wildlife. While there, she married a wonderful French physicist. In 2000, she settled for 3 years in Grenoble, as an IT teacher for the city. Later, she moved to Lyon, to be a project manager leading pharmaco-epidemiological studies, for 5 years. By the time she was 30, she had three wonderful —like their father— kids (the last two were twins for added fun). In 2009, she started to work at the International Agency for Research on Cancer (IARC/WHO), as a statistician, in the Cancer Surveillance section. There, she became acquainted with international cancer registry data. In 2013, she joined the American Cancer Society, in the Surveillance and Health Services Research program, as a senior epidemiologist in Atlanta, Georgia, USA. She started her research for her PhD in 2013, while still working at IARC and completed her thesis while working for the American Cancer Society. To be able to tackle her PhD while raising three children with her husband and having a full-time job, and still enjoy the journey, she turned to meditation… and kickboxing.

6.3 PHD PORTFOLIO

Name PhD student	Joannie Lortet-Tieulent
Erasmus MC Department	Public Health
PhD period	March 2013 – November 2016
Promotor:	Prof.dr. J.W.W. Coebergh
Copromotor:	Dr. I. Soerjomataram

			Workload (ECTS)
Courses			
Grant writing, IARC, Lyon, France	2012	1 day	0.5
Principals of oncology, Lyon, France	2012	2 hrs.	0.2
Seminars and workshops			
ACS seminars	2013 – 2016	60 hrs.	3
International Cancer Research Partnership, Atlanta, USA	2016	2 days	1
Attributable fraction of cancer due to preventable risk factors workshop, ACS, Atlanta, USA	2014	2 days	1
Tobacco regulation, Georgia State University, Atlanta, USA	2014	2 hrs.	0.1
Global Information Science workshops, ACS, Atlanta, USA	2013	4 hrs.	0.2
Infections and cancer, Emory University, Atlanta, USA	2013	2 hrs.	0.1
IARC priority research forum on Head and neck cancer, Lyon, France	2012	1 day	0.5
IARC seminars, Lyon, France	2012 – 2013	15 hrs.	1
Conferences and presentations			
International association of Cancer registries annual meeting, Mumbai, India (1 plenary presentation, chair of a plenary session, judge for posters)	2015	35 hrs.	1
Alliance des Ligues Francophones Africaines & Méditerranéennes fourth meeting (1 plenary session)	2015	32 hrs.	1

North American Association of Central Cancer Registries, Charlotte, USA (1 presentation in parallel session)	2015	32 hrs.	1
International association of Cancer registries annual meeting, Ottawa, Canada (1 plenary presentation, 2 posters [one First prize])		96 hrs.	3
Brazilian National Cancer Institute meeting, Head and Neck cancer in South America, Rio de Janeiro, Brazil (1 plenary presentation)	2012	32 hrs.	1
Scientific days of Rhone Alps Auvergne Cancer Center, Lyon, France (1 poster)	2012	32 hrs.	1
International association of Cancer registries annual meeting, Cork, Ireland (1 plenary presentation)	2012	32 hrs.	1
Teaching			
Assessing the burden of disease, University of Georgia, Athens, USA	2014	8 hrs.	0.3
Rate standardization, IARC Summer School, Lyon, France	2012	20 hrs.	1
Journal Club			
Chairing of the Surveillance Journal Club, American Cancer Society, Atlanta, USA	2013 – 2015	100 hrs.	3
Attendance at the Cancer Epidemiology Journal Club, IARC, Lyon, France	2012 – 2013	22 hrs.	1
Other external communication			
Launch of the Hindi version of the Cancer Atlas, Mumbai, India	2015	32 hrs.	1
Launch of the French version of the Cancer Atlas, Abidjan, Côte d'Ivoire	2015	32 hrs.	1
Total			23.9

6.4 ACKNOWLEDGMENTS

"Writing is like driving at night. You can only see as far as your headlights, but you can make the whole trip that way."

E.L. Doctorow

Likewise, writing a thesis is a race through the night. I knew where was the finish line, but when I started, the path lay in darkness. Nevertheless, I was able to complete this amazing race owing to the many people who have enlightened my path. I want to thank all of them.

Dear Jan Willem, thank you for accepting to be my promotor. I remember our first encounter in this loud restaurant in Ireland and after you agreed, I thought that my long-lasting dream of getting a PhD would finally come true. You have been the moon brightening my path through the night: high-level thoughts, and showing me my surroundings. "So what?" and "Who cares?" were your mottoes. Thank you for constantly challenging me intellectually, de-constructing what I had learned before, wrecking my beliefs, clearing space for new knowledge. You led me —always with benevolence— to my final stop.

Ma très chère Isabelle, I owe you this whole journey. You made this crazy dream of mine possible, first by convincing me it was feasible, then by launching me into the PhD program thanks to your network in Erasmus, and finally by offering to be my copromotor. You were like my flashlight: highlighting the obstacles and showing me how to overcome them, and advising me at crossroads in my career. You stayed close to me throughout the night, until it was dawn. Besides, I feel very fortunate to have you as a very close friend.

Dear members of the klein committee, Prof van Leeuwen, Prof Boezen, and Prof Aerts thank you for taking the time to read and assess my dissertation, all the more it was Summer time. Also to Prof Baas, Prof Mackenbach and Prof Janssen-Heijnen for accepting to be part of the opposition during my defense. I want to extend my thanks to the Erasmus Public Health for admitting me in the doctoral program. Furthermore, I express my gratitude to Yvonne van Loon for facilitating the administrative work and distributing my thesis to the members of the committees and to Pedel. It is precious to have such a great ally when I am so far away. All of you have brought some light at critical steps in my PhD.

Dear Ahmedin, thank you for offering me to work on manuscripts in line with both the American Cancer Society's (ACS) missions and with my PhD topic. Many thanks also for teaching me the importance of "telling a story" when writing an article. I appreciate your guidance on how to make a study attractive to scientific journals and their audience. Comparing drafts I wrote when I arrived at ACS three years ago with current ones, I clearly see your influence and how much I have grown professionally by your side.

Dear Freddie, you have been my inspiration in many ways. Your career path showed me the way to further my own career in public health. I have always admired your writing style, and I can see a connection when I write "albeit", "caveats" and "aforementioned" in manuscripts. I am grateful that you believed I could quickly acquire new talents even when I doubted it myself. In particular, you gave me no choice but to learn Stata, age-period-cohort modeling, and predictions. I am now a firm convert to the three (aforementioned).

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Joannie