



CrossMark

# Risk factors for lung cancer worldwide

Jyoti Malhotra<sup>1,2</sup>, Matteo Malvezzi<sup>3,4</sup>, Eva Negri<sup>4</sup>, Carlo La Vecchia<sup>3</sup> and Paolo Boffetta<sup>1</sup>

Number 1 in the series “Multidisciplinary questions in thoracic oncology: the team experience”

Edited by J-P. Sculier

## Affiliations:

<sup>1</sup>Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA.

<sup>2</sup>Rutgers Cancer Institute of New Jersey, Robert Wood Johnson Medical School, New Brunswick, NJ, USA.

<sup>3</sup>Dept of Clinical Sciences and Community Health, University of Milan, Milan, Italy.

<sup>4</sup>Dept of Epidemiology, IRCCS – Istituto di Ricerche Farmacologiche Mario Negri, Milan, Italy.

## Correspondence:

Carlo La Vecchia, Dept of Clinical Sciences and Community Health, Università degli Studi di Milano, Via Augusto Vanzetti 5, 20122 Milan, Italy.

E-mail: [carlo.lavecchia@unimi.it](mailto:carlo.lavecchia@unimi.it)

**ABSTRACT** Lung cancer is the most frequent malignant neoplasm in most countries, and the main cancer-related cause of mortality worldwide in both sexes combined.

The geographic and temporal patterns of lung cancer incidence, as well as lung cancer mortality, on a population level are chiefly determined by tobacco consumption, the main aetiological factor in lung carcinogenesis.

Other factors such as genetic susceptibility, poor diet, occupational exposures and air pollution may act independently or in concert with tobacco smoking in shaping the descriptive epidemiology of lung cancer. Moreover, novel approaches in the classification of lung cancer based on molecular techniques have started to bring new insights to its aetiology, in particular among nonsmokers. Despite the success in delineation of tobacco smoking as the major risk factor for lung cancer, this highly preventable disease remains among the most common and most lethal cancers globally.

Future preventive efforts and research need to focus on non-cigarette tobacco smoking products, as well as better understanding of risk factors underlying lung carcinogenesis in never-smokers.



@ERSpublications

**Tobacco smoking is the major determinant of lung cancer risk; genetics, occupation, pollution, poor diet also contribute** <http://ow.ly/4mRbUQ>

---

Editorial comment in *Eur Respir J* 2016; 48: 626–627.

Earn CME accreditation by answering questions about this article. You will find these at [erj.ersjournals.com/journal/cme](http://erj.ersjournals.com/journal/cme)

Received: Feb 17 2016 | Accepted after revision: April 04 2016 | First published online: May 12 2016

Support statement: This study was partly supported by the Italian Association for Cancer Research (AIRC; project no. 14360) Italian Foundation for Cancer Research (FIRC) and Ministero dell' Istruzione, dell' Università e della Ricerca (MIUR) Scientific Independence of Young Researchers (SIR) 2014 grant (project RBS11465UH). Funding information for this article has been deposited with FundRef.

Conflict of interest: None declared.

Copyright ©ERS 2016

## Introduction

Lung cancer is the most frequent malignant neoplasm among men in most countries and the main cause of cancer death in both sexes, accounting for an estimated 27% of total cancer deaths in the USA in 2015 and 20% in the European Union (EU) in 2016 [1, 2]. According to GLOBOCAN, in 2012 lung cancer accounted for an estimated 1 242 000 new cases among men, which is 17% of all cancers excluding non-melanoma skin cancer, and 583 000 (9%) of new cancer cases among women [3]. Approximately 58% of all cases occur in middle- and low-income countries [4]. Lung cancer also accounts for 19% of all cancer deaths [5]. Among both women and men, the incidence of lung cancer is low in people aged <40 years and increases up to age 75–80 years in most populations. The decline in incidence in the older age groups can be explained, at least in part, by incomplete diagnosis or by a generation (birth-cohort) effect, as in several countries the peak of the tobacco-related lung cancer epidemic has been reached by generations born in the 1930–1940s [6].

Table 1 presents the age-standardised mortality rates from lung cancer in men and women (at all ages) in selected countries worldwide and in the EU as a whole, in 2000–2004, 2005–2009 and 2012 (or closest year available for most countries), with the corresponding percent change. These figures were obtained from official lung cancer death certification data from the World Health Organization database [7]. Between 2002 and 2012, overall lung cancer mortality increased by 17.5% in the EU in women. Increases were observed in most European countries, with the exception of Denmark, Georgia and the Russian Federation. Worldwide, similar increases were also observed in most countries except for Central American countries (Mexico and Panama) and the USA. For men, overall lung cancer mortality between 2002 and 2012 decreased by 13.5% in the EU. Declines were also noted in several countries worldwide. Figure 1 shows joinpoint analyses of the trends in age-standardised mortality rates from lung cancer between 1980 and 2012 (or the most recent available year) in men and women from 23 selected European countries and the EU at all ages. Figure 2 shows the same statistics for eight other countries worldwide. In women, overall lung cancer mortality increased up to the most recent calendar year in most European countries, as well as worldwide. In a few countries characterised by earlier peaking (*i.e.* Denmark, UK and USA), mortality rates levelled off or declined over the most recent calendar year. Female lung cancer rates remain low and have not increased significantly in Russian women. Conversely, men showed a decline in lung cancer mortality in most countries except for a few, *i.e.* Brazil, Portugal and Bulgaria [8].

Thus, the decline in lung cancer mortality rates in men have continued over recent years, and are projected to persist in the near future [6]. Overall, female lung cancer mortality has been lower than in men but has been increasing up to recent years in most countries. Trends in lung cancer mortality can be interpreted in terms of different patterns of smoking prevalence in subsequent cohorts of people in various countries [9, 10]. An increase in tobacco consumption was paralleled a few decades later by an increase in the incidence of lung cancer, and a decrease in consumption is followed by a decrease in incidence. Similarly, the temporal lag in trends in female and male lung cancer mortality reflects historical differences in cigarette smoking between subsequent female and male cohorts [11, 12].

## Genetic risk factors

### Family history and high-penetrance genes

A positive family history of lung cancer has been found to be a risk factor in several registry-based studies that have reported a high familial risk for early-onset lung cancer [13]. Increased relative risks were found even after careful adjustment for smoking [14]. A linkage analysis of high-risk pedigrees identified a major susceptibility locus to chromosome 6q23–25 [15]. Lung cancer risk is also increased within the framework of the Li–Fraumeni syndrome, characterised by germline mutation in the tumour-suppressor gene p53 [16].

### Genetic polymorphisms

Recent genome-wide association (GWA) studies have been able to identify multiple genetic polymorphisms underlying lung cancer risk by utilising up to a million tagging single-nucleotide polymorphisms (SNP) to identify common genetic variations. Table 2 summarises the evidence of an association between genetic variants and lung cancer. The three main susceptibility loci identified are in the 15q25, 5p15 and 6p21 regions [20, 30, 31], but many other common variants have also been reported, as listed in table 2. GWA studies explain only a proportion of the overall genetic variance with lung cancer but the fact that only a minority of smokers develop cancer supports the hypothesis that genetic susceptibility might contribute to carcinogenesis.

Three separate GWA studies of lung cancer provided strong evidence for a susceptibility region in 15q25.1 with a consistent measure of effect between the studies [20, 30, 31]. Both the SNPs rs1051730 and rs8034191 corresponding to the region identified in these studies map to a 100-kb region of strong linkage disequilibrium on chromosome 15 extending from 76 593 078 bp to 76 681 394 bp. The 15q25 susceptibility region contains six identified coding regions, including three cholinergic nicotine receptor genes (*CHRNA3*,

TABLE 1 World standardised lung cancer death rates per 100 000 people (all ages) in selected countries in the periods 2000–2004, 2005–2009 and 2012 (or closest year available) and corresponding percent changes

	Men					Women				
	2000–2004	2005–2009	2012	% change 2007 versus 2012	% change 2002 versus 2012	2000–2004	2005–2009	2012	% change 2007 versus 2012	% change 2002 versus 2012
Argentina	32.28	29.84	27.18	−8.92	−15.81	7.14	8.09	8.97	10.81	25.60
Brazil	16.23	16.00	15.32	−4.24	−5.56	6.24	7.18	8.04	12.08	28.98
Canada	41.99	37.23	33.40	−10.28	−20.46	24.98	25.39	24.35	−4.11	−2.52
Chile	18.60	17.35	16.16	−6.89	−13.15	7.20	7.84	8.64	10.26	19.97
Colombia	13.80	14.38	12.98	−9.70	−5.92	7.04	7.36	6.78	−7.81	−3.57
Cuba	37.53	37.93	34.24	−9.74	−8.77	16.40	18.33	17.51	−4.46	6.74
Guatemala	5.85	5.68	4.63	−18.57	−20.91	3.98	3.83	2.56	−33.29	−35.78
Mexico	12.99	10.75	8.22	−23.52	−36.70	5.07	4.30	3.50	−18.64	−31.10
Panama	11.80	11.18	9.69	−13.34	−17.87	4.95	4.40	3.48	−20.86	−29.64
Puerto Rico	14.60	13.70	14.11	3.05	−3.34	5.63	5.83	5.38	−7.69	−4.40
USA	44.55	38.72	35.19	−9.12	−21.01	25.93	24.37	23.01	−5.61	−11.27
Uruguay	46.20	43.61	42.75	−1.97	−7.47	6.26	7.45	8.95	20.17	42.90
Venezuela	16.85	17.04	17.16	0.73	1.85	9.06	9.53	9.40	−1.34	3.82
Israel	26.51	25.19	23.73	−5.82	−10.50	8.88	8.99	9.44	4.92	6.21
Japan	29.91	28.87	27.40	−5.10	−8.39	8.03	7.95	7.76	−2.35	−3.30
Republic of Korea	43.44	39.44	35.06	−11.11	−19.30	10.08	9.46	8.89	−5.94	−11.78
Austria	35.84	32.43	29.27	−9.75	−18.33	11.53	12.60	14.42	14.47	25.02
Belgium	54.26	48.93	41.35	−15.48	−23.78	11.00	13.42	14.73	9.73	33.85
Bulgaria	39.41	43.93	41.40	−5.76	5.06	6.39	7.46	7.94	6.43	24.35
Croatia	62.11	57.06	52.40	−8.17	−15.64	10.72	11.74	13.07	11.26	21.92
Czech Republic	57.41	48.10	40.23	−16.35	−29.93	12.66	13.00	14.31	10.10	13.11
Denmark	41.60	37.32	33.11	−11.27	−20.41	28.01	28.56	26.77	−6.26	−4.42
Estonia	59.55	54.21	47.86	−11.71	−19.63	7.79	8.09	8.91	10.09	14.38
Finland	31.57	28.24	25.06	−11.26	−20.63	8.05	8.86	10.17	14.76	26.37
France	44.07	41.90	39.21	−6.43	−11.02	8.24	10.36	11.36	9.71	37.82
Georgia	24.87	17.72	23.77	34.12	−4.41	4.78	3.01	3.21	6.35	−32.94
Germany	39.17	34.99	32.08	−8.33	−18.11	11.12	12.76	14.50	13.65	30.40
Greece	47.73	46.45	46.33	−0.25	−2.94	7.34	7.72	9.24	19.71	25.85
Hungary	79.46	72.57	70.63	−2.67	−11.11	22.27	24.41	28.17	15.42	26.51
Iceland	26.14	29.18	24.32	−16.66	−6.98	25.14	25.86	23.59	−8.79	−6.17
Ireland	36.24	32.95	29.16	−11.50	−19.55	17.79	18.58	17.99	−3.19	1.13
Italy	45.44	38.39	34.43	−10.30	−24.22	8.61	9.44	10.30	9.11	19.69
Latvia	57.31	54.82	48.32	−11.86	−15.68	6.12	6.58	7.20	9.42	17.59
Lithuania	53.74	51.12	46.45	−9.14	−13.58	5.38	5.65	6.36	12.47	18.25
Luxembourg	43.90	37.12	32.90	−11.36	−25.05	10.80	12.90	15.95	23.67	47.65
Malta	37.49	32.54	32.90	1.11	−12.26	5.57	5.37	7.90	47.02	41.83
Netherlands	48.76	43.03	36.87	−14.32	−24.39	18.11	21.38	22.88	6.97	26.30
Norway	30.59	28.66	25.73	−10.22	−15.89	16.42	17.66	17.50	−0.91	6.58
Poland	67.64	61.95	53.58	−13.50	−20.78	13.28	15.21	16.44	8.11	23.82
Portugal	28.71	28.54	28.69	0.52	−0.09	4.97	5.68	6.13	7.79	23.36
Romania	46.76	47.93	47.85	−0.15	2.34	7.93	8.66	9.78	12.92	23.32
Russian Federation	57.11	51.21	46.77	−8.65	−18.09	5.80	5.55	5.50	−0.98	−5.15

Continued

TABLE 1 Continued

	Men					Women				
	2000–2004	2005–2009	2012	% change 2007 versus 2012	% change 2002 versus 2012	2000–2004	2005–2009	2012	% change 2007 versus 2012	% change 2002 versus 2012
<b>Serbia</b>	52.13	57.88	55.36	−4.35	6.20	12.35	15.11	17.65	16.80	42.96
<b>Slovakia</b>	53.63	46.69	43.14	−7.61	−19.57	7.67	8.43	10.01	18.74	30.54
<b>Slovenia</b>	50.61	46.93	43.84	−6.58	−13.38	11.39	12.76	13.10	2.66	15.05
<b>Spain</b>	45.71	42.89	39.72	−7.39	−13.10	5.14	6.31	8.02	27.00	56.01
<b>Sweden</b>	20.51	19.27	17.25	−10.48	−15.91	14.19	15.59	14.33	−8.03	1.04
<b>Switzerland</b>	32.06	28.72	24.33	−15.30	−24.13	10.96	12.24	13.06	6.73	19.18
<b>UK</b>	37.05	33.12	29.43	−11.13	−20.56	19.69	20.53	20.62	0.46	4.75
<b>Australia</b>	29.99	26.37	24.31	−7.79	−18.94	13.78	14.16	14.11	−0.36	2.33
<b>New Zealand</b>	30.15	25.79	23.74	−7.95	−21.26	18.59	18.48	18.68	1.08	0.46
<b>European Union</b>	44.85	41.07	38.78	−5.59	−13.54	11.30	12.62	13.27	5.10	17.46

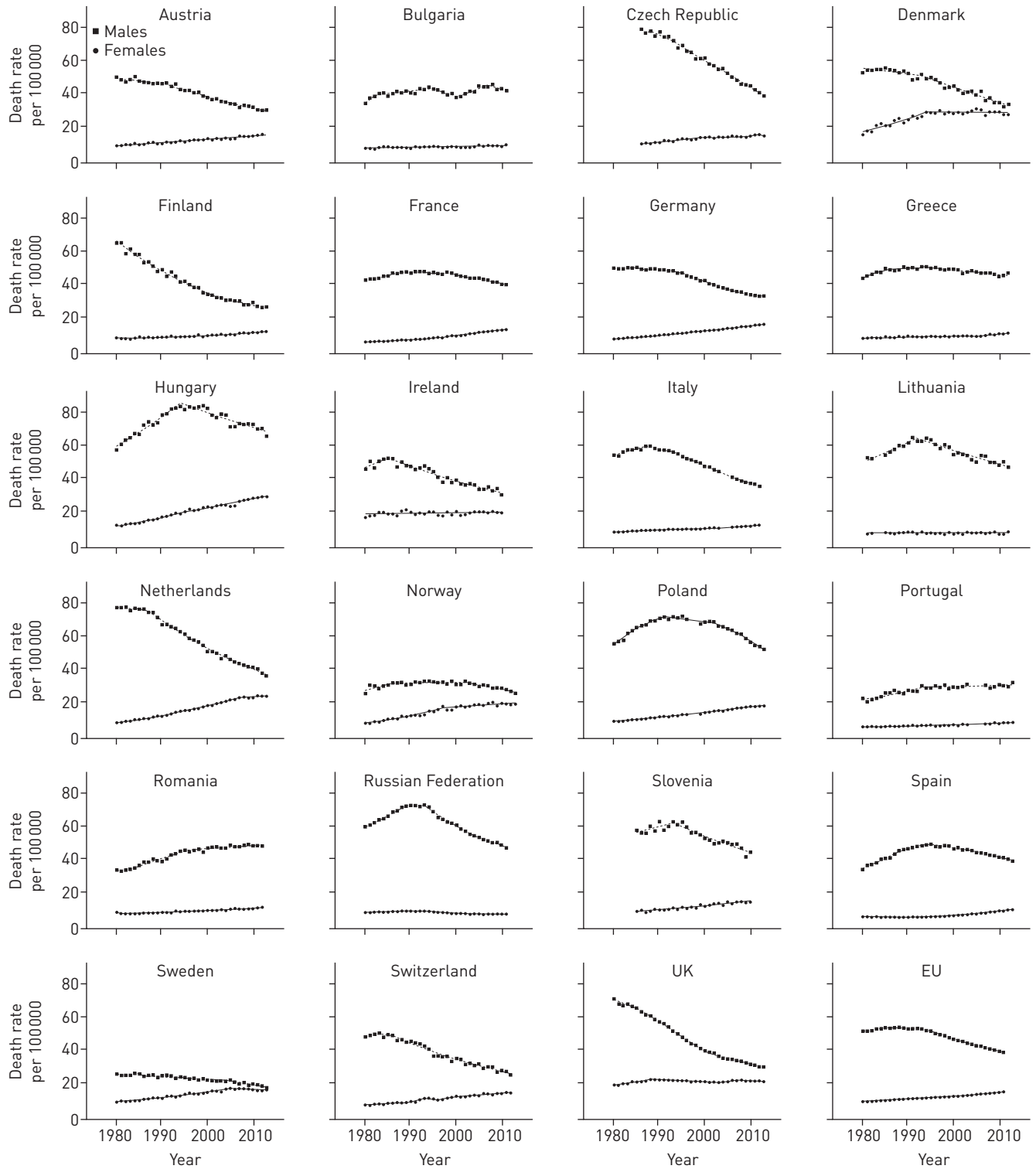


FIGURE 1 Trends in age-standardised (world standard population) death rates for lung cancer per 100,000 people (all ages) from 1980 to 2012 (or most recent available year) in 23 European countries and the European Union (EU).

*CHRNA5*, and *CHRN4*), encoding nicotinic acetylcholine receptors in neuronal and other tissues [30]. Variants on the 15q25 locus are also associated with increased vulnerability to tobacco addiction and altered smoking behaviour, including increasing the number cigarettes smoked per day [31, 34, 35]. In fact, a small increase in cigarette smoking leads to an association in the order of that reported for those loci. Since nicotinic acetylcholine receptors mediate sensitivity to nicotine, it has been proposed that variant receptors might increase addiction to tobacco and, therefore, exposure to tobacco carcinogens. 15q25 is the

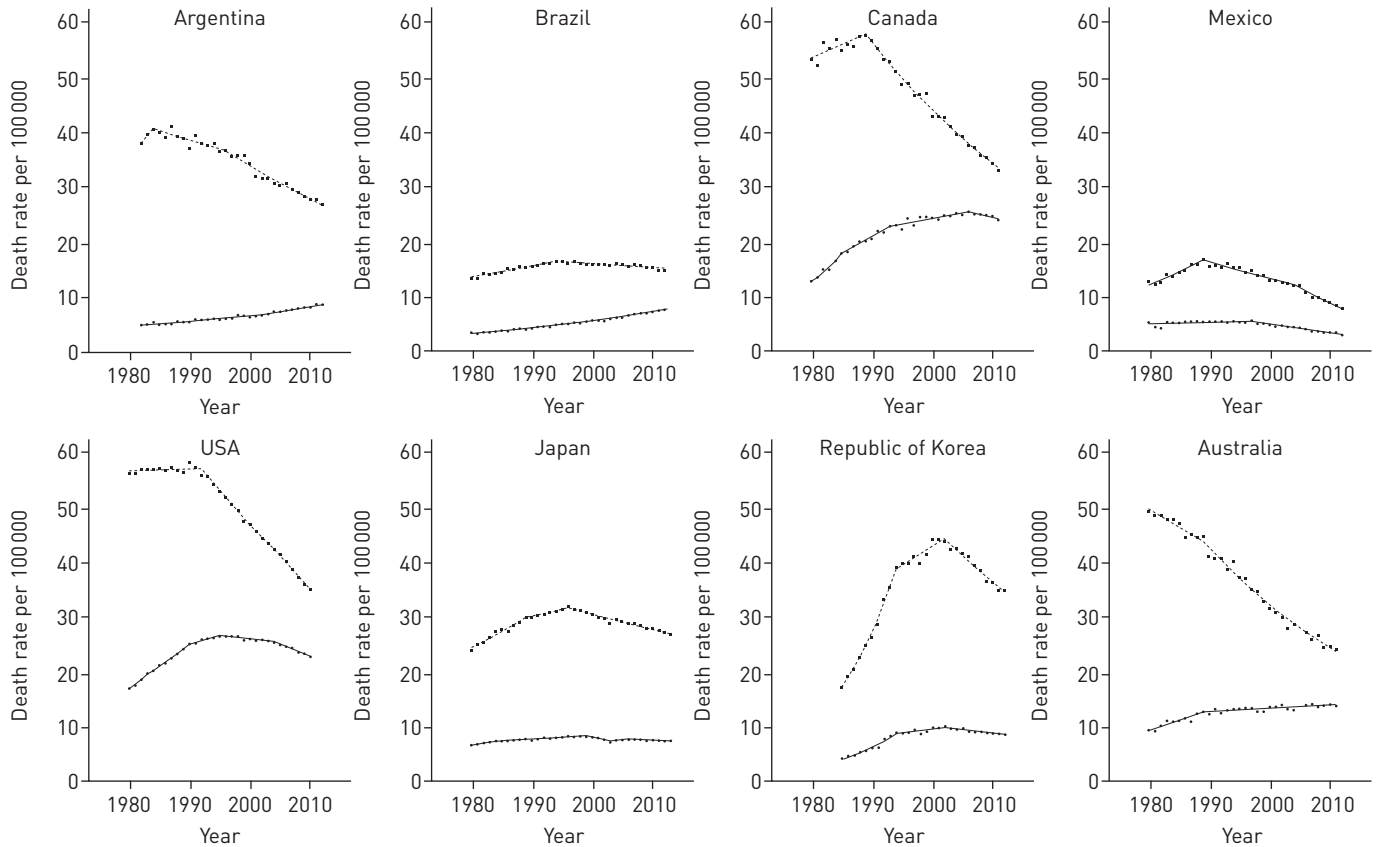


FIGURE 2 Trends in age-standardised (world standard population) death rates for lung cancer per 100000 people (all ages) from 1980 to 2012 (or most recent available year) in eight selected countries worldwide.

only locus which has been consistently replicated in all types of lung cancer, irrespective of lung cancer histology [26]. Another novel susceptibility locus at 9p21 reported in Caucasians is restricted to squamous cell lung cancer only [26].

The susceptibility locus in 5p15.33 represents a region that includes *TERT* (human telomerase reverse transcriptase gene) and *CLPTMIL* (cleft lip and palate transmembrane-1-like gene) [20]. Two variants in this region, rs402710 (OR 1.15; p-value:  $7 \times 10^{-5}$ ) and rs2736100 (OR 1.09; p-value: 0.016), which are not strongly associated with each other, were both reported to be associated with lung cancer risk. *TERT* is the reverse transcriptase component of telomerase that is essential for telomerase enzymatic activity and maintenance of telomeres. Telomerase is responsible for telomere regeneration and up to 90% of human tumours show telomerase activity [36]. There are some variations of race and ethnicity in the association between these susceptibility loci and lung cancer risk. A GWA study in Han Chinese subjects did not replicate the findings for 15q and 6p regions but confirmed previously identified loci in 5p region [17]. In addition, a number of new loci have been reported in Asians including 3q28 [17, 18] and 22q12.2 [17].

Some analyses have focused on pathway-based approaches to complement single SNP analysis by incorporating biological knowledge [37, 38]. A large pooled analysis of six studies to investigate associations between 7650 genetic variants in 720 genes related to inflammation pathways and lung cancer risk identified one novel variant (rs2741354 in *EPHX2* at 8q21.1; p-value:  $7.4 \times 10^{-6}$  after correcting for multiple comparisons), and confirmed the associations between the 5p and 6p regions with lung cancer risk [25]. Another analyses used imputation to the 1000 Genomes Project using pooled GWA data in European subjects and identified large-effect associations for squamous cell lung cancer with the rare variants BRCA2 p.Lys3326X (rs11571833) and CHEK2 p.Ile157Thr (rs17879961) [39]. This demonstrated that imputation can identify rare variants associated with cancer risk using pre-existing GWA data.

### Tobacco smoking

Tobacco smoking is the major cause of all major histological types of lung cancer. A carcinogenic effect of tobacco smoke on the lung was demonstrated in epidemiological studies conducted since the early 1950s and has been recognised by public health and regulatory authorities since the mid-1960s [40]. The

TABLE 2 Genetic variants identified to be associated with lung cancer risk

Susceptibility loci	Tagging SNPs	Genes	References
3q28	rs4488809	TP63	[17–19]
5p15.33	rs402710 rs2736100 rs401681	intron 1 of TERT CLPTM1L	[20–23]
6p21.33	rs4324798 rs3117582	APOM, BAG6	[20, 21, 24]
8q21	rs2741354		[25]
9p21	rs1333040	CDKN2B-AS1	[26]
10q25.2	rs7086803	VTI1A	[27]
12p13.33	rs6489769	RAD52	[27]
12q23.1	rs12296850		[28]
13q31.3	rs2352028	GPC5	[29]
15q25.1	rs1051730 rs8034191 rs16969968 rs12914385	<i>CHRNA3</i> , <i>CHRNA5</i> , and <i>CHRN4</i>	[20, 30, 31]
17q24.3	Rs7216064	BPTF	[32]
18p11.22	rs11080466 rs11663246	PIEZO2	[33]
22q12.2	rs17728461 rs36600	<i>HORMAD2</i> <i>LOC105372988</i>	[17]

SNP: single nucleotide polymorphism.

geographic and temporal patterns of the disease largely reflect tobacco consumption accumulated during previous decades [41, 42]. The excess risk among continuous smokers relative to that among never-smokers is in the order of 20- to 50-fold. Duration of smoking should be considered the strongest determinant of lung cancer risk in smokers [43]. Newer, low-yield cigarettes caused a shift in the site of disease (from trachea and bronchus to peripheral lung), and hence in the histology of lung cancer, from predominantly squamous cell to adenocarcinoma. Their impact on overall lung cancer risk, as compared to older, higher tar cigarettes, is still open to quantification [44]. The relative risk decreases in ex-smokers, and a favourable effect of stopping is apparent even for cessation later in life. However, an excess risk throughout life probably persists even in long-term quitters [42]. The importance of tobacco smoking in the causation of lung cancer complicates the investigation of other causes because tobacco smoking may act as a powerful confounder or modifier.

Although cigarettes are the main tobacco product smoked in western countries, an exposure–response relationship with lung cancer risk has also been shown for cigars, cigarillos and pipes, indicating a carcinogenic effect of these products [42]. An increased risk of lung cancer has also been shown following consumption of local tobacco products, such as bidi and hookah in India, khii yoo in Thailand and water pipe in China [42]. The higher rate of lung cancer among African-Americans compared to other ethnic groups in the USA is probably explained by their higher tobacco consumption [45]. The lower risk of lung cancer among smokers in China and Japan compared to Europe and North America might be due to the relatively recent introduction of regular heavy smoking in Asia, although differences in the composition of traditional smoking products and in genetic susceptibility might also play a role [46].

The epidemiological evidence and biological plausibility support a causal association between second-hand exposure to cigarette smoke and lung cancer risk in nonsmokers [47] with the excess risk in the order of



20–30% for a nonsmoker married to a smoker [48, 49]. The effect of involuntary smoking appears to be present for both household exposure, mainly from spousal and workplace exposure [49, 50], and perhaps from involuntary childhood smoking exposure [51]. Few studies have investigated the risk of lung cancer among users of smokeless tobacco products. In two large cohorts of US volunteers, the relative risk for spit tobacco use among nonsmokers was 1.08 (95% CI 0.64–1.83) and 2.00 (95% CI 1.23–3.24), respectively [52]. Overall, the evidence of increased risk of lung cancer from use of smokeless tobacco products is weak; the apparent protective effect detected in studies including smokers might be due to uncontrolled negative confounding, or reduced smoking among users of smokeless tobacco.

### Diet and alcohol

There is evidence from case–control studies that a diet rich in vegetables and fruits, especially cruciferous vegetables, may exert some protective effect against lung cancer [53, 54]. However, results of prospective studies with detailed information on dietary intake are less consistent in showing a similar effect [55]. Possible reasons for the inconsistent results include bias from retrospective dietary assessment, misclassification and limited heterogeneity of exposure in cohort studies, residual confounding by smoking, and variability in food composition. Isothiocyanates are a group of chemicals with cancer-preventive activity in experimental systems, and may be responsible for some reduced risk of lung cancer in relation to high intake of cruciferous vegetables.

High intake of meat, in particular fried or well-done red meat, may increase the risk of lung cancer [56] and this may be related to formation of nitrosamines during cooking [57]. A pooled analysis of eight cohort studies provided no evidence of an increased risk of lung cancer with a high intake of either total fat or saturated fat [58]. Many studies have addressed the risk of lung cancer according to estimated intake of either  $\beta$ -carotene or total carotenoids (which in most cases correspond to the sum of  $\alpha$ - and  $\beta$ -carotene) [59]. The evidence of a protective effect from most observational studies has been refuted by the results of randomised intervention trials based on  $\beta$ -carotene supplementation [60, 61]. In two of the studies, which included smokers or workers exposed to asbestos, a significant increase in the incidence of lung cancer was observed in the treated groups; in the remaining studies, no effect was ascertained [60, 61]. The difference in results between observational studies and preventive trials can be explained by confounding factors in fruits and vegetables other than  $\beta$ -carotene, or by the fact that high, nonphysiological doses of  $\beta$ -carotene might cause oxidative damage, in particular among smokers [62]. There is evidence from observational studies that low levels of vitamin D are associated with lung cancer risk [63]; however, results of randomised trials do not provide supportive evidence, arguing for caution when drawing conclusions.

Coffee drinking has been associated with lung cancer in a report from the NIH-AARP study (HR (95% CI) for  $\geq 6$  cups·day<sup>-1</sup> compared with none: 4.56 (4.08–5.10)) [64]. However, this association was substantially attenuated after adjusting for smoking (1.27 (1.14–1.42)) as coffee drinkers were more likely to be smokers than non-coffee drinkers [64]. Also, no evidence of an increased risk has been reported in studies of never-smokers [54]. There is some evidence of a chemopreventive effect of tea, notably green tea, in smokers [65]. However, the overall evidence is not consistent.

Given the strong correlation between alcohol consumption and tobacco smoking in many populations, it is difficult to elucidate the contribution of alcohol to lung carcinogenesis while properly controlling for the potential confounding effect of tobacco. Meta-analyses have indicated that the increased risk of lung cancer observed among alcoholics is mainly attributable to such residual confounding, since no consistent association was observed in never-smokers [66], but a smoking-adjusted association was suggested for high alcohol consumption [67, 68]. This conclusion was confirmed by a pooled analysis of seven cohort studies [69].

### Chronic inflammation from infections and other medical conditions

Patients with chronic obstructive pulmonary disease are at increased risk for lung cancer, and a number of studies have suggested that this is independent of smoking [70–72]. However, one study has not confirmed this and concludes that it is impossible to exclude a residual effect of smoking in the published literature [73]. A meta-analysis of lung cancer studies and asthma in never-smokers reported a relative risk of 1.8 (95% CI 1.3–2.3) [74]. These results are similar to analysis restricted to studies controlling for smoking, but this is mainly based on case–control studies [75].

Patients with pulmonary tuberculosis have been found to be at increased risk of lung cancer [76]. In the most informative study, involving a large cohort of tuberculosis patients from Shanghai, China [77], the relative risk of lung cancer in the subjects with a history of tuberculosis was 1.5 and 20 years after the diagnosis of tuberculosis was 2.0; a correlation was also seen with the location of the tuberculosis lesions. Whether the excess risk is caused by the chronic inflammatory status of the lung parenchyma or by the specific action of the *Mycobacterium* is not clear. Six studies exploring risk of lung cancer among individuals with markers of *Chlamydia pneumoniae* infection consistently detected a positive association [78]. However, studies based on



pre-diagnostic samples had lower risk estimates than studies based on post-diagnostic samples. No association between infection with human papilloma virus and lung cancer has been established [79, 80].

### **Ionising radiation**

Exposure to ionising radiation increases the risk of lung cancer [81]. This increased risk has been reported in atomic bomb survivors, as well as patients treated with radiotherapy (RR 1.5–2 for cumulative exposure in excess of 100 cGy) [82]. Underground miners exposed to radioactive radon and its decay products, which emit  $\alpha$ -particles, have been consistently found to be at increased risk of lung cancer [83]. A pooled analysis of 11 cohorts estimated an apparently linear, ~6% risk increase per working-level year of exposure (1 working-level year=1 working-level exposure $\times$ 170 h $\times$ 12 months) [84]. There was also evidence that smoking synergistically modifies the carcinogenic effect of radon [84]. Today the main concern about lung cancer risk from radon and its decay products comes from residential rather than occupational exposure. A pooled analysis of 13 European case-control studies resulted in a relative risk of 1.084 (95% CI 1.030–1.158) per 100 Bq·m<sup>-3</sup> increase in measured indoor radon [85]. After correction for the dilution caused by measurement error, the relative risk was 1.16 (95% CI 1.05–1.31). The exposure-response relationship was linear with no evidence of a threshold. A similar analysis of North American studies came to the same conclusion [86]. The US Environment Protection Agency estimates it to be the second leading cause of lung cancer in the USA. Thus, indoor radon exposure might be an important cause of lung cancer.

### **Occupational exposures**

Occupational exposures play a significant role in lung cancer aetiology, and the risk of lung cancer is increased among workers employed in a number of industries and occupations [87]. Two studies have reported an estimate of the proportion of lung cancer cases attributable to occupational agents in the UK to be 14.5% overall [88] and 12.5% in men in France [89]. The most important occupational lung carcinogens are reported to be asbestos, silica, radon, heavy metals and polycyclic aromatic hydrocarbons [90].

#### ***Asbestos***

All different forms of asbestos (chrysotile and amphiboles, including crocidolite, amosite and tremolite) are carcinogenic to the human lung, although the potency of chrysotile is lower than that of other types probably due to its earlier clearance [91, 92]. In many low- and medium-resource countries, occupational exposure remains widespread.

#### ***Metals and mixed occupation exposures***

Chromium [VI] compounds increase the risk of lung cancer among chromate production workers, chromate pigment manufacturers, chromium platers and ferrochromium producers. No such risk has been detected among workers exposed only to chromium [III] compounds.

Studies of nickel miners, smelters, electrolysis workers and high-nickel alloy manufacturers showed an increased risk of lung cancer [93]. The available evidence does not allow a clear separation between different nickel salts to which workers are exposed. An increased risk of lung cancer has also been reported among workers in cadmium-based battery manufacture, copper cadmium alloy workers and cadmium smelters, but the evidence is not as strong as for other agents [94]. High-level exposure to inorganic arsenic mainly occurs among workers employed in hot smelting; other groups at increased risk are fur handlers, manufacturers of sheep-dip compounds and pesticides, and vineyard workers [93]. An increased risk of lung cancer has also been reported among people exposed to high levels of arsenic in drinking water [95]. A non-linear exposure-response relationship was observed in most of the studies showing an association between lung cancer risk and arsenic, with no apparent effect for low-dose exposure.

#### ***Silica***

An increased risk of lung cancer has been consistently reported in cohorts of silicotic patients [96]. Many studies investigated crystalline silica-exposed workers in foundries, pottery making, ceramics, diatomaceous earth mining, brick making and stone cutting, some of whom might have developed silicosis. An increased risk of lung cancer was reported by some, but not all, studies and in the positive studies the increase was small, with evidence of an exposure-response relationship in the high-exposure range [97].

#### ***Polycyclic aromatic hydrocarbons***

Polycyclic aromatic hydrocarbons are a complex and important group of chemicals formed during combustion of organic material. An increased risk of lung cancer has been reported in several industries and occupations involving exposure to polycyclic aromatic hydrocarbons, such as aluminium production, coal gasification, coke production, iron and steel founding, tar distillation, roofing and chimney sweeping [98, 99]. An increase has also been suggested in a few other industries, including shale oil extraction, wood impregnation, roofing and

carbon electrode manufacture, with the suggestion of an exposure–response relationship. Motor vehicle and other engine exhausts represent an important group of mixtures of polycyclic aromatic hydrocarbons, since they contribute significantly to air pollution. The available epidemiological evidence shows an excess risk among workers with high occupational exposure to diesel engine exhaust [100].

### **Diesel exhaust**

Most studies of the association between diesel exhaust exposure and lung cancer suggest a modest, but consistent, increased risk [101]. The SYNERGY project pooled occupation and smoking information from 13304 lung cancer cases and 16282 controls from 11 case–control studies conducted in Europe and Canada. Cumulative diesel exposure was associated with an increased lung cancer risk with an odds ratio of 1.31 and a significant exposure–response relationship (p-value <0.01) [102].

### **Air pollution**

Indoor air pollution is considered to be a major risk factor for lung cancer in never-smoking women living in several regions of Asia. This includes coal burning in poorly ventilated houses, burning of wood and other solid fuels, as well as fumes from high-temperature cooking using unrefined vegetable oils such as rapeseed oil [103]. In Europe, a positive association between various indicators of indoor air pollution and lung cancer risk has also been reported [104].

Epidemiological studies exploring association between past exposure to air pollutants and lung cancer have been mainly limited by use of proxy indicators; for example, the number of inhabitants in the community of residence and residing near a major pollution source. However, these data are inconsistent, and mainly reflect present levels or levels in the recent past. In some cohort studies, environmental measurements of fine particles are suggestive of a small increase in risk among people classified as most highly exposed to air pollution [105–108]. The International Agency for Research on Cancer classifies outdoor air pollution as an established lung carcinogen in humans [109].

### **Other risk factors**

Oestrogen and progesterone receptors are expressed in the normal lung and in lung cancer cell lines, and oestradiol has a proliferative effect on the latter type of cells [110]. A small increased risk of lung cancer has been reported in early studies, while a decreased risk was detected in the more recent studies [111–119]. No effect was observed in the only randomised trial [112]. While the different results might be explained by changes in the formulations used for replacement therapy, the lack of an effect in the only study with an experimental design argues towards residual confounding by smoking and hence against an effect of this type of exposure on lung cancer.

There is some evidence that a reduced body mass index is associated with an increased risk of lung cancer. However, this inverse association can be explained, at least in part, by negative confounding by smoking and tobacco-related lung disease [120], and no clear association has been demonstrated among never-smokers. Subsequent studies supported this conclusion [121].

### **Conclusion**

For lung cancer prevention, control of tobacco smoking is the most important preventive measure. While the effects of tobacco control in the past few decades on the incidence and mortality of the disease can be appreciated, much remains to be done, in particular among women and in the area of lung cancer screening in smokers using low-dose computed tomography scans. Other priorities for the prevention of lung cancer include control of occupational exposures, as well as indoor and outdoor air pollution, and understanding the carcinogenic and preventive effects of dietary and other lifestyle factors.

### **References**

- 1 Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. *CA Cancer J Clin* 2015; 65: 5–29.
- 2 Malvezzi M, Carioli G, Bertuccio P, *et al.* European cancer mortality predictions for the year 2016 with focus on leukemias. *Ann Oncol* 2016; 27: 725–731.
- 3 Ferlay J, Soerjomataram I, Ervik M, *et al.* GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11. Lyon, IARC, 2013.
- 4 Foreman D, Bray F, Brewster DH, *et al.*, eds. Cancer Incidence in Five Continents. Volume X. Lyon, International Agency for Research on Cancer, 2014.
- 5 Ferlay J, Soerjomataram I, Dikshit R, *et al.* Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015; 136: E359–E386.
- 6 Malvezzi M, Bosetti C, Rosso T, *et al.* Lung cancer mortality in European men: trends and predictions. *Lung Cancer* 2013; 80: 138–145.
- 7 World Health Organization. WHO Statistical Information System (WHOSIS). [www.who.int/healthinfo/mortality\\_data/en/](http://www.who.int/healthinfo/mortality_data/en/) Date last updated: November 25, 2015. Date last accessed: December 15, 2015.

- 8 Hashim D, Boffetta P, La Vecchia C, *et al.* The global decrease in cancer mortality: trends and disparities. *Ann Oncol* 2016; 27: 926–933.
- 9 Graham H. Smoking prevalence among women in the European community 1950–1990. *Soc Sci Med* 1996; 43: 243–254.
- 10 Franceschi S, Naett C. Trends in smoking in Europe. *Eur J Cancer Prev* 1995; 4: 271–284.
- 11 Thun M, Peto R, Boreham J, *et al.* Stages of the cigarette epidemic on entering its second century. *Tob Control* 2012; 21: 96–101.
- 12 Malvezzi M, Bertuccio P, Levi F, *et al.* European cancer mortality predictions for the year 2012. *Ann Oncol* 2012; 23: 1044–1052.
- 13 Bailey-Wilson JE, Sellers TA, Elston RC, *et al.* Evidence for a major gene effect in early-onset lung cancer. *J La State Med Soc* 1993; 145: 157–162.
- 14 Lorenzo Bermejo J, Hemminki K. Familial lung cancer and aggregation of smoking habits: a simulation of the effect of shared environmental factors on the familial risk of cancer. *Cancer Epidemiol Biomarkers Prev* 2005; 14: 1738–1740.
- 15 Bailey-Wilson JE, Amos CI, Pinney SM, *et al.* A major lung cancer susceptibility locus maps to chromosome 6q23-25. *Am J Hum Genet* 2004; 75: 460–474.
- 16 Malkin D, Li FP, Strong LC, *et al.* Germ line p53 mutations in a familial syndrome of breast cancer, sarcomas, and other neoplasms. *Science* 1990; 250: 1233–1238.
- 17 Hu Z, Wu C, Shi Y, *et al.* A genome-wide association study identifies two new lung cancer susceptibility loci at 13q12.12 and 22q12.2 in Han Chinese. *Nat Genet* 2011; 43: 792–796.
- 18 Miki D, Kubo M, Takahashi A, *et al.* Variation in TP63 is associated with lung adenocarcinoma susceptibility in Japanese and Korean populations. *Nat Genet* 2010; 42: 893–896.
- 19 Hosgood HD III, Wang WC, Hong YC, *et al.* Genetic variant in TP63 on locus 3q28 is associated with risk of lung adenocarcinoma among never-smoking females in Asia. *Hum Genet* 2012; 131: 1197–1203.
- 20 McKay JD, Hung RJ, Gaborieau V, *et al.* Lung cancer susceptibility locus at 5p15.33. *Nat Genet* 2008; 40: 1404–1406.
- 21 Landi MT, Chatterjee N, Yu K, *et al.* A genome-wide association study of lung cancer identifies a region of chromosome 5p15 associated with risk for adenocarcinoma. *Am J Hum Genet* 2009; 85: 679–691.
- 22 Truong T, Hung RJ, Amos CI, *et al.* Replication of lung cancer susceptibility loci at chromosomes 15q25, 5p15, and 6p21: a pooled analysis from the International Lung Cancer Consortium. *J Natl Cancer Inst* 2010; 102: 959–971.
- 23 Hsiung CA, Lan Q, Hong YC, *et al.* The 5p15.33 locus is associated with risk of lung adenocarcinoma in never-smoking females in Asia. *PLoS Genet* 2010; 6: e1001051.
- 24 Wang Y, Broderick P, Webb E, *et al.* Common 5p15.33 and 6p21.33 variants influence lung cancer risk. *Nat Genet* 2008; 40: 1407–1409.
- 25 Brenner DR, Brennan P, Boffetta P, *et al.* Hierarchical modeling identifies novel lung cancer susceptibility variants in inflammation pathways among 10,140 cases and 11,012 controls. *Hum Genet* 2013; 132: 579–589.
- 26 Timofeeva MN, Hung RJ, Rafnar T, *et al.* Influence of common genetic variation on lung cancer risk: meta-analysis of 14 900 cases and 29 485 controls. *Hum Mol Genet* 2012; 21: 4980–4995.
- 27 Shi J, Chatterjee N, Rotunno M, *et al.* Inherited variation at chromosome 12p13.33, including RAD52, influences the risk of squamous cell lung carcinoma. *Cancer Discov* 2012; 2: 131–139.
- 28 Dong J, Jin G, Wu C, *et al.* Genome-wide association study identifies a novel susceptibility locus at 12q23.1 for lung squamous cell carcinoma in Han Chinese. *PLoS Genet* 2013; 9: e1003190.
- 29 Li Y, Sheu CC, Ye Y, *et al.* Genetic variants and risk of lung cancer in never smokers: a genome-wide association study. *Lancet Oncol* 2010; 11: 321–330.
- 30 Amos CI, Wu X, Broderick P, *et al.* Genome-wide association scan of tag SNPs identifies a susceptibility locus for lung cancer at 15q25.1. *Nat Genet* 2008; 40: 616–622.
- 31 Thorgeirsson TE, Geller F, Sulem P, *et al.* A variant associated with nicotine dependence, lung cancer and peripheral arterial disease. *Nature* 2008; 452: 638–642.
- 32 Lan Q, Hsiung CA, Matsuo K, *et al.* Genome-wide association analysis identifies new lung cancer susceptibility loci in never-smoking women in Asia. *Nat Genet* 2012; 44: 1330–1335.
- 33 Ahn MJ, Won HH, Lee J, *et al.* The 18p11.22 locus is associated with never smoker non-small cell lung cancer susceptibility in Korean populations. *Hum Genet* 2012; 131: 365–372.
- 34 Liu JZ, Tozzi F, Waterworth DM, *et al.* Meta-analysis and imputation refines the association of 15q25 with smoking quantity. *Nat Genet* 2010; 42: 436–440.
- 35 Saccone NL, Culverhouse RC, Schwantes-An TH, *et al.* Multiple independent loci at chromosome 15q25.1 affect smoking quantity: a meta-analysis and comparison with lung cancer and COPD. *PLoS Genet* 2010; 6: e1001053.
- 36 Fernandez-Garcia I, Ortiz-de-Solorzano C, Montuenga LM. Telomeres and telomerase in lung cancer. *J Thorac Oncol* 2008; 3: 1085–1088.
- 37 Zhao J, Gupta S, Seielstad M, *et al.* Pathway-based analysis using reduced gene subsets in genome-wide association studies. *BMC Bioinform* 2011; 12: 17.
- 38 Khatri P, Sirota M, Butte AJ. Ten years of pathway analysis: current approaches and outstanding challenges. *PLoS Comput Biol* 2012; 8: e1002375.
- 39 Wang Y, McKay JD, Rafnar T, *et al.* Rare variants of large effect in BRCA2 and CHEK2 affect risk of lung cancer. *Nat Genet* 2014; 46: 736–741.
- 40 Wynder EL. Tobacco as a cause of lung cancer: some reflections. *Am J Epidemiol* 1997; 146: 687–694.
- 41 Peto R, Boreham J, Lopez AD, *et al.* Mortality from tobacco in developed countries: indirect estimation from national vital statistics. *Lancet* 1992; 339: 1268–1278.
- 42 IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Tobacco Smoke. *In: Tobacco smoke and involuntary smoking*. Vol 83. Lyon, World Health Organization/IARC, 2004; pp. 51–1187.
- 43 Doll R, Peto R, Boreham J, *et al.* Mortality in relation to smoking: 50 years' observations on male British doctors. *BMJ* 2004; 328: 1519.
- 44 US Department of Health and Human Services. The Health Consequences of Smoking: 50 Years of Progress. A Report of the Surgeon General. Atlanta, U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2014.

- 45 Devesa SS, Grauman DJ, Blot WJ, *et al.* Cancer surveillance series: changing geographic patterns of lung cancer mortality in the United States, 1950 through 1994. *J Natl Cancer Inst* 1999; 91: 1040–1050.
- 46 Yuan J-M, Koh W-P, Murphy SE, *et al.* Urinary levels of tobacco-specific nitrosamine metabolites in relation to lung cancer development in two prospective cohorts of cigarette smokers. *Cancer Res* 2009; 69: 2990–2995.
- 47 IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Involuntary Smoking. *In: Tobacco smoke and involuntary smoking*. Vol 83. Lyon, World Health Organization/IARC, 2004; pp. 1191–1413.
- 48 Hackshaw AK, Law MR, Wald NJ. The accumulated evidence on lung cancer and environmental tobacco smoke. *BMJ* 1997; 315: 980–988.
- 49 Boffetta P. Involuntary smoking and lung cancer. *Scand J Work Environ Health* 2002; 28: Suppl. 2, 30–40.
- 50 Stayner L, Bena J, Sasco AJ, *et al.* Lung cancer risk and workplace exposure to environmental tobacco smoke. *Am J Public Health* 2007; 97: 545.
- 51 Boffetta P, Trédaniel J, Greco A. Risk of childhood cancer and adult lung cancer after childhood exposure to passive smoke: a meta-analysis. *Environ Health Perspect* 2000; 108: 73.
- 52 Henley SJ, Thun MJ, Connell C, *et al.* Two large prospective studies of mortality among men who use snuff or chewing tobacco (United States). *Cancer Causes Control* 2005; 16: 347–358.
- 53 Lam TK, Gallicchio L, Lindsley K, *et al.* Cruciferous vegetable consumption and lung cancer risk: a systematic review. *Cancer Epidemiol Biomark Prev* 2009; 18: 184–195.
- 54 World Cancer Research Fund/American Institute for Cancer Research. Food, Nutrition, Physical Activity and the Prevention of Cancer: A Global Perspective. Washington, AICR, 2007.
- 55 Vieira AR, Abar L, Vingeliene S, *et al.* Fruits, vegetables and lung cancer risk: a systematic review and meta-analysis. *Ann Oncol* 2016; 27: 81–96.
- 56 Sinha R, Kulldorff M, Curtin J, *et al.* Fried, well-done red meat and risk of lung cancer in women (United States). *Cancer Causes Control* 1998; 9: 621–630.
- 57 Sinha R, Kulldorff M, Swanson CA, *et al.* Dietary heterocyclic amines and the risk of lung cancer among Missouri women. *Cancer Res* 2000; 60: 3753–3756.
- 58 Smith-Warner SA, Ritz J, Hunter DJ, *et al.* Dietary fat and risk of lung cancer in a pooled analysis of prospective studies. *Cancer Epidemiol Biomark Prev* 2002; 11: 987–992.
- 59 Albanes D.  $\beta$ -Carotene and lung cancer: a case study. *Am J Clin Nutr* 1999; 69: 1345s–1350s.
- 60 Hennekens CH, Buring JE, Manson JE, *et al.* Lack of effect of long-term supplementation with  $\beta$  carotene on the incidence of malignant neoplasms and cardiovascular disease. *N Engl J Med* 1996; 334: 1145–1149.
- 61 The alpha-tocopherol, beta-carotene lung cancer prevention study: design, methods, participant characteristics, and compliance. The ATBC Cancer Prevention Study Group. *Ann Epidemiol* 1994; 4: 1–10.
- 62 Greenwald P.  $\beta$ -Carotene and lung cancer: a lesson for future chemoprevention investigations? *J Natl Cancer Inst* 2003; 95: E1–E1.
- 63 Herr C, Greulich T, Kocuzilla RA, *et al.* The role of vitamin D in pulmonary disease: COPD, asthma, infection, and cancer. *Respir Res* 2011; 12: 31.
- 64 Guertin KA, Freedman ND, Lofftield E, *et al.* Coffee consumption and incidence of lung cancer in the NIH-AARP Diet and Health Study. *Int J Epidemiol* 2015 [in press DOI: 10.1093/ije/dyv104].
- 65 Clark J, You M. Chemoprevention of lung cancer by tea. *Mol Nutr Food Res* 2006; 50: 144–151.
- 66 Bagnardi V, Rota M, Botteri E, *et al.* Alcohol consumption and lung cancer risk in never smokers: a meta-analysis. *Ann Oncol* 2011; 22: 2631–2639.
- 67 Bandera EV, Freudenheim JL, Vena JE. Alcohol consumption and lung cancer: a review of the epidemiologic evidence. *Cancer Epidemiol Biomark Prev* 2001; 10: 813–821.
- 68 Korte JE, Brennan P, Henley SJ, *et al.* Dose-specific meta-analysis and sensitivity analysis of the relation between alcohol consumption and lung cancer risk. *Am J Epidemiol* 2002; 155: 496–506.
- 69 Freudenheim JL, Ritz J, Smith-Warner SA, *et al.* Alcohol consumption and risk of lung cancer: a pooled analysis of cohort studies. *Am J Clin Nutr* 2005; 82: 657–667.
- 70 Mayne ST, Buenconsejo J, Janerich DT. Previous lung disease and risk of lung cancer among men and women nonsmokers. *Am J Epidemiol* 1999; 149: 13–20.
- 71 Wu AH, Fontham ET, Reynolds P, *et al.* Previous lung disease and risk of lung cancer among lifetime nonsmoking women in the United States. *Am J Epidemiol* 1995; 141: 1023–1032.
- 72 Gao YT, Blot WJ, Zheng W, *et al.* Lung cancer among Chinese women. *Int J Cancer* 1987; 40: 604–609.
- 73 Powell HA, Iyen-Omofoman B, Baldwin DR, *et al.* Chronic obstructive pulmonary disease and risk of lung cancer: the importance of smoking and timing of diagnosis. *J Thorac Oncol* 2013; 8: 6–11.
- 74 Santillan AA, Camargo CA Jr, Colditz GA. A meta-analysis of asthma and risk of lung cancer (United States). *Cancer Causes Control* 2003; 14: 327–334.
- 75 Rosenberger A, Bickeboller H, McCormack V, *et al.* Asthma and lung cancer risk: a systematic investigation by the International Lung Cancer Consortium. *Carcinogenesis* 2012; 33: 587–597.
- 76 Aoki K. Excess incidence of lung cancer among pulmonary tuberculosis patients. *Jpn J Clin Oncol* 1993; 23: 205–220.
- 77 Zheng W, Blot W, Liao M, *et al.* Lung cancer and prior tuberculosis infection in Shanghai. *Br J Cancer* 1987; 56: 501–505.
- 78 Littman AJ, Jackson LA, Vaughan TL. *Chlamydia pneumoniae* and lung cancer: epidemiologic evidence. *Cancer Epidemiol Biomark Prev* 2005; 14: 773–778.
- 79 Anantharaman D, Gheit T, Waterboer T, *et al.* No causal association identified for human papillomavirus infections in lung cancer. *Cancer Res* 2014; 74: 3525–3534.
- 80 Colombara DV, Manhart LE, Carter JJ, *et al.* Prior human polyomavirus and papillomavirus infection and incident lung cancer: a nested case-control study. *Cancer Causes Control* 2015; 26: 1835–1844.
- 81 IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Lung. *In: Ionizing Radiation, Part 1: X- and Gamma (y)-Radiation, and Neutrons*. Vol 75. Lyon, World Health Organization/IARC, 2000; pp. 253–254.
- 82 Boice JD. Ionizing radiation. *In: Schottenfeld D, Fraumeni JJ, eds. Cancer Epidemiology and Prevention*. New York, Oxford University Press, 1996; pp. 319–354.
- 83 International Agency for Research on Cancer, World Health Organization. Weight Control and Physical Activity. Volume 6. Lyon, IARC Press, 2002.



- 84 Lubin JH. Radon and lung cancer risk: a joint analysis of 11 underground miners studies. Washington, National Institutes of Health, 1994.
- 85 Darby S, Hill D, Auvinen A, *et al.* Radon in homes and risk of lung cancer: collaborative analysis of individual data from 13 European case-control studies. *BMJ* 2005; 330: 223.
- 86 Krewski D, Lubin JH, Zielinski JM, *et al.* A combined analysis of North American case-control studies of residential radon and lung cancer. *J Toxicol Environ Health Part A* 2006; 69: 533–597.
- 87 Coglianò VJ, Baan R, Straif K, *et al.* Preventable exposures associated with human cancers. *J Natl Cancer Inst* 2011; 103: 1827–1839.
- 88 Rushton L, Hutchings SJ, Fortunato L, *et al.* Occupational cancer burden in Great Britain. *Br J Cancer* 2012; 107: Suppl 1, S3–S7.
- 89 Boffetta P, Autier P, Boniol M, *et al.* An estimate of cancers attributable to occupational exposures in France. *J Occup Environ Med* 2010; 52: 399–406.
- 90 IARC Monographs. Chemical agents and related occupations. Volume 100 F. A review of human carcinogens. Lyon, World Health Organization/IARC, 2012.
- 91 Berman DW, Crump KS. Update of potency factors for asbestos-related lung cancer and mesothelioma. *Crit Rev Toxicol* 2008; 38: Suppl. 1, 1–47.
- 92 Gilham C, Rake C, Burdett G, *et al.* Pleural mesothelioma and lung cancer risks in relation to occupational history and asbestos lung burden. *Occup Environ Med* 2016; 7: 290–299.
- 93 Hayes RB. The carcinogenicity of metals in humans. *Cancer Causes Control* 1997; 8: 371–385.
- 94 IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Cadmium. In: Volume 58 Beryllium, Cadmium, Mercury and Exposures in the Glass Manufacturing Industry. Lyon, World Health Organization/IARC, 1993; pp. 119–238.
- 95 IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Arsenic in drinking-water. In: Volume 84 Some Drinking-water Disinfectants and Contaminants, including Arsenic. Lyon, World Health Organization/IARC, 2004; pp. 39–267.
- 96 Steenland K, Stayner L. Silica, asbestos, man-made mineral fibers, and cancer. *Cancer Causes Control* 1997; 8: 491–503.
- 97 Steenland K, Mannetje A, Boffetta P, *et al.* Pooled exposure–response analyses and risk assessment for lung cancer in 10 cohorts of silica-exposed workers: an IARC multicentre study. *Cancer Causes Control* 2001; 12: 773–784.
- 98 Bosetti C, Boffetta P, La Vecchia C. Occupational exposures to polycyclic aromatic hydrocarbons, and respiratory and urinary tract cancers: a quantitative review to 2005. *Ann Oncol* 2007; 18: 431–446.
- 99 Rota M, Bosetti C, Boccia S, *et al.* Occupational exposures to polycyclic aromatic hydrocarbons and respiratory and urinary tract cancers: an updated systematic review and a meta-analysis to 2014. *Arch Toxicol* 2014; 88: 1479–1490.
- 100 Benbrahim-Tallaa L, Baan RA, Grosse Y, *et al.* Carcinogenicity of diesel-engine and gasoline-engine exhausts and some nitroarenes. *Lancet Oncol* 2012; 13: 663–664.
- 101 Silverman DT, Samanic CM, Lubin JH, *et al.* The Diesel Exhaust in Miners study: a nested case-control study of lung cancer and diesel exhaust. *J Natl Cancer Inst* 2012; 104: 855–868.
- 102 Olsson AC, Gustavsson P, Kromhout H, *et al.* Exposure to diesel motor exhaust and lung cancer risk in a pooled analysis from case-control studies in Europe and Canada. *Am J Respir Crit Care Med* 2011; 183: 941–948.
- 103 IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 95 Household use of solid fuels and high-temperature frying. Lyon, World Health Organization/IARC, 2006.
- 104 Lissowska J, Bardin-Mikolajczak A, Fletcher T, *et al.* Lung cancer and indoor pollution from heating and cooking with solid fuels: the IARC international multicentre case-control study in Eastern/Central Europe and the United Kingdom. *Am J Epidemiol* 2005; 162: 326–333.
- 105 Krewski D, Jerrett M, Burnett RT, *et al.* Extended follow-up and spatial analysis of the American Cancer Society study linking particulate air pollution and mortality. *Res Rep Health Eff Inst* 2009; 140: 5–114.
- 106 Raaschou-Nielsen O, Andersen ZJ, Beelen R, *et al.* Air pollution and lung cancer incidence in 17 European cohorts: prospective analyses from the European Study of Cohorts for Air Pollution Effects (ESCAPE). *Lancet Oncol* 2013; 14: 813–822.
- 107 McDonnell WF, Nishino-Ishikawa N, Petersen FF, *et al.* Relationships of mortality with the fine and coarse fractions of long-term ambient PM10 concentrations in nonsmokers. *J Expo Anal Environ Epidemiol* 2000; 10: 427–436.
- 108 Laden F, Schwartz J, Speizer FE, *et al.* Reduction in fine particulate air pollution and mortality: extended follow-up of the Harvard Six Cities study. *Am J Respir Crit Care Med* 2006; 173: 667–672.
- 109 Loomis D, Huang W, Chen G. The International Agency for Research on Cancer (IARC) evaluation of the carcinogenicity of outdoor air pollution: focus on China. *Chin J Cancer* 2014; 33: 189–196.
- 110 Thomas L, Doyle LA, Edelman MJ. Lung cancer in women: emerging differences in epidemiology, biology, and therapy. *Chest J* 2005; 128: 370–381.
- 111 Schabath MB, Wu X, Vassilopoulou-Sellin R, *et al.* Hormone replacement therapy and lung cancer risk: a case-control analysis. *Clin Cancer Res* 2004; 10: 113–123.
- 112 Rossouw JE, Anderson GL, Prentice RL, *et al.* Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women’s Health Initiative randomized controlled trial. *JAMA* 2002; 288: 321–333.
- 113 Olsson H, Bladstrom A, Ingvar C. Are smoking-associated cancers prevented or postponed in women using hormone replacement therapy? *Obstet Gynecol* 2003; 102: 565–570.
- 114 Kreuzer M, Gerken M, Heinrich J, *et al.* Hormonal factors and risk of lung cancer among women? *Int J Epidemiol* 2003; 32: 263–271.
- 115 Blackman JA, Coogan PF, Rosenberg L, *et al.* Estrogen replacement therapy and risk of lung cancer. *Pharmacoepidemiol Drug Saf* 2002; 11: 561–567.
- 116 Taioli E, Wynder EL. Re: Endocrine factors and adenocarcinoma of the lung in women. *J Natl Cancer Inst* 1994; 86: 869–870.
- 117 Adami HO, Persson I, Hoover R, *et al.* Risk of cancer in women receiving hormone replacement therapy. *Int J Cancer* 1989; 44: 833–839.

- 118 Wu AH, Mimi CY, Thomas DC, *et al.* Personal and family history of lung disease as risk factors for adenocarcinoma of the lung. *Cancer Res* 1988; 48: 7279–7284.
- 119 Lipson D, Capelletti M, Yelensky R, *et al.* Identification of new ALK and RET gene fusions from colorectal and lung cancer biopsies. *Nat Med* 2012; 18: 382–384.
- 120 Henley SJ, Flanders WD, Manatunga A, *et al.* Leanness and lung cancer risk: fact or artifact? *Epidemiology* 2002; 13: 268–276.
- 121 Calle EE, Rodriguez C, Walker-Thurmond K, *et al.* Overweight, obesity, and mortality from cancer in a prospectively studied cohort of US adults. *N Engl J Med* 2003; 348: 1625–1638.