How do lung cancer rates in never smokers vary by country?

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EXECUTIVE SUMMARY

This report investigates how lung cancer mortality in lifelong never smokers varies by region and other factors.

Limited direct evidence from six epidemiological studies suggests that lung cancer rates in nonsmokers have not increased materially in recent years, though the overall data are not completely conclusive.

Only eight prospective studies provide direct data on variation in never smoker lung cancer rates by age and sex. While some of the studies demonstrate a rise in risk by age and higher rates in men than women, the data are of severely limited value for useful comparison across countries, being predominantly from the USA, often based on studies conducted 30 or 40 years ago and often involving very few deaths or cases.

41 studies provide estimates on lung cancer risk in never smokers that are sex- but not age-specific. 35 of the 56 rates are based on 20 cases at most and are open to substantial sampling error, and many of the populations studied are clearly unrepresentative of the national populations. Analysis of these data confirmed the tendency for rates to rise with age and be higher in males than females, and suggested that rates were higher for never smokers of cigarettes than for never smokers of any product. Rates were high in certain special populations (e.g. farmers in Xuanwei or miners in various countries). Omitting the rates for the special populations and restricting attention to never smokers of any product, there was no obvious difference in rates between studies in the US, UK and Scandinavia, the only regions that provided adequate data.

In an attempt to obtain further data on lung cancer risk in never smokers, an indirect estimation approach was also used. This involved a formula which combined ever/never smoker relative risk estimates from epidemiological studies with national estimates of overall lung cancer risk based on mortality data for the same region and period. Mortality data selected were for age 70-74 as data from the American Cancer Society CPS studies indicated our formula predicted actual never smoker lung cancer rates reasonably well for that age.

After excluding studies with an inappropriate age range, studies of populations that were clearly racially unrepresentative of the country in question and studies of certain occupational and other special groups, 216 indirect estimates of lung cancer risk in 70-74 year old never smokers were obtained. The estimates showed considerable heterogeneity and were clearly higher for males than for females. Rates were compared in Canada (10 estimates), USA (56), South and Central America (9), UK (26), Scandinavia (18), West Europe (31), East Europe (11), Japan (14), China (32) and Other regions (9).

In males, overall (random-effects) estimates of the rates (per 100,000 per year) were highest in China (120.3, 95% CI 101.3-142.8), with UK second (90.6, 64.2-127.8). No very marked variation was evident in the other eight regions where overall estimates ranged from 35.0 in Scandinavia to 54.8 in the USA. In females, overall estimates were much higher in China (93.4, 84.6-103.1) than in other regions, ranging from 19.2 in the "other regions" to 36.5 in Japan. Within China, rates in women were even higher in Hong Kong, with 5 study estimates ranging from 106.9 to 129.0. One study in Thailand produced very low estimates of 7.0 in males and 1.7 in females.

INDEX

Tables

1. Introduction

Lung cancer rates are available by age, sex and year for all major countries from national sources, and a WHO database provides extensive data since 1950. However, these rates are relevant to the whole population in the country and are not separately available by smoking habit. As smoking habits are not recorded on death certificates (and would perhaps be of dubious validity if they were), it is actually quite difficult to obtain national data on lung cancer rates in never smokers. This document presents some approaches to estimating such data. Given that, ideally, comparison between countries should be on an age, sex and period matched basis, it is important to get some insight into how rates in never smokers vary by these factors, and this document also supplies some information on this.

It should be noted at the outset that there is reason to expect some variation in rates. One knows, for example, that, in never smokers, risk varies by a number of factors. For example, a recent review of data from 23 studies[1] showed that asbestos exposure clearly increases risk of lung cancer in never smokers and there is also evidence[2] that other occupational factors do so as well. Similarly recent meta-analyses[3] showed that fruit and vegetable consumption was associated with a decreased risk of lung cancer, whilst dietary fat was associated with an increased risk of lung cancer. Given the known variation by country in diet and occupation, one would expect the risk of lung cancer in never smokers to vary also as a result, and variation in other environmental/lifestyle factors also may contribute, as may genetic factors.

2. Evidence on changes in lung cancer risk in never smokers by time period

We are aware of a number of relevant pieces of information here:

Comparison of CPS I and CPS II

Garfinkel and Silverberg[4] noted little change in age-adjusted lung cancer risk in never smokers between American Cancer Society prospective studies CPS I and CPS II.

	CPS I 1960-1964	1965-1968	1969-1972	CPS II 1982-1986
Male rates	14.6	16.6	16.7	15.4
Female rates	11.7	12.4	12.2	12.1

Data are rates per 100,000 per year standardized to the age distribution of the US population, 1970.

Further data from this study will be considered below.

US Veterans study

Doll and Peto[5] reported results from the US Veterans study which also showed no evidence of a trend in age-adjusted lung cancer risk in never smoking men with length of follow-up.

	Years since entry to study						
	1	2-4	5-7	8-10	11-13	14-16	All
Observed deaths	6	24	31	40	41	35	177
Expected deaths*	6.5	23.6	30.9	39.2	43.9	33.0	177.0
Observed/expected	0.9	1.0	1.0	1.0	0.9	1.1	1

* Number of deaths observed are compared with those expected if, among men of a given single year of age in a given sample, death rates were unrelated to calendar year.

British Doctors Study

In 1994, Doll and his colleagues[6] compared age-adjusted lung cancer rates per 100,000 per year in British never smoking male doctors in 1951-1971 and in 1971-1991. The rates were the same, 17, in both periods, based on a total of 19 lung cancer deaths, 10 in 1951-1971 and 9 in 1971-1991.

Hirayama study

In the book[7] describing the results of his Japanese study of a quarter of a million men and women, Hirayama presented a graph showing trends in age-standardized lung cancer rates over three periods, 1966-1972, 1973-1977 and 1978-1982. In both sexes some increase was seen in never smokers' rates over the period, from about 28 to 42 in males and from about 18 to 20 in females.

Swedish construction workers study

Boffetta and his colleagues[8] reported results from a study of Swedish male construction workers who consistently reported being lifelong never smokers at health examinations during 1971-1992. Over the period to the end of 1995, a total of 101 lung cancers were reported to the cancer registry. The authors noted that "only 1 case occurred before 1976; age standardized rates in subsequent quinquennia increased from 1.5/100,000 in 1976-80 (95% CI 1.0-2.9) to 5.4/100,000 in 1991-95 (95% CI 4.5-6.3) suggesting a period effect." No formal test of the statistical significance of the trend over time was reported, but given that the two sets of CI cited do not nearly overlap, this would have been quite highly significant.

Other data

Other indirect estimates and trends which suggest much larger variations in risk[9-13] tend to have clear technical weaknesses and be difficult to interpret.[14]

Conclusion

At this point in time, the more reliable evidence seems to suggest that lung cancer rates in nonsmokers have not increased materially in recent years, though the overall data are not completely conclusive.

3. Sex- and age-specific data on lung cancer risk in never smokers

Based on our in-house IESLC database[15] and including some additional data we identified eight prospective studies which provided sex- and age-specific data on lung cancer risk in never smokers. The data from these studies are given in Table 1.

The results from CPS I (study 1) and CPS II (study 2) are based on large numbers of lung cancer cases in never smokers, totalling 215 in males and 573 in females in CPS I and 123 in males and 309 in females in CPS II. Even so, rates for the younger age groups are often based on 10 deaths or less. Both studies show a clear tendency for risk to rise with age, with rates generally higher in males than in females, more clearly at age 65+ than in younger age groups. As indicated in the previous section, rates in the two studies are quite similar.

The results from the California American Legion Study (study 3), for males only, show rather higher rates, particularly at age 75+. Numbers of lung cancer deaths in never smokers are not available, but would have been quite small, since total lung cancer deaths in ever and never smokers combined were only 6 at age 35-44, 17 at age 45-54 and 16 at age 75+. Even though they were larger at age 55-64, 119, and at age 65-74, 143, the numbers in never smokers would not have been substantial. It should be noted that, whereas the definition of never smokers in other studies excludes pipe and cigar smokers, the population studied here is never smokers of cigarettes, and so will include some pipe and cigar smokers.

The results from the California Kaiser Permanente Study (study 4) are based on at most 5 lung cancer cases in never smokers in each age/sex cell, but still show a clear tendency for risk to rise with age and be higher in males.

The results from the US Veterans Study (study 5) for males are based on a total of 78 lung cancer deaths in never smokers for the age groups for which rates are reported. The rates are quite similar to those in the CPS studies.

The results from the US Nine State Study (study 6) for males are based on a total of only 12 lung cancer cases in never smokers, but rates are similar to those from the CPS studies. Note that whereas the rates for the other studies are calculated based on the age attained by the subject at the time of the lung cancer, these rates are based on the age of the subject at the start of the study. Given follow-up was short, less than 4 years, this is of little importance.

The final two sets of results (studies 7 and 8) are the only ones not for the USA.

Study 7 is based on an analysis carried out based on pooling results from three studies in Copenhagen. The data are only based on a total of 20 lung cancer cases in never smokers, 6 in males and 14 in females. The rates at age 50-64 are possibly somewhat higher than seen in the US studies, but those at age 65+ are not.

Study 8 is based on an analysis of male construction workers nationwide in Sweden, involving a total of 101 lung cancer cases in never smokers. The rates show an obvious tendency to rise with age. Boffetta *et al*[8] compared rates for age groups 55-64, 65-74 and 75-84 with those seen in CPS I (study 1), CPS II (study 2) and the US veterans (study 5) and concluded that they were "comparable to those from North American studies", although they look rather lower.

Overall it is clear that the data by sex and age are severely limited, being virtually all based on studies conducted in the USA, four of which were conducted 30 or 40 years ago, and often based on very few deaths or cases. They provide very little data for useful comparison across countries.

4. Sex- but not age- specific data on lung cancer risk in never smokers

Another approach to the problem is to study risk estimates from prospective studies that are not age-specific and attempt to relate them approximately to the average age of the population studied. Table 2 presents estimates from 41 studies, some of which provide data for one sex only (usually males) and some for both sexes.

Rates are calculated in two different ways. First, where the numbers of deaths (N) and person years at risk (P) are available for never smokers, the rate is obtained by the formula 100,000N/P. Second, where the number of deaths (N) and the numbers of subjects at risk (R) are available, the rate is obtained by the formula 100,000N/RY, where Y is the years of follow-up. For studies that provide the average number of years at risk, this is used as the estimate of Y. Otherwise Y is estimated from the start and finish of the follow-up period. The first estimate will tend to be higher than the second, though the difference will only be material for longer follow-up periods.

Many of the rates are based on quite small numbers of lung cancer cases in never smokers and are therefore open to substantial sampling error. Of the 56 rates where the numbers are known, 35 (63%) are based on 20 cases at most and only 8 (14%) on more than 100.

While most of the data relate to "never smokers" of any product, the definition of which may sometimes allow a very small number of cigarettes smoked in a lifetime (e.g. no more than 100), some of the data relate to "never smokers of cigarettes." This comes from studies which only asked about cigarette smoking, so that current or past smokers of pipes or cigars may be included. While the distinction between the two definitions is usually unimportant for women or in countries where products other than cigarettes are rarely smoked, it is relevant for men in, e.g., the US and UK where one would expect rates to be higher in "never smokers of cigarettes" than in "never smokers."

Data for many of the populations studied are clearly not representative of the national populations. For example, some industrial groups (e.g. tin miners, nickel workers, chrysotile miners) would be expected to have high risk because of the occupational exposure, while some of the populations (e.g. doctors, nurses and the participants in the CPS studies) may have lower than average risk.

For all but one of the studies, the age range of the population at the start of the follow-up period is known (or can be assumed from the nature of the population studied) and is presented in Table 2. In order to consider the lung cancer rate estimates more meaningfully, one would like to have an indication of the mean age of the study population during the follow-up period. For a number of studies this is given or can be calculated from the data presented in the source papers. These mean ages are marked with a superscript d in Table 2. For many studies, however, this is not available. Here, it was estimated by first calculating the mean age of the population at the start of the follow-up period (shown in Table 2 as the average age at start with no superscript), and then adding on an amount depending on the years of follow-up.

Both these stages involved a number of difficulties. Estimates of the mean age at the start of the follow-up were on occasion given in the source papers or could quite often be obtained with fair accuracy from data on the distribution of the population by age group. However, in some studies, all one had was the age range of the population at the start. Where this was not open-ended, it was possible to provide an estimate, likely to be quite accurate where the age range was narrow but less reliable where it was not. Where it was open-ended, e.g. age 15+ for some of the occupational studies, it was, however, not felt possible to come up with a reliable estimate, and a "?" has been entered in Table 2.

In order to estimate the mean age of the population in the follow-up period from the mean age at the start and the length of the follow-up period, it is necessary to take into account the decreased survival of older individuals.

From the data available, this cannot be done precisely, but based on national data on overall mortality rates it seemed reasonable to use the following algorithm, where d is the actual length of follow-up in the study.

Length of follow-up (years)	Increase in age
1-10	0.450d
11-15	0.425d
16-20	0.400d
21-25	0.375d
26-30	0.350d
31-35	0.325d
36-40	0.300d

The resultant mean age at follow-up is shown in the right-hand column of Table 2. The way it has been calculated is open to a number of objections, but errors are unlikely to be more than 2 or 3 years and it serves a purpose in indicating which groups are likely to have an unusually high or low average age and therefore an unusually high or low risk.

Table 3 shows the estimates given in Table 2 by gender, region and mean age in the follow-up period. Four regions were selected: Asia, where 6 rate estimates are available – 4 from China and 2 from Japan; "Scandinavia" (including somewhat arbitrarily Hungary), where 17 estimates are available – 4 from Denmark, 1 from Finland, 6 from Norway, 4 from Sweden and 2 from Hungary; UK, where 9 estimates are available; and USA/Canada, where 25 estimates are available – 23 from USA and 2 from Canada.

Looking at the results in Table 3 (and Table 2) various observations can be made:

High risk populations

All the extremely high rates, of over 100 per 100,000 per year, relate to special high risk populations. Thus, there are rates of 241.81 in farmers in Xuanwei (an area where cooking is typically carried out in unventilated kitchens with an indoor stove), 208.54 in tin miners in Yunnan, 167.56 in chrysotile miners in Quebec and 137.30 in nickel workers in Norway. US uranium miners also have a relatively high rate, of 60.96, as do US/Canada asbestos workers (56.12). A high rate of 56.07 is also seen in a study conducted in Renfrew and Paisley in Scotland, though here the explanation for this is less obvious.

Definition of never smoking

Rates appear to be higher (given age, gender and area) for "never smokers of cigarettes" than for "never smokers of any product."

Variation by age

There is some tendency for rates to be lower in younger age groups, with the rates all relatively low (1.91, 3.14, 7.47 and 15.53) in the age group 44-49 (ignoring the data for US asbestos workers). However, overall the pattern is far from clear (probably due to confounding by the types of population studied and the relatively large variability for many of the rates), and is much less obvious than that seen within-study in Table 1.

Variation by gender

There is also a tendency, as also seen in Table 1, for rates to be lower in females than males. Omitting the underlined (high risk) estimates in Table 3, the mean rate is always lower in females in all the 10 age x region categories with data for both genders ($p<0.01$).

Variation by region

There is no very obvious tendency for rates to differ by region. Of the 6 rates for Asia, 4 relate to high risk populations or to "never smokers of cigarettes" and the other 2, both from the Hirayama study in Japan, seem well in line with rates for the same age and gender in the other regions.

There are more data for the other three regions but there is no obvious indication of a difference. Omitting the rates for the special populations and for never smokers of cigarettes, the following average rates can be obtained:

Sex	Region	Number of estimates	Total cases	Rate (per 10^6 per yr) Mean	Geometric Mean
Male	Scandinavia[a]	9	202	19.3	14.8
	UK	6	54	25.9	21.2
	US[b]	10	578	18.8	17.9
Female	Scandinavia[a]	5	59	16.3	11.9
	UK	2	8	7.5	7.5
	US[b]	5	1137	14.4	13.8

[a] Including Hungary [b] Including Canada

Taking into account the variability of the populations studied and the small numbers of cases in many of the studies, these data provide little evidence of an effect of regional variation in lung cancer rates in never smokers. The above comparison is unadjusted for age, but comparison within age groups of the data in Table 3 does not affect the conclusions.

5. An alternative indirect approach

5.1 Theory

In theory it is possible to derive an estimate of the lung cancer risk in never smokers indirectly by combining relative risk estimates from a case-control or prospective study with an estimate of overall lung cancer risk based on mortality data for the same region and period. To illustrate this, let us define:

p_1 the proportion of ever smokers among cases

p_2 the proportion of ever smokers among controls (or the at risk population)

R the relative risk of lung cancer for ever/never smoking

L the overall lung cancer rate

L_N the lung cancer rate among never smokers

L_S the lung cancer rate among ever smokers

R is estimated by $R = p_1(1-p_2)/p_2(1-p_1)$

and we also have $L_S = RL_N$,

and $L = p_2L_S+(1-p_2)L_N$.

From this it is easy to calculate that

$L_N = L/(1-p_2+p_2R)$ or alternatively

$L_N = L(1-p_1)/(1-p_2)$

p_1, p_2 and R are obtained from the study and L from the national data.

The variance of log L_N can be estimated approximately as:

$$\text{var log } L_N = \frac{1}{N_0} + \frac{A_1}{B_1N_1} + \frac{A_2}{B_2N_2}$$

where N_0 is the number of lung cancers on which L is based

N_1 is the number of cases in the epidemiological study

A_1 is the number of cases who are ever smokers ($= N_1p_1$)

B_1 is the number of cases who are never smokers ($= N_1(1-p_1)$)

N_2 is the number of controls in the epidemiological study

A_2 is the number of controls who are ever smokers (= N_2p_2) and

B_2 is the number of controls who are never smokers (= $N_2(1-p_2)$)

For practical purposes, the contribution of $1/N_0$ will be negligible compared to the other two terms (particularly the term for the cases due to the rarity of lung cancer in never smokers) and can be ignored.

If A_2 and B_2 are unknown, we can use equivalent formulae:

$$P_2 = \frac{N_2}{RN_1 + N_2}$$

$$\frac{A_2}{B_2 N_2} = \frac{P_2}{(1-P_2)N_2}$$

Although this approach sounds simple, there are a number of problems with it:

Comparability of region/population

Given that usually only national lung cancer data are available, the method will not be appropriate for an epidemiological study that is based on a special population or is conducted in an area of high risk. It is obviously best if the population considered in the epidemiological study is nationally representative, but it may give some useful information if the study is conducted in a major town in the country.

Use standardized data or not?

As the objective is to try to obtain simple estimates of absolute lung cancer risk in never smokers, one does not want relative risk estimates to be adjusted for other lung cancer risk factors. However, given adjustment usually makes little difference to the relative risk, and one is embarking on an exercise which inevitably will lead to approximate estimates, use of such adjusted estimates is not necessarily ruled out.

Ensuring comparability of age and period

National lung cancer rates, in the form available in our International Mortality and Smoking Statistics System (IMASS)[16], are age, sex and period specific. There are large numbers of epidemiological estimates that are sex specific and we need not be concerned with data for combined sexes.

Lung cancer data in IMASS are available by 5 year period and data for single years are available from the WHO database. For the epidemiological data one can use the midpoint of the time the case-control study was conducted and the midpoint of the period of follow-up for prospective studies.

Problems relate more to ensuring comparability of age. The IMASS/WHO data are by 5 year age group, but the epidemiological data are typically for the whole age range considered (though some estimates are available for less broad age ranges). Can we apply estimates of L_N/L based on a wide age range to overall estimates across a range of 5 year age groups? Given that the proportion of ever smokers among both cases and controls will vary by age, L_N/L is likely to vary by age also. However, it seems reasonable to hope that, if one chooses an age group fairly typical of the average age of lung cancer victims and where the majority of the cases occur, then L_N/L based on the total data will be fairly accurate for that age group.

To test this idea, data for CPS I by Burns *et al*[17] giving lung cancer deaths and person years by age, sex and smoking status (never/former/current) for Whites were used. The actual rate of lung cancer (per 100,000 per year) among never smokers by age was estimated and compared with that predicted based on the overall lung cancer rates by age and an estimate of L_N/L derived from the total data ignoring age. The results are shown below for ages 45-49 up to 85-89 for both sexes.

Age group	Males: Lung cancers in never smokers	Males: Observed rate	Males: Predicted rate	Females: Lung cancers in never smokers	Females: Observed rate	Females: Predicted rate
45-49	2	2.62	5.54	14	3.69	7.12
50-54	10	6.87	10.02	30	5.01	9.80
55-59	22	11.82	17.65	49	6.94	11.05
60-64	29	17.41	29.49	95	14.39	17.32
65-69	41	31.41	38.67	92	16.78	20.05
70-74	32	33.42	44.28	86	21.01	19.79
75-79	32	52.30	47.88	100	38.39	30.76
80-84	26	85.99	41.21	63	47.58	33.35
85-89	17	48.61	41.51	35	67.05	47.19
Total	215	22.39	22.39	573	14.22	14.22
		$L_N/L = 0.1695$			$L_N/L = 0.7008$	

NB Data for age groups <45 and 90+ not shown.

As can be seen, the predicted rate tends to be an overestimate for younger age groups and an overestimate for older age groups. However, it is reasonably accurate for age groups 65-69, 70-74 and 75-79 (underlined in the table).

The table below shows similar findings for CPS II (Whites excluding cancers prevalent at baseline) based on data derived for INBIFO in 2001 from our in-house files.

Age group	Males: Lung cancers in never smokers	Males: Observed rate	Males: Predicted rate	Females: Lung cancers in never smokers	Females: Observed rate	Females: Predicted rate
45-49	2	3.01	1.63	6	3.11	3.67
50-54	3	2.60	3.78	15	5.53	5.78
55-59	4	3.48	7.23	18	6.12	9.89
60-64	11	10.66	13.30	26	9.24	13.26
65-69	12	14.32	18.35	34	15.24	20.50
70-74	15	26.77	26.24	29	18.16	21.32
75-79	10	33.30	33.79	27	26.48	22.66
80-84	10	78.71	39.81	26	50.80	23.37
85+	5	96.19	27.87	14	50.62	17.17
Total	73	11.47	11.47	196	11.25	11.25
		$L_N/L = 0.0956$			$L_N/L = 0.2743$	

NB Data for age groups <45 not shown.

Again, the correspondence between actual and predicted rates seem quite reasonable for the underlined age groups. Overall, the best correspondence is for age 70-74.

It does not seem unreasonable to use the epidemiological data to estimate L_N/L and then apply it to national data for age 70-74.

5.2 Practice

To apply the method, data were extracted from the IESLC database[15] of all studies published by the year 2000, relating to the ever smoker/never smoker relative risk (of any product if available, or of cigarettes if not). This was essentially the same data as the unadjusted results in Table 1 of the main IESLC report[18] but excluded studies in Turkey, India, Zimbabwe and South Africa as there were no national lung cancer mortality data available for them, also excluded estimates for the sexes combined, and those with missing data, and additionally included age-adjusted results from prospective studies.

For each study, a relevant year was calculated. For case-control studies this was the midpoint of the period during which the subjects were interviewed. For prospective studies, it was calculated as the midpoint of the baseline period plus an assumed length of follow-up using the function presented in section 4. If there were no mortality data for the relevant year for that country on the WHO database, then substitute years and countries were used as follows:

Country	Relevant year	Substitute year
USA	1941-1949	1950
Uruguay	1991-1995	1990
UK	1948	1950
Finland	1944-1951	1952
Switzerland	1946	1951
Germany	1936	1952
Hungary	1953	1955
Poland	1956	1959
China	1978-1987	1988
Taiwan	1993	1969

Country	Relevant year	Substitute country
Brazil	1991	Brazil South
Germany	1936-1986	West Germany

Relative risks were not included if:

(i) the upper age limit of the population studies was less than or equal to 60;

(ii) the population studied was clearly racially unrepresentative of the country in question – thus data for nonwhites, blacks, Hispanics and Japanese in the USA were rejected, though data for whites in USA, UK and Germany were accepted, as were data for Chinese in Singapore and Hong Kong, as these rates will be similar to national rates.

(As support for these decisions, it can be noted that the current percentages of the populations in the relevant ethnic groups are:

USA: non-Hispanic White	75%	and Hispanics	10%
UK: Whites	95%		
Germany: Germans	91%		
Singapore: Chinese	77%		
Hong Kong: Chinese	95%		

Source : www.library.uu.nl/wesp/populstat/populhome.html)

(iii) the population studied was an occupational group with a known or possible lung cancer risk – e.g. asbestos workers, uranium and coal miners,

(iv) the study related to special groups with unusual mortality risk, such as high coronary risk.

Following this weeding out process (which is inevitably somewhat arbitrary and subjective) there were 216 estimates of lung cancer risk for 70-74 year old never smokers. Of these, 128 related to males and 88 to females. Results of various fixed- and random-effects meta-analyses[19] are given in Table 4 and Table 5.

The overall weighted mean rate for nonsmokers aged 70-74 is estimated as 44.3 using fixed-effects estimates and 45.6 using random-effects estimates. There is considerable heterogeneity between the 216 individual estimates with the heterogeneity chisquared, 7010.2, far exceeding the value of 215 which would be expected from its degrees of freedom, were variation no more than due to chance. As a result, the confidence intervals for the fixed-effects analyses give a false impression of the accuracy of the estimates.

Table 4 shows that rates are higher for males than for females ($p<0.001$), the excess being similar for both the fixed-effects estimates (64.1 vs 40.9) and the random-effects estimates (57.1 vs 34.4). With one minor exception, this excess rate is present in all of the 10 location groups studied for both analyses (see Table 5), suggesting that it is a real finding. This is consistent with the data summarised in Sections 3 (Table 1) and 4 (Table 3).

There is no clear pattern in the estimates over time, though the rates tend to be lowest in the earliest studies conducted in 1930-60 and highest in the studies conducted in 1981-1990.

Of most interest is the evidence relating to variation by location. Rates are clearly highest in China ($p<0.001$), with both fixed- and random-effects estimates over twice the overall estimate. They are lowest in the "other" group, which consists of 3 estimates from Singapore, 2 from South Korea, 2 from Australia and 2 from Thailand. The low overall fixed-effects estimate of 25.5 (with very large heterogeneity) was mainly due to the data for Thailand, where ever smoking relative risks were only about 2 in each sex and national rates were an order of magnitude lower than seen in any of the other countries. Rates were less variable in the other eight regions, though were somewhat higher in the UK than elsewhere, where random-effects estimates were 61.5 as against 42.2, 40.7, 40.3, 37.8, 34.2, 32.3 and 29.1 in, respectively, Japan, USA, South/Central America, West Europe, Canada, East Europe and Scandinavia.

The difference between regions is evident in the individual sexes, as shown in Table 5. Thus, estimated nonsmoker rates are highest in China in both men and women and relatively low in the "other" region. The UK has relatively high rates in men, with an estimated rate of 90.6 using random-effects analysis, as compared to estimates of 35.0-54.8 for the remaining regions (ignoring China). The 17 estimates for UK males, in rank order, are as follows:

13.1, 20.4, 25.3, 51.6, 67.8, 73.3, 74.8, 98.3, 111.1, 117.0, 131.4, 134.1, 138.4, 141.9, 148.1, 149.1 and 655.4.

These rates show substantial variability, the very large estimate of 655.4 coming from a case-control study in which 12.2% (10/82) of cases reported never smoking, very similar to the 12.5% (14/112) of controls. While this result is extremely unusual, omitting it from the analysis only slightly reduced the estimates for UK males (from 88.6 to 82.8 for the fixed-effects analysis and from 90.6 to 81.1 for the random-effects analysis).

The individual rates are shown in Table 6. These are given separately by sex and region and are presented in descending order of rate within each sex x region combination. They illustrate further the considerable variability of the individual study estimates, even after the weeding out process.

Table 6 additionally includes results based on the age-range 35-69 for LIU4, the Chinese "million deaths" study, which was originally omitted because the all ages result, as used in the main IESLC report, was only available as adjusted. For both males and females, the weight for this study is about the same as for all other studies combined. Including it makes little difference to the meta-analysis results for China, where the random-effects estimates increased for males from 120.3 to 123.0 and for females decreased from 93.4 to 92.7. The random-effects estimates for all regions were also little affected (difference <0.5 for either sex), while the fixed-effects estimates changed more markedly (increasing for males from 64.1 to 95.0, and for females from 40.9 to 57.5).

It is interesting to note that, while, with one minor exception, all the individual study estimates for females in America, Europe and Japan are less than 50 per 100,000 per year, all the estimates in China (and one in Singapore) exceed 60. Furthermore, of the 17 estimates in China, the 5 from Hong Kong are in the highest 6, all exceeding 100. Koo[20,21] has often drawn attention to the high rates in Hong Kong.

The variability of the estimates is due to a large number of factors. One major cause is clearly the very small number of lung cancers in nonsmokers in some of the studies. However, this would not explain why the heterogeneity chisquared generally substantially exceeds that expected from its degrees of freedom within studies of the same gender in the same region. Other causes of the variability will include:

(i) the validity of assuming that estimates of L_N/L taken from studies of varying age range can be taken as valid for age 70-74,

(ii) the possible inclusion of some smokers of products of other than cigarettes among the group classified as never smokers, and

(iii) the unrepresentative nature of some of the populations studied.

The sources of variability in our estimates of risk in lifelong nonsmokers are certainly capable of further study, but though this might give some further insight, we doubt if the excess heterogeneity will ever be clearly explained in terms of such other causes of variability. Nor is further analysis of these data very likely to change the general conclusion that, with the exception of the high rates in China (and perhaps the low rates in Thailand), rates of lung cancer in nonsmokers tend not to vary very markedly by region. It is interesting to note that Ezzati and Lopez[22] have recently published estimates of global mortality attributable to smoking in 2000 that take account of variation in the never smoker lung cancer rate based on household use of poorly-vented stoves, previous estimates[23] having assumed they were the same worldwide. The use of poorly-vented stoves is common in various regions of China, and Ezzati and Lopez cite evidence of large variations in never smoker lung cancer rates in China, "largely a result of patterns of household energy use in China over the past decades" with "coal, a common household fuel in China and traditionally burned in stoves and buildings with poor ventilation … associated with increased risk of lung cancer."

5.3 Comparison with direct approach

The data presented in Table 1 give actual lung cancer rates by age taken directly from a limited number of studies. The data presented in Tables 4, 5 and 6 are indirect estimates of risk for age 70-74 derived using, in part, national data. It is of interest to see how similar these estimates are.

In Table 1, there are seven studies which provide risk estimates with associated numbers of deaths for males, either for age 70-74 precisely (studies 1, 2, 8) or for the very similar age groups, 65-74 (studies 4 and 5), 65-69 (study 6) or 65+ (study 7). The seven estimates vary from 28.6 to 48.2 per 100,000 per year and give an overall fixed-effects estimate of 32.5 (95% CI 27.6-38.4), based on a total of 141 lung cancers in never smokers. Four of these studies also provide corresponding data for females. These estimates are more variable, but together give an estimate of 25.1 (95% CI 21.5-29.3), based on a total of 160 deaths. These estimates derive predominantly from studies conducted in the USA, with some contribution from studies conducted in Scandinavia.

Compared with the results shown in Table 5, the direct estimate of 25.1 for females is quite similar to the indirect estimates of 26.6 for the USA and 37.8 for Scandinavia. For males, the direct estimate of 32.5 is rather lower, slightly so for Scandinavia, where the indirect estimate is 40.8, and more so for the USA, where it is 61.7. For the USA, five studies provide both direct and indirect estimates, the values being shown below:

	Rate (per 100,000 per year) in nonsmokers aged 70-74	
	Direct estimate	Indirect estimate
CPS I[17]	33.4	32.2
CPS II[24]	34.9	51.8
KAISE2[25][a]	43.6	143.0
DORN[26][a]	28.0	35.0
HAMMON[27][b]	28.6	22.5

([a] Direct data for age 65-74, [b] Direct data for age 65-69)

For the three earlier studies (CPS I, DORN, HAMMON), the correspondence between the direct and indirect estimates is good, but for the two later studies (CPS II, KAISE2) the direct estimates are lower. This is particularly so for the KAISE2 study), conducted in California, based on men attending for a health check-up, where the direct estimate is less than a third of the indirect estimate. It is interesting to note that in this study in males, lung cancer rates in ever smokers were substantially lower than the national rates for the whole US population. For the age group 65-74, rates (per 100,000 per year) were 43.6 in never smokers, 212.5 in ever smokers and 413.6 nationally. The discrepancy between the direct and indirect estimates is also evident for females (8.2 from Table 1 vs 35.2 from Table 6) and confirms the unusually low rates in this population. This may be due to the characteristics of the population studied.

There comparisons confirm the difficulty of obtaining good data on lung cancer rates in nonsmokers on a national basis. Using direct data by age gives limited information, except in the USA, while using indirect data provides far more results but involves a number of problems already discussed above.

6. Summary

This report investigates how lung cancer mortality in lifelong never smokers varies by region and other factors.

Limited direct evidence from six epidemiological studies suggests that lung cancer rates in nonsmokers have not increased materially in recent years, though the overall data are not completely conclusive.

Only eight prospective studies provide direct data on variation in never smoker lung cancer rates by age and sex. While some of the studies demonstrate a rise in risk by age and higher rates in men than women, the data are of severely limited value for useful comparison across countries, being predominantly from the USA, often based on studies conducted 30 or 40 years ago and often involving very few deaths or cases.

41 studies provide estimates on lung cancer risk in never smokers that are sex- but not age-specific. 35 of the 56 rats are based on 20 cases at most and are open to substantial sampling error, and many of the populations studied are clearly unrepresentative of the national populations. Analysis of these data confirmed the tendency for rates to rise with age and be higher in males than females, and suggested that rates were higher for never smokers of cigarettes than for never smokers of any product. Rates were high in certain special populations (e.g. farmers in Xuanwei or miners in various countries). Omitting the rates for the special populations and restricting attention to never smokers of any product, there was no obvious difference in rates between studies in the US, UK and Scandinavia, the only regions that provided adequate data.

In an attempt to obtain further data on lung caner risk in never smokers, an indirect estimation approach was also used. This involved a formula which combined ever/never smoker relative risk estimates from epidemiological studies with national estimates of overall lung cancer risk based on mortality data for the same region and period. Mortality data selected were for age 70-74 as data from the American Cancer Society CPS studies indicated our formula predicted actual never smoker lung cancer rates reasonably well for that age.

After excluding studies with an inappropriate age range, studies of populations that were clearly racially unrepresentative of the country in question and studies of certain occupational and other special groups, 216 indirect estimates of lung cancer risk in 70-74 year old never smokers were obtained. The estimates showed considerable heterogeneity and were clearly higher for males than for females. Rates were compared in Canada (10 estimates), USA (56), South and Central America (9), UK (26), Scandinavia (18), West Europe (31), East Europe (11), Japan (14), China (32) and Other regions (9).

In males, overall (random-effects) estimates of the rates were highest in China (120.3, 95% CI 101.3-142.8), with UK second (90.6, 64.2-127.8). No very marked variation was evident in the other eight regions where overall estimates ranged from 35.0 in Scandinavia to 54.8 in the USA. In females, overall estimates were much higher in China (93.4, 84.6-103.1) than in other regions, ranging from 19.2 in the "other regions" to 36.5 in Japan. Within China, rates in women were even higher in Hong Kong, with 5 study estimates ranging from 106.9 to 129.0. One study in Thailand produced very low estimates of 7.0 in males and 1.7 in females.

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TABLE 1 : Lung cancer rates (per 100,000 per year) by age among never smokers

1. USA – CPS I[17] 1959-1972 Whites

Attained age:		40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+
Male	R	6.0	2.6	6.9	11.8	17.4	31.4	33.4	52.3	86.0	129.5
	N	2	2	10	22	29	41	32	32	26	19
Female	R	1.7	3.7	5.0	6.9	14.4	16.8	21.0	38.4	47.6	59.0
	N	3	14	30	49	95	92	86	100	63	41

2. USA – CPS II[24] 1982-1988

Attained age:		40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+
Male	R	(2.2)	6.0	5.5	5.3	11.6	21.5	34.9	52.0	89.2	86.8
	N	0	4	7	7	14	22	25	21	16	7
Female	R	(0.6)	1.9	5.8	7.2	12.3	16.7	30.5	32.5	57.6	60.6
	N	0	4	18	25	42	47	63	44	41	25

(Rate estimates in brackets assume N=0.5)

3. USA – California American Legion Study[28] 1957-1962

Attained age:		35-44	45-54	55-64	65-74	75+
Male	R	8.6	7.2	45.1	41.3	328.8

(Rates are for never <u>cigarette</u> smokers; numbers of deaths not available)

4. USA – California Kaiser Permanente Study[25] 1979/86-1991

Attained age:		50-64	65-74	75+
Male	R	20.8	43.6	89.2
	N	5	5	4
Female	R	10.1	8.3	24.4
	N	5	2	3

5. USA – Veterans Study[26] 1954-1962

Attained age:		55-64	65-74	75+
Male	R	11.7	28.6	47.1
	N	25	49	4

6. USA – Nine State Study[29] 1952-1955

Actual age:		50-54	55-59	60-64	65-69
Male	R	3.0	9.1	7.2	41.1
	N	1	3	2	9

7. Denmark – Three pooled studies in Copenhagen[30] 1964/1992-1993

Attained age:		20-49	50-64	65+
Male	R	(4.7)	24.1	48.2
	N	0	3	3
Female	R	(3.6)	25.9	45.6
	N	0	5	9

(Rate estimates in brackets assume N=0.5)

8. Sweden – Construction workers[8] 1971/1992-1995

Attained age:		35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+
Male	R	0.9	1.9	2.2	3.3	6.8	13.0	28.8	30.7	40.2	48.7	64.5
	N	2	4	4	5	9	15	26	18	12	5	1

R Lung cancer rate per 100,000 per year.
N Number of deaths/cases.

TABLE 2 : Lung cancer risk in never smokers in prospective studies

Reference	Country	Further details of study	Year start	Year end	Age at start Range	Age at start Mean[e]	Never[a]	Sex	Person-years or Number at risk[b]	Deaths	Years	Rate per 10^5/yr	Mean age in follow-up[e]
[31]	China	Tin miners/Yunnan	1992	1995	40+	56	NA	M	N=7867	10	4	31.78	58
[32]	China	Farmers/Xuanwei	1976	1996	25-59	42	NA	M	N=2501	127	21	241.81	50
[33]	China	Tin miners/Yunnan	1976	1987	?	?	NA	M	N=999	25	12	208.54	?
[34]	China	4 communities/Shanghai	1986/89	1993	45-64	56	NC	M	N=7787	32	5.4	76.10	58
[7]	Japan	6 prefectures	1965	1982	40+	56	NA	M	P=310506	87	-	28.02	63
						55	NA	F	P=1816199	328	-	18.06	62
[35]	Denmark	Copenhagen	1976/78	1989	20+	49	NA	M	N=721	5	13	53.34	55
						54	NA	F	N=2159	7	13	24.94	60
[30]	Denmark	3 studies/Copenhagen	1964/92	1993	20+	53[d]	NA	M	P=29284	6	-	20.49	53
						58[d]	NA	F	P=53029	14	-	26.40	58
[36]	Finland	Mobile clinic	1968/72	1984	20-75	42	NA	M	N=6842	17	16	15.53	48
[37]	Norway	Random sample and siblings	1964/65	1993	38-72	66[d]	NC	M	P=58716	27	-	45.98	66
					33-72	66[d]	NC	F	P=207789	31	-	14.92	66
[38]	Norway	Nickel workers	1953	1979	15+	?	NA	M	P=8740	12	-	137.30	?
		General population	1966	1977	35-74	55	NA	M	P=29959	9	-	30.04	60
[39]	Norway	5 areas	1972/78	1988	35-49	42	NA	M	P=127325	4	-	3.14	48
						42	NA	F	P=157361	3	-	1.91	48
[40]	Sweden	Random sample	1963	1979	18-69	48	NA	M	-	23	-	19.6[c]	55
[41]	Sweden	Random sample	1963	1972	18-69	48	NA	M	N=6352	7	10	11.02	53
						49	NA	F	N=17679	19	10	10.75	54
[8]	Sweden	Construction workers	1971/92	1995	35+	52[d]	NA	M	P=1211504	101	-	8.34	52
[42]	Hungary	Industrial area/Budapest	1975/78	1994	40-77	54	NA	M	N=1397	3	18.5	11.61	61
						55	NA	F	N=4928	16	18.5	17.55	62
[43]	UK	Civil Servants/London	1967/69	1987	40-69	51	NA	M	N=3105	10	20	16.10	59
[44]	UK	X-ray volunteers in industry	1960	1963	40+	50	NC	M	N=6536	6	3	30.60	51
[6]	UK	British Doctors	1951	1991	20+	45	NA	M	-	19	-	14[c]	57
[45]	UK	British Doctors	1951	1973	20+	42	NA	F	-	4	-	7[c]	54
[46]	UK	Renfrew and Paisley	1972/76	1985	45-64	55	NA	M	N=1189	7	10.5	56.07	59
[47]	UK	Random sample/London	1967	1986	45-60	52	NA	M	N=1340	7	20	26.12	60
[48]	UK	Random sample and siblings	1964/65	1977	35-69	52	NA	M	N=867	4	13	35.49	58
		of migrants to USA				52	NA	F	N=3814	4	13	8.07	58
[49]	UK	Health checks/London	1975/82	1983	35-64	50	NA	M	N=6359	7	14.33	7.68	56
[50]	Canada	War Veterans	1955/56	1962	15+	55	NA	M	N=7063	10	6	23.60	58
[51]	Canada	Chrysotile miners/Quebec	1976	1988	50+	?	NC	M	N=1010	22	13	167.56	?

TABLE 2 : Lung cancer risk in never smokers in prospective studies(continued)

Reference	Country	Further details of study	Year start	Year end	Age at start Range	Mean[e]	Never[a]	Sex	Person-years or Number at risk[b]	Deaths	Years	Rate per 10^5/yr	Mean age in follow-up[e]
[28]	USA	American Legion/CA	1957	1962	25+	50	NC	M	NA	NA	NA	32.40	52
[52]	USA	Rancho Bernardo/CA	1972/74	1991	40-89	63	NC	M	N=502	5	18	55.33	70
						62	NC	F	N=1139	11	18	53.65	69
[53]	USA	CPS I/CA	1960	1969	30+	60[d]	NA	M	P=99741	18	-	18.05	60
						61[d]	NA	F	P=364464	46	-	12.62	61
			1960	1997	30+	67[d]	NA	M	P=249764	76	-	30.43	67
						68[d]	NA	F	P=896654	197	-	21.97	68
[25]	USA	Health check/CA	1979/86	1991	30+	55[d]	NA	M	P=69887	14	-	20.03	55
						57[d]	NA	F	P=131956	11	-	8.34	57
[54]	USA	Japanese/Oahu HI	1965/68	1990	46-68	55	NC	M	N=2393	13	22	24.69	63
[55]	USA	Random sample/IO	1986	1994	55-69	62	NC	F	P=195158	46	-	23.57	66
[56]	USA	Metal miners	1959/61	1975	15+	?	NC	M	P=25350	6	-	23.67	?
[57]	USA	Uranium miners	1950/60	1974	15+	?	NC	M	P=9842	6	-	60.96	?
[58]	USA	Lutheran brotherhood	1966	1986	35+	?	NA	M	P=58888	5	-	8.49	?
[26]	USA	War Veterans	1954	1962	35+	61[d]	NA	M	P=443856	78	-	17.57	61
[59]	USA	(+ Canada) Asbestos workers	1967	1976	15+	44[d]	NA	M	N=891	5	10	56.12	44
[29]	USA	9 states	1952	1955	50-69	59	NA	M	P=115859	15	-	12.95	61
[60]	USA	Physicians in β-carotene trial	1982	1995	40-84	60	NA	M	N=10919	23	12	17.55	65
[61]	USA	Nurses Health Study	1976	1992	30-55	49[d]	NC	F	P=776300	58	-	7.47	49
[17]	USA	CPS I	1959	1972	30+	61[d]	NA	M	P=960229	215	-	22.39	61
						61[d]	NA	F	P=4030268	573	-	14.22	61
[24]	USA	CPS II	1982	1988	35+	60[d]	NA	M	P=733033	124	-	16.92	60
						61[d]	NA	F	P=2073735	310	-	14.95	61

[a] NA = Never smoked anything   NC = Never smoked cigarettes
[b] N = Number of subjects at risk   P = Person-years at risk
[c] Age adjusted
[d] Average for person-years
[e] Estimated as described in the text

TABLE 3 : Lung cancer rates (per 100,000 per year) by gender, region and mean age in the follow-up period

Mean age in follow-up	Male				Female			
	Asia	Scandinavia[a]	UK	US[b]	Asia	Scandinavia[a]	UK	US[b]
44-49		15.53 3.14		56.12		1.91		7.47[c]
50-54	241.81	20.49 11.02 8.34	30.60[c]	32.40[c]		10.75	(7)	
55-59	31.78 76.10[c]	53.34 (19.6)	16.10 (14) 56.07 35.49 7.68	23.60[b] 20.03		26.40	8.07	8.34
60-64	28.02	30.34 11.61[a]	26.12	18.05 24.69[c] 17.57 12.95 22.39 16.92	18.06	24.94 17.55[a]		12.62 14.22 14.95
65-71		45.98[c]		55.33[c] 30.43 17.55		14.92[c]		53.65[c] 21.97 23.57[c]
Not known	208.54	137.30		167.56[bc] 23.67[c] 60.96[c] 8.49				

Underlined data relate to populations of tin miners, nickel workers, metal miners, asbestos workers, uranium miners and also farmers in Xuanwei, known to be a high risk area

Bracketed data are age adjusted rates, where the correspondence to the mean age in follow-up is not necessarily appropriate

[a] Including Hungary

[b] Including Canada

[c] Rates for never cigarette smokers

TABLE 4 : Indirectly estimated lung cancer rates (per 100,000 per year) in lifelong nonsmokers by gender, region and year of study based on fixed- and random-effects models

Gender	Region	Year of study	Rate (95%CI) - Fixed	Rate (95%CI) - Random	Heterogeneity chisquared	DF
All	All	All	44.3 (43.7-45.0)	45.6 (41.5-50.1)	7010.2	215
Male	All	All	64.1 (61.8-66.4)	57.1 (50.3-64.8)	1381.1	127
Female	All	All	40.9 (40.2-41.6)	34.4 (30.0-39.4)	5128.8	87
All	Canada	All	29.3 (25.6-33.4)	34.2 (24.3-48.0)	48.9	9
All	USA	All	36.1 (35.0-37.4)	40.7 (34.7-47.7)	1069.1	55
All	SCAmerica[1]	All	41.1 (35.9-47.2)	40.3 (28.6-56.7)	41.2	8
All	UK	All	49.0 (45.1-53.1)	61.5 (47.0-80.4)	210.4	25
All	Scandinavia[2]	All	38.3 (36.1-40.6)	29.1 (22.0-38.3)	175.6	17
All	W Europe[3]	All	30.9 (29.9-31.9)	37.8 (31.7-45.1)	388.4	30
All	E Europe[4]	All	35.2 (32.8-37.6)	32.3 (23.4-44.6)	118.5	10
All	Japan	All	42.6 (40.8-44.4)	42.2 (34.9-51.1)	123.7	13
All	China[5]	All	98.5 (95.4-101.8)	101.9 (93.1-111.4)	172.8	31
All	Other[6]	All	25.5 (23.8-27.4)	26.2 (9.7-70.8)	1346.2	8
All	All	1930 to 1960	31.8 (30.9-32.7)	24.8 (21.5-28.5)	401.0	35
All	All	1961 to 1970	33.5 (31.7-35.4)	43.5 (32.1-58.8)	662.1	28
All	All	1971 to 1980	41.1 (39.6-42.5)	51.4 (38.9-68.0)	2242.7	47
All	All	1981 to 1990	58.7 (57.3-60.2)	58.5 (51.1-67.1)	1821.4	72
All	All	1991 to 1998	56.3 (53.6-59.2)	45.3 (34.5-59.4)	688.0	29

[1] Including Argentina, Brazil, Cuba, Uruguay
[2] Including Denmark, Norway, Sweden, Finland, Iceland
[3] Including Spain, France, Belgium, Netherlands, Switzerland, Germany, Austria, Italy, Greece
[4] Including Czechoslovakia, Hungary, Poland
[5] Including China, Hong Kong
[6] Including South Korea, Thailand, Australia

TABLE 5 : Indirectly estimated lung cancer rates (per 100,000 per year) in lifelong nonsmokers jointly by gender and region based on fixed- and random-effects models

Region	Gender	Rate (95%CI) - Fixed	Rate (95%CI) - Random	Heterogeneity chisquared	DF
Canada	Males	55.4 (43.4-70.9)	53.1 (36.5-77.4)	10.1	5
	Females	22.5 (19.2-26.4)	22.5 (19.2-26.4)	2.3	3
USA	Males	61.7 (58.4-65.2)	54.8 (44.7-67.1)	362.6	32
	Females	26.6 (25.5-27.8)	27.6 (24.4-31.2)	146.6	22
SCAmerica[1]	Males	55.0 (45.2-66.9)	45.7 (31.3-66.7)	19.7	6
	Females	31.1 (25.7-37.7)	29.9 (19.3-46.4)	5.0	1
UK	Males	88.6 (77.2-101.7)	90.6 (64.2-127.8)	84.8	16
	Females	35.5 (32.1-39.3)	34.3 (29.0-40.6)	15.1	8
Scandinavia[2]	Males	40.8 (35.3-47.2)	35.0 (22.6-54.4)	64.5	10
	Females	37.8 (35.4-40.3)	22.7 (14.6-35.4)	110.2	6
W Europe[3]	Males	56.0 (50.8-61.7)	49.2 (35.0-69.2)	175.4	19
	Females	28.7 (27.7-29.7)	26.6 (23.5-30.1)	50.2	10
E Europe[4]	Males	61.4 (48.8-77.3)	37.4 (18.3-76.5)	32.0	5
	Females	33.3 (31.0-35.8)	27.4 (19.2-39.0)	61.6	4
Japan	Males	49.0 (42.7-56.2)	46.6 (30.0-72.3)	63.4	8
	Females	41.9 (40.2-43.8)	36.5 (29.2-45.6)	55.8	4
China[5]	Males	124.5 (113.4-136.6)	120.3 (101.3-142.8)	38.7	14
	Females	95.4 (92.2-98.8)	93.4 (84.6-103.1)	106.5	16
Other[6]	Males	22.4 (18.2-27.6)	39.3 (7.7-201.2)	149.6	3
	Females	26.0 (24.1-28.0)	19.2 (4.8-76.4)	1194.9	4

[1] Including Argentina, Brazil, Cuba, Uruguay
[2] Including Denmark, Norway, Sweden, Finland, Iceland
[3] Including Spain, France, Belgium, Netherlands, Switzerland, Germany, Austria, Italy, Greece
[4] Including Czechoslovakia, Hungary, Poland
[5] Including China, Hong Kong
[6] Including South Korea, Thailand, Australia

TABLE 6 Indirect estimates from individual studies of lung cancer rates (per 100,000) per year in lifelong nonsmokers

Gender	Region	Country	Study[a]	Study type[b]	Year	Race[c]	Lung cancer type[d]	Product[e]	Special occupational population	Rate	Weight
Male	Canada		MCDUFF	CC	1981	all	all	C		83.8	5.4
			HOROWI	CC	1962	all	all	C/A		77.8	19.5
			JAIN	CC	1983	all	all	C		59.1	11.1
			WIGLE	CC	1972	all	all	A		43.6	14.5
			SIEMIA	CC	1982	all	all	C		40.3	12.0
			BEST	prosp	1957	all	all	A	war veterans	6.2	1.0
Male	USA		BLOT2	CC	1976	all	all	C(3)		206.2	58.8
			KAISE2	prosp	1987	all	all	Conly/A		143.0	16.5
			STAYNE	CC	1970	all	all	A		134.4	59.7
			HENNEK	prosp	1988	all	all	A	doctors	128.9	26.6
			BLOT1	CC	1973	all	all	C(3)		120.1	60.2
			CHANG	prosp	1980	all	all	C		109.5	5.3
			BLOT3	CC	1978	all	all	C(1)		106.0	21.1
			PIKE	CC	1974	w-hi	all	A		86.2	15.2
			KHUDER	CC	1986	all	all	C		79.1	22.9
			SCHWAR	CC	1986	wh	all	C		74.7	100.2
			NAM	CC	1986	all	all	C		67.3	30.2
			KELLER	CC	1986	wh	all	A		62.6	272.0
			GOODMA	CC	1984	w+o	all	C/A		62.4	10.1
			WYNDE6	CC	1983	all	all	A		59.7	80.7
			BROSS	CC	1963	wh	all	A		55.7	33.2
			COMSTO	nested CC	1987	all	all	A		55.4	3.9
			DORGAN	CC	1982	wh	all	A		55.2	13.5
			WYNDE3	CC	1968	all	all	A		52.7	8.6
			CPSII	prosp	1984	all	all	Conly/A		51.8	83.9
			CHOW	prosp	1974	wh	all	A		47.3	6.2
			BUFFLE	CC	1978	wh	all	A		46.8	4.6
			OSANN	CC	1985	all	all	C		40.5	45.4
			DORN	prosp	1959	wh	all	A		35.0	82.3
			BLOT4	CC	1976	wh	all	C		38.8	7.7

TABLE 6 Indirect estimates from individual studies of lung cancer rates (per 100,000) per year in lifelong nonsmokers (continued)

Gender	Region	Country	Study[a]	Study type[b]	Year	Race[c]	Lung cancer type[d]	Product[e]	Special occupational population	Rate	Weight
Male (USA) contd			WYNDE2	CC	1963	all	all	A		33.4	7.7
			CPSI	prosp	1962	all	all	C/A		32.2	86.6
			SADOWS	CC	1941	wh	all	A		28.1	15.6
			TOUSEY	CC	1995	all	all	A		27.7	4.0
			GRAHAM	CC	1958	wh	all	A		26.4	17.7
			HAMMON	prosp	1953	wh	all	A		22.5	15.5
			LOMBAR	CC	1958	all	all	A		21.7	12.7
			BRESLO	CC	1951	all	all	A(2)		17.7	6.1
			WYNDE4	CC	1949	all	all	A		12.4	11.2
Male	SC America	Uruguay	DESTE2	CC	1995	all	all	A		85.1	28.9
		Uruguay	DESTEF	CC	1991	all	all	A		68.3	25.5
		Argentina	MATOS	CC	1995	all	all	C/A		50.2	10.8
		Brazil	WUNSCH	CC	1991	all	all	C/A		47.2	13.1
		Cuba	JOLY	CC	1979	all	all	A		35.7	11.7
		Argentina	PEZZO2	CC	1995	all	all	C		20.8	5.9
		Argentina	PEZZOT	CC	1989	all	all	Conly/C		18.2	4.0
Male	UK		GREGOR	CC	1977	all	all	C		655.4	6.7
			BRETT	prosp	1961	all	all	C	industrial workers	149.1	6.2
			MCCONN	CC	1948	all	all	A		148.1	3.7
			HOLE	prosp	1979	all	all	A		141.9	7.2
			DEAN3	CC	1971	all	all	A		138.4	25.0
			BENSHL	prosp	1973	all	all	A		134.1	6.2
			DEAN2	CC	1961	all	all	A		131.4	27.2
			GILLIS	CC	1979	all	all	C/A		117.0	12.3
			MIGRAN	prosp	1970	all	all	A		111.1	4.1
			PETO	prosp	1966	all	all	A	various groups	98.3	2.0
			ALDERS	CC	1980	all	all	A		74.8	13.9
			DOLL2	prosp	1963	all	all	A		73.3	19.2
			GOLLED	CC	1957	all	all	C/A		67.8	15.2
			STOCKS	CC	1954	all	all	A		51.6	43.0

TABLE 6 Indirect estimates from individual studies of lung cancer rates (per 100,000) per year in lifelong nonsmokers (continued)

Gender	Region	Country	Study[a]	Study type[b]	Year	Race[c]	Lung cancer type[d]	Product[e]	Special occupational population	Rate	Weight
Male (UK) contd			WILKIN	CC	1993	all	all	C		25.3	2.0
			DOLL	CC	1950	all	all	A		20.4	6.3
			DARBY	CC	1991	wh	all	A		13.1	3.0
Male	Scandinavia	Finland	KNEKT	prosp	1977	all	all	A		121.3	6.3
		Denmark	LANGE	prosp	1982	all	all	A		117.3	5.1
		Sweden	NOU	CC	1974	all	all	A		48.9	6.3
		Finland	TENKAN	prosp	1969	all	all	A		46.9	5.1
		Sweden	DAMBER	CC	1975	all	all	A		45.6	39.8
		Finland	PERNU	CC	1951	all	all	A(4)		44.3	84.3
		Norway	ENGELA	prosp	1970	all	all	A		39.1	7.4
		Sweden	AXELSS	CC	1991	sca	all	A		36.6	15.7
		Norway	KJUUS	CC	1981	all	all	A	employed persons	24.2	1.9
		Finland	KOULUM	CC	1944	all	all	A		8.9	4.7
		Norway	KREYBE	CC	1951	all	all	A	doctors and industrial workers	3.3	6.1
Male	W Europe	Germany	BROCKM	CC	1991	wh	all	C		375.0	1.0
		Netherlands	VANDER	CC	1961	all	all	C(3)		188.2	57.2
		Germany	EBELIN	CC	1983	all	all	A		101.9	12.6
		Netherlands	DORANT	case-cohort	1987	all	all	A		101.4	6.8
		Italy	RONCO	CC	1978	all	all	A		87.3	5.9
		Austria	VUTUC	CC	1978	all	all	C		84.7	18.6
		Italy	PASTOR	CC	1978	all	all	A		72.0	9.7
		Italy	TIZZAN	CC	1960	all	all	A		54.6	139.1
		Germany	JAHN	CC	1991	all	all	A		52.4	16.6
		Belgium	DROSTE	CC	1996	all	all	A		51.9	6.7
		Italy	BARBON	CC	1983	all	all	A		50.5	20.8
		Germany	BECHER	CC	1986	all	all	A		45.5	2.9
		France	BENHAM	CC	1978	all	all	C/A		32.7	35.3
		Germany	RANDIG	CC	1953	all	all	A		26.8	4.2
		Germany	DAVEYS	CC	1936	all	all	A		26.7	2.8

TABLE 6 Indirect estimates from individual studies of lung cancer rates (per 100,000) per year in lifelong nonsmokers (continued)

Gender	Region	Country	Study[a]	Study type[b]	Year	Race[c]	Lung cancer type[d]	Product[e]	Special occupational population	Rate	Weight
Male (W Europe) contd		Germany	KREUZE	CC	1993	all	all	A		23.9	22.3
		France	SCHWA2	CC	1957	all	all	A(2)		23.7	40.2
		Spain	ARMADA	CC	1988	all	all	A		22.4	3.9
		Switzerland	GSELL	CC	1946	all	all	A		10.5	1.9
		Switzerland	ABELIN	CC	1953	all	all	A		9.1	2.0
Male	E Europe	Poland	JEDRYC	CC	1984	all	all	C/A		92.3	44.0
		Hungary	ABRAHA	prosp	1984	all	q+s+a	A		69.5	10.3
		Poland	PAWLEG	CC	1993	all	all	A		44.0	4.0
		Czechoslovakia	KUBIK	prosp	1968	all	all	A		28.9	2.0
		Hungary	ORMOS	CC	1953	all	all	C/A		21.9	7.5
		Poland	STASZE	CC	1956	all	all	A		10.9	5.0
Male	Japan		WAKAI	CC	1990	all	all	A		92.2	9.2
			SOBUE	CC	1987	all	q+s+l+a	C		83.2	28.2
			ESAKI	CC	1966	all	all	C		75.8	11.6
			KIHARA	CC	1995	jap	all	A		69.9	20.5
			GAO2	CC	1990	all	all	C		69.7	11.4
			HIRAYA	prosp	1972	all	all	C/A		46.7	93.1
			HITOSU	CC	1963	all	all	A		43.9	7.2
			SEGI	CC	1950	all	all	A		12.9	19.5
			MATSUD	CC	1965	all	all	C		7.5	3.0
Male	China	China	LIU3	CC	1986	all	all	A	farmers	236.7	3.6
		Hong Kong	LAMWK2	CC	1978	all	q+s+l+a	A		200.4	17.2
		China	HU	CC	1986	all	all	C/A		172.0	37.2
		China	ZHOU	CC	1986	all	all	A		162.9	57.3
		China	FAN	CC	1991	all	all	C/A		148.0	37.5
		China	WANG	CC	1992	all	all	A		131.8	25.0
		China	XU	CC	1986	all	all	A		131.3	87.7
		China	LIU4[f]	CC	1987	all	all	A		129.9	3787.7
		China	HU2	CC	1978	all	all	C		119.8	43.0
		China	JIANG	CC	1984	all	all	A		115.7	5.5

TABLE 6 Indirect estimates from individual studies of lung cancer rates (per 100,000) per year in lifelong nonsmokers (continued)

Gender	Region	Country	Study[a]	Study type[b]	Year	Race[c]	Lung cancer type[d]	Product[e]	Special occupational population	Rate	Weight
Male (China) contd		China	LEI	CC	1986	all	all	A		93.7	35.2
		China	DU	CC	1985	all	all	A		89.6	23.0
		China	GAO	CC	1985	all	all	C		89.5	54.3
		China	LIU2	CC	1984	all	all	A		76.7	10.3
		China	XU3	CC	1981	all	all	A		63.5	6.5
		Hong Kong	CHAN	CC	1977	all	all	A		18.3	1.9
Male	Other	Australia	JONES	CC	1964	all	all	A(2)		125.1	25.6
		Singapore	MACLEN	CC	1973	ch	all	C		78.1	4.0
		S Korea	CHOI	CC	1987	all	all	C		37.3	12.2
		Thailand	SIMARA	CC	1972	all	all	C		7.0	47.1
Female	Canada		WIGLE	CC	1972	all	all	A		24.8	50.3
			HOROWI	CC	1962	all	all	C/A		23.7	22.8
			JAIN	CC	1983	all	all	C		23.0	52.1
			BEST	prosp	1958	all	all	Conly/A		17.6	29.3
Female	USA		CHANG	prosp	1980	all	all	C		44.0	13.8
			WU	CC	1982	wh	q+a	A		39.7	29.4
			ANDERS	prosp	1990	all	all	Conly/A		39.2	53.1
			GOODMA	CC	1984	w+o	all	C/A		39.1	22.4
			CPSII	prosp	1984	all	all	C/A		38.2	212.2
			NAM	CC	1986	all	all	C		37.9	59.8
			COMSTO	nested CC	1987	all	all	A		37.2	14.1
			KAISE2	prosp	1987	all	all	Conly/A		35.2	12.8
			SCHWAR	CC	1986	wh	all	C		33.3	187.2
			KELLER	CC	1986	wh	all	A		28.4	470.3
			TOUSEY	CC	1995	all	all	A		27.7	13.5
			DORGAN	CC	1982	wh	all	A		27.3	95.0
			OSANN	CC	1985	all	all	C		26.3	105.0
			LOMBA2	CC	1964	all	all	C		25.9	89.2
			WYNDE6	CC	1983	all	all	C		25.2	162.5

TABLE 6 Indirect estimates from individual studies of lung cancer rates (per 100,000) per year in lifelong nonsmokers (continued)

Gender	Region	Country	Study[a]	Study type[b]	Year	Race[c]	Lung cancer type[d]	Product[e]	Special occupational population	Rate	Weight
Female (USA) contd			BRESLO	CC	1951	all	all	A(2)		22.6	13.4
			WYNDE3	CC	1968	all	all	A		22.1	24.7
			PIKE	CC	1974	w-hi	all	A		21.7	36.0
			MILLER	CC	1978	all	all	C/A		20.5	33.5
			HAENSZ	CC	1956	all	all	A		19.7	137.7
			HORWIT	CC	1980	all	all	C		18.9	11.7
			BUFFLE	CC	1978	wh	all	A		18.5	39.7
			CPSI	prosp	1962	all	all	C		17.9	337.1
Female	SC America	Cuba	JOLY	CC	1979	all	all	C/A		37.0	63.6
		Brazil	WUNSCH	CC	1991	all	all	C/A		23.6	40.3
Female	UK		WILKIN	CC	1993	all	all	C		53.9	12.6
			DEAN3	CC	1971	all	all	MConly/A		43.6	55.4
			ALDERS	CC	1980	all	all	MConly/A		38.0	70.6
			DEAN2	CC	1961	all	all	A		36.7	155.6
			DARBY	CC	1991	wh	all	A		28.0	24.2
			MCCONN	CC	1948	all	all	A		26.9	7.9
			DOLL	CC	1950	all	all	A		25.1	42.7
			MIGRAN	prosp	1970	all	all	A		18.3	4.5
			GREGOR	CC	1977	all	all	C		13.2	1.0
Female	Scandinavia	Finland	PERNU	CC	1951	all	all	A(4)		45.1	701.5
		Denmark	LANGE	prosp	1982	all	all	A		36.8	7.8
		Norway	KREYBE	CC	1951	all	all	A	doctors and industrial workers	24.1	99.7
		Sweden	NOU	CC	1974	all	all	A		17.9	5.6
		Sweden	AXELSS	CC	1991	sca	all	A		17.5	19.8
		Norway	ENGELA	prosp	1970	all	all	A		15.7	26.0
		Sweden	SVENSS	CC	1985	all	all	A		15.2	39.8
Female	W Europe	Germany	BROCKM	CC	1991	wh	all	C		34.7	3.9
		Greece	KATSOU	CC	1988	all	all	A		34.7	68.4

TABLE 6 Indirect estimates from individual studies of lung cancer rates (per 100,000) per year in lifelong nonsmokers (continued)

Gender	Region	Country	Study[a]	Study type[b]	Year	Race[c]	Lung cancer type[d]	Product[e]	Special occupational population	Rate	Weight
Female (contd)	(W Europe)	Germany	JAHN	CC	1991	all	all	C/A		32.9	59.0
		Germany	KREUZE	CC	1993	all	all	A		32.6	108.2
		Austria	VUTUC	CC	1978	all	all	C		31.4	159.9
		Germany	DAVEYS	CC	1936	all	all	A		29.5	2379.3
		Spain	AGUDO	CC	1991	all	all	Conly/A		25.2	294.0
		Germany	RANDIG	CC	1953	all	all	A		21.1	31.5
		Germany	BECHER	CC	1986	all	all	A		20.9	11.4
		Italy	TIZZAN	CC	1960	all	all	A		18.1	46.0
		France	BENHAM	CC	1978	all	all	C/A		17.5	93.8
Female	E Europe	Hungary	ORMOS	CC	1953	all	all	C/A		38.4	503.3
		Hungary	ABRAHA	prosp	1984	all	q+s+a	A		37.0	40.6
		Poland	RACHTA	CC	1993	all	all	A		29.3	40.1
		Poland	JEDRYC	CC	1984	all	all	C/A		27.8	114.4
		Poland	STASZE	CC	1956	all	all	A		13.0	52.4
Female	Japan		SOBUE	CC	1987	all	q+s+l+a	C		49.3	352.7
			WAKAI	CC	1990	all	all	A		47.8	101.5
			HIRAYA	prosp	1972	all	all	C/A		42.0	1425.7
			ESAKI	CC	1966	all	all	C		29.6	61.9
			HITOSU	CC	1963	all	all	A		19.6	64.6
Female	China	Hong Kong	LAMTH	CC	1985	ch	all	A		129.0	293.4
		Hong Kong	LAMWK2	CC	1978	all	q+s+l+a	A		119.8	98.6
		Hong Kong	LAMWK	CC	1983	ch	all	A		117.5	114.5
		China	WANG	CC	1992	all	all	A		115.4	382.0
		Hong Kong	CHAN	CC	1977	all	all	A		106.9	117.4
		China	HU	CC	1986	all	all	C/A		97.0	64.4
		China	ZHOU	CC	1986	all	all	A		95.5	142.4
		China	GAO	CC	1985	all	all	C		91.5	906.5
		China	JIANG	CC	1984	all	all	A		85.8	22.7
		China	HU2	CC	1978	all	all	C		83.8	78.3
		China	LIU4[f]	CC	1987	all	all	A		81.7	13296.2

TABLE 6 Indirect estimates from individual studies of lung cancer rates (per 100,000) per year in lifelong nonsmokers (continued)

Gender	Region	Country	Study[a]	Study type[b]	Year	Race[c]	Lung cancer type[d]	Product[e]	Special occupational population	Rate	Weight
Female	(China) contd	China	WUWILL	CC	1986	all	all	C		80.4	508.8
		China	FAN	CC	1991	all	all	C/A		79.6	116.3
		China	DU	CC	1985	all	all	A		78.5	89.8
		China	LEI	CC	1986	all	all	A		67.3	111.7
		China	LIU2	CC	1984	all	all	A		64.1	52.4
		China	XU3	CC	1981	all	all	A		60.5	16.3
Female	Other	Singapore	SEOW	CC	1998	ch	q+s+l+a	C		90.8	192.7
		Singapore	MACLEN	CC	1973	ch	all	C		40.4	62.8
		S Korea	CHOI	CC	1987	all	all	C		32.4	288.5
		Australia	JONES	CC	1964	all	all	A(2)		12.6	24.6
		Thailand	SIMARA	CC	1972	all	all	C		1.7	116.3

[a] Study reference as used in IESLC database[15]
[b] cc = case-control, prosp = prospective
[c] wh or w = white, w-hi = white excluding Hispanic, o = oriental, sca = Scandinavian, jap = Japanese, ch = Chinese
[d] q = squamous, s = small, l = large, a = adeno
[e] A = any product, C = cigarettes, MC = manufactured cigarettes. The comparison is between "ever smoked the product" and "never smoked the product", except, where indicated, never smokers includes (1) smokers of low amount, (2) long term ex-smokers, (3) smokers of low amount and long term ex-smokers, (4) recent starters. Where only one product is shown, the "ever" and "never" definitions refer to the same product.
[f] Not included in Tables 4 and 5