Indirectly estimated absolute lung cancer rates in ever smokers and never smokers by gender, region, year and histological type

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EXECUTIVE SUMMARY

An indirect method is described for estimating lung cancer rates in never and ever smokers. This is based on combining estimates derived from epidemiological studies of the ever/never smoker relative risk and of the frequency of ever smoking in the population, with national estimates of lung cancer mortality 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 unrepresentative of the country in question and studies of certain occupational and other special groups, 216 estimates of lung cancer risk in 70-74 year old never smokers and ever smokers were obtained. The estimates, which were based on studies of varying designs reported between 1936 and 1998, showed considerable heterogeneity and were higher for males than females. After conducting random-effects meta-analyses, rates in never smokers were clearly highest in China, 101.4 per 100,000 per year, over twice the overall estimate of 46.0, and were particularly low in Thailand (though evidence there was sparse). In ever smokers, rates were also high in China, 319.0, but the difference from the overall estimate of 257.0 was less marked, and rates as high or higher were seen in the USA, 300.1, South/Central America, 320.0 and UK, 352.3. Again rates were low in Thailand. When the sexes were considered separately, the high rates in China were evident in never smokers of both sexes and in female ever smokers, but in male ever smokers rates in China were no higher than in many of the 10 regions considered. In males, ever smoker rates in Japan were about half as high as those in most of the other regions.

The method was also extended to estimate rates by histological type of lung cancer using data from epidemiological studies on the ever smoker/never smoker relative risk by type and on the proportion of lung cancer cases by type. 71 estimates of mortality rates for squamous cell carcinoma and 74 for adenocarcinoma could be obtained.

For never smokers the overall estimates were 10.4 for squamous cell carcinoma and 23.6 for adenocarcinoma. Compared to rates for females, male rates

were about twice as high for squamous cell carcinoma but similar for adenocarcinoma. For adenocarcinoma, rates were markedly higher in China (64.8) and Japan (47.1) than in Western populations. For squamous cell carcinoma, rates were also highest in China (23.7) but were low in Japan (5.0).

For ever smokers the overall estimates were 117.4 for squamous cell carcinoma and 67.3 for adenocarcinoma. For squamous cell carcinoma, rates in males were about three times those for females, but for adenocarcinoma rates in males were only about 40% higher. Although rates for both histological types were relatively high in China, similarly high rates were also evident in other regions and the variation by location was only marginally significant ($p<0.05$). Rates appeared to be low in Scandinavia.

Lung cancer rates were generally quite low for studies conducted up to 1960. Over the next four ten-year periods there was a striking increase in adenocarcinoma rates in ever smokers (35.2, 64.6, 97.9 and 126.6 in 1961-70, 1971-80, 1980-90 and 1991-98). There was also a less marked increase in adenocarcinoma rates in never smokers, and in squamous cell carcinoma rates in ever smokers, but there was no trend in squamous cell carcinoma rates in never smokers. The trend in adenocarcinoma rates is only really evident in non-Asian countries, though a more limited time spread of estimates for Asia makes interpretation difficult.

There are problems in reliable interpretation of the rates, due to the assumptions made and the heterogeneity of the estimates, but the indirect method may nevertheless be a useful tool.

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1. Background

In a first report [1], we presented direct and indirect estimates of absolute lung cancer risk in never smokers, while in a second report [2] we similarly presented direct and indirect estimates of absolute lung cancer risk in never smokers by histological type. Particularly for the evidence by histological type, direct evidence on absolute lung cancer risk in never smokers was very limited.

Although in our various reports on the IESLC project we had presented estimates of ever smoker/never smoker relative risk by various factors, we had never previously presented estimates of absolute risk in ever smokers. This report therefore extends the indirect estimation procedure to provide results for ever smokers, both overall and by histological type.

As a few of the estimates from our earlier reports have been revised, and as it is convenient to have all the relevant findings in one document, this report gives all the results for never and ever smokers, overall and by histological type. It also gives the whole of the theory for indirect estimation, although this too repeats some material in the earlier reports.

2. Methodology for indirect estimation of absolute lung cancer rates by smoking habit

2.1 Overall lung cancer rates

The general approach is to combine relative risk estimates from a case-control or prospective study with an estimate of overall lung cancer risk (for ever smokers and never smokers combined) based on mortality data from the same region and period. Suppose we know for a study the following:

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, and
L the overall lung cancer rate

We require to estimate:

L_N the overall lung cancer rate among never smokers, and
L_S the overall lung cancer rate among ever smokers

We can then write down the following three equations:

$$R = p_1(1-p_2)/p_2(1-p_1) \quad (1)$$
$$L_S = RL_N \quad (2)$$
$$L = p_2L_S+(1-p_2)L_N \quad (3)$$

These equations solve to give the two required rates:

$$L_N = L(1-p_1)/(1-p_2) \quad \text{or alternatively} \quad (4a)$$
$$= L/(1-p_2+p_2R) \quad (4b)$$
$$L_S = Lp_1/p_2 \quad \text{or alternatively} \quad (5a)$$
$$= LR/(1-p_2+p_2R) \quad (5b)$$

Let us further define the following:

N_0 the number of lung cancers on which L is based

N_1 the number of cases in the epidemiological study

N_2 the number of controls (or at risk population) in the epidemiological study

The variation of the logarithm of the rate estimates L_N and L_S can then be estimated approximately as:

$$\text{var log } L_N = \frac{1}{N_0} + \frac{p_1}{N_1(1-p_1)} + \frac{p_2}{N_2(1-p_2)} \quad (6)$$

$$\text{var log } L_S = \frac{1}{N_0} + \frac{(1-p_1)}{N_1 p_1} + \frac{(1-p_2)}{N_2 p_2} \quad (7)$$

In our previous reports, which were concerned with estimating lung cancer rates in never smokers, we assumed justifiably that 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 could be ignored. However, as this assumption is far less justifiable for ever smokers, particularly if the study in question is large, we have, in this report, taken account of $1/N_0$ in our calculations, both for never and ever smokers.

The inverse of var log L_N and var log L_S can then be used as the weighting factors in the meta-analyses, which assume that the rates L_N and L_S are log normally distributed.

Where, in a study, the number of never smoking cases (or in one study number of smoking cases) was zero, p_1, p_2 and R were estimated by adding 0.5 to each cell of the relevant 2x2 table (case/control [or at risk] x ever smoker/never smoker), so avoiding zeros in the denominator in some of the formulae above. This approach is somewhat open to question, but as the

estimate has very small weight, it contributes little to the meta-analysis anyway.

2.2 Lung cancer rates by histological type

Let the subscript h refer to data for a given histological type. Suppose we know for a study the following:

p_{1h} the proportion of ever smokers among cases of the given type,
p_{2h} the proportion of ever smokers among controls (or the at risk population)
R_h the relative risk of lung cancer of the given type for ever/never smoking, and
p_h the proportion of cases who are of the given type.

Note that, except for case-control studies where controls are specific to the type, p_{2h} and p_2 will be equal. Note also that in some studies, data on histological type are not available for all lung cancer cases (e.g. cases diagnosed on clinical evidence, with no pathology available). The proportion p_h should be based on the number of cases of the given type of interest divided by the total number of cases for which information on histological type was sought.

We can then estimate
L_N the lung cancer rate of the given type

by the formula:

$$L_h = Lp_h \qquad (8)$$

We also require to estimate:

L_{Nh} the lung cancer rate of the given type among never smokers, and
L_{Sh} the lung cancer rate of the given type among ever smokers.

We can write down the following equations:

$R_h = p_{1h}(1-p_{2h})/p_{2h}(1-p_{1h})$ (9)

$L_{Sh} = R_h L_{Nh}$ (10)

$L_h = p_{2h}L_{Sh} + (1-p_{2h})L_{Nh}$ (11)

These equations solve to give the two required rates:

$L_{Nh} = L_h(1-p_{1h})/(1-p_{2h})$

$= Lp_h(1-p_{1h})/(1-p_{2h})$ or alternatively (12a)

$= Lp_h/(1-p_{2h} + p_{2h}R_h)$ (12b)

$L_{Sh} = L_h p_{1h}/p_{2h}$

$= Lp_h p_{1h}/p_{2h}$ or alternatively (13a)

$= LR_h p_h/(1-p_{2h} + p_{2h}Rh)$ (13b)

Further defining

N_{1p} the number of cases with pathology information available (may = N_1)

N_{1h} the number of cases of the given type

N_{2h} the number of controls (or at risk population) corresponding to the cases of the given type

we can estimate the variance of the logarithm of the estimates L_{Nh} and L_{Sh} as follows:

$$\operatorname{var}\log L_{Nh} = \frac{1}{N_0} + \frac{(1-p_h)}{N_{1p}p_h} + \frac{p_{1h}}{N_{1h}(1-p_{1h})} + \frac{p_{2h}}{N_{2h}(1-p_{2h})} \quad (14)$$

$$\operatorname{var}\log L_{Sh} = \frac{1}{N_0} + \frac{(1-p_h)}{N_{1p}p_h} + \frac{(p_{1h})}{N_{1h}p_{1h}} + \frac{(1-p_{2h})}{N_{2h}p_{2h}} \quad (15)$$

2.3 Practice

To apply the method, data were extracted from the IESLC database [3] 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). These were essentially the same data as the unadjusted results in Appendix Tables A1 (total lung cancer), F1 (squamous cell carcinoma) and J1 (adenocarcinoma) of the main IESLC report [4] but excluded studies in Turkey, India, Zimbabwe and South Africa as there were no national lung cancer mortality data available for them and also excluded estimates for the sexes combined, and those with missing data, and additionally included age-adjusted results from prospective studies. For a small number of studies corrections to the database meant that some of the estimates in this report differ from those in the IESLC report [4].

When estimating L, the overall lung cancer rate, the WHO database was used, which provides the data by sex, single years, and five year age groups. To correspond to the particular epidemiological study concerned, mortality data were selected for age 70-74 and for the year corresponding to the midpoint of the period of the case-control study or, for prospective studies, the period of follow-up. 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 described in detail in section 5.2 of our first report [1]. The decision to choose the age group 70-74 was based on work carried out for CPS I and CPS II comparing actual age-specific lung cancer rates among never smokers with those predicted using our methods. As described in more detail in section 5.1 of our first report, the correspondence was closest for the age groups 65-69, 70-74 and 75-79 and best for the age group 70-74.

Epidemiological studies were selected from our main IESLC report [4] that satisfied certain criteria:

(i) relative risk and corresponding 2x2 table available,
(ii) lung cancer mortality rates available for country and period of study (or at least for a time close to the study period),

(iii) study population not grossly unrepresentative (e.g. a study of Chinese tin miners),

(iv) age range includes subjects of 60+ years (i.e. studies which only provided estimates for very young populations were rejected), and

(v) the race of the subjects represent either all in the country or a subset forming a major fraction of the total (e.g. whites in the USA).

Discussion of some of the issues involved in accepting/rejecting data is given in more detail in section 5.1 of our first report [1].

2.4 Meta-analysis

Inverse-variance weighted fixed- and random-effects meta-analyses were conducted by standard methods [5] to estimate overall rates, and rates subdivided by sex, region, year of study and definition of disease. As well as giving the estimated rates and 95% CIs, the table also presents the heterogeneity chisquared values for the total data (H_0 and D_0) as well as by subdivision of the data (H_1, … H_n and D_0, … D_n) where n is the number of levels of the subdivision. In attempting to assess the significance of variation in the rates by level, taking account of the extra-binomial variability of the data, we have assumed that the expression

$$\frac{(H_0 - \sum H_j)/(D_0 - \sum D_j)}{\sum H_i / \sum D_i}$$

(where summations are over the range 1 to n) can be considered an approximate F statistic on n-1, N-n degrees of freedom (where N is the total number of estimates in the analysis). The results of these F tests are given in the text below and do not appear in the tables.

3. Overall lung cancer rates

3.1 Data

There are 216 pairs of estimates of lung cancer risk for never smokers and ever smokers for 70-74 year olds. Of these, 128 relate to males and 88 to females. The individual rates (per 100,000 per year) and their weights are shown in Table 1, together with the corresponding sex, region, country, study, study type, year, race, and definition of lung cancer and product smoked. The rates are given separately by sex and region and are presented in descending order of never smoker rates within each sex x region combination.

3.2 Meta analyses

Table 2 shows the results of meta-analyses by sex, region and year of study separately, while Table 3 shows meta-analyses jointly by sex and region. Because of the considerable heterogeneity evident in the estimates, only results for random-effects estimates are presented. Results of the F tests described in section 2.4 looking for variation by subgroup are not shown in the Tables but are reported below where appropriate.

For never smokers, the overall estimate is 46.0. Rates are significantly ($p<0.001$) greater in males, 57.7, than in females, 34.8. This excess is present in all of the 10 location groups studied (see Table 3), indicating that it is a real finding.

While there is significant ($p<0.01$) variation by time, the pattern is not a simple trend, rates starting low in 1930 to 1960, increasing in 1981 to 1990 and then falling.

Of more interest is the evidence relating to variation by location. Overall this is significant ($p<0.001$), with rates in China clearly highest, 101.4, and over twice the overall estimate of 46.0. They are lowest in the "other" group, which consists of three estimates from Singapore, two from South Korea, two from Australia and two from Thailand. The low estimate, of 26.6, was mainly due to the data for Thailand (see Table 1), where estimates were 7.0 males and 1.7 for females. In Thailand 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 the estimates rates were 61.5 as against 42.5, 40.7, 40.2, 38.1, 34.5, 32.3 and 29.8 in, respectively, Japan, USA, South/Central America, West Europe, Canada, East Europe and Scandinavia.

The difference between the regions is evident in the individual sexes, as shown in Table 3. Thus estimated never smoker 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, as compared to estimates of 36.5-54.8 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 90.6 to 81.1.

It is interesting to note from inspection of Table 1 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 [6,7] 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 never smokers 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 never smokers 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 [8] 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 [9] 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."

For ever smokers, the overall estimate is 257.0. As for never smokers, the rates are significantly ($p<0.001$) higher in males, 367.4, than in females, 142.9, with the excess present in all location groups.

There is again a highly significant ($p<0.001$) variation by time, with the pattern of a rise up to 1981 to 1990, then a fall, the same as in never smokers.

Though significant ($p<0.001$), the variation by location differs from that for never smokers, with the rate in China, 319.0, similarly high to that in the USA, 300.1, South/Central America, 320.0 and UK, 352.3. The major differences in the combined sex estimates are the low rates in the "other" region of 76.2 (again due to abnormally low rates in Thailand) and in Japan (151.1).

The variation by location in fact differs between the sexes. In males, the major feature is the high rate in the UK, 530.0, and the low rates in Japan, 181.2, and the "other" region, 122.9. All the other regions have rates between 323.9 and 418.0. In females, the major features are the high rate in China, 263.7, intermediate rates (137.8-184.6) in USA, South/Central America, UK and Eastern Europe, lower rates (81.5-106.2) in Canada, Scandinavia, West Europe and Japan, and the low rate of 49.7 in the "other" region.

In addition to the sources of variability noted for never smokers, there are also the sources relating to smoking itself – prevalence of current smokers and quitters, amount smoked, duration of smoking, time quit, type of product smoked and manner of smoking it.

4. Squamous cell carcinoma

4.1 Data

There are 71 estimates of squamous cell carcinoma risk in never and ever smokers. Of these, 39 refer to males and 32 to females. The individual rates are shown in Table 4 and are laid out as in Table 1.

4.2 Meta-analyses

Results of the meta-analyses (again random-effects) are shown in Table 5.

For never smokers, the overall estimate is 10.4. Rates are significantly ($p<0.001$) higher in males, 15.8, than in females, 7.2.

Of the 71 estimates, 54 are specifically for squamous cell carcinoma, but 17 are for a wider definition (see footnote 1 to Table 5). As can be seen from Table 5, the estimates for each sex are quite similar whether all 71 estimates are used or whether the 54 specific estimates are used. This justifies using the wider definition (which allows more estimates into the analysis).

Table 5 also gives information on variation over time. Rates are lowest in 1930-60 (3.9), highest in 1961-70 (14.3), then declining somewhat thereafter (12.9, 10.1, 11.6 in, respectively, 1971-80, 1981-90, 1991-98). However, the variation over time is not statistically significant.

Table 5 also shows variation by location, though numbers of estimates are quite low for some of the 10 regions identified. This is statistically significant ($p<0.05$). Rates are highest in China at 23.7, intermediate, in the range 9.9 to 14.2, in USA, South Central America, UK, West Europe and the "other" grouping and lowest, in the range 4.4 to 5.7, in Canada, Scandinavia, East Europe and Japan.

The two countries with most data are China, with a rate of 23.7 (95% CI 16.8-33.4) based on 14 estimates and USA, with a rate of 9.9 (95% CI 6.7-

14.6) based on 22 estimates. The China-USA difference is evident in both males 35.7 vs 20.2 and females 20.1 vs 5.0 (not shown in Table 5).

For the USA, the 12 estimates for males vary from 7.2 to 51.0. Though, as noted above, rates for males are higher in China overall, there is also substantial variation there, with the five estimates varying from 18.3 to 71.8. While there is considerable overlap for males between rates in the USA and China, this is much less for females. Here the 10 estimates for the USA vary from 1.5 to 10.7, while the nine estimates for China vary from 9.9 to 41.7. Indeed, while in China 7 of the estimates exceed 12.0, none of the estimates in any of the other locations do. 4 of the 5 highest estimates come from Hong Kong.

For ever smokers, the overall estimate is 117.4. Rates are again significantly ($p<0.001$) higher in males, 182.2, than in females, 64.4. As for never smokers, it makes little difference whether analyses are based on a wider or more restrictive definition of squamous cell carcinoma.

Though rates are lower in 1930 to 1960, there is no clear pattern of variation over time since then.

There is some variation by country, though only just significant ($p<0.05$). Here the low rate of 43.8 in Scandinavia is the main feature, with rates highest in China, Canada and South/Central America (range 144.6 to 162.8) and intermediate in other countries (range 88.0 to 127.8).

5. Adenocarcinoma

5.1 Data

There are 74 estimates of adenocarcinoma risk in never and ever smokers. Of these, 40 refer to males and 34 to females. The individual rates are shown in Table 6.

5.2 Meta-analyses

Table 7 corresponds to Table 4, but giving results for adenocarcinoma.

For never smokers, the overall estimate is 23.6. Rates for males and females are quite similar, 22.2 vs 24.6, and the difference is not significant. Within location, where there are adequate numbers of estimates, rates are also similar for males and females (random-effects means 19.4 vs 15.2 for USA and 68.6 vs 63.3 for China, for example, results not shown).

Of the 74 estimates, 59 are specifically for adenocarcinoma, but 15 are for a wider definition (see footnote 1 to Table 6). As can be seen from Table 7, the means for each sex are quite similar whether all the estimates are used or whether the 59 specific estimates are used. As for squamous cell carcinoma, we conducted all the other analyses based on all the estimates.

There is a large variation by location ($p<0.001$) with high rates in China (64.8), Japan (47.1) and "Other" (30.4) which includes South Korea, Singapore and Australia. In all the other locations, rates are much lower, varying from 9.0 to 19.5.

There is also a significant variation by time ($p<0.05$) with a sharply increasing trend. The rates are 6.9, 17.5, 21.9, 29.0 and 33.9 for, respectively, 1930-60, 1961-70, 1971-80, 1981-90 and 1991-1998.

To investigate whether this increase is evident in both Asian and non-Asian populations (or whether this is partly because later data includes more Asian studies), we carried out additional meta-analyses as shown in Table 8. A number of things emerged from this analysis:

(i) There is a large difference and highly significant ($p<0.001$) between the rates for Asian and non-Asian populations, with rates estimates of 54.7 and 16.8.

(ii) There is little difference, in either Asian or non-Asian populations between adenocarcinoma rates for males and females, though the variation for non-Asian populations is in fact significant ($p<0.01$), with rates slightly higher in males (18.9 vs 14.9).

(iii) In Asian populations there is no significant evidence of any trend over time. However, of the 22 estimates available, 16 are for one period, 1981 to 1990, limiting the ability for a powerful test.

(iv) In non-Asian populations, there is significant ($p<0.05$) evidence of variation over time. This is due to an increasing trend ($p<0.01$), with rates of 6.9, 18.2, 15.0, 19.1 and 24.3 for the five successive periods considered. There is much better coverage of pre-1981 data here, with 25 estimates as against only 5 for Asia.

(v) The marked variation over time shown in Table 7 is to a considerable extent due to the combination of much lower rates in non-Asian populations and the fact that a much higher proportion of the later estimates were for Asia (17% pre-1981, 39% 1981 onwards).

Looking at the individual rates in Table 6 one can see that, though the rates are high generally in Asia, there are two quite low estimates for males – 1.3 for MATSUD, as against 73.8 and 64.7 for other Japanese studies, and 4.5 for CHAN, as against 130.7, 69.7, 65.8 and 30.6 for other studies in China. However, although the largest of the 52 adenocarcinoma rates outside Asia in either sex is only 45.3 (ABRAHA in Hungary – males), as many as 14 of the 22 Asian rates are higher than this, with two (LAMTH females and LAMWK2 males, both in Hong Kong) exceeding 100.

For ever smokers, the overall rate is 67.3. Though the rate is significantly ($p<0.01$) higher in males, 78.0, than in females, 55.9, the difference is far less than is the case for squamous carcinoma. As for never

smokers it makes little difference whether analyses are based on a wider or more restrictive definition of adenocarcinoma.

While there is variation by location, it is not highly significant ($p<0.05$). Rates are highest in China, Canada and South/Central America (range 88.5 to 106.5) – as is the case for squamous carcinoma in ever smokers – lowest in Scandinavia, East Europe and "Other" countries (range 24.5 to 41.6) and intermediate in other countries (range 55.0 to 73.7).

There is a highly significant ($p<0.001$) trend over time, with rates successively 9.8, 35.2, 64.6, 97.9 and 126.6 in 1930-60, 1961-70, 1971-80, 1981-90 and 1991-98.

As for never smokers, additional analysis has been conducted for Asian and non-Asian populations (Table 8). It can be seen that the male/female difference and the evidence of a time trend is restricted to non-Asian populations though, as noted earlier, the limited time spread hinders interpretation for the Asian studies.

6. Summary

An indirect method is described for estimating lung cancer rates in never and ever smokers. This is based on combining estimates derived from epidemiological studies of the ever/never smoker relative risk and of the frequency of ever smoking in the population, with national estimates of lung cancer mortality 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 unrepresentative of the country in question and studies of certain occupational and other special groups, 216 estimates of lung cancer risk in 70-74 year old never smokers and ever smokers were obtained. The estimates, which were based on studies of varying designs reported between 1936 and 1998, showed considerable heterogeneity and were higher for males than females. After conducting random-effects meta-analyses, rates in never smokers were clearly highest in China, 101.4 per 100,000 per year, over twice the overall estimate of 46.0, and were particularly low in Thailand (though evidence there was sparse). In ever smokers, rates were also high in China, 319.0, but the difference from the overall estimate of 257.0 was less marked, and rates as high or higher were seen in the USA, 300.1, South/Central America, 320.0 and UK, 352.3. Again rates were low in Thailand. When the sexes were considered separately, the high rates in China were evident in never smokers of both sexes and in female ever smokers, but in male ever smokers rates in China were no higher than in many of the 10 regions considered. In males, ever smoker rates in Japan were about half as high as those in most of the other regions.

The method was also extended to estimate rates by histological type of lung cancer using data from epidemiological studies on the ever smoker/never smoker relative risk by type and on the proportion of lung cancer cases by type. 71 estimates of mortality rates for squamous cell carcinoma and 74 for adenocarcinoma could be obtained.

For never smokers the overall estimates were 10.4 for squamous cell carcinoma and 23.6 for adenocarcinoma. Compared to rates for females, male rates were about twice as high for squamous cell carcinoma but similar for adenocarcinoma. For adenocarcinoma, rates were markedly higher in China (64.8) and Japan (47.1) than in Western populations. For squamous cell carcinoma, rates were also highest in China (23.7) but were low in Japan (5.0).

For ever smokers the overall estimates were 117.4 for squamous cell carcinoma and 67.3 for adenocarcinoma. For squamous cell carcinoma, rates in males were about three times those for females, but for adenocarcinoma rates in males were only about 40% higher. Although rates for both histological types were relatively high in China, similarly high rates were also evident in other regions and the variation by location was only marginally significant ($p<0.05$). Rates appeared to be low in Scandinavia.

Lung cancer rates were generally quite low for studies conducted up to 1960. Over the next four ten-year periods there was a striking increase in adenocarcinoma rates in ever smokers (35.2, 64.6, 97.9 and 126.6 in 1961-70, 1971-80, 1980-90 and 1991-98). There was also a less marked increase in adenocarcinoma rates in never smokers, and in squamous cell carcinoma rates in ever smokers, but there was no trend in squamous cell carcinoma rates in never smokers. The trend in adenocarcinoma rates is only really evident in non-Asian countries, though a more limited time spread of estimates for Asia makes interpretation difficult.

There are problems in reliable interpretation of the rates, due to the assumptions made and the heterogeneity of the estimates, but the indirect method may nevertheless be a useful tool.

TABLE 1: Indirect estimates from individual studies of lung cancer rates (per 100,000) per year in lifelong nonsmokers and in ever smokers

Sex	Region	Country	Study[a]	Study type[b]	Year	Race[c]	Lung cancer type[d]	Product[e]	p1[f]	p2[g]	Never smoker		Ever smoker	
											Rate	Weight	Rate	Weight
Male	Canada		MCDUFF	CC	1981	all	all	C	0.96	0.81	83.8	5.3	513.5	407.8
			HOROWI	CC	1962	all	all	C/A	0.91	0.73	77.8	18.6	278.4	300.7
			JAIN	CC	1983	all	all	C	0.97	0.77	59.1	11.0	591.3	611.6
			WIGLE	CC	1972	all	all	A	0.98	0.80	43.6	14.2	444.7	626.4
			SIEMIA	CC	1982	all	all	C	0.98	0.80	40.3	11.9	642.1	856.2
			BEST	prosp	1957	all	all	A	1.00	0.90	6.2	1.0	156.7	266.2
Male	USA		BLOT2	CC	1976	all	all	C(3)	0.80	0.59	206.2	58.5	577.4	346.8
			KAISE2	prosp	1987	all	all	Conly/A	0.85	0.53	143.0	16.5	772.5	506.6
			STAYNE	CC	1970	all	all	A	0.86	0.63	134.4	59.2	493.4	862.3
			HENNEK	prosp	1988	all	all	A	0.86	0.50	128.9	26.5	804.5	962.1
			BLOT1	CC	1973	all	all	C(3)	0.87	0.57	120.1	59.8	590.8	552.3
			CHANG	prosp	1980	all	all	C	0.94	0.75	109.5	5.3	569.6	985.3
			BLOT3	CC	1978	all	all	C(1)	0.93	0.68	106.0	21.1	605.5	670.9
			PIKE	CC	1974	w-hi	all	A	0.97	0.84	86.2	15.1	452.5	1709.4
			KHUDER	CC	1986	all	all	C	0.95	0.72	79.1	22.8	621.5	1889.8
			SCHWAR	CC	1986	wh	all	C	0.96	0.73	74.7	99.5	613.1	2889.0
			NAM	CC	1986	all	all	C	0.95	0.67	67.3	30.2	662.1	2244.7
			KELLER	CC	1986	wh	all	A	0.96	0.71	62.6	267.2	631.8	5420.3
			GOODMA	CC	1984	w+o	all	C/A	0.96	0.67	62.4	10.1	673.7	901.0
			WYNDE6	CC	1983	all	all	A	0.97	0.76	59.7	80.3	598.6	5040.3
			BROSS	CC	1963	wh	all	A	0.96	0.82	55.7	33.0	286.9	2219.5
			COMSTO	other	1987	all	all	A	0.97	0.78	55.4	3.9	599.2	882.9
			DORGAN	CC	1982	wh	all	A	0.98	0.83	55.2	13.5	542.5	2113.1
			WYNDE3	CC	1968	all	all	A	0.97	0.79	52.7	8.6	427.1	1141.2

TABLE 1 (continued) : Indirect estimates from individual studies of lung cancer rates (per 100,000) per year in lifelong nonsmokers and in ever smokers

Sex	Region	Country	Study[a]	Study type[b]	Year	Race[c]	Lung cancer type[d]	Product[e]	p1[f]	p2[g]	Never smoker		Ever smoker	
											Rate	Weight	Rate	Weight
Male	USA (contd)		CPSII	prosp	1984	all	all	Conly/A	0.96	0.68	51.8	83.5	664.9	11974.4
			CHOW	prosp	1974	wh	all	A	0.97	0.76	47.3	6.2	504.1	4110.0
			BUFFLE	CC	1978	wh	all	A	0.99	0.90	46.8	4.6	493.1	2886.8
			OSANN	CC	1985	all	all	C	0.96	0.55	40.5	45.3	815.2	1838.5
			BLOT4	CC	1976	wh	all	C	0.98	0.74	38.8	7.7	562.8	808.7
			DORN	prosp	1959	wh	all	A	0.95	0.74	35.0	80.7	246.3	3553.1
			WYNDE2	CC	1963	all	all	A	0.98	0.85	33.4	7.6	281.9	2151.2
			CPSI	prosp	1962	all	all	C/A	0.96	0.75	32.2	85.2	295.9	4642.6
			SADOWS	CC	1941	wh	all	A	0.96	0.87	28.1	15.4	108.7	1047.1
			TOUSEY	CC	1995	all	all	A	0.99	0.77	27.7	4.0	612.4	1602.8
			GRAHAM	CC	1958	wh	all	A	0.97	0.83	26.4	17.6	204.8	2385.0
			HAMMON	prosp	1953	wh	all	A	0.97	0.81	22.5	15.4	145.0	1863.0
			LOMBAR	CC	1958	all	all	A	0.99	0.89	21.7	12.7	192.0	2474.5
			BRESLO	CC	1951	all	all	A(2)	0.99	0.91	17.7	6.1	114.2	1284.3
			WYNDE4	CC	1949	all	all	A	0.98	0.85	12.4	11.1	112.8	1139.8
Male	SCAmerica	Uruguay	DESTE2	CC	1995	all	all	A	0.93	0.68	85.1	24.6	569.8	137.9
		Uruguay	DESTEF	CC	1991	all	all	A	0.95	0.67	68.3	22.1	580.8	139.7
		Argentina	MATOS	CC	1995	all	all	C/A	0.94	0.72	50.2	10.7	333.3	437.2
		Brazil	WUNSCH	CC	1991	all	all	C/A	0.95	0.82	47.2	12.9	219.6	657.6
		Cuba	JOLY	CC	1979	all	all	A	0.98	0.80	35.7	11.4	434.7	347.2
		Argentina	PEZZO2	CC	1995	all	all	C	0.98	0.80	20.8	5.8	312.4	678.0
		Argentina	PEZZOT	CC	1989	all	all	Conly/C	0.98	0.73	18.2	4.0	351.4	489.7
	UK		GREGOR	CC	1977	all	all	C	0.88	0.88	655.4	6.6	675.1	319.6
			BRETT	prosp	1961	all	all	C	0.96	0.88	149.1	6.2	487.6	1638.2

TABLE 1 (continued/2) : Indirect estimates from individual studies of lung cancer rates (per 100,000) per year in lifelong nonsmokers and in ever smokers

Sex	Region	Country	Study[a]	Study type[b]	Year	Race[c]	Lung cancer type[d]	Product[e]	p1[f]	p2[g]	Never smoker		Ever smoker	
											Rate	Weight	Rate	Weight
Male	UK (contd)		MCCONN	CC	1948	all	all	A	0.95	0.94	148.1	3.7	179.2	552.6
			HOLE	prosp	1979	all	all	A	0.96	0.83	141.9	7.2	767.8	2647.8
			DEAN3	CC	1971	all	all	A	0.96	0.80	138.4	24.9	812.6	2832.9
			BENSHL	prosp	1973	all	all	A	0.97	0.84	134.1	6.2	791.3	2968.5
			DEAN2	CC	1961	all	all	A	0.96	0.86	131.4	27.0	497.9	1703.2
			GILLIS	CC	1979	all	all	C/A	0.98	0.89	117.0	12.3	733.7	3445.4
			MIGRAN	prosp	1970	all	all	A	0.98	0.89	111.1	4.1	739.0	3227.9
			PETO	prosp	1966	all	all	A	0.98	0.89	98.3	2.0	604.8	2008.3
			ALDERS	CC	1980	all	all	A	0.98	0.84	74.8	13.9	784.3	2386.1
			DOLL2	prosp	1963	all	all	A	0.98	0.85	73.3	19.1	561.6	2915.3
			GOLLED	CC	1957	all	all	C/A	0.96	0.80	67.8	15.1	427.6	1623.4
			STOCKS	CC	1954	all	all	A	0.98	0.91	51.6	42.0	297.1	1793.5
			WILKIN	CC	1993	all	all	C	0.99	0.78	25.3	2.0	636.3	1166.6
			DOLL	CC	1950	all	all	A	0.99	0.96	20.4	6.3	185.2	1154.3
			DARBY	CC	1991	wh	all	A	1.00	0.82	13.1	3.0	648.1	3292.2
Male	Scandinavia	Finland	KNEKT	prosp	1977	all	all	A	0.95	0.74	121.3	6.2	771.3	299.4
		Denmark	LANGE	prosp	1982	all	all	A	0.98	0.89	117.3	5.0	570.1	445.7
		Sweden	NOU	CC	1974	all	all	A	0.93	0.67	48.9	6.1	297.7	184.2
		Finland	TENKAN	prosp	1969	all	all	A	0.98	0.75	46.9	5.0	687.1	224.2
		Sweden	DAMBER	CC	1975	all	all	A	0.93	0.64	45.6	35.7	333.2	251.1
		Finland	PERNU	CC	1951	all	all	A(4)	0.93	0.61	44.3	40.2	395.5	71.9
		Norway	ENGELA	prosp	1970	all	all	A	0.94	0.77	39.1	6.9	180.3	87.5
		Sweden	AXELSS	CC	1991	sca	all	A	0.95	0.68	36.6	15.2	310.9	279.6
		Norway	KJUUS	CC	1981	all	all	A	0.99	0.86	24.2	1.9	332.5	176.1
		Finland	KOULUM	CC	1944	all	all	A	0.99	0.82	8.9	4.4	315.2	72.9
		Norway	KREYBE	CC	1951	all	all	A	0.98	0.85	3.3	3.6	25.6	9.0

TABLE 1 (continued/3) : Indirect estimates from individual studies of lung cancer rates (per 100,000) per year in lifelong nonsmokers and in ever smokers

Sex	Region	Country	Study[a]	Study type[b]	Year	Race[c]	Lung cancer type[d]	Product[e]	p1[f]	p2[g]	Never smoker		Ever smoker	
											Rate	Weight	Rate	Weight
Male	W Europe	Germany	BROCKM	CC	1991	wh	all	C	0.98	0.98	375.0	1.0	401.2	1208.1
		Nethlands	VANDER	CC	1961	all	all	C(3)	0.63	0.44	188.2	50.0	404.5	65.7
		Germany	EBELIN	CC	1983	all	all	A	0.89	0.55	101.9	12.6	705.9	224.4
		Nethlands	DORANT	other	1987	all	all	A	0.99	0.90	101.4	6.8	750.7	1217.4
		Italy	RONCO	CC	1978	all	all	A	0.95	0.80	87.3	5.9	445.5	733.7
		Austria	VUTUC	CC	1978	all	all	C	0.95	0.75	84.7	18.0	590.6	454.1
		Italy	PASTOR	CC	1978	all	all	A	0.95	0.75	72.0	9.6	474.7	656.7
		Italy	TIZZAN	CC	1960	all	all	A	0.85	0.75	54.6	110.5	105.5	439.2
		Germany	JAHN	CC	1991	all	all	A	0.98	0.84	52.4	16.5	471.0	1877.1
		Belgium	DROSTE	CC	1996	all	all	A	0.99	0.83	51.9	6.6	733.3	804.9
		Italy	BARBON	CC	1983	all	all	A	0.97	0.75	50.5	20.7	558.0	1394.7
		Germany	BECHER	CC	1986	all	all	A	0.98	0.82	45.5	2.9	492.7	840.7
		France	BENHAM	CC	1978	all	all	C/A	0.98	0.77	32.7	34.9	406.9	2071.8
		Germany	RANDIG	CC	1953	all	all	A	0.99	0.94	26.8	4.1	134.7	699.6
		Germany	DAVEYS	CC	1936	all	all	A	0.97	0.86	26.7	2.8	127.9	369.3
		Germany	KREUZE	CC	1993	all	all	A	0.99	0.77	23.9	22.2	539.2	444.4
		France	SCHWA2	CC	1957	all	all	A(2)	0.96	0.80	23.7	38.0	144.4	577.7
		Spain	ARMADA	CC	1988	all	all	A	0.99	0.80	22.4	3.8	441.6	757.4
		Switzland	GSELL	CC	1946	all	all	A	0.99	0.81	10.5	1.9	185.5	77.4
		Switzland	ABELIN	CC	1953	all	all	A	0.98	0.65	9.1	2.0	284.0	99.8
Male	E Europe	Poland	JEDRYC	CC	1984	all	all	C/A	0.95	0.75	92.3	43.0	535.6	1022.1
		Hungary	ABRAHA	prosp	1984	all	q+s+a	A	0.96	0.75	69.5	10.2	607.5	755.4
		Poland	PAWLEG	CC	1993	all	all	A	0.98	0.73	44.0	4.0	699.7	597.2
		Czechslia	KUBIK	prosp	1968	all	all	A	0.98	0.65	28.9	2.0	813.4	776.8
		Hungary	ORMOS	CC	1953	all	all	C/A	0.93	0.57	21.9	7.1	204.4	113.0
		Poland	STASZE	CC	1956	all	all	A	0.98	0.83	10.9	4.8	116.1	171.5

TABLE 1 (continued/4) : Indirect estimates from individual studies of lung cancer rates (per 100,000) per year in lifelong nonsmokers and in ever smokers

Sex	Region	Country	Study[a]	Study type[b]	Year	Race[c]	Lung cancer type[d]	Product[e]	p1[f]	p2[g]	Never smoker		Ever smoker	
											Rate	Weight	Rate	Weight
Male	Japan		WAKAI	CC	1990	all	all	A	0.96	0.87	92.2	9.1	332.0	1426.3
			SOBUE	CC	1987	all	q+s+l+a	C	0.97	0.89	83.2	28.1	316.0	2720.6
			ESAKI	CC	1966	all	all	C	0.91	0.84	75.8	11.4	144.0	375.7
			KIHARA	CC	1995	jap	all	A	0.94	0.72	69.9	20.4	413.9	531.1
			GAO2	CC	1990	all	all	C	0.95	0.80	69.7	11.4	357.6	791.2
			HIRAYA	prosp	1972	all	all	C/A	0.93	0.81	46.7	88.6	203.5	1675.5
			HITOSU	CC	1963	all	all	A	0.95	0.88	43.9	7.1	120.8	624.6
			SEGI	CC	1950	all	all	A	0.89	0.82	12.9	16.5	22.1	99.9
			MATSUD	CC	1965	all	all	C	0.98	0.73	7.5	3.0	160.5	797.2
Male	China	China	LIU3	CC	1986	all	all	A	0.93	0.92	236.7	3.6	284.1	447.1
		HongKong	LAMWK2	CC	1978	all	q+s+l+a	A	0.91	0.79	200.4	15.2	567.2	105.5
		China	HU	CC	1986	all	all	C/A	0.75	0.58	172.0	36.6	359.5	142.9
		China	ZHOU	CC	1986	all	all	A	0.73	0.53	162.9	55.9	384.4	81.8
		China	FAN	CC	1991	all	all	C/A	0.86	0.68	148.0	37.0	420.3	619.4
		China	WANG	CC	1992	all	all	A	0.90	0.72	131.8	24.8	457.5	504.6
		China	XU	CC	1986	all	all	A	0.86	0.70	131.3	84.4	345.4	823.1
		China	HU2	CC	1978	all	all	C	0.86	0.66	119.8	42.2	362.9	415.7
		China	JIANG	CC	1984	all	all	A	0.93	0.83	115.7	5.5	314.8	307.7
		China	LEI	CC	1986	all	all	A	0.92	0.75	93.7	34.7	344.8	743.8
		China	DU	CC	1985	all	all	A	0.95	0.84	89.6	22.7	316.3	1155.0
		China	GAO	CC	1985	all	all	C	0.92	0.73	89.5	53.1	350.7	950.9
		China	LIU2	CC	1984	all	all	A	0.95	0.80	76.7	10.2	331.2	557.7
		China	XU3	CC	1981	all	all	A	0.93	0.69	63.5	6.4	380.2	171.7
		HongKong	CHAN	CC	1977	all	all	A	0.99	0.79	18.3	1.9	504.0	88.1

TABLE 1 (continued/5) : Indirect estimates from individual studies of lung cancer rates (per 100,000) per year in lifelong nonsmokers and in ever smokers

Sex	Region	Country	Study[a]	Study type[b]	Year	Race[c]	Lung cancer type[d]	Product[e]	p1[f]	p2[g]	Never smoker		Ever smoker	
											Rate	Weight	Rate	Weight
Male	Other	Australia	JONES	CC	1964	all	all	A(2)	0.91	0.79	125.1	23.9	337.9	255.4
		Singapore	MACLEN	CC	1973	ch	all	C	0.97	0.89	78.1	3.5	279.7	26.2
		SKorea	CHOI	CC	1987	all	all	C	0.95	0.83	37.3	11.7	156.6	241.8
		Thailand	SIMARA	CC	1972	all	all	C	0.55	0.38	7.0	17.2	13.9	18.9
Female	Canada		WIGLE	CC	1972	all	all	A	0.69	0.35	24.8	36.6	101.9	70.4
			HOROWI	CC	1962	all	all	C/A	0.60	0.45	23.7	17.1	43.2	28.4
			JAIN	CC	1983	all	all	C	0.88	0.48	23.0	45.9	188.1	180.0
			BEST	prosp	1958	all	all	Conly/A	0.27	0.27	17.6	17.7	39.5	3.8
Female	USA		CHANG	prosp	1980	all	all	C	0.79	0.51	44.0	13.7	162.1	178.6
			WU	CC	1982	wh	q+a	A	0.86	0.58	39.7	29.2	173.9	237.2
			ANDERS	prosp	1990	all	all	Conly/A	0.87	0.33	39.2	52.8	513.8	1754.5
			GOODMA	CC	1984	w+o	all	C/A	0.81	0.34	39.1	22.4	324.3	102.3
			CPSII	prosp	1984	all	all	C/A	0.82	0.36	38.2	204.8	311.4	2503.8
			NAM	CC	1986	all	all	C	0.85	0.36	37.9	59.3	379.6	512.5
			COMSTO	other	1987	all	all	A	0.87	0.43	37.2	14.1	333.3	122.8
			KAISE2	prosp	1987	all	all	Conly/A	0.86	0.40	35.2	12.8	355.1	456.5
			SCHWAR	CC	1986	wh	all	C	0.88	0.43	33.3	182.4	331.4	885.6
			KELLER	CC	1986	wh	all	A	0.90	0.41	28.4	440.9	354.3	1571.4
			TOUSEY	CC	1995	all	all	A	0.94	0.49	27.7	13.5	434.2	355.1
			DORGAN	CC	1982	wh	all	A	0.88	0.48	27.3	93.2	214.1	382.5
			OSANN	CC	1985	all	all	C	0.88	0.34	26.3	103.3	392.1	675.2
			LOMBA2	CC	1964	all	all	C	0.66	0.60	25.9	81.1	34.5	220.5
			WYNDE6	CC	1983	all	all	C	0.89	0.45	25.2	157.9	262.4	960.3
			BRESLO	CC	1951	all	all	A(2)	0.52	0.44	22.6	13.0	31.2	11.1
			WYNDE3	CC	1968	all	all	A	0.70	0.42	22.1	24.2	69.0	56.6

TABLE 1 (continued/6) Indirect estimates from individual studies of lung cancer rates (per 100,000) per year in lifelong nonsmokers and in ever smokers

Sex	Region	Country	Study[a]	Study type[b]	Year	Race[c]	Lung cancer type[d]	Product[e]	p1[f]	p2[g]	Never smoker		Ever smoker	
											Rate	Weight	Rate	Weight
Female	USA (contd)		PIKE	CC	1974	w-hi	all	A	0.82	0.48	21.7	35.4	105.0	136.3
			MILLER	CC	1978	all	all	C/A	0.83	0.31	20.5	33.2	232.3	515.7
			HAENSZ	CC	1956	all	all	A	0.48	0.30	19.7	112.2	42.4	65.8
			HORWIT	CC	1980	all	all	C	0.90	0.44	18.9	11.7	213.4	135.1
			BUFFLE	CC	1978	wh	all	A	0.91	0.59	18.5	39.2	131.9	506.0
			CPSI	prosp	1962	all	all	C	0.49	0.30	17.9	232.9	49.8	223.1
Female	SCAmerica	Cuba	JOLY	CC	1979	all	all	C/A	0.76	0.30	37.0	39.6	271.8	60.1
		Brazil	WUNSCH	CC	1991	all	all	C/A	0.67	0.32	23.6	35.9	103.7	64.8
Female	UK		WILKIN	CC	1993	all	all	C	0.88	0.55	53.9	12.6	308.4	167.2
			DEAN3	CC	1971	all	all	MConly/A	0.73	0.48	43.6	52.6	125.5	259.5
			ALDERS	CC	1980	all	all	MConly/A	0.88	0.60	38.0	67.7	175.9	526.8
			DEAN2	CC	1961	all	all	A	0.42	0.20	36.7	120.7	107.5	26.6
			DARBY	CC	1991	wh	all	A	0.93	0.51	28.0	24.0	343.4	642.9
			MCCONN	CC	1948	all	all	A	0.43	0.21	26.9	7.7	74.0	2.2
			DOLL	CC	1950	all	all	A	0.63	0.45	25.1	37.9	51.4	51.2
			MIGRAN	prosp	1970	all	all	A	0.89	0.52	18.3	4.5	132.0	204.7
			GREGOR	CC	1977	all	all	C	0.95	0.66	13.2	1.0	145.0	90.1
Female	Scandinavia	Finland	PERNU	CC	1951	all	all	A(4)	0.15	0.08	45.1	23.2	84.7	10.3
		Denmark	LANGE	prosp	1982	all	all	A	0.90	0.72	36.8	7.3	124.8	97.9
		Norway	KREYBE	CC	1951	all	all	A	0.29	0.33	24.1	9.9	19.3	6.6
		Sweden	NOU	CC	1974	all	all	A	0.71	0.26	17.9	5.2	127.1	20.7
		Sweden	AXELSS	CC	1991	sca	all	A	0.86	0.41	17.5	17.6	150.7	77.3
		Norway	ENGELA	prosp	1970	all	all	A	0.50	0.23	15.7	11.0	51.4	10.9
		Sweden	SVENSS	CC	1985	all	all	A	0.82	0.43	15.2	28.7	92.5	58.1

TABLE 1 (continued/7) : Indirect estimates from individual studies of lung cancer rates (per 100,000) per year in lifelong nonsmokers and in ever smokers

Sex	Region	Country	Study[a]	Study type[b]	Year	Race[c]	Lung cancer type[d]	Product[e]	p1[f]	p2[g]	Never smoker		Ever smoker	
											Rate	Weight	Rate	Weight
Female	W Europe	Germany	BROCKM	CC	1991	wh	all	C	0.86	0.75	34.7	3.9	69.5	86.5
		Greece	KATSOU	CC	1988	all	all	A	0.52	0.25	34.7	41.4	116.5	19.0
		Germany	JAHN	CC	1991	all	all	C/A	0.68	0.41	32.9	55.8	101.6	78.6
		Germany	KREUZE	CC	1993	all	all	A	0.68	0.36	32.6	100.2	113.9	74.3
		Austria	VUTUC	CC	1978	all	all	C	0.63	0.21	31.4	74.7	209.4	63.4
		Germany	DAVEYS	CC	1936	all	all	A	0.00	0.03	29.5	146.8	21.3	0.5
		Spain	AGUDO	CC	1991	all	all	Conly/A	0.22	0.11	25.2	127.5	57.7	13.0
		Germany	RANDIG	CC	1953	all	all	A	0.48	0.30	21.1	27.6	46.9	18.3
		Germany	BECHER	CC	1986	all	all	A	0.79	0.46	20.9	11.2	93.8	52.8
		Italy	TIZZAN	CC	1960	all	all	A	0.50	0.20	18.1	38.2	73.8	18.8
		France	BENHAM	CC	1978	all	all	C/A	0.48	0.17	17.5	73.4	77.7	25.4
Female	E Europe	Hungary	ORMOS	CC	1953	all	all	C/A	0.04	0.18	38.4	42.1	7.3	1.0
		Hungary	ABRAHA	prosp	1984	all	q+s+a	A	0.69	0.31	37.0	34.2	180.5	102.0
		Poland	RACHTA	CC	1993	all	all	A	0.72	0.30	29.3	37.0	171.7	46.4
		Poland	JEDRYC	CC	1984	all	all	C/A	0.61	0.16	27.8	88.9	222.0	31.3
		Poland	STASZE	CC	1956	all	all	A	0.29	0.08	13.0	25.8	56.2	6.9
Female	Japan		SOBUE	CC	1987	all	q+s+l+a	C	0.43	0.21	49.3	283.7	138.5	116.9
			WAKAI	CC	1990	all	all	A	0.43	0.18	47.8	95.3	169.7	23.7
			HIRAYA	prosp	1972	all	all	C/A	0.23	0.11	42.0	436.0	99.0	105.8
			ESAKI	CC	1966	all	all	C	0.46	0.26	29.6	53.7	72.8	17.4
			HITOSU	CC	1963	all	all	A	0.51	0.21	19.6	52.8	76.5	51.2

TABLE 1 (continued/8) : Indirect estimates from individual studies of lung cancer rates (per 100,000) per year in lifelong nonsmokers and in ever smokers

Sex	Region	Country	Study[a]	Study type[b]	Year	Race[c]	Lung cancer type[d]	Product[e]	p1[f]	p2[g]	Never smoker		Ever smoker	
											Rate	Weight	Rate	Weight
Female	China	HongKong	LAMTH	CC	1985	ch	all	A	0.55	0.24	129.0	94.8	491.5	61.7
		HongKong	LAMWK2	CC	1978	all	q+s+l+a	A	0.54	0.26	119.8	46.5	384.4	31.0
		HongKong	LAMWK	CC	1983	ch	all	A	0.54	0.22	117.5	58.8	483.9	30.8
		China	WANG	CC	1992	all	all	A	0.17	0.05	115.4	303.6	461.7	4.1
		HongKong	KOO	CC	1982	all	all	A	0.56	0.32	114.7	55.0	317.8	41.1
		HongKong	CHAN	CC	1977	all	all	A	0.56	0.26	106.9	47.9	372.0	32.0
		China	HU	CC	1986	all	all	C/A	0.39	0.27	97.0	60.8	167.8	15.5
		China	ZHOU	CC	1986	all	all	A	0.33	0.18	95.5	125.7	212.1	8.1
		China	GAO	CC	1985	all	all	C	0.35	0.18	91.5	491.8	232.5	100.1
		China	JIANG	CC	1984	all	all	A	0.44	0.24	85.8	22.2	213.6	5.6
		China	HU2	CC	1978	all	all	C	0.60	0.44	83.8	73.0	157.6	86.4
		China	WUWILL	CC	1986	all	all	C	0.56	0.37	80.4	345.3	177.7	282.6
		China	FAN	CC	1991	all	all	C/A	0.54	0.23	79.6	107.9	312.1	70.7
		China	DU	CC	1985	all	all	A	0.67	0.52	78.5	82.9	151.6	169.0
		China	LEI	CC	1986	all	all	A	0.59	0.29	67.3	101.2	234.9	63.1
		China	LIU2	CC	1984	all	all	A	0.59	0.25	64.1	50.0	273.1	24.3
		China	XU3	CC	1981	all	all	A	0.64	0.31	60.5	16.1	243.3	12.5
Female	Other	Singapore	SEOW	CC	1998	ch	q+s+l+a	C	0.40	0.11	90.8	35.2	502.0	10.8
		Singapore	MACLEN	CC	1973	ch	all	C	0.52	0.34	40.4	6.3	84.8	6.1
		SKorea	CHOI	CC	1987	all	all	C	0.20	0.14	32.4	80.7	51.3	11.9
		Australia	JONES	CC	1964	all	all	A(2)	0.58	0.35	12.6	13.7	32.2	11.7
		Thailand	SIMARA	CC	1972	all	all	C	0.31	0.16	1.7	7.5	4.0	5.6

[a] Study reference as used in IESLC database[3]

[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] Proportion of ever smokers among cases

[g] Proportion of ever smokers among controls (or the at risk population.

TABLE 2 : Indirectly estimated lung cancer rates (per 100,000 per year) in never smokers and ever smokers by sex, region and year of study based on random-effects models

				Never smokers		Ever smokers	
Sex	Region	Year of study	DF	Rate (95% CI)	Heterogeneity chisquared	Rate (95% CI)	Heterogeneity chisquared
All	All	All	215	46.0 (42.0-50.4)	3948.2	257.0 (238.2-277.2)	52354.0
Male	All	All	127	57.7 (51.1-65.1)	1168.1	367.4 (335.7-402.1)	41061.4
Female	All	All	87	34.8 (30.5-39.7)	2403.5	142.9 (125.2-163.1)	5942.1
All	Canada	All	9	34.5 (24.3-48.9)	43.5	223.4 (153.2-325.8)	979.8
All	USA	All	55	40.7 (34.8-47.6)	995.9	300.1 (258.9-347.8)	26390.3
All	SCAmerica[1]	All	8	40.2 (28.4-56.7)	36.4	320.0 (253.7-403.6)	310.6
All	UK	All	25	61.5 (46.8-80.8)	204.1	352.3 (294.4-421.6)	7378.6
All	Scandinavia[2]	All	17	29.8 (21.7-40.9)	90.2	193.2 (142.1-262.7)	900.2
All	W Europe[3]	All	30	38.1 (30.6-47.4)	319.9	231.1 (188.5-283.2)	5112.1
All	E Europe[4]	All	10	32.3 (22.3-46.8)	85.5	255.3 (178.2-365.6)	955.2
All	Japan	All	13	42.5 (34.5-52.4)	109.1	151.1 (115.5-197.6)	1986.5
All	China[5]	All	31	101.4 (92.4-111.4)	136.5	319.0 (290.1-350.8)	470.8
All	Other[6]	All	8	26.6 (12.5-56.7)	200.3	76.2 (38.8-149.8)	381.2
All	All	1930 to 1960	35	24.3 (20.5-29.0)	208.4	118.2 (100.7-138.8)	4138.4
All	All	1961 to 1970	28	43.7 (32.2-59.2)	563.8	201.2 (161.4-250.8)	8694.8
All	All	1971 to 1980	47	52.2 (41.8-65.1)	843.5	294.9 (255.3-340.7)	8774.2
All	All	1981 to 1990	72	58.6 (51.3-66.9)	1372.5	345.7 (316.3-378.0)	9115.3
All	All	1991 to 1998	29	45.3 (34.6-59.2)	489.9	323.3 (279.7-373.8)	2653.4

[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 3 : Indirectly estimated lung cancer rates (per 100,000 per year) in never and ever smokers jointly by sex and region based on random-effects models

			Never smokers		Ever smokers	
Region	Sex	DF	Rate (95%CI)	Heterogeneity chisquared	Rate (95%CI)	Heterogeneity chisquared
Canada	Males	5	53.1 (36.5-77.4)	9.9	395.5 (273.6-571.8)	524.1
	Females	3	22.7 (19.0-27.2)	1.5	81.5 (40.7-163.3)	68.0
USA	Males	32	54.8 (44.7-67.1)	359.9	418.0 (347.3-503.2)	20900.2
	Females	22	27.6 (24.5-31.1)	125.1	184.6 (146.2-232.9)	3611.0
SCAmerica[1]	Males	6	45.5 (31.1-66.5)	18.5	377.9 (300.5-475.3)	225.1
	Females	1	29.7 (19.1-46.1)	3.8	167.8 (65.3-431.2)	28.9
UK	Males	16	90.6 (64.2-127.8)	84.4	530.0 (442.7-634.5)	4745.8
	Females	8	34.3 (29.0-40.7)	14.4	146.2 (101.8-210.1)	435.3
Scandinavia[2]	Males	10	36.5 (23.8-55.8)	47.8	323.9 (243.4-431.1)	414.5
	Females	6	22.5 (15.5-32.8)	20.3	88.5 (63.4-123.5)	38.2
W Europe[3]	Males	19	49.2 (35.0-69.2)	162.5	360.4 (288.3-450.6)	4057.8
	Females	10	26.4 (22.7-30.6)	34.2	90.5 (69.8-117.2)	70.7
E Europe[4]	Males	5	37.5 (18.4-76.5)	31.0	407.5 (271.6-611.4)	683.7
	Females	4	27.6 (20.1-37.9)	22.2	137.8 (90.8-209.1)	21.1
Japan	Males	8	46.9 (30.5-71.9)	58.0	181.2 (131.8-249.1)	1760.8
	Females	4	36.5 (28.6-46.7)	46.1	106.2 (80.3-140.6)	21.6
China[5]	Males	14	120.1 (101.3-142.6)	37.7	369.5 (342.7-398.3)	131.7
	Females	16	92.2 (83.6-101.7)	67.8	263.7 (215.4-322.8)	142.8
Other[6]	Males	3	39.3 (9.0-172.2)	85.1	122.9 (53.6-282.1)	219.7
	Females	4	19.7 (7.2-54.4)	114.0	49.7 (11.9-207.0)	95.2

[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 4 : Indirect estimates from individual studies of squamous cell carcinoma rates (per 100,000) per year in lifelong nonsmokers and in ever smokers

Sex	Region	Country	Study[a]	Study type[b]	Year	Race[c]	Lung cancer type[d]	Product[e]	p1[f]	p2[g]	Lung cancer Rate	Lung cancer Weight	Ever smoker Rate	Ever smoker Weight
Male	Canada		JAIN	CC	1983	all	q	C	0.99	0.77	9.9	2.0	232.9	179.5
			SIEMIA	CC	1982	all	q	C	0.99	0.80	9.3	2.9	270.8	358.2
			BAND	CC	1987	all	q	Conly/A	0.99	0.79	5.7	6.8	213.9	766.4
Male	USA		STAYNE	CC	1970	all	q	A	0.86	0.63	51.0	22.2	176.9	164.2
			KHUDER	CC	1986	all	q	C	0.95	0.72	30.9	8.7	241.9	221.4
			BYERS1	CC	1961	wh	q	C	0.93	0.62	26.9	22.2	223.3	514.8
			COMSTO	other	1987	all	q	A	0.96	0.73	26.7	2.0	215.1	60.6
			BROWN2	CC	1987	wh	q	C	0.94	0.60	24.1	184.9	268.1	2821.2
			WYNDE6	CC	1983	all	KI	A	0.98	0.76	19.9	28.2	369.9	2394.8
			WYNDE3	CC	1968	all	KI	A	0.99	0.79	17.6	3.0	321.4	482.9
			DORGAN	CC	1982	wh	q	A	0.99	0.83	14.3	4.0	269.9	526.3
			BUFFLE	CC	1978	wh	q	A	0.98	0.80	13.8	3.4	194.2	222.7
			WYNDE2	CC	1963	all	KI	A	0.99	0.85	10.9	2.9	215.5	804.0
			HAMMON	prosp	1953	wh	not a	A	0.99	0.81	7.9	4.0	127.8	1033.6
			OSANN	CC	1985	all	q	C	0.98	0.55	7.2	8.0	258.9	402.9
Male	SCAmerica	Uruguay	DESTE2	CC	1995	all	q	A	0.99	0.91	18.3	3.6	240.9	124.4
		Argentina	MATOS	CC	1995	all	q	C/A	0.94	0.72	14.3	3.0	87.3	57.7
		Argentina	PEZZOT	CC	1989	all	q	Conly/C	1.00	0.73	2.2	0.5	140.9	109.5
Male	UK		ALDERS	CC	1980	all	q	A	0.99	0.87	24.8	1.8	364.3	290.6
Male	Scandinavia	Sweden	DAMBER	CC	1975	all	q	A	0.95	0.62	15.1	12.7	178.3	143.0
		Norway	ENGELA	prosp	1970	all	q	A	0.95	0.74	12.6	2.8	80.9	38.6
		Sweden	NOU	CC	1974	all	q	A	0.98	0.67	6.1	2.0	167.1	63.5
		Norway	KREYBE	CC	1951	all	KI	A	0.99	0.85	1.7	2.3	21.3	8.9
Male	W Europe	Italy	BARBON	CC	1983	all	q	A	0.98	0.75	13.8	5.9	198.6	314.1
		Germany	JAHN	CC	1991	all	q	A	0.99	0.84	8.7	3.0	201.3	462.2

TABLE 4 (continued) : Indirect estimates from individual studies of squamous cell carcinoma rates (per 100,000) per year in lifelong nonsmokers and in ever smokers

Sex	Region	Country	Study[a]	Study type[b]	Year	Race[c]	Lung cancer type[d]	Product[e]	p1[f]	p2[g]	Never smoker		Ever smoker	
											Rate	Weight	Rate	Weight
Male	E Europe	Poland	JEDRYC	CC	1984	all	q	C/A	0.98	0.78	18.9	5.9	291.1	346.4
		Hungary	ORMOS	CC	1953	all	q	C/A	0.93	0.57	6.5	2.0	66.2	29.5
		Hungary	ABRAHA	prosp	1984	all	q	A	1.00	0.75	2.8	0.5	260.5	187.3
		Poland	STASZE	CC	1956	all	q	A	1.00	0.83	1.1	0.5	62.1	108.3
Male	Japan		WAKAI	CC	1990	all	q	A	0.98	0.87	18.4	2.0	159.7	188.8
			SOBUE	CC	1987	all	q	C	0.99	0.89	7.2	2.9	127.8	562.4
			MATSUD	CC	1965	all	q	C	0.99	0.73	2.6	1.0	102.4	214.8
Male	China	China	ZHOU	CC	1986	all	q	A	0.78	0.53	71.8	41.0	225.4	73.9
		HongKong	LAMWK2	CC	1978	all	q	A	0.96	0.79	43.6	4.5	300.2	76.2
		China	XU3	CC	1981	all	KI	A	0.93	0.69	30.6	2.9	181.5	51.7
		China	GAO	CC	1985	all	q	C	0.96	0.73	21.6	12.6	188.4	393.4
		HongKong	CHAN	CC	1977	all	q+s	A	0.98	0.79	18.3	1.9	278.8	65.5
Male	Other	Australia	JONES	CC	1964	all	q	A(2)	0.94	0.81	35.8	4.9	146.7	91.0
		SKorea	CHOI	CC	1987	all	q	C	0.96	0.83	17.2	5.7	93.8	150.6
Female	Canada		JAIN	CC	1983	all	q	C	0.94	0.48	2.7	5.9	49.7	78.7
Female	USA		HAENSZ	CC	1956	all	not a	A	0.57	0.30	10.7	51.8	32.3	51.9
			LOMBA2	CC	1964	all	q+u	C	0.86	0.60	5.6	15.3	23.8	124.6
			WYNDE3	CC	1968	all	KI	A	0.83	0.42	5.5	5.2	37.5	27.8
			DORGAN	CC	1982	all	q	A	0.91	0.47	5.5	24.3	61.2	206.3
			BROWN2	CC	1987	wh	q	C	0.90	0.31	5.3	115.8	107.2	592.2
			ANDERS	prosp	1990	all	q	Conly/A	0.93	0.33	4.8	5.1	121.8	78.5
			OSANN2	NCC	1973	all	KI	C	0.94	0.51	3.7	6.8	56.9	77.8
			OSANN	CC	1985	all	q	C	0.93	0.34	3.3	12.1	84.6	155.9
			WYNDE6	CC	1983	wh	q	C	0.93	0.29	2.7	12.4	83.8	169.4
			COMSTO	other	1987	all	q	A	1.00	0.43	1.5	0.5	70.2	17.9

TABLE 4 (continued/2) : Indirect estimates from individual studies of squamous cell carcinoma rates (per 100,000) per year in lifelong nonsmokers and in ever smokers

Sex	Region	Country	Study[a]	Study type[b]	Year	Race[c]	Lung cancer type[d]	Product[e]	p1[f]	p2[g]	Never smoker		Ever smoker	
											Rate	Weight	Rate	Weight
Female	UK		ALDERS	CC	1980	all	q	MConly/A	0.93	0.41	5.2	7.9	31.7	69.2
Female	Scandinavia	Norway	KREYBE	CC	1951	all	KI	A	0.40	0.33	2.4	2.5	3.2	1.8
		Sweden	NOU	CC	1974	all	q	A	0.71	0.26	2.1	1.1	14.6	1.6
		Sweden	SVENSS	CC	1985	all	q	A	0.91	0.43	2.0	4.8	25.8	31.0
Female	W Europe	Greece	KATSOU	CC	1988	all	not a	A	0.67	0.25	11.3	13.6	69.1	14.6
		Germany	BECHER	CC	1986	all	q+s	A	0.93	0.55	5.4	2.1	57.4	33.5
Female	E Europe	Hungary	ABRAHA	prosp	1984	all	q	A	0.71	0.31	7.5	7.2	40.3	18.3
		Poland	STASZE	CC	1956	all	q	A	1.00	0.08	0.2	0.4	7.0	0.9
Female	Japan		SOBUE	CC	1987	all	q	C	0.72	0.21	4.1	14.5	38.5	35.1
			WAKAI	CC	1990	all	q	A	0.84	0.18	2.9	3.1	71.5	12.8
Female	China	HongKong	KOO	CC	1982	all	q+s	A	0.66	0.32	41.7	26.3	173.1	31.5
		HongKong	LAMWK2	CC	1978	all	q	A	0.70	0.26	27.6	13.7	179.4	21.1
		HongKong	CHAN	CC	1977	all	q+s	A	0.70	0.26	24.2	16.2	155.7	22.5
		China	ZHOU	CC	1986	all	q	A	0.45	0.18	23.6	37.9	90.1	7.0
		HongKong	LAMTH	CC	1985	ch	q	A	0.69	0.22	20.7	23.2	168.0	16.8
		China	WUWILL	CC	1986	all	q	C	0.71	0.37	15.5	59.3	65.0	134.9
		China	GAO	CC	1985	all	q	C	0.55	0.18	12.8	54.4	74.4	48.3
		HongKong	LAMWK	CC	1983	ch	q	A	0.75	0.22	11.0	6.8	115.5	14.5
		China	XU3	CC	1981	all	KI	A	0.88	0.31	9.9	2.1	168.1	9.9
Female	Other	Singapore	SEOW	CC	1998	ch	q	C	0.68	0.11	9.9	8.5	172.7	8.1
		SKorea	CHOI	CC	1987	all	q	C	0.52	0.14	4.3	10.1	29.6	8.2

Footnotes: See next page

TABLE 4 (continued/3) : Indirect estimates from individual studies of squamous cell carcinoma rates (per 100,000) per year in lifelong nonsmokers and in ever smokers

[a] Study reference as used in IESLC database[3]
[b] CC = case control prosp = prospective
[c] wh = white, ch = Chinese
[d] q = squamous cell carcinoma, KI = Kreyberg type I, not a = not adenocarcinoma, q+s = squamous cell + small cell carcinoma
q+u = squamous cell + undifferentiated carcinoma
[e] A = any product, C = cigarettes. The comparison is between "ever smoked the product" and "never smoked the product" except, where indicated by an X, never smokers include long-term ex-smokers. Where only one product is shown, the "ever" and "never" definitions refer to the same product.
[f] p_{1s} = ever smoking prevalence among squamous cell carcinoma cases
[g] p_{2s} = ever smoking prevalence among controls (or at risk population) used for squamous cell carcinoma analysis

TABLE 5 : Indirectly estimated squamous cell carcinoma rates (per 100,000 per year) in never smokers and ever smokers by sex, region, year of study and definition of squamous cell carcinoma based on random-effects models

					Never smokers		Ever smokers	
Sex	Region	Year of study	Lung cancer type[1]	DF	Rate (95%CI)	Heterogeneity chisquared	Rate (95%CI)	Heterogeneity chisquared
All	All	All	Any S	70	10.4 (8.3-12.9)	671.4	117.4 (102.3-134.7)	5215.7
Male	All	All	Any S	38	15.8 (12.3-20.2)	158.5	182.2 (160.8-206.5)	2117.3
Female	All	All	Any S	31	7.2 (5.4-9.6)	307.8	64.4 (52.6-78.9)	560.3
Male	All	All	Squamous	31	16.6 (12.6-21.8)	134.0	181.4 (160.8-204.6)	1074.0
Female	All	All	Squamous	21	6.4 (4.5-9.0)	212.7	68.3 (55.8-83.6)	278.8
All	Canada	All	Any S	3	5.4 (2.9-9.7)	4.5	162.8 (102.0-259.8)	188.9
All	USA	All	Any S	21	9.9 (6.7-14.6)	337.8	127.8 (100.1-163.0)	3207.1
All	SC America[2]	All	Any S	2	14.2 (6.8-29.7)	1.9	144.6 (83.4-250.5)	43.7
All	UK	All	Any S	1	9.9 (2.2-44.9)	3.7	107.6 (9.8-1179.5)	333.6
All	Scandinavia[3]	All	Any S	6	4.4 (1.9-10.2)	25.1	43.8 (21.2-90.6)	165.0
All	W Europe[4]	All	Any S	3	10.8 (7.3-16.0)	1.6	120.8 (81.5-179.1)	64.9
All	E Europe[5]	All	Any S	5	5.7 (2.2-14.4)	12.2	88.0 (43.7-177.2)	302.5
All	Japan	All	Any S	4	5.0 (2.8-8.7)	5.6	94.5 (69.1-129.3)	71.7
All	China[6]	All	Any S	13	23.7 (16.8-33.4)	98.5	156.5 (117.6-208.4)	212.4
All	Other[7]	All	Any S	3	12.2 (5.1-29.3)	16.9	96.9 (60.7-154.6)	27.0
All	All	1930 to 1960	Any S	6	3.9 (1.7-8.8)	20.5	37.0 (20.1-68.0)	196.3
All	All	1961 to 1970	Any S	8	14.3 (7.2-28.2)	62.2	114.3 (73.4-177.8)	885.2
All	All	1971 to 1980	Any S	10	12.9 (7.7-21.8)	42.3	140.6 (89.0-222.0)	497.2
All	All	1981 to 1990	Any S	39	10.1 (7.6-13.6)	520.9	125.3 (105.5-148.9)	3042.2
All	All	1991 to 1998	Any S	3	11.6 (7.3-18.4)	1.3	165.6 (111.5-246.1)	43.3

[1] "Any S" includes some results for squamous + small cell; Kreyberg I; and not adenocarcinoma, as well as for squamous specifically
[2] Including Argentina, Uruguay
[3] Including Denmark, Norway
[4] Including Germany, Italy, Greece

TABLE 6 : Indirect estimates from individual studies of adenocarcinoma rates (per 100,000) per year in lifelong nonsmokers and in ever smokers

Sex	Region	Country	Study[a]	Study type[b]	Year	Race[c]	Lung cancer type[d]	Product[e]	p1[f]	p2[g]	Never smoker		Ever smoker	
											Rate	Weight	Rate	Weight
Male	Canada		BAND	CC	1987	all	a	Conly/A	0.94	0.79	40.7	42.8	166.9	626.5
			JAIN	CC	1983	all	a	C	0.96	0.77	19.7	3.9	136.0	98.1
			SIEMIA	CC	1982	all	a	C	0.97	0.80	15.5	4.8	123.3	162.4
Male	USA		WYNDE6	CC	1983	all	KII	A	0.95	0.76	39.8	54.9	228.8	1297.1
			WYNDE3	CC	1968	all	KII	A	0.92	0.79	35.2	5.8	105.5	83.7
			COMSTO	other	1987	all	a	A	0.96	0.73	26.7	2.0	210.3	58.7
			BUFFLE	CC	1978	wh	a	A	0.95	0.80	25.8	5.3	116.0	115.2
			KHUDER	CC	1986	all	a	C	0.95	0.72	24.1	6.8	195.5	165.0
			BROWN2	CC	1987	wh	a	C	0.93	0.60	20.4	153.9	167.6	1700.3
			WYNDE2	CC	1963	all	KII	A	0.91	0.85	18.2	4.8	30.4	47.2
			DORGAN	CC	1982	wh	a	A	0.96	0.83	17.7	4.8	85.1	126.1
			STAYNE	CC	1970	all	a	A	0.86	0.63	16.2	7.0	58.6	46.2
			OSANN	CC	1985	all	a	C	0.96	0.55	12.6	14.0	234.6	360.2
			BYERS1	CC	1961	wh	a	C	0.87	0.62	8.6	7.0	35.1	50.3
			HAMMON	prosp	1953	wh	a	A	0.94	0.81	3.9	2.0	12.9	31.8
Male	SCAmerica	Uruguay	DESTE2	CC	1995	all	a	A	0.98	0.91	26.2	4.0	112.5	78.9
		Argentina	MATOS	CC	1995	all	a	C/A	0.94	0.72	24.5	5.0	150.2	113.3
		Cuba	JOLY	CC	1979	all	a	A	0.94	0.80	14.9	4.9	56.3	70.5
		Argentina	PEZZOT	CC	1989	all	a	Conly/C	0.95	0.73	13.7	3.0	100.0	71.6
Male	UK		ALDERS	CC	1980	all	a	A	0.96	0.78	14.2	1.8	101.2	43.1

TABLE 6 (continued) : Indirect estimates from individual studies of adenocarcinoma rates (per 100,000) per year in lifelong nonsmokers and in ever smokers

Sex	Region	Country	Study[a]	Study type[b]	Year	Race[c]	Lung cancer type[d]	Product[e]	p1[f]	p2[g]	Never smoker		Ever smoker	
											Rate	Weight	Rate	Weight
Male	Scandinavia	Sweden	DAMBER	CC	1975	all	a+al+br	A	0.80	0.63	17.6	11.7	42.2	41.6
		Norway	ENGELA	prosp	1970	all	a	A	0.87	0.74	14.1	4.4	32.9	16.8
		Sweden	NOU	CC	1974	all	a	A	0.90	0.67	12.3	3.5	54.7	16.4
		Norway	KREYBE	CC	1951	all	KII	A	0.93	0.85	1.7	2.3	4.3	7.6
Male	W Europe	Germany	JAHN	CC	1991	all	a	A	0.96	0.84	23.3	7.7	117.0	237.2
		Italy	BARBON	CC	1983	all	a	A	0.96	0.75	16.1	6.9	114.9	167.4
Male	E Europe	Hungary	ABRAHA	prosp	1984	all	a	A	0.88	0.75	45.3	8.1	108.7	65.7
		Poland	JEDRYC	CC	1984	all	a	C/A	0.93	0.78	22.0	6.7	85.6	72.2
		Hungary	ORMOS	CC	1953	all	a	C/A	1.00	0.57	1.3	0.5	8.8	3.7
		Poland	STASZE	CC	1956	all	a	A	1.00	0.83	1.0	0.5	8.9	18.8
Male	Japan	Japan	WAKAI	CC	1990	all	a	A	0.92	0.87	73.8	7.4	138.7	150.4
		Japan	SOBUE	CC	1987	all	a	C	0.94	0.89	64.7	23.1	119.1	512.0
		Japan	MATSUD	CC	1965	all	a	C	1.00	0.73	1.3	0.5	22.4	26.2
Male	China	HongKong	LAMWK2	CC	1978	all	a	A	0.78	0.79	130.7	11.2	121.6	40.6
		China	GAO	CC	1985	all	a	C	0.81	0.73	69.7	38.0	108.0	203.5
		China	ZHOU	CC	1986	all	a	A	0.60	0.53	65.8	39.4	86.2	54.8
		China	XU3	CC	1981	all	KII	A	0.91	0.69	30.6	2.9	135.0	35.5
		HongKong	CHAN	CC	1977	all	a+l	A	1.00	0.79	4.5	0.5	136.1	40.8
Male	Other	Australia	JONES	CC	1964	all	a	A(2)	0.87	0.79	27.5	3.4	48.5	27.6
		SKorea	CHOI	CC	1987	all	a	C	0.87	0.83	20.1	6.6	26.9	45.2

TABLE 6 (continued/2) : Indirect estimates from individual studies of adenocarcinoma rates (per 100,000) per year in lifelong nonsmokers and in ever smokers

Sex	Region	Country	Study[a]	Study type[b]	Year	Race[c]	Lung cancer type[d]	Product[e]	p1[f]	p2[g]	Never smoker		Ever smoker	
											Rate	Weight	Rate	Weight
Female	Canada		JAIN	CC	1983	all	a	C	0.78	0.48	10.6	22.6	41.4	68.4
Female	USA		ANDERS	prosp	1990	all	a	Conly/A	0.75	0.33	31.4	36.8	191.4	143.6
			COMSTO	other	1987	all	a	A	0.78	0.43	25.7	8.5	123.2	33.3
			LOMBA2	CC	1964	all	not q+u	C	0.44	0.60	20.2	57.9	10.7	47.2
			BROWN2	CC	1987	wh	a	C	0.74	0.30	18.9	413.3	130.7	748.8
			WYNDE3	CC	1968	all	KII	A	0.58	0.42	16.6	17.3	31.5	23.0
			DORGAN	CC	1982	all	a	A	0.83	0.55	13.2	48.4	51.4	217.4
			WYNDE6	CC	1983	wh	a	C	0.85	0.29	13.0	62.4	178.6	250.4
			OSANN	CC	1985	all	a	C	0.84	0.34	12.9	48.7	129.3	235.9
			OSANN2	NCC	1973	all	KII	C	0.73	0.48	11.1	19.0	32.9	39.6
			BUFFLE	CC	1978	wh	a	A	0.85	0.59	9.8	20.0	39.6	130.4
			HAENSZ	CC	1956	all	a	A	0.33	0.30	9.0	42.4	10.0	17.4
Female	SCAmerica	Cuba	JOLY	CC	1979	all	a	C/A	0.57	0.31	18.0	21.7	52.9	24.6
Female	UK		ALDERS	CC	1980	all	a	MConly/A	0.80	0.52	8.2	8.6	29.5	24.4
Female	Scandinavia	Sweden	NOU	CC	1974	all	a	A	0.24	0.26	29.8	15.6	26.3	6.8
		Norway	KREYBE	CC	1951	all	KII	A	0.27	0.33	21.7	9.6	16.0	5.9
		Sweden	SVENSS	CC	1985	all	a	A	0.69	0.43	8.8	18.5	26.9	31.8
Female	W Europe	Greece	KATSOU	CC	1988	all	a	A	0.38	0.25	24.3	28.2	44.5	11.3
		Germany	BECHER	CC	1986	all	not q+s	A	0.94	0.60	2.9	1.0	31.7	17.4
Female	E Europe	Hungary	ABRAHA	prosp	1984	all	a	A	0.54	0.31	17.2	17.2	45.1	20.7
		Poland	STASZE	CC	1956	all	a	A	0.09	0.08	8.6	13.9	9.3	1.0

TABLE 6 (Continued/3) Indirect estimates from individual studies of adenocarcinoma rates (per 100,000) per year in lifelong nonsmokers and in ever smokers

Sex	Region	Country	Study[a]	Study type[b]	Year	Race[c]	Lung cancer type[d]	Product[e]	p1[f]	p2[g]	Never smoker		Ever smoker	
											Rate	Weight	Rate	Weight
Female	Japan		WAKAI	CC	1990	all	a	A	0.22	0.18	44.0	81.8	58.0	10.8
			SOBUE	CC	1987	all	a	C	0.30	0.21	39.7	204.0	61.9	55.6
Female	China	HongKong	LAMTH	CC	1985	ch	a	A	0.38	0.24	100.4	73.4	187.8	31.3
		HongKong	LAMWK	CC	1983	ch	a	A	0.38	0.22	94.0	49.2	198.3	20.5
		HongKong	LAMWK2	CC	1978	all	a	A	0.39	0.26	75.5	32.8	132.9	17.4
		China	GAO	CC	1985	all	a	C	0.19	0.18	64.3	305.7	69.5	46.1
		HongKong	KOO	CC	1982	all	a+l	A	0.43	0.32	60.0	35.0	96.5	22.3
		China	ZHOU	CC	1986	all	a	A	0.24	0.18	54.0	77.0	77.3	6.8
		HongKong	CHAN	CC	1977	all	a+l	A	0.41	0.26	50.9	29.4	99.3	17.4
		China	WUWILL	CC	1986	all	a	C	0.45	0.37	45.7	184.2	62.6	124.3
		China	XU3	CC	1981	all	KII	A	0.36	0.31	34.5	7.9	44.9	3.5
Female	Other	Singapore	SEOW	CC	1998	ch	a	C	0.22	0.11	66.1	30.8	156.0	7.8
		SKorea	CHOI	CC	1987	all	a	C	0.09	0.14	20.9	50.9	13.4	4.3

[a] Study reference as used in IESLC database[3]

[b] CC = case control prosp = prospective

[c] wh = white, ch = Chinese

[d] q = squamous cell carcinoma, KI = Kreyberg type I, not a = not adenocarcinoma, q+s = squamous cell + small cell carcinoma
q+u = squamous cell + undifferentiated carcinoma

[e] A = any product, C = cigarettes. The comparison is between "ever smoked the product" and "never smoked the product" except, where indicated by an X, never smokers include long-term ex-smokers. Where only one product is shown, the "ever" and "never" definitions refer to the same product.

[f] p_{1s} = ever smoking prevalence among squamous cell carcinoma cases

[g] p_{2s} = ever smoking prevalence among controls (or at risk population) used for squamous cell carcinoma analysis

TABLE 7 : Indirectly estimated adenocarcinoma rates (per 100,000 per year) in never smokers and ever smokers by sex, region, year of study and definition of adenocarcinoma based on random-effects models

					Never smoker		Ever smoker	
Sex	Region	Year of study	Lung cancer type[1]	DF	Rate (95%CI)	Heterogeneity chisquared	Rate (95%CI)	Heterogeneity chisquared
All	All	All	Any A	73	23.6 (19.9-28.0)	1159.1	67.3 (58.3-77.7)	3280.8
Male	All	All	Any A	39	22.6 (17.8-28.8)	221.3	78.0 (66.0-92.2)	1741.1
Female	All	All	Any A	33	24.6 (19.3-31.4)	935.7	55.9 (43.3-72.2)	1131.0
Male	All	All	Adeno	32	23.4 (17.8-30.7)	191.5	81.2 (68.4-96.3)	1149.9
Female	All	All	Adeno	25	24.9 (18.8-32.9)	867.5	64.8 (50.0-84.1)	799.4
All	Canada	All	Any A	3	19.4 (8.4-44.4)	28.1	104.7 (64.3-170.5)	123.4
All	USA	All	Any A	22	16.9 (14.2-20.1)	115.0	73.7 (56.8-95.5)	1973.7
All	SC America[2]	All	Any A	4	18.6 (13.6-25.5)	1.4	88.5 (60.1-130.5)	53.2
All	UK	All	Any A	1	9.0 (4.9-16.6)	0.4	55.0 (16.4-184.3)	23.7
All	Scandinavia[3]	All	Any A	6	13.2 (7.8-22.6)	25.4	24.5 (14.9-40.4)	42.7
All	W Europe[4]	All	Any A	3	19.5 (12.3-31.1)	5.0	72.8 (48.3-109.8)	37.2
All	E Europe[5]	All	Any A	5	14.3 (7.0-29.1)	21.6	30.2 (13.2-68.9)	118.9
All	Japan	All	Any A	4	47.1 (35.2-63.1)	13.6	69.2 (43.3-110.7)	100.5
All	China[6]	All	Any A	13	64.8 (54.6-76.9)	61.5	106.5 (87.4-129.8)	70.5
All	Other[7]	All	Any A	3	30.4 (14.6-63.2)	26.8	41.6 (19.9-87.1)	27.1
All	All	1930 to 1960	Any A	6	6.9 (3.8-12.4)	19.4	9.8 (7.3-13.1)	9.3
All	All	1961 to 1970	Any A	8	17.5 (13.2-23.2)	11.8	35.2 (21.4-57.9)	183.3
All	All	1971 to 1980	Any A	13	21.9 (13.3-36.0)	134.1	64.6 (47.7-87.5)	179.1
All	All	1981 to 1990	Any A	39	29.0 (23.4-35.8)	822.8	97.9 (84.7-113.1)	1442.0
All	All	1991 to 1998	Any A	3	33.9 (17.6-65.3)	10.8	126.6 (108.4-147.9)	6.1

[1] "Any A" includes some results for adenocarcinoma and large cell; adenocarcinoma, alveolar and bronchiolar; not squamous or undifferentiated; not squamous or small; and Kreyberg II, as well as for adenocarcinoma specifically

[2] Including Argentina, Cuba, Uruguay

[3] Including Norway, Sweden

[4] Including Germany, Italy, Greece

[5] Including Hungary, Poland

[6] Including China, Hong Kong

[7] Including South Korea, Singapore, Australia

TABLE 8 : Indirectly estimated adenocarcinoma rates (per 100,000 per year) in never smokers and ever smokers – further random-effects meta-analyses

				Never smoker		Ever smoker	
Region	Sex	Year of study	DF	Rate (95%CI)	Heterogeneity chisquared	Rate (95%CI)	Heterogeneity chisquared
All	All	All	73	23.6 (19.9-28.0)	1159.1	67.3 (58.3-77.7)	3280.8
All	Male	All	39	22.6 (17.8-28.8)	221.3	78.0 (66.0-92.2)	1741.1
All	Female	All	33	24.6 (19.3-31.4)	935.7	55.9 (43.3-72.2)	1131.0
Asia	All	All	21	54.7 (45.8-65.4)	165.4	85.6 (69.4-105.6)	273.9
Asia	Male	All	8	54.2 (36.7-80.0)	27.9	85.4 (62.7-116.3)	173.8
	Female	All	12	54.0 (43.9-66.3)	133.3	85.7 (64.1-114.7)	77.4
Asia	All	1930 to 1960	No data				
	All	1961 to 1970	0	1.3 (0.1-20.1)	0.0	22.4 (15.3-32.8)	0.0
	All	1971 to 1980	3	69.7 (41.0-118.6)	11.3	124.3 (103.7-149.1)	1.3
	All	1981 to 1990	15	52.6 (43.2-64.0)	141.2	83.3 (66.0-105.2)	206.8
	All	1991 to 1998	0	66.1 (46.4-94.1)	0.0	156.0 (77.2-315.3)	0.0
Not Asia	All	All	51	16.8 (14.6-19.2)	213.4	61.1 (51.2-72.9)	102.1
Not Asia	Male	All	30	18.9 (15.2-23.4)	88.9	75.8 (62.5-92.0)	1455.7
	Female	All	20	14.9 (12.6-17.7)	95.5	43.9 (31.1-62.0)	1048.8
Not Asia	All	1930 to 1960	6	6.9 (3.8-12.4)	19.4	9.8 (7.3-13.1)	9.3
	All	1961 to 1970	7	18.2 (14.5-23.0)	8.2	37.2 (21.7-63.7)	173.9
	All	1971 to 1980	9	15.0 (11.3-19.9)	18.5	50.4 (36.0-70.5)	120.2
	All	1981 to 1990	23	19.1 (15.9-22.8)	122.4	108.1 (91.0-128.3)	1022.0
	All	1991 to 1998	2	24.3 (15.0-39.3)	0.0	125.5 (105.8-148.8)	5.7

References

1. Lee PN, Forey BA. *How do lung cancer rates in never smokers vary by country?* Unpublished. 2003.

2. Lee PN. *Lung cancer rates in never smokers by histological type*2006.

3. Lee PN, Forey BA, Young KJ. *International evidence on smoking and lung cancer (project IESLC). A first report. Part I: The databases, methods used to collect and analyse the data and scope of the information obtained.* Internal. 2003.

4. Lee PN, Forey BA, Young KJ. *International evidence on smoking and lung cancer (project IESLC). A first report. Part II: Results of selected meta-analyses.* Internal. 2003.

5. Fleiss JL, Gross AJ. Meta-analysis in epidemiology, with special reference to studies of the association between exposure to environmental tobacco smoke and lung cancer: a critique. *J Clin Epidemiol* 1991;**44**:127-39.

6. Koo LC, Ho JH-C, Lee N. An analysis of some risk factors for lung cancer in Hong Kong. *Int J Cancer* 1985;**35**:149-55.

7. Koo LC. Environmental tobacco smoke and lung cancer: is it the smoke or the diet? In: Bieva CJ, Courtois Y, Govaerts M, editors. *Present and future of indoor air quality, Proceedings of the Brussels Conference, 14-16 February 1989*. Amsterdam: Elsevier Science Publishers BV (Biomedical Division), 1989;65-75. International Congress Series 860.

8. Ezzati M, Lopez AD. Estimates of global mortality attributable to smoking in 2000. *Lancet* 2003;**362**:847-52.

9. Peto R, Lopez AD, Boreham J, Thun M, Heath C, Jr. *Mortality from smoking in developed countries 1950-2000. Indirect estimates from national vital statistics*. Oxford, New York, Tokyo: Oxford University Press; 1994.