IESLCN

13G

LEE2006A

Lung cancer rates in never smokers

by histological type

Author : P N Lee

Date : 26 January 2006

(T:/Pauline/Reports/LChisto.doc)

EXECUTIVE SUMMARY

A previous report, in 2003, investigated how lung cancer mortality in lifelong never smokers varies by region and other factors. Using a similar approach this report extends the investigation to specific types of lung cancer, with most attention given to squamous cell carcinoma and adenocarcinoma.

Only one direct comparison of nonsmoker lung cancer rates by histological type over time is available, based on CPS-I and CPS-II. While it demonstrated that rates were higher for adenocarcinoma than for squamous cell or small cell carcinoma, it showed no significant rise for any type, though numbers of deaths were too small for reliable inferences.

No prospective studies could be identified which provided data on variation by age and sex in never smoker lung cancer rates by histological type.

Eight prospective studies provided estimates on never smoker lung cancer risk by type that are sex- but not age-specific. All but 5 of the 28 sex-specific rates (for squamous cell, small cell or adenocarcinoma) are based on less than 20 cases and are open to substantial sampling error, and the populations studied are generally unrepresentative of national populations. For adenocarcinoma, where rates were always higher than for the other two types, the data seem consistent with risk rising with age, but did not reveal any clear differences between the countries or sexes. For squamous cell and small cell carcinoma, no clear patterns by sex, age or country were evident. However the age range for the available data was quite limited and all but 9 of the 28 rates came from one country, the US.

In the previous report an indirect estimation had been used to obtain further data. This approach was extended to deal with rates by histological type and involved a formula which combined estimates from epidemiological studies of

(a) the ever smoker/never smoker relative risk by histological type;

(b) the proportion of ever smokers among controls; and

(c) the proportion of cases of the type of interest among all cases, with national estimates of overall lung cancer risk based on mortality data for the same region and period. As before, the mortality data selected were for age 70-74.

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, 71 indirect estimates of squamous cell carcinoma risk in 70-74 year old never smokers were obtained. 74 estimates were obtained for adenocarcinoma. The estimates for both lung cancer types showed considerable heterogeneity.

For squamous cell carcinoma, the overall (random-effects) estimates of the rates (per 100,000 per year) were higher in males (15.6, 95% CI 12.1-20.0) than in females (6.9, 5.2-9.3). No variation over time was detected. The two countries with most data were China with a rate of 23.6 (17.0-32.8, n = 14) and USA with a rate of 9.9 (6.7-14.6, n = 22). The China-USA difference was evident in both sexes, particularly females (20.1 vs 5.0). Rates in China were higher than in all other regions studied, including Japan, though data were limited for some regions.

For adenocarcinoma, the rates were higher than for squamous cell carcinoma, but similar in males (22.2, 17.4-28.4) and females (24.6, 19.3-31.3). There is a large variation by location, with rates high in China, Japan and other Asian countries. For Asia, rates were 54.1 (36.7-79.7) in males and 53.7 (41.9-68.9) in females. Outside Asia, rates were 18.4 (14.8-23.0) in males and 15.0 (12.5-18.0) in females. Within either broad region, there was far less variation. In Asia, there was no clear evidence of a time trend, though interpretation was limited by 16 of the 22 Asian estimates being for 1981 to 1990, with very little data before 1970. Outside Asia, where studies covered a wider time range, there was evidence ($p<0.01$) of an increasing trend, with estimates of 7.1, 18.1, 15.2, 19.0 and 24.3 for, respectively, 1930-60, 1961-70, 1971-80, 1981-90 and 1991-98.

INDEX

Tables

1. Introduction

A previous report[1], "How do lung cancer rates in never smokers vary by country?", was divided into four sections:

(i) direct evidence on changes in lung cancer risk in never smokers by time period, based on six epidemiological studies;

(ii) direct evidence on variation in never smoker lung cancer rates by age and sex, based on eight epidemiological studies;

(iii) direct estimates of sex-specific, but not age-specific, rates of lung cancer in never smokers, based on 41 epidemiological prospective studies;

(iv) indirect estimation of lung cancer risk in never smokers. Ever smoker/never smoker relative risk estimates from epidemiological studies were combined with national estimates of overall lung cancer risk, based on mortality data for the same region and period, to give 216 indirect estimates of lung cancer risk in 70-74 year old never smokers.

The data considered in that report were for overall lung cancer rate, regardless of histological type. The present report investigates what useful additional information could be obtained on lung cancer risk in never smokers by sex, age and region.

2. <u>Evidence on changes in risk of specific histological types of lung cancer in never smokers by time period</u>

In the previous report[1] evidence from six epidemiological studies was summarized which suggested that lung cancer rates in never smokers have not increased materially in recent years, though the overall data are not completely conclusive.

As far as I am aware, the only such evidence by histological type of lung cancer comes from a comparison of CPS I and CPS II[2].

		Squamous cell carcinoma	Adeno-carcinoma	Small cell carcinoma
<u>CPS I (1959-61)</u>				
Males	Rate*	0.6	3.1	0.0
(180081 PY†)	Deaths	1	5	0
Females	Rate	0.8	1.9	0.6
(739145 PY)	Deaths	5	13	4
<u>CPS II (1982-84)</u>				
Males	Rate	1.5	2.3	0.4
(252731 PY)	Deaths	4	6	1
Females	Rate	0.3	2.2	0.6
(708413 PY)	Deaths	2	16	4

* Rate in never smokers per 100,000 per year, age-adjusted to the age distribution of the combined studies. Where numbers of deaths are less than five, the rates were not given in the source paper and have been estimated.
† Person-years of follow-up.

In considering these data it should be noted that microscopic or cytologic reports were only available for 70.0% of lung cancer deaths in CPS I and for 61.5% in CPS II. Assuming the distribution of histological type was approximately the same in those with and without a report, it seems that the rates in the table above, based on those actually cited by Thun *et al*[2], might be scaled upwards by 1/0.7 (CPS I) or 1/0.615 (CPS II) to allow a better picture of the true rate.

While it is clear that, in never smokers, rates of adenocarcinoma substantially exceed rates for squamous cell and small cell carcinoma, there is no statistically significant evidence of difference between the sexes or any trend over time for any of the three cell types for which data were available. This would be true whether rates were scaled up to allow for incomplete histological reporting or were as given in the source paper and reproduced here. Though the numbers of deaths are rather small to make any reliable inferences, it is interesting to note that there is no indication of a rise in adenocarcinoma risk in either sex between CPS I and CPS II.

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

In the previous report[1] evidence from eight prospective studies was summarized which provided direct data on variation in never smoker lung cancer rates by age and sex. I could identify no studies which provided corresponding data by histological type.

4. Sex- but not age-specific data in risk of specific histological types of lung cancer in never smokers

Another approach to the problem is to study risk estimates from prospective studies that are sex-specific, but not age-specific, and attempt to relate them approximately to the average age of the population studied. In the previous report[1] estimates were presented from 41 studies, some of which provided data for one sex only, and some for both sexes. Table 1 presents corresponding data by histological type, based on seven studies, five conducted in the USA and two in Scandinavia. The rates, R, are calculated by the formula

$$R = 100000N / (PH)$$

where N is the number of deaths, P the person-years at risk, and H the proportion of cases for which histology is known. The rates for CPS I and CPS II are thus somewhat different from those given in section 2.

Given the rates vary as regards average age of the population studied, and period of the study, with possible effects on classification of tumour type, and given many of the rates are based on very small numbers of deaths, it is difficult to draw any very reliable conclusions, other than that adenocarcinoma is the most common histological type in never smokers.

For adenocarcinoma, one can present the results in order of age as follows:

Mean age in follow-up	Rate	Cases	Sex	Country	Study
52	3.33	40	M	Sweden	Construction workers
55	3.86	6	M	USA	CPS II
56	3.67	16	F	USA	CPS II
56	3.97	5	M	USA	CPS I
56	2.51	13	F	USA	CPS I
61	8.63	27	M	USA	War veterans
61	4.32	2	M	USA	Nine states
66	18.89	33	F	USA	Iowa
66	14.72	7	M	Norway	Random sample/siblings

These data seem consistent with risk rising with age, but do not show up any clear differences between the countries or the sexes.

For squamous and small cell carcinoma, the data correspondingly laid out are as follows:

	Rates		Cases				
Mean age	Squamous	Small cell	Squamous	Small cell	Sex	Country	Study
52	1.58	2.42	19	29	M	Sweden	Construction workers
55	2.57	0.64	4	1	M	USA	CPS II
56	0.46	0.92	2	4	F	USA	CPS II
56	0.79	0.00	1	0	M	USA	CPS I
56	0.97	0.77	5	4	F	USA	CPS I
61	3.52	0.00	11	0	M	USA	War veterans
66	2.86	2.29	5	4	F	USA	Iowa
66	6.31	6.31	3	3	M	Norway	Random/siblings

Here one also cannot make any clear statement about differences between the countries or the sexes, though it is noticeable that in each of the eight studies with data for adenocarcinoma and squamous cell carcinoma, rates are higher for adenocarcinoma. The adeno/squamous ratios, 2.11, 1.50, 7.98, 5.03, 2.59, 2.45, 6.61, 2.33 for the 8 studies in order as above, have a geometric mean of 3.25. Rates for small cell carcinoma in never smokers are not markedly different from those for squamous cell carcinoma.

Recently, a large prospective study in Korea[3] reported results at 6 year follow-up of a population of 437,976 men aged 40+ as baseline (56.6% 40-49, 26.7% 50-59, 6.7% 60+). Unusually, they not only presented relative risks of different lung cancer types by smoking, but also presented absolute rates. The age-adjusted incidence rates per 100,000 person years for never smokers were as follows:

Lung cancer type	Rate (95% CI)	Cases
Squamous cell carcinoma	1.9 (1.1-3.1)	16
Adenocarcinoma	11.1 (8.3-14.8)	69
Small cell carcinoma	0.5 (02-1.4)	4

Again, rates in never smokers are substantially higher for adenocarcinoma than for squamous cell carcinoma.

5. An alternative indirect approach

5.1 Theory

As described in the previous report[1], one can 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 from the same region and period. Thus if we define:

p_1 the proportion of ever smokers among cases,

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

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

L the overall lung cancer rate

we can estimate L_N, the lung cancer rate among never smokers, based on the formulae

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

where L_S is the lung cancer rate among ever smokers, to give

$$L_N = L / (1-p_2+p_2R) \qquad \text{or alternatively}$$
$$L_N = L(1-p_1) / (1-p_2)$$

The previous report[1] also presents formulae for the variance of log N, the inverse of which can be used as a weighting factor in meta-analyses.

If we define, for a particular histological type of lung cancer, h,

P_{1h} the proportion of ever smokers among cases of the given type,

R_h the relative risk of the given type of lung cancer for ever/never smoking, and

L_h the overall rate of the given type of lung cancer

then

L_{Nh} the rate of the given type of lung cancer among never smokers

can be obtained using formulae corresponding to those for L_N

$$L_{Nh} = L_h / (1-p_2+p_2R_h) \qquad \text{or alternatively}$$
$$L_{Nh} = L_h(1-p_{1h}) / (1-p_2)$$

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 (which provided the data on relative risk and proportions of smokers in cases and controls), 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. The reasons for this are discussed in the earlier report[1].

For specific histological types, rates are not available from WHO but one can estimate L_h by multiplying L by a study-specific estimate of p_h, the proportion of all lung cancers that are of the given type. This estimate must take into account the fact 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 should be based on the number of cases of the histological type of interest divided by the number for which information on histological type was available.

5.2 Data extraction

In Appendix tables F1 (squamous cell carcinoma) and J1 (adenocarcinoma) of our main IESLC report[4], sex-specific data on relative risks for ever/never smoking were presented for more than 70 studies. Studies were selected satisfying various criteria:

(i) relative risk and corresponding 2x2 table (cases/controls x ever/never smoked) 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) information available on the proportion of lung cancer cases which were of the types considered (squamous cell carcinoma, adenocarcinoma)

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

(v) age range includes subjects of 60+ years (i.e. estimates for very young populations rejected), and

(vi) race 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 our earlier report[1].

Following this weeding out process (which is inevitably somewhat arbitrary and subjective), there were 71 estimates of risk of squamous cell carcinoma and 74 estimates of risk of adenocarcinoma for 70-74 year old never smokers. Of the estimates for squamous cell carcinoma, 39 related to males and 32 to females. Of the estimates for adenocarcinoma, 40 related to males and 34 to females.

5.3 Results – squamous cell carcinoma

Table 2 gives the results of various fixed- and random-effects meta-analyses for squamous cell carcinoma.

The overall weighted mean rate for nonsmokers aged 70-74 is estimated as 13.9 using fixed-effects estimates and 10.2 using random-effects estimates. There is considerable heterogeneity between the 71 estimates with the heterogeneity chisquared, 798.5, far exceeding the value of 70 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 2 gives heterogeneity chisquared values and degrees of freedom for the total data (H_0 and D_0) as well as corresponding values for levels of subdivisions of the data, such as location (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

$$\frac{(H_0 - \Sigma H_i)/(D_0 - \Sigma D_i)}{\Sigma H_i \quad / \quad \Sigma D_i}$$

(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 Table 2.

Table 2 shows that rates are higher for males than for females ($p<0.001$), the excess being similar for both the fixed-effects estimates (23.5 vs 10.2) and the - random-effects estimates (15.6 vs 6.9). Where there are estimates available, this excess rate is present in all the location groups considered in Table 3 (data by sex <u>and</u> location not shown), suggesting this is a real finding.

Of the 71 estimates, 54 are specifically for squamous cell carcinoma, but 17 are for a wider definition (see footnote 1 to Table 2). As can be seen from Table 2, the fixed- and random-effects means 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 2 also gives information on variation over time. The pattern is quite similar using fixed- or random-effects analysis, with the rates lowest in 1930-60 (random-effects mean 3.4), highest in 1961-70 (14.2), then declining somewhat thereafter (12.3, 10.1, 11.2 in, respectively, 1971-80, 1981-90, 1991-98). However, the variation over time is not statistically significant.

Table 2 also shows variation by location, though numbers of estimates are quite low for some of the 10 regions identified. This is statistically significant ($p<0.05$). Based on the random-effects results, rates are highest in China at 23.6, intermediate, in the range 9.9 to 14.3, in USA, South Central America, UK, West Europe and the "other" grouping and lowest, in the range 4.1 to 5.3, in Canada, Scandinavia, East Europe and Japan.

The two countries with most data are China, with a random-effects rate of 23.6 (95% CI 17.0-32.8) 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 35.6 vs 20.3 and females 20.1 vs 5.0 (not shown in Table 2).

Table 3 shows the individual rates. 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.

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.

5.4 Results - adenocarcinoma

Table 4 corresponds to Table 2, but giving results for adenocarcinoma.

The overall weighted mean rate for nonsmokers aged 70-74 is estimated as 35.4 using fixed-effects estimates and 23.4 using random-effects estimates. Again, there is considerable heterogeneity, with the chisquared of 2428.4 far exceeding the degrees of freedom of 73, were variation no more than due to chance. Again, we use F tests to assess statistical significance of variation over level.

The rates for males and females are quite similar, 29.7 vs 36.2 based on the fixed-effects estimates and 22.2 vs 24.6 based on the random-effects estimates, differences which are quite small and not significant. Within location, where there are adequate numbers of estimates, rates are also similar for males and females (random-effects means 19.3 vs 15.2 for USA and 69.2 vs 62.9 for China, for example).

Of the 74 estimates, 59 are specifically for adenocarcinoma, but 15 are for a wider definition (see footnote to Table 4). As can be seen from Table 2, 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 ($p<0.001$ based on an F test) with high rates in China (random-effects mean 64.6), Japan (46.4) and "Other" (30.3) which includes South Korea and Singapore. In all the other locations, rates are much lower, varying from 8.9 to 19.3.

There is also a significant variation by time ($p<0.01$) with a sharply increasing trend. The random-effects means are 7.1, 17.4, 22.3, 28.9 and 33.8 for, respectively, 1930-60, 1961-70, 1971-80, 1981-90 and 1991-1998. The fixed-effects means similarly show a clear increasing trend by a factor of about 5 over the period.

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 5. 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 random-effects estimates of 53.9 and 16.6.

(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 marginally significant ($p<0.05$) with rates slightly higher in males (18.4 vs 15.0).

(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 random-effects estimates of 7.1, 18.1, 15.2, 19.0 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 4 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).

Table 6 shows the individual rates, as for squamous carcinoma sorted in descending order separately within sex and region. Although the rates are high generally in Asia, it should be noted that 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 and LAMWK2 – both in Hong Kong) exceeding 100.

6. Summary

A previous report, in 2003, investigated how lung cancer mortality in lifelong never smokers varies by region and other factors. Using a similar approach this report extends the investigation to specific types of lung cancer, with most attention given to squamous cell carcinoma and adenocarcinoma.

Only one direct comparison of nonsmoker lung cancer rates by histological type over time is available, based on CPS-I and CPS-II. While it demonstrated that rates were higher for adenocarcinoma than for squamous cell or small cell carcinoma, it showed no significant rise for any type, though numbers of deaths were too small for reliable inferences.

No prospective studies could be identified which provided data on variation by age and sex in never smoker lung cancer rates by histological type.

Eight prospective studies provided estimates on never smoker lung cancer risk by type that are sex- but not age-specific. All but 5 of the 28 sex-specific rates (for squamous cell, small cell or adenocarcinoma) are based on less than 20 cases at most and are open to substantial sampling error, and the populations studied are generally unrepresentative of national populations. For adenocarcinoma, where rates were always higher than for the other two types, the data seem consistent with risk rising with age, but did not reveal any clear differences between the countries or sexes. For squamous cell and small cell carcinoma, no clear patterns by sex, age or country were evident. However the age range for the available data was quite limited and all but 9 of the 28 rates came from one country, the US.

In the previous report an indirect estimation had been used to obtain further data. This approach was extended to deal with rates by histological type and involved a formula which combined estimates from epidemiological studies of

(a) the ever smoker/never smoker relative risk by histological type;

(b) the proportion of ever smokers among controls; and

(c) the proportion of cases of the type of interest among all cases,

with national estimates of overall lung cancer risk based on mortality data for the same region and period. As before, the mortality data selected were for age 70-74.

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, 71 indirect estimates of squamous cell carcinoma risk in 700-74 year old never smokers were obtained. 74 estimates were obtained for adenocarcinoma. The estimates for both lung cancer types showed considerable heterogeneity.

For squamous cell carcinoma, the overall (random-effects) estimates of the rates (per 100,000 per year) were higher in males (15.6, 95% CI 12.1-20.0) than in females (6.9, 5.2-9.3). No variation over time was detected. The two countries with most data were China with a rate of 23.6 (17.0-32.8, n = 14) and USA with a rate of 9.9 (6.7-14.6, n = 22). The China-USA difference was evident in both sexes, particularly females (20.1 vs 5.0). Rates in China were higher than in all other regions studied, including Japan, though data were limited for some regions.

For adenocarcinoma, the rates were higher than for squamous cell carcinoma, but similar in males (22.2, 17.4-28.4) than in females (24.6, 19.3-31.3). There is a large variation by location, with rates high in China, Japan and other Asian countries. For Asia, rates were 54.1 (36.7-79.7) in males and 53.7 (41.9-68.9) in females. Outside Asia, rates were 18.4 (14.8-23.0) in males and 15.0 (12.5-18.0) in females. Within either broad region, there was far less variation. In Asia, there was no clear evidence of a time trend, though interpretation was limited by 16 of the 22 Asian estimates being for 1981 to 1990, with very little data before 1970. Outside Asia, where studies covered a wider age range, there was evidence ($p<0.01$) of an increasing trend, with estimates of 7.1, 18.1, 15.2, 19.0 and 24.3 for, respectively, 1930-60, 1961-70, 1971-80, 1981-90 and 1991-98.

7. References

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

2. Thun MJ, Lally CA, Flannery JT, Calle EE, Flanders WD, Heath CW, Jr. Cigarette smoking and changes in the histopathology of lung cancer. *J Natl Cancer Inst* 1997;**89**:1580-6.

3. Yun YH, Lim MK, Jung KW, Bae J-M, Park SM, Shin SA, *et al.* Relative and absolute risks of cigarette smoking on major histologic types of lung cancer in Korean men. *Cancer Epidemiol Biomarkers Prev* 2005;**14**:2125-30.

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. Engeland A, Haldorsen T, Andersen A, Tretli S. The impact of smoking habits on lung cancer risk: 28 years' observation of 26,000 Norwegian men and women. *Cancer Causes Control* 1996;**7**:366-76.

6. Boffetta P, Järvholm B, Brennan P, Nyrén O. Incidence of lung cancer in a large cohort of non-smoking men from Sweden. *Int J Cancer* 2001;**94**:591-3.

7. Anderson KE, Woo C, Olson JE, Sellers TA, Zheng W, Kushi LH, *et al.* Association of family history of cervical, ovarian, and uterine cancer with histological categories of lung cancer: the Iowa Women's Health Study. *Cancer Epidemiol Biomarkers Prev* 1997;**6**:401-5.

8. Herrold KM. Survey of histologic types of primary lung cancer in US veterans. *Pathol Annu* 1972;**7**:45-79.

9. Hammond EC, Horn D. Smoking and death rates - Report of forty-four months of follow-up of 187,783 men II. Death rates by cause. *JAMA* 1958;**166**:1294-308.

10. Burns DM, Shanks TG, Choi W, Thun MJ, Heath CW, Jr., Garfinkel L. The American Cancer Society cancer prevention study I: 12-year follow-up of 1 million men and women. In: Burns D, Garfinkel L, Samet JM, editors. *Changes in cigarette-related disease risks and their implications for prevention and control.* Rockville, Maryland: US Department of Health and Human Services, National Institutes of Health, National Cancer Institute, 1997;113-304. (Smoking and Tobacco Control. Monograph 8.) NIH Publication No. 97-4213.

11. Thun MJ, Day-Lally C, Myers DG, Calle EE, Dana Flanders W, Zhu B-P, *et al.* Trends in tobacco smoking and mortality from cigarette use in cancer prevention studies I (1959 through 1965) and II 1982 through 1988. In: Burns D, Garfinkel L, Samet JM, editors. *Changes in cigarette-related disease risks and their implications for prevention and control.* Rockville, Maryland: US Department of Health and Human Services, National Institutes of Health, National Cancer

Institute, 1997;305-82. (Smoking and Tobacco Control. Monograph 8.) NIH Publication No. 97-4213.

12. 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.

TABLE 1 : Lung cancer risk in never smokers in prospective studies – by histological type

Reference	Country	Period of follow-up	Mean age in follow-up[a]	Never[b]	Sex	Person-years at risk	% histology known	Lung cancer type	Deaths	Rate per 10^5 person-years[c]
[5]	Norway	1964-93	66	NC	M	58716	81.0	Squamous cell	3	6.31
	(Random sample and siblings)							Adenocarcinoma	7	14.72
								Small cell	3	6.31
[6]	Sweden	1971-95	52	NA	M	1211504	99.0	Squamous cell	19	1.58
	(Construction workers)							Adenocarcinoma	40	3.33
								Small cell	29	2.42
[7]	USA	1986-94	66	NC	F	195158	89.5	Squamous cell	5	2.86
	(Random sample from Iowa)							Adenocarcinoma	33	18.89
								Small cell	4	2.29
								Large cell	1	0.57
[8]	USA	1954-62	61	NA	M	443856	70.5	Squamous cell	11	3.52
	(War veterans)							Oat cell	4	1.28
								Adenocarcinoma	27	8.63
								Small cell	0	0.00
								Large cell	1	0.32
								Other	12	3.83
[9]	USA	1952-55	61	NA	M	115859	40.0	Adenocarcinoma	2	4.32
	(Nine states)							Not adenocarcinoma	4	8.63
[2,10]	USA	1959-61	56	NA	M	180081	70.0	Squamous cell	1	0.79
	(CPS I)							Adenocarcinoma	5	3.97
								Small cell	0	0.00
	USA	1959-61	56	NA	F	739145	70.0	Squamous cell	5	0.97
	(CPS I)							Adenocarcinoma	13	2.51
								Small cell	4	0.77
[2,11]	USA	1982-84	55	NA	M	252731	61.5	Squamous cell	4	2.57
	(CPS II)							Adenocarcinoma	6	3.86
								Small cell	1	0.64
	USA	1982-84	56	NA	F	708413	61.5	Squamous cell	2	0.46
	(CPS II)							Adenocarcinoma	16	3.67
								Small cell	4	0.92

[a] Estimated as described in the previous report[1] [b] NA = never smoked any tobacco product; NC = never smoked cigarettes [c] Calculated as described in the text

TABLE 2 : Indirectly estimated squamous cell carcinoma rates (per 100,000 per year) in lifelong nonsmokers by gender, region, year of study and definition of squamous cell carcinoma based on fixed- and random-effects models

Gender	Region	Year of study	Lung cancer type[1]	Rate (95%CI) - Fixed	Rate (95%CI) - Random	Heterogeneity chisquared	DF
All	All	All	Any S	13.9 (13.1-14.7)	10.2 (8.2-12.6)	798.5	70
Male	All	All	Any S	23.5 (21.4-25.8)	15.6 (12.1-20.0)	169.9	38
Female	All	All	Any S	10.2 (9.5-10.9)	6.9 (5.2-9.3)	429.9	31
Male	All	All	Squamous	24.7 (22.4-27.2)	16.6 (12.6-21.8)	139.7	31
Female	All	All	Squamous	9.2 (8.5-10.0)	6.2 (4.4-8.7)	285.7	21
All	Canada	All	Any S	5.0 (3.2-8.0)	5.3 (2.9-9.7)	4.7	3
All	USA	All	Any S	12.2 (11.3-13.2)	9.9 (6.7-14.6)	361.7	21
All	SC America[2]	All	Any S	14.3 (6.9-29.4)	14.3 (6.9-29.4)	1.9	2
All	UK	All	Any S	6.9 (3.7-12.8)	9.9 (2.2-44.8)	3.7	1
All	Scandinavia[3]	All	Any S	5.3 (3.8-7.3)	4.1 (1.8-9.3)	33.5	6
All	W Europe[4]	All	Any S	10.9 (7.6-15.5)	10.9 (7.6-15.5)	1.6	3
All	E Europe[5]	All	Any S	8.1 (5.2-12.6)	4.8 (1.8-13.0)	15.8	5
All	Japan	All	Any S	4.5 (3.1-6.5)	4.9 (2.8-8.4)	5.8	4
All	China[6]	All	Any S	22.4 (20.4-24.6)	23.6 (17.0-32.8)	125.5	13
All	Other[7]	All	Any S	8.6 (6.4-11.6)	12.0 (5.1-28.3)	22.7	3
All	All	1930 to 1960	Any S	8.3 (6.7-10.2)	3.4 (1.4-8.1)	35.0	6
All	All	1961 to 1970	Any S	19.6 (15.9-24.3)	14.2 (7.1-28.3)	67.6	8
All	All	1971 to 1980	Any S	15.9 (12.9-19.5)	12.3 (7.2-20.9)	54.7	10
All	All	1981 to 1990	Any S	14.0 (13.1-14.9)	10.1 (7.6-13.5)	602.9	39
All	All	1991 to 1998	Any S	11.2 (7.5-16.7)	11.2 (7.5-16.7)	1.5	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
5 Including Hungary, Poland
6 Including China, Hong Kong
7 Including South Korea, Singapore, Australia

TABLE 3 : Indirect estimates from individual studies of squamous cell carcinoma 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]	Rate	Weight
Male	Canada		JAIN	CC	1983	all	q	C	9.9	2.0
			SIEMIA	CC	1982	all	q	C	9.3	3.0
			BAND	CC	1987	all	q	C only/A	5.7	6.9
Male	USA		STAYNE	CC	1970	all	q	A	51.0	24.5
			KHUDER	CC	1986	all	q	C	30.9	9.0
			BYERS1	CC	1961	wh	q	C	26.9	22.8
			COMSTO	other	1987	all	q	C	26.7	2.1
			BROWN2	CC	1987	wh	q	C	24.1	194.1
			WYNDE6	CC	1983	all	KI	A	19.9	28.4
			WYNDE3	CC	1968	all	KI	A	17.6	3.0
			DORGAN	CC	1982	wh	q	C/A	14.3	4.0
			BUFFLE	CC	1978	wh	q	C	13.8	3.4
			WYNDE2	CC	1963	all	KI	A	10.9	3.0
			HAMMON	prosp	1953	wh	not a	A	7.9	4.1
			OSANN	CC	1985	all	q	C	7.2	8.1
Male	SCAmerica	Uruguay	DESTE2	CC	1995	all	q	A	18.3	3.7
		Argentina	MATOS	CC	1995	all	q	C	14.3	3.1
		Argentina	PEZZOT	CC	1989	all	q	C only	2.2	0.5
Male	UK		ALDERS	CC	1980	all	q	A	24.8	1.9
Male	Scandinavia	Sweden	DAMBER	CC	1975	all	q	A	15.1	13.5
		Norway	ENGELA	prosp	1970	all	q	C	12.6	3.0
		Sweden	NOU	CC	1974	all	q	A	6.1	2.0
		Norway	KREYBE	CC	1951	all	KI	A	1.7	3.0
Male	W Europe	Italy	BARBON	CC	1983	all	q	A	13.8	6.0
		Germany	JAHN	CC	1991	all	q	A	8.7	3.0
Male	E Europe	Poland	JEDRYC	CC	1984	all	q	C/A	18.9	6.0
		Hungary	ORMOS	CC	1953	all	q	C/A	6.5	2.1
		Hungary	ABRAHA	prosp	1984	all	q	A	2.8	0.5
		Poland	STASZE	CC	1956	all	q	A	1.1	0.5
Male	Japan		WAKAI	CC	1990	all	q	A	18.4	2.0
			SOBUE	CC	1987	all	q	C	7.2	3.0
			MATSUD	CC	1965	all	q	C	2.6	1.0

TABLE 3 : Indirect estimates from individual studies of squamous cell carcinoma 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]	Rate	Weight
Male	China	China	ZHOU	CC	1986	all	q	A	71.8	43.6
		HongKong	LAMWK2	CC	1978	all	q	A	43.6	4.7
		China	XU3	CC	1981	all	KI	A	30.6	3.0
		China	GAO	CC	1985	all	q	C	21.6	12.9
		HongKong	CHAN	CC	1977	all	q+s	A	18.3	2.0
	Other	Australia	JONES	CC	1964	all	q	AX	35.8	5.1
		SKorea	CHOI	CC	1987	all	q	C	17.2	5.9
Female	Canada		JAIN	CC	1983	all	q	C	2.7	6.3
	USA		HAENSZ	CC	1956	all	not a	A	10.7	70.4
			LOMBA2	CC	1964	all	q+u	C	5.6	16.7
			WYNDE3	CC	1968	all	KI	A	5.5	5.8
			DORGAN	CC	1982	all	q	C/A	5.5	26.5
			BROWN2	CC	1987	wh	q	C	5.3	127.7
			ANDERS	prosp	1990	all	q	C	4.8	5.4
			OSANN2	NCC	1973	all	KI	C	3.7	7.0
			OSANN	CC	1985	all	q	C	3.3	12.9
			WYNDE6	CC	1983	wh	q	C	2.7	12.9
			COMSTO	other	1987	all	q	C	1.5	0.5
Female	UK		ALDERS	CC	1980	all	q	A	5.2	8.3
Female	Scandinavia	Norway	KREYBE	CC	1951	all	KI	A	2.4	7.5
		Sweden	NOU	CC	1974	all	q	A	2.1	2.8
		Sweden	SVENSS	CC	1985	all	q	A	2.0	5.4
Female	W Europe	Greece	KATSOU	CC	1988	all	not a	A	11.3	19.5
		Germany	BECHER	CC	1986	all	q+s	A	5.4	2.2
Female	E Europe	Hungary	ABRAHA	prosp	1984	all	q	A	7.5	9.9
		Poland	STASZE	CC	1956	all	q	A	0.2	0.7
Female	Japan		SOBUE	CC	1987	all	q	C	4.1	19.4
			WAKAI	CC	1990	all	q	A	2.9	3.5

TABLE 3 : Indirect estimates from individual studies of squamous cell carcinoma rates (per 100,000) per year in lifelong nonsmokers (Continued 2)

Gender	Region	Country	Study[a]	Study type[b]	Year	Race[c]	Lung cancer type[d]	Product[e]	Rate	Weight
Female	China	HongKong	KOO	CC	1982	all	q+s	A	41.7	43.9
		HongKong	LAMWK2	CC	1978	all	q	A	27.6	20.6
		HongKong	CHAN	CC	1977	all	q+s	A	24.2	25.9
		China	ZHOU	CC	1986	all	q	A	23.6	60.9
		HongKong	LAMTH	CC	1985	ch	q	A	20.7	36.0
		China	WUWILL	CC	1986	all	q	C	15.5	74.9
		China	GAO	CC	1985	all	q	C	12.8	93.0
		HongKong	LAMWK	CC	1983	ch	q	A	11.0	9.2
		China	XU3	CC	1981	all	KI	A	9.9	2.2
Female	Other	Singapore	SEOW	CC	1998	ch	q	C	9.9	14.6
		SKorea	CHOI	CC	1987	all	q	C	4.3	18.8

[a] Study reference as used in IESLC database[12]
[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.

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

Gender	Region	Year of study	Lung cancer type[1]	Rate (95%CI) - Fixed	Rate (95%CI) - Random	Heterogeneity chisquared	DF
All	All	All	Any A	35.4 (34.5-36.4)	23.4 (19.6-27.8)	2428.4	73
Male	All	All	Any A	29.7 (27.4-32.2)	22.2 (17.4-28.4)	253.7	39
Female	All	All	Any A	36.2 (35.2-37.2)	24.6 (19.3-31.3)	2154.8	33
Male	All	All	Adeno	29.8 (27.3-32.6)	23.1 (17.6-30.5)	215.2	32
Female	All	All	Adeno	36.9 (35.8-38.0)	24.8 (18.8-32.8)	2013.0	25
All	Canada	All	Any A	23.4 (18.8-28.9)	19.3 (8.3-44.8)	33.0	3
All	USA	All	Any A	17.6 (16.7-18.6)	16.8 (14.1-20.1)	150.8	22
All	SC America[2]	All	Any A	18.4 (14.3-23.7)	18.4 (14.3-23.7)	1.5	4
All	UK	All	Any A	8.9 (5.1-15.8)	8.9 (5.1-15.8)	0.5	1
All	Scandinavia[3]	All	Any A	21.1 (18.7-23.8)	13.5 (8.5-21.5)	58.4	6
All	W Europe[4]	All	Any A	22.7 (18.1-28.3)	19.7 (12.6-30.9)	5.5	3
All	E Europe[5]	All	Any A	11.2 (9.5-13.1)	14.1 (7.1-27.8)	39.4	5
All	Japan	All	Any A	41.8 (38.6-45.2)	46.4 (36.5-59.1)	14.9	4
All	China[6]	All	Any A	64.7 (62.0-67.5)	64.6 (54.7-76.2)	129.6	13
All	Other[7]	All	Any A	32.8 (30.3-35.4)	30.3 (13.3-69.2)	194.5	3
All	All	1930 to 1960	Any A	11.3 (10.1-12.6)	7.1 (4.1-12.3)	73.1	6
All	All	1961 to 1970	Any A	18.6 (15.9-21.8)	17.4 (13.3-22.8)	13.1	8
All	All	1971 to 1980	Any A	33.4 (30.4-36.8)	22.3 (14.3-34.6)	214.5	13
All	All	1981 to 1990	Any A	38.4 (37.2-39.5)	28.9 (23.4-35.7)	1533.8	39
All	All	1991 to 1998	Any A	61.8 (54.7-69.9)	33.8 (16.7-68.8)	16.1	3

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 5 : Indirectly estimated adenocarcinoma rates (per 100,000 per year) in lifelong nonsmokers – further fixed-effects and random-effects meta-analyses

Region	Gender	Year of study	Rate (95% CI) - Fixed	Rate (95% CI) - Random	Heterogeneity chisquared	DF
All	All	All	35.4 (34.5-364)	23.4 (19.6-27..8)	2428.4	73
All	Male	All	29.7 (27.4-32.2)	22.2 (17.4-28.4)	253.7	39
All	Female	All	36.2 (35.2-37.2)	24.6 (19.3-31.3)	2154.8	33
Asia	All	All	52.9 (51.1-54.7)	53.9 (43.7-66.3)	601.2	21
Asia	Male	All	65.0 (55.3-76.3)	54.1 (36.7-79.7)	31.0	8
	Female	All	52.4 (50.6-54.2)	53.7 (41.9-68.9)	563.7	12
Asia	All	1930 to 1960				No data
	All	1961 to 1970	1.3 (0.1-19.5)	1.3 (0.1-19.5)	1 estimate	0
	All	1971 to 1980	65.6 (56.8-75.8)	70.4 (44.8-111)	17.4	3
	All	1981 to 1990	51.2 (49.4-53.1)	51.6 (40.4-66.1)	553.1	15
	All	1991 to 1998	66.1 (58.3-75.0)	66.1 (58.3-75.0)	1 estimate	0
Not Asia	All	All	17.8 (17.0-18.6)	16.6 (14.4-19.1)	347.8	51
Not Asia	Male	All	22.6 (20.5-24.9)	18.4 (14.8-23.0)	100.8	30
	Female	All	16.6 (15.8-17.5)	15.0 (12.5-18.0)	215.8	20
Not Asia	All	1930 to 1960	11.3 (10.1-12.6)	7.1 (4.1-12.3)	73.1	6
	All	1961 to 1970	18.8 (16.1-22.0)	18.1 (14.4-22.7)	9.4	7
	All	1971 to 1980	19.7 (17.4-22.4)	15.2 (10.7-21.7)	47.1	9
	All	1981 to 1990	19.3 (18.2-20.4)	19.0 (16.0-22.7)	141.1	23
	All	1991 to 1998	24.3 (15.2-39.0)	24.3 (15.2-39.0)	0.0	2

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

Gender	Region	Country	Study[a]	Study type[b]	Year	Race[c]	Lung cancer type	Product[e]	Rate	Weight
Male	Canada		BAND	CC	1987	all	a	C only/A	40.7	45.7
			JAIN	CC	1983	all	a	C	19.7	4.0
			SIEMIA	CC	1982	all	a	C	15.5	5.0
Male	USA		WYNDE6	CC	1983	all	KII	A	39.8	56.8
			WYNDE3	CC	1968	all	KII	A	35.2	6.2
			COMSTO	other	1987	all	a	C	26.7	2.1
			BUFFLE	CC	1978	wh	a	C	25.8	5.5
			KHUDER	CC	1986	all	a	C	24.1	7.0
			BROWN2	CC	1987	wh	a	C	20.4	164.7
			WYNDE2	CC	1963	all	KII	A	18.2	5.3
			DORGAN	CC	1982	wh	a	C/A	17.7	5.0
			STAYNE	CC	1970	all	a	A	16.2	8.0
			OSANN	CC	1985	all	a	C	12.6	14.5
			BYERS1	CC	1961	wh	a	C	8.6	7.9
			HAMMON	prosp	1953	wh	a	A	3.9	2.1
Male	SCAmerica	Uruguay	DESTE2	CC	1995	all	a	A	26.2	4.2
		Argentina	MATOS	CC	1995	all	a	C/A	24.5	5.1
		Cuba	JOLY	CC	1979	all	a	A	14.9	5.2
		Argentina	PEZZOT	CC	1989	all	a	C only	13.7	3.1
Male	UK		ALDERS	CC	1980	all	a	A	14.2	1.8
Male	Scandinavia	Sweden	DAMBER	CC	1975	all	a+al+br	A	17.6	13.9
		Norway	ENGELA	prosp	1970	all	a	C	14.1	5.9
		Sweden	NOU	CC	1974	all	a	A	12.3	4.3
		Norway	KREYBE	CC	1951	all	KII	A	1.7	3.2
Male	W Europe	Germany	JAHN	CC	1991	all	a	A	23.3	7.9
		Italy	BARBON	CC	1983	all	a	A	16.1	7.1
Male	E Europe	Hungary	ABRAHA	prosp	1984	all	a	A	45.3	9.1
		Poland	JEDRYC	CC	1984	all	a	C/A	22.0	7.3
		Hungary	ORMOS	CC	1953	all	a	C/A	1.3	0.6
		Poland	STASZE	CC	1956	all	a	A	1.0	0.5
Male	Japan		WAKAI	CC	1990	all	a	A	73.8	7.8
			SOBUE	CC	1987	all	a	C	64.7	24.0
			MATSUD	CC	1965	all	a	C	1.3	0.5

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

Gender	Region	Country	Study[a]	Study type[b]	Year	Race[c]	Lung cancer type	Product[e]	Rate	Weight
Male	China	HongKong	LAMWK2	CC	1978	all	a	A	130.7	14.3
		China	GAO	CC	1985	all	a	C	69.7	43.6
		China	ZHOU	CC	1986	all	a	A	65.8	46.3
		China	XU3	CC	1981	all	KII	A	30.6	3.1
		HongKong	CHAN	CC	1977	all	a+l	A	4.5	0.5
Male	Other	Australia	JONES	CC	1964	all	a	AX	27.5	3.7
		SKorea	CHOI	CC	1987	all	a	C	20.1	7.5
Female	Canada		JAIN	CC	1983	all	a	C	10.6	28.7
Female	USA		ANDERS	prosp	1990	all	a	C	31.4	44.0
			COMSTO	other	1987	all	a	C	25.7	9.8
			LOMBA2	CC	1964	all	not q+u	C	20.2	94.4
			BROWN2	CC	1987	wh	a	C	18.9	535.3
			WYNDE3	CC	1968	all	KII	A	16.6	22.5
			DORGAN	CC	1982	all	a	C/A	13.2	56.8
			WYNDE6	CC	1983	wh	a	C	13.0	66.4
			OSANN	CC	1985	all	a	C	12.9	55.1
			OSANN2	NCC	1973	all	KII	C	11.1	22.4
			BUFFLE	CC	1978	wh	a	C	9.8	22.1
			HAENSZ	CC	1956	all	a	A	9.0	98.7
Female	SCAmerica	Cuba	JOLY	CC	1979	all	a	A	18.0	41.9
Female	UK		ALDERS	CC	1980	all	a	A	8.2	10.1
Female	Scandinavia	Sweden	NOU	CC	1974	all	a	A	29.8	109.1
		Norway	KREYBE	CC	1951	all	KII	A	21.7	95.1
		Sweden	SVENSS	CC	1985	all	a	A	8.8	28.5
Female	W Europe	Greece	KATSOU	CC	1988	all	a	A	24.3	61.8
		Germany	BECHER	CC	1986	all	not q+s	A	2.9	1.0
Female	E Europe	Hungary	ABRAHA	prosp	1984	all	a	A	17.2	29.5
		Poland	STASZE	CC	1956	all	a	A	8.6	109.4
Female	Japan		WAKAI	CC	1990	all	a	A	44.0	166.5
			SOBUE	CC	1987	all	a	C	39.7	413.3

TABLE 6 : Indirect estimates from individual studies of adenocarcinoma rates (per 100,000) per year in lifelong nonsmokers (Continued 2)

Gender	Region	Country	Study[a]	Study type[b]	Year	Race[c]	Lung cancer type	Product[e]	Rate	Weight
Female	China	HongKong	LAMTH	CC	1985	ch	a	A	100.4	226.4
		HongKong	LAMWK	CC	1983	ch	a	A	94.0	128.4
		HongKong	LAMWK2	CC	1978	all	a	A	75.5	88.0
		China	GAO	CC	1985	all	a	C	64.3	997.0
		HongKong	KOO	CC	1982	all	a+l	A	60.0	86.7
		China	ZHOU	CC	1986	all	a	A	54.0	123.6
		HongKong	CHAN	CC	1977	all	a+l	A	50.9	82.0
		China	WUWILL	CC	1986	all	a	C	45.7	312.3
		China	XU3	CC	1981	all	KII	A	34.5	15.6
Female	Other	Singapore	SEOW	CC	1998	ch	a	C	66.1	240.7
		SKorea	CHOI	CC	1987	all	a	C	20.9	367.1

[a] Study reference as used in IESLC database[12]
[b] CC = case control prosp = prospective NCC = nested case-control
[c] wh = white, ch = Chinese
[d] a = adenocarcinoma, KII = Kreyberg type II, a+al+br = adenocarcinoma + alveolar carcinoma + bronchiolar carcinoma, a+l = adenocarcinoma + large cell, not q + u = not squamous cell or undifferentiated carcinoma, not q + s = not squamous or small cell 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.