INTERNATIONAL EVIDENCE

ON

SMOKING AND LUNG CANCER

(PROJECT IESLC)

A FIRST REPORT

PART II : RESULTS OF SELECTED META-ANALYSES

Peter N Lee
Barbara A Forey and
Katharine J Young

P N Lee Statistics and Computing Ltd
17 Cedar Road
Sutton
Surrey SM2 5DA
UK

April 2003

EXECUTIVE SUMMARY

Part I of this report describes how databases were set up containing almost 10000 relative risks from almost 300 epidemiological case-control or prospective studies, each involving 100 or more lung cancer cases. Part I gives details of how the relevant studies and the source papers were identified, the structure of the databases, the methods used for entry and checking of data and derivation of relative risks, as well as summary information about the characteristics of the studies and relative risks themselves. Part I ends by describing techniques for conducting meta-analyses and the format of the tables presenting the results.

This part of the report, Part II, presents results of preliminary analyses of the database aimed at giving insight into how the relative risk of lung cancer varies by type of product smoked; nature of exposure (ever, current, ex); dose of exposure; type of lung cancer; sex; location, timing and type of study; and extent of adjustment for confounding variables. Mainly the report consists of a series of meta-analyses, but some limited results from multiple regression analysis are also included.

The main conclusions reached from the analyses are as follows:

There is a strong association between smoking and **overall risk of lung cancer**, which is present for all types of product smoked, more marked for cigarette smoking than for pipe and cigar smoking, more clearly seen in current than former smokers, and evident in both males and females. This is illustrated in the table below which summarizes relative risks and 95% confidence limits from random-effects meta-analyses.

Product	Sex	Ever smoked (vs never smoked)	Current smoker (vs never smoked)	Ex-smoker (vs never smoked)
Any product	M	6.09 (5.46-6.85)	9.16 (8.00-10.49)	4.43 (3.92-4.99)
	F	4.45 (3.85-5.13)	6.95 (5.82-8.30)	3.47 (2.88-4.17)
Cigarettes only	M	7.86 (6.31-9.79)	11.81 (10.34-13.50)	5.43 (4.30-6.84)
	F	3.84 (3.23-4.58)	6.00 (4.56-7.90)	1.81 (1.07-3.07)
Pipes and/or cigars (not cigarettes)	M+F	2.92 (2.38-3.57)	4.64 (3.38-6.38)	2.00 (1.51-2.66)
Pipes only	M+F	3.12 (2.35-4.13)	5.20 (3.50-7.73)	2.69 (1.53-4.72)
Cigars only	M+F	2.95 (1.91-4.56)	4.67 (3.49-6.25)	2.85 (1.45-5.61)

There is no clear tendency for the strength of the association to vary by age.

The association is dose-related. This is most clearly evident from the relative risk estimates for any product and cigarette smoking, for which relative risks are summarized below, but can also be seen from more limited data for pipes and cigars.

Product	Sex	Low	Mid	High
Any product (ever)	M	3.13 (2.59-3.78)	6.81 (5.63-8.23)	12.58 (10.53-15.02)
	F	2.43 (1.91-3.09)	4.94 (3.81-6.39)	8.56 (5.39-13.61)
Any product (current)	M	4.88 (4.08-5.83)	9.18 (7.56-11.15)	16.22 (13.04-20.18)
	F	4.32 (3.42-5.46)	11.73 (9.80-14.05)	18.06 (14.06-23.21)
Cigarettes only (ever)	M+F	2.60 (1.88-3.60)	5.70 (3.88-6.36)	11.02 (8.05-15.39)
Cigarettes only (current)	M	5.25 (3.88-7.10)	12.59 (10.03-15.79)	24.69 (20.01-30.47)
	F	2.79 (1.71-4.56)	7.42 (5.10-10.80)	15.80 (10.75-23.21)

("Low" applies to relative risks for which the range of amount smoked includes 5 cigs/day and does not include 20 cigs/day, "Medium" to risks for which the range includes 20 cigs/day and does not include 5 or 45 cigs/day, and "High" to risks for which the range includes 45 cigs/day and does not include 20 cigs/day.)

There is quite clear evidence that, within smokers, risk of lung cancer is reduced in filter vs plain cigarette smokers and is increased in smokers of handrolled vs manufactured smokers. Limited evidence does not suggest any adverse effect of mentholation.

Comparison	Sex	Relative risk (95%CI)
Filter only vs plain only (or nearest equivalent)	M	0.67 (0.56-0.79)
	F	0.73 (0.62-0.86)
Filter ever vs plain only (or nearest equivalent)	M	0.70 (0.60-0.82)
	F	0.79 (0.68-0.93)
Filter only vs plain ever (or nearest equivalent)	M	0.69 (0.59-0.81)
	F	0.70 (0.59-0.82)
Handrolled vs manufactured	M	1.33 (1.16-1.53)
	F	0.92 (0.49-1.71)
Mentholated vs non-mentholated	M	1.15 (0.93-1.43)
	F	0.78 (0.63-0.98)

For any given exposure studied, the meta-analyses conducted nearly always showed highly significant heterogeneity between the individual relative risk estimates, which cannot be fully explained by systematic variation according to the factors studied. While further multivariate analyses will be needed to investigate sources of variation more fully, the results generally indicated that:

Sex: Although some of the meta-analyses above show somewhat higher relative risks for males than for females, the difference is not always statistically significant and may be due in part to confounding by other factors. Multivariate analysis of data for smoking of any product showed no significant variation in risk between sexes for ever smoking, but a significant 20% higher risk for current smoking.

Continent: The associations tended to be weakest in studies conducted in Asia and were stronger in studies conducted in North America or Europe. The tendency for Asian studies to give lower relative risks was particularly evident in the meta-analyses of smoking of any product. Multivariate analysis of data for smoking of any product showed that continent on its own explained about 95% of the variance between estimates. Although for cigarette smoking relative risks were generally higher in North American than in European studies, the reverse was true for pipe and cigar smoking. Lower risks in filter cigarette smokers are evident in studies conducted in Asia, North America and Europe.

Location within Europe: For most exposures associations were of a similar order of magnitude in different countries within Europe. For pipe/cigar smoking associations appeared weaker in the UK than in Scandinavia, Germany and other western countries.

Location within Asia: Limited data from India tended to show stronger associations than was the case for China or Japan.

Period of study: Studies starting more recently, particularly in North America or Europe, tended to show stronger associations than studies starting earlier.

Study type: For many exposures relative risk estimates from prospective studies tended to be somewhat greater than those from case-control studies.

Number of adjustment variables: Generally there was no strong evidence that the magnitude of the relative risk estimate was associated with the number of adjustment variables considered. Patterns of association were very similar whether meta-analyses were conducted based on estimates adjusted or unadjusted for confounding variables.

For a given exposure relative risk estimates are generally higher for **squamous cell carcinoma** than for **adenocarcinoma**. This is illustrated in the combined sex results below.

Exposure	All lung cancer	Squamous cell carcinoma	Adenocarcinoma
Ever any product	5.50 (5.08-5.95)	10.19 (8.65-12.01)	2.84 (2.41-3.36)
Current any product	8.58 (7.78-9.47)	16.41 (12.80-21.05)	4.11 (3.25-5.20)
Ex any product	4.24 (3.86-4.65)	8.24 (6.55-10.36)	2.65 (1.99-3.52)
Ever any product - low	2.78 (2.43-3.19)	4.25 (3.27-5.53)	1.69 (1.23-2.32)
Ever any product - mid	5.95 (5.12-6.92)	9.91 (7.21-13.61)	2.55 (1.97-3.30)
Ever any product - high	11.12(9.51-12.99)	22.19 (15.92-30.92)	4.23 (2.68-6.69)
Current any product - low	4.84 (4.25-5.50)	9.92 (7.41-13.28)	2.32 (1.59-3.58)
Current any product - mid	10.27 (9.02-11.68)	21.57 (16.77-27.73)	3.37 (1.88-6.02)
Current any product - high	17.74 (15.24-20.66)	39.16 (23.67-64.79)	5.71 (2.91-11.19)
Ever cigarettes only	6.46 (5.43-7.68)	11.56 (7.64-17.49)	3.15 (1.60-6.21)
Current cigarettes only	9.75 (8.09-11.76)	20.85 (14.84-29.29)	6.05 (3.69-9.92)
Only filter vs only plain	0.69 (0.61-0.78)	0.52 (0.40-0.68)	0.84 (0.66-1.08)

Ever filter vs only plain	0.73 (0.65-0.82)	0.55 (0.41-0.74)	0.99 (0.84-1.16)
Only filter vs ever plain	0.69 (0.62-0.77)	0.69 (0.57-0.83)	0.98 (0.80-1.21)
Handrolled vs manufactured	1.31 (1.14-1.52)	1.62 (1.18-2.21)	2.09 (0.83-5.25)
Ever pipes and/or cigars (not cigarettes)	2.92 (2.38-3.57)	3.65 (1.92-6.91)	0.93 (0.62-1.40)
Ever pipes only	3.12 (2.35-4.13)	3.43 (1.84-6.41)	0.50 (0.23-1.10)
Ever cigars only	2.95 (1.91-4.56)	3.87 (2.45-6.12)	0.55 (0.11-2.88)

(See previous table for definition of “low”, “mid” and “high”.)

It can also be seen that the lower risks in filter vs plain smokers seen for all lung cancer and for squamous cell carcinoma are not evident for adenocarcinoma. However the data do not support the suggestion that the switch to filter cigarettes has increased the risk of adenocarcinoma.

It is noticeable that the evidence does not suggest any increased risk of adenocarcinoma in smokers of pipes and/or cigars but not cigarettes.

Heterogeneity of the relative risks is less for squamous cell carcinoma than for all lung cancer, as Asian estimates for squamous cell carcinoma are higher and more comparable to those seen in Europe and North America. Estimates for adenocarcinoma are higher in North American than in European studies and some analyses show relative risks are higher in more recently conducted studies.

Ideas for further work on this valuable database will be discussed in Part III of this report.

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1. Introduction

The objective of the IESLC project is to collect and summarize published epidemiological evidence relating smoking to lung cancer, with a view to assessing how the strength of the association varies by the index of exposure to smoking considered and by the characteristics of the study reporting the findings.

Part I of this report describes how the studies were identified, how databases were set up to allow entry of relevant study details and of relative risks relating to defined smoking characteristics, the structure of the databases, and how data were entered and checked. It also summarizes characteristics of the 296 studies for which data have been included, each involving at least 100 lung cancer cases, and of the almost 10,000 relative risks recorded. Part I also gives details of the techniques used to carry out meta-analyses, including the method of selecting the relative risks and the method of combining them, and describes the content of typical output.

This part of the report, Part II, presents and discusses results of selected meta-analyses, showing how the relative risk of lung cancer varies by type of product smoked (any product, cigarettes, type of cigarette, pipes and cigars), nature of exposure (ever, current, ex), amount of exposure, type of lung cancer (any, squamous cell carcinoma, adenocarcinoma), sex, location of study, timing of study, type of study (case-control or prospective), number of adjustment factors considered and exact definition of the numerator and denominator of the relative risk. The intent is to give the reader a good idea of the amount of data available on the various topics and insight into the magnitude and variability of the relative risks. The analyses are not intended as a comprehensive assessment of the evidence, which *inter alia* would include fuller examination of apparently outlying results as well as multivariate analysis, which might take into account other variables of interest recorded on the database that are not considered in this report. Results of some limited multiple regression analyses are, however, included for smoking of any product.

The need for further analyses is considered in Part III of this report which suggests ideas for future research.

[Note that while preparing this report a small number of errors and omissions to the data were corrected following study of draft analyses. The effect of these changes is that some of the numbers of relative risks (but not studies) cited in Part I of this report are subject to minor error.]

2. Methods

2.1 Introduction

As described more fully in §4.3 in Part I of this report, each meta-analysis produces a cover page followed by eight sections of output, headed –1 to –8, respectively. The cover page describes the restrictions on the data included, the order of preference for selecting relative risks to be included and a short description of the contents of the table. §3 of the present report concerns results for overall lung cancer risk, while §4 and §5 concern results for, respectively, squamous cell carcinoma and adenocarcinoma. (Note that the word "section" is used to describe the sections of output, while sections of reports are indicated by the symbol §.)

The tables on overall lung cancer risk relate to five broad types of smoking indices, as follows:

A. Smoking of any product
B. Smoking of cigarettes (or any product if cigarettes not available)
C. Smoking of cigarettes only
D. Type of cigarette smoked
E. Pipes and cigars

Within each broad type of smoking index, there are a variable number of meta-analyses, described in the section of this report summarizing their results. Thus, for example, Appendix Table A2 (or Table A2) gives results for the second set of meta-analyses for smoking of any product, here relating to current vs never smoking.

The tables on squamous cell carcinoma and on adenocarcinoma consider the same types of smoking index with the exception of "smoking of cigarettes (or any product if cigarettes not available)". Thus we have the following tables:

Squamous cell carcinoma	Adenocarcinoma	
F.	J.	Smoking of any product
G.	K.	Smoking of cigarettes only
H.	L.	Type of cigarette smoked
I.	M.	Pipes and cigars

Note that the full output, including all of section-1 to section-8 is presented in Appendix Tables A to M. Reduced output, which usually only includes the cover page and section-3 giving the meta-analysis results for the adjusted data, is given in Tables A to M. Thus the reader who wishes only to see the meta-analysis estimates need refer only to the Tables but the more interested reader who wishes to see full details of the individual relative risks contributing to the estimates should refer to the corresponding Appendix Tables. The two sets of output always correspond directly; thus for example both Table G2 and Appendix Table G2 give results for smoking of cigarettes only for squamous cell carcinoma.

2.2 General restrictions to the analyses

The analyses presented all satisfy the following conditions for selecting relative risks:

Results complete enough for use in meta-analysis Adjusted relative risks which lack a confidence interval, and 2x2 tables with two zero cells are excluded from meta-analyses. Where a 2x2 table has a zero, the relative risk and confidence interval is calculated by adding 0.5 to each cell of the table. In practice, whether or not such data are included in meta-analyses makes little difference to the results as a relative risk calculated with a 0.5 in one cell will have a large standard error and therefore little weight.

Follow-up period for whole study or longest available This applies only to prospective studies. Where case-control studies present both interim and final results, only the final results are included on the database anyway (except if the

interim reports give results relating to comparisons not considered in the final report).

Race all or nearest available Results are chosen for the whole population (or nearest available). Otherwise results are chosen by separate racial group.

Principal rather than subsidiary studies See §3.3.3 of Part I for a discussion of the problem of overlapping studies and the definition of "principal" and "subsidiary" studies.

Age: whole study if available, otherwise by widest available age group.

Sex: single sex results rather than combined sex results.

2.3 Factors considered

The meta-analyses first give overall results for all the relative risks selected. Then results of an analysis of risk by the factor **sex** are shown with estimates shown, and compared, for combined sex results and those specifically for males and females. Further analyses are generally sex-specific, with results shown separately for males and for females (although in some analyses based on few studies, the further analyses are shown only for males, or are not sex-specific, or are omitted altogether). These analyses show results for the following factors:

Lung cancer type

For analyses of all lung cancer or nearest equivalent, the levels are All; and Other.

For analyses of squamous cell carcinoma, the levels are Squamous cell (q); Squamous or small cell (q+s); Squamous or undifferentiated (q+u); Kreyberg I (KI); and Not adenocarcinoma (not a). (Note that here and subsequently in §2.3 text in brackets indicates the abbreviations used in the tables.)

For analyses of adenocarcinoma, the levels are Adenocarcinoma (a); Adenocarcinoma or large cell (a+l); Adenocarcinoma, alveolar or bronchiolar (a+al+br); Kreyberg II (KII); Not squamous and undifferentiated (not q+u); and Not squamous or small (not q+s).

Continent

The levels are: North America (NAmer); South or Central America (SCAmer); Europe; Asia; Australasia (Auslia); and Africa.

Country in Europe

The levels are: Multicountry studies (Multi); UK; Germany; Scandinavia (Scand); Other West European countries, i.e. Italy, France, Spain, Belgium, Netherlands and Switzerland (othWest); East European countries, i.e. Poland, Hungary, Czechoslovakia, USSR (East); and Greece and Turkey (Balkans).

Country in Asia

The levels are: China; Japan; India; and Other, i.e. Hong Kong, Taiwan, Singapore, South Korea and Thailand.

Start year of study

The levels are: <1960; 1960-69; 1970-79; 1980-89; and 1990+. Note that a small number of studies with start year unknown are excluded.

Study type

The levels are: Case-control (CC); Prospective (Prosp); and Other, which includes nested case-control and case-cohort studies.

Number of adjustment variables

The levels are: 0;1;2;3-5;6-9; and 10+ or positive but not known (10+/nk).

The meta-analyses also include breakdown of results for factors relating to definition of the numerator and denominator of the smoking index used. These vary from analysis to analysis but may include:

Product

The levels are: All or unspecified (all/unsp); Cigarettes regardless of other products (cigs+/-ot); and Cigarettes only (cig only). For some analyses only the second and third of these levels are relevant. As discussed on p27 of Part I of this report, product was poorly defined for some studies, particularly in countries where smoking of pipes/cigars is rare. Then there is no meaningful difference between the categories and, to avoid excessive duplication, data were only entered in the "all/unsp" category.

Cigarette type

The levels generally are: All or unspecified (or not applicable if product is all or unspecified) (all/unsp); Manufactured cigarettes with or without handrolled (MC+-HR); and Manufactured cigarettes only (MC only).

When analyzing filter/plain relative risks, the levels are: Only filter (only f); Always filter (always f); Mainly filter (mainly f); Equal plain and filter (equal p&f); Both plain and filter (both p&f); and Ever filter (ever f).

When analyzing handrolled/manufactured relative risks the levels are: Only handrolled (only hr); Mainly handrolled (mainly h); Both manufactured and handrolled (both m&h); and Any handrolled (any hr).

Denominator

The levels generally are: Never any product (nev any); Never cigarettes (nev cigs); or Other, which always includes never smokers, but additionally includes light (i.e. maximum of 9 cigarettes per day) smokers (nev + 1), long term ex smokers (nev + 2), both light smokers and long term ex smokers (nev + 3),

smokers for whom amount smoked was missing (nev + 4) or smokers who only started smoking recently (nev + 5).

When analyzing filter/plain relative risks, the levels are: Ever plain (ever p); Mainly plain (mainly p); Plain (not otherwise specified) (p NOS); and Always plain (always p).

When analyzing handrolled/manufactured relative risks, the levels are: Ever manufactured (ever mc); Any manufactured (any mc); Only manufactured currently (mc cr); and Only manufactured (only mc).

Smoking status

The levels are: Ever; and Current.

2.4 Format of the meta-analysis output

§4.3 of Part I provides a detailed description of the output, including the meta-analyses shown in sections –3 (adjusted data) and –6 (unadjusted data). An example output is presented in Appendix H. That output includes the results, not only of fixed-effects and random-effects meta-analyses, but also of significance tests of pairwise differences between levels of the factors and, for some factors, of dose-related trend. These significance tests are based on the fixed-effects analyses and were found in practice to be of little value, partly as there is often very large heterogeneity between the individual relative risk estimates (when fixed-effects analyses assume homogeneity) and partly as the pattern of variation in risk by level is not always the same for the fixed-effects and random-effects estimates. Accordingly, the main output presented in this report omits these significance tests.

2.5 Meta-analysis of results by amount smoked

Results by amount smoked generally take the form of a relative risk for each of a set of categories (e.g. 1-10, 11-20 etc cigarettes) compared with a common base group, e.g. never smoked. These are not independent.

The approach adopted in this report is to define a set of levels of smoking, to select a relative risk from each study relevant to each level of smoking (if available), then to carry out a standard meta-analysis for each level. Effectively only one relative risk is chosen from each study for each level (or from each sex × age × race stratum), thus ensuring independent results for a valid meta-analysis. There are two opposing difficulties with this approach. Firstly, if a small number of broad categories are chosen, then some of the results from those studies which use many narrow categories will have to be omitted to avoid non-independent results. Conversely, if a large number of narrow categories is chosen, then results for broad original categories will have to be omitted because they are not sufficiently specific. More complex regression analyses modelling the dose response and allowing all the results to be retained are beyond the scope of this report.

Two schemes were chosen, the first with broad categories, and the second with narrow. Each scheme has a set of "key values". An interval is allocated to the category whose key value it includes and intervals which include none or more than one of the key values are excluded. (Note that on the database 99 indicates an open-ended upper limit.)

Scheme 1

Level	Key value	Maximum range
1	5	1-19
2	20	6-44
3	45	21+

Scheme 2

Level	Key value	Maximum range
1	1	1-9
2	10	2-19
3	20	11-29
4	30	21-39
5	40	31-98
6	99	41+

Thus, results for 21-39 cigs/day would be included as level 2 under scheme 1 but would be excluded under scheme 2 as the grouping is so broad it includes two key values.

An initial table (e.g. Table A5) shows all the available data by amount. Assignment to the categories of the two schemes is shown in sections –1 and –4 (NC1 and NC2, with 0 representing exclusion from that scheme). Where smoking of products other than cigarettes is included in the table, categorization is based on "cigarette equivalents", the definitions of which are shown at the end of those sections (with – representing "not applicable" and * representing "not known".) Only the two schemes are used as factors, with the excluded studies shown in the column headed "absent". Certain parts of the meta-analysis output are omitted (e.g. parts of the "absent" and "total" columns in sections –3 and –6 which would otherwise involve non-independent results.)

This is generally followed by three tables (e.g. Tables A6 – A8) corresponding to the levels of scheme 1, with the terms low, mid, high corresponding to levels 1, 2, 3 respectively, and all the usual factors are included here.

Note that although the same relative risks will usually appear in the subsequent tables as in the columns of the initial table, they may rarely include additional results[1]. Results from the subsequent tables are quoted in the text.

2.6 Meta-analysis of results by age

The approach adopted in this report is to define a set of age groups, and to carry out standard meta-analyses of the relative risks relevant to each age group separately. Although this is to some extent similar to the approach taken for results by amount smoked, a fundamental difference is that results for different age groups are independent, and there is therefore no constraint to choose just one result per study for each analysis.

Relative risks are only accepted for age ranges that fall completely within the age range specified. These are commonly age-specific results from studies with a wide age range, but may also include whole-study results from studies with narrow age criteria. Overlapping ranges of <56, 50-70 and 65+ have been chosen so as not to exclude data for common age ranges which could cross boundaries of the classification while still allowing one to compare relative risks in people of different average ages. Note that age is age at baseline for prospective studies, so results for prospective studies and case-control studies are not completely comparable.

Note also that it is in theory possible for relative risks for some age groups (e.g. 50-54 or 65-69) to fall into two of the age categories above. However use of non overlapping categories, e.g. <50, 50-70, >70 would have reduced the number of relative risks that could be used even more drastically.

[1] This occurs if a study originally used a different categorization scheme for adjusted and unadjusted results. For example in study JUSSAW, adjusted category 20+ is excluded (i.e. goes to the "absent" column) under scheme 1 (Table A5 – 3), while unadjusted categories 20-24 and 25+ are included in the mid and high categories respectively (Table A5 – 6), whereas in Tables A7 and A8, the unadjusted results are chosen as the best available in both sections –3 and –6.

2.7 More complex analyses

The output presented in the main tables allows some insight into the major factors that determine the magnitude of the relative risks associated with smoking. However, for some of the study factors, it is not straightforward to determine their true importance. There are two main reasons for this. First, these factors are not necessarily independent, so univariate analysis of the relationship between risk and differing levels of a single specific factor may be misleading. Second, the existence of huge unexplained heterogeneity between individual relative risk estimates implies that (as noted above) significance tests of pairwise comparison or trend based on the fixed-effects estimates are likely to have limited meaning. The significance levels should be based on a method that takes into account variation between study as well as within study. While the random-effects estimates take account of between-study variation, the estimations are carried out within factor level and cannot be readily compared statistically. To gain greater insight alternative approaches are needed.

Full multivariate analysis of the data is beyond the scope of this report. However, for certain sets of relative risks, results of some weighted multiple regression analyses are included, partly to provide additional information and partly to show the types of further analysis that might usefully be included in later reports. These analyses are presented in Appendix Table N (ever smoking of any product) and Appendix Table O (current smoking of any product). The analyses are carried out based on the logarithms of the individual relative risk estimates and their associated weights (inverse variances) and use a binomial error with no general mean fitted. The modeling shows how the deviance (and its associated degrees of freedom (d.f.)) is reduced by including various factors into the model (including continent, location in Europe, location in Asia, sex, start year of study, and study type).

Note that, in any model, the relative risks given for the last factor included represents overall estimates of the relative risk associated with each level of that

factor adjusted for the other factors. The relative risks for the other factor are relative to the base level for that factor (marked as “aliased”). The predicted relative risk for a given data point can be obtained by multiplying the relative risks for its factor levels (taking “aliased” as 1.0). Thus on the second page of Appendix N, in Model 4 (which includes continent, start year of study and study type) the fitted relative risk for a case-control study in North America starting in 1970-79 would be 1 x 1.440 x 4.310 = 6.206.

Note that, in the output, the significance of the drop in deviance is based on the assumptions of a fixed effects model (i.e. treating the deviance as chisquared on its given d.f.). Where the residual deviance is clearly not distributed as chisquared, exceeding its d.f. significantly, this p value may be misleading. A more conservative and reliable indicator of whether including the factor in the model reduces the deviance more than expected given the residual deviance may be to assume the ratio of (drop in deviance per d.f.)/(residual deviance per d.f.) is distributed as an F statistic.

3. Results for overall lung cancer risk

3.1 Further restrictions to the analysis

All analyses in §3 of this report have the further restriction that relative risks are selected for all lung cancer (i.e. regardless of lung cancer type) if available, and if not only for categories that at least include both squamous cell carcinoma and adenocarcinoma.

3.2 Smoking of any product (Tables A1 to A18)

All of Tables A1 to A18 relate to the smoking of any product, or to cigarette smoking if this is not available, in the order of preference:

1 = all/unspecified,

2 = cigarettes regardless of other products,

3 = cigarettes only.

They also all have the same order of preference for cigarette type:

1 = all/unspecified,

2 = manufactured cigarettes regardless of handrolled cigarettes,

3 = manufactured cigarettes only.

The unexposed group is never smokers, with the order of preference:

1 = never smoked anything,

2 = never smoked cigarettes,

with the exception of Table A4, where the unexposed group is non-current smokers, with the order of preference:

1 = nonsmoker of anything,

2 = nonsmoker of cigarettes.

The tables vary as follows:

A1	=	Ever smoking	A10	=	Current smoking - low
A2	=	Current smoking	A11	=	Current smoking - mid
A3	=	Ex smoking	A12	=	Current smoking - high
A4	=	Current smoking (vs non-current)	A13	=	Ever smoking - age <56
A5	=	Ever smoking by amount	A14	=	Ever smoking - age 50-70
A6	=	Ever smoking - low	A15	=	Ever smoking - age 65+
A7	=	Ever smoking - mid	A16	=	Current smoking - age <56
A8	=	Ever smoking - high	A17	=	Current smoking - age 50-70
A9	=	Current smoking by amount	A18	=	Current smoking - age 65+

In Tables A6 to A8 and Tables A10 to A12, the terms low, mid, high correspond to levels 1, 2 and 3 of scheme 1 as described in §2.5.

3.2.1 Ever smoking of any product (vs never smoking) (Table A1)

338 adjusted relative risks are available from 244 studies. Although there is extremely highly significant heterogeneity between the estimates (χ^2 = 7549.0 on 337 d.f.), there is enormous consistency in the direction of the effect, with only two of the estimates below 1.0. Both of these estimates, for females from studies DAVEYS and ORMOS, are based on very small numbers of exposed cases and are not statistically significant. The great majority of the individual relative risk estimates are significant and many exceed 10.0. The overall risk estimate is 4.24 (95% CI 4.18-4.30) from the fixed-effects analysis and 5.50 (5.08-5.95) from the random-effects analysis. Note that the LIU4 (million deaths) study from China, with its relatively low estimates and very narrow CI of 2.76 (2.69-2.83) for males and 2.86 (2.77-2.95) for females, contributes about a half of the total weight of the fixed-effects analysis. Random-effects estimates are rather lower for data for females (4.45, 3.85-5.13) than for males (6.09, 5.46-6.85) or sexes combined (6.09, 4.98-7.44). In view of the substantial heterogeneity between estimates, summary relative risks cited henceforth in the text will be based on random-effects analyses, unless they are specifically stated to be fixed-effects estimates.

Looking at how risks vary by level of the various factors studied the following comments can be made:

Lung cancer type Nearly all the estimates are for all lung cancer regardless of type. For those few where other definitions were used, estimates are lower (3.33 vs 6.21 for males, 3.46 vs 4.50 for females).

Continent In both sexes, estimates are substantially lower from Asian studies (males 3.46, females 2.84, again dominated by the LIU4 study with over 80% of the weight) than from European studies (males 6.94, females 4.34) or North American studies (males 7.39, females 6.62). For South/Central America, Australasia and Africa estimates are based on far less data, so are less reliable.

Country in Europe No evidence of significant variation by country within Europe is seen in females, but there is heterogeneity for males, with risk estimates lower for UK (5.98), Germany (6.51) and Scandinavia (6.94) than for other Western countries (7.78), Eastern countries (8.72) and multicountry studies (10.95).

Country in Asia Again there is no significant heterogeneity in females. In males, estimates are higher in India (8.74) than in China (2.98), Japan (3.40) or other countries (3.83). Note that there is no evidence on the database relating to smoking by women in India.

Start year of study There is some tendency for risk estimates to be higher in more recent studies. For example, for 1960-69 estimates are 5.92 in males and 4.15 in females while for 1980-89 they are 7.12 in males and 5.38 in females.

Study type In both sexes estimates are somewhat higher from prospective studies (males 6.55, females 5.64) than from case-control studies (males 5.94, females 4.24).

Number of adjustment variables Although there is a tendency for the fixed-effects estimates to decline with increasing number of variables adjusted for in females, this pattern is not clearly seen in the random-effects estimates, or in males.

Product In females, random-effects estimates are very similar according to the definition of product smoked (all/unspecified, cigarettes +/- others or cigarettes only) but in males the few estimates for cigarettes only tend to be higher (10.28 vs 6.21 for all/unspecified or 5.65 for cig +/- other).

Denominator In both sexes, risk estimates are highest where the denominator is never cigarettes (males 6.26, females 5.18), intermediate when it is never anything (males 6.20, females 4.31) and lowest when it is other definitions (males 4.20, females 2.05).

Turning now to the unadjusted data, it can be seen that the estimates are very similar to the adjusted estimates, overall (adjusted 5.50, unadjusted 5.47), for males (adjusted 6.09, unadjusted 6.23), for females (adjusted 4.45, unadjusted 4.36) and for the sexes combined (adjusted 6.09, unadjusted 5.79). Estimates by levels of the various factors studied are also quite similar for adjusted and unadjusted data.

3.2.2 Current smoking of any product (vs never smoking) (Table A2)

Here there are 194 adjusted relative risks from 131 studies. The heterogeneity (χ^2 = 2594.4 on 193 d.f.), though somewhat less per d.f. than for ever smoking, is still very highly significant. All the individual relative risk estimates are greater than 1.0 and all but seven are greater than 2.0, with a large proportion above 10.0. The overall risk estimate is 9.39 (9.17-9.62) from fixed-effects analysis and 8.58 (7.78-9.47) from random-effects analysis, substantially higher than the corresponding estimates for ever smoking. Random-effects

estimates are lower for females (6.95, 5.82-8.30) than for males (9.16, 8.00-10.49) or sexes combined (12.71, 9.89-16.32).

Looking at how risks vary by levels of the various factors studied, the following conclusions can be noted:

Lung cancer type Estimates are higher where the analysis includes all lung cancers (males 9.50, females 7.21) than in the few cases where it is based on other classifications that include squamous cell and adenocarcinoma (males 3.19, females 3.28).

Continent As for ever smoking, relative risk estimates are strikingly lower for Asia (males 3.91, females 2.80) than for Europe (males 9.52, females 6.51) or North America (males 11.75, females 10.68).

Country in Europe Though there is some evidence of heterogeneity for both sexes, there seems no consistent tendency in the two sexes for relative risks to be particularly high or low in any country.

Country in Asia There are no results for India. There is no significant variation between estimates for China, Japan or other countries, all the estimates being lower than in the USA or in any European country grouping considered.

Start year of study In both sexes there is a clear tendency for risk estimates to increase with later year of start, with estimates about twice as high for studies starting in 1990 or later (males 13.28, females 9.79) than for studies starting before 1960 (males 7.83, females 4.65). This pattern is clearer here than for the analyses of ever smoking shown in Table A1, perhaps because, with time, current smokers include a higher proportion with longer durations of smoking while ever smokers include a higher proportion of ex-smokers.

Study type Estimates, in both sexes, are similar for case-control and for prospective studies.

Number of adjustment variables No very clear tendency is seen for risk to vary by number of variables adjusted for.

Product In males, estimates are clearly higher for cigarette only (14.85) than for all or unspecified (8.09) or cigarettes +/- other products (9.67).

Denominator In females, estimates are rather higher where the denominator is never cigarettes (8.72) than where it is never any product (6.20). However for males, the reverse is true (8.49 for never cigarettes, 9.46 for never any product).

Turning now to the unadjusted data, it can be seen that the estimates are similar to the adjusted estimates, overall (adjusted 8.58, unadjusted 8.36), for males (adjusted 9.16, unadjusted 9.14), for females (adjusted 6.95, unadjusted 6.68) and for sexes combined (adjusted 12.71, unadjusted 11.47). As the pattern of results by levels of the various factors is quite similar for the adjusted and unadjusted data, and the same is true in Table A1 for ever smoking, in future attention will be restricted in the text to the adjusted estimates.

3.2.3 Ex-smoking of any product (vs never smoking) (Table A3)

185 relative risks are available from 126 studies. They are clearly substantially lower than the estimates for current smoking in Table A2, with values greater than 10.0 much less common. However, only seven are less than 1.0 and the association remains highly significant. Overall estimates are 5.68 (5.52-5.84) from the fixed-effects analysis and 4.24 (3.86-4.65) from the random-effects analysis. Interestingly, the overall estimates for ex-smoking are not that different from those ever smoking from Table A1. This may to some extent reflect the fact that estimates for ex-smoking tend less likely to be from Asia

(in particular, study LIU4 has no relevant data here) and more likely to be from recent studies than estimates for ever smoking.

		Ex-smoking		Ever smoking	
		Males	Females	Males	Females
Total estimates	N	100	64	181	108
From Asia	n	11	9	40	32
	%	11.0	14.1	22.1	29.6
	% weight	5.9	4.9	67.5	65.9
Started 1980 or later	n	43	36	59	51
	%	43.0	56.3	32.6	47.2
	% weight	58.6	78.7	77.1	83.2

Random-effects estimates are lower for females (3.47, 2.88-4.17) than for males (4.43, 3.92-4.99) or sexes combined (5.66, 4.34-7.38).

Looking at how risks vary by level of the various factors studied, we note:

Lung cancer type Estimates are higher where the analysis includes all lung cancers (males 4.49, females 3.57) than in the very few cases where it is based on a more limited classification (males 2.62, females 1.85).

Continent Estimates are lower for Asia (males 2.48, females 2.84) and Europe (males 3.68, females 2.54) than for North America (males 5.76, females 4.34).

Country in Europe There is some heterogeneity, but no very evident tendency that is consistent over the sexes for risks to be high in specific parts of Europe.

Country in Asia The data here are fairly limited and show no significant heterogeneity.

Start year of study There is a tendency for estimates to be higher in more recent studies in both sexes, but the trend is less clear than is the case for current smoking.

Study type In both sexes, estimates are lower for prospective studies (males 3.13, females 2.93) than for case-control studies (males 5.19, females 3.72). This may reflect the fact that deaths in short-term ex-smokers will be classified as such in case-control studies but not necessarily in prospective studies where smoking habits are recorded at baseline and the death occurs after some years of follow-up (when the death may well be classified as occurring in a current smoker). In other words, time since quit will tend to be greater at death in subjects classified as ex-smokers in prospective studies than in subjects so classified in case-control studies.

Number of adjustment variables Risk estimates tend to reduce with increasing number of adjustment variables in females, but not in males.

Product In males, risk estimates tend to be higher than average in the relatively few estimates where the product is cigarettes only, but the reverse is true in females.

Denominator In males, risk estimates tend to be lower where the denominator is never cigarettes rather than never any product, but the reverse is true in females.

3.2.4 Current smoking of any product (vs non current) (Table A4)

189 relative risks are available from 130 studies. As expected, with the denominator now including ex-smokers as well as never smokers, relative risks are generally less than those for current smokers in Table A2. Overall estimates

are 4.01 (3.94-4.08) from the fixed-effects analysis and 3.82 (3.55-4.11) from the random-effects analysis. Interestingly random-effects estimates are higher for females (4.74, 4.21-5.34) than for males (3.32, 3.01-3.67), a difference also evident for fixed-effects estimates. This may reflect the fact that ex-smokers will form a larger proportion of the denominator for males than for females, with giving up smoking much more common in males over the last 30 years or so.

Comparing the results by level of the various factors studied with those summarized in Table A2 for current vs never smokers, a number of features are similar, including lower estimates where the lung cancer type was not all, where the studies are conducted in Asia and where the product is not cigarettes only. However, there are some differences. Thus, while the clear tendency for estimates to be higher in recent studies seen in Table A2 for both sexes is also seen in Table A4 for females, it is not seen for males. This may reflect the increasing proportion of ex-smokers in the denominator in recent years in males. Also, while Table A2 shows little difference between results for prospective and case-control studies, estimates are higher for prospective studies (males 4.23, females 5.04) than for case-control studies (males 2.99, females 4.64) in Table A4. This may reflect the greater frequency of short-term ex-smokers in case-control studies as discussed in §3.2.3.

3.2.5 Ever smoking of any product (vs never smoking) by amount (Tables A5 to A8)

The analyses in Tables A1 to A4 are all based on smoking (ever, current or ex) not by amount smoked, i.e. the risks relate to those smoking any amount. The analyses in Tables A5 to A8 are based on ever smoking by amount smoked, usually expressed as cigarette equivalents, details being given at the end of Table A5-1 or Table A5-4 in the full output.

As noted earlier in §2.5, an attempt was made to classify relative risks by amount smoked into two sets of groupings. The first scheme successfully classified almost 70% of the relative risks into three broad groups: low, which

always included 5 cigs/day; mid, which always included 20 cigs/day; and high, which always included 45 cigs/day. Other relative risks could not be classified into one of these groups (labelled "absent" in Table A5) as the relative risk related to a range which spanned two or more of the key values 5, 20 and 45 (e.g. 1-20 cigs/day would be included under absent, as would 20+ cigs/day). For both sexes, there is a very clear tendency for risk to rise with increasing amount (Tables A6-A8): males: low 3.13 (2.59-3.78), mid 6.81 (5.63-8.23), high 12.58 (10.53-15.02); females: low 2.43 (1.91-3.09), mid 4.94 (3.81-6.39), high 8.56 (5.39-13.61).

The second scheme, which used key values of 1, 10, 20, 30, 40 and 99 (equivalent to the upper range being open-ended) left a higher proportion (53%) in the "absent" category, with rather few relative risks, particularly for females, in the higher categories. There is a clear increasing trend over the first four categories but then no evidence of any further increase over the next two (males: 2.39, 5.30, 7.37, 11.05, 5.93, 12.04; females 1.82, 3.97, 5.42, 8.51, 3.10, 9.22). Note that the estimates for the fifth category are only based on two relative risks for males and one relative risk for females.

The meta-analyses in Tables A6 to A8 also compare risk by level of the various factors separately within the low, mid and high levels of scheme 1. Various conclusions can be drawn:

(i) For both sexes, estimates are generally lower for Asia than for Europe or North America, though the difference is less marked in males for the high group (Table A8);

(ii) For females at all levels, and for males in the high group, estimates for North America are higher than those for Europe;

(iii) For males, estimates are higher for prospective than for case-control studies, there being too little data for females from prospective studies to allow valid comparison;

(iv) There is no clear pattern of variation by start year of study; and

(v) There is no clear pattern of variation by number of variables adjusted for or for the exact definition of product or of denominator.

3.2.6 Current smoking of any product (vs never smoking) by amount (Tables A9 to A12)

The analyses in Tables A9 to A12 correspond to those in Tables A5 to A8 but here current smoking rather than ever smoking is the numerator, so comparison can be made to Table A2, which is based on relative risks not by amount smoked.

For both sexes, estimates rise sharply with amount smoked using the three level scheme: males: low 4.88 (4.08-5.83), mid 9.18 (7.56-11.15), high 16.22 (13.04-20.18); females: low 4.32 (3.42-5.46), mid 11.73 (9.80-14.05), high 18.06 (14.06-23.21). Using the six level scheme the rise is clear over the first four levels and then is not so smooth (males 3.91, 6.34, 9.15, 16.52, 16.07, 44.20; females 2.89, 5.38, 12.26, 18.63, 19.31, 14.78). Numbers of individual relative risk estimates available are much lower for the three higher categories than for the three lower ones.

The meta-analyses in Tables A10 to A12 also compare risk by level of the various factors separately within the low, mid and high levels. Inspection of Tables A10 to A12 allows the following conclusions:

(i) Estimates are lower in Asia than in Europe or in North America for both sexes,

(ii) Estimates are lower in North America than Europe for females, with the reverse usually true for males,

(iii) There is no clear pattern of variation by start year of study,

(iv) There is some tendency in males for estimates to be higher when they relate to cigarettes only and when the denominator is never any product rather than never cigarettes.

3.2.7 Ever smoking of any product (vs never smoking) by age (Tables A13 to A15)

Whereas Table A1 is based on relative risks covering the whole age range considered in the study (or as near as is available), Tables A13 to A15 are based on age-specific relative risks. Table A13 relates to relative risks where the upper age limit is 55 at most, Table A14 to relative risks where the age limit is not outside the range 50 to 70 and Table A15 to relative risks where the lower age limit is at least 65. Some of the random-effects estimates are compared below.

	Table A1	Table A13	Table A14	Table A15
	All ages	Age <56	Age 50-70	Age 65+
Total	5.50 (5.08-5.95)	6.76 (5.03-9.10)	6.33 (4.86-8.25)	5.77 (4.80-6.93)
Males	6.09 (5.46-6.85)	7.04 (4.90-10.11)	8.93 (6.63-12.04)	5.81 (4.27-7.91)
Females	4.45 (3.85-5.13)	6.26 (3.76-10.45)	4.18 (2.94-5.94)	6.24 (4.19-9.29)

It should be noted that for the total data (males, females and combined) the all ages estimate from Table A1 is based on 338 individual relative risk estimates, whereas from Tables A13, A14 and A15 these estimates are based on, respectively, only 37, 33 and 37.

Two impressions can be gained from the data summarized above. First, the age-specific results, overall, show a stronger association than the non age-specific results. Second, there is no very clear trend for risk estimates to vary by age.

Analyses of how risk varies by factor level (not shown) are often based on relatively few individual relative risk estimates by level. In view of the similarity of the overall estimates by age, the data in Table A1 (already discussed) seem more useful to investigate how risk varies by factor level.

3.2.8 Current smoking of any product (vs never smoking) by age (Tables A16 to A18)

Comparing the random-effects estimates in Table A2 with those in Tables A16 to A18 we have

	Table A2	Table A16	Table A17	Table A18
	All ages	Age <56	Age 50-70	Age 65+
Estimates combined	194	24	23	25
Total	8.58(7.78-9.47)	6.84(4.83-9.67)	10.40(7.96-13.58)	10.10(7.91-12.91)
Males	9.16(8.00-10.49)	5.69(3.52-9.20)	12.84(9.28-17.77)	8.68(5.92-12.74)
Females	6.95(5.82-8.30)	10.27(7.26-14.52)	6.72(3.82-11.81)	11.80(9.05-15.37)

As for the data for ever smoking, there is no very clear evidence of variation with relative risk by age.

3.2.9 Conclusions from meta-analyses of data for smoking of any product

The results from the meta-analyses presented in Tables A1 to A18 allow a number of very clear conclusions to be made:

(i) There is a strong association between smoking and risk of lung cancer,

(ii) The association is stronger for current than for ex smoking,

(iii) The association with current smoking is stronger when comparisons are made with never smokers than with nonsmokers (i.e. never and ex smokers combined),

(iv) The association is stronger the more cigarettes are smoked,

(v) The association is stronger in North American and European populations than in Asian populations,

(vi) The association is little affected by adjustment for increasing number of potential confounding variables,

(vii) The association is similarly evident in different age groups,

(viii) The association is clearly seen in both prospective and case-control studies.

All these conclusions are unsurprising and consistent with those of many reviewers (albeit not based on so much evidence).

Though, as discussed in the preceding sections, some of the analyses show variations in relative risk by other aspects of study location, by when the study was started, by study type and by aspects of the definition of the numerator and denominator of the relative risk, there are difficulties in interpreting these findings for reasons already noted in §2.4 and 2.7. Results of some multivariate analyses, which may provide greater insight, are shown in the following subsections of §3.2.

3.2.10 Additional insights from weighted multiple regression analyses

Limited multiple regression analyses have been carried out based on the data for ever smoking (as in Table A1) and current smoking (Table A2). To simplify the modelling attention was restricted to studies where the start year was known, to case-control and prospective studies, to studies conducted in North America, Europe and Asia and to estimates for males and females (not combined). Detailed results of the fitted models are included in Appendix N (for ever smoking) and Appendix O (for current smoking).

Ever smoking of any product

The restriction results in 265 adjusted relative risks being available for analysis. Models were first fitted to the overall data, in which continent, start year of study, study type and sex were included in turn in the model. Before any of these factors were included in the model, the deviance was 35554.1 on 264 d.f. Including continent massively reduced the deviance, to 1967.3 on 261 d.f., explaining 94.5% of the total deviance. Including start year of study also had a marked effect, reducing the deviance to 1532.5 on 257 d.f. Study type had a smaller but still clear effect on the deviance, reducing it by a further 42.3 on 1 d.f., as compared with a residual deviance averaging 5.8 per d.f. Incorporating sex into the model only reduced the deviance by a further 3.9 on 1 d.f. Assuming

the variability between-study is no more than expected from the binomially distributed within-study variation, this represents a marginally significant ($p<0.05$) difference. However, given the deviance of the model, 1486.2 is very much more than expected based on its degrees of freedom, 255, it is clear this assumption did not apply and that evidence of any effect of sex is unconvincing.

The final model incorporating all four factors estimated that

(i) Compared to North American studies, the relative risk for European studies is lower by a factor 0.849 and the relative risk for Asian studies is lower by a factor 0.301;

(ii) Compared to studies conducted before 1960, the relative risks for studies conducted in 1960-69, 1970-79, 1980-89 and 1990+ are higher by factors of 1.696, 1.450, 2.221 and 2.804 respectively, i.e. showing a notable tendency to have higher relative risks in more recent studies;

(iii) Prospective studies give higher relative risks than case-control studies by a factor 1.247;

(iv) Relative risks for males are higher than those for females by only a factor of 1.032.

(Note that the output in Appendix Table N gives confidence limits for these relative risks, but these are based on the false assumption that there is no significant between-study variability.)

The next five pages of the detailed output show for each estimate the study (REF), relative risk number (NRR), actual value of the logarithm of the relative risk (LOGR), fitted value, (FITV), standard error of the fitted value (SEFITV) and the standardized residual (STDRES). The output is ranked in order of the standardized residual to draw easier attention to possible outliers. Estimates which are much lower than their fitted value are as follows (back-transformed to the original relative risk scale):

Study	Location	Start year	Sex	Relative risk Actual	Fitted	Standardized Residual
MILLS	N.America	1940	M	1.33 (1.09-1.63)	4.34	-11.6
LOMBA2	N.America	1960	F	1.33 (0.96-1.83)	7.13	-10.3
TIZZAN	Europe	1959	M	1.93 (1.57-2.36)	3.68	-6.2
KREUZE	Europe	1990	F	3.78 (2.68-5.34)	10.00	-5.5

Estimates which are much higher than their fitted values are:

Study	Location	Start year	Sex	Relative risk Actual	Fitted	Standardized Residual
JUSSAW	Asia	1964	M	16.83 (11.65-25.21)	2.21	+10.3
PERNU	Europe	1944	M	8.98 (6.92-11.53)	3.68	+6.8
BROWN2	N.America	1984	F	12.70 (11.50-13.90)	9.34	+6.4
SANKAR	Asia	1990	M	13.62 (9.00-20.62)	3.66	+6.2

It is beyond the scope of the current analyses to investigate why such unusually low or high values have arisen and to carry out additional analyses in which certain outliers are rejected or study-specific factors included.

In the next stage of the analysis the effect of adding specific additional factors to the previous model was considered. The results can be summarized as follows:

Factor included	Inclusion of factor Drop in deviance	df	Residual Deviance	df	F	p
Country in Europe	68.6	6	1408.5	247	2.01	<0.1
Country in Asia	157.2	3	1319.9	250	9.93	<0.001
Number of adjustment variables	22.5	5	1454.5	248	0.77	NS
Product definition	2.6	2	1474.5	251	0.22	NS
Denominator definition	19.0	3	1458.1	250	1.08	NS

(F = ratio of drop in deviance per df to residual deviance per df, p assumes this is distributed approximately as an F statistic)

Because of the large variation between studies, a more conservative test of significance has been used. This showed clear evidence of variation in risk by country within Asia, mainly due to higher risks in India, although risks in Japan were also higher than risks in China. There was also some evidence of variation in risk by country within Europe, with estimates higher in the UK and Scandinavia than in Germany particularly, though also than in other countries.

The next stage of the analysis was to run similar analyses separately for subsets of the data.

For **North American** studies, there is a massive effect of year of study with relative risks (in the model including sex and study type also) higher by a factor 1.65, 1.45, 2.63 and 4.31 for studies conducted in 1960-69, 1970-79, 1980-89 and 1990+ as compared to studies conducted before 1960 and a clear effect of study type (RR higher by 1.28 for prospective studies) but no effect of sex.

For **European** studies, there is also a massive effect of year of study, with relative risks higher by a factor 1.27, 1.43, 2.12 and 2.14 for studies conducted in 1960-69, 1970-79, 1980-89 and 1990+ as compared to studies conducted before 1960, and an effect of sex (relative risks for males higher by a factor 1.67 than those for females) but no real effect of study type. There is also some evidence of an effect of variation by country within Europe, and of variation by definition of product (higher relative risks for all/unspecified and cigarettes only than for cigarettes $\pm$ others) and of denominator (lower relative risks where it was never cigarettes).

For **Asian** studies, there is a large effect of year of study, but the pattern is erratic, with relative risks high for studies conducted in 1960-69 and 1990+ and low for studies conducted in 1970-1979 and 1980-1989. There is also the tendency noted for risks to vary by country within Asia.

When results are considered separately for **males**, there is clear evidence that relative risks are lower in Asia, higher in more recent studies and somewhat higher from prospective studies. There is also evidence of variation within Europe and within Asia. Estimates are very similar for North America and Europe.

When results are considered separately for **females**, there are some differences. Notably relative risks are lower for Europe than for North America, by a factor 0.628, and there is no real evidence of an effect of study type.

Current smoking of any product

The analyses involved 159 data points. In the first set of analyses, continent has a huge effect, on its own explaining 96% of the total deviance of 24920.5. The deviance drops further, by 195.3 from 982.6 to 787.4 on introducing start year of study and further improvements of 14.1 and 39.4 respectively are made by introducing study type and sex. Bearing in mind the extra-binomial variation, the effect of study type is not clearly significant, the p-value associated with the F statistic being 0.1, but the effect of sex is significant ($p<0.01$). From the model including all four factors, the relative risk in European studies is 0.581 times lower than that in North American studies, while that in Asian studies is 0.279 times lower. Compared to studies starting before 1960, the relative risks are higher by factors of 1.75, 1.58, 2.00 and 3.10 for studies conducted in, respectively, 1960-1969, 1970-1979, 1980-1989 and 1990+. Studies in males have relative risks higher by a factor of 1.20 than studies in females.

The listing for potential outliers showed less extreme values than was the case for ever smoking, the most notable being the low relative risk of 1.90 for the TIZZAN study in males, with a standardized residual of –7.31 and the high relative risk of 10.67 for the LUBIN2 study in males with a standardized residual of +6.01.

Bearing in mind the extra-binomial variation, no clear evidence of an effect is seen for any of the additional factors studied (country in Europe, country in Asia, number of adjustment variables, definition of product or definition of denominator).

For **North American** studies, there is again a clear effect of year of study, and some indication ($p<0.1$) of higher risks in prospective studies, but no effect of sex or any other factor.

For **European** studies, there is again a clear effect of year of study but the increased risk in prospective studies is less significant still. There is, however, evidence that relative risks are higher in males, by a factor 1.64, than in females. Bearing in mind the extra-binomial variation, the only other factor showing up as significant ($p<0.01$) is the fact that relative risks are higher if the denominator is "never anything" than if it is "never cigarettes".

For **Asian** studies, year of study has a clear effect but the pattern is not towards an increase in relative risk in the more recent studies. There is also clear evidence that relative risks are higher in males than in females. Interestingly, once year of study and sex were in the model (and also study type, which had no effect), the deviance reduced to 30.0 on 20 d.f. which is only slightly above that predicted by binomial variation ($p<0.1$).

For **females**, continent and year of study are the only significant factors, but for **males**, there is some evidence that relative risks are higher in prospective studies ($p<0.05$), but other factors are not significant (at $p<0.05$) when extra-binomial variation is accounted for.

The analyses confirm the independent relationships of location and of time of study to the relative risk and in some analyses show an effect of study type and sex. More detailed analyses could consider the apparent outliers and introduce other factors of potential importance into the modeling. The analyses presented here should be taken as illustrative of the sort of approach that can be taken, rather than being any sort of full analysis.

3.3 Smoking of cigarettes (Tables B1 to B18)

Tables B1 to B18 correspond to Tables A1 to A18 with the only difference being that the order of preference for the numerator of the relative risk is:

1 = cigarettes regardless of other products

2 = cigarettes only

3 = all/unspecified

In practice, the revised order of preference only made any difference at all to the relative risk estimate chosen, as compared to that used for smoking of any product, in a relatively small proportion of studies. For example, comparing the 194 estimates used for current smoking in Table B2 with those used in Table A2, only 36 (18.6%) differed. Not surprisingly overall estimates in Tables B1 to B18 tend not to differ much from the corresponding data in Tables A1 to A18 and the pattern of variation by level of the factors studied tends to be essentially the same as reported in §3.2. Accordingly we merely summarize the major (adjusted) estimates and do not discuss variation by level of the factors studied.

		Overall fixed-effects	Overall random-effects	Males random-effects	Females random-effects
B1	Ever	4.74 (4.67-4.80)	5.49 (5.10-5.92)	6.08 (5.52-6.71)	4.44 (3.85-5.13)
B2	Current	9.57 (9.35-9.80)	8.81 (7.99-9.71)	9.45 (8.28-10.79)	7.01 (5.86-8.38)
B3	Ex	5.70 (5.54-5.86)	4.25 (3.87-4.66)	4.45 (3.94-5.03)	3.47 (2.88-4.17)
B4	Current (vs non)	4.09 (4.02-4.16)	3.89 (3.62-4.18)	3.44 (3.12-3.80)	4.74 (4.21-5.35)
B6	Ever “low”	2.73 (2.65-2.82)	2.78 (2.43-3.19)	3.13 (2.59-3.78)	2.43 (1.91-3.09)
B7	Ever “mid”	4.00 (3.89-4.11)	5.95 (5.12-6.92)	6.81 (5.64-8.24)	4.94 (3.81-6.39)
B8	Ever “high”	7.93 (7.68-8.18)	11.17 (9.55-13.07)	12.67 (10.59-15.15)	8.56 (5.39-13.61)
B10	Current “low”	5.10 (4.87-5.34)	4.95 (4.35-5.62)	5.02 (4.20-6.00)	4.41 (3.49-5.59)
B11	Current “mid”	11.94 (11.45-12.45)	10.34 (9.09-11.75)	9.30 (7.66-11.29)	11.73 (9.80-14.05)
B12	Current “high”	21.25 (20.18-22.38)	17.80 (15.30-20.71)	16.31 (13.12-20.26)	18.06 (14.06-23.21)
B13	Ever Age <56	6.19 (5.47-7.01)	6.86 (5.09-9.25)	7.22 (5.01-10.41)	6.25 (3.75-10.44)
B14	Ever Age 50-70	6.31 (5.71-6.96)	6.48 (4.99-8.42)	9.32 (7.12-12.20)	4.20 (2.95-5.98)
B15	Ever Age 65+	2.89 (2.78-3.01)	6.03 (5.01-7.27)	6.29 (4.59-8.63)	6.24 (4.19-9.29)
B16	Current Age <56	8.58 (7.44-9.91)	7.01 (4.92-10.00)	5.70 (3.52-9.24)	10.38 (6.96-15.47)
B17	Current Age 50-70	12.75 (11.70-13.90)	11.06 (8.47-14.43)	13.22 (9.40-18.59)	6.84 (3.93-11.89)
B18	Current Age 65+	11.41 (10.35-12.57)	10.43 (8.30-13.11)	9.16 (6.42-13.06)	11.80 (9.05-15.37)

3.4 Smoking of cigarettes only (Tables C1 to C18)

Whereas Tables A1 to A18 and B1 to B18 allowed the inclusion in the numerator of smokers of products other than cigarettes, Tables C1 to C18 are restricted to estimates specifically for smokers of cigarettes only. Otherwise the preferences and layout of the tables are exactly the same. The restriction substantially reduces the number of relative risks available for study.

3.4.1 Ever smoking of cigarettes only (vs never smoking) (Table C1)

55 adjusted relative risks are available from 44 studies. Although there is extremely highly significant heterogeneity between the estimates (χ = 1208.5 on 54 d.f.) there is great consistency in that all the estimates are greater than 1.0. The lowest is 1.26 (MCCONN combined sexes) and the highest 53.81 (ABELIN males). The overall risk estimate is 4.38 (4.29-4.48) from the fixed-effects analysis and 6.46 (5.43-7.68) from the random-effects analysis. Random-effects estimates are higher for males (7.86, 6.31-9.79, n = 41) than for females (3.84, 3.23-4.58, n = 12) or sexes combined (3.57, 0.43-29.77, n = 2).

In view of the relatively small number of estimates for females, investigation of heterogeneity (though analysed for females) will only be discussed for males. Estimates were substantially higher for North America (8.45, n = 16) and Europe (8.79, n = 18) than for Asia (3.23, n = 4), with the two estimates from South America relatively high (13.8, 19.3). Within Europe estimates by country varied between 7.13 and 12.48. Estimates did not show any marked pattern by start year of study or study type but reduced somewhat with increasing number of adjustment variables (0-9.51; 1-7.76; 2-6.15). Cigarette type was “all/unspecified” and the denominator “never any” for nearly all the estimates, so variation by levels of these factors cannot usefully be studied.

3.4.2 Current smoking of cigarettes only (vs never smoking) (Table C2)

There are 38 adjusted relative risk estimates from 27 studies, of which the minimum is 3.58 (CPS I females) and the maximum 62.29 (BOUCOT males).

The overall estimate is 9.28 (8.84-9.74) from fixed-effects analysis and 9.75 (8.09-11.76) from random-effects analysis. Random-effects estimates are lower for females (6.00, 4.56-7.90, n = 12) than for males (11.81, 10.34-13.50, n = 25) or sexes combined (15.14, 5.53-41.44, n = 1). Estimates are virtually restricted to North America, UK and Scandinavia.

Within males, estimates are somewhat lower in Scandinavia (7.64) than in UK (11.75) or North America (13.26). Estimates reduce with increasing numbers of adjustment variables, but do not vary clearly by study type or by start year of study.

3.4.3 Ex-smoking of cigarettes only (vs never smoking) (Table C3)

23 relative risks are available from 18 studies. The overall estimates of 4.37 (4.07-4.70) from fixed-effects analysis and 4.28 (3.35-5.46) from random-effects analysis are clearly lower than those for current smoking in Table C2. Random-effects estimates are lower for females (1.81, 1.07-3.07, n = 7) than for males (5.43, 4.30-6.84, n = 16).

In males random-effects estimates are somewhat lower for Europe (4.25, n = 4) than for North America (6.19, n = 11), the only two continents with data apart from one estimate for South America (10.18). Estimates are somewhat lower for prospective studies (4.73) than for case-control studies (6.19) and also tend to decrease with increasing number of adjustment variables. No clear pattern of risk by start year of study is seen.

3.4.4 Current smoking of cigarettes only (vs non current) (Table C4)

29 relative risks are available from 20 studies. The overall estimate is 4.22 (4.07-4.38) from fixed-effects analysis and 4.61 (3.97-5.35) from random-effects analysis. Here estimates are higher for females (5.95, 4.25-8.33, n = 10) than for males (4.32, 3.60-5.18, n = 18). The most notable finding seen in the

analysis by factor level is the higher estimate in males for prospective studies (5.36) than for case-control studies (3.22).

3.4.5 Ever smoking of cigarettes only (vs never smoking) by amount (Tables C5 to C8)

There are a total of 59 estimates by amount, of which 43 can be classified successfully into scheme 1 with key values of 5, 20 and 45. The relative risks show a clearly increasing trend with estimates of, respectively, 2.17 (2.09-2.26), 3.65 (3.54-3.76) and 7.31 (7.07-7.57) from fixed-effects analysis and 2.60 (1.88-3.60), 5.70 (3.88-8.36) and 11.02 (8.05-15.09) from random-effects analysis. Using scheme 2 proved to be not very helpful, as 38 of the 59 estimates could not be classified and only two were in the top three levels. The evidence of a trend is strengthened by noting that, in all 18 studies that provided data, risk rose monotonically with amount smoked.

The great majority of the estimates classified into scheme 1 are for males, 12/16 for key value 5, 9/11 for key value 20 and 13/16 for key value 45, where relative risks are 2.83 (1.92-4.19), 6.63 (4.26-10.32) and 13.20 (9.19-18.96) from random-effects analysis (Tables C6-C8).

Although Tables C6 to C8 include analyses by factor level the numbers of estimates are too small to detect any patterns within smoking amount group that are different from those seen in Table C1.

3.4.6 Current smoking of cigarettes only (vs never smoking) by amount (Tables C9-C12

There are a total of 81 estimates by amount, of which 52 could be classified successfully into scheme 1. The relative risks show a clearly increasing trend with estimates of 3.88 (3.53-4.26), 10.46 (9.80-11.16) and 20.93 (19.29-22.72) from fixed-effects analysis for key values of, respectively, 5, 20 and 45. The random-effects estimates of 4.20 (3.09-5.71), 10.61 (8.44-13.34) and 21.86 (17.89-26.72) are quite similar. Of the 16 estimates for the highest group, the

lowest value is 9.20 (CPS I females for 40+ cigs/day) and the highest estimates 45.52 (CPS II males for 41+ cigs/day), 161.70 (BOUCOT males for 41+ cigs/day) and 246.50 (PEZZOT males for 41+ cigs/day). This last estimate, from a study in Argentina, has a lower confidence limit of 66.69.

For males, random-effects estimates are 5.25 (3.88-7.10), 12.59 (10.03-15.79) and 24.69 (20.01-30.47) based on, respectively, 13, 9 and 11 estimates for the three amount groups. For females, they are 2.79 (1.71-4.56), 7.42 (5.10-10.80) and 15.80 (10.75-23.21) based on 9, 5 and 5 estimates.

Looking at the analyses by factor level in Tables C9 to C12, it is notable that virtually all the estimates relate to prospective studies and many are for quite old studies starting before 1960 with no evidence from Asia. No patterns of risk by factor level are seen that were not already noted for Table C2.

3.4.7 Ever smoking of cigarettes only (vs never smoking) by age (Tables C13 to C15)

Here data are quite limited and the results can be summarized as follows:

			Relative risks (95% CI)	
Sex	Age	n	Fixed-effects	Random-effects
Both	<56	6	6.18 (4.83-7.89)	6.81 (4.48-10.36)
	50-70	6	6.31 (5.45-7.31)	9.22 (4.83-17.60)
	65+	11	5.86 (5.20-6.61)	6.11 (4.01-9.33)
Males	<56	3	9.96 (6.57-15.08)	9.96 (6.57-15.08)
	50-70	4	12.47 (10.00-15.56)	12.74 (9.49-7.09)
	65+	6	9.20 (7.80-10.86)	8.57 (6.62-11.09)
Females	<56	3	4.78 (3.53-6.48)	4.78 (3.53-6.48)
	50-70	2	3.69 (3.03-4.49)	3.69 (3.03-4.49)
	65+	5	3.56 (2.99-4.23)	4.42 (2.56-7.62)

Clearly there is no obvious tendency for risks to vary by age. The data are inadequate to permit useful analysis by factor level.

3.4.8 Current smoking of cigarettes only (vs never smoking) by age (Tables C16 to C18)

Again data are quite limited. The summary results are:

			Relative risks (95% CI)	
Sex	Age	n	Fixed-effects	Random-effects
Both	<56	10	6.50 (5.30-7.98)	7.26 (4.77-11.04)
	50-70	11	7.79 (6.79-8.95)	8.62 (4.91-15.11)
	65+	14	9.26 (8.39-10.23)	9.34 (6.21-14.06)
Males	<56	6	7.65 (5.75-10.16)	8.38 (4.18-16.81)
	50-70	7	15.47 (12.69-18.85)	13.40 (8.34-21.52)
	65+	9	13.30 (11.80-15.00)	12.03 (8.84-16.37)
Females	<56	4	5.46 (4.07-7.34)	5.46 (4.07-7.34)
	50-70	4	4.08 (3.36-4.94)	4.08 (3.36-4.94)
	65+	5	4.19 (3.51-5.00)	5.81 (3.16-10.67)

While there is some tendency for risks to rise with age in males, this is not very clear, and not evident in females.

3.4.9 Conclusions from meta-analyses of data for smoking cigarettes only

Although the number of relative risks for smoking of cigarettes only is much more limited than that for any product, the conclusions to be drawn are broadly the same in many respects. Thus it is clearly evident that associations are stronger for current than ex-smoking, are dose-related and are weaker in Asia than in Europe or North America. The strength of the associations with cigarette only smoking and with any product are not notably different, partly because many of the relative risks included in the any product analyses would in fact be for a group who smoked all or virtually all cigarettes. The cigarette only analyses are of more value for direct comparison with the estimates for pipe only and cigar only in §3.6.

3.5 Type of cigarette (Tables D1 to D5)

All of tables D1 to D5 relate to the smoking of cigarettes, with the order of preference

1 = cigarettes regardless of other products

2 = cigarettes only,

though the actual ordering is not crucial as only study ALDERS has data classified under both these headings.

They also have the same order of preference for smoking status:

1 = ever

2 = current.

(though this only affects the MATOS study)

They are also all concerned with results not by amount smoked, as data on cigarette type by amount smoked are very sparse and have not yet been analyzed.

Unlike the previous tables described in §3.2 to 3.4, both numerator and denominator relate to smokers, with the tables varying as follows:

Table D1	:	Filter (only)	vs.	Plain (only)
Table D2	:	Filter (ever)	vs.	Plain (only)
Table D3	:	Filter (only)	vs.	Plain (ever)
Table D4	:	Handrolled	vs.	Manufactured
Table D5	:	Menthol	vs.	Nonmenthol

The preferences for CIGTYP (numerator) and DENOM (denominator) are described in the subsections that follow.

3.5.1 Filter cigarettes (only) vs. plain cigarettes (only) (Table D1)

In a number of studies risks are compared in three groups:

1 = filter cigarettes only

2 = mixed filter and plain cigarettes

3 = plain cigarettes only,

where filter and plain cigarette smoking relates to lifetime smoking experience (or in some studies to current smoking or to smoking in a shorter period). Where the data are presented in this way, relative risks (with CI) have been entered for various comparisons including three of major interest: 1 vs. 3 (filter only vs. plain only); 1+2 vs. 3 (filter ever vs. plain only) and 1 vs. 2+3 (filter only vs. plain ever). Results for the first of these comparisons are analysed in Table D1 with results for the other two comparisons being analysed in Tables D2 and D3.

In practice, the data provided are often only given in two groups, and those not always clearly defined, so exact correspondence with these classifications is not possible. The results in Table D2 give the comparison for the most extreme categories available, corresponding to a great extent to analyses we published elsewhere (Lee, 2001). They use the following preference list for the numerator:

1 = filter only (or filter NOS)

2 = always filter cigarettes

3 = mainly filter cigarettes (as opposed to plain cigarettes)

4 = both filter and plain cigarettes

5 = equally filter and plain cigarettes

6 = ever filter cigarettes

and for the denominator:

1 = plain only (or plain NOS)

2 = always plain cigarettes

3 = mainly plain cigarettes (as opposed to filter cigarettes)

4 = ever plain cigarettes

There are 42 relative risks from 31 studies. These relate to the following comparisons:

Comparison			Estimates
Only filter	vs	Plain only (or NOS)	17
Only filter	vs	Always plain	8
Only filter	vs	Mainly plain	1
Only filter	vs	Ever plain	2
Always filter	vs	Always plain	3
Always filter	vs	Ever plain	3
Mainly filter	vs	Mainly plain	1
Ever filter	vs	Always plain	7

25 of the estimates are for males, 15 for females and 2 for sexes combined.

Overall risk is highly significantly ($p<0.001$) lower in filter cigarette smokers, with the relative risk 0.67 (0.63-0.71) from fixed-effects analysis and 0.69 (0.61-0.78) from random-effects analysis. 14 of the 42 individual relative risk estimates are significantly below 1.0 and none significantly above 1.0. Based on random-effects analysis, the reduction is slightly greater for males (0.67, 0.56-0.79) than for females (0.73, 0.62-0.86). An additional five estimates are not included in the analysis because no CI are available. All are below 1.0, consistent with the evidence of an advantage to filter cigarettes.

There is highly significant ($p<0.001$) heterogeneity between the estimates for males (chisquared = 108.44 on 24 df, $p<0.001$) but not for females (chisquared = 16.47 on 15 df, NS).

In males, there is evidence of a reduced risk in North America (0.72, 0.52-1.00, n = 6), Europe (0.69, 0.55-0.87, n = 12), Asia (0.51, 0.26-0.98, n = 4) and South/Central America (0.62, 0.29-1.33). All the estimates by country within Asia and Europe are below 1.0. Though the overall heterogeneity cannot be clearly explained, based on the factors studied, the advantage to filter cigarettes

tends to be greater in studies conducted in 1980-89, in case-control studies and for estimates based on ever rather than current smokers.

3.5.2 Filter cigarettes (ever) vs. plain cigarettes (only) (Table D2)

Here, compared to Table D1, the order of preference for filter cigarette smoking is reversed, but that for plain cigarettes remains the same.

There are again 42 relative risks from 31 studies (as changing the sequencing of preferencing will, except in unusual circumstances, not change the number of estimates). These relate to the following comparisons:

Comparison		Estimates
Ever filter	vs. Plain only/NOS	1
Ever filter	vs. Always plain	20
Always filter	vs. Ever plain	3
Mainly filter	vs. Mainly plain	1
Only filter	vs. Plain only/NOS	14
Only filter	vs. Mainly plain	1
Only filter	vs. Ever plain	2

The overall risk is highly significantly ($p<0.001$) lower in filter cigarette smokers, with the relative risk 0.79 (0.75-0.83) from fixed-effects analysis and 0.73 (0.65-0.82) from random-effects analysis. 14 of the 42 individual relative risk estimates are significantly below 1.0 and none significantly above 1.0. Based on random-effects analysis the reduction is somewhat clearer for males (0.70, 0.60-0.82) than for females (0.79, 0.68-0.93). An additional six estimates are not included in the analysis because no CI are available. Five of these are less than 1.0, consistent with the other evidence.

There is highly significant heterogeneity between the estimates for males (chisquared = 122.58 on 24 df, $p<0.001$) but not for females (chisquared = 17.81 on 14 df, NS).

In males, there is evidence of a reduced risk in North America (0.73, 0.53-1.01), Europe (0.76, 0.63-0.92) and Asia (0.53, 0.29-0.97), with all the estimates below 1.0 by country within Europe and Asia. There is no clear explanation of why the estimates are heterogeneous in males, based on the factors studied, though the estimated advantage to filter cigarettes tends to be greater in studies conducted in 1980-89, in case-control studies and for estimates based on ever rather than current smokers. It should be noted that almost half of the weight for the 25 estimates for males comes from the large multicentre LUBIN2 study which did not report a significant reduction in risk in filter cigarette smokers, with the relative risk 0.95 (0.87-1.04).

3.5.3 Filter cigarettes (only) vs. plain cigarettes (ever) (Table D3)

Compared with Table D2, the order of preference for both numerator and denominator is reversed.

Again there are 42 relative risks from 31 studies, this time relating to the following comparisons:

Comparison		Estimates
Only filter	vs. Ever plain	11
Only filter	vs. Mainly plain	1
Only filter	vs. Plain only/NOS	16
Always filter	vs. Ever plain	6
Mainly filter	vs. Mainly plain	1
Ever filter	vs. Always plain	7

The advantage to filter cigarettes is rather greater in these analyses than in those in Table D2, with the relative risk 0.67 (0.63-0.70) from fixed-effects analysis and 0.69 (0.62-0.77) from random-effects analysis. 16 of the 42 individual risk estimates are significantly below 1.0 and none significantly above 1.0. The advantage is similar in both sexes (males 0.69, 0.59-0.81; females 0.70,

0.59-0.82) though heterogeneity is much greater for males (chisquared = 107.9 on 24 df, $p<0.001$) than for females (chisquared = 22.6 on 14 df, $p<0.1$).

In both sexes, the advantage to filter cigarettes is similarly evident by continent, though within Europe the advantage seemed less evident in UK (males 0.79, females 0.76) and Scandinavia (males 0.81, females 0.75) than in the multicountry study (males 0.48, females 0.43), Germany (males 0.41, no data for females) or other western countries (males 0.70, females 0.22). However there are few estimates for some countries.

In males the estimated advantage to filter cigarettes appears more evident in studies conducted in 1980-89, in case-control studies and for estimates based on ever rather than current smokers, as was so for Table D1 and Table D2. As for Table D2, the estimate from LUBIN2 carried the greatest weight in the analysis for males, but here the relative risk (0.48, 0.41-0.55) showed a large advantage to filter cigarettes. As compared to the previous estimate, which was for "ever filter" vs. "always plain," the present estimate for LUBIN2 is for "only filter" vs. "ever plain."

Although there is unexplained heterogeneity of the results for males in Tables D1, D2 and D3, the analyses consistently show an advantage to filter cigarette smokers. It is only the magnitude of the advantage that seems open to question.

3.5.4 Handrolled vs. manufactured cigarettes (Table D4)

Here the numerator relates to handrolled cigarette smoking with the order of preference:

1 = any smoking of handrolled

2 = both (i.e. handrolled and manufactured)

3 = mainly handrolled (as opposed to manufactured)

4 = only handrolled.

The denominator relates to manufactured cigarette smoking with the order of preference:

1 = only ever manufactured

2 = only currently manufactured

3 = any manufactured

4 = ever manufactured.

There are 20 relative risk estimates from 15 studies. These relate to the following comparisons:

Comparison		Estimates
Both manufactured and handrolled	vs. only manufactured	11
Only handrolled	vs. only manufactured (or only manufactured currently)	7
Any handrolled	vs. only manufactured	2

11 of the estimates are for males, 4 for females and 4 for sexes combined.

The overall risk is highly significantly ($p<0.001$) increased in the handrolled smokers, with the relative risk 1.29 (1.17-1.42) from fixed-effects analysis and 1.31 (1.14-1.52) from random-effects analysis. Based on random-effects analysis there is an increased risk in males (1.33, 1.16-1.53) and in sexes combined (1.51, 0.97-2.34) but not in females (0.92, 0.49-1.71). Within males, increases are evident in both Europe (1.22, 1.00-1.48) and Asia (1.49, 1.21-1.84), the two continents with five estimates each. The data are not adequate to allow very reliable investigation of how risk varied by country within continent, but significant increases are noted in UK (1.54, 1.21-1.96, n = 2 studies), India (1.60, 1.09-2.33, n = 2) and in Hong Kong and Singapore (1.52, 0.03-2.24, n = 2). There is no obvious variation in risk by start year of study, study type, number of adjustment variables, or aspects of definition of the comparison made.

3.5.5 Mentholated vs. non mentholated cigarettes (Table D5)

Here the comparison is between those who have ever smoked menthol and those who smoke regular cigarettes but have never smoked menthol.

Only three studies provide data, all from the USA where smoking of menthol cigarettes is relatively popular. All three studies provide results for both males and females. Based on the combined data, the fixed-effects estimate is 0.99 (0.86-1.14) and the random-effects estimate is 0.98 (0.80-1.20). There is some evidence of heterogeneity between the six estimates (Chisquared = 9.47 on 5 df, $p<0.1$). This appears to be due to variation between sexes. For males, where the individual risk estimate from the KAISE2 study is significantly above 1.0 (1.45, 1.03-2.02), the combined estimate is also above 1.0 (1.15, 0.93-1.43), though not significant. For females, where all three estimates are below 1.0, the combined estimate (0.78, 0.63-0.98) shows a significant reduction in risk for smokers of mentholated cigarettes. The data are insufficient to explore other sources of variation.

3.5.6 Conclusions from meta-analyses for type of cigarette

The results for the meta-analyses presented in Tables D1 to D5 allow a number of conclusions to be made:

(i) The smoking of filter cigarettes is associated with a significantly smaller risk of lung cancer than is the smoking of plain cigarettes. The association is evident regardless of the precise comparison made and can be seen in all subsets of the data investigated.

(ii) The smoking of handrolled cigarettes is associated with a significantly larger risk of lung cancer than is the smoking of manufactured cigarettes. There is no obvious variation in the relative risk by location or timing of the study or by other factors studied. Although the association is not significant in females, the estimate has relatively wide CI and is not inconsistent with the estimate for males.

(iii) The evidence on mentholated cigarettes is limited, being based on only three studies. The combined data suggest a slightly lower risk for mentholated vs non mentholated cigarettes in females, but not in males.

3.6 Pipes and cigars

Tables E1 to E15 relate to the smoking of pipes and/or cigars (and not cigarettes), with never smoked anything as the denominator. Tables E1 to E5 relate to the smoking of pipes and/or cigars (and not cigarettes), Tables E6 to E10 to the smoking of pipes only and Tables E11 to E15 to the smoking of cigars only. Within each block of five tables, the first relates to ever smoking, the second to current smoking and the third to ex smoking, all not by amount smoked, while the fourth relates to ever smoking by amount and the fifth to current smoking by amount. Most of the estimates relate to males and virtually all are from North American or European studies. All the estimates relate to overall lung cancer risk. Unlike Tables A-C, analyses by factor are presented for sexes combined, rather than separately.

Note that for pipe and cigar smoking different schemes were used for the dose-response analysis. The first simply considered the lowest and highest categories, using key values 1 and 99. The second used three levels, using key values 1, 10 and 99. The different definitions of a "cigarette equivalent" may lead to lack of comparability between studies.

3.6.1 Pipes and/or cigars (Tables E1 to E5)

For ever smoking (not by amount) there are 38 estimates from 35 studies analyzed in Table E1. All but two are above 1.0 and the overall estimates are 3.46 (3.20-3.73) from fixed-effects analysis and 2.92 (2.38-3.57) from random-effects analysis. Of the 38 estimates, 34 are for males and two are for sexes combined (which will predominantly involve males, as females rarely smoke pipes and/or cigars). The two estimates for females are high, but based on extremely small numbers of exposed cases. Estimates are higher from European

studies (4.59) than from North American studies (2.25). Although there are few studies in any country within Europe, there appears to be considerable variation in the estimates – for example, compare the four estimates for the UK, 2.15, 3.13, 3.50 and 3.82, all with an upper 95% limit of less than 9, with estimates from Scandinavia, Germany and other western countries of 4.62, 6.81, 9.14, 11.04 and 30.49, the last estimate, from the ABELIN study, having a lower 95% limit of over 7. There is some tendency for estimates to be higher in more recent studies, and in case-control studies (3.11) rather than prospective studies (2.07), but no obvious pattern of variation by number of adjustment variables.

For current smoking (Table E2) there are 27 estimates from 21 studies. All but one are above 1.0 and the overall estimates are 3.71 (3.26-4.22) from fixed-effects analysis and 4.64 (3.38-6.38) from random-effects analysis. There is considerable heterogeneity with very large estimates for males in some studies, e.g. DARBY (44.22, 13.65-143.22) and KREUZE (30.37, 14.18-65.06), but not in other large studies, e.g. DORN (1.70, 1.21-2.37) and LUBIN2 (4.05, 3.18-5.16). Five of the 27 estimates are for females and provide an overall estimate of 10.64 (5.50-20.58) which is higher than that for males, 4.27 (3.08-5.93). Estimates are higher for Europe (6.33) than for North America (2.64), but there is no clear pattern of a difference by country within Europe, start year of study, study type or number of adjustment variables.

For ex-smoking (Table E3) there are eight estimates from eight studies, all for males. They are statistically homogeneous, with an overall estimate of 2.00 (1.51-2.66) based on individual values varying only from 1.46 to 3.29.

Only one study, WYNDE7, gives information on risk by amount smoked for ever smokers of pipes and/or cigars (Table E4). A dose-response is evident with the relative risks, 1.23, 2.75 and 4.10 for 1-4, 5-9 and 10+ cigarette equivalents.

Only two studies, WYNDE7 and DOLL2, give information on risk by amount smoked for current smokers of pipes and/or cigars (Table E5). Both studies show some dose-response relationship.

3.6.2 Pipes only (Tables E6 to E10)

For ever smoking of pipes only (not by amount) there are 24 estimates from 23 studies (Table E6). All but one are above 1.0 and the overall estimates are 3.24 (2.85-3.67) from fixed-effects analysis and 3.12 (2.35-4.13) from random-effects analysis. Virtually all the information relates to males, the only estimate for females (from the PERNU study in Finland) having huge confidence limits. Overall risks are higher from European studies (3.99 from 13 estimates) than from North American studies (2.03 from eight estimates). There is some indication that estimates are higher in Scandinavian studies. Note that the single estimate from Asia (3.00), for the XIANGZ study, relates to the smoking of bamboo, water or long stem pipes. Other factors do not clearly explain the heterogeneity between studies.

For current smoking of pipes only there are 12 estimates from 12 studies (Table E7), giving overall estimates of 5.28 (4.55-6.13) from fixed-effects analysis and 5.20 (3.50-7.73) from random-effects analysis. Most of the estimates are for European populations, where relative risks tend to be higher than for the two estimates from North America (DORN 2.14, WYNDE7 1.86). Estimates for males tend to be lower from the UK (2.15 and 4.52) than from Scandinavia (4.10, 7.20, 8.30, 9.16 and 10.20) or multicountry studies (5.85 and 12.50), though the single estimate for the sexes combined is from the UK, and high (12.30), though with wide CI (1.64-92.33).

For ex-smoking of pipes only there are five estimates from five studies (Table E8), all in males, giving overall estimates of 3.32 (2.42-4.55) from fixed-effects analysis and 2.69 (1.53-4.72) from random-effects analysis. Again estimates are lower from North America (1.44) than from Europe (3.67).

Dose-response data for ever smoking of pipes only (Table E9) is available for analysis from five studies, two of which (BEST, LUBIN2) show no obvious pattern, whereas the remaining three (BOFFET, DAMBER, DOLL) do appear to. One further study (SADOWS) presents relative risks without CI that indicate a weak dose-response and one (WYNDE7) presents a single amount-specific result.

Dose-response data for current smoking of pipes only (Table E10) is available for three studies. Two of the three studies give some evidence of an increase in risk with increasing consumption (CEDERL, DORN), but the other does not (DEAN3), and it is unclear whether the overall data show a significant dose-response relationship.

3.6.3. Cigars only (Tables E11 to E15)

For ever smoking of cigars only (Table E11) there are 15 estimates from 15 studies, all for males. Note that for the BOFFET study the estimates relate to the smoking of cigars and/or cigarillos. Results are also available for cigars and cigarillos separately but are not on the database as yet. All but one are above 1.0 and the overall estimates are 2.73 (2.32-3.21) from fixed-effects analysis and 2.95 (1.91-4.56) from random-effects analysis. Overall estimates are higher for Europe (4.75 based on six estimates) than for North America (2.05 based on eight estimates). Within Europe there is no clear pattern – note that here there are no data for the UK. There appears to be some trend towards an increase in risk with start year of study, although this may be confounded with the early data generally being from North America. Confounding by region may also explain the lower risks in prospective studies (all North American) than in case-control studies.

For current smoking of cigars only (Table E12) there are 15 estimates from 14 studies, 13 for males, 1 for females and 1 for sexes combined. Overall estimates are 4.05 (3.61-4.54) from fixed-effects analyses and 4.67 (3.49-6.25) from random-effects analyses. Estimates are higher for Europe (6.21) than for

North America (3.11). There is some tendency for estimates to be higher in more recent studies.

For ex smoking of cigars only (Table E13) there are five estimates from five studies, all for males. Overall estimates are 3.27 (2.36-4.52) from fixed-effects analysis and 2.85 (1.45-5.61) from random-effects analysis. The highest estimate is of 7.77 (4.38-13.81) from the European multicountry study BOFFET.

Dose-response data for ever smoking of cigars only (Table E14) with confidence limits was available for three studies, all of which showed the highest risks in the highest exposure group. This was not so in the SADOWS study where relative risks of 1.62, 4.51, 4.38 and 4.24 were reported without CI for 1, 2, 3 and >3 cigars/day.

Dose-response data for current smoking of cigars only (Table E15) is available for two studies. A clear dose-response is evident in the CPSI study, but the pattern is not so clear in the DORN study, where the data are very limited for higher exposures.

3.6.4 Conclusions from meta-analyses for pipes and cigars

The results from the meta-analyses presented in Tables E1 to E15 allow a number of very clear conclusions to be made:

(i) Both pipe and cigar smoking are associated with an increased risk of lung cancer,

(ii) The association is stronger in European (particularly non UK) studies than in North American studies,

(iii) The association is stronger for current smoking than for ex-smoking, and

(iv) The associations with pipe and cigar smoking are less strong than that with cigarette smoking.

For both pipe and cigar smoking there appears to be some evidence of a dose-response relationship. However the different groupings used in the different studies makes it difficult to quantify this statistically. There seems some case for carrying out some analyses attempting to estimate (with standard errors) risk per cigar smoked or per pipe smoked in each study with relevant data so as to allow easier assessment of the overall data.

4. Results for squamous cell carcinoma

4.1 Introduction

In §3 of this report, results are presented for all lung cancer, if available, and, if not, for categories of lung cancer type that at least include both squamous cell carcinoma and adenocarcinoma. In this section, lung cancer type is selected using the following order of preference:

1 = squamous cell carcinoma

2 = squamous or small cell carcinoma

3 = squamous or undifferentiated carcinoma

4 = Kreyberg I

5 = not adenocarcinoma

Generally, the great majority (70% or more) of the relative risks selected are for the simple definition "squamous cell carcinoma," data for categories 2, 3, 5 above only being entered on the database when categories 1 or 4 were not available. It should be noted that most of the results relate to case-control studies as most prospective studies base diagnosis on death certificate which does not routinely include information on cell type.

4.2 Smoking of any product

Apart from the choice of lung cancer type, the definitions used in Tables F1 to F15 are the same as described in §3.2 for Tables A1 to A15. The structure of the tables is the same also.

4.2.1 Ever smoking of any product (vs never smoking) (Table F1)

101 adjusted relative risks are available from 73 studies. Although there is extremely highly significant heterogeneity between the estimates (χ^2 = 518.8 on 100 d.f.), the heterogeneity, on a per d.f. basis, is considerably less (5.2) than was the case for the corresponding analysis in Table A1 (22.4). All the estimates apart from two show significant increases and they are clearly higher than is the case for all lung cancer. The overall relative risk estimate is 9.43 (8.87-10.04)

from the fixed-effects analysis and 10.19 (8.65-12.01) from the random-effects analysis. Random-effects estimates are rather lower for data for females (8.80, 6.80-11.39) than for males (11.49, 9.32-14.18) or sexes combined (10.70, 4.89-23.40).

Looking at how risks vary by level of the factors studied the following comments can be made:

Lung cancer type The estimate for squamous cell carcinoma specifically is very similar for males (10.83) and females (10.79). Estimates for other classifications tend to be higher (ranging from 14.10 to 15.54) in males and lower (ranging from 4.27 to 7.60) in females, though these are based on relatively few estimates.

Continent In males, estimates are only slightly lower from studies in Asia (9.63) than from studies in Europe (12.46) or North America (13.05). In females, estimates are actually slightly higher for Asia (6.89) than for Europe (5.17), but estimates are much higher in North America (13.94). Data from other continents are sparse and are only present for males.

Country in Europe Apart from one study in Turkey (DOSEME) which reports a relatively low risk for males of 3.60 (2.60-5.00), there is little evidence of variation in risk estimates by country within Europe for either sex.

Country in Asia For both males and females, estimates are higher for Japan (males 16.52, females 12.51) than for China (males 6.59, females 5.56). A single study in India in males has a high relative risk of 25.43 (13.87-46.63).

Start year of study In males, estimates are quite similar for all five start year groups (10.60, 11.66, 10.96, 12.46, 10.57 for <1960, 1960-1969, 1970-79, 1980-89, 1990+). In females relative risks are low in the early group (3.14) but do not

rise smoothly after than (12.83, 6.03, 10.92, 17.50), the last estimate being based on only one study.

Study type In both sexes estimates from the four prospective studies are somewhat higher than those from the case-control studies. However the prospective studies have relatively small numbers of cases and the estimates have wide variability.

Number of adjustment variables No tendency is seen for risk to vary by the number of adjustment variables considered.

Product In females estimates are higher for cigarettes +/- others (11.89) than for all/unspecified (6.39), but in males no such differences are seen (10.87 vs 11.31).

Denominator In females estimates are higher for never cigarettes (12.91) than for never anything (6.53) but in males, no such differences are seen (10.58 vs 12.64). This finding is highly correlated with the previous one in that studies which referred to smoking, regardless of what was smoked, tend to have "never anything" as the denominator and "all/unspecified" as the numerator, whereas those studies which allowed a product definition of "cigarettes +/- others" typically had "never cigarettes" as the denominator.

4.2.2. Current smoking of any product (vs never smoking) (Table F2)

Here there are 42 relative risks from 30 studies. Though the heterogeneity between the estimates (χ^2=289.2 on 41 d.f.) is significant, there is huge consistency in that all the individual estimates are significant and greater than 3.0, and the great majority are over 10.0. The overall risk estimate is 13.69 (12.68-14.78) from fixed-effects analysis and 16.41 (12.80-21.05) from random-effects analysis. The random-effects estimates are somewhat higher for males (17.43, 12.57-24.15) than for females (14.15, 9.16-21.85).

Looking at how risks vary by levels of the various factors studied, one can note:

Lung cancer type Estimates tend to be higher for Kreyberg I (males 28.68, females 19.36) than for squamous specifically (males 16.07, females 16.12). However numbers of estimates for Kreyberg I are low.

Continent In males, estimates are lower in Asia (9.30) than in Europe (19.27) or North America (21.38). In females estimates are lower in Asia (9.64) or Europe (7.84) than in North America (17.68).

Country in Europe Limited data preclude any inferences.

Country in Asia All the data are for Japan.

Start year of study No pattern is seen in males, but in females relative risks are low in the studies starting before 1960.

Study type Limited data for prospective studies show somewhat higher relative risks than for case-control studies.

Number of adjustment variables The pattern of findings is unclear and does not suggest that adjustment tends to reduce estimates.

Product/denominator No evidence of any significant variation is seen.

4.2.3 Ex-smoking of any product (vs never smoking) (Table F3)

35 relative risks are available from 26 studies. They are lower than the estimates for current smoking in Table F1, with fixed-effects analysis giving 10.05 (9.17-11.02) and random-effects analysis giving 8.24 (6.55-10.36).

Estimates are similar in males (7.92, 5.78-10.85) and females (7.57, 4.99-11.47), but this does not reflect the fact that the two largest studies give opposing results here. Thus BROWN2 has estimates which are clearly higher in females (19.20, 15.20-24.20) than in males (8.70, 7.40-10.20) while LUBIN2 has estimates which are clearly lower in females (4.70, 3.12-7.06) than in males (12.40, 9.39-16.36)

Numbers of relative risks available limit the extent to which variation by factor can be studied. In males, there is no clear evidence of variation by continent, but in females, estimates are higher for North America. In both sexes, the one relative risk estimate available for studies starting before 1960 is very low (HAMMON males 1.23; HAENSZ females 1.79) but otherwise no clear pattern is seen. Estimates tend to be higher for "cigarettes +/- other" vs "never cigarettes," than for "all/unspecified" vs "never anything."

4.2.4 Current smoking of any product (vs non current) (Table F4)

37 relative risks are available from 27 studies. Though all are greater than 1.0 and all but two are significant, the estimates, 3.61 (3.44-3.79) from fixed-effects analysis and 4.86 (3.94-5.99) from random-effects analysis, are clearly lower than in Table F1, where the denominator is never smoking. As in the corresponding table for all lung cancer types (Table A4) estimates are higher for females (6.70, 4.96-9.05) than for males (3.53, 2.90-4.29). There is considerable heterogeneity between estimates, but this cannot readily be explained by any of the factors studied, though in females there is a clear tendency (as in Table A4) for estimates to be higher in recent studies.

4.2.5 Ever smoking of any product (vs never smoking) by amount (Tables F5 to F8)

As explained in §2.5, the first table gives summary information by amount, while the next three give, respectively, results for amount classified as "low," "mid" and "high." 74% of the relative risks in Table F5 were successfully classified.

The relative risks show a clear trend by amount, overall and in each sex, with no great difference between the sexes.

	Low (F6)	Mid (F7)	High (F8)
Number of estimates	34	24	26
Overall - fixed effects	5.66 (5.10-6.28)	10.08 (8.72-11.66)	21.04 (17.92-24.69)
- random effects	4.25 (3.27-5.53)	9.91 (7.21-13.61)	22.19 (15.92-30.92)
Male - random effects	5.56 (4.13-7.49)	10.43 (6.65-16.37)	22.72 (15.33-33.68)
Female - random effects	3.48 (2.17-5.58)	9.56 (7.25-12.63)	21.10 (9.14-48.71)

The six group categorization did not prove any more useful in expressing the dose-response relationship.

Estimates do not vary much by continent within the low and mid dose relative risks, but in the high dose relative risk estimates are higher for North America (males 50.09, females 42.76) and in Asia (males 43.17, females 28.46) than in Europe (males 16.70, females 10.49). No consistent pattern of variation by year of start of study can be seen within the dose groups.

4.2.6 Current smoking of any product (vs never smoking) by amount (Tables F9 to F12)

The analysis in Tables F9 to F12 correspond to those in Tables F5 to F8 but here current smoking rather than ever smoking is the numerator. Again, the relative risks show a clear trend by amount, overall in each sex.

	Low (F10)	Mid (F11)	High (F12)
Number of estimates	8	7	12
Overall - fixed effects	9.92 (7.41-13.28)	21.57 (16.77-27.73)	49.56 (39.81-61.69)
- random effects	9.92 (7.41-13.28)	21.57 (16.77-27.73)	39.16 (23.67-64.79)
Male - random effects	11.94 (8.20-17.40)	18.53 (13.10-26.22)	48.33 (34.16-68.37)
Female - random effects	7.50 (4.73-11.90)	25.50 (17.71-36.72)	36.19 (9.06-144.51)

It is notable that for the high group, the relative risks are enormous in many of the studies, the highest relative risk estimates being 96.00 (SVENSS females), 94.40 (WU females) and 90.95 (WYNDE6 females) and five of the remaining estimates exceeding 40. A relatively low estimate for the HAENSZ study in females of 7.43 has brought the female estimate down. High estimates are seen in both sexes and in all three of the major continents. The data are insufficient to allow study of variation by factor level.

4.2.7 Ever smoking of any product (vs never smoking) by age (Tables F13 to F15)

Based on random-effects analysis, estimates are 14.73 (6.83-31.76) for age <56, 17.30 (10.78-27.74) for age 50-70 and 15.00 (6.46-34.80) for age 65+, based on respectively 10, 6 and 2 estimates. This does not suggest any material variation in relative risk by age. (Data on current smoking of any product, corresponding to Tables A16 to A18 are so sparse that analyses are not included in this report.)

4.3 Smoking of cigarettes only (Tables G1 to G12)

Note that since the results from Tables B1 to B18 were so similar to those for Tables A1 to A18, no attempt was made to run equivalent tables to B1 to B18 for squamous cell carcinoma. Tables G1 to G12 are the equivalent for squamous cell carcinoma to Tables C1 to C12 for all lung cancer. In view of the limited amount of data, analyses by age have not been run. Also analyses by factor level have not been conducted.

Overall estimates from the various analyses (mainly based on data for males) are as follows:

		Number of estimates	Relative risk (95% CI) Fixed-effects	Random-effects
G1	Ever	11	9.14 (7.93-10.54)	11.56 (7.64-17.49)
G2	Current	8	21.49 (16.73-27.61)	20.85 (14.84-29.29)
G3	Ex	3	8.73 (6.57-11.61)	6.01 (1.77-20.37)
G4	Current (vs non)	0	-	-
G6	Ever "low"	3	4.08 (2.84-5.86)	3.93 (2.18-7.10)
G7	Ever "mid"	3	12.85 (9.33-17.69)	11.56 (6.71-19.92)
G8	Ever "high"	3	19.56 (13.86-27.62)	16.79 (8.66-32.57)
G10	Current "low"	1	15.12 (4.93-46.37)	15.12 (4.93-46.37)
G11	Current "mid"	1	17.44 (6.30-48.28)	17.44 (6.30-48.28)
G12	Current "high"	2	61.43 (22.68-166.38)	61.43 (22.68-166.38)

4.4 Type of cigarette (Tables H1 to H5)

Tables H1 to H5 correspond to Tables D1 to D5 but relate to squamous cell carcinoma rather than to all lung cancer. Again results by factor level are not given due to limitations of the data.

Overall estimates from the various analyses are as follows:

		Sex	Number of estimates	Relative risk (95% CI) Fixed-effects	Random-effects
H1	Only filter vs only plain	M or F	13	0.58 (0.52-0.64)	0.52 (0.40-0.68)
		M	9	0.61 (0.55-0.68)	0.59 (0.45-0.75)
		F	4	0.38 (0.28-0.52)	0.42 (0.19-0.96)
H2	Ever filter vs only plain	M or F	11	0.85 (0.79-0.91)	0.55 (0.41-0.74)
		M	8	0.89 (0.83-0.95)	0.65 (0.50-0.85)
		F	3	0.36 (0.26-0.48)	0.41 (0.20-0.81)
H3	Only filter vs ever plain	M or F	13	0.87 (0.81-0.92)	0.69 (0.57-0.83)
		M	9	0.88 (0.82-0.94)	0.66 (0.51-0.84)
		F	4	0.74 (0.58-0.94)	0.74 (0.58-0.94)
H4	Handrolled vs manufactured	M	5	1.47 (1.24-1.76)	1.62 (1.18-2.21)
H5	Menthol vs non-menthol	M+F	1	1.04 (0.75-1.44)	1.04 (0.75-1.44)

Points to note are as follows:

(i) Every single one of the individual filter/plain relative risk estimates, whether adjusted or unadjusted, is less than 1.0 while every single one of the handrolled estimates is greater than 1.0;

(ii) for the filter/plain comparison, the reason some of the fixed-effects and random-effects estimates are so different is due to a high relative risk with large weight for the LUBIN2 study in males of 0.93 (0.86-1.00) for ever filter vs always plain. The corresponding estimate for only filter vs always plain was 0.53 (0.45-0.62), showing a much larger association with type of cigarette.

4.5 Pipes and cigars (Tables I1 to I9)

Tables I1 to I9 relate to the smoking of pipes and/or cigars (and not cigarettes) with never smoked anything as the denominator, and correspond to Tables E1-E3, E6-E8 and E11-E13. Because of the limitations of available data, no analyses are shown by factor level. There are no relevant data by amount, so no equivalents to E4-E5, E9-E10 and E14-E15 are presented.

Overall estimates from the various analyses are as follows:

		Number of estimates	Relative risk (95% CI) Fixed-effects	Random-effects
Pipe and/or cigars				
I1	Ever smoking	8	3.31 (2.35-4.66)	3.65 (1.92-6.91)
I2	Current smoking	2	5.62 (3.25-9.72)	5.62 (3.25-9.72)
I3	Ex smoking	2	2.75 (1.27-5.94)	2.75 (1.27-5.94)
Pipe only				
I4	Ever smoking	4	2.83 (1.93-4.14)	3.43 (1.84-6.41)
I5	Current smoking	1	4.64 (1.80-11.91)	4.64 (1.80-11.91)
I6	Ex smoking	1	0.97 (0.13-7.37)	0.97 (0.13-7.37)
Cigars only				
I7	Ever smoking	3	3.80 (2.63-5.49)	3.87 (2.45-6.12)
I8	Current smoking	1	7.63 (3.81-15.28)	7.63 (3.81-15.28)
I9	Ex smoking	1	3.58 (1.40-9.11)	3.58 (1.40-9.11)

Estimates for pipe and/or cigars and for cigars only tend to be somewhat higher than the estimates for all lung cancers in Tables E1 to E3 and E11 to E13. Estimates for pipe only tended to be somewhat lower than those in Tables E6 to E8.

4.6 Conclusions for squamous cell carcinoma

The main conclusion to be drawn from the analyses in §4 is that the strength of the association of squamous cell carcinoma with the smoking of any product or the smoking of cigarettes is substantially stronger than the corresponding associations for all lung cancer described in §3. For example, for current smoking of any product, the relative risk is 16.41 (2.80-21.05) for squamous cell carcinoma as against 8.58 (7.78-9.47) for any lung cancer. The heterogeneity is distinctly less for squamous cell carcinoma than for all lung cancer, mainly due to relative risks from Asian studies for squamous cell carcinoma being higher and more comparable to those seen in European and North American studies than is the case for all lung cancer. Variation in estimates by start year of study appears to be much less for squamous cell carcinoma than is the case for all lung cancer.

5. Results for adenocarcinoma

5.1 Introduction

The tables correspond to those given in §4 except that the preference for lung cancer type is:

1 = adenocarcinoma

2 = adenocarcinoma or large cell carcinoma

3 = adenocarcinoma, alveolar or bronchiolar cell carcinoma

4 = Kreyberg II

5 = not squamous or small cell carcinoma

5.2 Smoking of any product

The definitions used in Tables J1-J15 for adenocarcinoma correspond to those given in Tables F1 to F15 for squamous cell carcinoma.

5.2.1 Ever smoking of any product (vs never smoking) (Table J1)

There are 108 relative risks from 76 studies. Though there are eight relative risks above 10 (two of which, OSANN males 17.90, 10.40-31.00 and WYNDER females 13.99, 10.18-19.23, have a lower 95% confidence limit above 10.00), the great majority show a weaker association, with nine estimates below 1.0. Overall the estimates, 3.43 (3.27-3.61) from fixed-effects analysis and 2.84 (2.41-3.36) from random-effects analysis, though highly significant, show a much weaker association than is the case for squamous cell carcinoma (see Table F1). The random-effects estimates are somewhat higher for males (3.55, 2.83-4.45) than for females (2.31, 1.77-3.02).

Looking at how risks vary by level of the various factor studied the following comments can be made:

Lung cancer type The great majority (about 80%) of the estimates are for adenocarcinoma specifically, with most of the rest for Kreyberg II. Estimates

tend to be somewhat lower for Kreyberg II (males 2.92, females 1.81) than for adenocarcinoma specifically (males 3.73, females 2.55).

Continent In both sexes, estimates are higher for North America (males 5.33, females 3.65) than for Europe (males 3.00, females 1.84) and lowest for Asia (males 2.06, females 1.56).

Country in Europe There is little evidence of variation by country in Europe.

Country in Asia A single study for males in India has a high relative risk of 9.71 (5.01-18.82) but otherwise there is no marked variation.

Start year of study In both sexes there is a tendency for risk estimates to increase with year of start. For males, with estimates 2.64, 3.86, 3.02, 4.10 and 5.21 for <1960, 1960-69, 1970-79, 1980-89 and 1990+, the increase seems particularly evident.

Type of study Nearly all the studies are of case-control design and no clear difference between results from prospective and case-control studies can be seen.

Number of adjustment variables No tendency is seen for risk to vary by the number of adjustment variables considered.

Product/denominator Estimates tend to be higher in both sexes when the product is "cigarettes +/- others" and the denominator is "never cigarettes" than when the product is "all/unspecified" and the denominator is "never anything."

5.2.2 Current smoking of any product (vs never smoking) (Table J2)

There are 45 relative risks from 31 studies. Except for the male and female estimates from the TSUGAN study, all the estimates are above 1. The relative risk estimates, 4.73 (4.45-5.03) from fixed-effects analysis and 4.11

(3.25-5.20) from random-effects analysis, are higher than for ever smoking seen in Table J1, but substantially lower than the corresponding estimates for squamous cell carcinoma seen in Table F2. The random-effects estimates are somewhat higher for males (5.46, 3.98-7.49) than for females (3.14, 2.16-4.56).

Looking at how risks vary by levels of the various factors studied, one can note:

Lung cancer type Estimates tend to be higher for Kreyberg II (males 6.33, females 4.06) than for adenocarcinoma specifically (males 5.39, females 3.00). However numbers of estimates for Kreyberg II are low.

Continent In both sexes estimates are higher for North America (males 8.98, females 4.95) than for Europe (males 4.55, females 2.02) and lowest for Asia (males 2.34, females 1.50).

Country in Europe Limited data preclude any inferences.

Country in Asia All the data are for Japan.

Start year of study In males, no pattern is seen, but in females relative risks are low in the studies starting before 1960.

Study type No clear differences between results for prospective studies and case-control studies can be seen.

Number of adjustment variables The pattern of findings is unclear and does not suggest that adjustment tends to reduce estimates.

Product/denominator Estimates are higher in both sexes when the product is "cigarettes +/- other" and the denominator is "never cigarettes" than when the product is "all/unspecified" and the denominator is "never anything."

5.2.3 Ex-smoking of any product (vs never smoking) (Table J3)

36 relative risks are available from 26 studies. The overall estimate, 3.90 (3.62-4.21) from fixed-effects analysis and 2.65 (1.99-3.52) from random-effects analysis, are somewhat lower than those for current smoking in Table J2. The random-effects estimate for males (3.35, 2.32-4.85) is somewhat higher than that for females (2.14, 1.31-3.50).

Numbers of relative risks available limit the extent to which variation by factor can be studied. In both sexes estimates are higher in North America than in Asia (Japan) or Europe. In males, estimates increase with later start year of study, but in females they do not. Estimates are higher for the "cigarettes +/- others" vs "never cigarettes" comparison than for the "all/unspecified" vs "never anything" comparison.

5.2.4 Current smoking of any product (vs non-current) (Table J4)

39 relative risks are available from 28 studies. All but two are greater than 1.0 and the great majority statistically significant. The overall estimates are 2.64 (2.49-2.79) from fixed-effects analysis and 2.46 (2.07-2.92) from random-effects analysis, which are somewhat lower than in Table J1 where the denominator is never smoking. Estimates are similar for males (2.30, 1.86-2.84) and females (2.56, 1.85-3.55). In both sexes estimates are higher for North America than for Europe or Asia (Japan). There is no clear evidence of an effect of start year of study.

5.2.5 Ever smoking of any product (vs never smoking) by amount (Tables J5 to J8)

75% of the relative risks in Table J5 were successfully classified under scheme 1. The relative risks show evidence of a trend by amount overall and in

each sex. The excess risk (= relative risk –1) for a given amount is about five times lower than for the corresponding data for squamous cell carcinoma (see §4.2.5).

	Low (J6)	Mid (J7)	High (J8)
Number of estimates	32	22	24
Overall - fixed effects	2.74 (2.48-3.03)	2.73 (2.33-3.20)	5.75 (4.88-6.77)
- random effects	1.69 (1.23-2.32)	2.55 (1.97-3.30)	4.23 (2.68-6.69)
Male - random effects	1.95 (1.23-3.10)	2.80 (2.11-3.70)	4.76 (2.92-7.75)
Female - random effects	1.53 (0.94-2.48)	1.96 (0.94-4.06)	3.87 (1.17-12.80)

Relative risks tend to be highest for North American studies for the high dose data but differences between continent for the low and mid doses tend to be less clear.

5.2.6 Current smoking of any product (vs never smoking) by amount (Tables J9 to J12)

The somewhat limited data show a trend by amount, but clearly less strong than for squamous cell carcinoma (see §4.2.6).

	Low (J10)	Mid (J11)	High (J12)
Number of estimates	8	7	11
Overall - fixed effects	2.47 (1.97-3.11)	5.13 (4.28-6.15)	9.34 (7.79-11.18)
- random effects	2.32 (1.59-3.58)	3.37 (1.88-6.02)	5.71 (2.91-11.19)
Male - random effects	2.23 (1.24-3.99)	2.43 (1.06-5.57)	3.94 (1.08-14.39)
Female - random effects	2.50 (1.72-3.64)	7.40 (5.65-9.71)	7.09 (2.53-19.84)

5.2.7 Ever smoking of any product (vs never smoking) by age (Tables J13 to J15)

Based on random-effects analysis, estimates are 4.17 (1.86-9.35) for age <50, 5.31 (3.20-8.79) for age 50-70 and 1.73 (0.99-3.02) for age 65+ based on respectively 10, 4 and 2 estimates.

5.3 Smoking of cigarettes only (Tables K1 to K12)

These findings correspond to those in Tables G1 to G12 for squamous cell carcinoma. Overall estimates from the various analyses are as follows:

		Number of estimates	Relative risk (95% CI) Fixed-effects	Random-effects
K1	Ever smoking	11	1.96 (1.73-2.22)	3.15 (1.60-6.21)
K2	Current smoking	7	7.18 (5.71-9.04)	6.05 (3.69-9.92)
K3	Ex smoking	2	3.74 (2.72-5.14)	3.68 (2.56-5.30)
K4	Current (vs non)	0	-	-
K6	Ever “low”	3	2.81 (1.86-4.24)	2.81 (1.86-4.24)
K7	Ever “mid”	3	3.74 (2.48-5.63)	3.74 (2.48-5.63)
K8	Ever “high”	3	3.83 (2.48-5.91)	3.83 (2.48-5.91)
K10	Current “low”	1	1.83 (0.17-19.96)	1.83 (0.17-19.96)
K11	Current “mid”	1	2.83 (0.55-14.58)	2.83 (0.55-14.58)
K12	Current “high”	1	18.00 (1.01-320.16)	18.00 (1.01-320.16)

Note that not only are the data on amount for current smoking (K9 to K12) based on only one estimate per level, but also these estimates are hugely variable. Comparing the data with those for squamous cell carcinoma, it can be seen that, although there is a significant increase in risk of adenocarcinoma for smoking of cigarettes only, the association is clearly less strong than the estimates summarized in §4.3. There is also much less evidence of a dose-response relationship.

5.4 Type of cigarette smoked (Tables L1 to L5)

Tables L1 to L5 correspond to Tables H1 to H5 (squamous cell carcinoma) and Tables D1 to D5 (all lung cancer). Results are not given by factor level due to limitations of the data.

Overall estimates from the various analyses are as follows:

		Sex	Number of estimates	Relative risk (95% CI) Fixed-effects	Random-effects
L1	Only filter vs only plain	M or F	10	0.88 (0.75-1.03)	0.84 (0.66-1.08)
		M	7	0.91 (0.76-1.09)	0.89 (0.65-1.22)
		F	3	0.73 (0.49-1.10)	0.73 (0.49-1.10)
L2	Ever filter vs only plain	M or F	10	1.00 (0.89-1.12)	0.99 (0.84-1.16)
		M	7	1.01 (0.89-1.14)	0.99 (0.80-1.22)
		F	3	0.95 (0.67-1.34)	0.95 (0.67-1.34)
L3	Only filter vs ever plain	M or F	10	1.05 (0.93-1.18)	0.98 (0.80-1.21)
		M	7	1.09 (0.96-1.23)	1.01 (0.80-1.29)
		F	3	0.86 (0.64-1.15)	0.90 (0.60-1.35)
L4	Handrolled vs manufactured	M	4	2.12 (1.53-2.96)	2.09 (0.83-5.25)
L5	Menthol vs non-menthol	M+F	1	0.96 (0.73-1.27)	0.96 (0.73-1.27)

The advantage to filter cigarettes seen for squamous carcinoma (Tables H1 to H3) is not seen for adenocarcinoma. However, the data show no indication of an increased risk.

While the data for filter/plain are reasonably homogeneous, those for handrolled/manufactured are not, with three studies (JUSSAW 8.76, ALDERS 2.70, DESTEF 2.30) each showing statistically significant increases and one study (ENGELA 0.43) showing a statistically significant decrease.

5.5 Pipes and cigars (Tables M1 to M9)

Tables M1 to M9 correspond to Tables L1 to L9 for squamous cell carcinoma. Again there were no data by amount smoked.

Combined relative risk estimates, based on the rather sparse data available, are summarized in the table below:

		Number of estimates	Relative risk (95% CI) Fixed-effects	Random-effects
Pipe and/or cigars				
M1	Ever smoking	7	0.93 (0.62-1.40)	0.93 (0.62-1.40)
M2	Current smoking	2	0.84 (0.41-1.70)	0.84 (0.41-1.70)
M3	Ex smoking	2	1.56 (0.77-3.17)	1.56 (0.77-3.17)
Pipe only				
M4	Ever smoking	4	0.47 (0.24-0.91)	0.50 (0.23-1.10)
M5	Current smoking	1	0.40 (0.05-3.00)	0.40 (0.05-3.00)
M6	Ex smoking	1	0.51 (0.07-3.78)	0.51 (0.07-3.78)
Cigars only				
M7	Ever smoking	3	0.93 (0.48-1.82)	0.55 (0.11-2.88)
M8	Current smoking	1	0.80 (0.24-2.64)	0.80 (0.24-2.64)
M9	Ex smoking	1	1.87 (0.77-4.56)	1.87 (0.77-4.56)

The data provide no evidence of an effect of pipe or cigar smoking on the risk of adenocarcinoma. None of the individual or combined risk estimates in any analysis show a significant ($p<0.05$) increase in risk and most of the combined estimates are less than 1.0. Indeed the only statistically significant individual risk estimates show a reduction in risk. These are from the LUBIN2 West European multicentre study where the relative risk for ever smoking of pipe only was 0.27 (0.10-0.74) and that for ever smoking of cigars only was 0.09 (0.01-0.66). However there are certain inconsistencies between data presented in different tables of the source paper (Lubin et al., 1984) from which these estimates were derived, casting doubt on the validity of these estimates.

5.6 Conclusions for adenocarcinoma

The main conclusion to be drawn from the analyses in §5 is that the strength of the association of smoking is much weaker for adenocarcinoma than it is for squamous cell carcinoma. For example for current smoking of any product, the estimates are 16.41 (12.80-21.05) for squamous cell carcinoma and 4.11 (3.25-5.20) for adenocarcinoma. Indeed there is no evidence at all that adenocarcinoma is associated with the smoking of pipes or cigars. However, for the smoking of any product there is evidence of a dose-response relationship. There is no evidence to support the thesis that filter cigarette smoking increases

risk of adenocarcinoma relative to plain cigarette smoking, though the advantage to filter cigarettes seen for overall lung cancer risk and for squamous cell carcinoma is not clearly evident for adenocarcinoma. Relative risks for adenocarcinoma for smoking of any product appear to be highest in more recent studies and studies in North America.

Squamous cell carcinoma and adenocarcinoma are generally the most commonly-occurring types of lung cancer. At this stage analyses have not been conducted for other rarer types, including small cell lung cancer.

6. Conclusions

Part I of this report describes how databases were set up containing almost 10000 relative risks from almost 300 epidemiological case-control or prospective studies, each involving 100 or more lung cancer cases. Part I gives details of how the relevant studies and the source papers were identified, the structure of the databases, the methods used for entry and checking of data and derivation of relative risks, as well as summary information about the characteristics of the studies and relative risks themselves. Part I ends by describing techniques for conducting meta-analyses and the format of the tables presenting the results.

This part of the report, Part II, presents results of preliminary analyses of the database aimed at giving insight into how the relative risk of lung cancer varies by type of product smoked; nature of exposure (ever, current, ex); dose of exposure; type of lung cancer; sex; location, timing and type of study; and extent of adjustment for confounding variables. Mainly the report consists of a series of meta-analyses, but some limited results from multiple regression analysis are also included.

The main conclusions reached from the analyses are as follows:

There is a strong association between smoking and **overall risk of lung cancer**, which is present for all types of product smoked, more marked for cigarette smoking than for pipe and cigar smoking, more clearly seen in current than former smokers, and evident in both males and females. This is illustrated in the table below which summarizes relative risks and 95% confidence limits from random-effects meta-analyses.

Product	Sex	Ever smoked (vs never smoked)	Current smoker (vs never smoked)	Ex-smoker (vs never smoked)
Any product	M	6.09 (5.46-6.85)	9.16 (8.00-10.49)	4.43 (3.92-4.99)
	F	4.45 (3.85-5.13)	6.95 (5.82-8.30)	3.47 (2.88-4.17)
Cigarettes only	M	7.86 (6.31-9.79)	11.81 (10.34-13.50)	5.43 (4.30-6.84)
	F	3.84 (3.23-4.58)	6.00 (4.56-7.90)	1.81 (1.07-3.07)
Pipes and/or cigars (not cigarettes)	M+F	2.92 (2.38-3.57)	4.64 (3.38-6.38)	2.00 (1.51-2.66)
Pipes only	M+F	3.12 (2.35-4.13)	5.20 (3.50-7.73)	2.69 (1.53-4.72)
Cigars only	M+F	2.95 (1.91-4.56)	4.67 (3.49-6.25)	2.85 (1.45-5.61)

There is no clear tendency for the strength of the association to vary by age.

The association is dose-related. This is most clearly evident from the relative risk estimates for any product and cigarette smoking, for which relative risks are summarized below, but can also be seen from more limited data for pipes and cigars.

Product	Sex	Low	Mid	High
Any product (ever)	M	3.13 (2.59-3.78)	6.81 (5.63-8.23)	12.58 (10.53-15.02)
	F	2.43 (1.91-3.09)	4.94 (3.81-6.39)	8.56 (5.39-13.61)
Any product (current)	M	4.88 (4.08-5.83)	9.18 (7.56-11.15)	16.22 (13.04-20.18)
	F	4.32 (3.42-5.46)	11.73 (9.80-14.05)	18.06 (14.06-23.21)
Cigarettes only (ever)	M+F	2.60 (1.88-3.60)	5.70 (3.88-6.36)	11.02 (8.05-15.39)
Cigarettes only (current)	M	5.25 (3.88-7.10)	12.59 (10.03-15.79)	24.69 (20.01-30.47)
	F	2.79 (1.71-4.56)	7.42 (5.10-10.80)	15.80 (10.75-23.21)

("Low" applies to relative risks for which the range of amount smoked includes 5 cigs/day and does not include 20 cigs/day, "Medium" to risks for which the range includes 20 cigs/day and does not include 5 or 45 cigs/day, and "High" to risks for which the range includes 45 cigs/day and does not include 20 cigs/day.)

There is quite clear evidence that, within smokers, risk of lung cancer is reduced in filter vs plain cigarette smokers and is increased in smokers of handrolled vs manufactured smokers. Limited evidence does not suggest any adverse effect of mentholation.

Comparison	Sex	Relative risk (95%CI)
Filter only vs plain only (or nearest equivalent)	M	0.67 (0.56-0.79)
	F	0.73 (0.62-0.86)
Filter ever vs plain only (or nearest equivalent)	M	0.70 (0.60-0.82)
	F	0.79 (0.68-0.93)
Filter only vs plain ever (or nearest equivalent)	M	0.69 (0.59-0.81)
	F	0.70 (0.59-0.82)
Handrolled vs manufactured	M	1.33 (1.16-1.53)
	F	0.92 (0.49-1.71)
Mentholated vs non-mentholated	M	1.15 (0.93-1.43)
	F	0.78 (0.63-0.98)

For any given exposure studied, the meta-analyses conducted nearly always showed highly significant heterogeneity between the individual relative risk estimates, which cannot be fully explained by systematic variation according to the factors studied. While further multivariate analyses will be needed to investigate sources of variation more fully, the results generally indicated that:

Sex: Although some of the meta-analyses above show somewhat higher relative risks for males than for females, the difference is not always statistically significant and may be due in part to confounding by other factors. Multivariate analysis of data for smoking of any product showed no significant variation in risk between sexes for ever smoking, but a significant 20% higher risk for current smoking.

Continent: The associations tended to be weakest in studies conducted in Asia and were stronger in studies conducted in North America or Europe. The tendency for Asian studies to give lower relative risks was particularly evident in the meta-analyses of smoking of any product. Multivariate analysis of data for smoking of any product showed that continent on its own explained about 95% of the variance between estimates. Although for cigarette smoking relative risks were generally higher in North American than in European studies, the reverse was true for pipe and cigar smoking. Lower risks in filter cigarette smokers are evident in studies conducted in Asia, North America and Europe.

Location within Europe: For most exposures associations were of a similar order of magnitude in different countries within Europe. For pipe/cigar smoking associations appeared weaker in the UK than in Scandinavia, Germany and other western countries.

Location within Asia: Limited data from India tended to show stronger associations than was the case for China or Japan.

Period of study: Studies starting more recently, particularly in North America or Europe, tended to show stronger associations than studies starting earlier.

Study type: For many exposures relative risk estimates from prospective studies tended to be somewhat greater than those from case-control studies.

Number of adjustment variables: Generally there was no strong evidence that the magnitude of the relative risk estimate was associated with the number of adjustment variables considered. Patterns of association were very similar whether meta-analyses were conducted based on estimates adjusted or unadjusted for confounding variables.

For a given exposure relative risk estimates are generally higher for **squamous cell carcinoma** than for **adenocarcinoma**. This is illustrated in the combined sex results below.

Exposure	All lung cancer	Squamous cell carcinoma	Adenocarcinoma
Ever any product	5.50 (5.08-5.95)	10.19 (8.65-12.01)	2.84 (2.41-3.36)
Current any product	8.58 (7.78-9.47)	16.41 (12.80-21.05)	4.11 (3.25-5.20)
Ex any product	4.24 (3.86-4.65)	8.24 (6.55-10.36)	2.65 (1.99-3.52)
Ever any product - low	2.78 (2.43-3.19)	4.25 (3.27-5.53)	1.69 (1.23-2.32)
Ever any product - mid	5.95 (5.12-6.92)	9.91 (7.21-13.61)	2.55 (1.97-3.30)
Ever any product - high	11.12(9.51-12.99)	22.19 (15.92-30.92)	4.23 (2.68-6.69)

Current any product - low	4.84 (4.25-5.50)	9.92 (7.41-13.28)	2.32 (1.59-3.58)
Current any product - mid	10.27 (9.02-11.68)	21.57 (16.77-27.73)	3.37 (1.88-6.02)
Current any product - high	17.74 (15.24-20.66)	39.16 (23.67-64.79)	5.71 (2.91-11.19)
Ever cigarettes only	6.46 (5.43-7.68)	11.56 (7.64-17.49)	3.15 (1.60-6.21)
Current cigarettes only	9.75 (8.09-11.76)	20.85 (14.84-29.29)	6.05 (3.69-9.92)
Only filter vs only plain	0.69 (0.61-0.78)	0.52 (0.40-0.68)	0.84 (0.66-1.08)
Ever filter vs only plain	0.73 (0.65-0.82)	0.55 (0.41-0.74)	0.99 (0.84-1.16)
Only filter vs ever plain	0.69 (0.62-0.77)	0.69 (0.57-0.83)	0.98 (0.80-1.21)
Handrolled vs manufactured	1.31 (1.14-1.52)	1.62 (1.18-2.21)	2.09 (0.83-5.25)
Ever pipes and/or cigars (not cigarettes)	2.92 (2.38-3.57)	3.65 (1.92-6.91)	0.93 (0.62-1.40)
Ever pipes only	3.12 (2.35-4.13)	3.43 (1.84-6.41)	0.50 (0.23-1.10)
Ever cigars only	2.95 (1.91-4.56)	3.87 (2.45-6.12)	0.55 (0.11-2.88)

(See previous table for definition of “low”, “mid” and “high”.)

It can also be seen that the lower risks in filter vs plain smokers seen for all lung cancer and for squamous cell carcinoma are not evident for adenocarcinoma. However the data do not support the suggestion that the switch to filter cigarettes has increased the risk of adenocarcinoma.

It is noticeable that the evidence does not suggest any increased risk of adenocarcinoma in smokers of pipes and/or cigars but not cigarettes.

Heterogeneity of the relative risks is less for squamous cell carcinoma than for all lung cancer, as Asian estimates for squamous cell carcinoma are higher and more comparable to those seen in Europe and North America. Estimates for adenocarcinoma are higher in North American than in European studies and some analyses show relative risks are higher in more recently conducted studies.

Ideas for further work on this valuable database will be discussed in Part III of this report.

7. References

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