DRAFT 2

A REVIEW OF THE EPIDEMIOLOGY

OF LUNG CANCER

RELATED TO ACTIVE SMOKING

THE ROLE OF AMOUNT SMOKED, AGE OF STARTING TO SMOKE, DURATION OF SMOKING, PACK-YEARS OF SMOKING AND YEARS SINCE STOPPED SMOKING

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EXECUTIVE SUMMARY

A compilation is presented of the epidemiological evidence relating lung cancer risk to amount smoked, age at starting to smoke, duration of smoking, pack-years of smoking and years since stopped smoking. Data from all 59 case-control and prospective studies providing relevant information on at least 500 lung cancer cases have been systematically presented. Relative risks and 95% confidence intervals relating to all the aspects of smoking considered have been extracted, or calculated where necessary. Data relating to duration or pack-years of smoking that have not been age-adjusted have not been included so as to avoid gross bias.

Of the 59 studies, 10 were prospective (3 with over 25 years follow-up) and 49 case-control. Twenty-five were conducted in the USA, 10 in the UK, 11 in the rest of Europe, 9 in Asia, 3 in Canada and 1 in Cuba. The earliest studies reported results in 1950. Eight studies involved over 5000 lung cancer cases with 3 exceeding 10000. Common study weaknesses included failure to require histological confirmation of lung cancer, obtaining data from proxy respondents more frequently for cases than controls, and lack of control for lung cancer risk factors other than smoking. Studies varied in the extent to which lung cancer diagnosis would have been accurate, the depth in which questions were asked on smoking, the definitions used to categorize subjects by smoking category, the types of controls used in case-control studies, and the extent to which potential confounding factors were taken into account. Many of the studies concerned special groups (e.g. doctors or war veterans) which were not necessarily representative of the population at large.

In due course the data presented here (as well as those from other studies of 100 to 500 cases) will be placed on a computer database, which will allow formal meta-analyses to be conducted and a more detailed evaluation of how differences between study findings depend on the location and timing of the study and various aspects of its design and analysis. For the present conclusions are based on a simpler examination of the data presented.

Amount smoked Virtually all the studies show a very clear tendency for lung cancer risk to rise with the amount regularly smoked (or smoked at one specific point in time). An increased risk is clearly evident for those smoking less than 10 cigarettes a day. The relative risk associated with the highest level of exposure studied commonly exceeds 20. For a given amount smoked, relative risks tend to be higher for men than for women (although the data are not

completely consistent), and lower in Asia than in the USA, UK or Europe. For women, relative risks are clearly higher in more recent studies. A similar tendency is evident to some extent in men. For a given amount smoked, relative risks are clearly higher for squamous cell and small (oat) cell carcinoma than for adenocarcinoma. A dose-relationship with amount smoked is still evident for adenocarcinoma in most studies.

Age of starting to smoke With only minor exceptions, the data consistently show that an earlier age of starting to smoke is associated with an increased risk of lung cancer. The difference in risk between early and late starters is much more marked than would be expected were there a linear relationship of risk to duration of smoking. Evidence from one study indicates this difference is not materially explained by the tendency of earlier starters to smoke more. The relationship of earlier age of starting to smoke to increased risk is clearly evident for squamous carcinoma, but is less clearly seen for adenocarcinoma in the limited data available.

Duration of smoking Given age, risk of lung cancer was generally found to increase monotonically with duration of smoking. However, the way the data are presented and analysed in the source papers makes it difficult to get a clear idea of the true shape of the relationship of duration to risk. A relationship of lung cancer risk with duration of smoking was always evident for squamous and small cell carcinoma and was generally evident for other histological types also, and was generally evident within smokers of a given level of smoking. The relationship of lung cancer risk to duration of smoking was found to vary by amount smoked in the two American Cancer Society CPS studies, not being apparent at all in smokers of 1-9 cigarettes/day. Overall, the CPS data did show an association of lung cancer risk with duration of smoking, but only up to about 40 years smoked.

Pack-years smoked Pack-years as an index of exposure is open to the criticism that it multiplies together two aspects of smoking (duration and amount) that may relate very differently to risk. Unsurprisingly, given the evidence for duration and amount, risk of lung cancer (and all the major histological types) was found to increase steadily with increasing pack-years smoked.

Years stopped smoking Among ex-smokers, risk of lung cancer (and all the major histological types) clearly declines with increasing time given up. For those giving up smoking for 25 years or longer, an increased risk of lung cancer (compared to never smokers) is still evident, by about 2-fold. Compared to current smokers, risk declines with increasing time given up (an apparent increase in risk seen in some studies associated with very short-term giving up being likely to be an artefact caused by quitting because of disease). The decline can be seen within categories of amount smoked.

Overall, the data are clearly consistent with any aspect of dose reduction (smoking less cigarettes per day, smoking for a shorter duration, or giving up for longer periods) being associated with a reduced risk of lung cancer. This supports evidence reviewed separately that risk is reduced in relation to a reduced tar delivery of cigarettes.

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1. Introduction

1.1 Objective

The objective of this review is to provide a compilation of the epidemiological evidence from the larger case-control and prospective studies relating lung cancer risk to the major aspects of the smoking habit - specifically amount smoked, age of starting to smoke, duration of smoking, pack-years of smoking and years since stopped smoking.

1.2 Background/associated work

As part of another project (IESLC = International Evidence on Smoking and Lung Cancer), we aimed to identify all studies providing data relating smoking to lung cancer with at least 100 cases, and to accumulate the relevant evidence on a computer database. At the time of writing the literature searching and classification of the papers collected into separate studies is essentially completed, but the lengthy process of extracting the relevant data (often necessitating calculating relative risk and confidence interval estimates where these are not presented by the authors) is still ongoing. When this is completed (sometime in 2001) we will be in a better position to calculate meta-analyses of evidence relating to various aspects of the smoking habit.

As part of yet another project, we have reviewed the evidence relating lung cancer to type of cigarette smoked (filter/plain, tar level, handrolled/manufactured, black/blond, menthol, bidi/manufactured). This project involved review of the studies identified by IESLC to determine those with relevant data on cigarette type, extracting the relevant data into summary tables, performing a limited number of meta-analyses and then interpreting the data. A full report on this work is available, and a shorter paper for publication has been prepared.

1.3 This review

In order to achieve a useful review in a reasonable time, it was decided to limit attention to studies in IESLC involving a minimum of 500 lung cancer cases. Smaller studies would in any case not have allowed very reliable investigation of some of the more detailed aspects of the smoking habit to be studied here. Inasmuch as much of the

data presented here has not yet been entered onto the IESLC database, formal meta-analysis is not attempted at this stage. However, as will become evident, the main features of the results are clear enough without meta-analysis, and it is possible to draw conclusions satisfactorily.

Section 2 of this review concerns materials and methods, giving fuller details of how the studies were selected and the approaches used to extract relative risk estimates and confidence intervals.

The main characteristics of the 59 studies selected are summarized in section 3.

Section 4 discusses some general problems involved in studying the relationship of lung cancer to active smoking.

Sections 5 to 9 then consider, in turn, the evidence relating to the five aspects of smoking considered in this review; amount smoked, age of starting to smoke, duration of smoking, pack-years of smoking and years since stopped smoking.

Section 10 discusses the overall evidence and draws conclusions.

Following acknowledgements in section 11 and references in section 12, the tables of results are presented, the first digit of the table number relating to the section of the text to which the table refers. Finally, two appendices provide additional detail.

2. Methods

2.1 Selection of studies

IESLC aimed to identify all studies providing data relating smoking to lung cancer based on at least 100 cases. First, relevant papers were extracted from in-house files accumulated over many years. Next, additional papers were identified from Medline and Embase searches and obtained (if available though the British Library). Then any relevant new papers cited as references were obtained until ultimately no new papers were identified. These procedures should have identified all evidence published in English and much published in other languages. Care was taken to identify each study separately and which papers related to each study. The papers were filed by study, with papers relating to more than one study filed under each study. A total of 312 separate studies were identified by IESLC.

The study files were then gone through to identify all studies with at least 500 lung cancer cases, which provided information on at least one of the relative risks of interest.

2.2 Extraction of data

The objective was to obtain relative risk* estimates with 95% confidence limits (CIs) for the following comparisons:

1. Amount smoked by current smokers (vs. never smokers)
2. Age of starting to smoke by current smokers (vs. never smokers)
3. Duration of smoking (vs. never smokers)
4. Pack-years smoked (vs. never smokers)
5. Years stopped smoking by ex-smokers (vs. never smokers)
6. Years stopped smoking by ex-smokers (vs. current smokers)

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*For convenience the term "relative risk" is used not only for relative risks estimated directly in prospective studies but also for relative risks estimated approximately by odds ratios in case-control studies

For each comparison, data would be extracted for total lung cancer risk and for

risk by histological type of lung cancer.

Where data permitted, data would also be extracted for risk broken down by more than one of the five smoking aspects of smoking simultaneously. In practice data were found relating to the joint relationship of lung cancer risk to:

7. age of starting to smoke and amount smoked (vs never smokers)
8. age of starting to smoke and pack-years (vs never smokers)
9. duration of smoking and amount smoked (vs never smokers)
10. years stopped smoking and amount smoked (vs never smokers)

Note that, for case-control studies, data by duration of smoking or by pack-years smoked (which is the product of duration and amount smoked) were only extracted if adjustment had been made in analysis at least for age. As discussed further in section 4, unadjusted estimates are severely biassed, even when the cases and controls were matched on age.

Where, for one study, data on a specific aspect of smoking were available from more than one source, data were usually chosen that involved the largest number of cases (e.g. latest follow-up for prospective studies) and/or adjusted for the most potential confounding variables.

Where necessary, relative risks and CIs were estimated from reported numbers of cases and controls, using standard techniques which assumed that the logarithm of the relative risk was normally distributed. Occasionally the source paper presented crude numbers and adjusted relative risks with no confidence limits. In such situations the crude numbers were used to estimate unadjusted CIs, and adjusted CIs were calculated assuming that the width (on a log scale) of the unadjusted and adjusted CIs were the same. This will slightly underestimate the variance of the adjusted relative risk estimates, but such underestimation is unlikely to be important.

In some source papers relative risks and CIs were presented relative to a comparison group different from that required or for groupings which were very fine and

required combination. To estimate the required relative risks and CIs a procedure was employed which used the presented relative risks and CIs to generate "effective numbers" of cases and controls (or populations at risk) - i.e. those numbers that would produce the correct relative risk and CI values - and then used the effective numbers to estimate the required relative risks and CIs using standard theory.

On occasion, other methods were used to derive the required relative risk and CI estimates.

Appendix A gives details of the source(s) from which each presented relative risk and 95% CI was obtained and indicates whether the data come directly from the source or required calculation. The actual details of the calculations made are retained in-house.

3. Study characteristics

3.1 Introduction

The review focuses on the 59 studies which have presented relevant results. Table 3.1 gives, for each study, the study short name by which it will be referred, its title, its location and study type and the period during which the lung cancer cases died or were interviewed. The main references used for each study [1-86] (i.e. those which proved a source of the relative risk data used in this review) are given in Appendix B, although in some studies other references were used to obtain some of the information in the tables in this section.

3.2 Overlap of studies

The 59 studies are not completely independent. In particular, some points should be noted:

(i) What is referred to as YU is a meta-analysis of data from 15 Chinese case-control studies, three of which (GAO, FU, XU) also provided some separate results.

(ii) The French (BENHAM) and Scottish (GILLIS) case-control studies form part of the West European multicentre study (LUBIN). The LUBIN study also includes centres in Italy, Austria and Germany, for which separate results were not obtained in this review.

(iii) Following an early case-control study in three US states (WYNDER), the late Dr Ernest Wynder had been involved in case-control studies conducted in six cities on a continuing basis for many years, with numerous papers reporting results at different time points for cases and controls interviewed in different periods. For convenience, results for the period 1969-76 have been designated WYNDER2, those for 1977-84 WYNDER3, and those for 1981-94 WYNDER4. There may be some overlap of cases between WYNDER3 and WYNDER4.

3.3 Location

Nine studies (as defined in this review) were conducted in Asia (five in China, two in India and two in Japan), with 25 conducted in the USA (13 in single states, 12 nationwide or in multiple areas and one partly in Canada), three only in Canada and one

in Cuba. The remaining 21 studies were conducted in Europe; 10 in the UK, 10 in other European countries (two each in France and Sweden and one each in Denmark, Finland, Greece, Italy, Poland and Turkey) and one in five European countries. No studies included in this review have been conducted in South America, Africa, Australasia or the former USSR and only one has been conducted in Eastern Europe.

3.4 Study type

Of the 59 studies listed in Table 3.1, 10 were prospective, one a case-control study nested within a prospective study and the remaining 48 standard case-control studies. Of the prospective studies, four were conducted in the US (CPSI,CPSII,DORN,MRFIT), three in the UK (DOLL2,BENSHL,KINLEN) and one each in Canada (BEST), Denmark (PRESCO) and Japan (HIRAYA).

3.5 Period of study

Table 3.1 includes information on the period during which the lung cancer cases died in the prospective studies or during which they were interviewed (or in some studies died) for the case-control studies. This period is of relevance given the considerable change over time in the type of cigarette smoked.

The first three case-control studies to report findings were WYNDER, DOLL and BRESLO. WYNDER reported results in 1950 for a study presumably carried out in the late 1940s, DOLL reported interim results in 1950 and final results in 1953 for a study conducted in 1948-1952, and BRESLO reported results in 1954 for a study conducted in 1949-1952. Other early case-control studies included TRICHO, SCHWAR and STOCKS.

The first prospective studies started in 1951 (DOLL), 1954 (DORN), 1955 (BEST) and 1959 (CPSI). The longest periods of follow-up are 40 years (DOLL), 30 years (PRESCO) and 26 years (DORN), though with the exception of CPSII (6 years) and BEST (7 years), follow-up periods have always been at least 13 years.

As shown in Text-Table 3A, the number of studies with deaths or cases in a given

5-year period increased steadily to 1981-85, a period covered by about half the studies considered here. Subsequently, there has been a rapid decline, with only 5 studies reporting results relating to deaths or cases occurring in the 1990s. It is notable that relevant research started much later in Asia than in Europe or North America, with two case-control studies in India (JUSSAW,NOTANI) and one prospective study in Japan (HIRAYA) starting between 1963 and 1965.

TEXT-TABLE 3A

Number of studies with deaths or cases in the period stated

Period	North/Central America	Europe	Asia	Total
Up to 1950	2	2	0	4
1951-55	3	5	0	8
1956-60	5	4	0	9
1961-65	4	4	3	11
1966-70	6	5	3	14
1971-75	7	6	3	16
1976-80	10	13	2	25
1981-85	15	10	4	29
1986-90	8	8	5	21
1991-95	1	4	0	5
1996-2000	0	0	0	0

3.6 Lung cancer cases in the 59 studies

Table 3.2 presents some relevant details relating to the lung cancer cases in the 59 studies. Numbers of lung cancers shown usually relate to the total number in the study, though in some studies they relate to the actual number included in the analyses considered by the source paper. Further details of numbers of cases for some specific analyses are shown in later tables. The largest studies in terms of numbers of lung

cancer cases were LIU (29029), STOCKW (25400) and BROWNS (14596). Five other studies (LUBIN 7804, CPSI 5713, YU 5703, SCHWAR2 5588 and DORN 5097) exceeded five thousand cases, with a further five studies (CPSII 4382, WYNDER3 3097, SCHOEN 2044, MRFIT 2004 and PIKE 2001) exceeding two thousand. CPSI, CPSII and DORN are the prospective studies involving most lung cancer cases. In all the studies, the number of male cases exceeded the number of female cases. Seventeen of the studies were restricted to men (with a further study, DORN, including so few women that results for the overall population have been taken to apply to men).

The prospective (or nested case-control) studies generally relied on death certification for determining deaths from lung cancer, though PRESCO also included incidence data. However, as seen in the footnotes to Table 3.2, three studies (CPSI,CPSII,DORN) did have some histological data, and one (DOLL2) reported some analyses based on an independent review of medical records.

Of the 48 case-control studies, 19 required histological confirmation and 3 required histological or cytological confirmation. Of the remaining 26 studies, which did not require such confirmation, data on the percentage of confirmed cases (which varied from 41% to 84%) were presented by 10.

27 of the studies report usable data by histological type, only one of them (PRESCO) being a prospective study.

Proxy interviews were used in 100% of cases in 9 case-control studies, typically those in which cases were identified from death records. Some proxy interviews were also conducted in at least 14 of the other case-control studies. The prospective studies and about a half of the case-control studies relied on direct interview of the case.

3.7 Controls (or populations at risk) in the 59 studies

Table 3.3 similarly presents some relevant details of the controls (or populations at risk for prospective studies).

Of the 10 prospective studies, CPSI and CPSII involved over a million subjects, DORN, HIRAYA and MRFIT involved 248000 to 362000 subjects, with the others between 14000 and 92000 subjects. The largest case-control studies in terms of numbers of controls were LIU (87315), BROWNS (36438) and STOCKW (22704).

Numbers of controls were identical to the number of cases in 9 of the 49 case-control studies and were quite similar in a further 14. In a number of the other studies, numbers of controls were exactly or about twice as large as numbers of cases. In many of the studies, the relationship of the number of controls to cases was constrained by 1:1, 2:1 or 3:1 matching. Matching factors normally included age and sex, and commonly included race, location of residence, and period of interview.

The source of controls that was most popular was hospital patients, with population and decedent controls also quite frequent, and a few studies using cancer registry controls. Where controls were drawn from hospitals, cancer registries or decedents, many studies excluded any subjects with (or dying from) smoking-associated disease, but some studies only excluded cases with cancers or respiratory disease. The definition of which diseases were considered smoking-associated would have varied over time. Some studies used more than one type of control.

Proxy interviews were not used in cases or controls in about half the case-control studies. In eight of the studies (FU, LIU, BARBON, BECHER, DAMBER, GARSHI, NMFS, DEANN), cases and controls were selected after death, so all interviews were perforce proxy. In about a third of the case-control studies, some direct and some proxy interviews were used. In three of the studies (BLOT, SCHOEN, BUFFLE), case-control matching was done on vital status, with live subjects interviewed directly and proxies used for dead subjects. Some of the studies allowing for direct or proxy interviews did not state the frequency of each type, but among those that did proxy

interviews were always more common in cases. As shown in Text-Table B, the differences in frequency of proxy interviews was quite large in some studies, leading to the possibility of bias.

TEXT-TABLE 3B

Studies with difference in proxy interview use in cases and controls*

	Proxy interview use		
Study	Cases	Controls	Difference
SCHWAR2	58	8	50
DEANT	100	51	49
PERSHA	92	45	47
HUMBLE	47	2	45
RISCH	34	0	34
SIEMIA	18	0	18
CORREA	24	11	13
WYNDER	2	0	2

* To the list may be added DAMBER, which used decedent cases and a mixture of decedent and population controls, and PIKE, which used some proxy interviews in cases but very few in controls

3.8 Aspects of smoking considered

Table 3.4 shows which studies considered which aspects of smoking. Overall the numbers were:

Number of cigarettes smoked	52 studies
Age of starting to smoke	19
Duration of smoking	17
Pack years	11
Years since stopped	27
Age of starting x number	1

Age of starting x pack-years	1
Duration x number	8
Years stopped x number	3

3.9 Potential confounding variables adjusted for

Table 3.5 shows which studies adjusted for which potential confounding variables. Note that a study is included against a variable only if one or more of the analyses included in the tables of relative risks and CIs in sections 5 to 9 adjusted for the variable. This does not imply that all the relative risks cited were adjusted for the variable. The reader should refer to the tables of relative risks and CIs themselves to see which variables were adjusted for in any analysis.

By the definition used, 15 studies did not adjust for any confounding variables. Of the remaining 44 studies, age was adjusted for in all but one (YU), with race, area of residence, income/education/social class and occupation adjusted for in, respectively, 9, 4, 10 and 4 studies. Other adjustment factors occasionally used are noted in Table 3.5.

Most studies presented results separately for males and females. Those that did not generally adjusted for sex in analysis or used the fact that cases and controls were sex matched at the design stage. Exceptionally, the results cited for STOCKW do not take sex into account, either in analysis or design.

4. Some general problems in studying the relationship of lung cancer to smoking

There are a number of general problems in studying the relationship of lung cancer to smoking. These are discussed to some extent here, but may be considered further in subsequent sections.

4.1 Accuracy of diagnosis

As in all epidemiological studies of lung cancer, bias may arise if some of the subjects are misclassified as regards whether or not they have the disease. Lee [87] has reviewed the literature on accuracy of diagnosis, noting that numerous autopsy-based studies have found that 10% or more of clinically-based diagnoses of lung cancer are false-positives and that there may be at least as many false-negatives, where a lung cancer seen at autopsy is missed in-life. Requiring cases to be histologically confirmed will reduce the number of false-positives, but may not eliminate them completely, due to uncertainty about the primary site [88].

Given that cigarette smoking is more strongly associated with lung cancer than with the great majority of the diseases with which it might be confused, random misdiagnosis of lung cancer is likely to weaken the observed association of lung cancer with smoking. However, misdiagnosis may not be random, with the fact that a patient smokes making the doctor more likely to have their lung cancer detected during life [89]. There is also evidence [90] that lung cancer, when it appears on a death certificate, is much more likely to be considered an underlying (rather than a contributory) cause of death if the decedent is a smoker, though presumably this would not have applied early on when the relationship of smoking to lung cancer was not well recognised.

4.2 Accuracy of exposure

There are two major issues here. One relates to problems in defining what exposure actually is, the other to obtaining that information reliably.

4.2.1 Defining exposure

In a simple world, someone may start to smoke cigarettes at a given age, and then smoke at a steady rate until either the time of interview or the time at which cigarette smoking is stopped. Knowing the age of start, the age of stopping (if relevant) and the amount smoked per day when smoking then defines the smoking habit well, subjects being readily categorized as never smokers, ex-smokers or current smokers, with level and duration of smoking clearly defined.

In practice life is not so simple for a number of reasons, including the following:

(i) It is rarely the case that someone changes rapidly from having never previously smoked to being a smoker of, say, 20 cigarettes a day. There will often be a period of trial and experimentation before a smoker settles down to a regular habit. Age of starting to smoke is often not further defined on questionnaires, and "age first tried a cigarette" and "age first smoked regularly" may differ.

(ii) Even after the early phase of becoming a regular smoker, a smoker may modify the number smoked over time, for various reasons. Some studies record consumption only at a defined time point (e.g. at the start of follow-up in prospective studies), some record average over the smoking lifetime ("usual number smoked per day"), while others may attempt to determine a lifetime history (e.g. average number per day smoked in successive five-year periods), or ask about the maximum amount smoked.

(iii) Smokers may give up smoking more than once. Analyses usually compare risk in current smokers or in never smokers with risk in those who are not now smoking but gave up at various different times ago. It is possible that some of the reduction in risk in ex-smokers compared to current smokers may not actually be due to the benefits of the most recent period of giving up but may reflect the greater likelihood of having previous periods of giving up smoking in those not now smoking than in those currently smoking. Many studies do not record periods of ex-smoking before the latest one.

(iv) Some smokers may smoke very small amounts and/or for a very short period of time. Some studies do not include such smokers in their current or ex-smoker categories but among the never smokers, arguing that they have never smoked

regularly, so that this can be ignored for practical purposes. Some studies attempt to define smokers as those who have smoked to a minimum extent, say, as much as 100 cigarettes in their lifetime or at least 1 cigarette/day for as long as a year. Others may simply ask "have you ever smoked regularly?", the definition then depending on the respondent's view of what regularly is.

(v) Smokers do not only smoke cigarettes, but may smoke products such as pipes or cigars, which also increase the risk of lung cancer. Some studies may ask questions only about cigarettes, leaving open the possibility that the "never smoking" group may include pipe or cigar smokers, so tending to reduce the observed relative risk associated with smoking cigarettes, compared to that observed in studies where information is collected on smoking of other products and a base group can be defined who have never smoked any product. This may be unimportant in countries where smoking of other products is rare, but is more important in a number of countries where pipe and/or cigar smoking is or has been common. Where such data have been collected, some researchers use them to exclude from analysis all ever smokers of other products, restricting attention to a comparison of cigarette only smokers with a true never smoking base group. Or they may exclude smokers of pipes and cigars only, ignoring pipe and cigar smoking by those who also smoke cigarettes. Others try to avoid loss of data by converting numbers of pipes or cigars in terms of "cigarette-equivalents," but this entails assumptions which may be invalid.

It is evident that, even if all the data collected are accurate, relative risks presented are unlikely to be exactly comparable from study to study for the reasons stated. Investigating how lack of comparability affects the results is rendered difficult by the fact that many of the studies provide extremely limited details of the precise definition of the smoking categories they used.

Before turning to issues relating to the reliability of the information collected, it is important to refer to a problem specific to prospective studies. This is that subjects are often categorized into groups based on smoking habits determined at baseline, the analysis implicitly assuming that material changes will not occur during the follow-up

period. Especially where the follow-up period is a long one (and where additional smoking data are not collected to allow recategorization), this implicit assumption may be false. 20 year follow-up of a group classified as current smokers from information available at the start of the period may underestimate the true risk associated with continuing smoking if in fact a substantial proportion of this group have given up smoking during the follow-up period, and (less likely) some of the never smokers start smoking. Similarly analysis relating to amount smoked may be biassed if some heavy smokers reduce the amount they smoke during the follow-up period. Analyses of duration of smoking may also be affected by such incomplete data.

4.2.2 Reliability of reported exposure

Even if the questions are clearly defined, the answers obtained may be inaccurate. Estimates of current amount smoked are widely thought to be low, based on the fact that surveys typically only account for 70-80% of cigarettes actually sold. Probably this is because smokers are unwilling to admit the full extent of a habit known for many years to be unhealthy. Estimates of past amount smoked are likely to be subject to even more variability, mainly because of difficulties in accurately recalling the detailed past. The same applies to the timing of when the subject started to smoke and stopped, especially when the questions relate to multiple periods of smoking throughout life.

There is also evidence that some smokers deny their habit on interview, with many reports indicating that (i) a proportion of nonsmokers have cotinine levels consistent with current smoking, (ii) a proportion of never smokers have previously admitted smoking and (iii) misclassification rates are higher when questions are asked in a medical context [91].

If all these sources of inaccuracy are random, then the effect will be that the observed relationship of smoking with lung cancer will be weaker than the true relationship. However, in case-control studies, where the respondent is aware of the presence of the lung cancer, it is possible that recall bias may exist, with the extent or duration of smoking by cases over-reported relative to that by controls, in a conscious

or subconscious attempt to explain why the lung cancer has occurred. A major advantage of prospective studies is that the data are recorded before the lung cancer is present, so that recall bias is not an issue.

Bias can also arise in case-control studies if there are systematic differences between cases and controls in the circumstances in which the exposure data are collected. In studies where cases are hospital patients and controls are drawn from the normal population, the cases may be more ready to complete a detailed questionnaire in hospital (having more time available and more interest in the subject) than a control interviewed at home (who may be busy and keen to get onto other things). Differences between cases and controls in the proportion of proxy respondents may also cause bias - as noted in section 3, some but not all of the studies that use proxy respondents insist that if information for a case cannot be collected directly from the index subject (either because of illness or death) then the same is true for the control. Proxy questions are a particular problem for events long ago, e.g. subjects may have started smoking years before they met their spouse.

4.3 Selection of controls

Controls should be representative of the population from which the cases arise. There are two major concerns that affect case-control studies in this respect.

Firstly, in hospital (or decedent) case-control studies, it is important that the controls selected should not have diseases (or have died from diseases) that are associated with smoking, otherwise the frequency of smoking in the controls will be too high (or too low if the diseases are negatively associated with smoking) and the lung cancer relative risk associated with smoking will be too low (or too high). A problem is that, over the 50 years or so during which the studies we consider have been conducted, knowledge about the health effects of smoking has increased. For example, the first case-control study conducted in the UK (DOLL1) included heart disease patients in the controls, the association between smoking and heart disease not being known at the time the study was conducted, around 1950.

The second concern relates to the comparability of the source population from which the cases and controls are drawn. If cases with lung cancer and controls with some other disease come from different hospitals with different catchment areas, it is possible that differences observed between cases and controls may arise, in part, due to differences in smoking habits in the two areas. If controls are drawn from a list of drivers, for example, bias may arise if driving is associated with smoking, unless cases are restricted to those who drive. Similarly, if information is obtained by telephone from controls, but in hospital from cases, bias may arise if the cases include some who do not have a telephone. However, in a country such as the USA, where nearly everyone has a car or a telephone, such bias may be less, though even then one has to bear in mind that not driving may be for medical reasons.

4.4 Representativeness of study population

While case-control studies are usually drawn from the general population, prospective studies are often drawn from special populations, such as doctors (DOLL2), war veterans (DORN), or civil servants (BENSHL). Two large studies by the American Cancer Society (CPSI, CPSII) in which the data were collected by volunteers, are also known to have a far lower proportion of blacks and low income subjects than the US population. The absolute risk of lung cancer in these populations tends to be lower than the national average, due partly to less frequent exposure to lung cancer risk factors other than smoking. However, the estimated relative risk of lung cancer for, e.g. a 20-a-day smoker compared to a never smoker, may be less affected by the lack of representativeness of the population studied. Indeed, if these other factors are unassociated with smoking, and if they multiply risk independent of smoking (as has been demonstrated to be the case for asbestos{HAMMON1979}), then the relative risk estimates will be completely unaffected by the lack of representativeness of the population.

4.5 Confounding

In order to arrive at an unbiassed estimate of the risk of lung cancer associated with the aspects of smoking considered in this review, it is important that potential confounding factors are taken into account. These fall into three groups, which will

be considered separately: age, other aspects of smoking, and nonsmoking factors.

4.5.1 Age

Age is strongly related to risk of lung cancer and, as the average age of different smoking groups varies markedly (e.g. ex-smokers tend to be older), it is important to take it into account. This can be done in two ways, either by matching cases and controls at the design stage or by adjustment at the analysis stage; and in fact virtually every study has done one or the other. However, in principle, one should adjust for age in analysis, regardless of whether age-matching has been carried out or not, and many studies have not done so, using relative risk estimates that do not specifically take the matching into account.

Failure to take age into account at the analysis stage in age-matched case-control studies will lead to severe bias when analysing effects of duration of smoking or pack-years which are highly correlated with age, due to the relatively small variation in age of starting to smoke. The example in Table 4.1 illustrates the extent of such bias. For this reason we have decided to exclude such analyses from consideration in sections 7 and 8.

4.5.2 Other aspects of smoking

There are correlations between the various aspects of smoking that we are studying. Thus, it is known that, in many populations at least, those who start smoking younger tend to smoke more cigarettes a day than do those who start later, and that those who smoke more cigarettes a day are less likely to give up smoking and more likely to continue for a long duration than are those who smoke less cigarettes a day. Thus, for example, associations of lung cancer risk with age of starting to smoke, duration and time of giving up smoking may be confounded by differences in the average amount smoked between the groups being compared. Similarly associations of lung cancer risk with amount smoked may be confounded by age of starting to smoke, duration and time of giving up.

In an attempt to get round these intercorrelations and also to be able to take into

account reported variations in amount smoked and data on intermediate quit periods, some researchers have related lung cancer risk to a single index, "pack-years," which represents the sum of the product of duration and amount smoked over the periods during which they were smoking. Although we have presented results for this index in section 8, it should be noted that it is an oversimplification of the evidence if duration and amount smoked have a different relationship to lung cancer risk. If, as commonly suggested, duration has a fourth or fifth power relationship to risk and amount smoked only a first or second power relationship, the risk of someone smoking, say, 20 cigarettes a day for 50 years will be very different from that of someone smoking 50 cigarettes a day for 20 years, but they will have the same calculated pack-years.

It should also be noted that aspects of smoking other than the ones specifically studied in this report may cause bias. Heavier smokers may be more likely to inhale deeply or to smoke higher tar cigarettes, again with a propensity for confounding to occur if this is not taken into account.

4.5.3 Non smoking related factors

Smokers and nonsmokers differ in relation to a wide variety of factors (including occupation, education, income, diet, alcohol and coffee consumption) and many of these factors also differ between smokers of different numbers of cigarettes a day and between current and ex-smokers [93]. While many such factors are not causes of lung cancer, many are, and the possibility of some confounding exists, though it may be relatively minor given the much stronger association of lung cancer with smoking than with most of those other factors.

A more important confounding arises if in fact smoking habits (cutting down or giving up) have changed as a result of the lung cancer, and this is ignored in analysis. In case-control studies it will be more relevant to record smoking habits some time before diagnosis, otherwise the common tendency to give up smoking around the time of diagnosis will lead to confusion about the short-term benefits of giving up. Similarly, in prospective studies in which certified death from lung cancer is the

endpoint, bias from this source can be avoided by restricting the analysis to those not having lung cancer at interview.

5. Amount smoked

Table 5.1 presents the available evidence relating overall lung cancer risk (regardless of histological type). For each of the 52 studies providing information the table usually shows the risk (with 95% CI), relative to never smokers, of current smokers by level of cigarettes smoked per day. The table also shows the adjustment factors used, the sex to which the estimates apply and the number of cases included in the analysis. Where the base group is not never smokers (e.g. nonsmokers in 1980 in the LIU study) or the comparison groups are not current smokers (e.g. ever smokers in various studies), this is indicated in the table.

Based on the combined evidence, it is clear that there is highly significant evidence of a positive relationship of amount smoked to lung cancer risk. Of the sex-specific sets of relative risk, almost 90% show a strictly monotonic trend with risk estimates increasing with successive levels of cigarettes smoked. Even in those that do not, a positive trend is clearly evident in the great majority. Indeed, the only studies that show a rather erratic pattern of results are those of JUSSAW, BECHER (females), GARSHI and GILLIS, and even here the relative risks are substantially elevated in the highest cigarette smoking groups.

28 of the estimates for the lowest level of exposure relate to smoking less than 10 cigarettes a day. As is evident from the data, summarized in Text-Table 5.1, there is a clear elevation in risk even at this low consumption level, all but two of the estimates being above 1 (the other two being marginally and non-significantly below 1), and the median relative risk being estimated as 3.72 in males and 1.80 in females. Clearly, the evidence presented does not support the idea of a threshold (though it does not, in theory at least, rule out the possibility that, say, 1 cigarette a day does not increase risk).

TEXT-TABLE 5.1
Relative risk of lung cancer for lowest level of cigarette smoking,
if less than 10 cigarettes a day*

			Relative risk		
Study	Country	Level cigs/day	Males	Females	Combined
FU	China	1-4			0.85
YU	China	1-9		2.24	1.24
JUSSAW	India	1-4	17.1		
NOTANI	India	1-9	1.83		
HIRAYA	Japan	1-4	2.5	1.9	
JOLY	Cuba	1-9	5.38	4.73	
BEST	Canada	1-9	10.0		
BENHAM	France	1-9		1.23	
SCHWAR	France	1-9	2.57		
BARBON	Italy	1-9	2.7		
DAMBER	Sweden	1-7	2.3		
PERSHA	Sweden	1-9			5.43
LUBIN	W.Europe	1-9	4.83	1.69	
CPSI	USA	1-9	3.82	1.17	
CPSII	USA	1-9	14.3	4.30	
DORN	USA	1-9	3.7		
WYNDER	USA	1-9	2.25		
BENSHL	UK	1-9	4.00		
DOLL1	UK	1-4	3.72	0.94	

* See Table 5.1 for fuller details, including 95% CI

The relative risk associated with the highest level of exposure studies is very often extremely high. Text-Table 5.2 summarizes results for studies where the relative risk estimate exceeded 30 in at least one sex group. It can be seen that this occurred in as many as 11 of the 50 studies with such data.

TEXT-TABLE 5.2
Relative risk of lung cancer exceeding 30 in relation to the highest level of cigarette smoking studied*

			Relative risk		
Study	Country	Level cigs/day	Males	Females	Combined
JUSSAW	India	25+	94.2		
OSANN	USA	40+	42.8	40.9	
HUMBLE	USA	31+			39.7
CPSII	USA	41+	44.8	(24.0)	
KAUFMA	USA	45+			60.0
WYNDER	USA	35+	30.0		
WYNDER2	USA	41+	98.2	(15.9)†	
WYNDER3	USA	41+	44.5	47.7	
WYNDER4	USA	41+	35.9	34.0	
DARBY	UK	25+	143.0	41.6	
DEANN	UK	23+	31.6	(19.1)	

* See Table 5.1 for fuller details, including 95% CI. Bracketed data are corresponding results for females in the same study, where relative risks are <30.
† Female data are for 31+ cigs/day.

While such estimates are quite variable, depending *inter alia* on the choice of the highest dose level used, the accuracy with which exposure is determined, and the number of lung cancers in the never smoking group (which may be quite small), the results indicate that an extremely high RR estimate is not at all uncommon. Such relative risk estimates were in fact somewhat more common than estimates of less than 10, the majority being in the range 10-30.

At this stage we do not propose to conduct detailed formal analysis of how the slope of the relative risk estimate varies by sex, location, period, confounding variables considered, aspects of study design, etc. This will await the completion of our full computer database. In the meantime we will simply refer to some impressions gained from inspection of the data in Table 5.1.

Sex There were 22 studies in which comparable data were available for the two sexes. Of these, there were eight where the relative risk for a given amount smoked was very clearly higher in males (JOLY, LUBIN, CPSI, CPSII, WYNDER2, DARBY, DEANN, DOLL1), six where it was somewhat higher but the pattern seemed less clear (HIRAYA, PRESCO, BENHAM, SCHOEN, ALDERS, DOLL2), five where the relative risks were similar in the two sexes, or an excess at one level for males conflicted with an excess at another level for females (BECHER, OSANN, PIKE, WYNDER3, DEANT) and three where the pattern was towards a higher relative risk in females (BROWNS, NMFS, WYNDER4). Clearly, the overall pattern is towards men having a higher relative risk for a given amount smoked. The extent to which this is explicable in terms of differences in other aspects of smoking (e.g. age at starting to smoke, or inhalation) cannot be assessed from these data in isolation.

Location With the exception of the rather unusual results of JUSSAW, relative risks seem relatively low in the studies conducted in China, India and Japan. No clear differences could be seen between estimates for USA, UK and the rest of Western Europe.

Period In view of the striking results in the two CPS studies, with CPSII conducted in 1982-88 reporting substantially higher relative risks by amount smoked than seen in CPSI conducted in 1959-72, and the general thought that the percentage of smokers who had smoked for a long duration had increased over time, one might have expected to see clear evidence generally that risks were higher in studies conducted later than in those conducted earlier. This was studied by looking, for studies conducted other than in Asia, at relative risks for men associated with smoking 20 cigarettes a day (or the level that included 20 a day), and comparing results for those which involved lung cancers wholly

or predominantly before 1975 and those which involved lung cancers wholly or predominantly after 1975 (Text-Table 5.3).

TEXT-TABLE 5.3
Relative risk associated with smoking about 20 cigarettes a day*
separated by sex and period (excluding studies in Asia)

Relative risk	Males Pre 1975†	Post 1975†	Females Pre 1975†	Post 1975†
<2.00				
2.00-			PIKE	BECHER
3.00-		DOSEME		
4.00-	PIKE,BROSS			
5.00-		GARSHI,MRFIT		LUBIN,ALDERS
6.00-		BECHER,NMFS	CPSI,DEANN, DOLL1,DOLL2	JOLY
7.00-	TRICHO,DEANT	ALDERS,GILLIS	WYNDER2	
8.00-	SCHWAR,DAMBER		DEANT	NMFS,WYNDER3
9.00-	DORN,DEANN, DOLL1			
10.00-	STOCKS	BARBON,LUBIN, WYNDER4,BENSHL		
11.00-	WYNDER	WYNDER3		
12.00-				PRESCO,SCHOEN
13.00-	CPSI	JOLY,BENHAM		WYNDER4
14.00-	DOLL2	BROWNS,SCHOEN, KINLEN		OSANN,CPSII
15.00-	BEST	OSANN		BROWNS
20.00-		PRESCO,CPSII		BENHAM,DARBY
25.00-	WYNDER2			
30.00-				
>40.00		DARBY		

* i.e. the relative risk given in Table 5.1 for the group including 20 cigs/day
† The period is defined based on the midpoint of the period in which the cases occurred.

In men, there was a tendency for the relative risk to be slightly higher in the later studies,

but this was not very marked and the estimates for both periods showed a considerable scatter. The pattern was clearer for women, with relative risks of over 10 seen in more than half the estimates after 1975, but not at all before then.

Table 5.2 presents data by amount smoked and by histological type from 18 studies. Histological type is classified in various ways, but squamous cell carcinoma and adenocarcinoma are invariably kept separate - note that Kreyberg I includes squamous cell carcinoma and Kreyberg II includes adenocarcinoma. In some studies estimates of the current/never or ever/never smoking relative risk (regardless of amount smoked) are also shown to illustrate further the differences between the histological types.

There were almost 80 pairs of estimate where, in the same study, the relative risk for squamous cell carcinoma (or the classification including it) could be compared to that for adenocarcinoma (or the classification including it) at the same level of cigarette smoking. With the exception of 3 pairs (ALDERS females 1-17/day and DOLL1 females 1-4 and 5-14), where the difference was small and subject to considerable variation, the relative risk was higher for squamous cell carcinoma. In many studies, the ratio of the relative risks was 3-fold or more.

It has been suggested at one time that adenocarcinoma might not, in fact, be increased by cigarette smoking at all. Although low relative risks which were not statistically significant, or only weakly so, have been reported in some studies (e.g. SOBUE, LUBIN - females, DOLL1), other studies show a clear dose-related trend with a relative risk as high as 10-fold or more at the highest level of exposure (e.g. BARBON, OSANN, CORREA, BROWNS, WYNDER4).

A number of the studies report results for small cell (otherwise known as oat cell) carcinoma. Generally relative risks are strongly increased, similar to those for squamous cell carcinoma. However, the comparison may be somewhat different for the two sexes. In males, relative risks for small cell carcinoma, compared to those for squamous cell carcinoma, tend to be either lower (BARBON, LUBIN, GILLIS) or quite similar (SOBUE, BECHER, DAMBER, OSANN, BROWNS, SCHOEN), although a possible

exception is DOSEME. In females, however, relative risks for small cell carcinoma tend to be either higher (OSANN, BROWNS, SCHOEN) or quite similar (LUBIN) than those for squamous cell carcinoma.

Evidence relating to large cell carcinoma is sparser and more conflicting. In one study (BARBON), relative risks are higher than those for squamous cell carcinoma, in a second (WYNDER4) they are similar, in a third (DAMBER), they are intermediate between those for squamous cell carcinoma and adenocarcinoma and in a fourth (SOBUE), the increase in risk is much less than for squamous cell carcinoma and only somewhat greater than that for adenocarcinoma.

With the exception of some studies showing a weak relationship to adenocarcinoma, the dose-response relationship with number smoked is generally evident for all histological types of lung cancer.

Evidence is available that the diagnosis of histological type of lung cancer changes substantially when the same set of slides are reviewed at intervals by different pathologists[94, 95]. If, in fact, smoking only affects certain types of lung cancer and not others, misclassification may tend to lead to some relationship with smoking being seen for all types of lung cancer.

6. Age of starting to smoke

Based on data from 19 studies, Table 6.1 presents relative risks, generally compared to never smokers, by age of starting to smoke. The age of start categories are always decreasing from left to right so that, if risk is in fact greater with younger starting, the relative risk estimates should increase continuously from 1.0 for never smokers. The risks shown are generally for current smokers, though in some studies (as indicated in the table) they are for ever smokers. The table also shows the potential confounding factors adjusted for and the number of cases involved in the analysis.

In the great majority of the studies, the relative risk estimates do increase monotonically with decreasing age of starting to smoke. Exceptions are generally only minor (FU, ALDERS - females) or due to an estimate with very large variation (HIRAYA - females). The pattern was not evident in the DEANT study, but here information for (decedent) cases was wholly obtained from proxy interviews, with the dependent not necessarily having reliable knowledge about age of starting to smoke.

Text-Table 6.1 attempts to summarize the strength of the relationship by presenting estimates of the relative risk of the latest to earliest age of starting to smoke groups. This ratio tends to be lower where the comparison is between extremes of a multi-level grouping (e.g. 25+ vs <15) than simply between two adjacent categories (e.g. 20+ vs <20). This reflects the larger age of starting difference in the former situation.

In the table, estimates based both on comparisons of age of starting to smoke 10 years or more apart and on direct interviews are shown in bold face. The 12 estimates so marked are in the range 0.23 to 0.68, with the higher estimates from two very early studies (BRESLO, DOLL1). Half these estimates are below 0.3. These results suggest something like a 3-fold or even 4-fold increase in risk associated with perhaps an average 15 year difference in age of starting to smoke (though this cannot be estimated accurately, due to the open-ended nature of the categories).

TEXT-TABLE 6.1

Relative risk of lung cancer for latest to earliest age of starting to smoke groups*

Study	Country	Age of starting Comparison	Relative risk Males	Females	Both	Proxy interviews in cases
GAO	China	30+ v 10-19	**0.24**	**0.36**		No
FU	China	40+ v <20			0.27	100%
LIU	China	25+ v <20	0.60(urban) 0.74(rural)			100%
YU	China	30+ v <20		0.48	0.40	Yes
HIRAYA	Japan	20+ v <20	0.76	(3.15)†		No
JOLY	Cuba	25+ v <15	**0.23**	**0.26**		No
AUVINE	Finland	21+ v <15			0.77	Yes
BENHAM	France	20+ v <20	0.85	0.22		No
BARBON	Italy	20+ v <15	0.16			100%
BECHER	Poland	19+ v <17 23+ v <23	0.60	 0.56		100%
DAMBER	Sweden	21+ v <15	0.44			100%
BRESLO	USA	25+ v <15			**0.64**	No
CORREA	USA	21+ v <16			0.34	24%
CPSI	USA	25+ v <15	**0.25**	**0.26**		No
DORN	USA	25+ v <15	**0.29**			No
WYNDER4	USA	21+ v <18	0.60	0.44		No
ALDERS	UK	25+ v <15	**0.34**	**0.48**		No
DEANT	UK	25+ v <15	1.23	0.84		100%
DOLL1	UK	30+ v <20	**0.51**	**0.68**		No

* See Table 6.1 for further details. See text for explanation of relative risks shown in bold face.

† Unreliable estimate as relative risk for females starting before age 20 highly variable.

For a subject of age 70, for example, these results would suggest that an increase in duration from perhaps 40 to 55 years, i.e. by a factor of 1.375, is associated with a much higher proportional increase in risk. Noting that $(1.375)^3 = 2.60$, $(1.375)^4 = 3.57$, and $(1.375)^5 = 4.91$, those results give some support to the idea that risk is proportional to duration of smoking raised to a power of about 4. One should note, however, that there are a number of uncertainties. In particular, inaccuracy in determining age of starting to smoke may underestimate the true relationship while, on the other side of the coin, if younger starters smoke more or inhale more deeply, the true relationship with duration may be overstated by such analyses.

Table 6.2 gives data relating to age of starting to smoke broken down by histological type from 5 studies. For squamous cell carcinoma, the pattern of increasing risk with earlier age of starting to smoke is generally quite similar to that seen for overall lung cancer risk in Table 6.1. For other cell types the pattern is less consistent, with little evidence of an increased risk with earlier starting for BENHAM (Kreyberg II), BECHER (adenocarcinoma) and ALDERS (females - not squamous or small cell), but clearer patterns seen for BARBON and WYNDER4.

As shown in Table 6.3, one study (DORN) reported results for the joint relationship of lung cancer risk to age at starting to smoke and amount smoked. There was a clear tendency for risk to rise with increasing age of starting for each level of smoking, and for risk to rise with increasing amount smoked for each age of starting group. The relative risk for starting late (age 25+) to early (age <15) can be calculated as 0.28, 0.39, 0.33 and 0.32 for smokers of, respectively, 1-9, 10-20, 21-39 and 40+ cigarettes/day. These estimates tend to be slightly higher than that, 0.29, ignoring amount smoked (see Text-Table 6.1). This is because age of starting is negatively correlated with amount smoked. However, the difference in relative risk estimates is quite small, indicating that the great majority of the association of earlier starting with increased risk of lung cancer cannot be explained by heavier consumption in those who start early.

Table 6.4 presents results from the one study (HIRAYA) giving data jointly by age of starting to smoke and pack-years of smoking. The data show that each has an independent relationship with risk. Earlier starting to smoke is associated with increased risk at every level of pack-years, with the relative risk for starting late (age 30+) to early (age <20) calculated as 0.35, 0.44, 0.38, 0.58 and 0.60 for, respectively <10, 10-20, 20-30, 30-40 and 41+ pack-years.

7. Duration of smoking

Table 7.1 presents results from 13 studies which have provided data on relative risk in relation to duration of smoking, with adjustment for age. Most of the studies report risk by duration for ever smokers, though some of the studies (including CPSI and CPS II) concern current smokers, and one (PRESCO) concerns ex-smokers. The first nine studies shown found that risk increased monotonically with duration, and the last two studies (CPSI, CPSII) also found that it did in males. In CPSI and CPSII for females, risk rose with increasing duration up to about 40 years and then flattened out. In BUFFLE risk also tended to rise with duration but the trend was not quite smooth. The only study showing little or no relationship was HUMBLE. This study actually presented data for two very broad age groups (<65 and 65+) and although risk clearly rose with increasing age in the <65 group, there was no trend in the 65+ group. This may reflect inadequate age adjustment.

Leaving aside the HUMBLE study, Text-Table 7.1 compares risks in the shortest and longest duration groups. All 16 estimates are under 1 and with the exception of the data for PRESCO - females, which unusually, are for ex-smokers only, all the estimates lie in the range 0.19 to 0.47. the median being 0.36.

While it is clear that increasing duration (given age) is associated with an increased risk of lung cancer, it is difficult from these data to get a clear idea of the shape of the relationship of duration to risk. Partly this is because of the open-ended nature of the categories being compared (so that differences in average duration between the groups being compared are impossible to assess accurately). Also, in view of the very strong correlation of duration of smoking with age, precise estimates can only be obtained if the adjustment for age is very precise.

TEXT-TABLE 7.1
Relative risk of lung cancer in the shortest and longest duration groups

Study	Country	Durations being compared			Relative risks Males	Females	Both
SOBUE	Japan	30-39	v	50+	0.37		
BEST	Canada	1-19	v	40+	0.19		
PRESCO	Denmark	1-29	v	30+	0.36	0.62	
AUVINE	Finland	1-20	v	41+			0.42
BARBON	Italy	1-29	v	50+	0.22		
BECHER	Poland	1-19	v	40+	0.39		
DAMBER	Sweden	1-30	v	51+	0.29		
DOSEME	Turkey	1-10	v	21+	0.20		
SCHOEN	USA	<35	v	35+	0.34	0.36	
BUFFLE	USA	<34	v	50+	0.47		
CPSI	USA	1-29	v	50+	0.24	0.36	
CPSII	USA	1-29	v	50+	0.34	0.44	

Table 7.2 presents results for duration, broken down by histological type, from nine studies. Again, the risks usually concern ever smokers. For all histological types, the general pattern is for risk to increase clearly with increasing duration. There are some exceptions where the pattern is not clear (SOBUE- anaplastic, DAMBER - adeno, alveolar and bronchiolar, BUFFLE - adeno) but none for squamous cell carcinoma and small cell carcinoma, which show the strongest relationships with smoking.

Table 7.3 presents data for eight studies on the joint relationship of lung cancer risk to duration and amount smoked. Some of these data (BECHER, SCHOEN, WYNDER2) are also separated by histological type. Some concern risk in ever smokers, some risk in current smokers. In the majority of studies, risk clearly increases with increasing duration of smoking within level of smoking category and risk also clearly increases with increasing level of smoking within duration of smoking category. The increases in risk are, with very few exceptions, monotonic. In WYNDER2, though this pattern is evident for males, it is not so clear for females, with the data for smokers of

41+ cigarettes/day not fitting into the pattern. This may well be due to sampling error as there would have been very few heavy smoking women with lung cancer.

While the data for CPSI and CPSII generally show a tendency for risk to increase with increasing level of smoking given duration (though not so clearly in CPS II for the highest duration category), the relationship of risk to increasing duration given level of smoking is not so clear. Text-Table 7.2 shows estimates of relative risk for the shortest compared to the longest duration by sex, study and amount smoked. It can be seen that in CPSI light smokers (1-9 cigs/day) there was no indication of a relationship to duration at all, and for a number of the other study/sex/level subgroups the relative risk is larger than the relative risks ignoring level of smoking shown in Table 7.1 and Text-Table 7.1. The CPSI and CPSII data would bear more detailed analysis to clarify the joint relationship of lung cancer risk to duration and amount smoked

TEXT-TABLE 7.2
Relative risk of lung cancer in the shortest and longest duration groups by level of smoking in the CPS studies

	CPSI*		CPSII†	
Cigs/day	Males	Females	Males	Females
1-9	1.20	1.41		
10-19	0.26	0.61		
1-19			0.52	0.28
20	0.38	0.69		
20-39			0.41	0.25
21-39	0.19	0.36		
40+	0.45	0.63	0.63	0.63

* 25-29 v 50-54 years duration, except 30-34 v 40-44 years duration for 1-9 cigs/day females and 25-29 v 45-49 years duration for 40+ cigs/day females.

† 20-29 v 50+ years duration, except 30-39 v 50+ years duration for 40+ cigs/day males and females.

8. Pack-years smoked

Pack-years are the product of years smoked and average consumption, in 20s (packs per day), during the smoking period. As already noted, this index is open to the objection that risk of lung cancer may depend much more strongly on duration than on risk, so that two smokers with the same calculated pack-years may have quite different risks. Nevertheless it has become quite popular to express risk in terms of pack-years and Table 8.1 presents data from 11 studies, mainly for ever smokers, all of which provided relative risks adjusted at least for age. With one very minor exception (PRESCO - males - inhalers), all the analyses show a strictly monotonic increase in risk with increasing pack-years, with the risk in the highest category substantially elevated compared to that in the lowest category.

As shown in Table 8.2, eight studies provide evidence on risk by pack-years smoked separately by histological type of lung cancer. For squamous, small/oat or large cell carcinoma, all the studies show a marked rise in risk with increasing pack-years (with the exception of TNCS small cell carcinoma where there is large sampling variability due to few cases). The association with smoking is not so strong for adenocarcinoma, but most of the studies still show quite a clear trend of increasing risk with increasing pack-years.

9. Years stopped smoking

The relationship of lung cancer risk to years stopped smoking among ex-smokers is usually studied in one of two ways. First, by comparison with risk in never smokers, one can see whether, after a long enough period of cessation, risk reverts to a level similar to that seen in never smokers or whether risk remains somewhat elevated. Second, by comparison with risk in current smokers, one can see how long smoking has to be stopped before risk starts to decline relative to that group. Both types of analysis allow one to see the pattern of declining risk with increasing period given up.

9.1 Risk compared to that in never smokers

Table 9.1 summarizes evidence from 24 studies. Relative risks are shown for progressively decreasing numbers of years stopped across the table from left to right.

In virtually every study the relative risk of those giving up for the shortest period of time is significantly elevated, with the elevation usually very marked. Exceptions are DEANT and DOLL1 for females where numbers of ex-smoking cases were extremely low. Note that the numbers of cases shown in Table 9.1 include those for never smokers and for some of the early studies numbers of ex-smokers are much lower than this.

For men, and with limited exceptions (WYNDER2, WYNDER3, DEANT, DOLL1) for women, there is also an obvious tendency for risk to rise steadily with decreasing years of stopping smoking.

Eleven of the studies provide evidence relating to the risk of lung cancer following cessation of smoking for at least 15 years. The results are summarized in Text-Table 9.1, in order of period given up. It can be seen that all of the 21 estimates exceed 1 and that all but 4 of them are statistically significant at the 95% confidence level. For giving up smoking for 25 years or longer, the data suggest about a two fold increase in risk. For cessation periods of 15 years or longer, more like a three-fold increase is suggested. The data for women are much sparser than those for men but even here significant excess risks are seen in long-term quitters in two of the three studies.

TEXT-TABLE 9.1
Risk of lung cancer in long-term (15+ years) ex-smokers compared to never smokers*

Study	Period given up (years)	Relative risk (95% CI) Males	Females
DORN	40+	1.5 (1.1-2.0)	
BENSHL	31+	1.00 (0.32-3.10)	
DORN	30-39	2.0 (1.6-2.6)	
WYNDER3	30+	1.9 (1.1-3.1)	2.6 (1.2-5.3)
BARBON	25+	2.1 (1.0-4.3)	
LUBIN	20+	2.79 (2.4-3.47)	
CORREA	20+	3.9†	
DORN	20-29	3.3 (2.8-4.0)	
WYNDER3	20-29	3.7 (2.5-5.5)	1.6 (0.9-2.9)
BENSHL	20-29	2.59 (1.21-5.54)	
DEANT	19+	1.31 (0.57-3.02)	
CPSII	16+	3.83 (2.98-4.92)	1.76 (1.25-2.46)
WYNDER2	16+	4.14 (2.26-7.57)	0.72 (0.18-2.97)
GARSHI	15+	3.20 (2.18-4.69)	
DOLL2	15+	2.00 (0.70-5.70)	
BARBON	15-24	6.8 (3.6-12.8)	
LUBIN	15-19	3.80 (2.94-4.92)	

* Estimates are presented in order of period given up.
† CI not available.

Table 9.2 presents data similar to those in Table 9.1, but separated by histological type of lung cancer. Six studies provided suitable data. The pattern of decreasing risk with increasing years given up, but with risk still elevated compared to never smokers, even in long-term quitters, is generally evident for squamous, small and oat-cell carcinoma. For adenocarcinoma (or Kreyberg II) evidence of an excess risk for long-term quitters is less conclusive, as seen in Text-Table 9.2, where risks are shown for the longest quitting group in each study.

TEXT-TABLE 9.2
Risk of lung adenocarcinoma (or Kreyberg II lung cancer)
in long-term ex-smokers compared to never smokers*

Study	Period given up (years)	Relative risk (95% CI) Males	Females
BARBON	25+	1.8 (0.5-6.4)	
LUBIN	20+	1.42 (0.93-2.18)	
WYNDER2	16+	1.2 (0.4-3.3)	0.9 (0.2-3.8)
BENHAM	11+	1.0 (0.2-3.7)	

* Risks are shown for the longest quitting group in each study.

9.2 Risk compared to that in current smokers

Table 9.3 summarizes evidence from 23 studies. Relative risks (with 95% CI) are now shown for progressively increasing number of years stopped across the table from left to right, to show the pattern of decline from the risk in current smokers more clearly.

Data relevant to the decline in risk with increasing years given up are essentially the same as those in Table 9.1 (only the base group differs) and will not be discussed in detail. There are two other issues to be considered, however.

First, a number of the studies show that the lung cancer risk in very short-term quitters is actually higher than that of current smokers, significantly so in GAO, GRAHAM, CPSII, WYNDER2 and ALDERS in at least one of the two sexes. This does not indicate a short-term hazard of giving up smoking. Rather, it reflects the fact that diagnosis of lung cancer or symptoms associated with it may lead many smokers to give up smoking. Differences between studies in whether this elevated risk in short-term ex-smokers was seen may reflect differences in the actual time point at which smoking status was classified and/or whether, in prospective studies, ill patients were excluded from follow-up.

Of more interest is the timing of the decline in risk. To gain some more insight into this, Text-Table 3 shows, for each study, the first time period of quitting at which

risk, in ex-smokers, was reduced by 25%, 50% or 75% compared to that in current smokers. In other words, the first period at which the relative risk fell by 0.75, 0.50 and 0.25.

It can be seen that, in many of the studies, risk in ex-smokers was never observed to reduce by 75% compared to that in current smokers. In those where it did, it virtually always did not occur until a long period of giving up had occurred. Determining precisely the period of quitting necessary to reduce risk by 75% is not straightforward, due to the way the data are presented in open-ended intervals (except for RISCH) and due to sampling variability. However the overall impression of the data (which would require formal analysis to justify) is that one has to quit for something of the order of 20-25 years for risk to reduce this much. To reduce the risk by 25% takes perhaps about 6-8 years and to reduce the risk by 50% about 12-15 years.

Table 9.4 presents data similar to those in Table 9.3, but separated by histological type of lung cancer, with seven studies providing suitable data. A broadly similar pattern of decline with increasing years of quitting is evident for all types.

9.3 Joint relationship of risk to amount smoked when smoking and years of quitting

Table 9.5 presents data from three major prospective studies (CPSI, CPSII, DORN) on the joint relationship of amount smoked and years of quitting to risk of lung cancer. Risks here are presented relative to never smokers.

TEXT-TABLE 9.3
First time period at which risk was seen to have reduced
by 25%, 50% or 75% compared to that in current smokers

	Male			Female		
	Reduction in risk			Reduction in risk		
Study	25%	50%	75%	25%	50%	75%
GAO	10+	10+	-	-	-	-
HIRAYA	1-4	1-4	-	10+	10+	-
SOBUE*	5-9	10+	-			
JOLY	5+	5+	-	5+	-	-
RISCH	7	17	33	5	11	22
BARBON	5-14	15-24	25+			
BECHER	5-10	11+	-	5+	-	-
LUBIN	5-9	15-19	-	5+	5+	-
CORREA†	3-5	20+	-			
BROSS	6+	6+	-			
GRAHAM	6+	6+	-			
CPSI	1-4	5-9	10+			
CPSII	6-10	11-15	16+	3-5	6-10	16+
DORN	5-9	10-19	30-39			
GARSHI	5-14	15+	-			
WYNDER2	7-10	16+	16+	16+	16+	16+
WYNDER3	5-9	5-9	20-29	5-9	5-9	10-19
ALDERS	5-10	5-10	-	5-10	11+	-
DARBY	1-9	1-9	-	10+	10+	10+
DEANN	5-9	10+	-			
DEANT	1-4	9-18	19+	1-4	1-4	5-8
DOLL1	1-9	10+	-	10+	10+	-
DOLL2	5-9	5-9	15+			

* Based on average of results presented separately by age.
† Results are for sexes combined.
\- Risk was never observed to reduce by the given amount.

In CPSII, DORN and in the six-year follow-up data from CPSI, risk always rises

monotonically with amount smoked, given years stopped. Risk also, with only minor exceptions (CPSII females 1-19/day, DORN males 1-19/day), rises monotonically with decreasing years stopped, given level of smoking. The pattern is rather less clear in the 12 year follow-up data from CPSII, which is broken down by a large number of categories for both years stopped and cigarettes per day. Formal analysis of these data would be necessary to determine whether this apparent lack of clarity is real or is a result of sampling (or other) error.

10. Summary

A compilation is presented of the epidemiological evidence relating lung cancer risk to amount smoked, age at starting to smoke, duration of smoking, pack-years of smoking and years since stopped smoking. Data from all 59 case-control and prospective studies providing relevant information on at least 500 lung cancer cases have been systematically presented. Relative risks and 95% confidence intervals relating to all the aspects of smoking considered have been extracted, or calculated where necessary. Data relating to duration or pack-years of smoking that have not been age-adjusted have not been included so as to avoid gross bias.

Of the 59 studies, 10 were prospective (3 with over 25 years follow-up) and 49 case-control. Twenty-five were conducted in the USA, 10 in the UK, 11 in the rest of Europe, 9 in Asia, 3 in Canada and 1 in Cuba. The earliest studies reported results in 1950. Eight studies involved over 5000 lung cancer cases with 3 exceeding 10000. Common study weaknesses included failure to require histological confirmation of lung cancer, obtaining data from proxy respondents more frequently for cases than controls, and lack of control for lung cancer risk factors other than smoking. Studies varied in the extent to which lung cancer diagnosis would have been accurate, the depth in which questions were asked on smoking, the definitions used to categorize subjects by smoking category, the types of controls used in case-control studies, and the extent to which potential confounding factors were taken into account. Many of the studies concerned special groups (e.g. doctors or war veterans) which were not necessarily representative of the population at large.

In due course the data presented here (as well as those from other studies of 100 to 500 cases) will be placed on a computer database, which will allow formal meta-analyses to be conducted and a more detailed evaluation of how differences between study findings depend on the location and timing of the study and various aspects of its design and analysis. For the present conclusions are based on a simpler examination of the data presented.

Amount smoked Virtually all the studies show a very clear tendency for lung cancer risk to rise with the amount regularly smoked (or smoked at one specific point in time). An increased risk is clearly evident for those smoking less than 10 cigarettes a day. The relative risk associated with the highest level of exposure studied commonly exceeds 20. For a given amount smoked, relative risks tend to be higher for men than for women (although the data are not completely consistent), and lower in Asia than in the USA, UK or Europe. For women, relative risks are clearly higher in more recent studies. A similar tendency is evident to some extent in men. For a given amount smoked, relative risks are clearly higher for squamous cell and small (oat) cell carcinoma than for adenocarcinoma. A dose-relationship with amount smoked is still evident for adenocarcinoma in most studies.

Age of starting to smoke With only minor exceptions, the data consistently show that an earlier age of starting to smoke is associated with an increased risk of lung cancer. The difference in risk between early and late starters is much more marked than would be expected were there a linear relationship of risk to duration of smoking. Evidence from one study indicates this difference is not materially explained by the tendency of earlier starters to smoke more. The relationship of earlier age of starting to smoke to increased risk is clearly evident for squamous carcinoma, but is less clearly seen for adenocarcinoma in the limited data available.

Duration of smoking Given age, risk of lung cancer was generally found to increase monotonically with duration of smoking. However, the way the data are presented and analysed in the source papers makes it difficult to get a clear idea of the true shape of the relationship of duration to risk. A relationship of lung cancer risk with duration of smoking was always evident for squamous and small cell carcinoma and was generally evident for other histological types also, and was generally evident within smokers of a given level of smoking. The relationship of lung cancer risk to duration of smoking was found to vary by amount smoked in the two American Cancer Society CPS studies, not being apparent at all in smokers of 1-9 cigarettes/day. Overall, the CPS data did show an association of lung cancer risk with duration of smoking, but only up to about 40 years smoked.

Pack-years smoked Pack-years as an index of exposure is open to the criticism that it multiplies together two aspects of smoking (duration and amount) that may relate very differently to risk. Unsurprisingly, given the evidence for duration and amount, risk of lung cancer (and all the major histological types) was found to increase steadily with increasing pack-years smoked.

Years stopped smoking Among ex-smokers, risk of lung cancer (and all the major histological types) clearly declines with increasing time given up. For those giving up smoking for 25 years or longer, an increased risk of lung cancer (compared to never smokers) is still evident, by about 2-fold. Compared to current smokers, risk declines with increasing time given up (an apparent increase in risk seen in some studies associated with very short-term giving up being likely to be an artefact caused by quitting because of disease). The decline can be seen within categories of amount smoked.

Overall, the data are clearly consistent with any aspect of dose reduction (smoking less cigarettes per day, smoking for a shorter duration, or giving up for longer periods) being associated with a reduced risk of lung cancer. This supports evidence reviewed separately that risk is reduced in relation to a reduced tar delivery of cigarettes.

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T1

TABLE 3.1

The 59 studies selected

Continent (Country)	Country (State)	Study name	Study title	Study type[a]	Period of deaths/cases
Asia	China	GAO	Shanghai case-control study	CC	1984-86
	China	FU	Harbin case-control study	CC	1977-79
	China	LIU	Chinese million deaths study	CC	1986-88
	China	XU	Shenyang case-control study	CC	1985-88
	China	YU	15 Chinese case-control studies (includes GAO,FU,XU)	CC	1981-90
	India	JUSSAW	Greater Bombay case-control study	CC	1964-73
	India	NOTANI	Bombay Tata Memorial study	CC	1963-71
	Japan	HIRAYA	Japanese 29 health centres study	P	1965-81
	Japan	SOBUE	Osaka case-control study	CC	1986-88
Central America	Cuba	JOLY	Havana case-control study	CC	1978-80
North America (not USA)	Canada	BEST	Canadian veterans study	P	1955-62
	Canada	RISCH	Ontario case-control study	CC	1981-85
	Canada	SIEMIA	Montreal case-control study	CC	1979-85
Europe (not UK)	Denmark	PRESCO	Copenhagen prospective studies	P	1964-94
	Finland	AUVINE	Finnish nested case-control study	NC[b]	1986-92
	France	BENHAM	French case-control study	CC	1976-80
	France	SCHWAR	French case-control study	CC	1954-?
	Greece	TRICHO	Greek case-control study	CC	1950-62
	Italy	BARBON	Trieste case-control study	CC	1979-86
	Poland	BECHER	Cracow case-control study	CC	1980-87
	Sweden	DAMBER	North Sweden case-control study	CC	1972-77
	Sweden	PERSHA	Swedish case-control study	CC	1980-84
	Turkey	DOSEME	Istanbul case-control study	CC	1979-84
	Multicountry (inc. UK)	LUBIN	West European case-control study	CC	1976-80

T2

TABLE 3.1 (continued)

The 59 studies selected

Continent (Country)	Country (State)	Study name	Study title	Study type[a]	Period of deaths/cases
USA	California	BRESLO	California case-control study	CC	1949-52
	California	OSANN	Orange County case-control study	CC	1984-86
	California	PIKE	Los Angeles case-control study	CC	1972-75
	Florida	STOCKW	Florida case-control study	CC	1981-83
	Georgia	BLOT	Coastal Georgia case-control study	CC	1970-76
	Louisiana	CORREA	Louisiana case-control study	CC	1979-81
	Michigan	SCHWAR2	Detroit case-control study	CC	1984-87
	Missouri	BROWNS	Missouri case-control study	CC	1984-90
	New Jersey	SCHOEN	New Jersey case-control study	CC	1981-83
	New Mexico	HUMBLE	New Mexico case-control study	CC	1980-82
	New York	BROSS	Second Roswell Park case-control study	CC	1960-66
	New York	GRAHAM	First Roswell Park case-control study	CC	1956-60
	Texas	BUFFLE	Texas 6 counties case-control study	CC	1976-80
	25 States	CPSI	First American Cancer Society million person study	P	1959-72
	Nationwide	CPSII	Second American Cancer Society million person study	P	1982-88
	Nationwide	DORN	US veterans study	P	1954-80
	Nationwide	GARSHI	US railroad workers case-control study	CC	1981-82
	Multicentre (inc. Canada)	KAUFMA	US/Canada multicentre case-control study	CC	1981-86
	Multicentre	MRFIT	Multiple risk factor intervention trial	P	1973-86
	Nationwide	NMFS	National mortality followback survey	CC	1986
	9 areas	TNCS	Third national cancer survey	CC	1969-71
	3 states	WYNDER	Three state case-control study	CC	Late 1940s
	6 cities	WYNDER2	Six cities case-control study/1	CC	1969-76
	6 cities	WYNDER3	Six cities case-control study/2	CC	1977-84[c]
	6 cities	WYNDER4	Six cities case-control study/3	CC	1981-94[c]

T3

TABLE 3.1 (continued 2)

The 59 studies selected

Continent (Country)	Country (State)	Study name	Study title	Study type[a]	Period of deaths/cases
UK	England	ALDERS	10 hospital regions case-control study	CC	1977-82
	London	BENSHL	Whitehall civil servants study	P	1967-87
	S.W.England	DARBY	South West England case control study	CC	1989-93
	N.Ireland	DEANN	Northern Ireland case-control study	CC	1960-62
	Teesside	DEANT	Teesside case-control study	CC	1969-72
	England	DOLL1	Five hospital regions case-control study	CC	1948-52
	Britain	DOLL2	British doctors study	P	1951-91
	W.Scotland	GILLIS	West of Scotland case-control study	CC	1976-81
	London	KINLEN	London random sample	P	1967-86
	N.Wales and Liverpool	STOCKS	North Wales and Liverpool case-control study	CC	1953-55

Notes
[a] CC = case control PP = prospective NC = nested case-control
[b] Within a cohort of all Finns who lived in single-family houses for 19+ years
[c] There may be some overlap of the WYNDER3 and WYNDER4 studies

T4

TABLE 3.2

Lung cancer cases in the 59 studies

Study	Number of lung cancers[a] Men	Women	Histological confirmation	Results by histological type	Proxy interviews
GAO	733	672	53%	Yes	No
FU	523[b]		Not required	No	100%
LIU	20199	8830	Not required	No	100%
XU	729	520	83%M 73%F	Yes	No
YU	3535	2168	Not required	Yes	Yes
JUSSAW	792	-	41%[c]	No	No
NOTANI	683	-	42%[c]	No	No
HIRAYA	1454	463	No:DC[d]	No	No
SOBUE	1082	294	100%	Yes	No
JOLY	607	219	100%[c]	No	No
BEST	525	11	No:DC[d]	No	No
RISCH	403	442	98%	Yes	34%
SIEMIA	857	-	100%	Yes	18%
PRESCO	809	453	No:DC[d]	Yes[e]	No
AUVINE	479	38	Not required	No	Yes
BENHAM	1529	96	100%	Yes	No
SCHWAR	1159	-	Not required	No	No
TRICHO	862	-	Not required	No	?[f]
BARBON	755	-	100%	Yes	100%
BECHER	1432	198	44%	Yes	100%
DAMBER	604	-	98%[c]	Yes	100%
PERSHA	774	586	84%	No	92%
DOSEME	1210	-	100%	Yes	No
LUBIN	6920	884	100%	Yes	No
BRESLO	493	25	100%	Yes	No
OSANN	1153	833	100%	Yes	?[f]
PIKE	1425	576	Not required	No	Yes
STOCKW	17050[g]	8350[g]	100%	No	?[f]
BLOT	535	-	Not required	No	Yes
CORREA	1036	302	97%	Yes	24%

TABLE 3.2 (continued)

Lung cancer cases in the 59 studies

Study	Number of lung cancers[a] Men	Women	Histological confirmation	Results by histological type	Proxy interviews
SCHWAR2	3680	1908	100%	Yes	58%
BROWNS	9384	5212	100%	Yes	?[f]
SCHOEN	1050	994	100%	Yes	43%
HUMBLE	348	183	100%	No	47%
BROSS	974	-	Not required	No	No
GRAHAM	685	-	Not required	No	No
BUFFLE	475	460	100%[c]	Yes	84%
CPSI	4266	1247	No:DC[h]	Some[h]	No
CPSII	2920	1462	No:DC[i]	Some[i]	No
DORN	5097[j]	-	No:DC[k]	Some[k]	No
GARSHI	1256	-	No:DC[d]	No	100%
KAUFMA	534	347	Not required	No	No
MRFIT	2004	-	No:DC[d]	No	No
NMFS	641	342	No:DC[d]	No	100%
TNCS	570[l]	140[l]	No:DC[d]	Yes	No
WYNDER	644	40	98%	No	2%
WYNDER2	1051	314	100%	Yes	No
WYNDER3	2085	1012	100%	Yes	No
WYNDER4	1156	831	100%	Yes	No
ALDERS	819	630	53%	Yes	No
BENSHL	500	-	No:DC[d]	No	No
DARBY	667	315	71%	No	No
DEANN	803	151	Not required	No	100%
DEANT	616	150	Not required	No	100%
DOLL1	1357	108	68%	Yes	No
DOLL2	893	27	No:DC[m]	No	No
GILLIS	656	-	77%	Yes	No
KINLEN	718	-	No:DC[d]	No	No
STOCKS	576	-	Not required	No	Yes

T6

TABLE 3.2 (continued 2)

Lung cancer cases in the 59 studies

Notes

[a] Numbers of lung cancers usually relate to totals in study; in some studies they relate to smokers analyzed.

[b] Numbers between columns relate to sexes combined.

[c] % confirmed by histology or cytology.

[d] DC = death certificates.

[e] The numbers of lung cancers cited were deaths, incidence data with histological type were available for 867 cases.

[f] Data related to the smoking habits of the patients were taken from the patient history, no further details being given.

[g] Approximate data. Cases totalled 26398 and 67.1% of cases with race known were male.

[h] Hospital records were sought for all lung cancer deaths in the first two years of follow-up. Microscopic or cytologic reports were available for 70% of these. [52] gives limited results comparing overall risk of lung cancer in smokers and nonsmokers by histology.

[i] Hospital records were sought for all lung cancer deaths in the first two years of follow-up. Microscopic or cytologic reports were available for 61.5% of these. [52] gives limited results comparing overall risk of lung cancer in smokers and nonsmokers by histology.

[j] Less than 0.5% were female, and the analyses have generally been for the population combined.

[k] Although mortality analyses are presented based on death certificates with no reference to histological type, one paper[54] does report a survey of histological types in 2241 of the lung cancers occurring in the first 8½ years of follow-up. 1477 had histological sections available, with lung cancer confirmed in 1047. Data on the distribution of smoking by histological type were presented but not mortality rates.

[l] Approximate data.

[m] Although some analyses are based on lung cancers independently confirmed following a review of medical records.

T7

TABLE 3.3

Controls (or populations at risk) in the 59 studies

Study	Number of controls[a] Men	Women	Type of control[b]	Matching factors	Proxy interviews
GAO	760	735	Population: neighbourhood	Age (broadly)	No
FU	523[c]		Decedent: not RD	Age, sex, district	100%
LIU	52755	34560	Decedent: not CA,RD,VAD	None	100%
XU	788	577	Population: neighbourhood	Age (broadly), sex	No
YU	3173	2496	Varies by study	Varies by study	Some
JUSSAW	792	-	Population: Voters List	Age, community	No
NOTANI	1279	-	Hospital: not CA or RD	Age, community	No
HIRAYA	(122261)	(142857)	Prospective study	NA[d]	No
SOBUE	1141	1089	Hospital: not SAD	Sex	No
JOLY	1518[c]		Hospital: not SAD (479) and Population Neighbourhood (539)	Age, sex, race, hospital, date, area[e]	No
BEST	(77541)	(14226)	Prospective study	NA[d]	No
RISCH	362	410	Population	Age, sex, borough	No
SIEMIA	533	-	Population	Age (broadly)	No
PRESCO	(17452)	(13465)	Prospective study	NA[d]	No
AUVINE	479	38	Selected from cohort	Year of birth, sex	Yes
BENHAM	2899	192	Hospital: not SAD	Age, sex, hospital, interviewer	No
SCHWAR	1159	-	Hospital: ACC[f]	Age, interviewer, date of interview	No
TRICHO	613	-	Hospital: CA not R	None	?[g]
BARBON	775	-	Decedent: not SAC	Age, period of death	100%
BECHER	1343	198	Decedent: not RD	Age, sex, period of death	100%
DAMBER	1071	-	Decedent: not LUCA, SUI and Population	Age, year of death, year of birth, municipality[h]	100%, 0%[i]
PERSHA	1467	1380	Population: registers and Decedent: not SAD	Age, sex, residence, vital status	55%
DOSEME	829	-	Hospital: CA not SAD	None	No
LUBIN	13460	1747	Hospital: not SAD	Age, sex, study site	No
BRESLO	493	25	Hospital: not CA, RD	Age, sex, race	No

OSANN	1851	1656	CA. registry: not SAC	Sex	?[g]

TABLE 3.3 (continued)

Controls (or populations at risk) in the 59 studies

Study	Number of controls[a] Men	Women	Type of control[b]	Matching factors	Proxy interviews
PIKE	445	186	Population: neighbourhood	Age, sex	Very few
STOCKW	11530[j]	11170[j]	CA. registry: CO or RE CA	Sex	?[g]
BLOT	659	-	Hospital and decedent: not BL CA or RD	Age, sex, race, residence, vital status	Yes
CORREA	1073	320	Hospital: not RD, SAC	Age, sex, race	11%
SCHWAR2	1774	1918	Population: telephone	Sex	8%
BROWNS	36438[c]		Hospital: CA not SAC	Age	?[g]
SCHOEN	217[k]	995	Population: Drivers list and Decedent: not LUCA or RD	Age, sex, race, vital status, period of death	41%
HUMBLE	497	272	Population: telephone and Medicare	Age, sex, race	2%
BROSS	974	-	Hospital: not CA	Age, admission date	No
GRAHAM	1997	-	Hospital: not RD or SAD	None	No
BUFFLE	466	482	Population: State and federal records and Decedent	Age, sex, race, vital status, residence	84%
CPSI	(456491)	(594551)	Prospective study	NA[d]	No
CPSII	(508579)	(676527)	Prospective study	NA[d]	No
DORN	(248046)[l]	-	Prospective study	NA[d]	No
GARSHI	2385	-	Decedents: not CA, SUI, ACC or UK	Age, time of death	100%
KAUFMA	998	1572	Hospital: not CA or SAD	Sex	No
MRFIT	(361662)	-	Prospective study	NA[d]	No
NMFS	1590	1352	Decedents: not CA or CD or RD	Sex	100%
TNCS	1742	3162	Incident cancers: not SAC	Sex	No
WYNDER	780	-	Hospital: Not CA	None	No
WYNDER2	2519	831	Hospital: not SAD	Age, sex, race, city	No
WYNDER3	3948	1891	Hospital: not SAD	Age, sex, race, city, year of interview	No
WYNDER4	1122	948	Hospital: not SAD	Age, sex, race, city, year of interview	No
ALDERS	819	630	Hospital: not SAD	Age, sex, region, ward, time of interview	No

TABLE 3.3 (continued 2)

Controls (or populations at risk) in the 59 studies

Study	Number of controls[a] Men	Women	Type of control[b]	Matching factors	Proxy interviews
BENSHL	(19018)	-	Prospective study	NA[d]	No
DARBY	2108	1077	Hospital: not SAD and Population	Age, sex, residence	No
DEANN	803	151	Decedent: not RD	Age, sex, date of death	100%
DEANT	2563	2958	Population	Sex	51%
DOLL1	1357	108	Hospital: not SAC	Age, sex, hospital	No
DOLL2	(34439)	(6194)	Prospective study	NA[d]	No
GILLIS	1312	-	Hospital: not SAD	Age, sex, time of interview	No
KINLEN	(14085)	-	Prospective study	NA[d]	No
STOCKS	5960	-	Hospital: not CA	None	Yes

Notes

[a] Numbers of controls usually relate to totals in study; in some studies they relate to smokers analyzed. Bracketed numbers indicate size of baseline populations in prospective studies.

[b] ACC = accident, BL = bladder, CA = cancer, CD = circulatory disease, CO = colon, LU = lung, R = respiratory, RD = respiratory disease, RE = rectum, SAC = smoking associated cancers, SAD = smoking associated diseases, SUI = suicide, UK = unknown cause, VAD = vascular disease.

[c] Numbers between columns relate to sexes combined.

[d] NA = not applicable.

[e] Hospital and date for hospital controls, area for neighbourhood controls.

[f] A sample of controls with diseases other than cancer were interviewed but not used in the analyses of effects of smoking.

[g] Data related to the smoking habits of the patients were taken from the patient history, no further details being given.

[h] Year of death and age for decedent controls, year of birth for living controls.

[i] 100% for decedent controls, 0% for living controls.

[j] Approximate data. Controls totalled 22704 and 50.8% of controls with race known were male.

[k] Approximate data.

[l] Less than 0.5% were female, and the analyses have generally been for the population combined.

T10

TABLE 3.4

Aspects of smoking considered[a]

Study	Number of cigs smoked	Age of starting	Duration of smoking[b]	Pack years[b]	Years since stopped	Other
GAO	✓	✓	✓AO		✓	Duration x number
FU	✓	✓				Duration x number
LIU	✓	✓				
XU			✓AO			Duration x number
YU	✓	✓				
JUSSAW	✓					
NOTANI	✓					
HIRAYA	✓	✓			✓	Age start x pack years
SOBUE	✓H		✓H		✓	
JOLY	✓	✓			✓	
BEST	✓		✓			
RISCH[c]	(✓)	(✓)	(✓)	✓H	✓H	
SIEMIA				✓H		
PRESCO	✓		✓H	✓H		
AUVINE	✓	✓	✓			
BENHAM	✓H	✓H			✓H	
SCHWAR	✓					
TRICHO	✓					
BARBON	✓H	✓H	✓H	✓H	✓H	
BECHER	✓H	✓H	✓H	✓H	✓H	Duration x number
DAMBER	✓H	✓	✓H		✓	
PERSHA	✓					
DOSEME	✓H		✓H	✓H		
LUBIN	✓				✓H	
BRESLO	✓H	✓				
OSANN	✓H					
PIKE	✓					
STOCKW	✓					
BLOT	✓					

TABLE 3.4 (continued)

Aspects of smoking considered[a]

Study	Number of cigs smoked	Age of starting	Duration of smoking[b]	Pack years[b]	Years since stopped	Other
CORREA	✓H	✓		✓	✓	
SCHWAR2				✓		
BROWNS	✓H					
SCHOEN	✓H		✓H			Duration x number
HUMBLE	✓		✓			
BROSS	✓				✓	
GRAHAM					✓	
BUFFLE			✓H			
CPSI	✓	✓	✓		✓	Duration x number Years stopped x number
CPSII	✓		✓		✓	Duration x number, Years stopped x number
DORN	✓	✓			✓	Age start x number, Years stopped x number
GARSHI	✓			✓	✓	
KAUFMA	✓					
MRFIT	✓					
NMFS	✓					
TNCS				✓H		
WYNDER	✓					
WYNDER2	✓		✓AO		✓H	Duration x number
WYNDER3	✓H				✓	
WYNDER4	✓H	✓H	✓HO	✓H	✓HO	
ALDERS	✓H	✓H			✓H	
BENSHL	✓				✓	
DARBY	✓				✓	
DEANN	✓				✓	
DEANT	✓	✓			✓	

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TABLE 3.4 (continued 2)

Aspects of smoking considered[a]

Study	Number of cigs smoked	Age of starting	Duration of smoking[b]	Pack years[b]	Years since stopped	Other
DOLL1	✓H	✓			✓	
DOLL2	✓H				✓	
GILLIS	✓H					
KINLEN	✓					
STOCKS	✓					

Notes

[a] ✓ = relevant aspect of dose considered, H = relevant aspect also considered by histological type, HO = relevant aspect considered by histological type only, AO = relevant aspect considered by amount smoked only.

[b] Studies involving age-matched cases and controls which only present data on duration or pack-years unadjusted for age are not counted as such estimates are severely biassed.

[c] Results for number of cigarettes smoked, age of starting and duration only expressed as means for cases and controls, so that relative risks could not be calculated.

T13

TABLE 3.5

Potential nonsmoking confounding variables adjusted for

Study	None	Age	Race	Area of residence	Income/ education/ social class	Occupation	Other[a]
GAO		✓			✓		
FU		✓[a]			✓[a]		Centre[b]
LIU		✓					
XU		✓[a]			✓[a]		
YU							Centre[b]
JUSSAW	✓						
NOTANI	✓			✓			
HIRAYA		✓				✓	Period
SOBUE		✓					
JOLY	✓						
BEST		✓					
RISCH		✓		✓			
SIEMIA		✓	✓		✓	✓	Coffee, alcohol, beta-carotene
PRESCO		✓					Study cohort, period
AUVINE		✓					Vital status
BENHAM		✓					Hospital, interviewer
SCHWAR	✓						
TRICHO		✓					
BARBON		✓					
BECHER		✓			✓	✓	Air pollution
DAMBER		✓					
PERSHA	✓						
DOSEME		✓					Alcohol
LUBIN	✓						
BRESLO	✓						
OSANN		✓	✓				
PIKE	✓						
STOCKW	✓						

TABLE 3.5 (continued)

Potential nonsmoking confounding variables adjusted for

Study	None	Age	Race	Area of residence	Income/ education/ social class	Occupation	Other
BLOT	✓						
CORREA		✓					
SCHWAR2		✓					
BROWNS		✓				✓	
SCHOEN		✓	✓				Respondent type
HUMBLE		✓	✓				
BROSS	✓						
GRAHAM		✓					
BUFFLE		✓	✓		✓		Vital status
CPSI		✓					
CPSII		✓					
DORN		✓					
GARSHI		✓					
KAUFMA		✓	✓	✓	✓		Year of interview
MRFIT		✓	✓				Blood pressure, cholesterol
NMFS		✓					
TNCS		✓	✓				
WYNDER		✓			✓		
WYNDER2		✓	✓				
WYNDER3	✓						
WYNDER4		✓			✓		
ALDERS		✓					
BENSHL		✓					
DARBY	✓						
DEANN		✓					
DEANT		✓		✓	✓		

TABLE 3.5 (continued 2)

Potential nonsmoking confounding variables adjusted for

Study	None	Age	Race	Area of residence	Income/ education/ social class	Occupation	Other
DOLL1	✓						
DOLL2		✓					
GILLIS	✓						
KINLEN		✓					Tea
STOCKS		✓					

Notes

[a] Sex has not been considered. The four studies that presented results for sexes combined adjusted for sex, with the exception of FU, YU, BRESLO and PERSHA which matched cases and controls on sex and STOCKW, where the only analysis we could derive was not adjusted or matched for sex.

[b] Age, education and centre only adjusted for in joint analyses of XU + FU.

T16

TABLE 4.1

A (simplified) illustration of the magnitude of bias caused by failure to adjust for age when considering effects of smoking duration in age-matched case-control studies

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1. Assume that, at each of ages 40, 45, 50 ... 80, the number of smokers in the population who started to smoke at age 15 and at age 20 are equal and that there is no other age at which smokers started.

2. Assume that, at each age, the risk of lung cancer in those starting to smoke at age 15 is twice that in those starting at age 20.

3. It follows that, at each age, the frequency of lung cancer cases starting to smoke at age 15 will be twice that of those starting at age 20.

4. For a given age group, we sample an equal number of cases and controls. The relative distribution of cases and controls will therefore be as follows:

Controls	started age 15	3N
Controls	started age 20	3N
Cases	started age 15	4N
Cases	started age 20	2N

(where 6N is the number of pairs sampled).

5. Let $6N_{40}$, $6N_{45}$, ... be the number sampled at the successive ages, where N_{40}, N_{45} .... will rise with age initially and then fall due to the smaller number surviving to the highest age groups.

6. We then ignore age and subdivide the population by duration of smoking. We can then write down the numbers of controls and cases

Duration	Controls	Cases
20	$3N_{40}$	$2N_{40}$
25	$3N_{45} + 3N_{40}$	$2N_{45} + 4N_{40}$
30	$3N_{50} + 3N_{45}$	$2N_{50} + 4N_{45}$
35	$3N_{55} + 3N_{50}$	$2N_{55} + 4N_{50}$
.		
.		

TABLE 4.1 (Continued)

7. (In the above, the first column of cases and of controls derives from data for those starting at age 20, the second column from data for those starting at age 15.)

8. For any two successive duration groups (d, d+5), the true relative risk has been assumed to be 2:1 for higher:lower duration. The relative risk, as calculated by the cross product ratio will be

$$\frac{(2N_{d+25} + 4N_{d+20})(3N_{d+20} + 3N_{d+15})}{(2N_{d+20} + 4N_{d+15})(3N_{d+25} + 3N_{d+20})}$$

There is no reason why this estimate should be equal to 2. For example, if $N_{d+15} = N_{d+20} = N_{d+25}$ (numbers of cases not rising with age), it is easy to see that the estimate will be calculated as 1. Alternatively if $N_{d+15}:N_{d+20}:N_{d+25} = 1:2:5$ (numbers of cases rising with age), the estimate will be calculated as 0.96. Neither are remotely close to 2.

T18

TABLE 5.1

Relative risk (95% CI) of lung cancer by amount smoked (base = never smokers and comparison groups = current smokers, unless indicated)

Study/ adjustment factors	Number of cases	Sex	Relative risk (95% CI) by amount smoked			
GAO			0	1-19	20-29	30+cigs/day
None	671F	Female	1.00	1.32(0.93-1.87)	2.37(1.60-3.51)	10.55(5.71-19.50)
			(comparison groups = ever smokers)			
			0	1-4	5-9	10-14 cigs/day
FU			1.00	0.85(0.45-1.61)	1.34(0.85-2.10)	1.94(1.28-2.94)
None (not sex)	523M+F	Both				
			...	15-19	20-29	30+cigs/day
				2.09(1.36-3.19)	3.01(2.12-4.25)	5.93(3.39-10.4)
			(comparison groups = ever smokers)			
LIU			0	1-19	20	21+ cigs/day
Age	20199M aged 35-69	Male	1.00	2.11(2.02-2.20)	3.60(3.49-3.71)	6.98(6.73-7.23)
			(base group = nonsmoker in 1980)			
YU			0	1-9	10-19	20+cigs/day
Centre (not sex)	2019M+F,	Both	1.00	1.24(0.87-1.76)	2.19(1.43-2.79)	4.47(2.79-7.17)
	1048F	Female	1.00	2.24(1.70-2.95)	6.11(4.61-8.11)	12.20(8.84-16.85)
JUSSAW			0	1-4	5-9	10-14
None	726M	Male	1.00	17.1(9.07-32.1)	11.2(6.76-18.4)	6.60(4.73-9.20)
			...	15-19	20-24	25+ cigs/day
				11.1(6.44-19.1)	15.6(8.60-28.4)	94.2(48.8-182)
			(comparison groups = ever smokers of bidi only or cigarettes only)			
NOTANI			0	1-9	10-19	10-20+ cigs/day
None	646M	Male	1.00	1.83(1.33-2.51)	2.70(2.04-3.58)	4.71(3.65-6.08)
			(comparison groups = ever smokers of bidi only or cigarettes only)			
HIRAYA			0	1-4	5-14	15-24
Age, period	1200M,	Male	1.0	2.5(1.4 -4.3)	3.3(2.6 -4.3)	5.4(4.3-6.9)
	394F		...	25-34	35+ cigs/day	
				7.1(5.1-9.7)	8.4(5.7-12.3)	
			0	1-4	5-14	15+ cigs/day
		Female	1.0	1.9(1.0-3.2)	2.5(1.9-3.3)	3.1(1.8-5.1)

TABLE 5.1 (Continued)

Study/ adjustment factors	Number of cases	Sex	Relative risk (95% CI) by amount smoked			
SOBUE			1-19	20-29	30+ cigs/day	
Age, duration, inhalation, cig.type, fraction smoked	609M	Male	1.0	1.3(1.0-1.8)	1.7(1.2-2.3)	
			(results for current smokers only with base 1-19/day; age-adjusted RR for current/never = 4.1 [2.8-5.9])			
JOLY			0	1-9	10-19	20-29
None	564M, 217F	Male	1.0	5.38(2.41-12.0)	12.4(6.76-22.7)	13.1(7.00-24.4)
			...	30+ cigs/day		
				21.8(11.7-40.4)		
			0	1-9	10-19	20-29
		Female	1.0	4.73(2.72-8.21)	8.00(5.01-12.8)	6.93(3.68-13.0)
			...	30+ cigs/day		
				13.4(6.59-27.2)		
Duration			0	1-9	10-19	20-29	30+ cigs/day
		Male	1.0	1.0	2.1	2.3	3.6
		Female	1.0	1.0	1.2	1.2	2.3
			(comparison group = ever smokers)				
BEST			0	1-9	10-20	21+ cigs/day
Age	331M	Male	1.0	10.0(4.56-21.9)	16.4(7.73-34.9)	17.3(7.98-37.8)
PRESCO			0	1-14	15-24	25+ grams/day
Age, study cohort, period	809M, 453F	Male	1.0	10.7(4.7-24.5)	20.0(8.9-44.9)	24.6(10.8-56.3)
		Female	1.0	9.4(5.1-17.0)	12.6(6.8-23.1)	20.0(9.2-43.3)
AUVINE			0	1-10	11-20	21+ cigs/day
Age, sex	310 M+F	Both	1.00	4.69(3.12-7.03)	5.92(4.17-8.42)	6.98(4.63-10.5)
BENHAM			0	1-14	15-20	21+ cigs/day
None	1217M	Male	1.00	7.23(4.90-10.7)	13.5(9.28-19.5)	21.4(14.7-31.2)
Age, sex, hospital, interviewer	96F	Female	0	1-9	10-19	20+ cigs/day
			1.00	1.23(0.41-3.73)	2.88(1.16-7.15)	20.0(5.96-66.9)
			(comparison group = ever smokers)			
SCHWAR			0	1-9	10-19	20-29
None	1151M	Male	1.00	2.57(1.74-3.78)	5.61(3.94-8.00)	8.58(6.03-12.2)
			...	30+ cigs/day		
				16.4(10.6-25.3)		
			(base group = not smoked in last 10 years)			
TRICHO			0	1-10	11-20	21+ cigs/day
Age	862M	Male	1.00	1.71(1.15-2.56)	7.06(4.76-10.5)	27.1(16.4-44.8)

TABLE 5.1 (Continued 2)

Study/ adjustment factors	Number of cases	Sex	Relative risk (95% CI) by amount smoked			
BARBON			0	1-9	10-19	20-29
Age	755M	Male	1.00	2.7(1.5-5.1)	9.8(5.9-16.3)	10.9(6.7-17.8)
			...	30-39	40+ cigs/day	
				13.6(8.1-23.0)	17.7(10.7-29.2)	
				(comparison group = ever smokers)		
BECHER			0	1-19	20-29	30+ cigs/day
Age,	901M,	Male	1.00	3.48(2.33-5.19)	6.16(4.25-8.90)	7.69(5.15-11.5)
occupation,	198F	Female	1.00	6.37(2.66-15.2)	2.38(1.17-6.86)	7.37(2.2-24.7)
air pollution				(comparison group = ever smokers)		
DAMBER			0	1-7	8-15	16-25
Age	579M	Male	1.0	2.3(1.2-4.5)	7.3(4.4-12.9)	8.8(5.3-15.2)
			...	26+ cigs/day		
				14.9(6.8-34.0)		
PERSHA			0	1-9	10+ cigs/day	
None (not sex)	914M+F	Both	1.0	5.43(4.35-6.78)	10.3(8.32-12.8)	
DOSEME			0	1-10	11-20	21+ cigs/day
Age, alcohol	1210M	Male	1.0	2.2(1.4-3.3)	3.1(2.3-4.1)	6.6(4.4-10.2)
LUBIN			0	1-9	10-19	20-29
None	6074M,	Male	1.0	4.83(4.03-5.78)	8.03(6.79-9.50)	10.9(9.24-12.9)
	772F	Female	1.0	1.69(1.26-2.28)	3.80(3.03-4.76)	5.25(3.97-6.95)
				30+cigs/day		
		Male	...	12.5(10.5-14.9)		
		Female	...	5.25(3.39-8.14)		
BRESLO			0	1-19	20-39	40+ cigs/day
None	518M+F	Both	1.0	2.12(1.34-3.35)	5.57(3.66-8.47)	13.3(7.24-24.3)
				(consumption for current smokers based on smoking in 20 years prior to study)		
OSANN			0	1-39	40+ cigs/day	
Age, race	1153M,	Male	1.0	17.7(12.6-24.8)	42.8(30.5-60.1)	
	833F	Female	1.0	14.4(11.0-18.9)	40.9(29.3-57.1)	
PIKE			0	1-20	21-40	41+ cigs/day
None	1425M,	Male	1.00	4.83(3.15-7.40)	9.40(6.06-14.6)	9.46(5.60-16.0)
	576F	Female	1.00	2.57(1.72-3.83)	6.38(3.91-10.4)	16.6(5.03-54.5)
STOCKW	25398		0	1-19	20-40	41+ cigs/day
None (not sex)	M+F	Both	1.00	6.67(6.15-7.25)	14.5(13.5-15.5)	28.8(26.2-31.8)

TABLE 5.1 (Continued 3)

Study/ adjustment factors	Number of cases	Sex	Relative risk (95% CI) by amount smoked			
BLOT			0-9	10-39	40+ cigs/day	
None	535M	Male	1.00	4.27(3.08-5.93)	8.10(5.26-12.5)	
			(base group includes ex smokers for 10+ years and smokers of <10 cigs/day)			
CORREA			0	1-20	21+ cigs/day	
Sex	1253M+F	Both	1.0	9.3(6.8-12.7)	25.3(18.5-34.6)	
BROWNS			0	1-19	20+ cigs/day	
Age, occupation	5212M	Male	1.0	6.1(5.3-6.9)	14.1(12.7-15.5)	
	9384F	Female	1.0	8.4(7.2-9.7)	17.1(15.3-19.1)	
SCHOEN			0	1-19	20+ cigs/day	
Age, race,	763M	Male	1.0	7.1(3.9-13.0)	14.0(7.8-25.0)	
respondent type		Female	1.0	5.7(4.4-7.4)	12.2(9.3-16.0)	
	994F	(White)		(comparison group = ever smokers)		
HUMBLE			0	1-15	16-20	21-30
Age, race, sex	340M+F	Both	1.0	10.1(5.91-17.1)	15.2(9.19-25.0)	30.7(15.8-59.8)
				31+ cigs/day		
			...	39.7(21.0-74.9)		
BROSS			0	1-20	21+ cigs/day	
None	303M	Male	1.0	4.91(3.25-7.42)	7.20(4.46-11.6)	
			(comparison group = current filter or plain smokers)			
CPSI			0	1-9	10-19	20
Age	3633M,	Male	1.00	3.82(2.99-4.88)	8.62(7.28-10.2)	13.1(11.3-15.3)
	1132F	Female	1.00	1.17(0.86-1.59)	2.87(2.34-3.49)	6.17(5.25-7.26)
				21-39	40+ cigs/day	
		Male	...	18.8(15.9-22.0)	22.1(18.6-26.2)	
		Female	...	10.5(8.4-13.0)	12.6(9.33-17.1)	
CPSII			0	1-9	10-19	20
Age	1905M,	Male	1.00	14.3(11.0-18.5)	16.2(13.0-20.4)	23.6(19.4-28.8)
	1324F	Female	1.00	4.30(3.21-5.76)	8.47(6.99-10.3)	14.7(12.6-17.1)
				21-39	40	41+ cigs/day
		Male	...	24.5(19.7-30.4)	31.8(25.4-39.8)	44.8(34.5-58.1)
		Female	...	21.0(17.4-25.3)	23.5(18.9-29.2)	24.0(15.7-36.9)
DORN			0	1-9	10-20	21-39
Age	4316M	Male	1.0	3.7(3.1-4.5)	9.9(8.8-11.2)	16.9(15.0-19.0)
				40+cigs/day		
			...	22.9(19.8-26.6)		

TABLE 5.1 (Continued 4)

Study/ adjustment factors	Number of cases	Sex	Relative risk (95% CI) by amount smoked			
GARSHI			0	1-15	16-25	26-35
Age	909M	Male	1.00	3.29(2.22-4.87)	5.72(4.04-8.10)	7.69(5.20-11.4)
				36+ cigs/day		
			...	5.24(3.61-7.60)		
			(comparison groups = ever smokers of manufactured cigarettes only)			
KAUFMA			0	1-14	15-24	25-34
Age, race, sex, region, education, year of interview	649M+F	Both	1.0	8.0(5.0-13)	15(10-23)	28(17-44)
				35-44	45+ cigs/day	
			...	43(27-68)	60(35-102)	
MRFIT			0	1-15	16-25	26-35
Age, race, blood pressure, cholesterol	2004M	Male	1.00	2.58(2.12-3.13)	5.82(5.12-6.62)	7.31(6.38-8.39)
				36-45	46+ cigs/day	
			...	9.84(8.62-11.3)	10.7(8.91-12.8)	
			(base group includes ex-smokers)			
NMFS			0	1-24	25+ cigs/day	
Age	271M,	Male	1.00	6.67(4.17-10.7)	10.4(6.49-16.6)	
	185F	Female	1.00	8.93(5.76-13.9)	16.8(10.3-27.5)	
WYNDER			0	1-9	10-15	16-20
Age, social class	605M	Male	1.00	2.25(0.96-5.59)	5.97(2.75-13.0)	11.1(5.30-23.2)
				21-34	35+ cigs/day	
			...	30.2(14.1-64.5)	30.0(13.7-65.5)	
WYNDER2			0	1-10	11-20	21-30
None	298M,	Male	1.0	19.9(7.0-56.3)	29.6(12.0-73.0)	60.7(24.2-152)
	83F	Female	1.0	2.9(1.1-7.8)	7.8(4.3-14.2)	14.7(7.4-29.2)
	(Kreyberg I cases only)			31-40	41+ cigs/day	
		Male	...	77.8(31.2-194)	98.2(38.7-249)	
				31+ cigs/day		
		Female	...	15.9(8.3-30.7)		
WYNDER3			0	1-10	11-20	21-30
None	1151M,	Male	1.00	7.41(5.10-10.8)	11.4(8.67-14.9)	21.4(16.1-28.5)
	785F	Female	1.00	4.46(3.09-6.42)	8.29(6.45-10.6)	15.4(11.3-21.0)
				31-40	41+ cigs/day	
		Male	...	20.7(15.7-27.3)	44.5(33.1-59.7)	
		Female	...	34.4(25.2-46.8)	47.7(32.0-71.2)	
			(comparison groups = current smokers of 10+ years duration)			

TABLE 5.1 (Continued 5)

Study/ adjustment factors	Number of cases	Sex	Relative risk (95% CI) by amount smoked			
WYNDER4			0	1-10	11-20	21-40
Age	799M,	Male	1.00	2.47(1.62-3.75)	10.6(7.35-15.2)	19.9(14.0-28.4)
	549F	Female	1.00	5.16(3.22-8.24)	13.8(9.84-19.3)	30.7(21.3-44.3)
	(Squamous/			41+ cigs/day		
	epidermoid	Male	...	35.9(23.1-55.7)		
	or adeno-	Female	...	34.0(17.5-66.0)		
	carcinoma)					
ALDERS			0	1-17	18-27	28+ cigs/day
Age	400M,	Male	1.00	3.55(1.94-6.51)	7.97(4.61-13.8)	8.52(5.04-14.4)
	605F	Female	1.00	2.62(1.88-3.65)	5.28(3.79-7.36)	6.90(4.70-10.1)
			(comparison groups = ever smokers of manufactured cigarettes only)			
BENSHL			0	1-9	10-19	20+ cigs/day
Age	150M	Male	1.00	4.00(1.55-10.3)	9.05(3.91-20.9)	10.95(4.76-25.2)
DARBY			0	1-14	15-24	25+ cigs/day
None	325M,	Male	1.00	73.5(23.1-234)	95.4(29.9-304)	143(43.5-468)
	218F	Female	1.00	15.7(9.38-26.3)	21.5(12.9-35.8)	41.6(21.1-81.9)
DEANN			0	1-10	11-22	23+ cigs/day
Age	574M,	Male	1.00	4.61(0.29-7.29)	9.94(6.47-15.3)	31.6(9.2-51.9)
	150F	Female	1.00	2.27(1.06-4.88)	6.73(2.58-17.5)	19.1(3.36-108)
DEANT			0	1-12	13-22	23+ cigs/day
Age, social	362M,	Male	1.00	5.46(3.40-8.76)	7.42(4.74-11.6)	21.7(13.7-34.1)
class, district	143F	Female	1.00	3.16(1.96-5.09)	8.42(5.44-13.0)	24.2(14.5-40.5)
DOLL1			0	1-4	5-14	15-24
None	1357M,	Male	1.00	3.72(1.60-8.64)	7.48(3.39-16.5)	9.60(4.35-21.2)
	108F			25-49	50+ cigs/day	
		Male	...	16.6(7.4-37.1)	27.6(10.0-76.2)	
			0	1-4	5-14	15+ cigs/day
		Female	1.00	0.94(0.45-1.99)	1.97(0.95-4.09)	6.88(2.61-18.1)
			(comparison group = ever smoked, average consumption in last 10 years)			
DOLL2			0	1-14	15-24	25+ cigs/day
Age	376M,	Male	1.00	7.50(4.51-12.5)	14.8(9.19-24.0)	25.4(15.7-40.8)
	22F	Female	1.00	1.29(0.14-11.5)	6.43(1.81-22.8)	29.7(9.46-93.3)
GILLIS			0	1-14	15-24	25-34
None	503M	Male	1.0	4.5(2.5-8.1)	7.6(4.2-13.8)	8.6(4.6-16.1)
				35-49	59+ cigs/day	
		Male	...	9.7(5.1-18.4)	7.8(3.7-16.4)	

TABLE 5.1 (Continued 6)

Study/ adjustment factors	Number of cases	Sex	Relative risk (95% CI) by amount smoked			
KINLEN			0	1-14	15-24	25+ cigs/day
Age, tea	718M	Male	1.00	10.6(4.99-22.5)	14.1(6.67-30.0)	21.7(10.2-46.4)
STOCKS			0	2-99	100-149	150-199
Age	576M	Male	1.00	8.49(3.43-21.0)	10.7(4.35-26.2)	19.3(7.57-49.0)
				200-249	250+ cigs/week	
		Male	...	11.2(4.33-28.8)	17.8(6.95-45.7)	

T25

TABLE 5.2

Relative risk (95% CI) of lung cancer by amount smoked - by histological type (base = never smokers, comparison groups = current smokers unless indicated)

Study/ adjustment factors	Sex	Histological type	Relative risk (95% CI) by amount smoked			
SOBUE			0	20-29	30+	Current/Never
Age,duration,	Male	Squamous	1.0	1.5(1.0-2.3)	1.9(1.2-2.9)	18.1(7.9-41.3)
inhalation,		Adeno	1.0	1.2(0.8-1.8)	1.2(0.8-1.9)	1.9(1.3-3.0)
cig.type,		Small	1.0	0.8(0.4-1.5)	2.3(1.3-4.2)	21.4(5.3-87.1)
fraction smoked		Large	1.0	2.1(0.8-5.3)	2.6(1.0-6.6)	3.8(1.2-12.1)
				(results by level for current smokers only; current/never RRs adjusted for age only)		
BENHAM			0	1-14	15-20	21+
None	Male	Kreyberg I	1.00	6.94(4.68-10.3)	13.9(9.56-20.2)	21.6(14.7-31.5)
		Kreyberg II	1.00	2.9(1.1-7.5)	2.9(1.2-7.3)	5.8(2.3-15.0)
				Ever/Never		
		Kreyberg I	...	17.2(11.2-26.8)		
		Kreyberg II	...	3.6(1.6-8.3)		
BARBON			0	1-9	10-19	20-29
Age	Male	Squamous	1.0	3.9(1.4-11.0)	13.2(5.4-31.9)	15.2(6.4-35.7)
		Adeno	1.0	2.2(0.7-6.4)	7.4(3.2-17.5)	6.5(2.8-14.9)
		Small	1.0	1.1(0.3-4.5)	9.2(3.7-22.6)	11.8(5.0-28.0)
		Large	1.0	10.9(1.3-94.6)	21.6(2.8-168)	25.0(3.3-187)
				30-39	40+	Current/Never
		Squamous	...	18.5(7.7-45.2)	23.5(9.9-55.9)	18.8(8.2-43.4)
		Adeno	...	9.7(4.1-23.1)	9.6(4.1-22.1)	7.9(3.6-17.4)
		Small	...	13.4(5.4-33.0)	19.8(8.3-47.1)	14.3(6.2-33.0)
		Large	...	31.4(4.1-243)	54.4(7.3-404)	34.3(4.7-250)
				(comparison group = ever smokers)		
BECHER			0	1-19	20-29	30+
Age, education,	Male	Squamous	1.0	7.51(3.09-18.3)	13.5(5.8-31.5)	21.4(9.1-50.7)
occupation		Adeno	1.0	2.19(0.84-5.72)	4.38(1.87-10.3)	5.11(2.09-12.5)
		Small	1.0	7.85(2.28-27.0)	11.7(3.53-38.4)	16.8(5.02-56.2)
DAMBER				Ever/never		
Age	Male	Squamous		11.8(6.4-23.0)		
		Adeno, alveolar, bronchiolar		2.4(1.1-5.3)		
		Small cell		13.8(5.2-45.6)		
		Large cell and poorly diff.		7.3(2.0-32.5)		

TABLE 5.2 (Continued)

Study/ adjustment factors	Sex	Histological type	Relative risk (95% CI) by amount smoked			
DOSEME			0	1-10	11-20	21+
Age, alcohol	Male	Squamous	1.0	2.6(1.5-4.6)	3.2(2.2-4.6)	7.0(4.1-12.0)
		Small	1.0	1.7(0.6-5.2)	5.0(2.6-9.8)	13.5(6.1-30.0)
		Other	1.0	1.8(0.8-4.1)	2.7(1.6-4.7)	3.2(1.4-7.0)
			(comparison group = ever smokers)			
LUBIN			0	1-9	10-19	20-29
None	Male	Squamous	1.00	9.23(6.91-12.3)	14.6(11.1-19.3)	20.2(15.3-26.7)
		Adeno	1.00	1.38(0.96-1.98)	2.77(2.05-3.73)	3.46(2.57-4.64)
		Oat	1.00	4.21(2.86-6.18)	7.36(5.15-10.5)	10.5(7.39-15.0)
		Other KI	1.00	3.93(2.38-6.51)	5.91(3.70-9.45)	7.15(4.49-11.4)
				30+		
		Squamous	...	23.6(17.8-31.2)		
		Adeno	...	3.97(2.91-5.42)		
		Oat	...	11.5(7.97-16.5)		
		Other KI	...	8.24(5.10-13.3)		
			0	1-9	10-19	20-29
	Female	Squamous	1.00	2.67(1.70-4.20)	6.37(4.54-8.95)	9.09(6.13-13.5)
		Adeno	1.00	0.93(0.57-1.52)	1.61(1.11-2.32)	1.01(0.55-1.84)
		Oat	1.00	2.45(1.45-4.14)	5.78(3.92-8.51)	8.78(5.65-13.6)
		Other KI	1.00	1.39(0.52-3.71)	4.82(2.64-8.80)	10.7(5.83-19.7)
				30+		
		Squamous	...	7.56(4.12-13.9)		
		Adeno	...	1.97(0.94-4.16)		
		Oat	...	8.80(4.63-16.7)		
		Other KI	...	9.21(3.73-22.7)		
BRESLO			Ever/never			
None (not sex)	Both	Adeno	2.10(0.87-5.07)			
		Other	4.99(3.24-7.69)			
			(based on smoking in 20 years prior to study)			
OSANN			0	1-39	40+	Ever
Age, race	Male	Squamous	1.0	35.3(17.0-73.3)	76.0(36.8-157)	36.1(17.8-73.3)
		Adeno	1.0	16.5(9.3-29.3)	37.5(21.3-66.0)	17.9(10.4-31.0)
		Small	1.0	27.6(9.8-77.4)	95.3(34.7-262)	37.5(13.9-202)
	Female	Squamous	1.0	24.0(12.7-45.5)	72.3(36.8-142)	26.4(14.5-48.1)
		Adeno	1.0	8.8(6.1-12.8)	24.2(15.8-37.2)	9.5(6.8-13.8)
		Small	1.0	76.7(27.5-215)	316.1(111-900)	86.0(31.6-234)
CORREA			0	1-20	21+	
Sex	Both	Squamous and small	1.0	23.2(14.6-37.0)	54.8(35.6-89.2)	
		Adeno	1.0	4.3(2.6-7.2)	12.0(7.3-19.7)	

TABLE 5.2 (Continued 2)

Study/ adjustment factors	Sex	Histological type	Relative risk (95% CI) by amount smoked			
BROWNS			0	1-19	20+	
Age, occupation	Male	Squamous	1.0	7.6(6.2-9.4)	17.2(14.6-20.3)	
		Adeno	1.0	6.2(4.9-7.9)	10.7(8.9-13.0)	
		Small	1.0	7.3(5.4-9.9)	19.2(15.2-24.4)	
		Other/ mixed	1.0	4.0(3.1-5.1)	11.2(9.5-13.3)	
	Female	Squamous	1.0	11.7(8.7-15.8)	26.1(20.7-32.8)	
		Adeno	1.0	5.8(4.7-7.1)	8.6(7.3-10.1)	
		Small	1.0	25.6(18.1-36.3)	53.1(39.5-71.3)	
		Other/ mixed	1.0	6.2(4.7-8.1)	15.4(12.7-18.7)	
SCHOEN			0	1-19	20+	
Age, race	Male (White)	Squamous	1.0	11.8(4.2-32.9)	23.3(8.5-63.4)	
		Adeno	1.0	3.3(1.2-8.8)	5.7(2.2-14.4)	
		Small	1.0	11.9(1.6-90.6)	28.4(3.9-206)	
	Female	Squamous	1.0	7.8(4.9-12.4)	16.4(10.2-26.3)	
		Adeno	1.0	2.9(2.0-4.1)	5.4(3.7-7.8)	
		Small	1.0	41.2(14.8-114)	99.9(36.0-278)	
				(Comparison group ever smokers)		
WYNDER3			0	1-10	11-20	21-30
None	Male	Kreyberg I	1.00	13.3(8.35-21.0)	15.8(10.7-23.4)	29.6(19.8-44.2)
		Kreyberg II	1.00	2.44(1.29-4.62)	8.42(5.81-12.2)	15.4(10.2-23.1)
				31-40	41+	
		Kreyberg I	...	37.7(25.6-55.5)	64.1(43.1-95.2)	
		Kreyberg II	...	11.1(7.46-16.5)	28.4(18.3-44.0)	
			0	1-10	11-20	21-30
	Female	Kreyberg I	1.00	6.56(3.90-11.0)	18.2(12.4-26.5)	26.5(16.9-41.5)
		Kreyberg II	1.00	3.06(1.83-5.11)	4.50(3.22-6.28)	9.40(6.13-14.4)
				31-40	41+	
		Kreyberg I	...	95.2(60.7-149)	88.7(52.3-150)	
		Kreyberg II	...	13.8(9.01-21.1)	20.7(11.2-38.2)	
WYNDER4			0	1-10	11-20	21-40
Age (and education for large cell)	Male	Squamous	1.0	14.1(7.6-26.4)	16.0(9.5-27.0)	38.9(23.1-65.3)
		Adeno	1.0	4.4(2.5-7.6)	7.2(4.9-10.4)	12.1(8.4-17.4)
				41+		
		Squamous	...	66.8(36.8-121)		
		Adeno	...	19.3(12.0-30.3)		
			0	1-19	20-39	40+
		Large	1.0	8.3(3.4-20.6)	14.6(6.4-33.1)	37.0(16.4-83.2)
			0	1-10	11-20	21-40
	Female	Squamous	1.0	9.3(3.9-22.1)	33.0(16.3-66.6)	74.9(37.0-152)
		Adeno	1.0	4.5(2.7-7.7)	14.2(9.6-20.9)	27.2(17.8-41.6)
				41+		
		Squamous	...	85.3(29.5-247)		
		Adeno	...	34.3(16.2-72.5)		
			0	1-19	20-39	40+
		Large	1.0	6.0(2.6-13.7)	21.0(11.0-40.1)	72.9(35.4-150)

TABLE 5.2 (Continued 3)

Study/ adjustment factors	Sex	Histological type	Relative risk (95% CI) by amount smoked			
ALDERS			0	1-17	18-27	28+
Age	Male	Squamous/				
		Oat	1.00	3.79(1.19-12.1)	7.19(1.55-20.3)	8.78(3.22-23.9)
		Other	1.00	2.80(0.85-9.24)	2.67(0.84-8.46)	3.32(1.19-9.24)
	Female	Squamous/				
		Oat	1.00	2.55(1.34-4.84)	9.24(4.82-17.7)	14.5(6.7-31.7)
		Other	1.00	2.77(1.44-5.31)	4.58(2.24-9.36)	3.31(1.54-7.11)
			(comparison groups = ever smokers of manufactured cigs only)			
DOLL1			0	1-4	5-14	15-24
None	Male	Kreyberg I	1.0	4.7(1.4-16.0)	10.6(3.3-34.1)	14.3(4.4-46.0)
		Kreyberg II	1.0	0.5(0.1-3.6)	0.8(0.2-3.6)	1.2(0.3-5.3)
				25+		
		Kreyberg I	...	25.4(7.8-82.4)		
		Kreyberg II	...	1.1(0.2-5.6)		
			0	1-4	5-14	15-24
	Female	Kreyberg I	1.0	1.0(0.4-2.6)	1.7(0.6-4.5)	8.3(2.8-24.8)
		Kreyberg II	1.0	1.1(0.2-6.2)	2.3(0.6-9.5)	4.1(0.6-25.9)
DOLL2			0	1-14	15-24	25+
Age	Male	Squamous	0.00	1.00	1.50	2.00
		Oat	0.10	1.00	2.00	3.80
		Adeno	0.00	1.00	4.00	2.33
			(there were no deaths in nonsmokers for squamous and adeno, so risks estimated relative to 1-14/day - confidence limits could not be estimated, total numbers of deaths 55, 40 and 13 for squamous, oat and adeno respectively)			
GILLIS			0	1-14	15-24	25-34
None	Male	Squamous	1.0	4.4	8.2	9.8
		Oat	1.0	3.0	7.6	7.0
		Adeno	1.0	1.8	1.4	3.0
				35+		
		Squamous	...	10.4		
		Oat	...	5.8		
		Adeno	...	2.6		
			(approximate estimates from graph)			

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TABLE 6.1

Relative risk (95% CI) of lung cancer by age of starting to smoke (base = never smokers, comparison groups = current smokers, unless indicated)

Study/ adjustment factors	Number of cases	Sex	Relative risk (95% CI) by age of starting to smoke			
GAO			Never	30+	20-29	10-19
Age, education	732M,	Male	1.0	1.2(0.8-1.9)	4.7(3.3-6.5)	5.1(3.6-7.2)
	672F	Female	1.0	2.0(1.4-3.0)	3.8(2.6-5.8)	5.6(3.4-9.0)
			(comparison group = ever smokers)			
FU			Never	40+	30-39	20-29
None (not sex)	523M+F	Both	1.0	0.91(0.47-1.77)	0.95(0.57-1.56)	2.54(1.88-3.43)
				<20		
			...	3.34(2.31-4.83)		
LIU		Male	Non	25+	20-24	<20
Age	16317M	Urban	1.00	2.45(0.05)	2.94(0.05)	4.11(0.07)
	Urban	Rural	1.00	2.26(0.09)	2.62(0.09)	3.07(0.11)
	3882M		(base group = nonsmoker in 1980; bracketed			
	Rural		numbers are standard errors)			
YU			Never	30+	20-29	<20
Centre (not sex)	2812M,	Both	1.00	1.31(0.88-1.93)	2.42(1.93-3.06)	3.29(2.36-3.57)
	1142F	Female	1.00	1.55(1.17-2.04)	2.84(2.18-3.70)	3.20(2.43-4.32)
HIRAYA			Never	20+	<20	
Age	1323M,	Male	1.00	4.35(3.51-5.39)	5.71(4.51-7.27)	
	426F	Female	1.00	2.46(1.93-3.13)	0.78(0.10-6.16)	
JOLY			Never	25+	15-24	<15
None	552M,	Male	1.00	4.67(2.14-10.2)	11.0(6.03-20.02)	20.4(11.2-37.3)
	166F	Female	1.00	3.05(1.69-5.51)	7.76(4.82-12.5)	11.8(7.18-19.4)
			(comparison groups = ever smokers)			
AUVINE			Never	21+	16-20	<15
Age, sex	310M+F	Both	1.00	5.36(3.66-7.85)	5.63(3.94-8.07)	6.94(4.59-10.51)
BENHAM			Never	20+	<20	
None	121M,	Male	1.00	12.2(8.43-17.7)	14.4(10.0-20.8)	
	96F		Never	31+	21-30	<20
		Female	1.00	1.77(0.48-6.55)	3.72(1.61-8.58)	8.16(3.99-19.6)
BARBON			Never	20+	15-19	<15
Age	755M	Male	1.00	8.2(5.0-13.3)	9.9(6.2-15.8)	50.8(27.2-95.0)
			(comparison group = ever smokers)			

TABLE 6.1 (Continued)

Study/ adjustment factors	Number of cases	Sex	Relative risk (95% CI) by age of starting to smoke			
BECHER			19+	17-18	<17	
Age,	901M,	Male	1.0	1.30(1.00-1.68)	1.66(1.19-2.32)	
occupation,	198F		23+	<23		
air pollution		Female	1.0	1.77(0.68-4.60)		
DAMBER			Never	21+	16-20	<15
None	579M	Male	1.00	4.56(2.87-7.26)	6.80(4.65-9.95)	10.4(6.91-15.7)
BRESLO			Never	25+	15-24	<15
None (not sex)	518M+F	Both	1.00	3.33(1.81-6.15)	4.29(2.83-6.51)	5.22(3.34-8.16)
CORREA			Never	21+	16-20	<16
Sex, age	2731M+F	Both	1.00	8.3	17.4	24.2
CPSI			Never	25+	20-24	15-19
Age	1094M,	Male	1.00	4.16(2.85-6.09)	9.83(7.52-12.9)	14.2(11.2-18.0)
	309F	Female	1.00	2.31(1.68-3.16)	3.70(2.49-5.47)	5.04(3.53-7.20)
				<15		
		Male	...	16.4(12.6-21.4)		
		Female	...	9.00(3.84-21.1)		
DORN			Never	25+	20-24	15-19
Age	1132M	Male	1.00	5.02(3.72-6.79)	8.97(6.92-11.6)	12.8(10.1-16.4)
				<15		
		Male	...	17.3(13.0-23.1)		
WYNDER4			Never	21+	18-20	<18
None	997M,	Male	1.00	6.33(4.33-9.25)	8.30(5.86-11.8)	10.5(7.61-14.5)
	691F	Female	1.00	4.19(3.07-5.73)	6.40(4.76-8.60)	9.54(7.16-12.7)
ALDERS			Never	25+	20-24	15-19
Age	397M,	Male	1.00	3.76(1.54-9.18)	7.75(3.98-15.1)	9.41(5.29-16.7)
	604F	Female	1.00	3.59(2.44-5.30)	5.39(3.60-8.08)	4.57(3.31-6.31)
				<15		
		Male	...	11.1(6.12-20.0)		
		Female	...	7.49(4.64-12.1)		
			(comparison groups = ever smokers of manufactured cigarettes only)			
DEANT			25+	20-24	15-19	<15
Age,	280M,	Male	1.00	1.57(0.89-2.78)	1.85(1.13-3.02)	0.81(0.46-1.45)
amount smoked	91F	Female	1.00	1.51(0.61-3.72)	1.75(1.05-2.93)	1.19(0.61-2.33)
DOLL1			Never	30+	20-29	<20
None	1357M,	Male	1.00	4.79(1.87-12.3)	8.29(3.72-18.5)	9.46(4.31-20.8)
	108F	Female	1.00	1.68(0.83-3.4)	2.26(1.05-4.86)	2.46(1.08-5.58)
				(comparison groups = ever smokers)		

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TABLE 6.2

Relative risk (95% CI) of lung cancer by age of starting to smoke - by histological type (base = never smokers, comparison groups = current smokers, unless indicated)

Study/ adjustment factors	Sex	Histological type	Relative risk (95% CI) by age of starting to smoke			
BENHAM			Never	20+	1-19	
None	Male	Kreyberg I	1.00	12.5(8.58-18.1)	14.5(10.0-20.9)	
		Kreyberg II	1.00	3.0(1.2-7.4)	4.1(1.8-9.7)	
BARBON			Never	20+	15-19	<15
Age	Male	Squamous	1.00	9.4(4.2-23.4)	13.7(5.9-31.7)	71.3(27.6-184)
		Adeno	1.00	5.7(2.5-12.9)	6.0(2.7-13.3)	33.4(13.1-84.9)
		Small	1.00	8.8(3.7-20.8)	10.4(4.5-24.2)	47.5(18.1-125)
		Large	1.00	22.7(3.0-169)	24.2(3.3-177)	146(18.6-999)
			(comparison group = ever smokers)			
BECHER			19+	17-18	<17	
Age, education, occupation	Male	Squamous	1.0	1.26(0.92-1.73)	1.43(0.96-2.12)	
		Adeno	1.0	1.28(0.78-2.10)	1.11(0.56-2.18)	
		Small	1.0	1.26(0.82-1.93)	1.36(0.80-2.32)	
WYNDER4			Never	21+	18-20	<18
None	Male	Squamous/ epidermoid	1.00	13.9(6.42-30.0)	16.9(8.04-35.3)	25.1(12.3-51.2)
		Adeno	1.00	3.37(2.15-5.30)	4.19(2.80-6.26)	5.29(3.69-7.58)
		Small/oat	0.00	1.00	1.69(0.99-2.89)	1.56(0.96-2.56)
	Female	Squamous/ epidermoid	1.00	6.15(3.14-12.0)	9.17(4.84-17.4)	13.9(7.48-26.0)
		Adeno	1.00	2.77(1.91-4.01)	4.76(3.40-6.66)	6.54(4.72-9.06)
		Small/oat	1.00	23.9(7.27-78.5)	27.0(8.28-88.0)	50.0(15.6-160)
ALDERS			Never	25+	20-24	15-19
Age	Male	Squamous/ oat	1.00	2.62(0.50-13.7)	3.35(0.94-11.9)	11.65(3.89-34.9)
		Other	1.00	4.44(0.64-3.07)	6.79(1.79-25.7)	3.23(1.14-9.16)
				<15		
		Squamous/ oat	...	14.56(4.67-45.4)		
		Other	...	2.39(0.81-7.03)		
			Never	25+	20-24	15-19
	Female	Squamous/ oat	1.00	3.49(1.72-7.06)	5.73(2.82-11.6)	4.42(2.37-8.23)
		Other	1.00	3.21(1.45-7.06)	4.26(1.82-9.95)	3.15(1.63-6.07)
		Squamous/ oat		<15		
		Other	...	5.45(2.37-12.6)		
			...	6.17(2.35-16.2)		
			(comparison groups = ever smokers of manufactured cigarettes only)			

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TABLE 6.3

Joint relationship of lung cancer risk to age of starting to smoke and amount smoked (base = never smokers, comparison groups = current smokers)

Study/ adjustment factors	Sex	Relative risks (95% CI) by age starting and amount smoked				
			Age at starting to smoke			
DORN		Cigs/day	25+	20-24	15-19	<15
Age	Male	1-9	1.75(0.81-3.80)	3.58(2.02-6.34)	3.44(1.87-6.34)	6.34(2.00-20.1)
		10-20	4.70(3.22-6.87)	7.66(5.66-10.4)	10.6(8.07-13.9)	12.1(7.99-18.3)
		21-39	8.00(5.35-12.0)	12.5(9.21-16.9)	15.8(12.1-20.7)	23.9(16.9-33.6)
		40+	9.00(4.51-18.0)	17.0(11.1-25.9)	23.5(17.0-32.7)	28.3(18.0-44.3)

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TABLE 6.4

Joint relationship of lung cancer risk to age of starting to smoke and pack years (base = never smokers, comparison groups = ever smokers)

Study/ adjustment factors	Sex	Relative risks (95% CI) by age of starting to smoke and pack years					
HIRAYA		Age of			Pack-years		
Age, sex		start	<10	10-20	20-30	30-40	41+
	Both	30+	1.6	1.5	2.3	3.4	4.1
		25-29	1.6	3.9	4.1	3.4	7.9
		20-24	2.0	2.8	4.8	5.4	7.1
		<20	4.6	3.4	6.0	5.9	6.8

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TABLE 7.1

Relative risk (95% CI) of lung cancer by duration of smoking (base = never smokers, comparison groups = smokers unless indicated)

Study/ adjustment factors	Number of cases	Sex	Relative risk (95% CI) by duration of smoking			
SOBUE			1-29	30-39	40-49	50+ years
Age,amount smoked, inhalation, cig.type, fraction smoked	609M	Male	1.0	1.5(1.0-2.2)	2.8(2.0-4.1)	4.1(2.7-6.2)
			(results for current smokers only with base 1-29 years; age-adjusted RR for current/never = 4.1 [2.8-5.9])			
BEST			0	1-19	20-29	30-39 years
Age	240M	Male	1.0	2.68(1.12-6.37)	4.10(1.75-9.61)	13.9(6.31-30.4)
				40+ years		
			...	14.2(6.64-30.3)		
PRESCO			0	1-29	30+ years	
Age, study cohort	76M,	Male	1.0	2.5(1.0-6.4)	7.0(3.0-16.3)	
	37F	Female	1.0	2.6(1.2-5.5)	4.2(1.8-9.8)	
			(comparison groups = ex-smokers)			
AUVINE			0	1-20	21-40	41+ years
Age, sex	310M+F	Both	1.0	2.51(2.73-7.43)	4.76(2.37-9.57)	5.97(4.25-8.78)
			(comparison groups = current smokers)			
BARBON			0	1-29	30-39	40-49
Age	755M	Male	1.0	3.2(1.8-5.7)	7.9(4.7-13.5)	11.4(7.0-18.8)
				50+ years		
			...	14.5(9.0-23.3)		
BECHER			0	1-19	20-39	40+ years
Age, education, occupation	600M	Male	1.00	3.59(1.59-8.08)	8.57(4.87-15.08)	9.21(5.31-15.97)
DAMBER			0	1-30	31-40	41-50
Age	589M	Male	1.00	3.19(1.73-5.89)	6.95(3.81-12.7)	9.87(5.81-16.64)
				51+ years		
			...	10.9(6.54-18.3)		
DOSEME			0	1-10	11-20	21+ years
Age, alcohol	1210M	Male	1.0	1.0(0.6-1.7)	3.8(2.6-5.7)	4.9(3.5-7.0)
SCHOEN			0	<35	35+ years	
Age, race, respondent type	763M	Male (White)	1.0	5.5(3.0-10.0)	16.0(8.9-28.7)	
	994F	Female	1.0	4.2(3.2-5.6)	11.7(9.1-15.2)	

TABLE 7.1 (Continued)

Study/ adjustment factors	Number of cases	Sex	Relative risk (95% CI) by duration of smoking			
HUMBLE			0	1-29	30-39	40-49
Age, race, sex	339M+F	Both	1.0	15.5(6.19-38.6)	17.5(8.47-36.4)	19.6(11.2-34.3)
				50-59	60+ years	
			...	18.8(11.0-31.9)	11.9(5.88-24.1)	
			(comparison groups = current smokers)			
BUFFLE			0	<34	34-43	44-50
Age, race, education, vital status	475M	Male	1.0	6.8	11.1	9.4
				50+ years		
			...	14.5		
CPSI			0	1-29	30-34	35-39
Age	3650M,	Male	1.00	4.21(3.08-5.77)	7.42(5.65-9.73)	10.3(8.26-12.8)
	1132F	Female	1.00	2.16(1.70-2.74)	4.60(3.72-5.70)	5.06(4.16-6.14)
				40-49	45-49	50+ years
		Male	1.00	12.1(10.0-14.8)	14.6(12.2-17.5)	17.7(15.1-20.7)
		Female	1.00	5.96(4.85-7.33)	6.76(5.08-9.01)	6.08(4.08-9.07)
			(comparison groups = current smokers)			
CPSII			0	1-29	30-34	35-39
Age	1905M,	Male	1.00	9.96(6.98-14.2)	16.6(11.9-23.3)	23.9(18.0-31.7)
	1324F	Female	1.00	6.56(5.14-8.36)	12.4(9.80-15.7)	15.0(12.1-18.6)
				40-49	45-49	50+ years
		Male	...	25.5(20.0-32.5)	27.9(21.9-35.5)	29.2(23.7-35.9)
		Female	...	14.9(12.3-18.1)	16.3(13.2-20.1)	15.0(12.3-18.4)
			(comparison groups = current smokers)			

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TABLE 7.2

Relative risk (95% CI) of lung cancer by duration of smoking - by histological type (base = never smokers, comparison groups = ever smokers unless indicated)

Study/ adjustment factors	Sex	Histological type	Relative risk (95% CI) by duration of smoking			
SOBUE			1-29	30-39	40-49	50+ years
Age,amount smoked, inhalation, cig.type, fraction smoked	Male	Squamous	1.0	2.1(1.2-3.8)	4.3(2.4-7.7)	8.0(4.3-14.9)
		Adeno	1.0	1.1(0.7-1.8)	2.0(1.3-3.2)	2.1(1.2-3.7)
		Small	1.0	2.4(0.9-6.2)	4.3(1.7-10.9)	7.6(2.8-20.0)
		Large	1.0	1.3(0.5-3.2)	2.1(0.8-5.3)	1.6(0.5-4.9)
			(results for current smokers only with base = 1-29 years; see Table 5.2 for current/never age-adjusted RRs)			
PRESCO			0	1-29	30+ years	
Age, study group	Male	Squamous	1.0	1.0(0.1-9.1)	18.3(6.3-53)	
		Adeno	1.0	2.7(0.9-8.2)	3.1(1.1-8.7)	
		Anaplastic	1.0	2.8(0.7-11)	9.7(3.6-26)	
	Female	Squamous	1.0	1.8(0.3-9.6)	4.2(0.8-23)	
		Adeno	1.0	4.3(1.5-12)	5.5(1.6-19)	
		Anaplastic	1.0	0.8(0.1-7.0)	2.2(0.3-18)	
BARBON			0	1-29	30-39	40-49
Age	Male	Squamous	1.0	2.1(0.7-6.5)	9.6(3.9-23.9)	14.6(6.1-34.6)
		Adeno	1.0	3.7(1.4-9.7)	5.1(2.1-12.5)	8.2(3.6-18.7)
		Small	1.0	3.1(1.1-8.7)	8.8(3.5-21.8)	12.6(5.3-30.0)
		Large	1.0	7.3(0.8-64.7)	24.0(3.1-185)	28.6(2.9-214)
				50+ years		
		Squamous	...	21.2(9.1-49.3)		
		Adeno	...	8.3(3.7-18.7)		
		Small	...	15.5(6.5-36.5)		
		Large	...	41.2(5.6-306)		
BECHER			0	1-19	20-39	40+ years
Age, education, occupation	Male	Squamous	1.00	5.83(1.79-19.0)	12.5(5.21-29.7)	13.0(5.54-30.5)
		Adeno	1.00	1.10(0.20-5.95)	3.47(1.40-8.58)	4.41(1.86-10.5)
		Small	1.00	5.54(1.12-27.3)	11.4(3.37-38.7)	11.8(3.57-39.1)
DAMBER			0	1-30	31-40	41-50
Age	Male	Squamous	1.0	4.4(1.8-10.7)	8.4(4.0-18.3)	13.8(6.8-29.1)
		Adeno, alveolar, bronchiolar	1.0	1.8(0.6-5.4)	1.2(0.2-6.0)	3.4(1.3-9.1)
		Small	1.0	3.65(1.0-14.3)	10.5(3.4-38.4)	19.6(6.5-69.3)
				51+ (years)		
		Squamous	...	16.7(8.5-34.0)		
		Adeno, alveolar, bronchiolar	...	2.5(0.9-6.7)		
		Small	...	25.1(8.2-89.0)		

TABLE 7.2 (Continued)

Study/ adjustment factors	Sex	Histological type	Relative risk (95% CI) by duration of smoking			
DOSEME			0	1-10	11-20	21+ (years)
Age, alcohol	Male	Squamous	1.0	1.2(0.6-2.5)	3.9(2.3-6.7)	4.9(3.2-7.5)
		Small	1.0	1.7(0.5-5.3)	7.0(3.2-15.6)	8.4(4.0-17.6)
		Other	1.0	0.8(0.3-2.5)	3.3(2.2-7.5)	4.1(2.2-7.5)
SCHOEN			0	≤35	35+ (years)	
Age	Male	Squamous	1.0	9.5(3.4-26.6)	26.1(9.6-71.2)	
	(White)	Adeno	1.0	2.1(0.8-05.9)	6.7(2.7-17.1)	
		Small	1.0	12.0(1.6-89.6)	32.0(4.4-232)	
	Female	Squamous	1.0	4.3(2.5-7.3)	15.8(10.0-24.9)	
		Adeno	1.0	2.4(1.6-3.6)	5.1(3.6-7.3)	
		Small	1.0	25.9(9.1-73.7)	93.5(33.9-258)	
BUFFLE			0	0-33	34-43	44-50
Age, race, education, vital status	Male	Squamous	1.0	9.0(2.9-27.9)	14.8(4.8-45.3)	12.6(4.0-38.8)
		Adeno	1.0	4.4(1.7-11.5)	5.7(2.2-14.8)	4.3(1.6-11.4)
		Small	1.0	7.4(1.3-41.1)	17.1(3.2-90.9)	13.9(2.6-74.5)
				50+		
		Squamous	...	22.1(7.2-67.7)		
		Adeno	...	3.5(1.3-9.7)		
		Small	...	20.2(3.8-108.1)		
WYNDER4			0	1-19	20-39	40+
Age, education	Male	Large	1.0	2.9(1.2-7.3)	10.6(4.9-22.9)	23.1(10.4-50.8)
	Female	Large	1.0	2.9(1.2-6.9)	11.5(6.3-21.1)	30.1(15.8-57.4)

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TABLE 7.3

Joint relationship of lung cancer risk to duration of smoking and amount smoked (base = never smokers, comparison groups = ever smokers unless indicated)

Study/ adjustment factors	Sex	Relative risks (95% CI) by duration and amount			
GAO			Duration of smoking (years)		
Age, education		Cigs/day	1-29	30-39	40+
	Male	1-19	0.9	3.2	3.8
		20-29	2.1	7.1	7.2
		30+	3.0	10.8	15.4
			1-29	30+	
	Female	1-9	1.4(0.9-2.2)	2.4(1.4-4.1)	
		10-19	2.6(1.2-5.7)	3.2(2.0-5.1)	
		20+	8.9(2.0-40.2)	14.1(7.1-28.0)	
XU			Duration of smoking (years)		
Age, education		Cigs/day	1-29	30-39	40+
	Male	1-19	1.8	2.1	3.3
		20-29	1.5	2.7	6.0
		30+	5.3	4.9	17.1
	Female	1-19	1.4(NS)	3.1	3.4
		20+	2.1(NS)	3.4	9.4
XU+FU[4]			Duration of smoking (years)		
Age, education, centre		Cigs/day	1-29	30-39	40+
	Female	1-19	1.3(1.0-1.7)	2.6(1.9-3.5)	3.2(2.4-4.3)
		20+	1.8(0.9-3.6)	3.3(1.8-6.2)	5.7(2.9-11.5)
BECHER			Duration of smoking (years)		
Age, education, occupation		Cigs/day	1-19	20-39	40+
	Male Kreyberg I	1-19	4.14(1.52-11.3)	9.98(4.11-34.3)	7.89(3.55-27.5)
		20-29	9.36(3.94-22.2)	14.5(6.78-31.2)	12.9(6.22-26.6)
		30+	10.2(3.97-26.3)	22.2(9.95-49.3)	21.3(10.1-45.2)
			1-39	40+	
	Male adeno-carcinoma	1-29	3.03(1.19-7.70)	3.96(1.64-9.55)	
		30+	4.34(1.55-12.2)	5.28(1.93-14.4)	
SCHOEN		Cigs/day x duration of smoking (years)			
Age, race, respondent type	Male (white)	<20, <35	20+, <35	<20, 35+	20+, 35+
	All	2.8(1.4-5.7)	7.3(3.9-13.5)	11.3(6.0-21.2)	17.9(9.9-32.2)
	Squamous	4.8(1.5-14.8)	12.4(4.4-35.1)	18.0(6.3-51.1)	29.0(10.6-79.3)
	Adeno	1.1(0.29-4.2)	2.8(1.0-7.9)	5.2(1.9-14.4)	7.4(2.9-18.9)
	Small	4.1(0.42-39.6)	16.5(2.2-125)	20.4(2.60-157)	35.8(4.9-260)
	Female				
	All	3.2(2.3-4.4)	6.5(4.5-9.4)	8.4(6.2-11.2)	16.0(11.9-21.7)
	Squamous	2.7(1.4-5.1)	7.7(4.1-14.3)	12.0(7.4-19.6)	21.4(13.1-34.9)
	Adeno	2.0(1.3-3.2)	3.4(2.0-5.6)	3.9(2.6-5.9)	6.8(4.5-10.1)
	small	19.0(6.4-56.5)	40.6(13.5-122)	62.5(22.3-176)	140(49.8-391)

TABLE 7.3 (Continued)

Study/ adjustment factors	Sex	Relative risks (95% CI) by duration and amount			
CPSI			Duration of smoking (years)		
Age		Cigs/day	25-29	30-34	35-39
	Male	1-9	4.42(1.96-9.96)	-	3.45(1.88-6.33)
		10-19	2.37(0.98-5.76)	5.69(3.69-8.76)	6.93(5.07-9.48)
		20	6.18(4.08-9.37)	11.0(8.60-14.1)	9.85(7.96-12.2)
		21-39	4.77(2.60-8.76)	14.0(10.7-18.4)	16.9(13.7-20.9)
		40+	11.1(6.44-19.0)	16.0(11.6-22.1)	19.5(15.3-24.7)
	Female	1-9	-	1.97(1.16-3.35)	1.71(0.96-3.03)
		10-19	2.34(1.40-3.91)	2.96(2.01-4.36)	3.26(2.27-4.68)
		20	4.41(2.97-6.54)	7.09(5.46-9.21)	7.05(5.47-9.09)
		21-39	7.27(3.89-13.6)	12.3(8.38-17.9)	12.4(8.64-17.6)
		40+	12.3(5.49-27.4)	11.2(5.77-21.6)	12.8(7.19-22.6)
			40-44	45-49	50-54
	Male	1-9	4.06(2.47-6.66)	4.29(2.68-6.87)	3.69(2.15-6.35)
		10-19	8.55(6.60-11.1)	9.64(7.56-12.3)	9.00(6.90-11.7)
		20	14.1(11.7-16.9)	14.2(11.8-17.0)	16.1(13.3-19.5)
		21-39	17.4(14.3-21.2)	20.8(17.1-25.3)	25.2(20.5-31.0)
		40+	22.3(18.0-27.6)	28.3(22.9-34.9)	24.5(19.0-31.6)
	Female	1-9	1.40(0.66-2.95)	-	-
		10-19	4.37(3.01-6.35)	3.00(1.55-5.80)	3.82(1.43-10.2)
		20	6.75(4.98-9.15)	9.23(6.27-13.6)	6.41(2.87-14.3)
		21-39	13.1(8.76-19.5)	12.3(6.58-23.0)	20.4(8.47-49.3)
		40+	18.9(11.1-32.2)	19.4(9.19-40.3)	-
			(comparison groups = current smokers, - = less)		
CPSII			Duration of smoking (years)		
Age		Cigs/day	20-29	30-39	40-49
	Male	1-19	10.6(3.18-29.7)	9.6(5.3-17.3)	21.5(14.6-31.7)
		20-39	22.1(10.7-45.8)	13.7(8.9-21.2)	28.8(20.4-40.6)
		40+	Only 1 death	32.8(21.1-51.3)	40.3(28.1-57.7)
	Female	1-19	4.6(2.1-9.9)	9.3(6.3-13.7)	10.1(7.2-14.2)
		20-39	10.8(6.3-18.6)	15.7(11.6-21.2)	20.5(15.9-26.4)
		40+	Only 1 death	18.1(10.7-30.7)	37.2(26.7-51.9)
			50+		
	Male	1-19	20.5(11.4-36.9)		
		20-39	53.4(36.6-78.0)		
		40+	52.0(32.5-83.1)		
	Female	1-19	16.5(7.7-35.5)		
		20-39	43.3(28.1-66.7)		
		40+	28.8(10.6-78.3)		
			(comparison groups = current smokers, data are for age 60-69, duration as at start of study)		

TABLE 7.3 (Continued 2)

Study/ adjustment factors	Sex	Relative risks (95% CI) by duration and amount		
WYNDER2			Duration of smoking (years)	
Age, race		Cigs/day	21-40	41+
	Male,	1-20	1.0	1.6
	Kreyberg I	21-40	1.8	4.4
	(480 cases)	41+	3.8	5.5
	Male,	1-20	1.0	1.6
	Kreyberg II	21-40	1.4	1.9
	(211 cases)	41+	1.5	3.7
	Female,	1-20	1.0	1.3
	Kreyberg I	21-40	2.7	4.8
	(98 cases)	41+	2.8	2.2
	Female	1-20	1.0	1.6
	Kreyberg II	21-40	1.7	7.1
	(73 cases)	41+	1.2	8.7
			(Results are for current smokers, risks relative to a smoker of 1 to 20 cigs/day, with duration 21 to 40 years)	

TABLE 8.1

Relative risk (95% CI) of lung cancer by pack-years smoked (base = never smokers, comparison groups = ever smoked unless indicated)

Study/ adjustment factors	Number of cases	Sex/smoking status	Relative risk (95% CI) by pack-years smoked			
RISCH			0	<30	30-59	60+
Age, borough,	403M,	Male	1.00	5.22(2.37-11.5)	11.0(5.39-22.3)	22.6(9.98-51.2)
years since quit	442F	Female	1.00	7.30(4.11-13.0)	26.7(14.0-50.6)	81.9(25.2-267)
			(Comparison groups = current smokers)			
SIEMIA			0	1-10	10-20	21-30
Age, race,	844M	Male	1.0	4.4(2.2-8.6)	9.9(5.3-18.7)	16.1(8.5-30.8)
income,				31+[a]		
occupation,		Male	...	28.0(14.5-54.0)		
coffee, alcohol, beta-carotene						
PRESCO		Inhaler	0	<15	15-29	30-44
Age, study	482M,	Male	1.0	4.7(1.2-19.2)	11.1(4.8-25.4)	19.7(8.6-45.1)
cohort	175F	Female	1.0	5.5(2.2-13.9)	10.1(5.6-18.2)	13.5(7.2-25.5)
				45-59	60+	
		Male	...	19.2(8.4-43.7)	24.2(10.6-55.3)	
		Female	...	15.1(7.7-29.5)	21.4(9.2-49.7)	
		Non-inhaler	0	<30	30-59	60+
		Male	1.0	4.8(1.9-11.7)	7.5(3.1-17.9)	10.8(4.4-26.3)
		Female	1.0	2.4(1.2-5.1)	4.5(2.0-10.5)	12.0(3.9-36.6)
			(Comparison groups = current smokers)			
BARBON			0	<45	45-89	90+
Age	755M	Male	1.0	6.5(4.0-10.5)	12.7(7.9-20.5)	20.5(12.3-95.0)
BECHER			0	1-25	25-50	50+
Age, education, occupation	600M	Male	1.00	2.79(1.48-5.24)	8.82(5.11-15.24)	13.86(7.94-24.19)
DOSEME			0	1-10	11-20	21+
Age, alcohol	1210M	Male	1.0	1.8(1.2-2.6)	4.3(3.0-6.4)	6.8(4.4-10.4)
CORREA			0	1-20	21-40	41+
Age, sex	2731M+F	Male/White	1.0	3.6	9.5	24.5
		Male/Black	1.0	4.0	14.6	18.2
		Female/White	1.0	1.5	7.7	26.2
		Female/Black	1.0	13.3	19.5	52.8

TABLE 8.1 (continued)

Study/ adjustment factors	Number of cases	Sex/smoking status	Relative risk (95% CI) by pack-years smoked			
SCHWAR2			0	1-40	41+	
Age	3226M,	Male	1.00	3.52(2.87-4.33)	12.2(9.99-14.9)	
	1807F	Female	1.00	5.66(4.69-6.84)	21.3(17.3-26.2)	
GARSHI			0	1-50	51+	
Age	989M	Male	1.00	3.98(2.81-5.64)	8.22(5.84-11.6)	
TNCS			0	-20	>20-<40	40+
Age, race	570M,	Male	1.00	2.74(1.81-4.16)	5.52(3.85-7.92)	9.93(7.14-13.8)
	140F	Female	1.00	3.42(1.97-5.74)	11.5(6.96-18.9)	16.4(10.0-26.9)
WYNDER4			0	1-19	20-39	40-49
Age	798M,	Male	1.0	3.17(2.02-4.97)	9.60(6.53-14.1)	17.7(12.3-25.5)
	547F	Female	1.0	6.33(4.10-9.76)	13.0(9.14-18.5)	25.4(17.5-36.1)
	(Squamous/			50+		
	epidermoid	Male	...	25.3(17.6-36.3)		
	or adeno-	Female	...	40.4(24.5-66.6)		
	carcinoma)			(Comparison groups = current smokers)		

Notes

[a] Groupings were actually 1-500, 501-1000, 1001-1500 and 1501+ cigarette years.

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TABLE 8.2

Relative risk (95% CI) of lung cancer by pack-years smoked - by histological type (Base = never smoked, comparison groups = ever smoked unless indicated)

Study/ adjustment factors	Sex	Histological type	Relative risk (95% CI) by pack-years smoked			
RISCH			Never	Per 40 pack-years (fitted model)		
Matching factors, years since quit	Male	Squamous	1.00	15.5(5.65-42.3)		
		Adeno	1.00	5.44(2.04-14.5)		
		Small/oat	1.00	14.9(3.97-55.8)		
		Large/giant	1.00	11.7(1.31-104)		
	Female	Squamous	1.00	101(15.3-660)		
		Adeno	1.00	8.75(3.68-20.8)		
		Small/oat	1.00	87.3(26.7-286)		
		Large/giant	1.00	18.0(2.53-127)		
			(Comparison group = current smokers)			
SIEMIA			Never	1-10	11-20	21-30
Age, race, income, occupation, coffee, alcohol, beta-carotene	Male	Squamous	1.0	7.5(2.1-26.7)	17.9(5.4-59.7)	26.8(8.0-89.9)
		Adeno	1.0	2.2(0.7-6.7)	5.3(2.0-14.1)	8.0(3.0-21.7)
		Oat	1.0	6.5(1.4-29.8)	11.8(2.7-50.6)	22.8(5.3-98.4)
				31+[a]		
		Squamous	...	50.2(14.9-169.0)		
		Adeno	...	13.0(4.8-35.0)		
		Oat	...	31.8(7.3-138.6)		
PRESCO	Inhalers		Never	1-29	30-60	61+
Age, study cohort	Male	Squamous	1.0	22.6(7.9-65)	44.5(16.2-122)	45.5(15.9-130)
		Adeno	1.0	8.4(3.6-20)	11.8(5.3-26)	12.1(4.9-03.0)
		Anaplastic	1.0	12.2(4.8-31)	18.3(7.6-44)	35.1(4.2-87)
	Female	Squamous	1.0	5.6(1.7-19)	16.0(5.2-49)	43.5(10.9-170)
		Adeno	1.0	7.0(2.9-17)	8.5(3.4-22)	20.5(5.3-80)
		Anaplastic	1.0	10.1(3.9-26)	17.7(6.9-45)	10.1(1.2-84)
	Non-inhalers					
	Male	Squamous	1.0	8.3(2.3-29)	17.5(5.6-54)	30.2(9.6-95)
		Adeno	1.0	2.1(0.5-8.0)	3.6(1.1-11)	4.3(1.1-17)
		Anaplastic		1.0	10.0(3.3-30)	16.3(5.2-51)
	Female					
		Squamous	1.0	3.0(0.8-12)	2.2(0.2-19)	25.0(4.6-140)
		Adeno	1.0	1.0(0.2-5.0)	1.5(0.2-12)	0.0
		Anaplastic		1.0	8.9(2.5-32)	28.8(5.8-140)
			(Comparison groups = current smokers. For adenocarcinoma and squamous cell carcinoma reference category is never smokers for sexes combined. For anaplastic carcinoma reference is never plus 1-29 pack-years for sexes combined.)			

BARBON			Never	<45	45-89	90+
Age	Male	Squamous	1.0	8.4(3.6-19.8)	17.1(7.3-39.8)	28.8(12.1-68.6)
		Adeno	1.0	4.8(2.1-10.8)	8.1(3.6-18.1)	11.6(5.0-27.0)
		Small	1.0	6.1(2.6-14.6)	13.9(5.9-32.5)	22.4(9.3-54.1)
		Large	1.0	17.2(2.3-128)	30.0(4.1-221)	63.2(8.5-473)

TABLE 8.2 (Continued)

Study/ adjustment factors	Sex	Histological type	Relative risk (95% CI) by pack-years smoked			
BECHER			Never	1-25	25-50	50+
Age, education, occupation	Male	Squamous	1.00	4.56(1.77-11.8)	12.3(5.26-28.9)	20.0(8.48-47.1)
		Small	1.00	3.47(0.91-13.3)	12.2(3.72-40.3)	18.4(5.54-61.1)
		Adeno	1.00	0.97(0.30-3.10)	4.10(1.75-9.63)	5.96(2.48-14.3)
DOSEME			Never	1-10	11-20	21+
Age, alcohol	Male	Squamous	1.0	1.8(1.1-3.0)	4.4(2.7-7.0)	7.1(4.2-11.8)
		Small	1.0	2.8(1.2-6.6)	7.8(3.6-17.2)	12.9(5.3-29.0)
		Other	1.0	2.3(1.2-4.5)	4.3(2.3-8.3)	3.5(1.6-7.7)
TNCS			Never	<18	18-56	>56
Age	Male	Squamous	1.0	1.0(0.4-2.3)	2.8(1.5-4.9)	4.0(2.5-6.4)
		Adeno	1.0	2.2(0.8-5.7)	2.9(1.1-7.7)	3.4(1.5-8.2)
		Small	1.0	0.0	47(14-154)	7.1(2.8-17.6)
WYNDER4			Never	1-19	20-39	40-49
Age	Male	Squamous	1.0	6.5(2.7-15.4)	24.1(11.0-52.4)	48.9(22.9-101)
		Adeno	1.0	2.4(1.4-4.1)	5.6(3.6-8.7)	11.6(7.7-17.6)
				50+		
		Squamous	...	82.1(39.5-171)		
		Adeno	...	13.8(9.2-20.9)		
			Never	1-19	20-39	40-49
	Female	Squamous	1.0	11.9(4.9-28.8)	26.4(13.1-53.4)	48.8(24.9-95.8)
		Adeno	1.0	6.8(4.1-11.4)	11.2(7.5-16.8)	21.4(14.3-32.2)
				50+		
		Squamous	...	95.2(43.4-209)		
		Adeno	...	32.7(19.0-56.2)		

(Comparison groups = current smokers)

[a] Groupings were actually 1-500, 501-1000, 1001-1500 and 1501+ cigarette years.

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TABLE 9.1

Relative risk (95% CI) of lung cancer in relation to years stopped smoking (base = never smokers)

Study/ adjustment factors	Number of cases	Sex	Relative risk (95% CI) by years stopped			
GAO			Never	10+	5-9	1-4
Age, education	204M,	Male	1.0	1.1(0.5-2.2)	3.1(1.7-5.9)	6.9(4.4-10.8)
	502F	Female	1.0	2.2(1.0-4.6)	3.9(1.5-9.9)	7.2(3.4-15.1)
HIRAYA			Never	10+	5-9	1-4
Age	<1323M,	Male	1.00	1.38(0.59-3.22)	1.59(0.66-3.81)	2.03(1.10-3.74)
	<426F	Female	1.00	0.97(0.03-30.95)	3.29(0.56-19.53)	3.72(1.12-12.40)
JOLY			Never	5+	1-4	
None	113M,	Male	1.0	7.68(4.00-14.7)	19.2(9.16-40.1)	
	86F	Female	1.0	4.30(2.05-8.99)	12.9(5.38-31.1)	
RISCH			Never	11+	2-10	
Age, borough	403M,	Male	1.0	2.24(1.07-5.03)	8.04(3.90-18.2)	
	442F	Female	1.0	1.20(0.56-2.53)	8.03(4.29-15.9)	
BENHAM			Never	11+	4-10	1-3
None	343M	Male	1.00	4.17(2.65-6.56)	9.00(5.88-13.8)	26.7(17.2-41.6)
BARBON			Never	25+	15-24	5-14
Age	755M	Male	1.0	2.1(1.0-4.3)	6.8(3.6-12.8)	9.1(5.3-15.5)
				1-4		
			...	13.9(6.8-28.5)		
DAMBER			Never	11+	6-10	1-5
Age	579M	Male	1.0	2.6(1.6-4.5)	4.3(2.2-8.0)	7.8(4.5-13.3)
LUBIN			Never	20+	15-19	10-14
None	1906M,	Male	1.00	2.79(2.24-3.47)	3.80(2.94-4.92)	5.78(4.66-7.16)
	388F			5-9	1-4	
			...	7.49(6.15-9.11)	11.7(9.72-14.0)	
			Never	5+	1-4	
		Female	1.00	1.73(1.18-2.52)	4.25(2.87-6.29)	
CORREA			Never	20+	6-20	3-5
Age, sex	2731M+F	Both	1.0	3.9	7.0	7.7
BROSS			Never	6+	1-5	
None	250M	Male	1.00	2.44(1.46-4.06)	11.3(7.18-17.7)	
GRAHAM			Never	6+	>1-5	≤1
Age	168M	Male	1.00	2.59(1.18-5.67)	8.50(4.32-16.7)	35.8(20.5-62.5)

TABLE 9.1 (Continued)

Study/ adjustment factors	Number of cases	Sex	Relative risk (95% CI) by years stopped			
CPSI			Never	10+	5-9	1-4
Age	193M	Male	1.00	1.28(0.73-2.25)	5.15(3.35-7.91)	8.09(5.55-11.8)
				≤1		
		Male	...	14.7(9.78-22.2)		
CPSII			Never	16+	11-15	6-10
Age	1150M,	Male	1.00	3.83(2.98-4.92)	8.61(6.60-11.2)	11.4(8.81-14.8)
	424F	Female	1.00	1.76(1.25-2.46)	3.52(2.33-5.31)	4.79(3.35-6.85)
				3-5	1-2	≤1
		Male	...	18.6(14.3-24.2)	28.1(21.6-36.4)	38.8(28.9-52.2)
		Female	...	9.26(6.75-12.7)	15.4(11.4-20.8)	23.4(16.4-33.5)
DORN			Never	40+	30-39	20-29
Age	1106M	Male	1.00	1.5(1.1-2.0)	2.0(1.6-2.6)	3.3(2.8-4.0)
				10-19	5-9	≤5
		Male	...	5.1(4.2-6.1)	7.8(5.7-10.5)	16.1(10.4-24.8)
GARSHI			Never	15+	5-14	0-4
Age	989M	Male	1.00	3.20(2.18-4.69)	5.06(3.47-7.36)	7.70(5.48-10.8)
WYNDER2			Never	16+	11-15	7-10
None	298M,	Male	1.00	4.14(2.26-7.57)	11.2(6.26-20.0)	13.9(8.16-23.8)
	120F	Female	1.00	0.72(0.18-2.97)	7.02(3.36-14.6)	4.66(2.33-9.32)
				4-6	1-3	
		Male	...	15.9(9.32-27.0)	31.2(18.9-51.5)	
		Female	...	4.19(2.10-8.35)	8.00(5.05-12.7)	
WYNDER3			Never	30+	20-29	10-19
None	598M,	Male	1.0	1.9(1.1-3.1)	3.7(2.5-5.5)	6.1(4.5-8.4)
	320F	Female	1.0	2.6(1.2-5.3)	1.6(0.9-2.9)	2.2(1.4-3.3)
				5-9	1-4	
		Male	...	7.2(5.1-10.3)	17.4(12.5-24.1)	
		Female	...	4.8(3.2-7.1)	9.3(6.4-13.4)	
ALDERS			Never	11+	5-10	1-4
Age	192M,	Male	1.00	3.31(1.67-6.58)	4.45(2.20-9.00)	18.7(10.0-35.0)
	361F	Female	1.00	1.30(0.77-2.20)	3.02(1.92-4.75)	9.67(6.64-14.1)
BENSHL			Never	31+	20-29	10-19
Age	68M	Male	1.00	1.00(0.32-3.10)	2.59(1.21-5.54)	4.08(2.03-8.20)
				1-9		
		Male	...	8.68(4.00-18.9)		
DARBY			Never	10+	1-9	
None	288M,	Male	1.00	23.2(7.34-73.3)	55.1(17.4-175)	
	137F	Female	1.00	2.67(1.49-4.78)	16.8(9.98-28.3)	

TABLE 9.1 (Continued 2)

Study/ adjustment factors	Number of cases	Sex	Relative risk (95% CI) by years stopped			
DEANN			Never	10+	5-9	1-4
Age	131M	Male	1.00	3.67(2.06-6.54)	5.28(2.39-11.7)	6.56(3.80-11.3)
DEANT			Never	19+	9-18	5-8
Age	87M, 48F	Male	1.00	1.31(0.57-3.02)	2.99(1.51-5.90)	4.16(1.92-9.02)
				1-4		
		Male	...	4.67(2.62-8.34)		
			Never	9+	5-8	1-4
		Female	1.00	0.72(0.17-3.01)	1.09(0.15-8.13)	1.63(0.57-4.63)
DOLL1			Never	10+	1-9	
None	77M, 185F	Male	1.00	2.49(0.93-6.65)	6.51(2.71-15.3)	
		Female	1.00	0.74(0.06-8.41)	2.21(0.73-6.70)	
DOLL2			Never	15+	10-14	5-9
Age	50M	Male	1.00	2.00(0.70-5.70)	5.30(1.97-14.2)	5.90(2.32-15.0)
				1-4		
		Male	...	16.0(6.52-39.2)		

TABLE 9.2

Relative risk (95% CI) of lung cancer in relation to years stopped smoking - by histological type (base = never smokers)

Study/ adjustment factors	Sex	Histological type	Relative risk (95% CI) by years stopped			
BENHAM			Never	11+	4-10	1-3
None	Male	Kreyberg I	1.00	4.29(2.71-6.79)	9.21(5.98-14.2)	27.2(17.3-42.6)
		Kreyberg II	1.00	1.0(0.2-3.7)	2.1(0.6-7.2)	6.7(2.0-24.2)
BARBON			Never	25+	15-24	5-14
Age	Male	Squamous	1.0	1.9(0.5-7.2)	8.1(2.8-23.2)	11.9(4.8-29.8)
		Adeno	1.0	1.8(0.5-6.4)	4.6(1.5-13.8)	7.3(3.0-17.6)
		Small	1.0	2.2(0.6-7.9)	7.6(2.7-22.6)	7.7(3.0-19.8)
		Large	1.0	9.7(1.0-95.6)	13.9(1.4-137)	22.0(2.8-175)
				1-4		
		Squamous	...	18.7(6.2-56.3)		
		Adeno	...	9.4(3.0-29.7)		
		Small	...	10.9(3.3-35.6)		
		Large	...	46.2(5.1-41.7)		
LUBIN			Never	20+	15-19	10-14
None	Male	Squamous	1.00	4.55(3.26-6.36)	6.79(4.68-9.84)	10.2(7.39-14.1)
		Adeno	1.00	1.42(0.93-2.18)	2.02(1.21-3.36)	1.99(1.27-3.12)
		Oat	1.00	1.91(1.15-3.16)	2.58(1.41-4.70)	5.00(3.18-7.86)
		Other KI	1.00	3.25(1.82-5.79)	3.01(1.43-6.32)	5.66(3.20-10.0)
				5-9	1-4	
		Squamous	...	14.6(10.0-19.7)	23.0(17.2-30.8)	
		Adeno	...	2.60(1.77-3.83)	3.38(2.38-4.79)	
		Oat	...	6.11(4.03-9.26)	10.1(6.92-14.9)	
		Other KI	...	4.89(2.79-8.57)	7.62(4.58-12.7)	
			Never	5+	1-4	
	Female	Squamous	1.00	3.21(1.88-5.49)	7.45(4.39-12.6)	
		Adeno	1.00	0.92(0.48-1.76)	0.93(0.39-2.21)	
		Oat	1.00	1.26(0.53-3.00)	7.41(4.12-13.3)	
		Other KI	1.00	3.02(1.20-7.58)	6.53(2.69-15.9)	
WYNDER2			Never	16+	11-15	7-10
Age, race	Male	Kreyberg I	1.0	5.0(2.2-11.5)	13.7(6.0-31.1)	17.2(7.9-37.3)
		Kreyberg II	1.0	1.2(0.4-3.3)	5.4(2.3-12.6)	6.6(3.1-14.1)
				4-6	1-3	
		Kreyberg I	...	24.9(11.6-53.4)	53.8(25.7-112)	
		Kreyberg II	...	5.9(2.7-13.1)	14.2(7.0-28.8)	
			Never	16+	11-15	7-10
	Female	Kreyberg I	1.0	0.0	8.8(3.0-26.0)	5.1(1.7-14.9)
		Kreyberg II	1.0	0.9(0.2-3.8)	5.6(2.1-14.7)	4.1(1.7-9.9)
				4-6	1-3	
		Kreyberg I	...	6.2(2.3-16.5)	13.6(7.2-25.7)	
		Kreyberg II	...	3.6(1.4-9.3)	6.7(3.5-12.8)	
WYNDER4			Never	11+	6-10	1-5
Age, education	Male	Large	1.0	6.1(2.8-13.6)	12.9(5.3-31.1)	12.4(5.2-29.6)
	Female	Large	1.0	4.2(2.0-9.0)	11.5(5.0-26.7)	15.9(7.1-35.4)

TABLE 9.2 (Continued)

Relative risk (95% CI) of lung cancer in relation to years stopped smoking - by histological type (base = never smokers)

Study/ adjustment factors	Sex	Histological type	Relative risk (95% CI) by years stopped			
			Never	11+	5-10	1-3
ALDERS Age	Male	Squamous/Oat	1.00	2.33(0.62-8.82)	4.00(1.09-14.7)	23.3(7.18-75.7)
		Other	1.00	2.40(0.69-8.31)	4.11(0.85-20.0)	5.45(1.75-17.0)
	Female	Squamous/Oat	1.00	0.64(0.17-2.43)	8.03(3.41-19.0)	16.1(7.78-33.2)
		Other	1.00	1.86(0.75-4.64)	0.83(0.29-2.33)	7.13(3.16-16.1)

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TABLE 9.3

Relative risk (95% CI) of lung cancer in relation to years stopped smoking (base = current smokers, unless stated)

Study/ adjustment factors	Number of cases	Sex	Relative risk (95% CI) by years stopped			
GAO			Current	1-4	5-9	10+
Age, education	671M,	Male	1.00	1.77(1.22-2.56)	0.79(0.45-1.40)	0.28(0.14-0.57)
	237F	Female	1.00	2.48(1.15-5.38)	1.34(0.51-3.53)	0.76(0.34-1.67)
HIRAYA			Current	1-4	5-9	10+
Age	<1323M,	Male	1.00	0.46(0.26-0.81)	0.36(0.15-0.84)	0.31(0.14-0.71)
	<426F	Female	1.00	1.59(0.47-5.35)	1.41(0.24-8.37)	0.41(0.01-13.37)
SOBUE		Male	Current	1-4	5-9	10+
Amount smoked	1023M	Age 55-64	1.00	0.85(0.49-1.47)	0.47(0.25-0.92)	0.34(0.18-0.64)
		60-69	1.00	0.87(0.50-1.49)	0.61(0.34-1.10)	0.35(0.20-0.59)
		65-74	1.00	0.96(0.51-1.80)	0.69(0.36-1.32)	0.41(0.23-0.72)
		70-79	1.00	0.85(0.43-1.70)	0.49(0.23-1.06)	0.50(0.27-0.94)
JOLY			Current	1-4	5+	
None	552M,	Male	1.00	1.23(0.76-1.97)	0.49(0.36-0.68)	
	166F	Female	1.00	1.73(0.73-4.11)	0.57(0.28-1.19)	
RISCH			Current	Per 10 years stopped (fitted model)		
Age, borough,	403M,	Male	1.00	0.65(0.50-0.85)		
pack-years	442F	Female	1.00	0.52(0.35-0.78)		
BARBON			Current	1-4	5-14	15-24
Age	755M	Male	1.0	1.01(0.57-1.79)	0.66(0.47-0.92)	0.49(0.31-0.79)
				25+		
			...	0.15(0.08-0.28)		
BECHER			0-4	5-10	11+	
Age,	901M,	Male	1.0	0.66(0.45-0.98)	0.40(0.29-0.56)	
occupation,	198F		0-4	5+		
air pollution		Female	1.0	0.51(0.17-1.50)		
LUBIN			Current	1-4	5-9	10-14
None	5870M,	Male	1.00	1.10(1.00-1.22)	0.71(0.62-0.80)	0.55(0.47-0.63)
	484F			15-19	20+	
			...	0.36(0.29-0.44)	0.26(0.23-0.31)	
			Current	1-4	5+	
		Female	1.00	1.11(0.75-1.64)	0.45(0.31-0.66)	
CORREA			Current	3-5	6-20	20+
Age, sex	2731M+F	Both	1.00	0.61	0.56	0.31

TABLE 9.3 (Continued)

Study/ adjustment factors	Number of cases	Sex	Relative risk (95% CI) by years stopped			
BROSS			Current	1-5	6+	
None	777M	Male	1.00	1.91(1.40-2.60)	0.41(0.28-0.61)	
GRAHAM			Current	≤1	>1-5	6+
Age	618M	Male	1.00	4.94(3.54-6.89)	1.17(0.70-1.94)	0.35(0.19-0.69)
CPSI			Current	≤1	1-4	5-9
Age	977M	Male	1.00	1.07(0.77-1.49)	0.59(0.44-0.78)	0.37(0.26-0.53)
				10+		
		Male	...	0.09(0.06-0.15)		
CPSII			Current	≤1	1-2	3-5
Age	2228M	Male	1.00	1.77(1.44-2.18)	1.28(1.10-1.49)	0.85(0.72-0.99)
	822F	Female	1.00	1.88(1.34-2.63)	1.23(0.93-1.63)	0.74(0.56-1.00)
				6-10	11-15	16+
		Male	...	0.52(0.45-0.61)	0.39(0.33-0.46)	0.17(0.15-0.20)
		Female	...	0.38(0.27-0.54)	0.28(0.19-0.42)	0.14(0.10-0.19)
DORN			Current	1-4	5-9	10-19
Age	4772M	Male	1.00	1.39(0.91-2.12)	0.67(0.50-0.90)	0.44(0.38-0.51)
				20-29	30-39	40+
		Male	...	0.28(0.25-0.33)	0.17(0.14-0.21)	0.13(0.10-0.17)
GARSHI			0-4	5-14	15+	
Age	948M	Male	1.00	0.65(0.52-0.81)	0.41(0.32-0.52)	
WYNDER2			Current	1-3	4-6	7-10
None	969M,	Male	1.00	1.60(1.27-2.02)	0.81(0.61-1.09)	0.72(0.53-0.97)
	247F	Female	1.00	1.49(0.99-2.24)	0.78(0.40-1.50)	0.87(0.45-1.68)
				11-15	16+	
		Male	...	0.57(0.40-0.83)	0.21(0.14-0.32)	
		Female	...	1.30(0.64-2.64)	0.13(0.03-0.54)	
WYNDER3			Current	1-4	5-9	10-19
None	1641M,	Male	1.00	1.09(0.87-1.36)	0.45(0.35-0.59)	0.38(0.31-0.47)
	878F	Female	1.00	0.85(0.61-1.19)	0.44(0.31-0.64)	0.20(0.14-0.29)
				20-29	30+	
		Male	...	0.23(0.17-0.32)	0.12(0.07-0.19)	
		Female	...	0.15(0.09-0.26)	0.23(0.11-0.48)	
ALDERS			Current	1-4	5-10	11+
Age	385M,	Male	1.00	1.81(1.24-1.65)	0.43(0.26-0.71)	0.32(0.20-0.52)
	530F	Female	1.00	2.08(1.49-2.91)	0.65(0.43-0.99)	0.28(0.17-0.46)
DARBY			Current	1-9	10+	
None	607M,	Male	1.00	0.61(0.48-0.77)	0.26(0.20-0.32)	
	289F	Female	1.00	0.81(0.56-1.18)	0.13(0.08-0.20)	

TABLE 9.3 (Continued 2)

Study/ adjustment factors	Number of cases	Sex	Relative risk (95% CI) by years stopped			
DEANN			Current	1-4	5-9	10+
Age	767M	Male	1.00	0.86(0.57-1.31)	0.69(0.34-1.41)	0.48(0.30-0.76)
DEANT			Current	1-4	5-8	9-18
Age	399M, 109F	Male	1.00	0.62(0.40-0.96)	0.56(0.29-1.10)	0.40(0.23-0.70)
				19+		
		Male	...	0.18(0.09-0.38)		
			Current	1-4	5-8	9+
		Female	1.00	0.27(0.10-0.75)	0.18(0.03-1.32)	0.12(0.03-0.49)
DOLL1			Current	1-9	10+	
None	1350M, 68F	Male	1.00	0.68(0.48-0.98)	0.26(0.14-0.48)	
		Female	1.00	1.06(0.35-3.21)	0.35(0.03-4.03)	
DOLL2			Current	1-4	5-9	10-14
Age	279M	Male	1.00	1.02(0.61-1.72)	0.35(0.20-0.63)	0.28(0.14-0.54)
				15+		
		Male	...	0.11(0.05-0.23)		

TABLE 9.4

Relative risk (95% CI) of lung cancer in relation to years stopped smoking - by histological type (base = current smokers, unless stated)

Study/ adjustment factors	Sex	Histological type	Relative risk (95% CI) by years stopped			
RISCH			Current	Per 10 years stopped (fitted model)		
Age, borough, pack-years	Male	Squamous	1.00	0.63(0.39-1.00)		
		Adeno	1.00	0.85(0.51-1.40)		
		Small/oat	1.00	0.43(0.22-0.82)		
		Large/giant	1.00	0.96(0.40-2.32)		
	Female	Squamous	1.00	0.50(0.20-1.29)		
		Adeno	1.00	0.48(0.23-1.00)		
		Small/oat	1.00	0.39(0.15-1.03)		
		Large/giant	1.00	1.07(0.43-2.71)		
BARBON			Current	1-4	5-14	15-24
Age	Male	Adeno	1.0	1.15(0.47-2.78)	0.89(0.54-1.47)	0.56(0.24-1.29)
		Squamous	1.0	0.97(0.45-2.07)	0.62(0.40-0.96)	0.42(0.21-0.84)
		Small	1.0	0.75(0.31-1.83)	0.53(0.32-0.89)	0.52(0.26-1.06)
		Large	1.0	1.33(0.48-3.71)	0.63(0.32-1.27)	0.40(0.12-1.34)
				25+		
		Adeno	...	0.22(0.08-0.62)		
		Squamous	...	0.10(0.03-0.29)		
		Small	...	0.15(0.05-0.42)		
		Large	...	0.28(0.09-0.91)		
BECHER			0-4	5-9	10+	
Age, education, occupation	Male	Squamous	1.00	0.58(0.36-0.94)	0.31(0.19-0.52)	
		Adeno	1.00	0.81(0.44-1.49)	0.52(0.28-0.94)	
		Small	1.00	1.08(0.57-2.04)	0.42(0.19-0.90)	
LUBIN			Current	1-4	5-9	10-14
None	Male	Squamous	1.00	1.17(1.04-1.32)	0.74(0.64-0.86)	0.52(0.43-0.63)
		Adeno	1.00	1.01(0.78-1.29)	0.78(0.57-1.05)	0.59(0.41-0.86)
		Oat	1.00	0.99(0.82-1.20)	0.60(0.46-0.77)	0.49(0.36-0.67)
		Other KI	1.00	1.27(0.96-1.69)	0.82(0.57-1.18)	0.94(0.64-1.39)
				15-19	20+	
		Squamous	...	0.35(0.27-0.45)	0.23(0.19-0.28)	
		Adeno	...	0.60(0.38-0.94)	0.42(0.30-0.60)	
		Oat	...	0.25(0.15-0.42)	0.19(0.13-0.87)	
		Other KI	...	0.50(0.27-0.92)	0.54(0.37-0.80)	
			Current	1-4	5+	
	Female	Squamous	1.00	1.21(0.73-2.01)	0.52(0.31-0.87)	
		Adeno	1.00	0.65(0.27-1.56)	0.64(0.33-1.26)	
		Oat	1.00	1.19(0.68-2.08)	0.20(0.09-0.47)	
		Other KI	1.00	1.24(0.53-2.90)	0.57(0.24-1.39)	

TABLE 9.4 (Continued)

Study/ adjustment factors	Sex	Histological type	Relative risk (95% CI) by years stopped			
WYNDER2			Current	1-3	4-6	7-10
Age, race	Male	Kreyberg I	1.0	1.7(1.3-2.2)	0.8(0.6-1.1)	0.5(0.3-0.7)
		Kreyberg II	1.0	1.3(0.9-2.0)	0.6(0.3-1.0)	0.6(0.4-1.0)
				11-15	16+	
		Kreyberg I	...	0.4(0.3-0.6)	0.2(0.1-0.3)	
		Kreyberg II	...	0.5(0.3-0.9)	0.1(0.04-0.2)	
			Current	1-3	4-6	7-10
	Female	Kreyberg I	1.0	1.3(0.8-2.2)	0.6(0.2-1.5)	0.5(0.2-1.4)
		Kreyberg II	1.0	1.5(0.8-2.7)	0.8(0.3-2.0)	0.9(0.4-2.1)
				11-15	16+	
		Kreyberg I	...	0.8(0.3-2.2)	0.0	
		Kreyberg II	...	1.3(0.5-3.3)	0.2(0.05-0.8)	
WYNDER4			Current	1-5	6-10	>10
None	Male	Large	1.00	0.70(0.43-1.13)	0.69(0.41-1.14)	0.35(0.25-0.49)
	Female	Large	1.00	0.71(0.38-1.31)	0.52(0.26-1.01)	0.19(0.11-0.34)
ALDERS			Current	1-3	5-10	11+
Age	Male	Squamous/Oat	1.00	2.10(1.08-4.09)	0.36(0.15-0.86)	0.21(0.08-0.52)
		Other	1.00	2.07(0.89-4.83)	1.56(0.39-6.25)	0.91(0.34-2.44)
	Female	Squamous/Oat	1.00	3.02(1.68-5.43)	1.51(0.72-3.18)	0.12(0.03-0.43)
		Other	1.00	1.38(0.61-3.13)	0.16(0.06-4.45)	0.36(0.14-0.90)

TABLE 9.5

Joint relationship of lung cancer risk to years stopped smoking and amount smoked when smoking (base = never smokers)

Study/ adjustment factors	Sex	Relative risk (95% CI) by years stopped and amount smoked		
CPSI			Years stopped	
Age		Cigs/day	10+	5-9	1-4
	Male	1-19	0.44(0.11-1.79)	1.25(0.31-5.11)	3.31(1.43-7.67)
		20+	1.81(1.00-3.30)	6.50(4.19-10.1)	10.1(6.84-15.0)
			<1		
	Male	1-19	7.13(2.86-17.7)		
		20+	17.7(11.5-27.2)		

(The above table is taken from 6 yr follow-up data, where the findings are presented in a form that allows confidence limits to be calculated; below is a more detailed table from 12 year follow-up data for which confidence limits could not be estimated)

CPSI			Years stopped						
Age		Cigs/day	35-39	30-34	25-29	20-24	15-19	10-14	5-9	2-4
	Male	1-9	1.89	1.38	0.58	-	-	1.22	1.68	2.83
		10-19	-	1.68	2.16	0.96	2.04	2.91	3.50	7.96
		20	4.10	1.55	1.12	1.86	2.22	5.03	10.49	11.68
		21-39	3.69	4.13	-	2.04	4.88	4.85	9.18	14.30
		40+	-	-	0.89	3.99	3.74	7.77	12.36	27.88
	Female	1-9	-	-	1.81	2.38	-	0.45	1.89	2.13
		10-19	-	-	3.65	2.42	3.06	0.61	0.95	-
		20	-	-	-	1.66	0.98	0.76	-	4.31
		21-39	-	-	-	10.90	16.99	-	-	-
		40+	-	-	-	-	-	-	-	-

CPSII			Years stopped		
Age		Cigs/day	16+	11-15	6-10
	Male	1-20	3.1(2.4-4.1)	6.0(4.4-8.3)	8.7(6.4-11.8)
		21+	5.5(4.1-7.3)	12.6(9.4-16.9)	15.0(11.2-20.0)
	Female	1-19	1.4(0.9-2.2)	1.5(0.7-3.4)	1.0(0.4-2.7)
		20+	2.6(1.6-4.2)	5.9(3.7-9.4)	9.1(6.2-13.3)
			3-5	1-2	<1
	Male	1-20	16.5(12.1-22.4)	22.4(16.3-30.8)	26.7(17.8-4.0)
		21+	20.9(15.5-28.1)	33.2(25.0-44.1)	50.7(36.5-70.4)
	Female	1-19	2.9(1.4-6.2)	9.1(5.2-16.0)	7.9(3.2-19.2)
		20+	14.6(10.4-20.4)	19.5(13.9-27.3)	34.3(23.4-50.2)

TABLE 9.5 (Continued)

Study/ adjustment factors	Sex		Relative risk (95% CI) by years stopped and amount smoked		
DORN				Years stopped	
Age		Cigs/day	40+	30-39	20-29
	Male	1-19	1.1(0.6-1.9)	0.5(0.2-1.3)	1.7(1.0-2.8)
		10-20	1.6(1.0-2.4)	2.1(1.5-2.9)	3.3(2.6-4.1)
		21-39	1.8(0.9-3.3)	2.8(1.9-4.3)	3.4(2.6-4.5)
		40+	2.3(0.9-6.2)	4.5(2.6-7.9)	5.9(4.2-8.3)
			10-19	5-9	<5
	Male	1-9	2.2(1.3-3.6)	3.6(1.5-9.0)	7.6(2.3-24.9)
		10-20	4.3(3.4-5.4)	5.1(3.3-8.0)	12.5(7.1-21.7)
		21-39	6.8(5.4-8.7)	11.5(7.8-17.0)	20.6(11.9-35.6)
		40+	7.8(5.6-10.9)	13.6(8.0-22.9)	26.9(13.6-53.4)

APPENDIX A

Sources for the main tables

This appendix gives details of the sources used for each of the main tables in sections 5 to 9. For each study included in the table, the appendix provides details of

(i) the reference number (in square brackets) of the publication which was used as source,

(ii) the tables in that reference that were used, and

(iii) whether the relative risks and CIs used were taken directly from the source or whether some calculation was necessary. Details of the calculations used are available on request.

Sources for Table 5.1

GAO	Calculated from numbers of ever smokers in Table I of [1] and numbers of never smokers in Table 1 of [2]
FU	Calculated from Table IV of [3]
LIU	Table 2 of [5]
YU	Tables 3 and 6 of [8]
JUSSAW	Calculated from numbers of never smokers in Table VI and numbers of bidi only and cigarette only smokers combined in Table VI of [9]
NOTANI	Calculated from Table II of [10]
HIRAYA	Table 2 of [11]
SOBUE	Tables II and IV of [14]
JOLY	Calculated from Tables 2, 4 and 5 of [15]
BEST	Calculated from Table 8.2 of [16] noting that the expected values are estimated based on only 7 deaths in never smokers
PRESCO	Table 4 of [19]
AUVINE	Table 3 of [21]
BENHAM	Calculated from Table 3 of [22] (Males); direct from Table III of [23] (Females)
SCHWAR	Calculated from Tables 6, 7A and 7C of [24]
TRICHO	Calculated from Table 3 of [25] using age groups <50, 50-59, 60-69, 70+
BARBON	Table 1 of [26]
BECHER	Tables VI and VII of [27]
DAMBER	Estimated approximately from Figure 2 of [29] using Model A data
PERSHA	Calculated from numbers in Table 4, combining over radon levels [30]
DOSEME	Table 2 of [31]
LUBIN	Calculated from Table 3 of [32]
BRESLO	Calculated from Table 4 of [33]
OSANN	Table V of [34]

Sources for Table 5.1 (continued)

PIKE	Calculated from Table 1 of [35]
STOCKW	Calculated from Table 2 of [36]
BLOT	Calculated from Table 3 of [37]
CORREA	Table 3 of [39]
BROWNS	Table 2 of [41]
SCHOEN	Calculated from Tables 2 and 6 of [42]
HUMBLE	Calculated from Table 3 of [44]
BROSS	Calculated from Table 1 of [45]
CPSI	Calculated from Appendices B and C of [49]
CPSII	Calculated from Appendices 26, 27 and 30 of [51]
DORN	Table III of [57]
GARSHI	Calculated from Table 3 of [58]
KAUFMA	Table 2 of [59]
MRFIT	Calculated from Table 1 of [60]
NMFS	Calculated from Table 2 of [61]
WYNDER	Calculated from Figure 3 of [64]
WYNDER2	Calculated from Figure 1 of [66]
WYNDER3	Calculated from Tables 3 and 4 of [68]
WYNDER4	Calculated from Tables 4 and 5 of [70]
ALDERS	Calculated from Table 1 of [72]
BENSHL	Calculated from Table IV of [74]
DARBY	Calculated from Table 3 of [75]
DEANN	Calculated from Table IV (females) and Table V (males) of [76]
DEANT	Calculated from Table 5 of Supplement to [77]
DOLL1	Calculated from Table V of [78]

Sources for Table 5.1 (continued 2)

DOLL2	Calculated from Table III of [83] - males, and Table III of [82] - females, with additional data supplied as personal communication by R Peto
GILLIS	Table 2 of [84]
KINLEN	Calculated from Tables VIII and IX of [85]
STOCKS	Calculated from Tables 31 and 34 of [86]

Sources for Table 5.2

SOBUE	Tables II and IV of [14]
BENHAM	Calculated from Table 3 and direct from Table 2 of [23]
BARBON	Table 2 of [26]
BECHER	Table 3 of [28]
DAMBER	Table 4 of [29] using model A data
DOSEME	Table 2 of [31]
LUBIN	Calculated from Table 3 of [32]
BRESLO	Calculated from Table 3 of [33]
OSANN	Table V of [34]
CORREA	Table 3 of [39]
BROWNS	Table 2 of [41]
SCHOEN	Calculated from Tables 3-6 of [42]
WYNDER3	Tables 3 and 4 of [68]
WYNDER4	Tables 4 and 5 of [70] and Table 3 of [69]
ALDERS	Calculated from Tables 2 and 3 of [72]
DOLL1	Calculated from Tables I and II of [79] and Table X of [78]
DOLL2	Calculated from Table 8 of [80]
GILLIS	Estimated from Figure 1 of [84]

Sources for Table 6.1

GAO	Table 3 of [2]
FU	Calculated from Table V of [3]
LIU	Table 3 of [5]
YU	Tables 3 and 6 of [8]
HIRAYA	Calculated from Table 17 of [12]
JOLY	Calculated from Tables 2 and 6 of [15]
AUVINE	Table 3 of [21]
BENHAM	Calculated from Table 3 of [22] (Males); direct from Table III of [23] (Females)
BARBON	Table 1 of [26]
BECHER	Tables VI and VII of [27]
DAMBER	Calculated from Tables I and II of [29]
BRESLO	Calculated from Table 5 of [33]
CORREA	Table 4 of [38]
CPSI	Calculated from Tables 2 and 4 of [50]
DORN	Calculated from Appendix A (p30) and Appendix D (p103-4) of [56]
WYNDER4	Calculated from Table 3 of [70]
ALDERS	Calculated from Table 1 of [72]
DEANT	Calculated from Table 9 of Supplement to [77]
DOLL1	Calculated from Table VI of [78]

Sources for Table 6.2

BENHAM	Calculated from Table 3 of [22]
BARBON	Table 2 of [26]
BECHER	Table 3 of [28]
WYNDER4	Calculated from Table 3 of [70]
ALDERS	Calculated from Tables 2 and 3 of [72]

Sources for Table 6.3

DORN	Calculated from Appendices A and D of [56]

Sources for Table 6.4

HIRAYA	Table 18 of [12]

Sources for Table 7.1

SOBUE	Tables II and IV of [14]
BEST	Calculated from Table 9.3 of [16] noting that the expected values are estimated based on only 7 deaths in never smokers
PRESCO	Table 2 of [20]
AUVINE	Table 3 of [21]
BARBON	Table 1 of [26]
BECHER	Calculated from Table 3 of [28]
DAMBER	Calculated from Tables IV and V of [29]
DOSEME	Table 2 of [31]
SCHOEN	Calculated from Tables 2 and 6 of [42]
HUMBLE	Calculated from Table 3 of [44]
BUFFLE	Table 3.1 of [48]
CPSI	Calculated from Appendices B and C of [49]
CPSII	Calculated from Appendices 38, 39, 44 and 46 of [51]

Sources for Table 7.2

SOBUE	Table IV of [14]
PRESCO	Table 3 of [20]
BARBON	Table 2 of [26]
BECHER	Table 4 of [28]
DAMBER	Table V of [29]
DOSEME	Table 2 of [31]
SCHOEN	Calculated from Tables 3-6 of [42]
BUFFLE	Table 3.3 of [48]
WYNDER4	Table 3 of [69]

Sources for Table 7.3

GAO	Male data in Table II of [2] Female data in Table I of [1]
XU	Table 1 of [7] and Table 3 of [6]
BECHER	Tables 6 and 7 of [28]
SCHOEN	Tables 2-6 of [42]
CPSI	Calculated from Tables 1 and 2 and Appendices B and C of [49]
CPSII	Calculated from Appendices 2, 3, 18-21 of [51]
WYNDER2	Table 14 of [65]

Sources for Table 8.1

RISCH	Table 5 of [17]
SIEMIA	Table 3 of [18]
PRESCO	Table 2 of [20]
BARBON	Table 1 of [26]
BECHER	Calculated from Table 4 of [28]
DOSEME	Table 2 of [31]
CORREA	Table 3 of [38]
SCHWAR2	Calculated from Table 3 of [40]
GARSHI	Calculated from Table 3 of [58]
TNCS	Calculated from Tables 4, 5, 6 and 7 of [63]
WYNDER4	Calculated from Tables 4 and 5 of [70]

Sources for Table 8.2

RISCH	Table 6 of [17]
SIEMIA	Table 3 of [18]
PRESCO	Table 3 of [20]
BARBON	Table 2 of [26]
BECHER	Table 4 of [28]
DOSEME	Table 2 of [31]
TNCS	Calculated from Table 4 of [62]
WYNDER4	Tables 4 and 5 of [70]

Sources for Table 9.1

GAO	Table 3 of [2]
HIRAYA	Calculated from Table 19 of [12]
JOLY	Calculated from Tables 2 and 6 of [15]
RISCH	Table 2 of [17]
BENHAM	Calculated from Table 3 of [22]
BARBON	Table 1 of [26]
DAMBER	Estimated from Figure 4 of [29]
LUBIN	Calculated from Tables 2 and 5 of [32]
CORREA	Table 4 of [38]
BROSS	Calculated from Table 2 of [45]
GRAHAM	Calculated from adjusted numbers in Table 4 of [46]
CPSI	Calculated from Table 3 of [50]
CPSII	Calculated from Table 3 (Chapter 4) of [53]
DORN	Table 4 of [55]
GARSHI	Calculated from Table 3 of [58]
WYNDER2	Calculated from Tables 9 and 10 of [65]
WYNDER3	Tables 2 and 3 of [67]
ALDERS	Calculated from Table 1 of [72]
BENSHL	Table 4 of [73]
DARBY	Calculated from Table 3 of [75]
DEANN	Calculated from Table IX of [76]
DEANT	Calculated from Table 9 of Supplement to [77]
DOLL1	Calculated from Table VI of [78]
DOLL2	Calculated from Table IX of [81]

Sources for Table 9.2

BENHAM	Calculated from Table 3 of [22]
BARBON	Table 2 of [26]
LUBIN	Calculated from Tables 2 and 5 of [32]
WYNDER2	Calculated from Tables 9 and 10 of [65]
WYNDER4	Table 3 of [69]
ALDERS	Calculated from Tables 2 and 3 of [72]

Sources for Table 9.3

GAO	Calculated from Table 3 of [2]
HIRAYA	Calculated from Table 19 of [12]
SOBUE	Table 2 of [13]
JOLY	Calculated from Table 6 of [15]
RISCH	Table 6 of [17]
BARBON	Calculated from Table 1 of [26]
BECHER	Table 3 of [28]
LUBIN	Calculated from Table 5 of [32]
CORREA	Calculated from Table 4 of [38]
BROSS	Calculated from Table 2 of [45]
GRAHAM	Calculated from adjusted numbers in Table 4 of [46]
CPSI	Calculated from Table 3 of [50]
CPSII	Calculated from Table 3 (Chapter 4) of [53]
DORN	Calculated from Table 4 of [55] and Table 1 of [57]
GARSHI	Calculated from Table 3 of [58]
WYNDER2	Calculated from Tables 9 and 10 of [65]
WYNDER3	Calculated from Tables 1 to 3 of [67]
ALDERS	Calculated from Table 1 of [72]
DARBY	Calculated from Table 3 of [75]
DEANN	Calculated from Table IX of [76]
DEANT	Calculated from Table 9 of Supplement to [77]
DOLL1	Calculated from Table VI of [78]
DOLL2	Calculated from Table IX of [81]

Sources for Table 9.4

RISCH	Table 6 of [17]
BARBON	Calculated from Table 2 of [26]
BECHER	Table 3 of [28]
LUBIN	Calculated from Table 5 of [32]
WYNDER2	Calculated from Tables 9 and 10 of [65]
WYNDER4	Calculated from Table 3 of [69]
ALDERS	Calculated from Tables 2 and 3 of [72]

Sources for Table 9.5

CPSI	Calculated from Table 3 of [50]; also Table 3 of [49]
CPSII	Calculated from Table 3 (Chapter 4) of [53]
DORN	Table 4 of [55]

APPENDIX B

Main references for studies

For each of the 59 studies considered in this report, this appendix gives the references to the publication(s) which provided the source(s) of the relative risks and CIs presented. On occasion, additional publications may have been used to provide information on the study details presented in section 3.

Continent	Country (State)	Study	Main references
Asia	China	GAO	[1, 2]
	China	FU	[3, 4]
	China	LIU	[5]
	China	XU	[4, 6, 7]
	China	YU	[8]
	India	JUSSAW	[9]
	India	NOTANI	[10]
	Japan	HIRAYA	[11, 12]
	Japan	SOBUE	[13, 14]
Central America	Cuba	JOLY	[15]
North America	Canada	BEST	[16]
(not USA)	Canada	RISCH	[17]
	Canada	SIEMIA	[18]
Europe	Denmark	PRESCO	[19, 20]
(not UK)	Finland	AUVINE	[21]
	France	BENHAM	[22, 23]
	France	SCHWAR	[24]
	Greece	TRICHO	[25]
	Italy	BARBON	[26]
	Poland	BECHER	[27, 28]
	Sweden	DAMBER	[29]
	Sweden	PERSHA	[30]
	Turkey	DOSEME	[31]
	Multicountry	LUBIN	[32]

Continent	Country (State)	Study	Main references
USA	California	BRESLO	[33]
	California	OSANN	[34]
	California	PIKE	[35]
	Florida	STOCKW	[36]
	Georgia	BLOT	[37]
	Louisiana	CORREA	[38, 39]
	Michigan	SCHWAR	[40]
	Missouri	BROWNS	[41]
	New Jersey	SCHOEN	[42]
	New Mexico	HUMBLE	[43, 44]
	New York	BROSS	[45]
	New York	GRAHAM	[46]
	Texas	BUFFLE	[47, 48]
	25 States	CPSI	[49, 50]
	Nationwide	CPSII	[51-53]
	Nationwide	DORN	[54-57]
	Nationwide	GARSHI	[58]
	Multicentre (inc. Canada)	KAUFMA	[59]
	Multicentre	MRFIT	[60]
	Nationwide	NMFS	[61]
	9 areas	TNCS	[62, 63]
	3 states	WYNDER	[64]
	6 cities	WYNDER2	[65, 66]
	6 cities	WYNDER3	[67, 68]

Continent	Country (State)	Study	Main references
	6 cities	WYNDER4	[69, 70]
UK	England	ALDERS	[71, 72]
	England	BENSHL	[73, 74]
	S.W.England	DARBY	[75]
	N.Ireland	DEANN	[76]
	Teesside	DEANT	[77] and supplement
	England	DOLL1	[78, 79]
	Britain	DOLL2	[80-83]
	W.Scotland	GILLIS	[84]
	London	KINLEN	[85]
	N.Wales and Liverpool	STOCKS	[86]