A REVIEW OF THE EPIDEMIOLOGY OF LUNG CANCER AND TYPE OF CIGARETTE SMOKED

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June 2000

EXECUTIVE SUMMARY

This review focuses on 54 studies which have presented results relating type of cigarette smoked to risk of lung cancer, 17 conducted in the USA (one partly in Canada), 10 in the UK, 12 in the rest of Europe, nine in Asia and six in South and Central America. Thirteen of the studies were prospective, 39 case-control and two of other designs.

Difficulties in assessing the relative risk of lung cancer associated with smoking different types of cigarette from the available evidence include the following:

(i) Inaccuracy in classifying subjects into the groups being compared;

(ii) Inadequate adjustment for potential confounding variables. Of the 54 studies reviewed, 15 did not adjust for any potential confounding factors at all, only 34 adjusted for age, 29 for number of cigarettes smoked, 12 for duration of smoking and 17 for any factor other than age or smoking;

(iii) Difficulties in obtaining results from different studies in a comparable format;

(iv) Limited nature of the evidence on some aspects of type of cigarette smoked. Despite the continuing decline in tar levels of cigarettes smoked, there is virtually no evidence at all in relation to deaths or cases of lung cancer occurring in the 1990s;

(v) Inadequate reporting of some major studies. Of the two largest case-control studies, one (the West European study conducted in five countries) failed to adjust for age in any of its analyses, while the other (American Health Foundation Multicentre Study II) failed to adjust for any variable in its analyses of tar level. Of the two largest prospective studies, one (CPSI) never presented any results for filter/plain smoking, while the other (CPSII) has, for males, never presented any results by tar level of brand smoked and has only presented results for filter/plain smoking graphically, without any indication of variability;

(vi) Many of the analyses only relate to smoking specific types of cigarette for a limited period of time and do not provide direct information on lifetime smoking of that type of cigarette.

Despite these difficulties a number of consistent findings emerge from the review.

Filter/plain (36 studies) Over half of the studies provide statistically significant evidence of a lower risk of lung cancer in smokers of filter cigarettes. Meta-analyses of relative risks for

filter/plain (comparing the most extreme groups where results were presented in more than two categories) demonstrated a highly significant ($p < 0.001$) advantage to filter (RR = 0.58, CI = 0.55-0.62 for males, n = 28 and RR = 0.67, CI = 0.59-0.75 for females, n = 14). The advantage was evident separately in studies conducted in the USA, in the UK, in Europe, and in Asia and South America. Although studies varied in respect of confounding variables taken into account, there was no evidence that this had an important effect on the conclusions.

Eight studies provided evidence on filter/plain relative risk by histological type. For squamous cell carcinoma (or Kreyberg I), all the sex-specific estimates were below 1, with the combined estimate (RR = 0.56, CI = 0.50-0.62, n = 11) showing a highly significant ($p < 0.001$) advantage to filter cigarettes. For adenocarcinoma (or Kreyberg II) the advantage was less marked (RR = 0.84, CI = 0.70-1.00, n = 8). However, there was no indication of an increase in risk associated with the switch to filter cigarettes, contrary to indirect inferences drawn from the observed rise in incidence of adenocarcinoma in the USA and the assumed greater distribution of smoke components distally in the lung when filter cigarettes are smoked (Thun et al, 1997a).

Tar level (16 studies) The results show a clear pattern of decreasing risk with declining tar levels. For males, meta-analysis of results comparing the lowest and highest tar categories gave a highly significant ($p < 0.001$) lower risk in the low tar category (RR = 0.77, CI = 0.69-0.86, n = 13). For females, a similar advantage was seen (RR = 0.82, CI = 0.70-0.97, n = 9). The advantage to filter cigarettes is equivalent to a 2-3% reduction in risk for each mg tar per cigarette. Limited evidence suggests that these conclusions were not materially affected by failure to adjust for potential confounding variables in some studies. Only one study reported results by histological type. That study reported a lower risk of Kreyberg I lung cancer in lower tar smokers in females, but no effect of tar on risk of Kreyberg I lung cancer in males or in Kreyberg II lung cancer in either sex.

Hand rolled/manufactured (12 studies) Compared to smokers of manufactured cigarettes only, a significantly higher risk of lung cancer was seen in smokers who had ever smoked hand rolled cigarettes (RR = 1.41, CI = 1.26-1.57, n = 15), in smokers of hand rolled cigarettes only (RR = 1.27, CI = 1.09-1.48, n = 12) and in mixed smokers of hand rolled and manufactured cigarette smokers (RR = 1.26, CI = 1.06-1.49, n = 11). Adjustment for potential confounding variables was generally quite poor in these studies. Limited evidence did not clarify the

relevance of cell type in this comparison.

Black (dark)/blond (light) (10 studies) Compared to smokers who have never smoked black cigarettes, a remarkably consistent higher risk of lung cancer was seen in those who have ever smoked black cigarettes (RR = 1.71, CI = 1.50-1.96, n = 12). The increase was evident both for smokers of black cigarettes only (RR = 1.72, CI = 1.44-2.05, n = 8) and for mixed smokers of black and blond cigarettes (RR = 1.47, CI = 1.21-1.79, n = 8). The increase in lung cancer for ever smokers of black cigarettes was evident both for squamous cell carcinoma (RR = 1.96, CI = 1.44-2.67, n = 4) and for adenocarcinoma (RR = 1.64, CI = 1.17-2.32, n = 4).

Mentholated cigarettes (3 studies) The combined evidence is difficult to interpret, showing a non-significantly increased risk in smokers of mentholated cigarettes in men (RR = 1.18, CI = 0.91-1.53) but a significantly decreased risk in women (RR = 0.70, CI = 0.52-0.95).

Other cigarette types The report also presents limited evidence relating lung cancer risk to the nicotine level of the brand smoked, to the smoking of bidis, to the smoking of brands local to Okinawa and to the smoking of pillis and pöllis, but no clear conclusions could be drawn.

Note All the combined relative risk estimates cited above are based on fixed-effects meta-analysis. Estimates from random-effects meta-analyses, also shown in the main body of the report, were generally quite similar.

INDEX

Appendices

A. Summary of each study and its main results

B. References to the 54 studies

1. Introduction

1.1 Objectives

The objective of this review is to provide a comprehensive compilation, analysis and interpretation of the epidemiological data relating type of cigarette smoked to risk of lung cancer.

1.2 Previous reviews

I have conducted quite detailed unpublished reviews on the epidemiological evidence relating lung cancer to type of cigarette smoked on two previous occasions (Lee, 1979a; Lee, 1993). Data from the earlier review were published in shortened form in two papers (Lee and Garfinkel, 1981; Lee, 1984).

Although sections on the differential effects of type of cigarette on lung cancer appear in various reviews on health effects of smoking (e.g. IARC, 1986; US Surgeon-General, 1982), and some of the papers considered in this review include some tables summarizing relevant evidence from a range of published studies (e.g. Sidney et al, 1993; Wynder and Kabat, 1988), there does not appear to be any comprehensive review on the subject in the recent literature.

In view of the continuing decline in tar yield of cigarettes smoked in many countries and the resultant increase in the number of smokers who have smoked low-tar cigarettes for a substantial period of time, this is a surprising omission, which this review hopes to rectify.

1.3 Structure of the review

Section 2 of this review concerns materials and methods, including the criteria used for selecting studies, the approaches used to extract relative risk estimates and the way in which meta-analyses were conducted.

The main characteristics of the 54 studies selected are summarized in Section 3 and described in more detail in Appendices.

Section 4 discusses some general problems involved in studying the relationship between lung cancer and type of cigarette.

The data concerning the relative lung cancer risk of filter and plain cigarette smokers, the most commonly considered aspect of type of cigarette smoked, are considered in detail in Section 5.

Data on lung cancer risk by tar level, handrolled/manufactured cigarette smoking and black (dark)/blond (light) cigarette smoking are then considered in Sections 6, 7 and 8 respectively.

Section 9 considers the evidence in relation to other less commonly considered aspects of cigarette smoking, including mentholation, nicotine level and the smoking of bidis.

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

Relevant papers were obtained from previous reviews updated by a literature search. A search for relevant data on risk related to type of cigarette smoked was also made among papers obtained in another project aimed at collecting together all published papers on risk of lung cancer in relation to smoking.

Although our search procedures are likely to have obtained essentially all relevant evidence published in English, and did identify many papers published in other languages, it is possible that some foreign language papers were missed. I would be pleased to hear from anyone of any papers that have been overlooked.

A paper was considered to be relevant if it presented data comparing risk of lung cancer according to type of cigarette smoked. Some papers had to be excluded as, although they collected data on tar level, they only presented results relating to lifetime cumulative tar, an index which is the product of number smoked x duration x tar yield and does not allow any proper comparison of risk in high and low tar cigarette smokers.

Care was taken to identify each study separately and which papers presented multiple reports on the same study. In the case of some studies, there were large numbers of papers and the references cited exclude those that provided duplicated results.

2.2 Extraction of data

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

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

Reference group (base)	Comparison group
Plain	Filter
High tar	Low tar
Manufactured	Handrolled
Blond (light)	Black (dark)
Nonmentholated	Mentholated
High nicotine	Low nicotine
Manufactured	Bidi
Non-local	Local brand
Pölli	Pilli

Where necessary, relative risks and CIs were estimated from reported numbers of cases and controls or from numbers of cases and populations at risk (or rates) using the CIA program based on the methods described by Morris and Gardner (1988) and made available by the British Medical Journal. Occasionally the source paper presented crude numbers and adjusted relative risk estimates with no CIs. In these cases, 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 estimate, but such underestimation is unlikely to be important.

Often source papers reported relative risks and CIs with the opposite reference group to the one required, e.g. plain/filter rather than filter/plain. Where it was a simple two group comparison, it was straightforward to convert the relative risks and CIs by taking reciprocals. However, the data were often presented as multiple groups, e.g. always filter (base), switched to filter, always plain. To convert such estimates to have the required base (here always plain) was not straightforward for groups other than the first and last. Here a procedure was employed which used the presented relative risks and CIs to generate effective numbers of cases and controls by level (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 in the usual way. A similar procedure was used to convert risks expressed relative to nonsmokers or never smokers to risks expressed relative to the required reference group. On occasion, other methods were used to derive the required relative risks and CIs. The source of the derived data

for each study is made clear in Appendix A.

2.3 Meta-analysis

Combined estimates of relative risk (with CIs) based on results from multiple studies for similar comparisons were in some cases estimated by fixed-effects and random-effects meta-analyses (Fleiss and Gross, 1991). Unless specifically stated to the contrary, cited meta-analysis estimates are fixed-effects.

3. Study characteristics

3.1 Introduction

The review focuses on 54 studies which have presented results relating type of cigarette smoked to risk of lung cancer. 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. A summary of each study, together with its main results, is presented, using a standard proforma in Appendix A, while the main references used for each study are listed in Appendix B. As noted earlier, Appendix A also gives details of how relative risk estimates, with their associated CI, were derived.

3.2 Overlap of studies

The 54 studies are not completely independent. In particular some points should be noted:

(i) The French, Italian, Austrian and Scottish case-control studies (BENHAM, BERRIN, VUTUC and GILLIS) form part of the West European multicentre study (LUBIN). The LUBIN study also includes centres in Germany, for which separate results were not obtained in the literature review.

(ii) What has been called the TANG study is a study of four British cohorts; the BUPA (British United Provident Association) study and the UK Heart Disease Prevention Project, lung cancer results for which have not separately been presented, the Whitehall study (also analyzed separately under BENSHL), and the Renfrew/Paisley study (part of which is included under HAWTHO).

(iii) Some of the data from DESTEF1, conducted in one Montevideo hospital, may have been included in some analyses of DESTEF2, conducted in multiple hospitals in the same city.

(iv) Wynder has been involved in case-control studies on a continuing basis for many

years. As far as could be determined, there appeared to be three main studies; WYNDER, conducted in New York in 1966-69, AHF1, conducted in six US cities in 1969-76, and AHF2, conducted in 45 hospitals in 1977-95. It is possible, however, that there is some overlap of cases.

3.3 Location

Nine studies have been conducted in Asia, six in South and Central America, 17 in the US (10 in specific states, seven nationwide or multicentre), 10 in the UK and 12 in the rest of Europe (11 in specific countries, one multicentre). No studies have been conducted in Africa, Australasia or the former USSR. Only one study has been conducted in Eastern Europe (ZEMLA in Poland), and only one study (KAUFMA) included any Canadian cases and that study had six centres, five in the US.

3.4 Study type

Of the 54 studies listed in Table 3.1, 39 were of the case-control design and 13 were prospective. The prospective studies were, with only one exception, conducted in the US or Europe, the exception being the Japanese study HIRAYA, which had very limited reporting indeed of results relating to type of cigarette smoked.

There were two studies of unusual design, WEINBE and KNOTH. WEINBE, conducted in Allegheny County, Pennsylvania, involved a comparison of risk factors (including smoking) in areas identified as being of high and of low lung cancer risk, with no information actually being collected from lung cancer cases. This study does not allow an estimate to be made of the relative risk of lung cancer associated with smoking different types of cigarettes.

KNOTH, conducted in three German cities, involved a comparison of age of death from lung cancer in decedents identified as having smoked filter and plain cigarettes. The study is unsound as it lacks any control. Any difference in age of death seen may reflect differences in the age distribution of living smokers of filter and plain smokers, and cannot be used to make inferences about risk. (Schoolboys who die as schoolboys die younger than schoolmasters who die as schoolmasters, but this tells us nothing about

whether being taught is more hazardous than is doing the teaching!).

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 in view of the considerable change over time in the type of cigarette smoked.

Table 3.2 shows the number of studies which covered specific periods of time. The earliest were the case-control studies PERNU (1944-58) and DOLL1 (1948-52). The latest were the case-control studies of MATOS (1994-96) and DESTEF2 (1993-96), both conducted in South America, an area where quite a large number of studies have been conducted in the last 15 years. The period covered by the most studies was 1976-80 (26 studies), with the next most common periods 1981-85 (20 studies) and 1986-90 (18 studies).

3.6 Lung cancer cases in the 54 studies

Table 3.3 presents some relevant details of the lung cancer cases in the 54 studies. Numbers of lung cancers shown usually relate to the total number in the study for smokers and nonsmokers combined, though in some studies they relate to the number of cases among the smokers analyzed. Further detail of numbers of cases for some specific analyses are shown in later tables. Most of the studies concerned some hundreds of cases. Larger studies, involving over 900 cases, included the prospective studies HIRAYA, CPSI and CPSII and the case-control studies CORREA, BROSS, BUFFLE, AHF1, AHF2, PERNU, ALDERS, DEAN, DOLL1 and particularly LUBIN, whose 7804 cases included 1721 from BENHAM and 1101 from BERRIN.

None of the 13 prospective studies required full histological confirmation of their cases, most being based on diagnosis as recorded on death certificates. Nor did they present results by histological type, with the exception of ENGELA, which obtained histological confirmation from the Norwegian Cancer Registry for 80% of their cases.

Histological confirmation was required for every case in 16 of the 39 case-control studies, two in Asia, three in South and Central America, six in the USA and five in Europe. The rate of histological confirmation was clearly much higher for US than for UK case-control studies. Results (for type of cigarette) were presented by histological type for 12 of the 39 case-control studies. It was interesting to note that in the USA, despite histological confirmation rates being high, results were only presented by histological type in the three studies associated with Wynder (WYNDER, AHF1, AHF2).

Proxy interviews were used for all cases in four of the studies and for some cases in a further four. Other studies involved direct interview of the case (case-control studies) or of the subject (prospective studies).

3.7 Controls (or populations at risk) in the 54 studies

Table 3.4 similarly presents some relevant details of the controls (or populations at risk for prospective studies). Of the 13 prospective studies, two (CPSI and CPSII) involved over a million subjects, one (HIRAYA) involved over a quarter of a million. and one (SPEIZE) involved over a hundred thousand. Others involved tens of thousands of subjects except for MIGRAN which involved some 6000.

Numbers of controls were identical to the numbers of cases in 13 of the 29 case-control studies and were similar in a further five. In many 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 numbers of controls to cases was constrained by 1:1 or 2:1 matching. Matching factors normally included age, and commonly included race, location of residence, and hospital of admission and time of interview.

Hospital controls, usually with diseases not associated with smoking, were used in 29 of the case-control studies, while population controls were used in eight and decedent controls in four. Some studies used more than one type of control.

Proxy interviews were used for controls in six of the case-control studies. In three studies using proxy interviews for cases (FU, BUFFLE, DEAN) controls were

individually matched on proxy interview use. However, there were some studies where proxy interviews were used more for cases than controls (CORREA 24 vs 11%, WILCOX 44 vs 37%, PATHAK 47 vs 0%, DEAN2 100 vs 0%). One study (KNOTH) did not have any controls at all.

3.8 Aspects of cigarette type considered

Table 3.5 shows which studies considered the various aspects of cigarette type. Overall the totals by cigarette type were:

Filter/plain	37	studies
Tar level	16	
Hand rolled/manufactured	12	
Black/blond	10	
Menthol/nonmenthol	3	
Nicotine level	1	
Bidis	2	
Brands local to Okinawa	1	
Pillis and pöllis	1	

3.9 Potential confounding variables adjusted for

Table 3.6 shows which studies adjusted for which potential confounding variables in at least some of their analyses relating lung cancer risk to type of cigarette smoked. 15 studies did not adjust for any potential confounding variables at all.

Of the remaining 39 the numbers of studies taking into account particular confounding variables were as follows:

Age	34	studies
Aspects of cigarette smoking		
Cigarettes/day	29	
Duration	12	
Pack-years	6	
Age at starting to smoke	5	
Years quit	4	
Inhalation	4	
Other	5	
Any aspect	32	
Factors other than age or smoking		
Race	7	
Area of residence	6	
Education/social class	9	
Time of interview or admission	2	
Other	8	
Any factor other than age or smoking	17	

4. Some general problems in studying the relationship of lung cancer to type of cigarette smoked

4.1 Misdiagnosis of lung cancer

As in all epidemiological studies of lung cancer, bias may arise if some of the subjects classified as having lung cancer in fact do not do so. Lee (1994) has reviewed evidence 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. 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 (Faccini, 1989).

Given that cigarette smoking is likely to be more strongly associated with lung cancer than with other diseases with which it might be confused, random misdiagnosis of lung cancer is likely to weaken the observed association of lung cancer with smoking and probably also with type of cigarette smoked. In theory, however, the observed association may be biased in either direction if type of cigarette is associated with accuracy of diagnosis. This might arise if, for example, lower social class is associated both with the smoking of one type of cigarette and with less accurate diagnosis of disease. This is a possibility not considered in any of the papers reviewed here which generally assume implicitly that diagnosed lung cancer is true lung cancer.

4.2 Misreporting of cigarette smoking status

The analyses relating risk to type of cigarette smoked concern smokers, most authors restricting attention to current cigarette smokers, but some also including former smokers. While there is abundant evidence that a proportion of ever smokers deny current or former smoking on interview (Lee and Forey, 1995), it is generally felt that the possibility of never smokers claiming to be smokers can be disregarded (except perhaps in studies of prevalence of smoking in children). Though the subjects included in the analyses are likely to be smokers, it is possible in theory that the exclusion of some true smokers may somewhat bias the comparison of risks of smokers of different types of cigarette. This might occur if, for example, denial of smoking is commoner both for

smokers of one type of cigarette and for smokers with some characteristic which makes them at higher risk.

4.3 Misreporting of cigarette type

Bias may arise if smokers are incorrectly classified by type of cigarette smoked. The chance of incorrect classification will be greatest when it is based on detailed past smoking history, which the respondent may not accurately recall. A striking example of this is the study by Peach et al (1986) which reinterviewed 429 men interviewed 12 years earlier, who had claimed to smoke at that time. Of the 429 men, 43 (10%) claimed not to have been smoking 12 years ago, 216 (50%) could not recall the brand smoked, with only 170 (40%) recalling a brand. In **49%** of those who did recall a brand, the brand differed from that previously stated!

The effect of incorrect classification is likely to be to underestimate differences in risk between smokers of different types of cigarette. This will also occur if subjects are classified by the type they predominantly smoke, when in fact they smoke other types as well. Classification of subjects based on tar level, using data on tar levels by brand smoked, that inadequately account for changes over time, is another problem that may reduce the power to detect true differences in risk.

Generally, the studies reporting results on risk of lung cancer in relation to type of cigarette smoked have given little or no attention to the possibility of inaccuracy in their classification by cigarette type. It is interesting, in this context, to note that in the report on the largest case-control study so far conducted (Lubin et al, 1984a), a table was presented showing that among lifetime filter cigarette smokers, 13% of male and 11% of female controls had smoked cigarettes for 40 years or more, and that 27% of male and 24% of female controls had smoked cigarettes for 30-39 years. This is despite interviewing being conducted in 1976-1980 and the market share of filter cigarettes being very small before 1955.

4.4 Relevance of results to lifetime smoking of a particular type of cigarette

It is important to bear in mind that many of the comparisons of lung cancer risk

carried out concern smokers who have used the "new" product for only a limited length of their smoking career. Thus some studies compare lifetime smokers of plain cigarettes with smokers who switched to filter cigarettes having smoked plain cigarettes for a considerable period before. Similarly smokers in the lowest tar groups will not have smoked cigarettes with this level of tar for more than a few years.

Because of this it is important not to interpret relative risks of, say, 0.7 for lifetime plain vs. switched to filter as indicating that lifetime filter vs. lifetime plain will only be associated with a 30% reduction in risk. In view of the importance of duration of smoking on the risk of lung cancer, the reduction may be markedly greater than this (provided, of course, that the relative risk of 0.7 is itself unbiased and not due, for example, to uncontrolled confounding due to earlier switchers smoking less or inhaling less than average or being more health conscious than later switchers).

4.5 Confounding

As noted in section 3.9, 15 of the 54 studies did not adjust for any potential confounding factors. For many of these studies the authors would appear to have assumed that the matching of cases and controls would have controlled for bias due to the factors matched for. There are two errors in this assumption however. Firstly, matching of the total set of cases and controls does not imply that the cases and controls who smoke cigarettes and will be included in the analysis are necessarily matched. Second, it is generally recognized that, to avoid bias, one should adjust in analysis for those factors considered important enough to be matching factors (Breslow and Day, 1981; Rothman and Greenland, 1998).

What factors should be adjusted for in analysis? Age is clearly important as age is strongly related to risk of lung cancer and the uptake of different types of cigarette varies by age, and indeed age has been adjusted for in 34 of the 39 studies that did adjust for any potential confounding variables.

Of non smoking related factors, one should include those that are known to be

related to risk of lung cancer and to differ in prevalence between smokers of the types of cigarettes being compared. Race, education/social class and area of residence are the only factors that have been considered in even a moderate number of studies. Only one study has considered occupation and none diet, despite the evidence relating both to lung cancer and the likelihood that these are related to type of cigarette smoked.

Risk of lung cancer is known to depend on various aspects of the smoking habit, including amount smoked, inhalation and age of starting to smoke. Smokers of different types of cigarette may differ in these characteristics and it seems natural to adjust for them in analysis to obtain an unbiased analysis. It should be clear, however, that such analyses are attempts to answer the question "Is a given 'dose' of cigarette A less associated with risk of lung cancer than is the same 'dose' of cigarette B?"

However, from a public health point of view, a reduced risk for a filter or low-tar cigarette smoker, demonstrated in analyses of this type, is not much use if in fact smokers switching from plain to filter, or from high-tar to low-tar cigarettes, smoke more cigarettes or inhale them more deeply. In this context, adjustment for number of cigarettes currently smoked or for depth of inhalation may be viewed as over-adjustment. However, not adjusting for these variables may lead to under-adjustment if those who switch to filter or low-tar cigarettes are "less committed" smokers than those who do not and smoked or inhaled less before they switched. When attempting to answer the question "Is switching from one type of cigarette to another associated with a reduced risk of lung cancer?", an appropriate procedure would be to adjust for variables measured at an earlier time when switchers and non-switchers were both smoking the same cigarette. However, this leads to problems relating to accuracy of recall. It should also be noted that the value of adjustment for self-reported inhalation is rather dubious in that such self reports are unlikely to be very reliable.

4.6 Compensation

As noted in the previous section, smokers switching to filter or low-tar cigarettes may "compensate" by increasing the number of cigarettes they smoke, or the depth of inhalation. They may also increase the number of puffs they take per cigarette and block

the ventilation holes used to achieve lower machine-smoked tar deliveries.

In fact, evidence from various sources suggests that compensation in terms of increasing amount smoked is at most minor. This evidence includes the following:

(i) Data from short-term experimental brand-switching studies indicating only modest increases in consumption in relation to massive decreases in brand delivery (Stepney, 1980);

(ii) Results from a large epidemiological study (CPSI) showing very similar changes in the number of cigarettes smoked over a 12 year period in those who did or did not change the tar/nicotine yield of the brand they smoked (Garfinkel, 1979);

(iii) Evidence from cross-sectional national surveys showing that smokers of low tar cigarettes smoke less cigarettes per day than smokers of middle tar cigarettes (Lee, 1982);

(iv) Evidence from many countries (e.g. USA, UK, Canada) that consumption per smoker has only risen modestly over a period when tar levels have declined markedly, and there has been a huge switch from plain to filter cigarettes (Nicolaides-Bouman et al, 1993). The increase in consumption observed may, in any case, not be due to compensation but to the decline in prevalence of smoking, with lighter smokers more likely to give up than heavier smokers.

Far more attention in the literature has been given to the possibility that smokers compensate for reduced machine tar and nicotine yields by altering the way they smoke their cigarettes. It has been suggested that smokers will adjust their manner of smoking to achieve a desired intake of nicotine, and that, if tar and nicotine levels are proportional, switching to brands with reduced tar and nicotine yields will have no effect at all on the dose of tar received. In fact, the evidence demonstrates that though some smokers may indeed compensate in this way, many do not, and on average compensation is far from complete. Some of the more relevant evidence supporting this view is summarized below:

(i) Stephen et al (1989) reviewed evidence from 17 intervention and observational studies which had related marker levels (M) of carbon monoxide and nicotine to machine yields (Y). Defining compensation (C) by the relationship $M = \alpha Y^{1-C}$

where C = 0 implies no compensation (marker level proportional to yield) and C = 1 implies complete compensation (marker level invariant of yield), they estimated C as 0.73 for carbon monoxide and 0.66 for nicotine. They also calculated that smokers who reduced their tar yield by half, on average reduced their intake by 24%.

(ii) Adlkofer et al (1989) analyzed data from two studies in which serum cotinine was measured on multiple occasions and details of brands smoked and cigarette consumption recorded. Compensation indices for nicotine were estimated as 0.75 within-smoker and 0.57 between-smoker.

(iii) Pritchard and Robinson (1996) reviewed eight data sets relating usual-brand nicotine yield to blood cotinine concentration. They found that on average, blood cotinine concentrations were roughly midway between complete compensation and the value expected if there was no compensation.

(iv) Woodward and Tunstall-Pedoe (1992) studied expired-air carbon monoxide, serum thiocyanate and serum cotinine values in 2754 Scottish smokers in three tar groups (mean yields 7.8, 13.3 and 16.0 mg/cig respectively) and estimated an index of tar consumption assuming that the intake of different smoke components relative to one another is in proportion to their concentration in the smoke. The average tar indices increased with increasing tar group (2.1, 2.9 and 3.1) but less than indicated by the mean yields.

For a more detailed review of the literature, reaching the same conclusion that compensation for different smoke yields is only partial, the interested reader is referred to Scherer (1999).

5. Lung cancer risk in filter and plain cigarette smokers

In the USA, in 1950 less than 1% of cigarettes smoked had filter tips. Over the following years, there was a dramatic switch to filter cigarettes, 19% in 1955, 51% in 1960, 80% in 1970 and 93% in 1980 (USDA, 1996). Associated with this switch there has been a marked decline in the tar levels of cigarettes smoked, from over 35 mg in 1950 to 14 mg in 1980.

Similar trends, though differing in the exact time scale, have occurred in many other countries. In the UK, the proportion of filter cigarettes sold started rising somewhat later than in the USA, from 2% in 1955 to 16% in 1960, 53% in 1965, 78% in 1970, 87% in 1975 (Lee, 1976) and over 95% in 1985 (Wald and Nicolaides-Bowman, 1991). In France, the rise was later still, from 11% in 1960, to 37% in 1970, 61% in 1980 and 72% in 1985 (Hill, 1990). In Germany, however, the rise was similar to that in the USA, from 18% in 1956 (Weber, 1976), to 68% in 1960, 84% in 1970 and 88% in 1980 (Merzdorf et al, 1982). In Japan, the switch was very rapid, from 8% in 1960, to 43% in 1965, 90% in 1970 and 99% in 1980 (Lee, 1979b).

There are 37 studies (10 prospective, 25 case-control and two others) which have presented data comparing risk of lung cancer in filter and plain cigarette smokers.

Table 5.1 summarizes some relevant details of the studies. Points to note from this table are as follows:

(i) 12 of the studies were conducted in the USA, 3 in Asia, 4 in South America, 9 in Western Europe and 1 in Eastern Europe.

(ii) The LUBIN case-control study is a multicentre study conducted in seven centres, two of which, BENHAM and BERRIN, have presented results specific to their centres.

(iii) The prospective study referred to as TANG is an analysis of combined data from four cohorts. For two of these, HAWTHO and MIGRAN, some results from earlier follow-up have been presented separately.

(iv) While many of the studies have considered cigarette smokers in their analysis regardless of whether the subjects also smoke pipes or cigars or smoke

manufactured or handrolled cigarettes, some have restricted attention to cigarette only smokers or to manufactured cigarette only smokers. Some studies have restricted attention to those who smoked for a given minimum number of years.

(v) The great majority of the prospective studies have simply related the type of cigarette smoked at baseline to risk of lung cancer. Many of the case-control studies have related risk of lung cancer to filter/plain classifications based on a lifetime history of smoking (e.g. always plain, switched to filter, always filter).

(vi) Of the 10 prospective studies, four started in the 1960s, five in the 1970s and one in the 1980s. The follow-up periods ended in the 1970s for three studies, in the 1980s for six studies and in the 1990s for one.

(vii) The earliest case-control study (DOLL) was conducted in 1948-1952. Interviews were conducted in the 1960s in five studies, in the 1970s in nine studies, in the 1980s in 16 studies and in the 1990s in seven studies.

Table 5.2 gives relative risks from the studies. In all cases these have been organized so that the base group is plain cigarette smokers or the group containing least filter cigarette smokers, so that the relative risks represent filter/plain ratios and not plain/filter ratios, i.e. they should be below 1.0 if filter cigarette smoking is associated with less risk than plain cigarette smoking. The table shows the adjustment factors used in the analysis, the number of lung cancer cases on which the actual analysis is based (except where stated) and the sex corresponding to the relative risk estimates presented.

Statistically significant ($p < 0.05$) advantages to filter cigarette smoking were evident in at least some of the analyses in the following 21 studies:- HIRAYAMA, SIDNEY (females only), CPSII, RIMING, CHOI (males only), PEZZOT, DESTEF1, CORREA, PATHAK, BROSS, WYNDER, KHUDER, AHF2, LUBIN, BENHAM, JOCKEL, ARMADA, ALDERS (females only), DEAN2, DOLL and WEINBE. In contrast significant disadvantages were only noted in two analyses, MATOS (for ex-smokers only) and KNOTH (which is an invalid comparison, based on average age at death). In some studies, it was not possible to determine statistical significance due to inadequate information.

It is clear that the overall picture is of an advantage to filter cigarettes. In order to show this more clearly, Table 5.3 summarizes results comparing the most extreme categories for those studies which provide relative risks and CIs. Where multiple results have been presented, the data adjusted for most potential confounding variables have been used. The results in Table 5.3 are shown in rank order, separately for each sex.

For males, there are 28 estimates in Table 5.3, five above 1 and 23 below, 13 significantly (at $p < 0.05$). Using fixed-effects meta-analysis, the combined relative risk estimate was 0.58 (CI = 0.55-0.62). There was highly significant heterogeneity between studies ($P^2_{het} = 140.74$ on 27 d.f., $p < 0.001$), the relative risk from random-effects meta-analysis being somewhat higher, at 0.64 (CI = 0.55-0.75).

Difference between continents was investigated as one possible source of this heterogeneity. Fixed-effects relative risk estimates were shown to be higher (though still significantly below 1) for UK studies (0.83, CI = 0.72-0.96, n = 8) than for studies conducted in the USA (0.54, CI = 0.49-0.58, n = 8), Europe (0.51, CI = 0.45-0.59, n = 6) or Asia or South America (0.59, CI = 0.50-0.71, n = 6). However heterogeneity between continents ($P^2_{het} = 29.90$ on 3 d.f., $p < 0.001$) only explained part of the story, highly significant ($p < 0.001$) heterogeneity still being evident within the UK studies, within the USA studies and within the Asia/South America studies. Random-effects estimates were UK (0.77, CI = 0.56-1.06), USA (0.63, CI = 0.48-0.82), Europe (0.55, CI = 0.43-0.71) and Asia/South America (0.57, CI = 0.34-0.97).

One problem with the above estimates is, as noted above, that there is some degree of overlap between the populations studied for some of them. Another is that the estimate for the large CPSII study is approximate, the relative risk being estimated from data presented graphically and the CI being based only on a rough idea of the numbers of lung cancer cases occurring in the groups being compared. Excluding this study, and also HAWTHO (part of TANG) and BENHAM (part of LUBIN) from the meta-analysis gave a relative risk of 0.64 (CI = 0.59-0.69), based on 25 estimates, that was slightly higher than the figure of 0.58, based on all 28 estimates. Though there was still marked heterogeneity between the 24 estimates, however ($P^2_{het} = 111.83$ on 24 d.f., $p < 0.001$),

the random-effects relative risk estimate of 0.65 (CI = 0.53-0.75) was similar.

For females, there are 14 estimates in Table 5.3, two above 1 and 12 below, five significantly (at $p < 0.05$). The fixed-effects meta-analysis relative risk estimate was 0.67 (CI = 0.59-0.75). Heterogeneity was less than for males, but still significant (P^2_{het} = 27.61 on 13 d.f., $p < 0.05$). The random-effects estimate was 0.65 (CI = 0.51-0.83).

Here there was no significant difference between results for the different continents (P^2_{het} = 1.37 on 2 d.f., NS), with fixed-effects relative risk estimates similar for studies conducted in the UK (0.71, CI = 0.50-1.02, n = 4), USA (0.68, CI = 0.59-0.78, n = 5) and Europe (0.54, CI = 0.37-0.79, n = 5). Random-effects estimates were UK (0.78, CI = 0.38-1.59), USA (0.69, CI = 0.50-0.95) and Europe (0.50, CI = 0.30-0.85).

Excluding, as before, results from CPSII and also BENHAM (in LUBIN), made little difference, the fixed-effects estimate changing to 0.69 (CI = 0.57-0.84, n = 12) and the random-effects estimate to 0.67 (CI = 0.50-0.91).

Based on all the results for males and females combined, and including the results of the CORREA study, which did not report results separately by sex, gave an overall fixed-effects relative risk estimate of 0.59 (CI = 0.56-0.63, n = 43) and a random-effects estimate of 0.64 (CI = 0.56-0.73). With the same exclusions as before the fixed-effects estimate was 0.64 (CI = 0.60-0.69, n = 38) and the random-effects estimate was 0.65 (CI = 0.56-0.75).

There were nine studies in which the comparison group was "always filter," based on lifetime smoking history (or at least the last four brands smoked) - AGUDO, ARMADA, ALDERS,AHF2, BUFFLE, CPSII, DESTEF1 and LUBIN (including BENHAM). Overall results from these studies gave a fixed-effects relative risk estimate for males and females combined of 0.55 (CI = 0.51-0.59, n = 14) and a random-effects estimate of 0.64 (CI = 0.53-0.78). Excluding BENHAM and CPSII the fixed-effects estimate was 0.62 (CI = 0.55-0.69, n = 10) and the random-effects estimate was 0.71 (CI = 0.53-0.94). These estimates are not clearly different from those using all the data

summarized in Table 5.3.

Table 5.4 summarizes the available data by histological type, with results mainly being reported for squamous carcinoma and adenocarcinoma or the broader groupings Kreyberg I and Kreyberg II. Some studies report results only for Kreyberg I, the type most strongly associated with smoking. Results for small cell, bronchioalveolar and oat cell carcinoma are only occasionally reported.

Similarly to Table 5.3, Table 5.5 summarizes results for squamous carcinoma (or Kreyberg I) and adenocarcinoma (or Kreyberg II) comparing the most extreme categories of plain and filter smoking. As can be seen, all 11 estimates for squamous carcinoma (or Kreyberg I) are below 1, four significantly, and the fixed-effects meta-analysis estimate of 0.56 (CI = 0.50-0.62) and random-effects estimate of 0.50 (CI = 0.37-0.67) are both highly significantly ($p < 0.001$) reduced. For adenocarcinoma (or Kreyberg II), the results are less indicative of a reduction, with only five of eight estimates below 1, and all eight higher than the corresponding estimates from the same study for squamous carcinoma (or Kreyberg I). However, two of the estimates are significant, and the fixed-effects meta-analysis estimate of 0.84 (CI = 0.70-1.00) is marginally significant, though the random-effects estimate, though lower, at 0.80 (CI = 0.61-1.06) is not.

In view of the much stronger association of smoking with squamous carcinoma than with adenocarcinoma, the larger reduction in risk associated with filter cigarette smoking for squamous carcinoma is not surprising. However, in view of recent suggestions in the literature (e.g. Thun et al, 1997a) associating the reported rise in adenocarcinoma in the USA with tar reduction and the switch to filter cigarettes, it is important to note that the data provide no evidence that the switch to filter cigarettes has increased risk of adenocarcinoma.

As noted in section 4.5, different adjustments for confounding variables (notably amount smoked and inhalation) can affect interpretation of the filter/plain relative risk. It is difficult to assess the effect that covariate adjustment had in many of the studies, since they only presented results for one particular set of confounding variables. There

were, however, 10 studies that presented results adjusted for more than one set of variables. Table 5.6 summarizes relevant results from Table 5.3 for those studies. Note that for two of the studies (AHF2 and BENHAM) the analyses compared are from different source papers and may differ in the populations considered and other relevant aspects.

There were four studies (RIMING, PEZZOT, DEAN, DEAN2) where one could identify specifically the effect of additional adjustment for number smoked. For the six sex-specific comparisons, the effect was to increase the filter/plain ratio in four and to decrease it in two. The effect was usually quite small, the largest being in PEZZOT, where the relative risk changed from 0.23 to 0.29. In no case did additional adjustment for number smoked affect the conclusions at all.

There were two studies (AHF2, DEAN) where one could identify specifically the effect of additional adjustment for inhalation and one study (MIGRAN) where one could identify the effect of additional adjustment for inhalation and age of starting. Of the six sex-specific comparisons, the filter/plain ratio was increased in three and decreased in three, the effect of adjustment again never affecting the conclusions.

The general impression from Table 5.6 is that the effect of adjustment was not great, the only apparent exception being in BENHAM where the relative risk, adjusted for age only, 0.38, changed to 0.70, after additional adjustment for number smoked and duration of smoking. However, the two relative risks are derived from different source papers (Benhamou et al, 1989, 1994) and seem not to be completely comparable, inasmuch as in the first paper 99/1030 cases were classified as always smoking filter cigarettes, whereas in the second paper only 24/1114 were.

Although the results in Table 5.6 do not suggest an important effect of adjustment on the conclusions, it should be noted that they mainly relate to other aspects of the smoking habit. Few of the studies have considered non-smoking related factors at all, and none have made it clear what effect adjustment for them had on the filter/plain relative risk.

The evidence discussed in section 4.6 does not suggest that on average smokers switching from plain to filter cigarettes increase the number of cigarettes they smoke, and the results in Table 5.6 do not suggest that adjustment for amount smoked has a material effect on the conclusions. It should be noted, however, that an analysis of data from AHF2 by Augustine et al (1989) reported that risk of lung cancer was increased in those who did increase the amount they smoked after switching. Compared with those who did not increase amount smoked after switching, and after adjustment for duration of plain smoking, duration of filter smoking, age at switch and number of plain cigarettes smoked, at time of switching the relative risks of lung cancer in males who increased the amount they smoked by 1-10, 11-20 and 21+ cigs/day were, respectively, 1.19 (CI = 0.93-1.51), 1.75 (CI = 1.33-2.29) and 2.37 (CI = 1.64-3.41). In females, the corresponding relative risks were 1.66 (CI = 1.23-2.24), 2.97 (CI = 2.09-4.20) and 3.83 (CI = 2.31-6.34). It should be noted that, because of errors in reporting of amount smoked, these risk estimates are likely to be biassed due to what is often referred to as "regression to the mean." This can be illustrated by considering what would happen if there were no true increase in amount smoked following switching, changes being reported only due to errors in recall. Thus, comparing two men, one of whom reported changing from 20 to 10 cigarettes a day, the other changing from 20 to 30 cigarettes a day, one is likely to see a higher lung cancer risk in the man reporting an increase simply because he probably smoked more cigarettes per day originally (current best estimate 25) than the other man (current best estimate 15).

6. Relative risk of lung cancer in relation to tar level

There are 16 studies (seven prospective, eight case-control and one other) which have presented data relating risk of lung cancer to the tar level of cigarettes smoked. Excluded from these studies are those which have only related lung cancer risk to total lifetime tar - such analyses are unhelpful because they do not allow separation of the effects of amount smoked, duration and tar level of brand smoked.

Table 6.1 summarizes some relevant details of the studies. Points to note from this table are as follows:

(i) Nine of the 16 studies were conducted in the USA, four in the UK and three in Western Europe.

(ii) The LUBIN case-control study is a multicentre study conducted in seven centres, three of which were BENHAM, VUTUC and GILLIS, which have presented results specific to their centre.

(iii) The prospective study referred to as TANG is an analysis of combined data from four cohorts. For one of these, BENSHL, some results from an earlier follow-up have been presented separately.

(iv) While many of the studies have considered cigarette smokers in their analysis regardless of whether the subjects also smoke pipes or cigars or smoke manufactured or hand rolled cigarettes, some have restricted attention to cigarette only smokers or to manufactured cigarette only smokers. One study (AHF2) restricted attention to current filter cigarette smokers.

(v) All the prospective studies and some of the other studies have restricted attention to current cigarette smokers, but four studies (LUBIN, BENHAM, VUTUC, ALDERS) have also included former smokers.

(vi) Most of the prospective studies estimated tar level based on the brand reported to be currently smoked at baseline interview. The classifications of tar level used in the case-control studies depended on brand histories reported at interview.

(vii) For the prospective studies, the baseline periods ranged from 1959 to 1985. The follow-up periods extended into the 1990s only in one study (SPEIZE), and then only to 1992. All the case-control studies related to lung cancer cases interviewed between 1976 and 1986. There is therefore virtually no evidence

whatsoever related to the smoking of cigarettes in the 1990s.

(viii) In line with the fact that the evidence relates to lung cancer cases occurring mainly in the 1960s, 1970s and 1980s, the lowest tar category used in analysis is often high by the standard of modern cigarettes.

Only one of the studies (AHF2) presented evidence on risk of lung cancer related to tar level separately for different histological types of lung cancer.

Table 6.2 gives relevant results from the 16 studies. Due to the differences in expressing the relative risks in the studies, it is not straightforward to combine the findings by formal meta-analysis. However, it is evident that there is a clear pattern of decreasing risk with declining tar levels. This can be seen clearly if, as in Table 6.3, one summarizes the results comparing the lowest and highest tar categories (using the data adjusted for most potential confounding variables where multiple results are presented) and putting the findings into rank order.

For males, the summary in Table 6.3 includes 13 relative risks from 12 studies (counting the two follow-up periods of CPSI as independent data). Twelve relative risks are less than one, four significantly so (at $p < 0.05$), and a fixed-effect relative risk estimate from the individual risks is 0.77 (CI = 0.69-0.86). There is non-significant heterogeneity between the estimates ($P^2_{het} = 18.00$ on 12 d.f.), but using a random-effects analysis gives a very similar answer of 0.77 (CI = 0.66-0.88). The heterogeneity is mainly due to the relative risk estimate of 1.32 in the AHF2 study. This estimate is unadjusted even for age, calculated from data presented only in a figure, and only applies to current filter cigarette smokers. Excluding it, and also subsets of LUBIN to avoid overlap, reduces the relative risk estimate somewhat to 0.75 (CI = 0.66-0.85) and removes the heterogeneity ($P^2_{het} = 7.03$ on 8 d.f.). The summary for males in Table 6.3 does not include results from the TANG and WEINBE study, both of which (see Table 6.2) also suggested a lower risk of lung cancer in low tar smokers.

For females, Table 6.3 includes nine relative risks. Six are less than one, four significantly so (at $p < 0.05$), and the fixed-effects relative risk estimate of 0.82 (CI =

0.70-0.97) is similar to that for males and is also statistically significant. Here there is marginally significant heterogeneity between the estimates (P^2_{het} = 17.65 on 8 d.f., $p < 0.05$) but the random-effects estimate of 0.79 (CI = 0.60-1.02) is very similar. The estimate for the SPEIZE study is dubious (R. Peto, personal communication) because the effect of additional adjustment for daily cigarette consumption implausibly changed a relative risk estimate of 0.50 to 1.00. Excluding the results from this study and also, as for males, from AHF2 and subsets of the LUBIN study, reduced the fixed-effects relative risk estimate to 0.77 (CI = 0.62-0.95), but did not remove the heterogeneity (P^2_{het} = 12.71 on 5 d.f., $p < 0.05$) though again the random-effects estimate of 0.75 (CI = 0.52-1.09) is very similar to the fixed-effects estimate. The summary for females excludes results from the CPSII study which also reported a statistically significant advantage to low tar (see Table 6.2).

The only study to report results by histological type was AHF2. As can be seen from Table 6.2, this study found no evidence of an advantage to low tar in males for Kreyberg I or Kreyberg II lung cancer or in females for Kreyberg II. For Kreyberg I, compared to smokers of 15+ mg tar cigarettes, the relative risk in females was estimated as 0.60 (CI = 0.39-0.91) for smokers of 10-14 mg tar cigarettes and 0.77 (CI = 0.44-1.34) for smokers of < 10 mg tar cigarettes. As noted above, these estimates are unadjusted for any covariate and are for current filter cigarette smokers.

It is difficult to assess effects of covariate adjustment as most of the studies presented only one set of results adjusted for those potential confounding variables they thought to be most relevant. Of the four studies that did provide relative risk estimates adjusted for more than one set of variables, one (BENSHL) reported somewhat lower relative risks in the low tar group when adjustment was made for number smoked and duration of smoking, as compared with adjustment for either factor individually, one (BENHAM) reported quite similar relative risks whether or not a range of variables in addition to age were adjusted for, one (GILLIS) found that adjustment for number smoked had virtually no effect on the relative risk estimates, and one (SPEIZE) reported, as noted above, an implausibly large effect of adjustment for number smoked. Apart from the SPEIZE study, these results do not suggest that adjustment has a major effect

on conclusions, though clearly more evidence is needed.

It should be noted that the estimates in Table 6.3, and the estimates per mg tar for the CPSII and TANG studies (see Table 6.2) are virtually all adjusted for number smoked, the only exception being the AHF2 study. The fixed-effects relative risk estimates of 0.74 for each sex (excluding AHF2 and SPEIZE) therefore should be viewed as answering the question "For smokers of a given number of cigarettes per day, is smoking lower tar cigarettes associated with a reduced risk of lung cancer?".

It is difficult to equate exactly the estimates of 0.74 for relative risk of lowest to highest tar level to risk per mg tar, due to the open-ended tar categories used (see Table 6.2). Though there is variation from study to study, it seems that on average those in the lowest tar category had a tar level 10-15 mg lower than those in the highest tar category. If so, this would imply a reduction in risk of 2-3% per mg tar decrease, consistent with the values reported in the two studies (CPSII, TANG) which only presented their results in this way.

7. Lung cancer risk in hand rolled vs. manufactured cigarette smokers

Although manufactured cigarettes are predominantly smoked in most countries, hand rolled cigarettes are commonly smoked in a number of countries, e.g. Norway and Australia (Nicolaides-Bouman et al, 1993). Compared to manufactured cigarettes, hand rolled cigarettes tend to have a higher tar level, a poorer inhalation cone and require an increased number of puffs to smoke (IARC, 1986).

Twelve studies, nine case-control and three prospective, have been conducted comparing lung cancer risk in smokers of hand rolled and manufactured cigarettes. Four studies were conducted in Asia, two in China (HU, FU), one in Hong Kong (CHAN) and one in Singapore (MACLEN). In all these studies hand rolled cigarette smokers would have used Chinese tobacco. Of the other studies, two were conducted in Uruguay (DESTEF1, DESTEF2), one in the USA (BUFFLE), and one in France (BENHAM), one in Norway (ENGELA), two in England (ALDERS, MIGRAN) and one in Scotland (HAWTHO).

Table 7.1 compares lung cancer risks, relative to smokers of manufactured cigarettes only, of ever hand rolled smokers, mixed manufactured and hand rolled cigarette smokers and smokers of hand rolled cigarettes only. All three relative risks could not be estimated for each study. In most of the studies, the relative risks are calculated for current and former smokers combined, with the classification by type of cigarette smoked based on lifetime smoking habits (or in the case of BENHAM, the last four brands smoked). Exceptionally, as indicated in the table footnotes, results are for current smokers only and/or are based on brand usually smoked.

Adjustment for potential confounding variables was generally quite poor. Thus four studies did not adjust for any variables at all and one only adjusted for district. Of the remaining seven studies, one adjusted for age only, four for age and smoking variables (such as amount or duration) only and two for age and nonsmoking variables (such as education) only. None of the 12 studies adjusted for age, smoking variables and other potential confounding variables.

Generally, the studies show some tendency for risk of lung cancer to be higher in ever hand rolled cigarette smokers. As shown in Table 7.2, which presents results of meta-analyses, the fixed-effects relative risk estimate (based on 15 data points, 10 for males, 5 for females) is 1.40 (CI = 1.26-1.57), with the random-effects estimate of 1.42 (CI = 1.21-1.66) very similar.

Table 7.2 also presents fixed-effects meta-analysis relative risk estimates for hand rolled only smokers (RR = 1.27, CI = 1.09-1.48, based on 12 estimates) and for mixed hand rolled and manufactured smokers (RR = 1.26, CI = 1.06-1.49, based on 11 estimates). Random-effects estimates are very similar.

In the analyses for females, there was evidence of significant ($p < 0.05$) heterogeneity between estimates for ever hand rolled and hand rolled only. Here there was contrast between high relative risks for HU and ENGELA and low relative risks for CHAN and MACLEN.

Variation between estimates may arise for a number of reasons, including differences in types of tobacco smoked in hand rolled cigarettes in different countries, differences in average amounts of tobacco in a hand rolled cigarette, differences in use of filters, differences in cigarettes making up the comparison group in different studies, differences in adjustment factors considered and, of course, sampling variation.

Table 7.3 summarizes the rather limited evidence relating lung cancer risk of hand rolled and manufactured cigarette smokers by cell type. In the DESTEF1 study, relative risks for hand rolled smoking were particularly high for small cell lung cancer, the authors (De Stefani et al, 1994) considering that "the possibilities of a chance finding and of misclassification of the disease appears to be an unlikely explanation of this strong and rather specific association." In contrast to the markedly raised risk in this study (4.5, CI = 1.9-10.9 for ever hand rolled in men), the results from the ENGELA study showed a marginally significant lowered risk of small cell lung cancer for the same comparison (0.43, CI = 0.18-1.00). In the ENGELA study, the association with hand rolled smoking appeared to be concentrated among squamous cell carcinoma cases (1.91, CI = 1.00-

3.64), a cell type not significantly elevated in the DESTEF1 study (1.2, CI = 0.8-1.8).

Although the overall findings do suggest that hand rolled cigarette smoking is more strongly associated with lung cancer risk than is the smoking of manufactured cigarettes, the relevance of cell type in this comparison remains unclear.

8. Lung cancer risk in black (dark) vs. blond (light) cigarette smokers

Ten studies, all case-control, have been conducted comparing lung cancer risk in smokers of black tobacco vs. non-black (blond) tobacco cigarettes. All have been conducted in Southern Europe and Latin America, two in Spain (AGUDO, ARMADA), two in Argentina (MATOS, PEZZOT), two in Uruguay (DESTEF1, DESTEF2) and one each in Brazil (SUZUKI), Cuba (JOLY), France (BENHAM) and Italy (BERRIN). With the exception of the Cuban, French and Italian studies, which were conducted in the late 1970s, all the studies were conducted between 1987 and 1996. Based on the control populations in the various studies, the proportion of male smokers smoking black tobacco cigarettes varies considerably by country, being 90% or more in Cuba, France and Italy, about 50% in Uruguay and lower in Argentina and Brazil. Matos et al (1998) point out that there has been a big shift away from black tobacco cigarettes in recent years in Uruguay, from 52% of the market in 1960 to 3% in 1985. As noted by Joly et al (1983), dark tobacco has a higher concentration of phenols and nicotine and is more alkaline than the light, Virginia-grown type of tobacco.

Table 8.1 presents risks, based on each of the ten studies, compared to smokers of blond (light) cigarettes only. For each study, relative risks are shown for ever smokers of black (dark) cigarettes. For six of the studies, relative risks are also shown for smokers of black cigarettes only and for mixed smokers of black and blond cigarettes. In one of the studies (DESTEF2), the source paper merely presented data for "blond" and "black" smokers (with numbers totalling those for all smokers). It has been assumed arbitrarily that the comparison is actually never black vs. ever black, so that the results can be included in the table. In another study (BENHAM, female results) results were given for $\leq$ 50%, 51-99% and 100% dark tobacco. For convenience, the first group has been taken to be blond only and the second mixed black/blond, in the table (and later meta-analyses).

All of the studies based their answers on a lifetime history of brand smoked, with the minor exception of BENHAM, which based the classification on the four most recent brands smoked. Results were always presented for current and former smokers combined, with one study (MATOS) also giving results separately for the two groups.

All of the studies except one (JOLY) adjusted for age in analysis. The other studies varied in the confounding factors allowed for, only six studies (MATOS, PEZZOT, SUZUKI, BENHAM [male analyses], BERRIN and ARMADA) taking into account other aspects of the smoking habit such as amount smoked or pack years.

For current and former smokers combined, the studies show remarkably consistently a higher risk in smokers who have ever smoked black cigarettes than in those who have never smoked. All relative risk estimates are elevated and, as shown in Table 8.2, which presents results of meta-analyses, the overall fixed-effects relative risk estimate (based on 12 data points, eight for males, three for females and one for sexes combined) is highly significant (RR = 1.71, CI = 1.50-1.96), the random-effects estimate being similar (RR = 1.75, CI = 1.47-2.09).

The evidence is less consistent about whether risk is higher in smokers of black cigarettes only, or in mixed smokers of black and blond cigarettes, but, again as shown in Table 8.2, the overall fixed-effects estimates are both significantly increased relative to blond only smokers (black only RR = 1.72, CI = 1.44-2.05; mixed black/blond RR = 1.47, CI = 1.21-1.79), as are the overall random-effects estimates (black only RR = 1.72, CI = 1.42-2.09; mixed black/blond RR = 1.63, CI = 1.18-2.27).

Where the authors of a paper present relative risks adjusted for more than one set of potential confounding variables, the main results shown in Table 8.1 are those adjusted for the greatest number of variables. Shown in square brackets in the table are additional results from the SUZUKI, BENHAM and ARMADA studies adjusted for fewer variables. The results of all three studies suggest that further adjustment tends to decrease risk estimates. Not included in Table 8.1 are additional results (shown in Appendix A) from DESTEF1 and BENHAM adjusted for various different sets of confounding variables but based on interim analyses on smaller numbers of cases or results unadjusted for age.

In the study by MATOS relative risks for black tobacco smokers were found to be elevated in both current and former smokers, though the increases were not

significant.

Table 8.3 summarizes relevant results comparing ever black with blond only by histological type of lung cancer. All estimates are increased for each type studied. For the four studies presenting data both for squamous cell carcinoma and for adenocarcinoma, the combined fixed-effects relative risk estimates were 1.96 (CI 1.44-2.67) for squamous cell carcinoma and 1.64 (CI 1.17-2.32) for adenocarcinoma, random-effects estimates being very similar.

Overall the evidence strongly indicates that smokers of black tobacco cigarettes have higher risks of lung cancer than smokers of blond cigarettes only. Although some of the excess seen in the meta-analyses may result from uncontrolled confounding, a number of the studies have reported statistically significant excess risks after adjustment for quite a wide range of variables.

9. Lung cancer risk by other aspects of type of cigarette smoked

9.1 Mentholated cigarettes

In the USA, use of mentholated cigarettes has been widespread since the 1960s, being more common in women than men and in Blacks than Whites (Kabat and Hebert, 1991). Black US men have higher age-adjusted lung cancer rates than do White US men, and there has been interest in whether this might be explained by their increased use of mentholated cigarettes. Table 9.1 summarizes results from the three US studies that have compared the risk of lung cancer in cigarette smokers according to menthol use. Two of these are case-control studies (AHF2, CARPEN) and one is prospective (SIDNEY).

In the first study (AHF2), involving most lung cancer cases, neither short-term nor long-term menthol use was significantly associated with risk of lung cancer in either sex. Nor was there any evidence of an association with menthol usage for specific histological types of lung cancer.

The second study (SIDNEY) raised the possibility that menthol usage might be associated with an increased risk of lung cancer in men, reporting marginally significant associations with ever menthol use (RR = 1.45, CI = 1.03-2.02) and with duration of menthol use (trend p = 0.02). However, no such evidence was seen in women, risk being nonsignificantly reduced in ever menthol users (RR = 0.75, CI = 0.51-1.11). Compared to AHF2, which collected information on brands smoked during life, this study only asked about the brand of cigarettes usually smoked.

Whereas the first two studies concerned current cigarette smokers, the final study (CARPEN) also included ex-smokers in their analyses, making adjustments for total pack-years and years since quit. Data on menthol smoking was obtained from a question which asked “On average over your lifetime, out of every 100 cigarettes you smoked, how many were menthol?”. No significant associations were reported with menthol use in either sex, or for sexes combined, but it was interesting to note that, like the SIDNEY study, also conducted in California, there was some positive association in males and negative association in females.

In view of this, it is of interest to combine the sex-specific results from the 3 studies using meta-analysis. As shown in Table 9.2, the combined evidence shows a nonsignificant increased risk in men, whether using fixed-effects meta-analysis (RR = 1.18, CI = 0.91-1.53) or random-effects meta-analysis (RR = 1.23, CI = 0.88-1.72), but a significant **decrease** in women (RR = 0.70, CI = 0.52-0.95 using either fixed-effects or random–effects meta-analysis).

Clearly, more evidence is needed to confirm whether or not mentholated cigarette smoking in women is associated with a lower risk of lung cancer than is smoking of non-mentholated cigarettes. It seems clear, however, that the increased risk of lung cancer in Blacks vs Whites in the US (which Sidney et al, 1995, state to be by about 60% in men and about 10% in women for 1985-1989) cannot be explained by increased smoking of mentholated cigarettes by Blacks. Kabat and Hebert (1991) summarize evidence suggesting that about 45% of black male smokers and about 15% of white male smokers use mentholated cigarettes. To explain a 60% higher lung cancer incidence in Blacks purely in terms of menthol smoking would require at least a 4-fold higher lung cancer risk associated with menthol than non-menthol smoking.

Four further points should be made on the evidence described:

(i) Only the CARPEN study reported results relating to menthol smoking separately by race. For sexes combined, they found no indication of a trend with pack-years of mentholated cigarettes either in Caucasians or in African Americans (results not shown in Table 9.1).

(ii) All three studies adjusted for amount smoked, either directly or via pack-years, so estimating risk per cigarette smoked. In the SIDNEY study, data were presented showing that mentholated cigarette smokers smoked less cigarettes/day on average (men 20.7, women 17.4) than did non-mentholated cigarette smokers (men 23.3, women 19.7). However, whether or not adjustment was made for amount smoked "did not substantially alter" the estimate of relative risk for mentholated cigarette use.

(iii) Although AHF2 adjusted for inhalation, they noted that their data, and those of

other studies, did not suggest that smokers of mentholated cigarettes inhaled more. SIDNEY also reported that inhalation was similar in mentholated and non-mentholated cigarette smokers.

(iv) Although all three studies adjusted for race and two adjusted for education, none of the studies adjusted for occupation. The fact that mentholated cigarette smokers are more often black and the fact that Blacks more often work in dirtier occupations with higher lung cancer risks suggests occupation may be a relevant confounding variable.

(v) No study in any country other than the USA has reported results relating to use of mentholated cigarettes.

9.2 Nicotine level of brand smoked

Only one study, MRFIT, has attempted to estimate risk of lung cancer solely according to the machine nicotine yield of the brand smoked. As shown in Table 9.3, that prospective study reported somewhat lower risks in smokers of 1.1-1.4 mg or $\leq$1.0 mg nicotine cigarettes than in smokers of 1.5+ mg nicotine cigarettes. However these differences, based on only 95 lung cancer cases, were not significant. Nor was any significant relationship seen between lung cancer risk and mg nicotine in multivariate analysis which reported results as regression coefficients with standard errors. It is interesting to note that the relative risks per mg nicotine, calculated by exponentiation from the regression coefficients, were rather different when based on one paper (Kuller et al, 1991; 1.51, CI = 0.74-3.09) than when based on the other paper (Ockene et al, 1990; 6.75, CI = 0.49-94.2). This is presumably because of differences in the potential confounding variables adjusted for. Notably only the analyses by Ockene et al (1990) adjusted for tar level, a procedure which may lead to unstable results given the strong correlation of nicotine and tar yield.

9.3 Bidis

Two studies have compared the risk of lung cancer in smokers of Indian bidi cigarettes and smokers of Western style manufactured cigarettes. Both were case-control studies conducted in Bombay over a similar time period. One study, NOTANI, involved patients (lung cancer cases and non cancer controls) attending the Tata Memorial Hospital between 1963 and 1971. The other study, JUSSAW, compared lung cancer cases in patients admitted to collaborating hospitals in 1964 to 1973 with population controls interviewed at an unstated time. Although both studies matched cases and controls for age and community, neither study adjusted in analysis for any risk factors, though they presented data subdivided by cigs/day (NOTANI) and by cigs/day, duration of smoking and religion (JUSSAW), which allowed some adjusted relative risks to be calculated.

As can be seen from Table 9.4, both studies reported a higher risk of lung cancer in smokers of bidis only than in smokers of cigarettes only, though the relative risk (adjusted for number of cigarettes/day) in the JUSSAW study (RR = 3.60, CI = 2.43-5.34) was substantially higher than that in the NOTANI study (RR = 1.38, CI = 1.01-1.88). Mixed smokers of bidis and cigarettes had a very much higher unadjusted risk of lung cancer than smokers of cigarettes only in the JUSSAW study (RR = 6.72, CI = 2.78-16.2), but a somewhat lower risk in the NOTANI study (RR = 0.70, CI = 0.43-1.13).

Drawing firm conclusions from these data is difficult for a number of reasons, including the following:

(i) The results from the two studies are highly significantly different and cannot usefully be combined. It is not apparent what features of the study designs might have caused this difference.

(ii) Both studies were conducted in the same area, and the effect of bidis, which contain locally-grown tobacco, may be different in other areas.

(iii) Control for potential confounding variables is poor. Matching for age of overall cases and controls does not ensure that the selected bidi and cigarette smokers

were of comparable age so that failure to control for age in analysis may have caused bias. In the JUSSAW study, separate adjustment for number smoked, duration of smoking and religion affected the bidi/cigarette relative risk, but it was not possible to estimate the joint effect of adjusting for all these (and other factors) simultaneously.

9.4 Brands local to Okinawa

One case-control study, WAKAI, conducted in Okinawa, Japan, in 1998-1991, compared the lung cancer risk in smokers of local Okinawan brand cigarettes with that of Japanese national brands. This study was carried out because the lung cancer risk in Okinawa was higher than in the rest of Japan. Okinawa was returned from the USA to Japan in 1972 and the study participants were asked about the brand most frequently consumed after then. As shown in Table 9.5, lung cancer risk, after adjustment for a wide range of relevant variables, was significantly higher in smokers of the local brands (RR = 1.45, CI = 1.02-2.07), with an excess seen for both squamous cell carcinoma and for adenocarcinoma, though only the former was statistically significant. It is noted by Wakai et al (1997) that the average tar yield of Okinawan brands is higher than that of non-Okinawan brands.

9.5 Pillis and Pöllis

PERNU, a large case-control study, conducted in Finland as long ago as 1944-1958, reported results comparing the risk of lung cancer in smokers of pillis and pöllis. A pilli "has an attached 'holder' made of cardboard, but no actual filter", while a pölli "includes short cigarettes smoked with short wooden mouthpiece and cigarettes of American-type" (Pernu, 1960). As shown in Table 9.6, there was essentially no difference in risk of lung cancer between male pilli and pölli smokers, based on results from over 1000 cases. A lower risk in pilli smokers was seen in women, but was based on only 17 cases and was not statistically significant. One weakness of this study, which is largely of anecdotal interest, is the failure to control for age, either in the study design or in analysis.

10. Discussion and conclusions

There are a variety of difficulties in assessing the relative risk of lung cancer associated with smoking different types of cigarettes based on epidemiological data. Some arise from general problems in the conduct of epidemiological studies (see also section 4), some from particular problems associated with the conduct or reporting of results from specific studies. Below the most important difficulties are summarized.

Inaccuracy in classifying subjects into the groups being compared

In prospective studies, classification by type of cigarette is usually based on what the subject reported (or was reported) to be smoking at baseline, and there is no guarantee that switches in smoking habits did not occur over the follow-up period, especially where the follow-up period is long with no further interviews conducted. While, in case-control studies, attempts are usually made to obtain a lifetime history of smoking, this depends on memory, which has been shown to be unreliable, especially in respect of such detailed aspects as brand smoked or tar level.

Inadequate adjustment for potential confounding variables

It is clear that, at the very least, studies should take into account age and number of cigarettes smoked in their analysis, and it would also seem appropriate that they adjust for other relevant aspects of the smoking habit, including duration of smoking, and some relevant non-smoking related factors known to be linked to lung cancer. However, of the 54 studies reviewed, 15 did not adjust for any potential confounding factors at all, only 34 adjusted for age, 29 for number of cigarettes smoked, 12 for duration of smoking and 17 for any factor other than age or smoking. That said, however, there was little evidence from the studies reviewed that conclusions depended materially on the particular set of confounding variables adjusted for.

Difficulty in identifying the relevant studies and avoiding overlap

Although our attempts to obtain relevant data were extensive, it is possible that some studies have been missed. I would be happy to receive information on additional studies from any readers.

Avoidance of unnecessary duplication of data from the same study is another problem

which is difficult to avoid. This is particularly so for the series of reports over the last 30 years or more from Wynder and his colleagues.

Difficulty in obtaining results from different studies in a comparable format

Reports are inconsistent about how they present relative risks. For example, they may present risks for type A vs type B, type B vs type A or type A vs nonsmokers and type B vs nonsmokers. As far as possible, risks have been presented in this review relative to a common base. However, this has in some studies required estimation procedures which involve assumptions that may be open to debate and may introduce uncertainty. Even after such reorganisation of the relative risks, it is impossible to obtain precise comparability. Thus, for example, filter/plain relative risks may be based on always filter vs always plain, mainly filter vs mainly plain, filter for 20+ years vs always plain, filter vs plain based on one time point, etc.

Limited nature of the evidence on some aspects of type of cigarette smoked

Although there are over 30 studies providing data on the relative risk of lung cancer associated with filter and plain cigarette smoking, the number of studies providing evidence relating to other aspects of cigarette type is much less, 15 on tar, 12 on hand-rolled/manufactured, nine on black/blond and only 3 on menthol.

Of particular importance is the fact that, despite the continuing decline in tar levels of cigarettes smoked, there is virtually no evidence at all in relation to deaths or cases of lung cancer occurring in the 1990s. The need for additional studies here is particularly evident.

It should also be borne in mind that many of the analyses presented do not provide direct information on lifetime smoking of the cigarette types being compared. Thus many of the filter/plain analyses compare lifetime plain cigarette smokers with smokers who had switched to filter cigarettes, while many of the analyses of risk by tar level are based on brands smoked at one time point or over a limited time period. Evidence relating to risk of very low tar cigarettes is nonexistent.

Inadequate reporting by some of the largest studies

A remarkable feature of the evidence reviewed is the inadequate reporting of data from some of the largest studies. Particularly obvious examples are the following:

LUBIN The combined results from this large case-control study, involving 7804 lung cancer cases, was analysed without any adjustment for age, reliance being placed on the age-matching of the total cases and controls, which of course did not apply to the smoking groups being compared. (It was notable that BENHAM, a subset of LUBIN, also did not adjust for age in early papers on the study, but did in later studies, as if the study group suddenly realised the importance of this!)

AHF2 Though results for the filter/plain comparison from this large case-control study have been presented adjusted for age, amount smoked and other variables, the only results reported comparing risk by tar level (Wynder and Kabat, 1988) were simple distributions of cases and controls by tar level, allowing estimation only of unadjusted relative risks. Results, adjusted for age and other variables, have been presented for lifetime tar, based on the product of tar yield, amount smoked and duration (Zang and Wynder, 1992), but such analyses do not allow comparisons of risks in smokers of lower and higher tar cigarettes.

CPSI Although results relating to tar and nicotine yield have been presented from this million person prospective study, no results have been reported comparing risk in filter and plain cigarette smokers, despite relevant questions being asked at baseline (in 1959). It must be noted though that at that time most smokers of filter cigarettes would have smoked cigarettes only for a very limited period of time, as the switch to filter cigarettes really only started in the early 1950s.

CPSII Considering the large size of this 1.2 million person prospective study, the reporting of results relating to lung cancer and type of cigarette smoked is very limited indeed. This is particularly so for men, where the only results cited, in Thun and Heath (1997), are in a figure which shows age-adjusted lung cancer death rates for those smoking non-filter, mixed and filter cigarettes at enrolment, with no indication presented

of variability of the estimates and relative risks difficult to estimate precisely from the data as presented.

SPEIZE To date relevant results from the well-known Nurses Health Study have only appeared in a single paragraph of one paper. The text of that paragraph stated that tar levels at baseline had been divided into tertiles, without stating what the cut-points were. It then reported results comparing risk in the top and bottom quartiles (sic) without giving relative risks for the intermediate tar group (or groups). The results presented adjusted for age and age at start only and adjusted for age, age at start and number smoked were in any case so different as to be implausible (R. Peto, personal communication).

HIRAYA Numerous papers have been published based on this well-known Japanese prospective study of over a quarter of a million people. It is remarkable that the only results relating to filter and plain cigarette smoking in any of them that could be found was a single sentence in a paper entitled "Lung Cancer in Japan : Effects of Nutrition and Passive Smoking" (Hirayama et al, 1984) which stated "The lung cancer-standardized mortality rate was observed to be 18.3% lower in smokers who do not inhale compared to regular deep inhalers, and 48.9% lower in smokers of filter tip cigarettes compared to smokers of nonfiltertip cigarettes, according to our cohort study."

Despite these difficulties, the available data show consistent and large enough differences in risk for a number of the cigarette type breakdowns for conclusions to be drawn. Results of meta-analyses for the major cigarette type comparisons are brought together in Table 10.1. As can be seen, when the data are considered overall, there is quite clear evidence of an increased risk of lung cancer associated with smoking black cigarettes compared with blond cigarettes or handrolled cigarettes compared with manufactured cigarettes, and of a decreased risk associated with smoking filter rather than plain cigarettes and lower tar rather than higher tar cigarettes. For all four comparisons, about 30 to 40% of the individual study estimates are statistically significant (at $p<0.05$) in the direction indicated, with none of them significant in the opposite direction, and the meta-analysis relative risks are all highly significant

($p<0.001$) statistically. In contrast, the evidence that mentholated cigarette smokers have a different lung cancer risk from non-mentholated cigarette smokers is inconsistent, a marginally significant advantage to menthol in females in the three studies presenting evidence being countered by a non-significant disadvantage in males.

While it is clear that adjustment for potential confounding variables is inadequate in a number of the studies, there was little evidence to indicate that more complete adjustment would have materially affected the conclusions obtained.

In the USA, various pieces of evidence point to the fact that lung cancer rates have risen faster than might be expected, bearing in mind trends in the prevalence, frequency and duration of smoking. This conclusions has been reached based on mathematical modelling (Swartz, 1992), confirmed by our own analyses (Lee and Forey, 1996), and also by a comparison of lung cancer rates in men in CPSI and CPSII, conducted 25 years apart, after adjustment for age, amount smoked and duration of smoking (Thun et al, 1997b). It has also been observed that there has been a marked rise in recent years in the relative frequency of adenocarcinoma compared to squamous carcinoma (Thun et al, 1997a, Lee, 1998).

Thun et al (1997a) suggested that these observations could be explained by the switch to lower tar filter cigarettes, compensation for reduced nicotine yields leading smokers to inhale more deeply and distribute relevant smoke components more distally into the lung, with a consequent greater propensity to adenocarcinoma.

This suggestion fails to take into account evidence from two studies (Brownson et al , 1995; Yesner et al, 1973) in which pathologists reevaluated slides originally assessed 5 to 10 years before, both reporting a markedly increased tendency to classify lung cancers as adenocarcinoma. The suggestion also does not appear to fit in with the evidence reviewed here, which shows clearly (see Table 10.1) that not only do filter cigarette smokers have a markedly reduced risk of squamous cell carcinoma, compared to plain cigarette smokers, but they also appear to have a somewhat **reduced** risk of adenocarcinoma. There is nothing in these findings to explain the rise in lung cancer risk

in the USA apparently unexplained by trends in the prevalence, frequency and duration of smoking, or to explain the quite substantial rises in risk of adenocarcinoma that have been observed in some studies. In any case, hypotheses that tar reduction and the switch to filter cigarettes might lead to an increased risk of lung cancer would hardly explain lung cancer trends in the UK, which have declined markedly in younger age groups, indeed rather more than would be expected based on trends in smoking **and** tar reduction (Lee and Forey, 1998).

The epidemiological evidence, taken as a whole, seems quite clear that the switch to filter cigarettes and the tar reduction mainly associated with this has resulted in a decline in the risk of lung cancer to the smoker. A major concern, however, is the lack of recent published studies on the issue, with only one of the studies providing evidence on tar reduction being based on smoking habits since 1986. More studies are clearly needed as one cannot infer that reductions in risk associated with reductions in tar yield from 35 to 15 mg/cig can readily be extrapolated to predict reductions in risk associated with further reductions in tar yield down to 10, 5 or 1 mg/cig.

11. Acknowledgements

This report would not have been possible without the help of many of my colleagues. Katharine Young spent many hours collecting together the database of epidemiological studies on lung cancer and smoking from which those considered in this review were selected. Barbara Forey not only assisted with the database but also estimated many of the relative risks used. Jan Hamling helped in identifying data on trends in tar levels and the switch to filter cigarettes and with the meta-analyses. John Fry provided valuable comments on the draft, as did those already mentioned. Pauline Wassell and Diana Morris typed the numerous drafts rapidly and accurately. I thank them all, and also Philip Morris who provided financial support.

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