Chapter 1

The Epidemiology of Tobacco and Lung Cancer: Some Conclusions from a Lifetime of Research

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/67167

Abstract

This review summarizes evidence on the smoking/lung cancer relationship, based on the author's 50 years' experience. It starts by illustrating variations in national rates by time and sex. It then demonstrates that the relationship of smoking to overall lung cancer risk is strong, consistently seen and dose-related with amount smoked, duration, age of start and time of quitting. Relative risks vary markedly by country, but little by sex, age, race, occupation, genetics and other factors. Though precisely estimating the smoking risk is difficult, the relationship is clearly causal, not explained by bias or confounding. The risk from smoking is reduced in lower tar filter cigarettes, and essentially independent of mentholation and type of curing. Lung cancer risk is not increased by smokeless tobacco use. The relative risk is much greater for squamous/small-cell carcinoma than for adeno/large-cell carcinoma. The argument that the increasing ratio of squamous to adenocarcinoma results from changes in cigarettes is shown to be weak, the increase also being seen in never smokers, starting before filters were introduced, and associated with diagnostic changes. Most of the weak association of lung cancer with passive smoking is explicable by confounding and by misclassification of some ever smokers as never smokers.

Keywords: smoking, lung cancer, trends, dose response, quitting smoking, confounding, bias, cigarettes, tar reduction, compensation, mentholation, flue-cured, blended, histological type, passive smoking

1. Introduction

While, at the beginning of the twentieth century, lung cancer was a rare disease, it was diagnosed progressively more often over the next 50 years, and various suggestions were made during this period that cigarette smoking might be the cause, deriving mainly from the simple fact that the incidence and cigarette consumption were increasing concomitantly [1]. Although

earlier case-control studies had been conducted in Germany [2, 3], it was not until studies in the UK [4] and in the USA [5] published in the 1950s that serious attention was given to the possibility that smoking might cause lung cancer. Following additional evidence from a number of large prospective studies, the US Surgeon General concluded [6] that 'cigarette smoking is a cause of lung cancer in men, and a suspected cause of lung cancer in women', and later reports [7–9] have confirmed and extended the conclusions.

Following a section which concerns trends in lung cancer rates, this review summarizes the evidence on a number of aspects of the relationship of smoking with lung cancer, and also considers the evidence on environmental tobacco smoke (ETS) or 'passive smoking'. In general, less attention is given to those aspects that are well-known and non-contentious, while dealing more fully with areas where the evidence is more open to interpretation. Concentration also tends to be in areas where the author and his colleagues have been involved in detailed reviews of the evidence. As the author has some 50 years of experience, this covers quite a wide range of topics, though not all.

2. Trends in lung cancer rates

Figure 1 shows trends in lung cancer rates in eight countries over the period 1946–2010. They are presented separately for males and females and for age 15+, weighted according to the age distribution of the European standard population. As can be seen, rates in males always substantially exceed rates in females. While in each country rates in males have risen to a peak and then declined, rates of females have tended to rise over the whole period, though there is evidence of flattening out in some countries. The differing trends in the two sexes are consistent with differing trends in the take up of smoking, which can be clearly seen in the detailed data presented in International Smoking Statistics [10].

For both sexes, there is striking variation by country in the trends seen. Points to note are the relatively low rates in Sweden and in Japan, and the rapidly accelerating rates in Hungary, so that in males, rates are now almost double those elsewhere. It is interesting that the lung cancer rates in Canada and the USA are so similar, given the type of tobacco predominantly used in Canada is made only from flue-cured tobacco, while American cigarettes are blended, a topic discussed further in Section 3.5.

Trends in the UK are markedly different from those in other countries, particularly in males. In the 1950s, rates in males were much higher than in other countries, but following a much earlier and steeper decline than elsewhere, are now below those in all countries except Japan and Sweden. In 1998, Lee and Forey [11] attempted to determine whether the trends could be fully explained by trends in cigarette consumption, concluding that they could not, with factors other than cigarette smoking contributing importantly to risk. A contributor to the declining trend may have been the introduction of the Clean Air Act in the UK in 1956.

The trends in the UK are very different from those in the USA. Thus, UK rates, once much higher than in the USA, are now lower in both sexes. To some extent, this may have coloured differing national opinions on the benefits (or otherwise) of changes from high tar plain

http://dx.doi.org/10.5772/67167

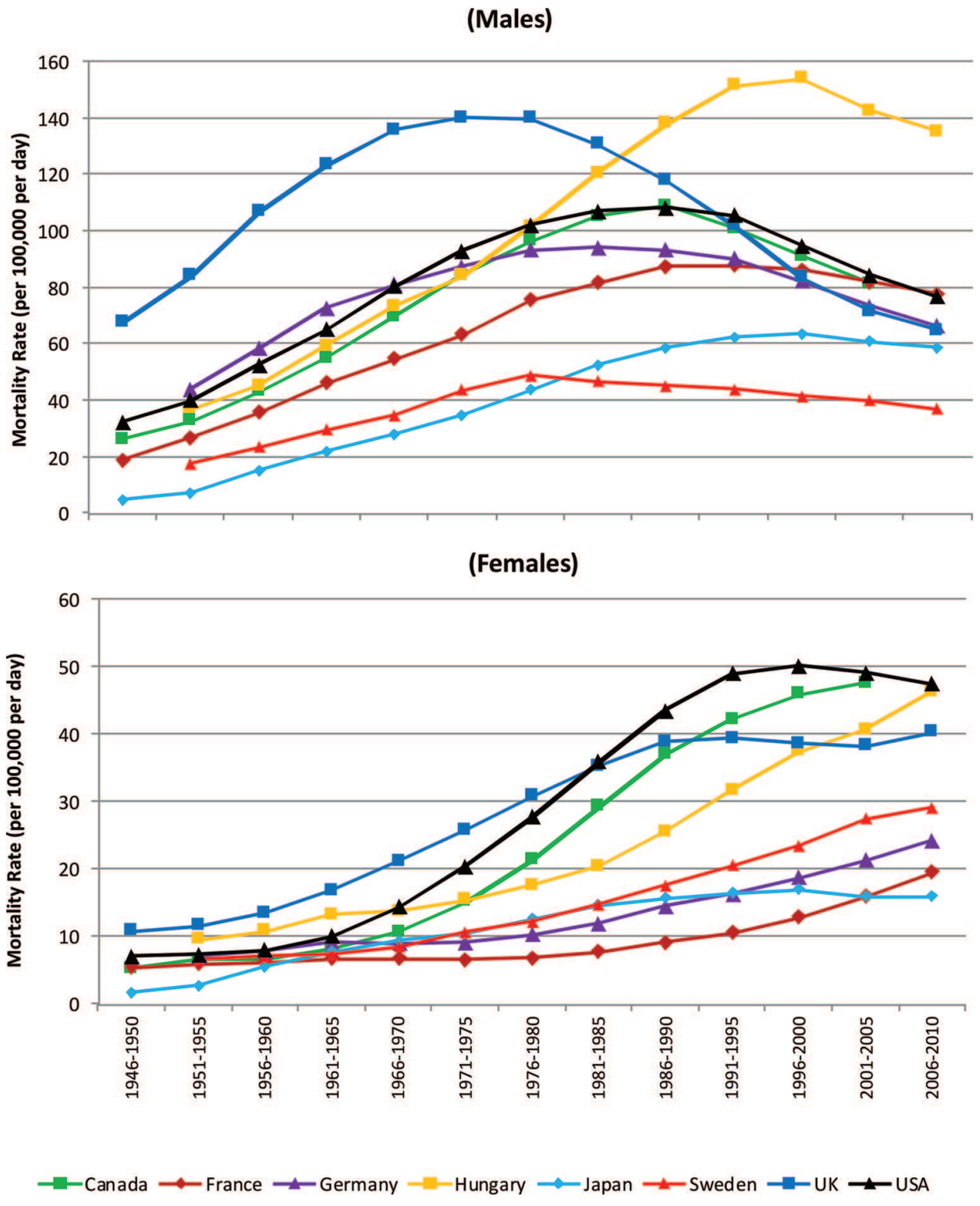

Figure 1. Lung cancer mortality rates by country and period.

cigarettes to low-tar filtered cigarettes. In 2003, Lee and Forey [12] looked in detail at the question as to why the trends in the US and UK are so different. Their analyses took into account detailed data on trends in the age of starting and stopping smoking, amount smoked

per smoker and tar levels, and demonstrated clearly that the differing trends in lung cancer rates could not be explained by these factors. They concluded that the explanation must lie in changes over time in aspects of smoking not considered in the analyses and/or exposure to risk factors other than smoking. Evidence relating to a number of possible such smoking variables or other risk factors was considered, but no clear explanation of the differing trends could be found. Lee and Forey [12] also criticised views expressed in NCI Monograph 13 [13], in particular that tar reduction has been ineffective in lowering lung cancer risk, and that trends in US lung cancer rates fit in well with trends in smoking habits.

3. Relationship of smoking to overall lung cancer risk

In order to describe the main characteristics of the relationship, this section leans heavily on a recently published systematic review with meta-analysis by Lee et al. [14]. This involved all epidemiological studies published before 2000 which included at least 100 lung cancer cases, and which provided relevant information on risks associated with smoking. The meta-analyses involved almost 300 studies, far more than in any other published meta-analysis.

3.1. Dose-related increase in risk in current and former smokers

Although the relative risk (RR) estimates vary considerably between studies, the evidence of an association is extremely clear from the meta-analyses [14], with overall random-effects relative risk estimates of 5.50 (95% confidence interval [CI] 5.07–5.96) for ever smokers, 8.43 (7.63–9.31) for current smokers and 4.30 (3.93–4.71) for ex-smokers, these *RRs* all being expressed relative to those who have never smoked. Although the individual RR estimates are variable in magnitude, they are highly consistent in direction. Thus, of 195 sex-specific RR estimates for current smoking, every single one is greater than 1.0, and all but seven are individually statistically significant at $p < 0.05$, with as many as 27 of the *RRs* exceeding 20. These estimates are for smoking of any product or for cigarettes if results for any product were not available. Estimates for cigarette only smokers were less commonly available but were somewhat higher, with a combined estimate of 8.95 (7.76–10.33) for current smokers.

That there is a tendency for the RR to increase with number of cigarettes smoked per day is abundantly clear. Because studies vary in the groupings used to categorize amount smoked, analyses were included in the systematic review [14] comparing ever smoking *RRs* for three groups: 'about 5 cigs/day' (the category for which results provided includes 5 but not 20 cigs/day), 'about 20 cigs/day' (includes 20 but not 5 or 45 cigs/day), and 'about 45 cigs/day' (includes 45 but not 20 cigs/day). The *RRs* increased steadily with increasing amount smoked, being 3.49 (95% CI 3.13–3.89), 7.33 (6.29–8.54) and 13.69 (11.80–15.89) for the three groups.

Later Fry et al. [15], based on model-fitting techniques, successfully fitted the linear with baseline model $\log_e RR = 0.833 \log_e (1 + 0.81c)$ to 97 independent data blocks, where c is cigarettes smoked per day. This model predicted quite a linear relationship between c and RR, with the RR estimated as 3.86, 6.30, 10.71, 14.77, 18.62 and 22.31 for, respectively, 5, 10, 20, 30, 40 and 50 cigs/day (see **Figure 2**).

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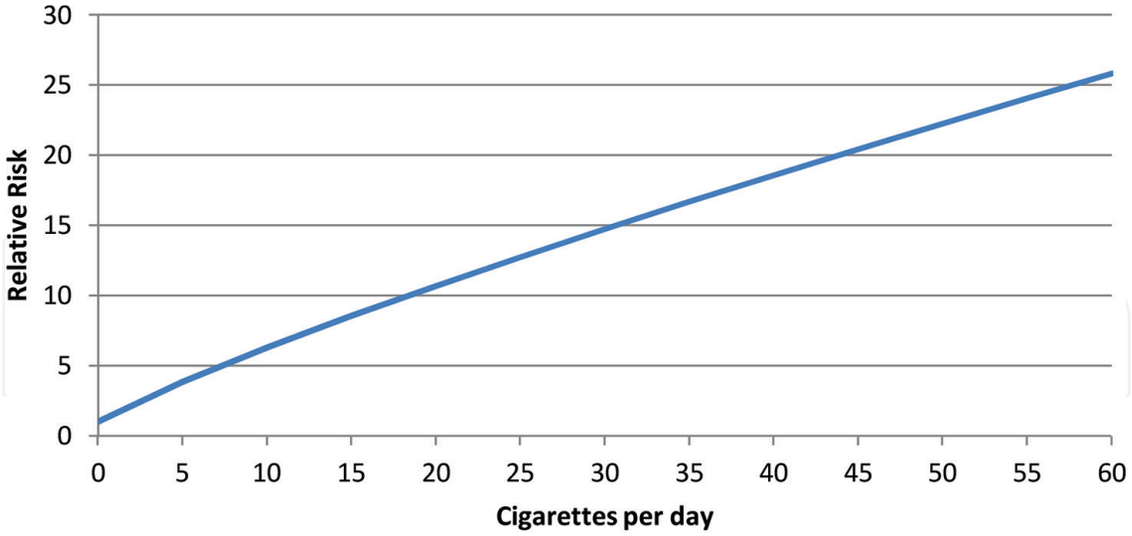

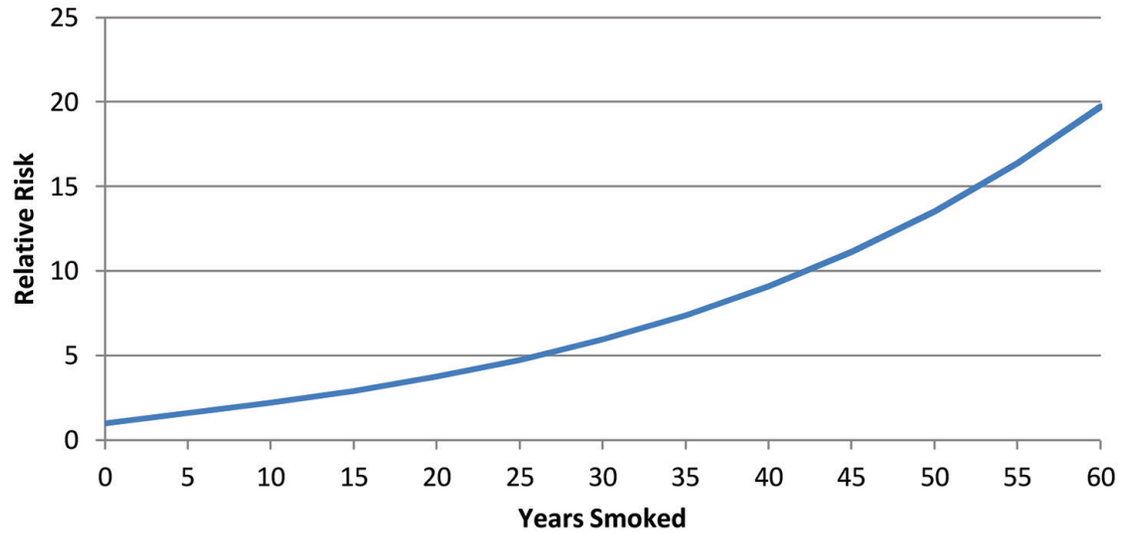

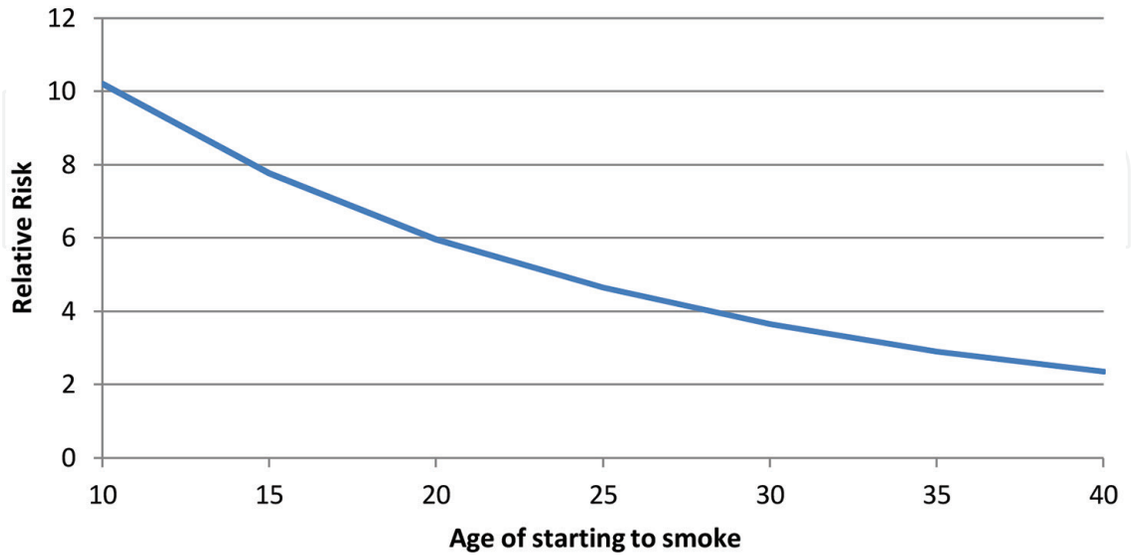

Figure 2. Dose-response relationships for current smoking fitted to 97, 35 and 27 independent data blocks for amount smoked, duration of smoking and age of starting to smoke.

For years smoked, the shape of the dose response was best fitted by a power model $\log_e RR = 0.792\,(y/10)^{0.74}$, where y is years smoked. When applied to 35 data sets, this predicted *RRs* of 2.21, 3.75, 5.96, 9.11 and 13.54 for, respectively, 10, 20, 30, 40 and 50 years smoked (**Figure 2**). Model-fitting techniques were also applied to data by age of starting to smoke, the best model being $\log_e RR = 0.176\,(7-a/10)^{1.44}$, where a is age of start. Here, based on 27 data sets, the *RRs* declined sharply with increasing age of start, being 8.94, 7.80, 6.83, 5.99, 4.66 and 3.66 for, respectively, 12.5, 15, 17.5, 20, 25 and 30 years (**Figure 2**).

Although there is uncertainty as to the actual shape of the true dose-relationship, and misclassification of smoking status and dose may bias the fitted relationships to some extent, it is abundantly clear that risk of lung cancer increases markedly with increasing dose, whether quantified by increased daily amount smoked, increased duration of smoking, or earlier age of starting to smoke.

It is also clear that risk declines, relative to continuing smokers, in those who quit smoking. This is evident, not only from the lower *RRs* in ex-smokers than in current smokers noted above, but also from those studies that report results by time quit. In a review of studies published in the 1900s [14] it was estimated that, compared to current smokers, those who had quit for 'about 12 years' (the category for which results are provided includes 12 but not 7 years), 'about 7 years' (includes 7 but not 3 or 12 years), and 'about 3 years' (includes 3 but not 7 years) had, respectively, *RRs* of 0.28 (0.24–0.32), 0.57 (0.50–0.64) and 0.95 (0.84–1.08). The lack of any clear reduction in the short-term quitters is considered to be due to 'reverse causation' with some smokers quitting due to incipient disease.

A later paper [16], investigated whether the decline in RR of lung cancer following quitting (expressed relative to never smokers) could be adequately fitted by a simple, negative exponential, model. In this model, the excess relative risk ER (= $RR - 1$) following t years of quitting was estimated by multiplying the ER for a continuing smoker by the factor $\exp(-\frac{t \log_e 2}{H})$, where H is the estimated half-life. Thus, for example, if H is 10 years, and the *RR* for a continuing smoker is 11 ($ER = 10$), the *RR* for a quitter will be 6 after 10 years of quitting (the *ER* of 10 being halved to 5), 3.5 after 20 years, and 2.25 after 30 years, and will still be doubled after 35 years. Based on 106 independent data sets from 85 studies, published up to 2011, it was found that if reverse causation was ignored, the model fit was poor, but the fit was much improved if reverse causation was allowed for, either by ignoring short-term quitters, or by considering them to be smokers. For the best-fitting analysis (ignoring short-term quitters), H was estimated as 9.93 (95% 9.31–10.60), but varied by sex (females 7.92, males 10.71) and age (increasing from 6.98 for age <50 years to 12.99 for age 70+ years). It was concluded that the model adequately described the decline in ER, although precise estimates of H may be biased by misclassification of smoking status and failure to update smoking habits during follow-up in long-term prospective studies. The large value of H illustrates clearly the persistent effects of smoking.

As shown subsequently [17], the negative exponential model can quite simply be adapted to predict risk following changes in exposure more generally. The adaptation was shown to satisfactorily predict results from those (relatively few) studies that have investigated the effect of reducing cigarette consumption, and suggests it may be useful for predicting changes in risk following switching to a reduced exposure product.

3.2. Factors affecting risk

The age-specific absolute risk of lung cancer is known to be related to many factors other than smoking. These include alcohol, occupation, air pollution, diet, viruses and genetic factors [18].

However, the evidence considered in this section relates not to which factors modify the risk of lung cancer, but to which affect the RR associated with smoking.

3.2.1. Sex

There has been considerable discussion about whether smoking increases the risk of lung cancer more in women than in men, e.g. [19]. Based on the systematic review of Lee et al. [14], there was little evidence of any difference, though RR estimates generally tended to be higher for men than for women. This conclusion was supported by additional analyses comparing *RRs* within individual studies using the same definition of exposure and similar levels of amount smoked. The slightly higher *RRs* in men do not necessarily indicate any greater susceptibility, as they may reflect increased exposure to occupational carcinogens, differences in duration of smoking or increased use of higher tar and plain cigarettes. Note, however, that in prospective studies in which smoking habits are determined at baseline, the greater tendency of males to quit during follow-up may tend to understate the male/female ratio. Though it is difficult to get a precise answer on the male/female difference, these results appear to agree with the conclusion of Bain et al. [20] that 'women do not appear to have a greater susceptibility to lung cancer than men, given equal smoking exposure'.

3.2.2. Age

Though the absolute risk of lung cancer rises steeply with age, both in never and ever smokers, it is far less clear whether the RR also does, particularly when the great majority of published studies do not give results by age. However, a number of studies considered in the systematic review [14] did provide RR estimates for ever or current smoking separately by age, and it was possible to carry out meta-analyses based on the ratio within study of the estimate for the oldest age group for which data were available, compared to that for the youngest. While the meta-analysis did show a significantly higher risk in the oldest age group, the estimated average ratio (1.17, 95% CI 1.10–1.25) was quite modest. Clearly, any variation in RR by age is much smaller than the RR itself.

3.2.3. Location

There is a striking variation between study locations in the estimated RR associated with smoking. For current smoking, where the overall RR estimate for the sexes combined from meta-analyses [14], based on 195 estimates, was 8.43 (95% CI 7.63–9.31), the estimate was higher than this for studies based in North America (11.68, 10.61–12.85), and markedly lower than this for studies in China (2.94, 2.23–3.88), Japan (3.55, 3.05–4.14), and other parts of Asia (2.90, 2.04–4.13), with estimates intermediate in the United Kingdom (7.53, 5.40–10.50), Scandinavia (8.68, 7.14–10.54) and other parts of Europe (8.65, 5.98–12.51). The pattern of

variation by location is similar if comparisons are based on ever rather than current smoking. The extent to which these quite clear differences are due to the product smoked, amount smoked, genetics or other factors, is a question which deserves further attention.

3.2.4. Time

The systematic review [14] generally showed a tendency for *RRs* to be lower in studies which started a long time ago. Thus, current smoker *RR* estimates rose continuously from 6.39 (95% CI 4.70–8.69) for studies starting before 1960 to 12.81 (8.70–18.85) for studies starting in the 1990s. Indeed, in the meta-regression analyses, start year of study and location were the most highly significant ($p < 0.001$) independent predictors of the current smoker RR. There are a number of possible reasons for the time trend, including changes in the use of cigarettes relative to pipes and cigars, and improvement in the quality of studies. However, the most plausible reason seems to be changes in patterns of uptake of smoking, with smokers in the earliest studies, born around the turn of the nineteenth century, being less likely to have had a lengthy smoking career than later-born smokers in more recent studies. Note that this increase occurs despite evidence, discussed in Section 3.4, that cigarettes have become somewhat less harmful due to reductions in tar and the switch to filters.

3.2.5. Race

Few studies considered in the systematic review [14] provided comparable *RRs* for ever or current smoking by race, and these results gave no indication that *RRs* for Whites differed systematically from those for Blacks (or non-Whites). Comparison of risks in Blacks and Whites is in any case made difficult by various differences in their smoking characteristics [21]. Thus, while in the USA. Blacks are more often current smokers, are less likely to quit smoking, smoke higher-tar cigarettes and have higher cotinine levels, all characteristics which would predict a higher risk of lung cancer, they are also less likely to have ever smoked, have lower daily cigarette consumption, and start smoking later, all characteristics predictive of a lower risk.

Other risk factors were not considered in detail in the systematic review [14]. However, reference is briefly made below to some of these.

3.2.6. Asbestos and other occupational exposures

It is well-known that asbestos exposure increases risk of lung cancer, though the increase depends materially on the type of asbestos. In an early large study of US insulation workers [22] *RRs*, compared to men who had never smoked cigarettes and who were unexposed to asbestos, were 5.17 for those exposed only to asbestos, 10.85 for those who had ever smoked only, and 53.24 for those exposed to both risk factors. These results, while suggesting a multiplicative relationship and an extremely high risk in those with both exposures, do not suggest that the smoking RR varies materially by asbestos exposure. A meta-analysis conducted in 2001 [23] involving 23 epidemiological studies confirmed that asbestos exposure and smoking have an approximate multiplicative relationship with lung cancer risk.

There are, of course, numerous occupational factors which affect risk of lung cancer. Nearly all, such as arsenic, chromium, nickel, chloromethyl ethers and polycyclic aromatic hydrocarbons increase risk, though a reduced risk has been reported for exposure to endotoxins [24]. The author is not aware of any occupation known to materially affect the RR associated with smoking. As smokers are more likely to work (or have worked) in 'dirty' occupations, there is a possible confounding effect of occupation. However, numerous epidemiological studies have adjusted for occupation (or indicators of it such as social grade) and the systematic review [14] found that the RR for smoking was hardly affected at all by the extent of adjustment for other risk factors.

3.2.7. Genetics and family history

A review by Lee in 1993 [25] considered the limited evidence then available on family history, concluding that risk was approximately doubled in those who have a relative with lung cancer. The association has been confirmed in a recent pooled analysis [26] of data from 24 studies, with the RR of lung cancer associated with having a first degree relative with lung cancer estimated as 1.51 (1.39–1.63). The *RR* was somewhat higher for ever smokers (1.55, 1.42–1.68) than for never smokers (1.25, 1.03–1.52). Similar results were reported in an earlier meta-analysis [27]. From the pooled meta-analysis results, one can estimate that the RR for ever versus never smoking is somewhat lower in those with a family history of lung cancer than in those without, by a factor which can be estimated as 1.25/1.55 = 0.81 (95% CI 0.65–1.00), a factor which is of considerably smaller magnitude than the *RR* for ever smoking of 5.50 (5.07–5.96), noted in Section 3.1.

The demonstration of an association of family history with lung cancer does not necessarily prove there is a genetic determinant of lung cancer, as family members may share aspects of smoking such as amount smoked, depth of inhalation and type of product smoked, or be exposed to common environmental factors other than smoking (e.g. heating and cooking practices). In recent years, there have been a very large number of studies aiming at looking more directly at how a whole range of genotypes are associated with lung cancer risk or with propensity to smoke. The author's impression of the literature is that associations reported are often non-significant and never strong. Even for well-studied relationships, such as chromosome 15q25, the evidence [28–31] only suggests that the variants are associated with an increased cigarette consumption of about one cigarette per day, and an increased lung cancer risk of about 30–50%. Furthermore, evidence obtained on whether the variants differentially affect lung cancer risk in never smokers is very limited. There seems to be no evidence that *RRs* associated with smoking are strongly affected by genetic factors.

3.3. Difficulties in the precise estimation of risk from smoking

3.3.1. Inaccuracy of diagnosis of lung cancer

A review in 1994 by Lee [32] demonstrated substantial evidence of disagreement between autopsy, clinical and death certificate diagnosis of lung cancer. Even though autopsy does not ensure 100% accuracy even if clinical history is taken into account, it offers the possibility of substantially improving the level of accuracy of death certificate data, which is affected

by fashion and the particular interests and perceptions of certifying doctors. For example, knowledge that a person is a smoker affects diagnostic procedures so that lung cancer in a non-smoker is less likely to be detected clinically than in a non-smoker. The review also bemoaned the decline in autopsy rates, noting that advances in clinical diagnostic techniques seem not to be compensating for this in reducing inaccuracy.

While in many Western countries, autopsy rates are very low, this is not so in Hungary, or other countries in the old Austro-Hungarian empire. Autopsies were for many years routinely carried out there on all patients dying in hospital. A study there [33] showed a substantial discrepancy between pre- and post-autopsy diagnosis. In that study, 59% (36/61) of lung cancer seen at autopsy were not detected pre-autopsy, while 50% (25.50) of those diagnosed pre-autopsy were not confirmed at autopsy. Accuracy of diagnosis increased with the number of diagnostic techniques applied, but was still far from perfect in the absence of necropsy. Under-diagnosis was commoner in non-smokers and over-diagnosis commoner in smokers. Although improved diagnostic procedures could have increased accuracy of diagnosis, the results certainly imply the possibility of considerable bias to the estimated RR for lung cancer and smoking.

3.3.2. Inaccuracy in determining smoking habits

In comparing the risk of ever smokers and never smokers, random misclassification of smoking habits tends to dilute any true association with lung cancer risk. Thus, if the true *RR* is 10, and there are 50% ever and 50% never smokers random misclassification of 5% of the population into the wrong group would lead to the observed *RR* being $(47.5 \times 10 + 2.5 \times 1)/(47.5 \times 1 + 2.5 \times 10) = 6.59$. The major determinant of the bias is misclassification of ever as never smokers rather than the reverse. The association would also be diluted, if cases deny or understate their smoking, though this would not be relevant in prospective studies, where smoking habits are determined before onset of disease. Any tendency for current smokers to claim to be ex-smokers, as might happen in a situation where patients have been advised to stop smoking, would tend to increase the RR for ex-smokers and reduce the RR for current smokers. Generally, plausible levels of misclassification of smoking habits cannot explain the observed association of smoking with lung cancer.

3.3.3. Confounding factors

In the systematic review of Lee et al. [14] adjustment for age and other factors was found to have very little effect on the overall estimate of the RR associated with smoking. The conclusion of a minimal effect of confounding is consistent with that from an analysis of data from the very large US Cancer Prevention Study II [34]. It is in any case clear that the smoking RR is too large to be explained by confounding. For an RR which comfortably exceeds 10 for heavy smokers to be an artefact of confounding would require there to be another risk factor which is both extremely strongly related to lung cancer and to which smokers are very much more commonly exposed than non-smokers. While some rare risk factors (e.g. bis(chloromethyl) ethyl exposure) increase lung cancer risk very markedly, and smokers and non-smokers do differ in a range of characteristics, no factor (or group of factors) has emerged which can come

close to explaining the observed RR for smoking in terms of confounding. Certainly there is no good evidence to support early theories by Fisher [35] and Burch [36] that the association of smoking with lung cancer might be totally explained by genetic factors. This theory seems, in any case, to be refuted by the observation that in smoking-discordant identical twins, risk of lung cancer was much higher in the twin who smoked [37–38].

Confounding is a more relevant issue when considering the dose-related aspects of smoking. As shown in the systematic review [14], adjustment for other aspects of smoking (typically including amount smoked) consistently reduces associations of lung cancer risk with age of starting to smoke, duration of smoking, years quit and tar level. This is because earlier starters and high tar smokers tend to smoke more heavily than do later starters and low-tar smokers, and lighter smokers tend to be more ready to quit smoking.

3.3.4. Publication bias

The tendency for researchers to be more likely to want to publish, and editors more likely to accept for publication, studies finding a statistically significant association may cause important bias for some relatively weak associations of exposure to disease [39, 40]. However, the association of smoking with lung cancer is too strong and consistently reported for publication bias to be a material explanation of the strong relationship.

3.3.5. Recall bias

In case-control studies, the smoking habits reported by a case may be affected by knowledge of the disease, particularly where the disease is widely reported to be caused by smoking. However, the fact that smoking *RRs* are quite similarly elevated in prospective studies (where such recall bias is not a possibility, smoking habits being reported before onset of the cancer) as in case-control studies (where it is a theoretical possibility) appears to rule out recall bias as an explanation for the observed association.

3.3.6. Assessment of conclusions

While there are a number of factors that affect precise estimation of the risk of lung cancer from smoking, it is very clear that smoking is an important determinant of risk. Looking back at the Bradford Hill criteria for determining whether an association is due to causation [41] the available evidence discussed above clearly demonstrates strength, consistency, temporality (with the exposure preceding the disease) and biological gradient (or dose response). The relationship also satisfies plausibility, given the numerous known carcinogens in tobacco smoke, and coherence, the evidence not conflicting with known facts concerning the natural history and biology of lung cancer. There is also experimental evidence, partly in humans in relation to the decline of risk following quitting, and partly in animals, with exposure to tobacco for having been shown to increase risk of skin cancer in mice and exposure to tobacco smoke having been shown to elicit lung tumours in rodents [9]. One could also argue analogy with regular inhalation of other pollutants increasing risk of lung cancer. Of the nine Bradford Hill criteria, the only one it fails is specificity. Smoking is clearly not a necessary condition for lung cancer to arise, inasmuch as there are other causes of lung cancer. Nor is it sufficient,

as many smokers do not contract the disease. Though some old dictionary definitions appear to equate 'cause' to 'necessary and sufficient cause', this is not what is meant by saying that smoking causes lung cancer.

3.4. Types of product

While in most countries the majority of cigarette smokers smoke manufactured cigarettes, with relatively few smokers using hand-rolled cigarettes, in some countries, e.g. the Netherlands and Norway, hand-rolled smoking is relatively common [10]. The systematic review of studies in the 1900s [14] included 20 independent within-study estimates of the ratio of risk in hand-rolled versus manufactured cigarette smokers, which produced a combined *RR* estimate of 1.29 (95% CI 1.12–1.49), based mainly on lung cancers in men. The conclusion of a somewhat higher risk for hand-rolled cigarette smokers is consistent with that in an earlier review relating lung cancer to type of cigarette smoked [42].

That systematic review [14] also included results indicating that the RR of lung cancer was substantially lower for smokers of pipes and cigars than for cigarette smokers. Thus, for current smoking, while the *RRs* for cigarette only and for mixed cigarette and pipe/cigar smokers were, respectively, 9.57 (95% CI 7.90–11.59) and 9.60 (8.37–11.00), they were consistently lower for smokers of pipes only (5.20, 3.50–7.73), cigars only (4.67, 3.49–6.25) and smokers of pipes and/or cigars only (4.76, 3.44–6.59). Lower risks for smokers of pipes and cigars were also evident when results for ex-smokers or ever smokers were considered. Data on the types of cigars or pipes smoked were not considered, but the increased risk was evident in each continent. However, it is doubtless true that risk does vary to some extent by the type of pipe and cigar smoked.

There has been considerable research into the health risks of smokeless tobacco in Western populations, mainly based on data for Sweden, where a type of moist snuff known as snus is the dominant product, and for the USA, where chewing tobacco is common, and moist and dry snuff are also used [43–45]. The results provide no indication of any increased risk of lung cancer associated with smokeless tobacco use. They may help to explain the relatively low risk of lung cancer in Sweden (see **Figure 1**), where snus use is a common alternative to cigarette smoking.

3.5. Type of manufactured cigarette

Over the second half of the last century, the characteristics of manufactured cigarettes have changed substantially [10]. In the mid-1950s, cigarettes were typically of the non-filter plain variety with average tar levels exceeding 30 mg/cigarette. By now, nearly all cigarettes smoked have filters and average tar levels are around 10 mg/cigarette in many countries. Nicotine yields per cigarette have reduced by a similar factor.

An important question is whether these changes, introduced in order to reduce risk, have actually done so. Two points are worth making at the outset. The first is that, though the observed rise in RR for current smokers over the second half of the last century which was noted above would appear to suggest that the risk of cigarettes might have increased, this is

not necessarily so, as changes in average duration of smoking by smokers have clearly had a major effect, and may mask any effects of the switch to lower tar filter cigarettes.

The second is that there is clear evidence of what is commonly termed 'compensation'. Thus, whereas one might expect smokers switching from cigarettes with a nicotine yield (machine-measured under standard smoking conditions) of, say, 2 mg/cigarette, to cigarettes with a nicotine yield of 1 mg/cigarette to halve their nicotine uptake, the reduction in measured dose is typically much less than this. This may, in theory, be because smokers increase their daily consumption or because they change how they smoke the cigarettes, the second possibility being more plausible given that consumption per smoker has changed little over the years in most countries [10].

Scherer and Lee [46] recently reviewed the available evidence on the extent of compensation, based partly on brand-switching and partly on cross-sectional studies. Using estimates based on nicotine biomarkers, commonly cotinine, they estimated a weighted mean compensation index of 0.781 (95% CI 0.720–0.842), where a value of 1 indicates complete and 0 no compensation. The index is estimated from a formula in which the biomarker, B, is related to the yield, Y, the formula $B = \mu Y^{1-C}$ where μ is a constant and C is the index. Thus, if $C = 1$, the biomarker is independent of the yield, while if $C = 0$, the biomarker is directly proportional to it. Using their estimated value of C of 0.781 would imply that a 50% reduction in yield would only produce a 14% reduction in dose, as assessed by the biomarker. This suggests that any effects of a reduction in nicotine yield on lung cancer risk are likely to be much less than would be suggested by the reduction in yield.

Various reviews have assessed the evidence on risk associated with the switch to lower tar filter cigarettes. In one of the earliest reviews [42], it was calculated, based on 43 sex-specific estimates, that the risk of lung cancer was 36% lower (95% CI 27–44%) in filter than in plain cigarettes, and 23% lower (95% CI 27–44%) for lower than higher tar cigarettes. The estimated reduction, seen in both sexes, equated to 2–3% risk reduction per mg tar per cigarette. Following publication of a report by the National Cancer Institute [13] claiming that the apparent benefits of lower delivery cigarettes may be illusory if *RRs* are adjusted for daily consumption, Lee and Sanders [47] investigated the claim by comparing *RRs* unadjusted and adjusted for consumption. They found clear reductions in risk associated with both filter and lower tar cigarette consumption, regardless of adjustment, reductions which were evident regardless of sex, study location, time period or study design. Their 2012 systematic review [14] also included a number of relevant results, among which were an estimated *RR* of 0.69 (95% CI 0.61–0.78) for only filter versus only plain smoking, and of 1.42 (1.18–1.71) for higher versus lower tar smoking.

It should be noted that the evidence considered is limited by the range of tar levels tested in any one study being often quite small (as all long-term smokers have experienced reducing tar levels), and also by there being essentially no evidence on risk of ultra-low (≤3 mg) tar cigarettes. Also, there are various other limitations, including difficulties in obtaining individual results in a comparable format, inadequate reporting of results, possible unreliability of the data recorded on cigarette type, and lack of adjustment in some studies for potential confounding variables. However, the results clearly suggest that the switch to lower

tar filter cigarettes has been beneficial, though the benefit has been substantially reduced by compensation.

That cigarette mentholation might increase risk of lung cancer has some plausibility. First, the acute respiratory effects of menthol might affect inhalation of cigarette smoke, and secondly, in the USA, Black men (who have a very strong preference for mentholated cigarettes) have lung cancer rates that are substantially higher than those for White men. However, a systematic review by Lee [21] concluded that the epidemiological evidence is actually consistent with mentholation having no effect on the lung carcinogenicity of cigarettes. That review identified eight generally good quality studies, all but one conducted in the USA, which gave a combined RR estimate for ever versus never use of mentholated cigarettes of 0.93 (95% CI 0.84–1.02), with no significant evidence of any effect in males or females, or in Blacks or Whites. Noting also that, in the USA, Black women (who also have a very strong menthol preference) have lung cancer rates which are no higher than in Whites, the high rates in Black men cannot be explained by their greater preference for mentholated cigarettes.

Based on the tobacco they include, most cigarettes sold can be divided into two categories; flue-cured (or 100% Virginia) cigarettes, and blended (or American blended) cigarettes. The tobacco in flue-cured cigarettes is cured over a short period (about a week) at high temperatures, while blended cigarettes are based on three types of tobacco (flue-cured, Burley or Oriental) blended together [48]. Burley and Oriental tobaccos are air-cured over a period of about 6 weeks, the three tobacco types being genetically different. Different countries tend to predominantly use the different types of cigarettes. For example Austria, Denmark, Germany and the US use mainly blended cigarettes, while Australia, Canada and UK use mainly flue-cured cigarettes [10]. Comparing lung cancer risk for smokers of flue-cured and blended cigarettes is not straightforward since epidemiological studies are typically conducted in a single country where the smokers are likely to all (or virtually all) use one cigarette type or the other. An alternative approach tried by Lee et al. [49] was to compare lung cancer risk (for 1971–2000) by sex, age and period for those four countries listed above which traditionally use blended cigarettes, and those three listed countries which use flue-cured cigarettes. The comparisons were made both unadjusted and adjusted for prevalence of current and former smoking and for consumption per smoker. This approach was not particularly sensitive, due to the limited number of countries which (a) could both be clearly categorized by type, (b) had relevant data available and (c) did not have a large proportion of smokers of products other than cigarettes. However, it did not suggest any material effect of cigarette type on risk. Particularly noteworthy are the quite similar lung cancer rates and trends in the USA and in Canada shown in **Figure 1**, with one country using blended and the other flue-cured cigarettes.

4. Differential effect of smoking on histological type of lung cancer

4.1. Classification and diagnosis of histological type

The classification of lung cancer based on its microscopic characteristics, formulated nearly 100 years ago [50], has changed little in general structure, with the great majority of lung

cancers classified into one of four basic types—squamous cell carcinoma, adenocarcinoma, small-cell carcinoma and large-cell carcinoma. However, successive WHO classifications [51–53] have differed in how tumours should be ascribed to these types, and there are considerable difficulties in ensuring an accurate and consistent diagnosis, with evidence of intra- and inter-observer variability of classification [54–56]. Part of the problem lies in the morphological heterogeneity of lung cancers with some tumours, and occasionally even in a single tissue block, presenting evidence of more than one type of lung cancer [57]. It is also clear that the morphological type of tumour is influenced by its site within the lung and by how the specimen was obtained.

4.2. Variation in relative risk of lung cancer by histological type

In their systematic review of studies published in the twentieth century [14], Lee et al. presented a range of RR estimates, not only for all lung cancer but also for squamous cell carcinoma. More limited results are also shown for small-cell and large-cell carcinoma. For current smoking overall *RRs* were strikingly higher for small-cell carcinoma (18.17, 95% CI 12.92–25.56) and squamous cell carcinoma (16.43, 12.66–21.32) than for adenocarcinoma (4.05, 3.15–5.22), with that for large-cell carcinoma (8.56, 5.29–13.86) being intermediate. The same pattern was seen for ever smoking.

For all lung cancer types *RRs* varied substantially by location, being much higher for North America than for China, with no clear pattern seen for other regions, some with sparse data. Evidence that risk increases with increasing amount smoked and duration of smoking and earlier age of starting to smoke was seen for both squamous cell carcinoma and for adenocarcinoma, though RR estimates were much higher for squamous cell carcinoma. Indeed, for squamous cell carcinoma, combined *RRs*, each based on a substantial number of estimates, were of order 30 for heavy smokers (about 45 cigs/day), long-term smokers (about 50 years) and early starting smokers (about age 14 years). *RRs* for ex-smokers were also substantially higher for squamous cell carcinoma (8.74, 95% CI 6.94–11.01) than for adenocarcinoma (2.85, 2.20–3.70). In a separate publication [58], based on data from 85 studies comparing cancer risks in current smokers, quitters (by time quit) and never smokers, it was found that the rate of decline in RR following quitting was somewhat less rapid for adenocarcinoma than for squamous cell carcinoma, where the half-lives were estimated, respectively, as 14.45 (11.92–17.45) and 11.68 (10.22–13.34). The slower decline in risk for adenocarcinoma was evident in subgroups by sex, age and other factors.

4.3. Possible explanations for the time shift in the relative frequency of adenocarcinoma and squamous cell carcinoma

A shift in the relative frequency of adenocarcinoma to squamous cell carcinoma over time has been clearly evident in many countries [59], and in 2014, the US Surgeon General [7] argued that the increasing incidence and relative frequency of adenocarcinoma has resulted 'from changes in the design and consumption of cigarettes since the 1950s'. The argument that the switch from higher tar, plain cigarettes to lower tar, filtered cigarettes is responsible for the rise in adenocarcinoma had been made previously [60–62] and supported by various

researchers [63, 64]. However, there are a number of reasons which indicate that this conclusion is, to say the least, over-simplistic.

One reason for doubting the claim is that the observed shift in the relative frequency of adenocarcinoma to squamous cell carcinoma began well before the increase in consumption of low-tar filtered cigarettes started [65].

Had there been an adverse effect of low-tar filter cigarettes on risk of adenocarcinoma, one might have expected to see that for adenocarcinoma, the filter versus plain RR would be significantly increased. However, this is not the case [14, 42, 47], the systematic review [14] giving *RRs* close to 1, whether comparison was made between only filter and only plain smokers (0.84, 95% CI 0.66–1.08), ever filter and only plain smokers (0.99, 0.84–1.16) or only filter versus ever plain (0.98, 0.80–1.21). In contrast, significantly reduced risks were seen for the same three comparisons for squamous cell carcinoma 0.52 (0.40–0.68), 0.55 (0.41–0.74) and 0.69 (0.57–0.83), respectively. That the switch to lower tar filtered cigarettes has not resulted in an increase in risk for adenocarcinoma is also consistent with evidence from more recent studies [63, 66, 67]. Note that the reduced *RRs* for filtered cigarette smoking for squamous cell carcinoma suggests that the switch has been beneficial, not adverse, though the magnitude of effect is not enough to explain the observed large rise seen in the relative frequency of adenocarcinoma to squamous cell carcinoma.

Although the US Surgeon General [7] dismissed changes in diagnostic procedures as unimportant, there is quite clear evidence they are relevant, as indicated by three facts. First, schemes for classifying histological type of lung cancer have changed over time, notable being the reallocation of one of the four classes of large-cell carcinoma in the WHO classification [51] to adenocarcinoma in the 1981 classification [52]. Secondly, large studies where diagnoses of histological type made some years earlier were reviewed later by pathologists using later classification schemes generally report an increase in numbers of adenocarcinoma [68]. Finally, studies using standard criteria to review cases collected over a period of at least 10 years found no increase in the proportion of lung cancers classified as adenocarcinoma [68, 69]. Interestingly one of those studies [69] reported a substantial rise in the rate of bronchioloalveolar carcinoma, which affected smokers and non-smokers alike, and which the authors suggested may have a viral origin.

A huge weakness in the Surgeon General's argument [7] is that it would predict that the shift from squamous cell carcinoma to adenocarcinoma would be confined to smokers. Two pieces of work clearly indicate that there has been a clear change in never smokers. An analysis in 2013 [70] indirectly estimated absolute lung cancer mortality rates by smoking habit, time period- and histological-type-based studies published in the twentieth century, coupled with WHO mortality data for the same country and period. Thus, while in never smoker rates of squamous cell carcinoma per 100,000 per year were estimated to vary little by time period (7.6, 12.6, 12.7, 10.2 and 11.6 for, respectively, 1930–1960, 1961–1970, 1971–1980, 1981–1990 and 1991–1999) the corresponding rates for adenocarcinoma increased sharply for the same time period, (6.9, 17.0, 18.1, 29.0 and 33.9).

The change in never smokers is illustrated more clearly in a recent publication [68] which examined how the proportion of adenocarcinoma in never smokers varied by time, sex and

region, based on 219 sex- and period-specific blocks of data drawn from 157 publications. Compared to the period 1950–1960, the ratio of adenocarcinoma to squamous cell carcinoma was higher by factors of 1.67, 1.97, 2.35 and 3.93 for, respectively, 1970–1979, 1980–1989, 1990–1999 and 2000 onwards. This publication presents arguments that the time trends could not be explained by changes in ETS exposure, or misclassification of ever smokers as never smokers.

While the switch to lower tar filtered cigarettes may have affected the relative frequency of adenocarcinoma to squamous cell carcinoma, the epidemiological evidence suggests that this is because changes in cigarettes have reduced risk of squamous cell carcinoma, not because they have increased risk of adenocarcinoma. The evidence also suggests that the differing trends by histological type are due partly to changes in diagnosis and classification and partly to other factors that have affected both non-smokers and smokers. What these factors are requires further research.

5. Relationship of ETS exposure to lung cancer risk

As active smoking causes lung cancer, and as ETS contains many of the carcinogens in tobacco smoke, one might expect there to be some increased risk from ETS exposure. However, exposure to smoke constituents from ETS is very much less than exposure from active smoking, with studies based on cotinine (the major metabolite of nicotine) suggesting relative exposure factors of order 0.06% [71]–0.4% [72]. For particulate matter, a series of studies conducted in different countries by Phillips et al., e.g. [73, 74], suggests a lower factor still, of about 0.005–0.02%. Given that the chemical compositions of ETS and of tobacco smoke are not identical, and given doubts about the shape of the dose response at low doses, it is not clear what increase in risk one might expect to be associated with ETS exposure. However, two things are evident. First, any increase in risk is likely to be quite low, if it exists at all, making it extremely difficult to detect reliably using epidemiological methods. Second, any increase in risk is only likely to be demonstrable in never smokers or in those with a smoking history that is very limited or ceased a long time ago [75].

Since the first publications in the early 1980s [76–79], reports of studies of ETS and lung cancer in never smokers have proliferated, and a recent meta-analysis [80] presented a systematic review of 102 studies. Except where noted, the conclusions reached are based on this review.

5.1. Relative risk by source of exposure

The early studies were mainly conducted in women, comparing risk in never smokers married to smokers and in never smokers married to non-smokers. There were good reasons for this: a much larger proportion of women than men had, at that time, never smoked; whether a spouse smoked or not could be determined quite reliably; and studies showed that cotinine levels in never smokers married to smokers were clearly (about three times) higher than in never smokers married to non-smokers [81]. However, over the years, evidence has been collected on a wide range of markers of ETS exposure, with some studies collecting extremely detailed histories of exposure.

Based on the meta-analyses [80] using random-effects estimates to account for the substantial between-study heterogeneity, significant ($p < 0.05$) positive associations were found with all the most commonly studied indices of exposure. The estimated *RRs* were 1.22 (95% CI 1.14–1.31) for smoking by the husband (or nearest equivalent exposure for which results were available), 1.14 (1.01–1.29) for smoking by the wife, 1.22 (1.15–1.30) for workplace exposure, 1.15 (1.02–1.29) for childhood exposure and 1.31 (1.10–1.45) for total exposure, each RR being based on a substantial number of studies. Based on very much less evidence no significant association was seen with ETS exposure in travel or in social situations, and interestingly a significant negative relationship was seen for ETS exposure in childhood specifically from the parents, with the relative risk of 0.78 (0.64–0.94). The *RR* for smoking by the husband could also be expressed as 1.10 (1.07–1.14) per 10 cigarettes smoked, using available dose-response data.

5.2. Factors affecting relative risk estimates

In order to study heterogeneity further the review [80] looked at the 119 relative risk estimates for smoking by the husband or wife (or nearest equivalent), where the overall estimate was 1.21 (95% CI 1.14–1.29), and found evidence that the largest relative risks were seen in small studies of fewer than 50 cases (1.47, 1.15–1.88), in the earliest studies, published before 1990 (1.38, 1.24–1.54), and in studies that did not adjust for age (1.42, 1.18–1.71). However, with one minor exception, some increase was seen in all the subgroups studied (which included location and study design).

There was also evidence of an increase, for spousal smoking, both for squamous cell carcinoma and adenocarcinoma.

5.3. Difficulties in interpreting the association

Whereas the RR for active smoking is large and cannot plausibly be attributed to bias or confounding, that for ETS exposure is substantially smaller, making a causal conclusion difficult to establish with any certainty. In the recent review [80], various potential sources of bias were discussed. Some sources were dismissed as being unlikely to be very relevant. These include publication bias, because large studies, which contribute most to the overall estimates, seem likely to publish their findings regardless of the results; recall bias, because the overall estimates varied little according to whether the study design was prospective (where recall bias is not an issue) or case-control (where it is), or according to diagnostic inaccuracy, because estimates were quite similar for studies that did or did not require full histological confirmation. Bias due to the reference group (never smokers married to never smokers) actually having some ETS exposure was considered, with comments made in the review [80] on the 'background correction' of Hackshaw et al. [81] aimed at converting an RR for marriage to a smoker to an RR expressed relative to never smokers with no ETS exposure at all. It was noted that this background correction only makes sense when the original association, with marriage to a smoker, derives from a causal relationship, and only applies to the *RRs* for marriage to a smoker, and does not affect the estimates of the increase in risk for amount smoked by the husband.

http://dx.doi.org/10.5772/67167

However, the review [80] did demonstrate clearly that confounding and misclassification of active smoking were extremely important issues which had a profound effect on the interpretation of the observed association of ETS exposure with lung cancer risk. The evidence that confounding may be a material issue derived from observations made some years ago [82, 83] strongly suggesting that, for a wide range of risk factors, exposure to the risk factor is higher in non-smokers exposed to ETS than in those not exposed to ETS. For some of these risk factors, available data are inadequate to provide any sort of reliable quantitative estimate of their relationship to lung cancer risk in non-smokers, but for four, increased dietary fat consumption, reduced fruit consumption, reduced vegetable consumption and fewer years of education, it was established that they were associated both with increased lung cancer risk and with increased ETS exposure in non-smokers. The review [80] found that adjustment for confounding reduced the *RR* for husband smoking from 1.219 (95% CI 1.138–1.305) to 1.139 (1.062–1.221), and for 10 cigs/day smoked by the husband from 1.102 (1.065–1.140) to 1.062 (1.027–1.099). Taking into account that adjustment is only for some risk factors, this illustrates the considerable potential for bias.

Bias from misclassification of active smoking arises partly because some current or former smokers are known to deny having smoked, so being wrongly described as never smokers [84, 85], and partly as smokers tend to marry smokers [75, 81]. Taken together, these two tendencies, if ignored, will bias the observed association of smoking by the husband to lung cancer risk in never smokers [81, 86, 87]. Based on what were regarded as reasonable estimates of the extent to which misclassification occurs and of the magnitude of the concordance between spouse's smoking habits it was found that correction for misclassification of smoking habits further reduced the confounder-adjusted estimates to 1.077 (0.999–1.162) for husband smoking and to 1.032 (0.994–1.071) for 10 cigs/day.

Given that adjustment for confounding and misclassification correction substantially weakens the association of lung cancer with the index of ETS exposure that is most usually considered (smoking by the husband) and renders it non-significant, and given that these adjustments and corrections may be incomplete, it seems that one cannot reliably conclude that any true causal effect of ETS exposure on lung cancer risk has been demonstrated. If there were any true relationship, it would certainly be much weaker than suggested by meta-analyses that do not adjust for confounding and misclassification.

6. Final comments

Some of the conclusions expressed here may disagree with those of other researchers. These include the risks of smoking being similar in men and women; the modest benefits of the switch to lower tar filter cigarettes; the inaccuracy of many diagnoses of lung cancer; the lack of evidence that cigarettes made from blended tobaccos (as used in the USA) are more harmful than cigarettes made from flue-cured tobacco (as used in the UK); the rise in the relative frequency of adenocarcinoma to squamous cell carcinoma (seen in never smokers, and affected by changes in diagnosis and classification) not being explained by changes in cigarettes; and the observed association of ETS exposure to lung cancer risk being to a large

extent due to bias and confounding. However, it should be emphasised that all the conclusions arrived at from a detailed and careful study of the evidence, including as far as possible all relevant papers that have been published on these subjects, with in some cases reference back to the raw data.

Acknowledgements

I thank Japan Tobacco International who supported my time in preparing their paper. I also thank them and the numerous other tobacco companies and organizations who have supported my work over the last 50 years. The late Dr. Francis Roe provided inspiration for much of my work. Particular thanks are also due to the staff of my company P.N. Lee Statistics and Computing Ltd. who have, over many years, made an invaluable contribution to my research. These include Barbara Forey, John Fry, Jan Hamling, Alison Thornton and Katharine Coombs who have all featured as co-authors in many of my papers, and Diana Morris, Pauline Wassell and Yvonne Cooper who typed my manuscripts and obtained relevant references.

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