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Passive Smoking and Cancer Risk: the Nature and Uses of Epidemiological Evidence

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The apparent effect of passive smoking on cancer risk has become an important social and political issue. For this reason alone the strength of the epidemiological evidence warrants close examination. The research published to date indicates a positive association of passive smoking with lung cancer, but there is no consistent evidence of associations with cancer at other sites. We have summarised the epidemiological evidence, and examined the major criticisms raised against these studies. These criticisms include alleged bias arising from misclassification of exposure to environmental tobacco smoke (ETS) or of personal smoking history, and from differential publication of positive findings. In their strongest form, these critiques challenge the ability of epidemiology to establish causation on any issue. We argue that epidemiology is not inherently different from other branches of science—in each of which scientific "proof" of cause and effect involves judgement based on measurement and logical inference. We also describe the application of epidemiological data to establishing proof, in courts of law, of the lung cancer risk of passive smoking.
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INTRODUCTION

THE CANCER risk of passive smoking is not a subject of mere scientific curiosity. The risk of cancer in non-smokers is often the main reason given for prohibiting or restricting smoking in public places. From an economic point of view, much hinges on such prohibitions or restrictions. An obvious example is the reduction in cigarette consumption that is likely to follow workplace smoking bans; Chapman *et al.* estimate that if half the white collar worksites in Australia were to ban smoking the Australian tobacco industry would lose sales of $6.5 million annually [1]. Because the stakes are so high, the issue of passive smoking and cancer also casts a spotlight on the scientific and legal assessment of risk, revealing different views on how cause and effect should be judged, and what constitutes "scientific proof".

Over the last 10 years passive smoking—or environmental tobacco smoke (ETS)—may well have been examined more closely than any other single environmental factor associated with cancer. Here we do not attempt to repeat the comprehensive reviews published by the US Surgeon General [2], the National Research Council [3], the Environmental Protection Agency (EPA) [4] and others. We have summarised the available evidence and concentrated on the interpretation of the results, including the application of epidemiological research to legal judgements about passive smoking and cancer.

EVIDENCE OF CANCER RISKS

Passive smoking and lung cancer

The evidence of an association between passive smoking and lung cancer comes principally from epidemiological studies. Counting the number of such studies reported in the scientific press entails chasing a moving target. The EPA's report in mid-1990 [4] documented 21 case-control studies and three cohort studies. One doctoral dissertation has since been published [5], and at least one further new study has been reported [6]. (This enumeration includes only papers published in English language journals.)

The case-control studies have generally been based on married women who report that they have never smoked, and the studies have predominantly used the smoking behaviour of the spouse as a surrogate measure of passive smoking. Otherwise the studies vary greatly in the questions used to obtain information on spouse's smoking, in the units of exposure, in the choice of controls, and in the methods of analysis. Detailed descriptions of the individual studies are given in the major reviews cited above. The findings of the case-control studies are summarised in Fig. 1, which shows the risk of lung cancer in "exposed" non-smokers relative to "non-exposed" non-smokers, with the studies ordered by size. Those studies in which the 95% confidence interval around the risk estimate did not include 1.0 (i.e. the statistically significant studies) are shown as solid circles. It can be seen that the risk estimates vary from 0.75 to 2.55, that this variability is most evident amongst the smaller studies, and that most (17/22) of the risk estimates exceed 1.0.

There have been three cohort studies of passive smoking and lung cancer published, from Japan [7], the USA [8] and Scotland [9]. The Japanese and American studies are well-known. Both were published in 1981, and were based on cohorts of hundreds of thousands of adults followed for 20 years or more. Both reported increases in lung cancer amongst non-smoking women married to smoking men. The increase in the American study was small (relative risk = 1.1 for women with husbands smoking 20 or more cigarettes per day compared with wives of non-smoking husbands) and not statistically significant. In the

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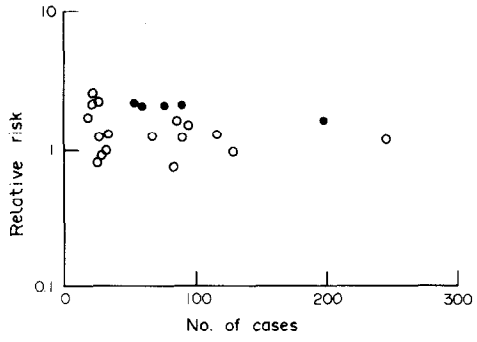

Fig. 1. Results of case-control studies of lung cancer and passive smoking. Relative risk shown on logarithmic scale, men and women combined. Where more than one exposure category recorded, relative risk for highest exposure group is shown. Relative risk estimates that are statistically significant ($P<0.05$) are shown as solid circles.

Japanese cohort, the relative risks of lung cancer in non-smoking wives were 1, 1.42, 1.58 and 1.91 when the husbands were non-smokers, or daily smokers of 1–14, 15–19 or 20 or more cigarettes per day. The Scottish study [9] was considerably smaller than the other two, including only 9 lung cancer deaths among non-smokers, and reported a rate ratio for lung cancer of 2.41 (95% CI 0.45–12.83) for persons with a partner who had ever smoked.

Passive smoking and other cancers in adults

Relatively little has been published on cancers other than lung cancer. Table 1 summarises the statistically significant ($P<0.05$) findings in the literature, and is an updated version of the table published in 1986 in the NRC Report [3]. Not shown are two recent ecological studies relating breast cancer amongst women to national measures of tobacco consumption [10,11]. Ecological studies of this particular relationship are unlikely to be persuasive, because of the problems of confounding by other lifestyle-related risk factors for breast cancer, and because of the difficulty in distinguishing the effects of active and passive smoking.

Passive smoking and childhood cancers

Much has been published on the subject of parental smoking and childhood cancer, but few studies have clearly distinguished passive smoking after birth from exposure *in utero*. Pershagen summarised the findings of six major studies on the effects of maternal smoking during pregnancy on childhood cancer [12]. Only one study reported a clear dose-response relation and a statistically significant increase in risk of cancer (all sites) [13]. Overall, there was no consistent pattern to indicate an underlying association; neither did this apply when the findings for the most common childhood cancer (leukaemia) were examined separately. Research on smoking in pregnancy and childhood cancer published since Pershagen's review has included both positive [14] and negative [15] findings.

Some studies have reported a stronger association of childhood cancer with paternal smoking than with maternal smoking [16, 17]. Sandler *et al.* also reported that cancer in adulthood was more strongly related to father's smoking than to maternal smoking history [18]. From this evidence it seems unlikely that childhood passive smoking strongly affects cancer risk, since smoking by the mother contributes much more to passive smoking in early years of life than does smoking by other adults [19]. Further evidence against a causal role of childhood passive smoking comes from the study by Stjernfeldt *et al.* [13] who reported that the association of maternal smoking and childhood leukaemia was strongest for smoking during the 5-year period before pregnancy, intermediate for smoking during pregnancy, and weakest for maternal smoking postnatally.

INTERPRETING THE EVIDENCE ABOUT CANCER RISKS

We intend to concentrate our attention on the evidence relating to lung cancer. It is still the case that relatively little is known about passive smoking and adult cancers other than lung cancer. Some of the cancers (for example, breast cancer) that have been linked to passive smoking in epidemiological studies are not known to be associated with active smoking. It may be that the carcinogenic action of passive smoking is different in kind to that of active smoking; however, there is no evidence at present that this is so. Passive smoking can therefore be presumed to increase the risk of cancers at non-lung sites related to active smoking more than at other sites. However, there is yet too little information from which to draw firm conclusions. If there is an association of parental smoking with childhood cancer, it is probably due to transplacental exposure to tobacco products rather than to postnatal passive smoking.

There may well have been more reviews of lung cancer and passive smoking published than there have been original papers.

Table 1. *Studies of passive smoking and cancers other than lung cancer with significantly increased risks* ($P<0.05$)

Author [ref.]	Study type	Tumour outcome	Relative risk	Comment
Hirayama, 1990 [54]	Cohort	Brain Nasal sinus Leukaemia Breast	4.78 3.29 2.04 1.73	Non-smoking wives with heavy smoking husbands vs. wives with non-smoking husbands
Miller, 1984 [55]	Case-control	All sites	1.4	
Fukuda, 1990 [56]	Case-control	Maxillary Sinus	1.4 5.7	1 smoker in house > 1 smoker
Sandler, 1985a [57] (exposure in early life)	Case-control	All sites Cervix Haematopoietic	1.5 1.7 2.4	Paternal smoking
Sandler, 1985b [58] (adult exposure)	Case-control	All sites Breast Cervix Endocrine	1.6 1.8 1.8 3.2	Smoking by spouse
Sandler, 1985c [59] (lifetime exposure)	Case-control	All sites Breast Cervix Leukaemia and lymphoma	2.6 3.3 3.4 6.8	≥ 3 household exposures to smoke
Slattery, 1989 [60] (recent exposure)	Case-control	Cervix	3.4	Non-smokers

Adjusted relative risks given where provided.

Nevertheless, there are a number of issues that commonly arise in these reviews, as presented recently by Fleiss and Gross [20].

Two important and inter-related questions are repeatedly raised. Does the epidemiological evidence establish that risk of cancer is increased following passive smoking? More fundamentally, can epidemiological research ever establish causation? Fleiss and Gross concentrate on the first of these questions, but also allude to the second. They point to many deficiencies in the epidemiological studies of passive smoking and lung cancer, and conclude that it is "questionable whether any of the epidemiological studies meets even minimal standards of [scientific] quality". Indeed, they imply that this lack of scientific quality is inherent in all observational (i.e. non-experimental) research since it is very unlikely that biases will ever be removed from epidemiological studies [20]. The standard of scientific quality that is applied—implicitly here, but explicitly in other reviews [21, 22]—is the double-blinded randomised controlled trial.

The deficiencies and limitations of observational research have been emphasised in many of the reviews of passive smoking. Fleiss and Gross list the major suspected sources of bias, including misclassification and publication bias [20]. They give examples of possible confounding (which they also label as "bias"). The dangers of unrecognised systematic error weigh heavily in their summing up, which states "given the biases that exist in each individual study, the safest conclusion is a negative one". However, their review includes no evidence that the biases actually exist, nor any exploration of what their effect might be on estimates of risk.

There is debate over the role of statistical significance in interpreting the passive smoking and lung cancer studies. Fleiss and Gross calculate an overall odds ratio of 1.12 (95% CI 0.95–1.30) based on US studies only [20]. Since the 95% confidence interval includes the null value of 1.0, they conclude that "there is no convincing scientific evidence from the epidemiologic literature of an association between exposure to ETS and risk of lung cancer in the United States".

An important issue not discussed by Fleiss and Gross is whether regard should be given to scientific considerations other than statistical confidence intervals—such as the biological and toxicological evidence on passive smoking. Another source of contention only alluded to by Fleiss and Gross, although developed fully elsewhere [23, 24], is the comparison of epidemiological estimates of lung cancer risk associated with passive smoking with the risks (generally much lower) that are calculated by extrapolating from the lung cancer risks of active smoking, based on a standardised measure of exposure.

We examine these issues in more detail below.

ISSUES ARISING

Statistical "significance"

Some published critiques of the epidemiological literature [25–27] display a preoccupation with tests of statistical significance as the arbiter of whether an association exists. A piecemeal approach to the literature, examining the statistical significance of each individual study, is inappropriate for two reasons.

Firstly, in all comparative quantitative research, a test of statistical significance is just one guide to the interpretation of the research results. The $P<0.05$ criterion of "significance" is a convention—albeit a widely accepted one—which has no absolute meaning in itself.

Secondly—and more importantly—when the relationship at issue is likely to involve small increases in risk (e.g. relative risks less than 1.5) then it is quite probable that any one study, conducted within one location and with access to only a limited number of study subjects, will have inadequate statistical power. In such circumstances—and the study of passive smoking is an obvious example—epidemiologists recognise that drawing inferences about causality requires examination of the pattern of results from a large number of studies. Indeed, a more formal approach to this situation is to use meta-analysis, which produces a statistically more robust summary estimate based on weighted averaging of study-specific results.

Meta-analysis is itself only a guide to judgement since, especially in epidemiology, assumptions must often be made regarding the comparability of measurements of exposure, selection of study participants, and other important aspects of study design [28]. As well as taking into account the overall pattern of point estimates, epidemiologists should take into account the evidence of dose-response relationships, the biological plausibility of the findings, and the degree of corroborative support from other scientific disciplines.

Extrapolation of dose-response relationship

The qualitative composition of ETS mirrors that of actively-inhaled smoke [2]. Therefore, it is a reasonable presumption that the risk of lung cancer is of the order that would be estimated by backwards extrapolation of the dose-response data for active smoking to the level of active smoking equivalence represented by average exposure to ETS.

However, there are three methodological problems. Firstly, the specific components of cigarette smoke that cause lung cancer remain unidentified. Secondly, the dimensions of exposure that determine the risk are uncertain—and probably complex. They seem likely to include age at first exposure, duration of exposure and rate of exposure. Further, these various dimensions may act differentially at different stages of carcinogenesis [29]. Thirdly, there is the practical problem of validly measuring exposure to ETS in non-smokers. Interviews can only provide an indirect measure of exposure.

Alternatively, biological measures can be made of metabolites—particularly cotinine—that derive from inhaled ETS. However, to have quantitative validity such metabolites must have a known, constant relationship to the components of cigarette smoke that account for the risk of cancer. It is not known what relation cotinine levels in various body fluids have to concentrations of carcinogens in the lung, and this relation is almost certainly not constant; due, at least, to the variables that influence the metabolism of nicotine [30].

There are also differences between the exposures from passive and active smoking that may be important. Sidestream smoke is produced at lower temperatures than mainstream smoke, and consequently in undiluted form it contains higher concentrations of many respiratory irritants and potential carcinogens [2]. The dose of smoke products received by the passive smoker will depend on the "age" of the smoke. Passive smoking ranges from the "direct" exposure that Hirayama [31] suggests may be especially risky (breathing within 1.5 metres of a burning cigarette) to inhalation of smoke that has settled and "aged" so that only the gaseous constituents remain. In mainstream smoke, nicotine is present on the surface of smoke particles, but evaporates with aging of the smoke [32], hence blood and saliva measures of nicotine and metabolites in passive smokers may over-represent exposure to particle phase smoke compounds, relative to active smokers. Passive smokers chiefly take in smoke

through the nose, with shallow inhalation; active smokers take in smoke through the mouth and typically inhale deeply.

These differences complicate the dosimetric approach to risk assessment. Extrapolation from the dose-response relationship of active smoking and lung cancer sheds some light on the possible effects of passive smoking, but it does not constitute a definitive assessment.

Misclassification bias and confounding

As in all epidemiological studies—indeed all comparative studies—the use of imperfect classification procedures that affect equally each of the compared groups of subjects introduces a conservative bias in the estimation of the strength of the relationship between exposure and disease outcome [33]. Thus, in both cohort and case-control studies the random misclassification of either the exposure variable or of the disease outcome leads to a point estimate that is biased towards the null value.

The most practically important source of misclassification of individuals in studies of passive smoking and cancer is the inadvertent inclusion of active smokers or ex-smokers in studies that are intended to be restricted to lifelong non-smokers. In their meta-analysis of epidemiological studies reported to 1986, Wald *et al.* made a careful attempt to take account of "bias" from this source [34]. Lee, however, has concluded that there is a real likelihood that the observed increases in risk of lung cancer reported in those various studies could be attributable to "bias due to misclassification of smoking habits" [35].

It is important to examine this methodological issue critically. In particular, the word "bias" has been used freely by various commentators to encompass all circumstances in which the observed value (i.e. the estimate) of risk tends systematically to differ from the true value of that risk. A biased estimate may result from two distinct sources: (1) biased procedures in the selection and classification of study subjects such that the relationship between exposure and disease is misrepresented, or (2) uncontrolled confounding in which the coexistent effect of some other risk factor causes a spurious increase or decrease in the risk attributed to the risk factor (exposure) of interest.

Active smoking is a very potent cause of lung cancer, and many other cancers, and displays clearcut monotonic dose-response relationships [34]. If the distribution of active smoking is statistically independent of passive smoking within any study population of individuals, the presence of active smokers, by elevating the average background risk of study subjects, will reduce the statistical power of the study to detect an effect of ETS. (We assume here that the effects of the two exposures are additive or, at least, less than multiplicative.) For this basic reason, epidemiologists have preferred to confine their studies of the effects of passive smoking to groups of lifelong non-smokers.

However, it is not easy to preclude all current smokers or ex-smokers from such a study. Ineligible persons (i.e. unidentified smokers) inadvertently included in the study will carry a substantively increased risk of cancer as a result of their own active smoking. If such persons are evenly distributed between the groups to be compared in a cohort study, or are distributed independently of husband's smoking habit in a case-control study, their presence necessarily leads to an underestimation of the true relative risk attributable to passive smoking. This represents a particular form of misclassification bias, arising not from the usual source of bias in epidemiological research—that is, defects in the sampling or classification of otherwise eligible individuals—but from the inadvertent inclusion of ineligible individuals.

In reality, unidentified smokers in the study population may have a different profile of spouse smoking from that of the true lifelong non-smokers. Indeed, there is a likelihood of overestimation of the true effect of passive smoking because of the widely-reported tendency of smokers to marry smokers and of non-smokers to marry non-smokers. Note that this tendency to spouse concordance for smoking habit introduces confounding to the study. That is, within the study population the exposure of interest (spouse's smoking status) is associated with another risk factor (study subject's smoking status) which itself is strongly predictive of the outcome of interest (cancer).

It follows that the potential for such confounding, other things being equal, is in proportion to the prevalence of smoking among women in the population from which the study population of non-smoking women is being recruited. If a very small proportion of women smoke—as was the case within the Greek and Japanese populations that were the settings for the first two reported studies of passive smoking and lung cancer [7, 37]—then confounding from this source will be much less than in, say, a Western population where the prevalence of women in the general population who are smokers is 25–40%.

Lee has argued, using illustrative data relevant to high-prevalence populations, that positive confounding between spouse smoking and subject smoking, in accord with the reported levels of assortative mating between smokers and non-smokers, could account for apparent increases in relative risk of the order of 1.5 [35]. However, by the same arithmetic, it can be shown that the effect of any such positive confounding in low-prevalence populations would be much smaller, and even negligible. Indeed, it might be argued that in such populations women would have enjoyed less freedom to select their prospective husband on the basis of his smoking habit than is the case in higher-prevalence Western populations. Lee, however, suggests that in countries such as Japan and Greece the cultural pressure on women smokers to report themselves as non-smokers to an interviewer might augment their misclassification [35].

Wald and colleagues [34] estimated a considerably lower confounding effect from inadvertent inclusion of smokers than did Lee [35]. They estimated that an observed value of 1.35 (the value obtained from their unadjusted meta-analysis) might result from bias to an underlying true value of 1.30.

This remains an important methodological issue in relation to studies of passive smoking and cancer. Since the inadvertent inclusion of smokers in an intended study population of non-smokers is virtually unavoidable it is relevant to seek direct empirical evidence, using biological markers, of such faulty recruitment of study subjects.

There have been a number of studies of the relationship of self-reported smoking habits to various biological indicators, and these are reviewed elsewhere [35]. A recent multicentre study, conducted in 13 centres in 10 countries and coordinated by the IARC [38], was conducted explicitly to elucidate this methodological issue in studies of ETS and cancer risk. The study estimated the prevalence of unidentified smokers in study populations of ostensible (self-reported) non-smokers on the basis of urinary cotinine measurements. That study found a very high correlation between self-reported smoking habits and urinary cotinine, indicating that 2–3% of "non-smokers" were actually likely to be smokers.

Publication bias

Since the most persuasive epidemiological evidence on passive smoking and cancer is the outcome of pooled analysis or meta-analysis, publication bias is an important consideration. Pooled or meta-analyses reduce error due to random variability, but if these analyses are based on published data, as they generally are, then they remain vulnerable to any systematic tendency to favour submission and publication of papers that report the presence of an association between passive smoking and cancer. Such a bias has been shown to exist in other areas of medical research [39].

There are two means of investigating publication bias—examination of patterns in the published data, and comparison of published and unpublished results.

Vandenbroucke applied the technique of funnel plots to the published findings on passive smoking and lung cancer in search of empirical evidence of publication bias [40]. With this technique, risk estimates are plotted against a measure of study size. In the absence of publication bias, the risk estimates should be symmetrically distributed around the true value, with decreasing variability as study size increases (hence the "funnel"). If there is a tendency to suppress papers that report no association, the pattern should be asymmetric, with the most notable gap occurring in the small study/negative result quadrant of the plot. Vandenbroucke concluded that there was no evidence of such a deficiency in the published results for women, but that there were some signs of a bias operating in the much smaller number of studies of men.

Vandenbroucke included only those studies published up to 1986. When more recent studies of passive smoking and lung cancer are added, there is still no obvious deficiency in the pattern of results (Fig. 1).

Publication bias may operate most strongly with the first papers that are written on a particular topic, the so-called "pipeline effect" [41]. In other words, positive findings may be more publishable initially, but if interest in the topic remains high, well-conducted negative studies subsequently become just as attractive to publish as papers with positive findings. Indeed, it has been suggested that journals are now so sensitive to the danger of false positive papers that there may be "a preference for publishing findings which refute a previous claim, rather than confirmatory results" [42]. In the instance of passive smoking and lung cancer, there is no evidence that positive findings were reported more commonly in the early years of publications. In fact the tendency is the reverse: between 1981 and 1984, 3 out of 6 published studies reported a relative risk of more than 1; from 1985 to 1991 14 out of 16 published studies did so. In the presence of a "pipeline effect", one would expect the risk estimates obtained from pooled analyses to diminish as more studies were published. There is no evidence that this is occurring with passive smoking and lung cancer. In 1986 Wald *et al.* calculated a relative risk of 1.35, based on 13 studies [34]. In 1990 the EPA, following a similar methodology, calculated a pooled relative risk of 1.41, based on 22 studies [4].

There is no readily available source of information on unpublished studies of passive smoking and cancer. In response to Vandenbroucke [40], Wells presented unpublished data on passive smoking and lung cancer in men that he had obtained by personal contacts with investigators [43]. The risk estimates derived from the unpublished data were greater than most of those calculated from the published data. The numbers of men were small, but this is evidence against a publication bias.

To obtain further information, we wrote to 22 persons listed in the Directory of Ongoing Research in Cancer Epidemiology in 1986 [44] and 1987 [45] who reported that they were researching cancer risks of passive smoking. We asked these persons whether they had findings from their research that had either not been submitted for publication, or had been submitted but not published. We asked also whether they had any personal experience of a bias favouring publication of positive papers. Replies were received from 14 researchers; two researchers were not contactable since they had moved and left no forwarding address.

The respondents all reported that they had no personal experience of a publication bias in the area of passive smoking and cancer. One respondent provided the results of a negative study of passive smoking and bladder cancer that had not been submitted for publication. Otherwise, there were no reports of research that had been completed but not published.

We wrote also to the Tobacco Institute of Australia, on the assumption that if anyone were to know of unpublished research showing no association of passive smoking and cancer then it should be the public relations arm of the tobacco industry. We received in reply a copy of the unpublished thesis of Varela [46]. This is not strong evidence of the suppression of negative results, since the delay in publication from Varela's thesis was due to the death of the author, and the results have subsequently been presented by others [5]. We conclude it is most unlikely that publication bias explains the predominance of positive findings amongst the published research papers on passive smoking and lung cancer.

"Scientific proof"—scientists and policy-makers

The causal process *per se* can never be observed. Causality must therefore be inferred (induced) from the juxtaposition of events—the putative antecedent "cause" and its "consequence"—observed in satisfactory, interpretable, circumstances. Since the time of David Hume, the sixteenth century British philosopher, the limits of inductive logic have been recognised [47]. Absolute "proof" of causation cannot be attained by scientific research. This applies to all scientific research—whether experimental or observational, laboratory-based or epidemiological.

Popper's amelioration of this seeming logical dilemma for science has been to point out that scientific research proceeds not by "proving" but by "disproving" [48]. An hypothesis of causality is sustained when there is sufficient supportive evidence and when potential alternative hypotheses (i.e. alternative explanations of the observed data) can be refuted.

The question then arises as to what constitutes sufficient evidence. This is a matter of judgement; there is no simple criterion of sufficiency.

In relation to the causation of human disease, a secondary question is: "sufficient evidence for what?" The argument is sometimes made that scientific proof is of a higher order than proof for purposes of public health policy-making. This turns upon the view that scientists are seeking "truth" and, properly, they adopt a position of conservative scepticism. In contrast, on this same view, policy-makers are expected to promote and protect the public's health and therefore to recommend action when there is a reasonable likelihood that the available evidence indicates a causal relationship [49].

In practice, there is no explicit or formally recognised difference between the approach of the scientist and that of the public health practitioner. The approach of either also varies as a function of context. Both types of professional must judge where, along a continuum of increasing certainty, the cumulative

body of evidence currently lies. This they necessarily do without either quantitative precision or reference to an agreed benchmark of "sufficiency".

LEGAL TESTS OF PROOF OF CANCER RISKS

While within the arenas of science and policy-making the criteria of causality are intrinsically inexact and are subject to professional judgement, within the legal context there is a need for a more formalised approach. Judgements in courts of law often require decisions within a binary mode to determine who "wins" and who "loses".

Two recent legal cases in Australia illustrate the approach of the judiciary to the question of passive smoking as a cause of human disease, and of cancer in particular. Both cases have been at the forefront, internationally, of the legal exploration of these tissue.

In July 1988, Sean Carroll, an ex-bus driver and long-time employee of the public transport authority in Victoria, Australia, sought compensation for lung cancer that he claimed was due to his long-term occupational exposure to ETS. To win the case, it was necessary for Carroll to establish that there was a greater than 50% probability (i.e. "on the balance of probabilities") that his cancer was attributable to that exposure.

Three factors strengthened Carroll's claim. Firstly, his lung cancer had been cytologically diagnosed as small cell (oat cell) carcinoma—i.e. a type of lung cancer with a particularly strong association with active cigarette smoking [36] and, where results have been reported by histological type, with passive smoking [6,50, 51]. Secondly, occupational exposures typically entail higher levels of ETS than do domestic exposures [2]. Further, Carroll and his family were self-reported lifelong non-smokers. Thirdly, both anecdotal evidence and reasonable deduction indicated that occupational exposure to ETS was relatively high within Carroll's particular occupational environment; corroboration for this came from comparative data for ETS levels in different categories of occupational environments in the USA [2]. Evidence given in court by an expert witness estimated that the confluence of these factors would have resulted in Carroll having had a 4-fold increase in risk of developing small cell carcinoma relative to his risk had he not been occupationally exposed to ETS. This estimate entailed taking a baseline average relative risk of ETS-induced lung cancer in lifelong non-smokers of 1.4 [34] and multiplying it up, in compounding fashion, in accordance with the epidemiological and environmental data pertaining to the three factors mentioned above. An estimated relative risk of approximately 4.0 results. Since three of the four "units" of risk—i.e. the excess relative risk—are attributable to ETS, the estimation indicated an approximately three in four, or 75%, probability that Carroll's lung cancer was due to ETS.

Immediately after the presentation of that evidence the case was settled out of court, at the instigation of the defendant. Carroll was paid both compensation and damages. He died in January 1991.

The second court case resulted from a claim by the Australian Federation of Consumer Organisations (AFCO) that a statement published by the Tobacco Institute of Australia (TIA) that "there is little evidence, and nothing which proves scientifically, that cigarette smoke causes disease in non-smokers" was false and misleading, and therefore in breach of Trade Practices legislation. This statement was part of an advertisement published in capital city daily newspapers in Australia on 1 July 1986.

The case was conducted in the Federal Court of Australia during 1989 and 1990, and was heard by a judge, Mr Justice Morling. The case focused primarily upon evidence given by various "expert witnesses" called by either side—and included an extramural hearing in London involving British and American epidemiologists. The case culminated in a judgement that included the statement that "there is compelling scientific evidence that passive smoking does indeed cause lung cancer" (AFCO vs. TIA, 1991, p.139) [52].

The significance of this case was that it produced the first legal judgement anywhere in the world in relation to the totality of the scientific evidence pertaining to the effects of ETS upon human health.

Because of the nature of the proceedings brought under Section 52 of the Commonwealth Trade Practices Act (1974), for an injunction and not for criminal penalties, the burden of proof was—as in the Carroll case—"on the balance of probabilities". That is, the plaintiff (AFCO) had to establish that, on the balance of probabilities, there was more than a little evidence and/or the evidence did prove scientifically that passive smoking causes disease in non-smokers. However, the court was also required to consider how the part of the advertisement complained of might be interpreted, in order to determine whether it was misleading or deceptive. Accordingly, the judge formulated the following test:

> "I think that in the context of the advertisement, the words 'nothing which proves scientifically that cigarette smoke causes disease in non-smokers' mean 'nothing which affords compelling or convincing evidence that cigarette smoke causes disease in non-smokers'. This is the meaning which I think most readers would give to the words." (AFCO vs. TIA, 1991, p. 15.)

A review of the judgement indicates that Mr. Justice Morling accepted the primary argument that the interpretability of the epidemiological evidence depended in particular upon the pattern of findings across studies, and on its coherence with the substantial evidence from studies of active smoking and cancer and from corroborative animal experimental and other bioassay studies—and did not depend on the compilation of a scorecard of statistical significance tests in a series of individual studies.

CONCLUSION

The weight of the epidemiological evidence indicates that lung cancer is associated with passive smoking, and, in our view, the association is most probably causal. There are nevertheless limitations in the information that is available. How might researchers obtain better evidence about the cancer risk of passive smoking?

It may be helpful to reflect on the research concerned with active smoking that has been especially influential on scientists and policy-makers. Perhaps the most compelling evidence of the harmful effect of smoking cigarettes was the consistent decline in the excess risk of cancer that followed cessation of smoking. The equivalent evidence for passive smoking would be the relative risk of lung cancer amongst spouses of ex-smokers, stratified by time since the spouse last smoked. Such an analysis would require large numbers of cases to fill the various age/duration of exposure strata. Hirayama [37] reported the risk of lung cancer for wives of ex-smokers was intermediate between the risks of wives of never-smokers and the wives of

current smokers, but showed no breakdown of risk by duration of spouse's cessation of smoking.

Better evidence will be provided by studies that incorporate more sophisticated measures of passive smoking than the relatively crude questionnaire assessments that have been used so far. Better measures of exposure should lead to risk estimates that are less subject to bias, and provide more detailed information on the dose-response relation of passive smoking to cancer risk. Such dose-response information has been important evidence in support of cancer caused by active smoking. In relation to lung cancer, significant advances in the measurement of exposure may come from the development of personal monitors [53]. Such monitors are likely to provide a more direct assessment of the respiratory impact of passive smoking than do metabolite studies.

The findings of conventional epidemiological studies on their own seem unlikely to complete the picture. Advances in molecular epidemiology may enable the identification of similar genetic effects (for example, oncogene activation or suppressor gene deletion) amongst active and passive smokers. Similarly, the conclusions of epidemiological studies would be strengthened if there was supporting evidence available from biological studies based on animal models or cell cultures showing, for example, common mechanisms of action of active and passive smoking in the pathogenesis of cancer.

The search for better and more precise estimations of the cancer risk of passive smoking should provide a stimulus to the further development and incorporation of interdisciplinary strategies in epidemiological research.

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Meeting Report: Long-term Antihormonal Therapy for Breast Cancer

Alberto Costa and V. Craig Jordan

TAMOXIFEN IS a non-steroidal anti-oestrogen that is available to treat selected patients with all stages of breast cancer [1]. Early laboratory studies demonstrated [2] that long treatment schedules might be an appropriate strategy to use as adjuvant therapy following mastectomy in node-positive and node-negative disease. Clinical trials organisations have focussed on long-term tamoxifen therapy which has become an important part of the therapeutic armamentarium to prevent the recurrence of breast cancer following mastectomy.

During a 3-day international meeting (Chairman, V.C. Jordan) in Orlando, Florida (29 June–2 July 1991), the University of Wisconsin Comprehensive Cancer Center (Director, P.P. Carbone) hosted a review of progress to evaluate the efficacy and safety of tamoxifen therapy. The goal of the conference was also to discuss possible mechanisms of drug resistance to tamoxifen that have been identified in the laboratory and to consider the prospects for new breast cancer treatment strategies.

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EFFICACY OF TAMOXIFEN

Paul Carbone noted that the concept of extended (5+ years) adjuvant tamoxifen therapy was piloted at Wisconsin as a direct result of the early laboratory data [2]. The studies that demonstrated the effectiveness of long-term tamoxifen therapy in preventing rat mammary carcinogenesis were first presented at a meeting in Cambridge, UK in 1977. The laboratory and clinical results [3] provided the information to establish ECOG trials of chemotherapy and different durations of tamoxifen therapy (1, 5 or indefinite years) in both premenopausal and postmenopausal patients. At present early analysis of ECOG trials demonstrate an increase in disease-free survival for patients receiving at least 5 years tamoxifen (10 mg twice daily) (D.C. Tormey, Madison). Oestrogen receptor (ER) positive disease is more likely to respond to tamoxifen in ECOG studies and in the Stockholm trial of adjuvant tamoxifen (2 or 5 years) the presence of the ER was a prerequisite for a response to tamoxifen (L. Rutqvist, Stockholm). In contrast, tamoxifen was noted to be efficacious in ER-poor patients from both CRC (M. Baum,