Assessment of risk from active and passive smoking, with particular reference to the epidemiological evidence

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1. Introduction

Many claims of possible health effects of active and passive smoking are made in the scientific literature and in the media. This document is intended to assist the lay reader in gaining a better understanding of the strengths and weaknesses of such claims. It is divided into 8 main sections;

2. Types of epidemiological study
3. Quantification of risk
4. Problems of causal inference
5. Types of bias and error
6. Some major sources of epidemiological data on smoking and health
7. Risks of smoking
8. Risks of ETS exposure.
9. Effects in pregnancy, infancy and childhood

Thus sections 2 and 3 describe techniques used, 4 and 5 processes by which conclusions are reached, and 6, 7, 8 and 9 look at the evidence itself.

Attention is primarily given to epidemiological evidence, i.e. studies of the relationship between disease and exposure in humans, because this is the evidence on which estimates of risk are based. Some reference is, however, made in sections 4, 7 and 8 to evidence of other sorts, e.g. from animal and chemical studies.

2. Types of epidemiological study

Epidemiological studies fall into two main classifications, observational studies and experimental studies. The essential distinguishing feature of experimental studies is that they involve some action, manipulation or intervention on the part of the investigators, that is something is done to at least some of the study subjects. In observational studies, on the other hand, investigators take no action other than to simply observe the situation.

The most useful types of observational study collect information on exposure and on risk of disease in the individuals. There are three main types:

a) Prospective (forward-looking) studies in which a sample of the healthy living population is interviewed to determine smoking habits, ETS exposure and other relevant risk factors and is then followed up for a period to see which subjects die from specified causes of death, contract certain diseases, or show an increase in symptoms or clinical signs seen initially. In this type of study, subjects may be re-interviewed at intervals to obtain updated information on risk factors, symptom prevalence, etc. Note that prospective studies (or cohort studies as they are often termed) are called prospective because they look forward to onset of the disease. They may (and in fact should for smoking studies) collect information on past exposure to risk factors.

b) Retrospective (backward-looking) studies in which details of smoking habits, ETS exposure and other associated factors are obtained for "cases" who have died or are suffering from certain smoking-related diseases and compared with those obtained for "control" groups not suffering from these diseases. Control groups can either be a random sample of the living population or can be people who have died or are suffering from certain diseases assumed to be unrelated to the risk factor under investigation (and who therefore should be representative of the living population in this respect). Retrospective studies (or case-control studies as they are often termed) are called retrospective because they look backwards from the disease to its potential cause.

c) Cross-sectional studies, in which information on smoking habits, ETS exposure and prevalence of disease is recorded at one point in time on a sample of the living population.

A fourth type of observational study, the case report, is really a type of retrospective study that is not properly controlled. Here a doctor might report a number of patients with a disease all having being exposed to a particular risk factor, without explicitly measuring the frequency of the risk factor in the population at large (though implicitly assuming it is substantially lower). Where the disease is rare and the risk factor unusual, a short paper might even describe a single case.

In some circumstances it may also be possible to carry out observational studies of groups rather than individuals. If, for

example, data are available on sales of cigarettes and on death rate from lung cancer, in each of a number of different regions of the country, a number of different countries, or in a particular region or country at a number of different time points, it may be possible to relate the two together by statistical analysis without the necessity for interviews or questionnaires at all. Such studies are sometimes referred to as ecological correlation studies.

Experimental studies are always of the prospective type inasmuch as the investigator must take his action first and study the consequences later. The traditional way of defining the treated and control groups is to identify one large group of all study subjects and then divide them randomly into two (or more) groups. (One can also randomize at the group rather than at the individual level in some situations.) The randomization ensures that the groups being compared differ systematically only in respect of treatment, so that any differences seen in frequency of disease between the groups cannot be explained by other risk factors. It is this ability to make the comparison of exposed and non-exposed individuals unbiassed by differences in other risk factors that gives experimental studies their great advantage, and explains why they are used (e.g. in randomized clinical trials of new drugs) whenever it is practical to do so. The problem of course is that in the context of smoking or passive smoking, such studies are usually not practical. One cannot insist that people smoke or not smoke for a lifetime, and the few applications of experimental studies in the smoking and health literature relate mainly to studies of the effect of advice to give up smoking, which are far less powerful at

detecting a true effect because many people ignore the advice (and because the advice may seep through indirectly to the group not supposed to receive it).

Most smoking and health studies are observational by nature, and it is worth commenting briefly on the advantages and disadvantages of the different types of observational studies in the context of smoking and passive smoking.

Of the five types mentioned, case reports and cross-sectional studies are of least importance. Case reports are often the reason for starting an investigation (e.g. Consultant X notes that all [or none] of his patients with disease Y smoke) but are rarely cited as direct evidence, while cross-sectional studies are really only applicable to study of easily measured non-fatal diseases (e.g. correlation of cough or wheezing with smoking), and are not relevant to fatal diseases to which most interest is usually given.

Ecological correlation studies are quite often conducted, but are usually regarded as providing evidence that is of much less value then prospective or case-control studies. We have all heard the numerous examples of spurious inferences from such studies, especially when trends over time are considered (e.g. rise in birth rate over a period when the stork population increased). The particular problems with such studies in the smoking and health situation is that one has no direct evidence as to whether the people dying of the disease of interest actually are smoking or not, that one very often has no relevant information on other risk factors of interest, and that correlation between incidence of

disease and frequency of smoking at the same time may be irrelevant to testing a theory as to whether risk relates to lifetime exposure to smoking.

Prospective and case-control studies are by far the most important sources of data on risks from active and passive smoking. Case-control studies are in fact more commonly conducted than prospective studies for four main reasons: they produce results more quickly, they are cheaper because they involve the collection of risk factor data on far fewer people (particularly where the disease is rare), they can often be conveniently conducted in a hospital, and because in many countries there is no easy method of determining easily whether people have died or from what, thus rendering prospective studies difficult to carry out. (In Scandinavia and in the UK one can automatically track down via computer systems who has died, but this is not so in all countries). Nevertheless prospective studies have a number of theoretical advantages which renders their results generally more reliable then those from case-control studies. The problems of inference from case-control studies will be discussed in more detail in sections 4 and 5. For the moment, it is worth mentioning a few of these problems: the difficulty of choosing an appropriate control group, the reliance on recall of past exposure to risk factors, and the possibility that presence of the disease might have affected one's habits or how they are reported. There is no doubt that results from prospective studies are of particular importance in assessing the risks from active and passive smoking.

3. Quantification of risk

Risk is the probability of an adverse event happening to an individual on a defined occasion. Suppose I am told that the risk of a fatal accident per ride on a motor-cycle is 1 in 5,000 what does this tell me? There are various points to be made.

Firstly, if the risk remains constant at 1 in 5,000 per ride then one should be able to predict with reasonable accuracy the number of deaths occurring as a result of a large number of rides. For example after 500,000 rides, while one would be surprised to see exactly 100 deaths, one would not expect, from statistical considerations, much over 120 deaths or much under 80 deaths. An insurance company paying out £5,000 per death and insuring a very large number of motorcyclists would not need to take in much over £1 a ride to ensure a profit in the long-term.

Secondly, while the information is highly relevant on a large sample basis and of value to insurance companies, it is less directly relevant to individuals. Some may be unlucky after 10 rides, others may survive 10,000. The information is of itself no use in telling an individual which accident will be the fatal one - the risk remains at 1 in 5,000 (all other things equal) for each trip, regardless of whether one has had 4,999 successful trips beforehand. It may, however, help individuals to decide which of alternative actions to take. If the risk for a ride in a car is 1 in 100,000, for example, many would prefer to go by car on this basis, though other considerations come into it, such as enjoyment

of feeling of speed, likelihood of getting into traffic jams, cost, comfort, etc.

Thirdly, an estimate of risk is only relevant to the amount of knowledge assumed about the prevailing circumstances. If one actually knew all the facts about each trip one might, in theory at least, be able to determine which trip might be fatal and which not. Certainly, one can easily determine circumstances which affect risk (weather, traffic, speed, experience of the driver, state of repair of the motor-cycle, etc.) This may not affect the insurance company's position, if the risk estimate is applicable to the average situation, but is highly relevant to the individual. In some situations, probably not the case with motor-cycling, some individuals may actually not be at risk (e.g. a disease which is genetically determined).

In the smoking and health context, one is normally concerned with chronic diseases, such as cancer or heart disease, or risk of overall mortality. Two important considerations come into play.

Firstly, risk is usually expressed per unit of time, usually a year. Partly this is because data on lifetime risk are not often directly available, but more so because lifetime risk is not particularly informative - after all we all die.

Secondly, risk is related to the age of the individual. For many chronic diseases, annual risk rises markedly by age, so it is of little value to know the risk of a group without knowing its age. Sometimes one presents risk for a specific age-group, as an age-specific rate, e.g. the lung cancer rate for French men aged 55-64 is 180 per 100,000 per year. Sometimes, if one wants to

present a rate for the whole age range, one presents an age-standardised rate. One common method is to take a population with a standard age distribution and then compute what the overall rate would be if the population under study had this standard distribution. This technique, known as direct standardisation, can be used to compare mortality rates of different countries when rates are standardised to that of the world population. A second method, known as indirect standardisation, divides the number of deaths that occurred in the population of interest by the number that would have occurred if the population had the age-specific rates of a standard population. This ratio, multiplied by 100, is known as the standardised mortality ratio (SMR). It is a standard technique used to compare risk in different occupational groups. With 100 the risk for all men aged 20-64, the lung cancer risk of medical practitioners in 1981 was 25 and that of tobacco workers was 157.

A fundamental difference between prospective and case-control studies, is that the former, but not the latter, can provide estimates of absolute risk. Case-control studies draw samples of cases and of controls but typically do not collect information on the total numbers of cases and controls from which the samples are drawn. However both types of study allow estimation of the relative risk of groups being compared. It is clear for prospective studies one can calculate relative risk - one just computes risk estimates for each group and divides one by the other. It is less clear how one can calculate relative risk in case-control studies. How this is done is shown in the next paragraphs.

Consider a population consisting of n_1 unexposed individuals and n_2 exposed individuals of a given age, and suppose that in a short period of time there are d_1 deaths in the unexposed individuals and d_2 deaths in the exposed individuals. In the prospective study situation, one estimates relative risk by

$$R = \frac{d_2/n_2}{d_1/n_1}$$

One can see that this expression can be rewritten as

$$R = \frac{d_2/d_1}{n_2/n_1}$$

d_2/d_1 can be estimated from the relative frequency of exposed and unexposed in the cases, and n_2/n_1 from the relative frequency of exposed and unexposed in the controls. (Strictly the latter relative frequency is actually an estimate of $(n_2-d_2)/(n_1-d_1)$ but provided deaths are only a small fraction of the population, the difference is trivial.) Often results from case-control studies are displayed in a form such as

	Cases	Controls
Non-smokers	40	70
Smokers	60	30

Here since the above expression can be written

$$R = \frac{d_2 n_1}{d_1 n_2}$$

it is often convenient to estimate risk by the cross-product ratio here giving

$$R = \frac{60 \times 70}{40 \times 30} = 3.5$$

Various techniques are available for estimating age-standardised or age-adjusted relative risks, described in standard

statistical text books. A value of 3.5 would indicate that, all other things being equal, someone in the exposed group would have 3.5 times the risk of dying from the disease of interest in the next year as someone of the same age in the unexposed group. Three general comments should be made about such estimates:

a) They are subject to sampling error. It is common not only to present an estimate of relative risk, but also its 95% confidence limits, e.g. RR = 3.5 (95% CL = 1.75 to 7.0). This means that we can be 95% certain the true relative risk lies somewhere between 1.75 and 7.0.

b) Where they are age-adjusted, they are essentially some sort of average of individual relative risk estimates made at each age. They do not necessarily imply the relative risk at each age is the same. It may be that young exposed individuals have 5 times the risk of young non-exposed individuals, but old exposed individuals have only 2 times the risk of old non-exposed individuals.

c) An unstandardised or age-adjusted relative risk does not take into account the possibility of "confounding" by other risk factors. Individuals exposed to the factor of interest may be more (or less) exposed to other risk factors. If information is available on other risk factors it may be possible to adjust relative risk estimates for these, similarly to the way one adjusts relative risk estimates for age. The example below shows how an unadjusted relative risk may give a false association, when subdividing the data by another risk factor makes the association disappear completely.

	Unexposed to confounding factor		Exposed to confounding factor		Ignoring confounding factor	
	Cases	Controls	Cases	Controls	Cases	Controls
Unexposed to factor of interest	7	21	15	9	22	30
Exposed to factor of interest	3	9	35	21	38	30
Relative risk (R)	1.00		1.00		1.73	

Here there is no evidence of an association (R = 1.00) between the factor of interest and the disease either in those unexposed to the confounding factor or in those exposed to the confounding factor, so that a confounder-adjusted relative risk would show no association. If the confounder is ignored, however, there is an association (R = 1.73). This is because the confounder is strongly related to the disease:

	Cases	Controls
Unexposed to confounder	10	30
Exposed to confounder	50	30
Relative risk for confounder	5.00	

and because in the population at large (controls) the confounder is strongly related to the factor of interest:

	Unexposed to factor of interest	Exposed to factor of interest
Unexposed to confounder	21	9
Exposed to confounder	9	21

Suppose that in a population a proportion p are exposed to an agent and that their risk, relative to the unexposed proportion (1-p), is R. If risk of the population is 1 unit, that of the total population is given by

$$pR + (1-p) = 1 + p(R-1)$$

Thus a proportion

$$\frac{p(R-1)}{1 + p(R-1)}$$

of the total cases of the disease are associated with exposure. This is often termed the attributable risk fraction in epidemiology and, when multiplied by the total number of deaths from the disease, is termed the number of deaths attributable to the agent or the number of deaths due to the agent. Three points need to be made about this:

a) The terminology, by its use of the words "attributable" and "due to", implies cause and effect. However it is in fact no more than another index of an association. In the hypothetical case-control study example above, if we ignored the confounding factor we could compute p = 30/(30+30) = 0.5, R = 1.73, giving an "attributable risk fraction" of 0.27, and 16 of the 60 deaths "due to the agent". Had we taken the confounding factor into account, both the "attributable risk fraction" and the numbers of deaths "due to the agent" would have dropped to zero.

b) The attributable risk fraction depends both on R and on p, so is only valid to situations where both apply. There has been an increasing tendency to use attributable risk fraction

estimates for smoking-related lung cancer calculated from US or UK based data and then apply them gaily to other countries not only with very different proportions of smokers (p) but also with very different types and amounts of cigarettes smoked and durations of smoking (all of which may affect R).

c) In some situations, if one computes numbers of deaths from a disease due to agent A and also computes numbers of deaths due to agent B, one can end up with more deaths than actually occur. Does this mean the statistic is in some way wrong? I think the answer to this is actually no. Suppose a disease only occurs if one is exposed to both agents (perhaps one requires a gene plus a chemical exposure). One can easily see that, by the calculations above, all the deaths can be attributed to each agent. But, from the point of view of each agent, none of the deaths would have occurred in the absence of exposure, so this seems to me correct. Of course a more precise explanation would be to say that the attributable risk fraction for the combined exposure is 1.00.

In the above concern is with quantifying risk in terms of the probability, or relative probability, of an event occurring. An obvious alternative is to compute statistics based on length of life. One problem is that though in an animal study it may be easy enough to follow an exposed and unexposed group for life and to compare average length of life in the two groups, such information is not available in the human situation. Prospective studies rarely

follow subjects for much over 20 years and one is reduced to indirect estimation, which is full of traps and fallacies.

If one has estimates of risk of death by age it is possible to calculate what is known as expectation of life. One starts with an arbitrary number of individuals and then, for each successive year of age, computes the number dying at that age and the number surviving to the next year. The average age of all the deaths is then the expectation of life. This statistic, which is routinely calculated for each sex at national level as an index of overall mortality, has value but its interpretation is not straightforward. The problem lies in the fact that it is calculated from information from people born over a wide range of years and is not really an index of how long a person born today expects to live. Given, in many countries, there is a trend for age-specific mortality rates to decline over the years, it will underestimate how long a person born today expects to live. One could try an alternative procedure, based on extrapolation of rates, to estimate this but it would be highly speculative. After all, we do not really know what death rates in the second half of the next century are likely to be.

Despite its problems in interpretation, expectation of life is quite a useful method for comparing risk in different groups, such as smokers and non-smokers, although of course it is only an index of association. The difference between expectations of life for an exposed and unexposed group is an estimate of the years of life lost. By restricting attention to deaths before, say, age 65 one can also calculate years of active life lost.

Average age at death is different from expectation of life, although it sounds similar (after all expectation, in a statistical sense, means average). Here, the calculation is much simpler, involving averaging the ages at death for a population dying in a given year, but its value is much more limited. Indeed it is renowned as a method for generating spurious results. To illustrate this consider the following examples:

a) Comparison of the age at death of schoolmasters and schoolchildren. Clearly that of schoolchildren must be less than 19, and that of schoolmasters much higher but this does not mean being a schoolchild is particularly hazardous.

b) Comparison of the age at death of filter and plain cigarette smokers. In the years after filter cigarettes were introduced, smokers of them were much younger on average than smokers of plain cigarettes. Because of this, one would expect, all things being equal, filter cigarette smokers to die at a younger age than plain cigarette smokers. Miller (1977) noted this and concluded erroneously that filter cigarettes were more hazardous than plain cigarettes. The problem really is one of comparing numerators (deaths) without considering denominators (population). It is the same type of error as example 1, only less obvious.

c) A water authority inadvertently introduces a chemical into the water supply which doubles death rates in those aged 60+ but has no effect on those of younger age. The average age at death increases. Has the water authority done well?

The above discussion on average age at death and on expectation of life refers to what are indices of total mortality. One can also try to construct indices of risk of death from specific diseases based on length of life. Here too, there is plenty of scope for misleading arguments.

One point to make is that even in animal studies where risk of death from a disease is strongly related to level of exposure to an agent, there need not necessarily be any marked relationship between average age at death from the disease and level of exposure. Unless the exposure is large enough to materially affect the total death rate, a doubling of risk at each age may simply have the effect of doubling the number of deaths at each age (which clearly leaves the average the same). When one further takes into account the fact that the age distributions of heavy and light smokers differ, the observation of Passey (1962) that the average age of death of heavy smoking lung cancer patients did not differ from that of light smoking lung cancer patients is no sort of evidence that increased smoking does not increase risk of lung cancer.

A second point is that it is unsound to argue that, because average age at death from diseases associated with a factor is higher than the average age at death from all diseases, therefore the association cannot be due to cause and effect. To illustrate this consider a hypothetical situation in which all deaths below age 40 are due to a disease A and all deaths in later life are due to disease B. The agent of interest does not affect disease A, but causes disease B to occur closer to age 40. The average age of death from the disease (B) associated with the agent is lower than that

from all deaths, but the agent still causes B. Thus, arguing that many of the smoking associated diseases, such as stroke and chronic obstructive lung disease are diseases of the elderly, may have some value in describing the situation but is not evidence against cause and effect.

Given estimates of each year of age of the proportion of the population who die, one can, as noted above estimate expectation of life. In estimating it one actually constructs a life-table which gives, for each year of age, the proportion surviving to that age. This life-table can be used not only to calculate expectation of life, but also to calculate two additional types of statistic:

a) the age at which a given percentage die. For a percentage of 50, this median age at death will be close to the expectation of life.

b) the probability of dying by a given age, given survival to an earlier age. The probability of dying by retirement for smokers and non smokers of age 35 has, for example, been compared.

It can also be useful simply to plot the life-table graphically.

It is also possible to construct a deleted life-table in which deaths only from a specific cause of interest are considered. Although one cannot construct the complete table, because one would need observations past age 100, one can still usefully compare groups in terms of the ages at which a small percentage die, or in terms of proportions surviving to a given age.

Finally, in this section, some references should be made to statements such as that by Diehl (1969) who stated that "on average the time by which a habitual cigarette smoker's life is shortened is about 5½ minutes for each cigarette smoked". This statistic, calculated by dividing estimated loss of life expectation from smoking by average number of cigarettes smoked in a lifetime, is really more a method of expressing a result emotively than of providing a useful statistical approach. One problem with this "statistic" is that it is not calculated correctly. To compute average loss of life per cigarette, one should technically compute loss of life per cigarette for each individual and then average the answers over individuals. This is not the same as dividing average loss of life by average number of cigarettes. The reason the proper calculation has not been made is of course that it is not possible, on an individual basis, to measure life shortening. Another worrying thing about the whole concept is the fact that one might be averaging effects which are very different at different times of life. It can be shown (see Appendix A) that the assumption that each exposure has an equal effect implies a particular relationship between the life-tables of the exposed and non-exposed groups, which does not actually exist.

Further, more technical, detail about quantification of risks is given in a paper I wrote in 1978 on "Estimation of loss of life in relation to a disease or to a factor causing it; with particular reference to smoking". This paper also computes values of a variety of statistics based on UK and US data. This is attached for information as Appendix A.

References to Section 3

Miller, G.H. (1977) Journal of Breathing, 40, 6-7, 11-13.

Passey, R.D. (1962) Lancet, 2, 107-

Diehl, H.S. (1968) Tobacco and your health. McGraw-Hill, New York.

4. Problems of causal inference

Consider evidence from a single epidemiological study in which, for each individual, there is information on presence or absence of the disease and on presence or absence of the risk factor of interest, be it smoking or passive smoking. Suppose an association is observed between the factor and the disease - either in a prospective study the frequency of disease is greater in the exposed group, or in a retrospective study the frequency of exposure is greater in the case group. Under what circumstances can one conclude cause and effect?

It is necessary in the first place to point out that one is not talking about cause in the sense of necessary and sufficient cause. For most, if not all, diseases associated with smoking some cases arise in non-smokers. For all diseases associated with smoking some smokers do not get the disease. One is concerned with cause in the sense of the risk being increased as a consequence of smoking - one is arguing whether or not some smokers would not have got the disease had they not smoked.

Some have argued that it is impossible to demonstrate a cause and effect relationship from a non-randomized observational epidemiological study, but this argument appears to be incorrect. If all alternative plausible possible explanations can be excluded, then it is legitimate to conclude that the association arose as a result of a cause and effect relationship. This may not be mathematical proof but is an eminently sensible practical approach. The key lies in taking all the alternative plausible possible

explanations properly into account. It is in fact possible to classify the possibilities that have to be considered. These are discussed in the sections that follow.

Chance Standard statistical techniques can attach a probability (p) value to an association. This is an assessment of the chance that an association as strong as or stronger than that observed might have arisen if in fact there were no relationship between the disease and the factor of interest at all. Clearly any result might in theory have happened by chance, but as the p value gets lower one becomes less ready to accept a chance explanation. Most experimenters will consider values in the range 0.1 - 0.01 as suggestive, those in the range 0.01 - 0.001 as quite convincing, and those less than 0.001 as very convincing evidence that the association is not due to chance, though their prior beliefs will also be relevant. Note that strictly a p value is only appropriate to testing a clearly defined prior hypothesis. Where one is carrying out multiple analyses involving many factors and many diseases, care in interpreting p values is required, as if one looks at enough combinations one would actually expect by chance alone to come up with some demonstrating an association which is "statistically significant" (i.e. with a low p value). Unless the association seen after such "data dredging" has a very low p value, it should be regarded more as indicating a hypothesis to be tested by further studies than as any strong evidence of a true relationship.

Sequence of events In theory an association might arise because presence of the disease affects the risk factor. Such a possibility

is more relevant in case-control studies or in prospective studies with a short follow-up period (undiagnosed disease might still affect habits) than in prospective studies with a long follow-up period. In most smoking and health situations this explanation is not relevant, because it can be demonstrated that the exposure occurred many years before onset of the disease. In fact, more often effects of the disease act in the opposite direction, with onset of lung cancer or chronic obstructive lung disease often resulting in the sufferer giving up or cutting down smoking.

Misclassification of disease or exposure Misclassification of exposure and disease is a problem in all studies, though the magnitude of it will vary with the nature of the disease and the type of exposure considered. It is a well known statistical fact that random misclassification of one or both of two variables being associated tends to result in the observed association being weaker than the true association that actually exists. It is therefore not a valid argument to argue that random misclassification might explain an observed association. For an association to have arisen as an artefact of misclassification, a mechanism for differential misclassification has to exist. There are two possibilities here. One is that knowledge of disease (or the disease itself) might affect recall of exposure, making diseased subjects more likely to be classified as exposed. This is only a problem in case-control studies, but can be quite a severe problem there, especially in studies using healthy controls who do not have the incentive of cases to search the past in an effort to explain why their disease arose. The second possibility for differential misclassification is

that knowledge of exposure might increase the likelihood the disease is diagnosed. Recent studies have shown that a lung cancer was more likely to be diagnosed in life if the patient was a smoker, thus resulting in overestimation of the association of lung cancer with smoking. However this bias is inadequate to explain more than a small part of the total association. In theory differential misclassification can be prevented by collecting the data "double-blind" (i.e. the diagnoser of the disease should not know the patients' risk factor details, and the person supplying details of risk factors should not know of the disease) but this is not always practical.

Inadequate control group Suppose one observes in a case-control study that the frequency of smokers is higher in the subjects with the case disease than in those with the control disease. The inference that smoking is associated with an increased risk of the case disease rests on the assumption that those with the control disease have smoking habits typical of the population at large. Without this assumption one cannot exclude the alternative possibility that smoking is associated with a reduced risk of the control disease, smoking not actually affecting risk of the case disease at all.

Non-response Only some subjects approached provide usable data, and the relative risk estimate may be biassed as a result. Suppose, for example, in a case-control study, cases are personally interviewed in hospital and all or virtually all respond, while controls are interviewed by telephone or mailed questionnaire and only a proportion respond. If smokers are less willing to respond than

non-smokers (and there is some evidence for this), the recorded proportion of smokers in the control population will be falsely low, so biassing the comparison of the smoking habits of the cases and controls. Note, however, that bias will not occur just because the level of non-response depends on disease status, or because it depends on the risk factor. It needs an interaction between disease and factor in the level of non-response to cause bias. Bias may then be in either direction.

Confounding Let us turn now to explanations of the association involving another factor. That smokers have higher liver cirrhosis rate than non-smokers is not because of any direct effect of smoking, but because smokers drink more than non-smokers, and because alcohol predisposes to liver cirrhosis. Here alcohol is said to confound the smoking/cirrhosis relationship, in that failure to take it into account generates a false picture. It is precisely to avoid confounding that randomized studies are desirable. Because virtually all studies of smoking and passive smoking are not randomized, and because smokers and passive smokers differ in many ways from non-smokers and from non-passive smokers, great care has to be taken to exclude the possibility of confounding in such studies. For a variable to be a confounder it must be associated both with the disease and the factor of interest. When judging whether an association might result from confounding, it is necessary not only to consider whether the confounding variable is associated both with disease and the factor, but also to consider the strength of the two associations, as well as how often the confounder occurs. To illustrate this point, let us consider some

mathematics. Define R_C as the relative risk of disease from the confounder, and p_1 and p_2 as the frequency of the confounder among people exposed and not exposed to the factor, and assume the factor itself does not affect risk of the disease. An apparent relative risk in relation to the factor, R_F, will then be observed given by the formula:

$$R_F = [R_C p_1 + (1-p_1)]/[R_C p_2 + (1-p_2)]$$

Examination of this formula allows a number of observations to be made:

a) If $R_C = 1$, $R_F = 1$. (As noted above, we must have an association of the confounder with the disease, i.e. $R_C > 1$, to generate confounding, i.e. $R_F > 1$).

b) If $p_1 = p_2$, $R_F = 1$. (As noted above, we must also have an association of the confounder with the risk factor, i.e. $p_1 > p_2$, to generate confounding).

c) Given p_1 and p_2, R_F increases with R_C reaching a maximum of p_1/p_2 when R_C is infinite. Thus if 60% of smokers are occupationally exposed to an agent, and only 40% of non-smokers are, an observed relative risk greater than 1.5 (60/40) cannot be explained in terms of a confounding effect.

d) Given p_2, the largest value of R_F that can be achieved is $1/p_2$, when $p_1 = 1$ and R_C is infinite. This implies that to generate a large relative risk by confounding, the confounder must be rare in those not exposed.

TABLE 1

Some combinations of circumstances that might produce a spurious relative risk from exposure of 10.0

Relative risk for the confounder (R_C)	Frequency of the confounder among the exposed (p_1)	Frequency of the confounder among the non-exposed (p_2)
∞	1	0.1
46	1	0.08
91	0.9	0.08
∞	0.8	0.08
19	1	0.05
23.5	0.9	0.05
46	0.7	0.05
∞	0.5	0.05
12.25	1	0.02
16	0.8	0.02
23.5	0.6	0.02
46	0.4	0.02
∞	0.2	0.02
11	1	0.01
13.9	0.8	0.01
23.5	0.5	0.01
46	0.3	0.01
∞	0.1	0.01

N.B. For each value of p_2, the maximum and minimum value of p_1 is shown, together with the corresponding minimum and maximum value of R_C.

A general conclusion is that it is relatively easy to generate relative risks by confounding that are slightly greater than 1, but it requires special circumstances to explain a large relative risk. To obtain a spurious relative risk of 10.0, for example, one requires the frequency of the confounder among the not exposed to be less than 10%, a much higher frequency of the confounder among the exposed, and a very high relative risk in relation to the

confounding variable. Table 1 indicates some possibilities. It can be readily seen that in most circumstances, it is quite unlikely such conditions would apply for any confounding variable. This is why strength of an association is so important in coming to a conclusion as to whether it is causal or not.

Misclassification of confounding variables Often, statistical adjustment for a confounding variable reduces, but does not eliminate, the association of interest. Many workers assume that if the association remains after adjustment then the confounding variable cannot fully explain the unadjusted association. This inference is only valid if the confounding variable is measured without error. When a confounder is measured inaccurately, adjustment will tend to be incomplete so that there will be an association remaining due to what is termed "residual confounding". One should in fact be particularly wary in drawing conclusions concerning causality where one knows the confounding variable is likely to be measured inaccurately and adjustment for it materially reduces the magnitude of the association with the risk factor of interest. Examples of confounding variables which are likely to be measured inaccurately are diet (people do not accurately remember what and how much they eat, especially in years gone by) and variables which are obvious surrogates for some difficult to measure true factor, such as social class (which does not of itself kill people, but may act as a marker for things that do), and indices of sexual activity (which may be inaccurate markers of exposure to a sexually transmitted agent). It is in fact true that where there is a major risk factor which is inaccurately measured, it becomes very

difficult, if not impossible, to come up with reliable evidence as to whether a weaker association seen with another factor, which is correlated with the major risk factor, is a true effect or is a result of confounding. A good example of this is the relationship of smoking to cervix cancer. One knows risk of cervix cancer is strongly affected by a sexually transmitted agent (probably a virus), and that smokers have many more sexual partners than non-smokers, and for this reason the multitude of reports of an association between smoking and cervix cancer are generally not treated as proof of a causal relationship.

Where there is a major factor known to be very strongly associated with a disease and the effect of another minor factor is to be investigated, some researchers investigate the effect of the minor factor by restricting attention to those not exposed to the major factor. However, bias may still occur if the subjects are misclassified according to the major factor. The main example of this occurs in study of the association between lung cancer and marriage to a smoker, where attention is restricted to those who have never smoked. As I have discussed in detail elsewhere in a book and numerous papers, if (as can be demonstrated to be true) a small proportion of ever smokers are misclassified as never smokers, and if (as is also the case) smokers tend to marry smokers more than expected by chance, then an apparent association between risk of lung cancer and marriage to a smoker will be seen even when marriage to a smoker carries no actual risk of lung cancer at all. In judging whether an observed association between risk of lung cancer and marriage to a smoker represents a true effect or not, it is

necessary to try to estimate whether it is or is not greater than the association which might be expected as a result of misclassification of active smoking status.

Dose-response Often, subjects will be classified not simply as exposed or not exposed, but by degree of exposure. Normally, a true relationship will be stronger with increasing exposure, and emphasis should be given to statistical tests that are powerful for the detection of such a dose-related trend. One should be cautious about accepting as evidence of a causal effect studies which show an association at low doses but not at high doses or which show a very irregular dose response relationship. Even where the dose-response does rise smoothly, a causal relationship must not be concluded too readily, since many of the mechanisms already discussed that produce bias in a simple association between a risk factor and disease will also produce a spurious dose-response relationship. Since heavy smoking and heavy drinking are strongly correlated, one would expect to see a dose-related relationship between smoking and liver cirrhosis even though there is no true effect.

Effect of stopping exposure In some studies (particularly of active, but not of passive smoking) evidence is available of individuals who were exposed to the risk factor of interest for a period after which time exposure ceased. For acute effects one would expect to see risk drop shortly after exposure to a level similar to that in the never exposed group, while for chronic effects one would expect to see a risk intermediate between that of those never exposed and those continuously exposed, with risk approaching that of those never exposed the longer the time after exposure stops.

Evidence of patterns along these lines strengthens the argument that a causal relationship exists, though it must be pointed out that they might occur as a result of confounding - for example if ex-smokers drink less than continuing smokers, but more than never smokers, ex-smokers would have an intermediate risk of liver cirrhosis though smoking has nothing to do with liver cirrhosis. Evidence that risk is higher in ex-smokers than in continuing smokers (or is higher in long term ex-smokers than in short term ex-smokers) tends to cast doubt on the causal nature of an association, though it might not rule it out if presence of the disease makes people give up smoking.

Representativeness and consistency If one observes an association between a disease and a risk factor in a particular population that seems difficult or impossible to explain by chance or one of the various forms of bias that have been considered, it still does not necessarily mean that the risk factor causes disease in other populations. In some situations such a conclusion would indeed be false (e.g. effects of sunlight on white-skinned men do not apply to black-skinned men). For this reason, consistency of an association in studies in differing populations adds strength to an argument of causality. A few points need to be made however:

a) The example of sunlight is the exception rather than the rule, and many agents affect risk in a wide variety of populations. For this reason it is probably better to assume, in the absence of evidence to the contrary, that an effect seen in one population is likely to be applicable to other populations.

b) Specific sources of bias can produce the same artefactual association in every study, so that consistency of an association does not of itself prove cause and effect.

c) Where the association is weak, and studies not large, it will often be the case that some studies show and some studies do not show a statistically significant relationship. This of itself should not be construed as evidence of inconsistency. A better test is to see statistically whether the variation in strength of the association about the average is greater than expected by chance. However, even where such a "test of heterogeneity" shows the variation is greater than expected, it does not necessarily mean that the association is not causal. Populations may vary in the type of exposure (e.g. by smoking different cigarettes or with different frequency) or have a different frequency of susceptible subjects.

d) Where the association is weak, and studies not large, "meta-analysis" - i.e. statistical combining of results from all the studies - may demonstrate whether, taken as a whole, the evidence shows an association that cannot be explained by chance. It should be noted that this process involves a further potential source of bias, "non-reporting bias" or the "file drawer problem", due to the studies being reported not being representative of all the studies carried out. It is well documented that estimates of an association may be biassed upwards if scientists tend not to submit to journals, or journal editors tend not to publish, studies finding no association or an association in an unexpected direction.

Extraneous evidence and plausibility Finally, in coming to a judgment, it is necessary to take into account extraneous evidence and to consider whether the claimed effect is plausible. Among points that should be considered are the following:

a) Is the site of action likely or unlikely given the nature of the exposure?

b) Is the magnitude of effect plausible given the extent of exposure?

c) Is the type of effect expected or unexpected from what is known about related exposures?

d) Is there relevant evidence from animal studies?

e) Is there evidence that the exposure of interest is mutagenic or contains known carcinogens (for a cancer endpoint)?

f) Is there a plausible mechanism for the claimed effect? How strong is the evidence supporting this mechanism?

g) Is the association consistent with what is known about regional and temporal variation in incidence of the disease and in frequency of exposure to the risk factor?

Having considered all the possibilities noted above, it may be possible to conclude with reasonable certainty that an epidemiologically observed association is due to a cause and effect relationship. It should be noted that this does not imply that one can conclude whether any specific individual died from or contracted the disease of interest as a result of exposure.

5. Types of bias and error

In the preceding sections reference has already been made to a number of types of bias and error that can occur in epidemiological studies. For convenience this section brings together these and other types of bias and error. The types are listed in alphabetical order, with a brief definition of each, and in many cases an example illustrating how it may work. The interested reader is referred for further reading to the books "Methodological errors in medical research" by B. Andersen (Blackwell, 1990) and to "Follies and fallacies in medicine" by P. Skrabanek and J. McCormick (Tarragon Press, 1989), and also to a whole issue of the Journal of Chronic Diseases in 1979 "The case-control study: consensus and controversy" which contains a lot of relevant information on the type of study which is the most frequent source of various categories of bias and error. Some of the types of bias and error and their descriptions are drawn from these sources.

Admission rate bias. If the admission rates of exposed and unexposed cases and controls differ, the estimated relative risk of disease for the risk factor of interest will be distorted in hospital-based studies. This bias is often discussed when considering the relationship between diseases (i.e. are patients with disease A more likely to also have disease C than those with disease B) where it is often referred to as Berkson's bias. To show how this works, consider a population of one million adults of which 1% have both A and B. Thus there are 1,000 persons with each. Suppose 10% have C and in fact C is independent of A and B. There

will thus be 100 with A and C, 100 with B and C, 900 with A but not C, and 900 with B but not C. Let us assume admission rates A = 20%, B = 60%, and C = 40%, which operate independently. A hospital will therefore receive the following numbers of patients:

A alone : 180 (= 20% of 900)

B alone : 540 (= 60% of 900)

A and C : 52 (= 20% of 100 from A, plus 40% of remaining 80 from C)

B and C : 76 (= 60% of 100 from B, plus 40% of remaining 40 from C)

Our study thus shows 232 patients with A of which 52 = 22.4% have C and 616 patients with B of which 76 = 12.3% have C. 22.4% is greater than 12.3% but it is a false inference to argue that condition C predisposes to A.

Attention bias. Study subjects may systematically alter their behaviour when they know they are being observed.

Author bias. The author of an article may cite evidence that supports his case more readily than evidence that does not. While apparently routine for a politician, this is not acceptable in science.

Average age at death. It is an error to attempt to compare risk of disease in two populations by comparing their average age of death, based on information collected at one time point. One needs to have data not only on the age distribution of those who have died but also on those who have not before any meaningful comparison can be attempted. It is also an error to expect to see a correlation

between average age at death from a disease and level of exposure to a factor causing it, unless two conditions are present:

a) the disease is common enough to materially affect overall risk of death and

b) there is no relationship between age and extent of exposure. (See also section 3).

Berkson bias. See "admission rate bias".

Confounding. An association between the factor of interest and the disease may be confounded if exposure to the factor of interest is associated with exposure to another (confounding) factor that affects risk of the disease. The effect of confounding is illustrated in the table below:

True effect of confounding factor	Association of factor of interest and confounding factor	Effect on association of interest
Increases risk	Positive	Spurious increase
Increases risk	Nil	Nil
Increases risk	Negative	Spurious decrease
No effect on risk	Any	Nil
Decreases risk	Positive	Spurious decrease
Decreases risk	Nil	Nil
Decreases risk	Negative	Spurious increase

The possibility of confounding is the principal reason for being unable to directly infer "causation" from "association" in observational epidemiological studies.

Control group inadequate. The control group should be representative, as regards the risk factor of interest, of the population at large. Some early case-control studies of smoking and lung cancer were biassed because they included heart disease patients in the control group, not realising at that time that smoking was associated with heart disease. There are many

mechanisms by which the control group may be inadequate, considered separately in this section.

Data dredging. When data are reviewed for all possible associations without any prior hypothesis, the results are usually suitable only for forming hypotheses not for testing them.

Detection signal bias. See "unmasking bias".

Diagnostic bias. The same illness may receive different diagnostic labels at different points in space or time. For example, rates of "chronic bronchitis" in the UK have massively declined in recent years because many are now categorized under "chronic airways obstruction". There has also long been a tendency for "emphysema" to be used in the US to describe diseases categorised under "bronchitis" in the UK. In addition, ability to diagnose a disease may improve over time as additional techniques become available. For lung cancer it has been estimated that over the period 1900-1950 about a 10-fold increase in recorded mortality rate arose simply as a result of the introduction of X-rays and other means of detecting the disease, which, as early autopsy studies show, was once almost impossible to detect in-life.

Diagnostic suspicion bias. A knowledge of the subject's prior exposure to a putative cause may influence both the intensity and the outcome of the diagnostic process. It has been demonstrated that given lung cancer is present, it is more likely to be discovered in smokers than non-smokers. It in fact seems generally to be true that once the public or the medical profession has strong suspicion of a relationship between a risk factor and a disease, it becomes more difficult to carry out an unbiassed study of that

relationship.

Exposure suspicion bias. A knowledge of the patient's disease status may influence both the intensity and the outcome of a search for exposure to the putative cause.

Family information bias. Once a person has a disease there is a tendency for that person to take time to accumulate information about other family members who have had the disease. As a result, spurious evidence of a tendency for diseases to cluster in families can often be collected. This bias has been demonstrated by showing that people with certain diseases are more likely to report their parents had had the disease than are their disease-free siblings.

File drawer problem. See "publication bias".

Fishing expeditions. See "data dredging".

Fraud. There are some well documented examples. There is actually quite a fine line between presenting one's data in the best way to make a point clearly and fudging one's results.

Hawthorne effect. In 1920 the Western Electric Company carried out a series of experiments at the Hawthorne plant in Chicago to determine the effect of illumination on production. The control groups worked under constant illumination whereas the experimental groups worked under varying illumination. Production increased in both test groups and controls, to a similar extent. It seems that increases in production were caused by the increased interviews which workers received from management. It is possible that some part of the well-known differences between participants and non-participants in medical research have a comparable cause.

Like with like. In case-control studies, cases and controls should as far as possible be identical in terms of the conditions under which the data were collected. Interviewing cases in hospital and controls at home may impart differences in response due to the environment rather than the disease. Having different interviewers for cases and controls may also cause bias, especially if the questions are not precisely defined. There are many possibilities.

Membership bias. Membership in a group (the employed, joggers, etc.) may imply a degree of health which differs systematically from that of the general population. This bias particularly affects study of the benefits or otherwise of physical activity. The undoubted tendency for the sick to take less physical activity, renders it difficult or impossible to interpret a reduced level of disease in the physical active as a direct beneficial effect of the physical activity.

Migrator bias. Migrants may differ systematically from those who stay at home.

Misclassification. This refers to simple errors in determining the data in an epidemiological study, whether it be disease, factor of interest, confounding variables, or the variables by which subjects are to be included in the study or not. Though misclassification of disease or risk factor can only generate a spurious positive relationship if it is differential, random misclassification of confounding variables or of the variables determining the subjects to be included in the study (e.g. smoking status in ETS studies) can produce spurious positive relationships. Random misclassification of

disease or risk factor tends to underestimate true associations. (See section 4 for further discussion.)

Neyman bias. See "prevalence-incidence bias".

Non-respondent bias. People who do not respond to a questionnaire may have a different distribution of risk factors than do respondents. It has been repeatedly demonstrated, for example, that cigarette smokers are less likely to return mailed questionnaires than are non-smokers. It is often stated in the literature that a good research study should have high response rates and should compare responders and non-responders, but many studies fail in this respect.

Placebo effect. It has often been demonstrated that participants in drug trials taking the inert control "placebo" pill show an improvement in response, because the patients think they are being treated. This demonstrates the need to have a suitable control group and not to infer simply, from observations of improvement in the test group, that the test treatment was actually effective.

Prevalence-incidence bias. The effect of a factor which predisposes to fatal or short episodes of disease may be underestimated if only longer term survivors are studied. Suppose smoking had no effect on onset of a disease, but in fact led to an increase in survival. A typical case-control study would then find that interviewed (surviving) cases were more often smokers and expected.

Publication bias. Studies published in the literature may be unrepresentative because of a tendency for scientists not to submit, or journals not to publish studies showing no association or an association is an unexpected direction.

Recall bias. The recall of cases and controls may differ both in amount and accuracy, even if the case disease has no patho-physiological effect on memory. It has been reported, for example, that when questioning mothers whose pregnancies ended in fetal death or malformation, and a matched group of mothers whose pregnancies ended normally, more of the former group reported exposures to drugs that could not be substantiated in interviews during the pregnancy or in other health records. This bias tends to be most marked when the exposure of interest is rare, or when controls are community-based rather than hospitalized - hospitalized individuals have more time and inclination to think of possible past exposures.

Selection bias. Any process of selecting one's cases or controls so that they are not representative of the population of which they are supposed to be representative.

Time trend bias. Correlation over time of average incidence of disease with average level of a risk factor may be misleading because of differences in the age structure of the diseased and healthy population. A rise in death rate from a disease which commonly occurs in the elderly cannot sensibly be related to changes in level of a habit predominantly carried out by the young. For a chronic disease, risk is in any case usually a result of cumulative exposure over many years, so that even knowing current exposure for people of the same age as those who are dying may be of little relevance.

Unacceptable disease bias. When disorders are socially unacceptable, e.g. VD, suicide or insanity, they tend to be

under-reported.

Under-exhaustion bias. The failure to exhaust the hypothesis space (i.e. to consider all possibilities) may lead to authoritarian rather than authoritative interpretation.

Unmasking bias. An innocent exposure may become suspect if, rather than causing a disease, it causes a sign or symptom which precipitates a search for the disease. It has been suggested, for example, with some supporting evidence presented, that post-menopausal oestrogens might cause the search for endometrial cancer (by causing symptomless patients to bleed) rather than the cancer itself.

Volunteer bias. The opposite of "non-respondent bias".

There are doubtless many other types of error, but this gives a reasonable flavour of the many ways in which false conclusions can be reached.

6. Some major sources of epidemiological data on smoking and health

In this section a brief description is given of some of the more important sources of data on smoking and health. These are divided into prospective studies, case-control studies and other sources of information.

6.1 Prospective studies

The British Doctor's Study. In 1951, the British Medical Association forwarded a questionnaire to all British doctors concerning their smoking habits. A total of 34,440 men and 6,194 women provided information complete enough to be used, representing 69% of men and 60% of women alive when the questionnaire was sent. Further inquiries about smoking have been made at intervals. A number of papers described the relationship of mortality by cause to smoking habit, initially by Doll and Hill and then by Doll and Peto. The most recent papers describe 20 year follow-up in males (Doll and Peto, 1976) and 22 year follow-up in females (Doll et al, 1980), based on 10,072 and 1,090 deaths respectively. The study gave great attention to tracing the doctors, with the proportion lost to follow-up very low (mainly Indians returning to the sub-continent). The study provides considerable information on effects of giving up smoking, since over the period of the study many of the 83% of doctors who smoked initially gave up, the reduction being much greater than in British men generally. Limitations of the study are the lack of information on other risk factors and the fact that doctors are not representative of the population at large.

The American Cancer Society million person study (Cancer Prevention Study CPS I). In late 1959 and early 1960, the American Cancer Society enrolled 1,078,894 men and women in 25 US states in a prospective study. These represented 3% of the population over the age of 45 years. A lengthy initial questionnaire was administered that contained information on age, sex, race, education, place of residence, family history, past diseases, present physical complaints, occupational exposures, and various habits. Information on smoking included: type of tobacco used, number of cigarettes smoked per day, inhalation, age started smoking, and the brand of cigarettes used, from which tar and nicotine content of the cigarette could be calculated. Because data were collected by family (a family had to contain at least one member over age 45 and if it did all members over 35 were interviewed) it was possible to classify subjects by their own and their spouse's smoking habits, for study of the effects of ETS exposure. Nearly 93% of the survivors were successfully followed for a 12-year period. Numerous papers have been published, with Hammond the main author of earlier papers and Garfinkel the main author of later ones. Some of the major findings are summarized in the 1989 Surgeon-General's Report where comparisons are made with those from CPS II (see below). Strengths of the study are its enormous size, the ability to take into account numerous potential confounding variables, and the careful statistical methodology used to analyze the results. It should be noted that the study sample is not representative, being predominantly white and middle-class. Results relating to ETS have only been reported for lung cancer, though it is clear the material

is available for important analyses relating to other causes.

The American Cancer Society Prevention Study CPS II This study, started in 1982, was conducted in all 50 US mainland states and had the same general method of data collection as CPS I, though the questionnaire was more extensive. It involved over 1.2 million persons, again predominantly white and more educated than the general population. Follow-up is until 1988. The 1989 Surgeon-General's Report contained results for 1982-1986 follow-up, by which time virtually all deaths during this period had been ascertained, though cause of death was not yet available for about 10% at that time. No results on ETS have yet been reported. It seems quite possible that in a year or two comprehensive results on ETS will be reported for both CPS I and CPS II.

US Veterans Study This study followed the mortality experience of 250,000 US veterans who held Government life insurance policies in December of 1953 and who completed a smoking questionnaire in 1954 or 1957. Almost all policy holders were white males. A paper by Kahn (1966) reports very detailed results from 8½ years follow-up. Rogot and Murray (1980) give shorter results for 16 years follow-up. One limitation of the study is the fact that despite the long follow-up period, information on smoking habits was obtained only at the start of the study.

Japanese Study of 29 Health Districts (Hirayama study) In late 1965, a total of 265,118 men and women in 29 health districts in Japan were enrolled in a prospective study. Interviews were carried out at home by trained public health nurses and midwives using a very simple single page questionnaire which included items on age,

occupation, marital status, age at first marriage, number of children, length of breast feeding, dietary history, smoking habits, and alcoholic and non-alcoholic drinking habits. The population were followed up from census records of residence and death certificates, but no further information was collected. Questions on ETS exposure were not asked. Rather, information on spouse's smoking habits was obtained from the interview with the spouse carried out at the same time (since all subjects in the same household aged 40+ were interviewed). Hirayama has published many papers describing the relationship of active and passive smoking to risk of a range of diseases. The most recent are based on 16 year follow-up, to 1981. A number of authors have criticised various features of this study. For a discussion see Lee (1991).

WHO MONICA project MONICA is an acronym for monitoring of trends and determinants of cardiovascular disease. The project was established to clarify the reasons why national mortality trends in coronary heart disease in the 1970's were declining in several countries, but constant or rising in many others. One specific objective is to study the relationship of 10 year trends in incidence rate of coronary heart disease and stroke with 10 year trends in the major cardiovascular risk factors serum cholesterol, blood pressure and cigarette consumption. 39 centres in 26 countries in Europe, USA, Asia and Australasia are participating with a total population of 15 million people aged 25-64 being monitored. Attempts to collect information on risk factors were made from a total of some 100,000 individuals with participation rates varying from 54% to 91% by centre. Data were collected on smoking, age, height,

body weight and blood pressure with a blood sample taken for cholesterol determination. As the interviews were in the main conducted in the mid 1980's, full results are not yet available, though the study will clearly be of major importance when it is completed. The 1989 World Health Statistics Annual gives data on heart disease and stroke mortality and on the distribution of the risk factors in each centre, but no statistical analysis of the extent to which variation in mortality can be explained by variation in risk factor level.

The Multiple Risk Factor Intervention Trial (MRFIT). This is probably the most expensive epidemiological study ever conducted. In the 1970's some 360,000 men in 18 US cities were screened for three major risk factors for coronary heart disease: serum cholesterol, cigarette smoking, and blood pressure - and almost 13,000 men with levels most predictive of subsequent risk were randomly assigned to two groups. The test group "special intervention" (SI) were given dietary and anti-smoking advice and treated for hypertension if their diastolic blood pressure exceeded 90 mm Hg. No intervention program was offered to the control group "usual care" (UC). Over the 6 year period during which intervention took place the proportion of cigarette smokers in the SI group halved (from 64% to 32%), while cholesterol and blood pressure also reduced. Reductions also occurred in the UC group (the news travelled), though not to the same extent - the proportion of cigarette smokers reduced from 64% to 45%. The latest paper comparing mortality in the SI and UC groups - after 10½ years follow up - was last year (MRFIT Research Group, 1990), a small reduction in all cause and heart disease mortality

being seen in the SI group, which was not evident at the end of the intervention. A limitation of the study is that it is a test of the overall intervention strategy and that it is not possible reliably to distinguish effects of changes in smoking from those of changes in blood pressure and cholesterol. It should be noted that the study provided some information on ETS, since, of the high risk group originally identified, 1245 were married never smokers, 286 to women who smoked and 959 to women who did not. However there have only been 41 deaths to date (see Svendsen et al 1987 for some results here).

National Child Development Study This study involved all people born in the week 3-9 March 1958. Originally studied at birth by the National Birthday Trust Fund, the 17,000 members of this cohort have been followed up at the ages of 7, 11, 16 and 23, and a fifth follow-up is planned for their early 30's. A huge amount of information has been collected from this sample, in particular concerning the relationship between mother's smoking during pregnancy and neonatal mortality, birthweight and subsequent development of the child. The most recent report is by Fogelman and Manor (1988). TAC sponsored some analysis based on the 16 year follow-up, culminating in a paper by Fogelman (1980). It will be interesting to see whether the sample is followed for life, or at least to a time at which it will be useful to study their mortality.

Swedish Twin Study The famous statistician R A Fisher, once a consultant to the Tobacco Manufacturers Standing Committee, said that one reason why the association between smoking and lung cancer could not be considered proof of cause and effect was the

possibility that there was a gene which made people both more likely to smoke and more likely to get lung cancer. One way of obtaining evidence as to the plausibility of this hypothesis is from studies of smoking discordant identical twins, i.e. identical twins one of whom smokes and one of whom does not (or smokes to a lesser extent). It is difficult to gain good data on this because lung cancer is a relatively rare disease, identical twins are rare (about 1 in 100 births are twin births and only 1 in 3 of these are identical), and because identical twins often have identical rather than discordant smoking habits. Nevertheless some relevant data have been obtained from two studies, the Swedish and Finnish twin studies, both conducted in countries which have registration numbers, record twin-ness at birth, and have excellent computer systems to track down mortality. The Swedish twin study concerned all like-sexed twins born between 1886 and 1925 for which both members of the pair were alive in 1961. In 10,945 out of 12,889 twin pairs, both members responded to a mailed questionnaire in 1961. Floderus et al (1988) report results from a 21-year follow-up during which some 6,447 deaths occurred, of which 309 occurred in smoking discordant identical twin pairs. In interpreting results from twin studies it should be noted that although a genetic explanation for a difference in risk between the smoking-discordant identical twin pairs is ruled out, the theoretical possibility of confounding is not.

Finnish Twin Study The Finnish Twin Cohort was compiled from the national population registry of all Finnish citizens in 1974 and consists of all like-sexed pairs born prior to 1958 with both members alive in 1967. Information on smoking habits and zygosity

was obtained in 1975. 556 smoking discordant twin pairs were followed for 12 years, during which 52 died. Results of these studies are described in two recent papers by Kaprio and Koskenvuo (1989, 1990), the latter one presenting some combined analysis from the Swedish and Finnish studies.

There are of course many more prospective studies that have been carried out, but the above are those that have assumed a particular importance in evaluating the relationship between smoking and health, or are likely to do so in the future.

6.2 Case-control studies

There are myriads of case-control studies of the relationship between smoking or ETS and risk of specific diseases. Only a few of particular interest are noted below.

American Health Foundation Studies Wynder, who along with Doll in the 1950's conducted the pioneering studies demonstrating a strong association between smoking and lung cancer, has for many years conducted continuing case-control studies of lung and other cancers in hospitals mainly in the New York area. The technique has been to interview patients in hospital with an extensive questionnaire (including questions on demographic factors, occupation, alcohol, smoking and ETS exposure) and then to select out cases with a specific smoking-related cancer and controls matched for age, sex, race, hospital and time of interview with diseases that were not tobacco-related. Recent papers of interest on lung cancer are those by Kabat and Wynder (1984), Wynder and Kabat (1988) and Kabat (1990).

National Cancer Institute Western European Study Lubin et al (1984a, 1984b) describe results from a case-control study of lung cancer conducted in 1976-80 involving interviews with 7,804 cases and 15,207 controls carried out in hospitals in seven locations in Western Europe. Controls, who were matched to each case by sex, age and study site, were in hospital with diseases that were not related to smoking, and were interviewed to obtain a detailed smoking history. ETS exposure was not studied, a major interest being to relate lung cancer risk to type of cigarette smoked.

Alderson hospital case-control study In this Tobacco Research Council sponsored study, 12,693 interviews were conducted in 46 hospitals in 10 English hospital regions between 1977 and 1982. There were four case diseases, lung cancer, chronic bronchitis, ischaemic heart disease and stroke. For each case patient, a control with a disease not associated with smoking was selected matched for sex, age, hospital and time of interview. A detailed questionnaire asked about smoking history including brand smoked - the main objective of the study was to relate risk to type of cigarette smoked - and about a whole range of possible confounding variables. Questions on passive smoking were introduced part way through the study. Results are reported in Alderson et al (1985) and in Lee et al (1986).

6.3 Other sources of data

National mortality data Each year, in their World Health Statistics Annual, the WHO publish data on mortality rates by year, age, sex and cause of death for a wide variety of countries. These data are available on application to WHO and have been the source of

numerous studies of trends in various diseases. Many countries, including the UK, also publish similar data by region of the country. The source of all these data is a combination of the census, to determine population, and death certificates, to determine numbers of deaths by cause. As smoking is not recorded in the census (at least in most countries) or on death certificates, it is not possible to obtain national information on death rates for smokers or non-smokers from these sources. Such rates can only be estimated indirectly.

National smoking data The TRC, in their Research Paper 6, used, until the early 1970's, to publish annual estimates of sales and consumption per head for quite a wide range of countries worldwide. Since this was discontinued there has been no simple single source of such data. Research Paper 6 was in any case limited by being only based on sales data, so not giving estimates of the frequency of smoking or of consumption per head broken down by age and sex, which is very important to have if any useful relationship to risk of smoking-associated diseases is to be made. While many surveys have been carried out in many countries there is no single document published so far that summarizes all the relevant data. This omission will be partly repaired when a compilation by my colleague, Mrs Forey, and myself is published as a book, probably in 1992. This concerns data in 22 developed countries up to 1985. A comprehensive summary of UK data has been prepared by Wald et al (1988).

Occupational mortality tables Although smoking is not considered, it is important to be aware of the existence of the

decennial reports of the Registrar General. Every ten years, the distribution of occupation as recorded in the census year (which ends in a 1), is compared with the distributions of occupations as recorded on death certificates in that year and in the preceding and following year or two. This enables calculations of risk of any given disease of people in a given occupation relative to all people, and thus identifies occupations with especially high risks.

Other particularly important sources of information are the US Surgeon-General's annual reports on Smoking and Health and, earlier, the various reports of the Royal College of Physicians. While I do not agree with all their conclusions, they are a most valuable literature source (particularly the Surgeon-General's reports) and provider of useful summaries of information on specific aspects of smoking and health.

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7. Risks of smoking

In this section I summarize briefly the evidence concerning diseases associated with smoking. Many are claimed adverse effects of smoking, some are diseases less common in smokers, and in one or two cases I refer to some important diseases where there has been some discussion in the literature of possible positive or negative effects, though the overall evidence in fact suggests no association. What is presented is not intended to be a detailed discussion of the evidence. Rather it is intended to be a summary which brings into context smoking's relevance by (i) giving the magnitude of the association (normally presented as the relative risk for current smokers compared with never smokers); (ii) indicating the numbers of deaths occurring nationally per year from the diseases; (iii) giving an opinion, with the main supportive evidence, as to whether the association can be considered causal, an artefact due to bias, or some intermediate position; and (iv) indicating important factors other than smoking known to contribute to the disease. For all the diseases, my commentary is based on some experience of the literature, based on a continuing review of important papers. It should be noted, however, that there are some diseases for which my knowledge of the literature is much more extensive than others. Thus, while I refer to recent detailed reviews I have conducted for some diseases, for others (such as stroke where there is a large literature, with many recent important papers, which I have not had time to study in detail) my views are less reliably based. Nevertheless I hope this section will be of

value to someone who wants to get a quick briefing on the relationship of smoking to specific diseases.

Overall risk of mortality. In England and Wales in 1988, the most recent year for which I have detailed data from the Registrar General, there were 280,931 deaths in males and 290,477 deaths in females. 25.2% were from cancer, 46.9% from diseases of the circulatory system, 10.6% from diseases of the respiratory system, with the major groupings with the next highest percentages, "injury and poisoning" and "diseases of the digestive system", contributing much less to the total, 3.1% each. Numerous epidemiological studies have shown that smokers have higher overall risks of mortality than non-smokers. In earlier studies the risk for current smoking males relative to never smoking males was about 1.7 or 1.8, with females having lower relative risks. In more recent studies, relative risks have increased in both sexes. The table below shows results from the two large American Cancer Society CPS studies. For both current and former smokers (aged 35+) the risk relative to never smokers is shown, together with 95% confidence limits in brackets.

	Current smokers	Former smokers
CPS-I 1959-1965		
Males	1.80 (1.75-1.85)	1.38 (1.33-1.42)
Females	1.23 (1.18-1.28)	Not available
CPS-II 1982-1986		
Males	2.34 (2.26-2.43)	1.58 (1.53-1.64)
Females	1.90 (1.82-1.98)	1.32 (1.27-1.37)

Exact computation of the attributable risk is not possible since relative risks are not given by age group, but were the later estimates to be applied to smoking frequency data for UK men and women aged 35+ (for 1982), I estimate attributable risks of 46% for men and 27% for women. While there are obvious problems in applying US experience (and that for a non-representative population) to the UK, it is important to note these estimates are in fact larger than those of Peto who estimated that of 1,000 children born today 250 would die because of tobacco, illustrating the fact that even if one argues that a substantial proportion of the excess mortality in smokers is not a consequence of their smoking, one can still end up with large attributable risks.

The same can be said for numbers of deaths associated with smoking. Applying the attributable risks to 1982 figures for total deaths one would actually get in excess of 200,000 deaths so that the commonly made claims of 100,000 deaths "due to smoking" could actually allow for a large proportion of the association to be non-causal in origin.

Although analysis of overall mortality has the advantage of not being dependent on accuracy of diagnosis, it is in fact not very useful for assessing causation as it arises from a multitude of diseases, with varying associations with smoking and varying aetiologies. The extent to which smoking causes disease I will address below in the sections dealing with the specific diseases.

Lung cancer. In 1988 in England and Wales there were 24,671 deaths in males and 10,631 deaths in females from "malignant tumours of the trachea, bronchus and lung", the category most

commonly used for the purposes of quantifying "lung cancer" deaths. (Tracheal cancers are extremely rare, and most other cases do not distinguish the bronchus from the lung on the death certificate). An absolutely vast body of evidence has been collected on the relationship between smoking and lung cancer. It is abundantly clear that:

(i) The association is very consistent - an excess lung cancer rate in smokers has been observed in a very great number of studies carried out in many different parts of the world. No large well-conducted study has contradicted this observation.

(ii) The association is very strong. Many studies have found that cigarette smokers have a risk of lung cancer that is ten times or even more that of non-smokers. The most recent evidence from CPS-II gives relative risks of lung cancer for current smokers of 22.4 in males and 11.9 in females.

(iii) The association is dose-related in various ways:

a) Risk increases steadily with number of cigarettes smoked per day.

b) Risk is much greater in those starting to smoke early rather than late. It has been shown that risk is proportional to the fourth or fifth power of duration of smoking independent of age. The increased duration of smoking in older men and particularly in older women explains why relative risk estimates for CPS-II are much higher than those seen 20 or so years earlier in CPS-I (males 11.4, females 2.7).

c) Risk is reduced in those who stop smoking relative to those who continue to smoke.

d) Risk is greater in those who inhale (though see below), and in those who take more puffs of each cigarette, keep the cigarette in the mouth between puffs and re-light half smoked cigarettes.

e) Risk is reduced in those who smoke filter-tipped cigarettes or cigarettes with reduced tar delivery compared to those who smoke plain cigarettes or cigarettes with higher tar delivery.

(iv) Although there is a wide range of factors that have been found to cause lung cancer (I am currently completing a review on confounding factors in lung cancer which will list them all), the great majority of them do not increase lung cancer risk to anything like the extent of the increase seen in smokers. Agents that do cause a more marked increase in risk are generally, like biochloromethyl ether, agents to which few are exposed, or, like various types of heating or cooking methods used in parts of Asia, specific to certain populations and therefore not capable of explaining the more general association.

(v) Cigarette smoke condensate is carcinogenic to mouse skin.

(vi) The lungs of smokers, when examined post-mortem, consistently show changes in the bronchial epithelium which are virtually never found in non-smokers.

These findings all appear to point to a causal role for smoking but it is important to consider the main objections that have been raised to this conclusion.

Most vociferous of the objectors has been the late Philip Burch, who postulates that a particular genotype predisposes both to smoking and to getting lung cancer. The explanation could in theory account for (i), (ii), (iii) and (vi) above, it being understood that groups more exposed to cigarette smoking tend to contain more people with the genotype and thus be more at risk of lung cancer. However Burch's theory totally fails to account for 3 major observations:

a) The results from the Finnish and Swedish studies of smoking discordant monozygotic identical twins which show significantly increased risk of lung cancer in the smoking (or heavier smoking) twin.

b) The lack of convincing evidence of a marked familial tendency for lung cancer which one would expect to find if genetic effects were to explain such a strong association as that seen between smoking and lung cancer.

c) Various features of trends in lung cancer seen in the UK. Burch argues that changes in ability to diagnose lung cancer can explain trends in lung cancer, but though they contribute importantly to trends in the first half of this century, they do not explain why rates for women are catching up dramatically with rates in men, nor differential trends in men and women of different age groups. A recent analysis by myself and my colleagues (Lee et al, 1990) shows broad similarities in each

sex between trends in lung cancer and trends in cumulative cigarette consumption in the UK which cannot be explained on a genetic basis.

Burch also comments on a number of apparent anomalies which he finds difficult to reconcile with a smoking causation hypothesis, two of which I will refer to.

One is that inhalation studies in animals have not demonstrated an increased risk of lung cancer in the smoke-exposed groups. Here one should note firstly that some recent studies have demonstrated an increased risk, though not so clearly as in epidemiological studies, and secondly that it is very doubtful that the dose to the lungs received by animals in inhalation experiments is really comparable to that of the smoker who willingly takes in hundreds of lungfuls of smoke a day for 40 or 50 years or more.

Secondly Burch noted that some studies have found that heavy smokers who inhale have a lower risk of lung cancer than heavy smokers who do not inhale. The explanation for this anomaly is unclear - accuracy of statements about inhalation is probably poor, and it may be that deep inhalation actually results in deposition of the smoke at parts of the lung that are less susceptible to its effects - but I do not find this evidence anything like sufficient to weigh against the impressive array of other evidence that smoking does cause lung cancer.

Nor do the claims of Eysenck or Sterling impress. Both try to explain away the association in terms of a confounding variable (Eysenck - psychological variables; Sterling - occupational

variables). While there is, as they point out, good evidence for an association of these variables to both smoking and lung cancer, they totally overlook that both the relationships for which they cite evidence are so much weaker than that between smoking and lung cancer that it is mathematically impossible for the former to explain the latter.

I have no doubt that smoking causes lung cancer, the evidence being strong and coherent and the objections weakly based.

It does not necessarily follow that the susceptibility to cigarettes is equal for all people. This comment is not based on the observation that some smokers and not others get lung cancer (the same is true for Russian roulette and does not prove some are more susceptible to bullets than others). Rather it is based partly on the general principle that biological variation will tend to ensure variation in susceptibility and partly on some limited recent evidence indicating a genotype with a particularly high risk of lung cancer. It is not beyond the bounds of possibility that there is some characteristic which strongly affects the risk of people who smoke, so that perhaps some people could smoke with virtual impunity if the relevant facts were known, but at present there is little evidence to support this belief.

Despite my views, I do not think that all recorded changes in lung cancer mortality over time or differences in lung cancer mortality between countries can be explained by smoking. My Thorax paper (Lee et al, 1990) presents evidence supporting the existence of a non-smoking related factor which has resulted in a decline in lung cancer rates in younger men and women in the UK. I do not also

believe the massive recent increase in lung cancer in Japan can be accounted for by trends in smoking. Such evidence does not provide an argument that smoking does not cause lung cancer, merely that there are other things that do.

Larynx cancer. Larynx cancer is much rarer than lung cancer. In England and Wales in 1988 there were only 669 deaths in males and 175 in females, some 40 times less than for lung cancer. A consistent positive relationship to smoking has been reported in a large number of studies. In recent large studies of populations which have smoked for a long time, the association is very strong. For example, relative risks for current vs. never smokers exceeded 10 for both males and females in CPS-II. There is a strong relationship of risk to amount smoked. It is clear alcohol consumption is also a factor with relative risks very high in heavy smoking heavy drinkers but there is no evidence that the association with smoking can be explained as a result of confounding by alcohol - risk is strongly related to smoking in non-drinkers and in drinkers of a given amount. Risk is reduced in ex-smokers. Inhalation of tobacco smoke has been shown to produce larynx tumours in hamsters, though not in other rodents. The evidence that smoking causes larynx cancer is very clear.

Oral cancer. In 1988 in England and Wales there were 1,077 deaths in males and 610 in females from cancers of the lip, oral cavity and pharynx. In many ways the epidemiological evidence is very similar to that for larynx cancer, with the association very strong (in CPS-II current smokers had relative risks of 27 in males and 5.6 in females) and dose-related, with risk reduced in

ex-smokers and alcohol similarly implicated. (Note that alcohol itself is not carcinogenic to animals but may act to increase absorption of carcinogens from other sources.) Oral cavity cancer has not been produced by cigarette smoke or cigarette smoke condensates, but despite this the strength and consistency of the association makes it difficult to believe that oral cancer is not caused by smoking.

Oesophageal cancer. In England and Wales in 1988 there were 2,954 deaths in males and 1,930 in females from cancer of the oesophagus. The epidemiology is similar to that for larynx and oral cancer, with the association very strong (in CPS-II current smokers had relative risks of 7.6 in males and 10.3 in females) and dose-related, with risk reduced in ex-smokers and alcohol similarly implicated. In some countries, other factors may be relevant (e.g. the drinking of very hot drinks), but there is no evidence of any confounding factor that might explain the relationship with smoking. Although the oesophagus is not directly exposed to inhaled tobacco smoke, there is no doubt that the oesophagus is exposed to smoke constituents, either by swallowing what condenses on the mucous membranes of the mouth and pharynx or mucous cleared from the lungs by the cilia or by coughing. Again it is difficult not to conclude that smoking causes oesophageal cancer.

Bladder cancer. In 1988 in England and Wales there were 3,296 deaths in males and 1,489 in females from bladder cancer. A large number of epidemiological studies have indicated a consistent increase in risk of bladder cancer in smokers, though the association is much weaker than that for lung, larynx, and cavity

and oesophageal cancer, the latest results from CPS-II, showing a relative risk of 2.86 in men and 2.58 in women, being reasonably typical. The overall evidence suggests some dose-relationship and an intermediate risk elevation in ex-smokers. A number of occupational exposures produce an increased risk of bladder cancer, and the inter-relationship of smoking and occupation in their effects on bladder cancer is unclear. While quite possible that smoking causes bladder cancer, the evidence that it does so is not completely conclusive.

Kidney cancer. In 1988 in England and Wales there were 1,315 deaths in males and 848 in females from kidney cancer. The epidemiological evidence, more limited than that for bladder cancer, has generally shown a weak association (CPS-II gave current smoker relative risks of 2.95 in males and 1.41 in females, the latter not statistically significant), with some evidence of a dose-response relationship and a weaker association in ex-smokers. The aetiology of kidney cancer is little understood - while a number of factors, such as lead, cadmium, hormones, radiation, and genetic factors have been discussed as possible agents, no dominant role of any factor has emerged. The evidence that smoking causes kidney cancer is not conclusive.

Pancreas cancer. In England and Wales in 1988 there were 2,905 deaths in males and 3,103 in females from pancreas cancer. Most of the epidemiological studies report that smokers have about twice the risk of pancreas cancer of those who have never smoked (CPS-II gives relative risks of 2.1 for males and 2.3 for females) and there is some evidence of a dose-response relationship. Pancreas cancer is

notoriously difficult to diagnose reliably and it is possible that the association might arise as a result of a true association between smoking and some other cancer misdiagnosed as pancreas cancer. Dietary fat, alcohol, and coffee consumption have all been implicated in some studies, though the evidence is unclear. It is not clear whether smoking causes pancreas cancer or not.

Stomach cancer. In England and Wales in 1988 there were 5,639 deaths in males and 3,786 in females from stomach cancer. Some studies have noted an association of smoking with stomach cancer but never more than a relatively weak one. Although Hirayama has claimed smoking causes stomach cancer - he found a dose-related trend in his study - other authorities generally agree that the evidence that it does is far from conclusive.

Cervix cancer. In England and Wales in 1988 there were 1,942 deaths in females from cervix cancer. There is quite a large number of studies that have shown a positive association of smoking with cervix cancer, and the latest CPS-II results, with a relative risk of 2.14, are consistent with this. However, incidence of cervix cancer is very strongly related to aspects of sexual habits (probably a sexually transmitted virus), with early and frequent coitus, multiple sexual partners, pregnancy at an early age, and the presence of sexually transmitted diseases all showing a strong relationship to risk; and there is clear evidence that these risk factors are strongly associated with smoking. Although some association of cervix cancer with smoking persists after adjustment for recorded aspects of sexual habits, such adjustment must be seriously incomplete (because one is not actually adjusting for the

sexually related cause) so that what one observes could easily be due to "residual confounding". There is no particular reason to believe that smoking causes cervix cancer.

Endometrial cancer. In England and Wales in 1988 there were 544 deaths in females from cancer of the body of the uterus, mainly endometrial. Nearly all studies have shown that smokers have a somewhat reduced risk of endometrial cancer, with risk reduced by an average perhaps about 30%. There is evidence of a dose-relationship, and of a reduced reduction in ex-smokers. The risk reduction cannot be explained by adjustment for body weight, a major correlate of endometrial cancer risk and is somewhat greater in post-menopausal than in pre-menopausal women and in users than non-users of post-menopausal oestrogens. Wald et al (1990) conclude the negative association probably results from a causal relationship.

Breast cancer. In England and Wales in 1988 there were 13,723 deaths in females from breast cancer (the most common cause of cancer in females) and also 73 in males. Because of the probable anti-oestrogenic evidence of smoking (see Wald et al, 1990) it has been suggested that smoking might reduce risk of breast cancer, and there are indeed a few reports of a statistically significant reduction in risk. In fact, the overall evidence suggests a very slight positive association, with a relative risk of about 1.1. Because of the numerous possibilities of confounding and other sources of bias, it is not possible to conclude an association of this magnitude ~~as~~ is causal and no authority has claimed smoking causes breast cancer.

Colon cancer. This is mentioned, as it is one of the commoner causes of cancer, with 5,208 deaths in males and 6,286 deaths in females in England and Wales in 1988. However, the epidemiological evidence shows no consistent association whatsoever with smoking, and indeed colon cancer patients have often been used in case-control studies to form part or all of the controls with non-smoking related cancer.

Rectum cancer. Like colon cancer, this disease, from which 2,904 males and 2,287 females died in England and Wales in 1988, shows no evidence of an association with smoking.

Chronic obstructive lung disease. In 1988, 18,817 men and 9,932 women in England and Wales died from "chronic obstructive pulmonary disease and allied conditions". The major contributors to those numbers were "chronic airways obstruction" (CAO) (11,430 male and 5,375 female deaths) and "chronic bronchitis" (CB) (4,556 male and 2,233 female deaths), it being notable that over the last 20 years there has been an increasing tendency to classify deaths which would previously have been called CB under the term CAO. Other important contributors are "emphysema" (E) (1,511 male and 578 female deaths), a term more commonly used in the US than in the UK, and "asthma" (832 male and 1,174 female deaths). Many epidemiological studies have shown that the combined incidence of CAO + CB + E is considerably increased in smokers - recent results from CPS-II show relative risks for current smokers of 9.7 in males and 10.5 in females. Asthma, on the other hand, shows little association with smoking. The evidence that smoking is an important cause of CAO + CB + E rests on a number of factors:

a) the consistency, strength, and dose-relationship of the association;

b) pathology studies showing that advanced E, while present in 20% of heavy smokers, is virtually unknown in non-smokers;

c) studies demonstrating that in identical twins with differing smoking habits, respiratory symptoms are on average more frequent and respiratory function poorer in the heavier smoking twin of the pair; and

d) the observation that lung function deteriorates more rapidly during periods when people are smoking than during periods when they are not. Lung function, as measured by forced expiratory volumes in 1 second, is extremely highly correlated with extent of chronic obstructive lung disease.

The twin evidence is important because it undermines the possibility of the association being due to genetic factors affecting both the desire to smoke and the susceptibility to disease. The evidence on lung function decline is also important because being made <u>within</u> smokers, it overcomes the theoretical problem normally encountered relating to possible differences <u>between</u> smokers and non-smokers due to self-selection.

Unlike lung cancer, however, it seems reasonably clear that there are a number of other very important determinants of CAO + CB + E. There are, for example, huge social class differences in mortality rates that cannot be explained by smoking - indeed they were present at a time when the social classes smoked to much the same extent. There has also been, as shown in my Thorax paper (Lee

et al, 1990), a huge decline in CAO + CB and a smaller decline in E, that cannot be explained by smoking. Reductions in air pollution since the Clean Air Act are a contributor to the decline but not the only one.

Evidence that in only a minority of smokers (about 15%) lung function deteriorates abnormally fast, whilst in the remainder the deterioration is no different from that in non-smokers, suggests that smoking may only be a cause of bronchitis in those who are at risk for other reasons. There is also some evidence from family studies that this could be an inherited susceptibility, a view strengthened by the observation that emphysema is particularly prevalent in those with a deficiency of the enzyme alpha-1-antitrypsin.

Ischaemic heart disease. In 1988 in England and Wales there were 84,880 deaths in men and 68,204 in women from what is now more commonly called ischaemic heart disease (IHD) and what used to be known as coronary heart disease. This is the most common cause of death in most westernized countries, and is a major contributor to numbers of deaths associated with smoking or "due to" smoking. The evidence available on IHD is enormous and complex. A review of the available data notes the following important observations:

a) There is consistent evidence that cigarette smokers are at increased risk of IHD.

b) The magnitude of the association is much weaker than for lung cancer. In CPS-II, for example, the relative risk for current cigarette smokers was 1.94 in men and 1.78 in women. 20 years earlier, in CPS-I, relative risks were 1.83 and 1.40.

c) There is evidence of a dose-relationship.

d) Ex-smokers are usually found to have a reduced risk compared with current smokers.

e) Many studies show a larger association in younger than in older people.

f) There is a very wide range of factors that have been associated with smoking. High blood pressure and raised serum cholesterol are two for which an association has been reported in numerous studies, but there are many others. (A review paper written over 10 years ago listed 246 risk factors for IHD!)

g) Adjustment for confounding factors has never been found to affect materially the association between smoking and IHD.

h) Smokers who give up smoking after a first myocardial infarction (heart attack) have a markedly reduced risk (about half) of a second infarct.

i) Autopsy studies have indicated a significant positive association of smoking with degree of atherosclerosis.

j) Intervention trials have tended to show some reduction in IHD incidence or mortality. However, in these trials, subjects have usually been encouraged to modify other behaviour as well as smoking.

The evidence that smoking is actually a cause of IHD is certainly far less convincing than it is for lung cancer or chronic obstructive lung disease, for example. The fact that the association is much weaker means that confounding is a possibility. That statistical adjustment for many and varied lists of other risk

factors has not explained the smoking association is not completely convincing because it is not usually possible to determine all the candidate risk factors accurately or at all, especially those relating to genetic, dietary, psychological or stress factors. Some studies have shown quite a strong association in younger people which is difficult in theory to explain by confounding. It could be that there is a sub-group of people susceptible to the effects of smoking which is progressively eliminated, with the smaller association in older men due to a confounding effect, although it could be argued that if smoking is a major cause of IHD in the young, it is probable it has some effect in the old.

Overall I feel that the evidence is suggestive, but not conclusive, that smoking causes IHD. In any event the multifactorial nature of IHD makes two things clear. Firstly, any estimate of deaths due to smoking is likely to be subject to very considerable uncertainty as the relative risk estimated from the epidemiological studies is rather unlikely to accurately indicate the true extent to which smoking might increase risk. Secondly, it will be remarkably difficult to obtain any useful test of the hypothesis that smoking causes IHD by study of trends in IHD against trends in smoking (because of the likelihood that trends in other risk factors may have masked the true picture).

Cerebrovascular disease (stroke). There were 25,519 deaths in males and 43,080 in females from stroke in England and Wales in 1988. 73% of deaths occur in those aged 75 or older. It is interesting to note that this is a disease for which the US Surgeon-General has changed his conclusions. In 1979 he noted the

epidemiological data produced results which "have not been congruent", that "no conclusion can be stated with confidence", and that "the relationship of smoking to the incidence of stroke is not established" though he noted "an association with subarachnoid haemorrhage has been reported in women". In 1989 he noted that "current evidence indicates that cigarette smoking is a cause of stroke", noting "an increased risk for stroke among smokers compared with non-smokers that is independent of other risk factors, a dose-response relationship, and a decrease in stroke risk with smoking cessation". Though in fact the 1989 report did not contain a detailed analysis to fully describe the reasons for a change in view one was the increase in relative risk of stroke for current smokers between CPS-I (1.9 for men and 1.5 for women) and CPS-II (3.7 for men and 4.9 for women). A recent meta-analysis by Shinton and Beevers (1989) estimated the relative risk associated with cigarette smoking to be 1.5 for all studies, but noted considerable variation in risk by age (with a 3 fold risk in those under 55, and virtually no association in those aged 75+) and by type of stroke (cerebral infarction 1.9, cerebral haemorrhage 0.7 and subarachnoid haemorrhage 2.9). The relationships could not be explained by confounding by blood pressure or obesity, two major risk factors for stroke. While it is possible that smoking may cause stroke, my view of the evidence I have seen is that it is not conclusive, although I would actually prefer to do a detailed analysis of the extensive available data before coming to a firm view.

Peripheral vascular disease. Atherosclerotic peripheral vascular disease (PVD) is primarily a stenosing or occlusive

disorder of the arteries, usually of the legs. Blood supply to the extremities becomes limited with tissue atrophy and gangrene occurring in some cases. A number of studies have demonstrated that patients with PVD are predominantly smokers, the incidence of smoking being markedly higher than that in control populations. Clinical experience demonstrates that continuation of smoking worsens prognosis after surgical therapy. While the evidence that smoking causes PVD is quite compelling, evidence that it causes a rare form of the disease (Buerger's disease or thromboangiitis obliterans) seems completely conclusive. I reviewed evidence from 27 published papers in 1986 which showed that the disease, to all intents and purposes, only occurred in smokers, occurred much more often in heavy smokers, was uniformly progressive (resulting frequently in amputations) if smokers continued to smoke and did not progress further if smokers stopped smoking permanently. It is quite plausible that the disease, which virtually only occurs in men, is caused by a hypersensitivity to a specific tobacco component. Note that inference of a causal relationship is particularly solid here for two reasons - virtual absence of the disease in non-smokers, and the fact that one can study the relationship <u>within</u> smokers of changes in smoking habits on progress of disease.

<u>Aortic aneurysm</u>. Abdominal aortic aneurysm refers to the dilatation or expansion of the aortic wall due to degenerative or inflammatory destruction of the components of the wall. If the wall ruptures as a result death usually occurs rapidly. A number of the large epidemiological studies have demonstrated an increased risk of death from aortic aneurysm in smokers with a relative risk around

3-5. A large autopsy study found aneurysms eight times more frequently in heavy smokers than non-smokers. Possible confounding by other causes of aneurysm have not been considered in the studies but the magnitude of the association makes it quite probable smoking is a cause. In England and Wales in 1988 there were 5,081 deaths in males and 2,833 deaths in females from aortic aneurysm.

Peptic ulcer. There is evidence of a positive association between smoking and peptic (or gastric) ulcer from a number of directions. Thus prospective studies show that mortality from ulcer is more than twice as high among smokers as non-smokers, cross-sectional studies show a higher prevalence of the disease in smokers, while clinical studies show a reduced rate of healing in smokers. The underlying causes of the disease are not clearly understood, although drugs (Tagamet, Zantac) have been successfully developed to counter the excessive acid secretion which characterizes it and thus successfully heal and prevent recurrence in many people. It seems quite probable from the evidence that smoking is harmful as regards peptic ulcer, especially in view of the fact that part of the evidence comes from a classic randomized intervention study of Doll et al (1958) in which smokers with ulcer were randomized to receive or not receive advice to give up smoking, a considerably improved healing rate being seen in those receiving the advice.

Osteoporosis. The term "osteoporosis" refers to reduced bone density, which typically occurs post-menopausally in women. The greater the degree of osteoporosis, the greater the risk of fracture, especially of the hip, wrist and spine though, of

course, risk of fracture also depends on the risk of falling. A number of studies have indicated that smokers have reduced bone mineral density and an increased risk of fracture, though the evidence is not totally consistent. Even if there is an association, there are a number of possible explanations. These include confounding by body weight (smokers are thinner and fat people have higher bone density and less risk of fracture), or by alcohol (smokers drink more and heavy drinkers have lower bone density and fall over more readily), as well as a direct effect of smoking on oestrogen synthesis and metabolism. Smoking would not seem to explain the dramatic rise in incidence of hip fracture in the last 30 years in many Western countries, there being some hundreds of thousands of cases annually in the UK. Smoking may contribute to risk of osteoporosis and to risk of fractures but the evidence of a causal role has not been conclusively demonstrated.

Parkinson's disease (paralysis agitans). This is one of the few common conditions for which there is clear evidence that smoking is associated with a reduced incidence. I reviewed the epidemiological evidence in detail in 1987 (TJ696). There are of the order 50,000 patients with Parkinson's Disease in England and Wales (as with all virtually essentially non-fatal diseases prevalence in the population is not reliably known). The evidence is consistent that those who have ever smoked have about a half the risk of those who have never smoked, and the epidemiological data are all consistent with a true causal protective effect of smoking. Parkinson's Disease is characterized by a deficiency of dopamine in the brain and a direct effect of nicotine in stimulating dopaminergic pathways in

the central nervous system is a possible mechanism. It should be noted, however, that there is as yet no known common cause of Parkinson's Disease and it is not impossible that were one discovered which happened to be negatively related with smoking, the judgment might change. Wald et al (1990) consider the relationship probably causal.

Inflammatory bowel disease. In 1987 I collaborated in a review (Cope et al, 1987) of cigarette smoking and inflammatory bowel disease. There are two major types of inflammatory bowel disease, ulcerative colitis (UC) and Crohn's Disease (CD). Their combined incidence worldwide is less than 20 per 100,000 so it is a relatively uncommon disorder, though quite well studied. The relationship of smoking to the diseases is complex. Compared to those who have never smoked, current smokers have a strikingly reduced prevalence of UC, by an estimated factor of about 4, very consistently seen in over 10 studies. There is however a suggestion that ex-smokers have an increased risk of UC in some studies, though the evidence here is somewhat conflicting. Despite this, virtually all studies show a reduction in UC in ever versus never smokers. In contrast the evidence on CD shows a positive association, clearer in current smokers (risk about doubled) than in ex-smokers. A clear explanation of why these differing associations have occurred has not yet emerged. Various possibilities are discussed in our review. It should be noted that CD is strongly associated with refined sugar consumption and that smokers take more refined sugar than non-smokers.

Age at menopause. Women who smoke cigarettes have very consistently been found to have a natural menopause at an earlier age than women who do not smoke, current smokers having a menopause one to two years earlier than never-smokers. Ex-smokers have only a slightly earlier menopause. The difference in age at menopause has remained after statistical adjustment for a number of confounding variables. From the evidence I have seen, though I have not studied it systematically, I would not disagree with the verdict of Wald et al (1990) that it is probably causal.

References to section 7

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8. Risks of ETS exposure

This is not intended to be a detailed discussion of epidemiological evidence here. The interested reader is referred to my own draft book, hopefully to be published this year by Karger, "A detailed review of epidemiological evidence relating environmental tobacco smoke (ETS) to the risk of cancer, heart disease and other causes of death in adults who have never smoked" and to various reviews in the Proceedings of the 1989 Montreal Conference, published last year with editors D.J. Ecobichon and J.M. Wu by McGill University. Rather it is a summary of key points and conclusions.

Some general points

In order to disentangle the possible effects of active and passive smoking, most studies of the effects of passive smoking limit attention to people who have never smoked, or at least report they have never smoked.

Some diseases, particularly those that are rare and strongly associated with smoking, are very difficult to study. Larynx cancer in a never smoker, for example, is extremely uncommon and no reliable data on possible effects of ETS exposure has been accumulated.

Virtually none of the studies of risk estimate exposure by objective by measurements of smoke constituents in air or in body fluids. They tend to rely on questionnaire data, with marriage to a smoker being the most commonly used index of ETS exposure. Studies relating objective measurements (such as cotinine - a major

metabolite of nicotine - in blood, urine or saliva) to questionnaire statements confirm, however, that exposed or more-exposed subjects acccording to questionnaire answers do in fact have more actual exposure than subjects reporting no or less exposure.

Because tobacco smoke contains various carcinogens and other toxic chemicals, ETS exposed nonsmokers will have some exposure to these. The level of exposure from ETS is, however, very much lower than that arising from active smoking. The factor varies according to the smoke constituent in question; it is about 0.5% if based on inhaled particulate matter or cotinine, and about 0.05% if based on particulate matter retained in the lung. (In other words the average ETS exposed non-smoker retains in the lung an amount of particulate matter derived from tobacco smoke that is about 1/2000th of that retained by an average smoker). Although higher factors can be calculated for certain vapour phase constituents, it would be surprising, a priori, if risk from ETS exposure were to be at most more than a small fraction of risk from active smoke exposure. Claims of relative risk from ETS exposure of a similar magnitude to those from exposure to active smoking, are difficult to reconcile with the dosimetric evidence.

It is clear that on average smokers have considerably more ETS exposure than do ETS-exposed never smokers. This makes it difficult to reconcile claims that ETS exposure increases risk of any disease not associated with active smoking.

In studies of diseases strongly associated with smoking which use marriage to a smoker as the index of ETS exposure, an artefactual association may arise simply because of the (documented)

tendency for a small proportion of current or past smokers to report that they have never smoked. The magnitude of this bias depends on a number of factors: the strength of the association of active smoking with the disease, the proportion of ever smokers denying they had even done so, the proportion of ever smokers in the population, and the extent to which smokers tend to marry smokers (it is well documented that the smoking habits of a man and his wife are not independent).

Lung cancer

There are almost 30 published studies, mainly case-control, providing some evidence. The studies show a clear positive association in females between risk of lung cancer and smoking by the spouse (or other household members), with never smoking women married to a smoker having an average 1.2 to 1.5 times the (low) risk of lung cancer of never smoking women married to a non-smoker. This association is also evident in males, though the data here are less extensive. There is no consistent evidence of an association between risk of lung cancer and exposure to ETS at work or in childhood. The association between lung cancer and spouse smoking is present in studies in the US, Europe and Asia, and is dose-related. The epidemiologically observed increase in lung cancer associated with spouse smoking averages about 10% to 20% of that associated (in the same studies) with active smoking. This contrasts with the much lower relative exposure to smoke constituents noted above. Though the magnitude of the epidemiologically observed associations is surprisingly large when viewed against the dosimetric evidence, it is still well within the

range of values which epidemiology is notoriously poor at detecting reliably.

There are two major sources of bias in the epidemiological evidence. One results from lack of comparability in a non-smoker of the studies between cases and controls in the circumstances under which data were collected. The second results from misclassification of ever smokers as never smokers. This can explain all of the association between ETS and spouse smoking seen in men and can explain most of the association seen in US and Western European women. Lack of evidence on misclassification rates in Asian women preclude any reliable conclusion as to its importance there. Other sources of bias to be noted include publication bias (for which there is some evidence), failure to adjust for confounding factors, and specific weaknesses evident in some studies. Generally the epidemiological studies regarding the strongest associations were those which were of the lowest quality.

The epidemiological evidence does not convincingly demonstrated that the observed association of lung cancer with spouse smoking results from a causal effect of ETS exposure.

Cancer of sites other than the lung

The evidence on ETS as a possible risk factor for cancer at sites other than the lung is fragmentary and inconclusive. For no site is there any consistent association with ETS to be explained. There are isolated reports in particular studies of associations of ETS with risk of cancer of the colon, brain, endocrine glands, breast, cervix and nasal sinus, but none provide convincing evidence of any cause and effect relationship. Chance, evaluation of

multiple endpoints, and biases due to poor study design doubtless explain most of the associations. The reported association with cervix cancer seems likely to have arisen from failure to adjust fully for sexual habits.

Heart disease

There is evidence from 11 studies (although full results have only been reported in eight). Although there is evidence of an association between ETS exposure and risk of heart disease from the data presented, this is not convincing evidence of a true effect for four reasons:

i) many of the studies are based on very small numbers of deaths;

ii) the only two studies with relatively large numbers are both open to a number of important criticisms:

iii) some studies report a relative risk estimate which is implausibly high, bearing in mind the magnitude of the association of heart disease with active smoking; and

iv) it is highly probable publication bias has occurred to a major extent.

It is notable that the American Cancer Society million person study (CPS-I) is known to have relevant data on more deaths from heart disease among never smoking women than have occurred in all the published studies combined, but has not reported findings, presumably because no relationship with ETS was found.

Other fatal diseases in adults

Relative few studies have investigated the relationship of ETS to diseases other than cancer or heart disease. Isolated unconvincing reports of a relationship of ETS to stroke, chronic

obstructive lung disease, and to suicide require confirmation from other studies before it can be determined whether in fact any association exists.

Respiratory disease in adults

Possible respiratory effects of ETS have been studied by various techniques, including epidemiological studies of pulmonary function (as reflected by spirometry) and/or respiratory symptoms (e.g. cough, phlegm or wheeze) or disease in non-smokers exposed chronically to ETS, as well as experimental studies of the acute effects of ETS on pulmonary function in normal and/or asthmatic individuals. Witorsch (1990) has summarized the evidence from the various types of study. He notes that the epidemiologic studies are too variable in results to permit any conclusion concerning an association between long-term ETS exposure and impaired respiratory health on pulmonary function in non-smoking adults, and that if ETS does in fact affect the pulmonary health of non-smokers its effect is likely to be subtle. He also noted that acute exposure studies in normal individuals generally failed to demonstrate an adverse effect of short-term exposure on pulmonary function, even under artificially extreme conditions. Acute exposure studies in asthmatics have yielded contradictory and inconsistent results. While most asthmatics do not appear to respond, there seems to be a sensitive sub-group in whom ETS exposure does result in increased airflow obstruction. It seems fairly generally accepted that ETS exposure may cause attacks of asthma, possibly by a psychological rather than a physiological mechanism in some cases,

but no evidence has been presented that it will make someone become an asthmatic.

Reference to Chapter 8

Witorsch, P. (1990) In: Environmental Tobacco Smoke. Proceedings of the International Symposium at McGill University 1989. eds. D.J. Ecobichon and J.M. Wu. Lexington Books, 169-185.

9. Effects in pregnancy, infancy and childhood

This section is concerned with possible effects of smoking on children before they themselves smoke, on infants, or in pregnancy. There are two general points to be made that apply to many if not all of the health endpoints that have been considered.

The first is that it is difficult to disentangle various possible types of effect. Maternal smoking has often been used as an index of exposure, but for endpoints that occur after the birth of the child, it may not be possible to distinguish between possible effects of smoking in pregnancy (via transfer of smoke constituents to the fetus) and possible effects of ETS (from the cigarettes smoked by the mother). Similarly paternal smoking might also produce effects via ETS exposure or by effects on sperm. In some studies conducted more recently, the health of the child has been related to ETS exposure of the mother, i.e. the mother herself is a non-smoker but she may be exposed to the smoke of others - if one of those others is the father, one again has the problem of distinguishing effects on sperm from those of ETS exposure.

The second is that there is a major problem with regard to potential confounding by other factors. Many of the health endpoints studied have numerous risk factors that are correlated with them. Adjustment for some of these materially affects some of the associations with parental smoking. For risk factors such as social class, which are inherently inaccurately measured or surrogates for a true risk factor, the association remaining after adjustment may represent "residual confounding" rather than a true

association.

I am currently collecting together evidence for a detailed review later in the year of this area, with particular attention to possible effects of ETS. My views at the current time on some of the more important of the various areas are summarized briefly below.

Birth weight. There is abundant evidence that smoking mothers have babies that are lighter than those of non-smoking mothers by an average about 200 grams. The difference has been found to be independent of all other factors known to influence birth weight, and is dose-related. If a woman gives up smoking by the fourth month of gestation her risk of delivering a low birth-weight baby is similar to that of a non-smoker. This reduction in birth weight is probably a consequence of the smoking by the mother. Although there have been reports of birth weight reduction resulting from paternal smoking or from maternal ETS exposure, the evidence of an association is inconsistent. A causal relationship has certainly not been demonstrated.

Birth malformations. There is no consistent evidence that smoking is teratogenic, i.e. that it leads to malformations in the offspring.

Spontaneous abortion. There is evidence from several studies of a statistically significant association between maternal cigarette smoking and spontaneous abortion. Some of these studies have shown a dose-response relationship between incidence and number of cigarettes smoked. Spontaneous abortions are difficult to study because of problems in ascertainment. Although an association exists, it is not clear whether this results from a causal relationship.

Perinatal mortality. A number of studies, some of substantial size, have shown an association of fetal and infant mortality to maternal smoking. A recent large study in Missouri reported that risk in first-born children was increased by 25% in mothers smoking less than a pack a day and by 56% in heavier smoking mothers. The problem in interpreting this, and other studies, as indicating a true effect of smoking was the wide range of other factors affecting risk and the fact that statistical adjustment for them substantially reduced the relationship with maternal smoking. While it is possible that smoking does increase risk of perinatal mortality, it is also possible that part or all of the association is due to residual confounding or to confounding by other unmeasured risk factors.

Sudden infant death syndrome (SIDS). A number of studies have shown an association between maternal smoking and SIDS with a relative risk of about 2. The main problem in interpreting this association as a cause and effect relationship lies in the difficulty of fully accounting for the affects of many confounding factors, including the huge association with social class. A Welsh study showed that lower social class infants had a 14 times higher risk of SIDS than did higher social class infants.

Child development. Much of the evidence on this has come from the follow-up of children born in one week in 1958 (see section 6). Children born to mothers who smoke have shown reductions in height and in educational achievement compared to children born to mothers who did not smoke. It is clear that these deficits, which are in any case quite small in magnitude, are reduced by adjustment for numerous risk factors for height and educational attainment. Again

social class related factors are important and it remains unclear the extent to which the association represents residual confounding or a true effect.

Childhood cancer. Although there have been isolated reports of an increased incidence of childhood cancer in relation to parental smoking or ETS exposure, the evidence is inconsistent and inconclusive. A recent review by Doll (1989) of the epidemiology of childhood leukaemia, a major contributor to the overall incidence of childhood cancer, did not even mention parental smoking or ETS.

Respiratory health in children and infants. There is very clear evidence of an association between parental smoking and the incidence of bronchitis, pneumonia, and other lower respiratory tract infections in infants during the first year of life. The evidence is less clear for older children though the overall data still suggest some association. Although much of the evidence of an association has been in the literature for many years now, it remains far from certain which of 4 possible mechanisms explain it: a direct effect of ETS exposure, effects of maternal smoking in pregnancy, cross-infection from the parents (smokers have higher rates of infection than non-smokers), or confounding by social class related or other variables. Although studies have adjusted for parental infection, social class and other potential confounding factors, it is far from certain adjustment has been complete. An effect of maternal smoking in pregnancy is perhaps the least likely of the explanations, but none of the others can really be ruled out. This is certainly one of the areas where evidence of a possible effect of smoking on other people is strongest, though not

completely conclusive.

Lung function in children. There has been a relatively large number of studies relating lung function in school age children to parental smoking. (It is difficult to administer the tests to infants.) The results, recently summarized by Witorsch (1990), are variable. Where studies have reported a reduction in lung function, by a decreased FEV_1 (forced expiratory flow in 1 second) or FEF_{25-75} (rate of airflow between the 25% and 75% points of the forced vital capacity), the effect has been small and levels within what are considered to be the normal range. Difficulties in interpreting an association, if it exists, are similar to those for interpreting possible effects on respiratory health in children and infants.

Chronic ear infections ("glue ear"). In recent years a number of studies have reported an association between parental smoking (or ETS exposure) and chronic ear infections (referred to as glue ear, middle ear effusions, or secretory otitis media). The interpretation of these findings seems in many ways similar to that for respiratory infections in infants and children, but I have not examined the evidence in detail.

References to Chapter 9

Doll, R. (1989) Journal of the Royal Statistical Society, 152, 341-351.

Witorsch, R. (1990) In: Environmental Tobacco Smoke. Proceedings of the International Symposium at McGill University. Eds. D.J. Ecobichon and J.M. Wu, Lexington Books, 205-226.