Environmental Tobacco Smoke and Lung Cancer

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Introduction

Unfortunately, passion and prejudice nowadays compete with objectivity in most discussions of this topic. As a non-smoker, who not infrequently suffers from irritation to the nose, throat and eyes from other people's smoke, I am arguably not the right person to prepare an objective review of the subject. However, hopefully, my basic scientific training and long experience of less emotionally evocative issues, will enable me to rise above any prejudices that I may have.

In setting the scene for my talk I must first make it clear that I intend to stick stoically to its title. Thus I will not be discussing the possible relationships between exposure to ETS and diseases other than lung cancer. Although most people know, in superficial terms, what ETS is, and what lung cancer is, it is necessary, first, to consider in some detail what exposure to ETS really entails and secondly to be aware of the fact that death from lung cancer as shown on death certificates is subject to high false positive and false negative rates. The first two sections of this paper concern these topics.

Most humans living and working in temperate climates spend much more of their time indoors than outdoors. Nevertheless, until relatively recently the possible dangers to health from outdoor air pollution have attracted far more concern and research than those of indoor air pollution. Before the importance of the contribution of cigarette smoking to lung cancer risk was appreciated, numerous investigators concluded that city dwellers and persons exposed to industrial air pollution and vehicular exhaust fumes are 50% to 100% more at risk of developing lung cancer

than persons living in rural areas[1,2,3]. Some of the difference could be explained by differences in smoking habits between city and country dwellers, particularly during the period between the two world wars[4,5]. On the other hand, the ease with which it is possible to induce skin cancers in mice by applying to them extracts from particulate city air material[6,7] indicated that oudoor air pollutants should not be dismissed as unimportant.

Restrictions on smoke emission by factories and domestic chimneys and more recently introduced restrictions on the emission of fumes by traffic vehicles, has led to striking reductions in outdoor air pollution and as this has happened, interest has increasingly switched to the quality of indoor air. In parallel, there have been striking advances in chemical analytical technology such that it is now possible to detect the presence in air of chemicals that are present in only extremely low concentrations (e.g. parts per billion). Unfortunately, whereas most toxicologists are aware of the wise words of the Swiss physician, Paracelsus, to the effect that "it is the dose that makes the poison", many politicians and many members of the public who are led by them, think that they are living in a world made up of a large number of "safe" substances and just a few toxic substances, and believe that no dose of a "safe" substance is toxic and no dose of a toxic substance is "safe". They have also been led to believe that it would be possible to eliminate cancer as a disease by excluding a relatively few carcinogens from the environment.

These considerations have served to transform a scientifically rather boring and fruitless area of toxicology into an emotion-driven hot political debate.

What is Environmental Tobacco Smoke?

There are 3 characteristics of ETS that distinguish it from other indoor air pollutants. Firstly, tobacco and tobacco smoke has a unique odour which anyone with average olfactory acuity can very easily detect even when the levels of airborne smoke components are exceedingly low. Moreover, the absorption and subsequent slow emission of these odorous smoke components by furnishing fabrics serves to prolong the period during which earlier smoking can be detected. Secondly, there are present in smoke irritant substances - particularly aldehydes such as acetaldehyde and acrolein - which are irritant to the eyes and upper respiratory tract. And thirdly, it is easy to see the source of ETS in the form of a smoker puffing away at his cigarette or pipe, etc.

If it were not for these 3 characteristics, indoor air pollution by ETS would not have become such a prominent issue as it is.

From a chemical viewpoint, ETS is not a clearly definable entity. The smoker of a cigarette emits into the air 4 kinds of smoke:-

(1) That derived initially from a match or lighter
(2) Exhaled mainstream smoke (that has been taken into the lungs)
(3) Exhaled 'waste' smoke (that has only been taken into the mouth)
(4) Sidestream smoke emitted by cigarettes, cigars, etc. between puffs.

Each of these types of smoke consists of a few main components plus a very large number of substances present in low or minute concentrations.

Physically, smoke components fall into 3 groups: volatiles, semi-volatiles and particulates, and individual substances within each of these groups vary widely in stability. After their emission, the various smoke components are progressively diluted by admixture with air, and the rate of dilution is greatly influenced by the efficiency of the indoor ventilatory system. Even under relatively poor ventilatory conditions, however, the concentrations of the volatile components fall rapidly because they escape through vents and cracks.

Whenever organic material is burned under conditions where there is insufficient oxygen for complete combustion, a wide range of so-called pyrolysis products are produced. This is true for open fires, bonfires and the toasting, roasting, frying or grilling of foods. In other words, the spectrum of chemicals present in tobacco smoke is closely similar to that in many other forms of smoke that may contaminate indoor air. The main exception is that tobacco smoke contains nicotine and related alkaloids, plus pyrolysis products derived from them, which are generally not present in smoke from other sources.

It has been claimed that carcinogenic nitrosamines derived from nicotine and related alkaloids contribute importantly to lung cancer risk from tobacco smoke[8]. Insofar as these same substances are present in sidestream smoke they add to the potential carcinogenicity of ETS. However, the concentrations of these substances are very low in comparison with those of chemical carcinogens of another type - the polycyclic aromatic hydrocarbons and related heterocyclic compounds - which are present in all kinds of smoke derived by the pyrolysis of organic substances[9].

These various considerations illustrate why it is exceedingly difficult to characterise exposure to ETS in any meaningful or quantifiable way. They also illustrate that quantification of exposure to ETS per se is likely to be meaningless unless it is paralleled by the collection of quantitative exposure data for exposure to other kinds of smoke, including cooking and heating fumes, smoke derived from various industrial processes, bonfire smoke, etc.

What does a diagnosis of "lung cancer" as recorded on the death certificate mean?

Pathologists distinguish different types of primary lung cancer according to the type of cells of which they are composed, and according to where in the lung they arise. The main types are: squamous, oat (small) cell, large cell and adenocarcinoma. Suspicion that a person has developed lung cancer is engendered by: a history of smoking, a history of exposure to an industrial lung carcinogen, symptoms of cough, especially if accompanied by haemoptysis, and a chest X ray shadow. The presence of cancer cells in sputum or pleural fluid or the presence of cancerous tissue in a sample of lung tissue taken at bronchoscopy confirms that a patient has cancer but does not establish that the cancer arose originally in the lung. Biopsy specimens taken from metastases from adenocarcinomas of the colon, pancreas or breast, for instance, are indistinguishable from those derived from primary adenocarcinomas of the lung.

Hungary is almost unique among developed countries in having a very high autopsy rate for persons dying in hospital. In a recent study, Kendrey et al[10] compared pre-autopsy and post-autopsy diagnoses in 1000 deaths at the Postgraduate Medical School and 1000 deaths here at the Semmelweis Medical University. It transpired that 59%

(31/61) primary lung cancers seen at autopsy were not detected pre-autopsy, and 50% (25/50) pre-autopsy diagnoses of primary lung cancer were not confirmed at autopsy.

Given the availability of a range of sophisticated diagnostic techniques, these very high false negative and false positive diagnostic rates for primary lung cancer may seem surprising. However, it has to be realised that many of the patients in whom the clinical diagnoses were wrong, were in fact too old or too ill when admitted to hospital to be submitted to a full range of diagnostic procedures. The commonest error was to misdiagnose the site of origin of a cancer which, by the time of admission to hospital, had spread to other tissues, including the lungs.

The figures derived from this recent Budapest Study are broadly similar to those in many other studies of the same kind that have been reported in various countries during the last 50 years, and there are no grounds for suspecting that clinical diagnostic standards are lower in Hungary than elsewhere. Indeed, the overall picture in Hungary, with its high autopsy rate, is better than that in other countries since, where an autopsy is performed it is the autopsy diagnosis and not the clinical diagnosis which goes on to the death certificate. In Japan, where the autopsy rate is only 3-4% of all deaths, the error rate for the diagnosis of lung cancer on death certificates is undoubtedly very much higher.

Even if an autopsy is carried out, death certification errors may still occur, for instance, because of coding errors or because death certificates completed on the day of autopsy are subsequently not corrected when diagnoses are amended following the microscopic examination of tissue samples.

The evidence needed for determining whether exposure to ETS predisposes to lung cancer

Latent intervals extending over 15-20 or more years usually separate first exposure to known occupational carcinogens and the appearance of cancers. In assessing whether ETS poses a lung cancer risk, therefore, one needs reliable exposure data, not only for the few months or years before the diagnosis of lung cancer is made, but for much longer periods and preferably going back to childhood. Because such data are never available, many epidemiologists have adopted the ploy of assuming that the smoking habits of a person's spouse and/or other cohabitees constitute a suitable surrogate for actual measurements of ETS exposure during the years before lung cancer is diagnosed. On this basis they have compared, mainly in case:control studies, the incidence of lung cancer in non-smokers (usually women) living with smokers with those of non-smokers living with non-smokers. Despite the many obvious reasons why the use of this surrogate measurement is wildly inaccurate, epidemiologists argue that unless accompanied by bias, such inaccuracy serves more to obscure real differences than to invent them. Hence the question needs to be posed. Are the spouses of smokers and the spouses of non-smokers alike in all ways relevant to the development of lung cancer other than their exposure to ETS in the home? As is made clear, below, the answer to this question is a very clear and definite 'No!'.

The results of both laboratory and epidemiological studies indicate that, in the case of carcinogenesis by genotoxic agents, the length of the period during which exposure has occurred is an important determinant of risk. One may deduce from this that if exposure to ETS is a risk

factor for lung cancer, then comparisons of lung cancer incidence in persons exposed to ETS during childhood with those not so exposed should provide evidence of increased risk. The fact that in the studies so far reported, no evidence of increased risk has been seen also undermines the theory that ETS exposure is a risk factor for lung cancer.

Finally, if ETS exposure predisposes to lung cancer, then one might have expected workplace exposure to ETS over many years to be associated with increased lung cancer risk. Again, the negative results that have emerged from studies of this run counter to the view that ETS exposure increases lung cancer risk.

Misclassification of people who are current smokers or ex-smokers as lifetime non-smokers

A serious problem in relation to assessing exposure to ETS on the basis of data derived by questionnaires, is that the answers people give concerning their present and past smoking habits are unreliable.

Current smokers are easily distinguished from current non-smokers by measuring the level of the nicotine metabolite, cotinine, in their saliva or urine. In a study in the UK[11], salivary cotinine measurements revealed that 2.5% of 808 persons who claimed to be non-smokers were in fact current smokers. In the same paper it was reported that among 540 subjects who completed the same questionnaire in 1980 and again in 1985 there were high levels of inconsistency between the answers given on the two occasions to questions concerning their smoking habits. Thus 17/174 men (10.9%) who claimed to be life-long non-smokers in 1980, claimed in 1985 to be ex-smokers who started smoking before 1980. Similarly, of 166 subjects who claimed in 1985 to be

lifelong non-smokers, 4 had said they were current smokers and 10 said they were ex-smokers when they completed the questionnaire in 1980 (giving a rate of 8.4% for this type of discrepancy).

There are nowadays an increasing number of reasons, other than sheer carelessness, and resentment at having their privacy invaded, why people do not tell the truth about their smoking habits. For instance, both men and women try to conceal from their spouses, children and physicians that they have failed to keep promises to stop smoking. More importantly, the practice of life insurance companies of charging smokers higher premiums has been a prescription for entering falsehoods on questionnaires about smoking.

In Japan, a woman's status in the marriage market is devalued if she admits to being a smoker. In a study of 400 women in Japan 22/106 (20.8%) who were found to be current smokers on the basis of urinary cotinine measurements claimed to be life long non-smokers[12].

Plausibility

It can and has been argued that, since smokers are at higher risk of developing lung cancer than non-smokers and since ETS contains many of the same chemicals as mainstream tobacco smoke, it is plausible that exposure to ETS increases the risk of developing lung cancer. Some of the estimates of relative risk of lung cancer in the non-smoking spouses of smokers, however, exceed those that have been calculated for light smokers. Clearly these are highly implausible since the smoker himself is more heavily exposed to ETS than the non-smoker in this vicinity.

Epidemiological studies aimed at investigating whether exposure to ETS predisposes to lung cancer

Three kinds of epidemiological studies have addressed this question: spousal/cohabitee studies, workplace studies and childhood exposure studies.

Spousal/cohabitee studies

In 33 studies of this kind, of which 4 were prospective and 29 were case:control, the risk (unadjusted for covariates) for a non-smoker married to a smoker relative to that for a non-smoker married to a smoker ranged from 2.5 down to 0.75. Meta-analysis of the data in these studies, provides weakly significant ($p<0.05$) evidence of an apparent association between exposure to ETS and lung cancer risk. However, in most studies, no data were collected in relation to several of the most important known confounding variables. The list of these includes radon, diet, heating and cooking fumes in the home, outside air pollution and the keeping of pet birds. Indeed, fewer than half the studies adjusted their findings for any risk factor other than age and some studies did not even adjust for age!

During recent years the importance of unhealthy diets (e.g. diets low in fresh fruit, vitamin C, beta carotene and antioxidants generally and/or high in saturated fat) as risk factors for lung cancer has become increasingly into prominence[13, 14, 15]. Failure to allow for dietary variables, however, does not lead merely to imprecision in assessing whether ETS predisposes to lung cancer, but it also leads to bias since it transpires that non-smokers exposed to ETS tend to eat significantly less healthy diets than non-smokers not exposed to ETS[16, 17].

Apart from failure to correct properly for bias due to misclassification of smokers as non-smokers, and failure to consider important confounders, many of the 33 studies have other weaknesses such as inappropriate matching of cases and controls, differences in method of collection of data with regard to smoking habits of cases and controls and their respective spouses, failure to require anything like a stringent basis for the diagnosis of lung cancer, only small numbers of cases and controls, failures to consider histological type of lung cancer, etc. etc. Lee [18] has pointed out that the studies with the fewer weaknesses exhibit lower relative risk values than studies with more weaknesses, and many of the studies giving the highest relative risks values involve fewer than 50 comparisons of cases and controls. Another point of interest is that later studies are giving lower relative risk values than earlier studies. Thus a meta-analysis of 11 studies reported between 1989 and 1992 indicated a relative risk of 1.02 (with 95% confidence limits of 0.95 - 1.15) compared with 1.29 (1.09 - 1.52) for studies reported in 1981 to 1985 and 1.42 (1.20 - 1.68) for studies reported in 1986 to 1988.

In the light of these many considerations and in the light of the fact that death certification in respect of lung cancer is subject to both high false-positive and high false-negative results it is impossible to have any confidence in the conclusion that living with a smoker increases the risk that a non-smoker will develop lung cancer.

Workplace exposure to ETS

A meta-analysis of data from 12 comparisons (9 studies) aimed at determining whether exposure to ETS at work is associated with increased lung cancer risk indicated

a relative risk of 0.98 (with 95% confidence limits of 0.89 - 1.08)[19]. In other words, this analysis provided no evidence of increased risk from such exposure.

Childhood exposure to ETS

A meta-analysis of the data from 13 comparisons (12 studies) aimed at determining whether exposure to ETS during childhood (i.e. as a consequence of parental smoking or smoking by other family members) increases the risk of lung cancer indicated a relative risk of 0.98 (95% confidence limits of 0.86 - 1.12)[19]. In other words, this analysis provided no evidence of increased risk from such exposure.

Conclusions

Personally, I would judge it is unlikely that exposure to ETS can do one any good. However, if, in the words of the playwright, George Bernard Shaw[29], such exposure "stimulated the phagocytes", I could be wrong in this judgement! Be that as it may, it is abundantly clear that the evidence for there being an association between exposure to ETS and increased risk of lung cancer is both insubstantial and unsatisfactory. Furthermore, given the impossibility of actually measuring and recording exposure to ETS over periods of 20 years or more while at the same time collecting reliable information with regard to diet and other factors which predispose to, or protect against, lung cancer, I see no prospect of it being possible to design a definitive study. The question is, therefore, should further costly resources be used up in chasing this 'Will-o'-th'-Wisp' problem, when potentially more tractable medico-scientific problems are crying out for support? I, personally, think "not"!

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