



Evidence for Smoking Causing Lung Cancer

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This medical discussion paper will be useful to those seeking general information about the medical issue involved. It is intended to provide a broad and general overview of a medical topic that is frequently considered in Tribunal appeals.

Each medical discussion paper is written by a recognized expert in the field, who has been recommended by the Tribunal's medical counsellors. Each author is asked to present a balanced view of the current medical knowledge on the topic. Discussion papers are not peer reviewed. They are written to be understood by lay individuals.

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Preamble

Most physicians working in lung cancer research hold firmly to the view that the association between cigarette smoking and lung cancer was established fifty years ago by Doll and Hill's study of British physicians. Yet some advocates for the tobacco industry still believe that there is no proof for smoking being the main cause of this dreadful condition, which in spite of great advances in cancer treatment carries a virtual death sentence on its diagnosis. Two main causes for this paradox may be identified—first, that there are many factors (genetic, environmental, life-style, etc) that contribute to cancer causation; and second, that “proof, like beauty, lies in the eye of the beholder”. People's perception of what constitutes adequate proof differs widely; in spite of the recent popularization of so-called “evidence-based medicine” the quality of the evidence remains necessarily subjective.

In retrospect, the first evidence was provided by data on the prevalence of smoking, and increasing mortality from lung cancer, but the lag between cause and effect delayed recognition of a relationship between the two. Differences between men and women in both smoking habits and mortality provided later clues, but it was not until prospective studies of smoking versus non-smoking adults, and of individual smoking load, that the effects were clearly demonstrated. More recent work has helped to define other contributory factors, and improve the scientific and statistical methodology. Age-standardized mortality ratios, and such concepts as “pack-years” have been used to provide risk factors for individuals, but there are still gaps in our understanding that make it difficult to quantify risk; such as, for example, the contribution of an occupational or environmental exposure relative to the risk of smoking.

The present brief review will summarize the major studies carried out during the past half-century that have built the case for smoking being the cause for lung cancer, and that provide quantitative evidence that may help to apportion blame when assessing lung cancer occurring in the workplace.

Introduction

The historical background to the study of smoking related cancer deaths includes the trends in smoking consumption and in cancer mortality [2]. The prevalence of cigarette smoking was small in 1900, but the *per capita* consumption in the USA increased ten-fold between 1900 and 1920 to reach about 700 cigarettes per annum per head of the population. The distribution of free cigarettes to the armed services led to sharp increases between 1915-20 and 1940-45, and overall *per capita* consumption in North America reached 3,500 in 1950, peaking at 4,300 in 1963. Data on smoking habits first appeared in a survey by the Milwaukee Journal; in 1935, 62% of males in the area were regular smokers, compared to 17% of females; by 1960 there was little further increase in males, to 70%, but the prevalence of adult female smokers had dramatically increased to 50%. Thereafter, a number of surveys showed a steady decline in cigarette consumption; in 1980 approximately 30% of both adult females and males smoked regularly [12]. These historical figures contribute to the rates at which lung cancer mortality increased, both in the general population and in males versus females.

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The fact that smoking reached its peak in the mid-1960s implies that lung cancer rates will be highest in people that are now aged 60-80, but should then gradually decline.

Of course, such smoking statistics can never tell the whole story, because of large differences between individuals in smoking habits, including number of cigarettes smoked per day, the type of cigarette smoked (filter vs. plain, tar and nicotine content, depth of inhalation, etc). Surveys have shown that daily consumption in men has always been higher than women, that more men inhale deeply and also smoke cigarettes with higher tar and nicotine content. Also, women have used filter-tip cigarettes in greater numbers than men; a survey in 1964 showed 79% of adult women smokers and 54% of men used filter-tips.

The average age that adults begin smoking has also changed; in the 1930s the average age at which women began to smoke was 35, but this has now dropped to 16, similar to men. Indeed the prevalence of smoking among teen aged women exceeds that of men.

Lung cancer incidence and mortality

Before the 1920s, lung cancer was rare. However, over the subsequent two decades, an increasing incidence was noted, but put down to improved diagnosis and related factors. Incidence and mortality increased rapidly. An age effect was noted, with 60 year-olds being roughly 100 times more likely to be diagnosed than 40 year-olds, together with a gender effect- men being approximately 7 times more likely than women. In the 1960s, incidence in men peaked and began to fall, whereas in women the incidence continued to increase; by 1983 the ratio of males to females had fallen to 2.8 [14].

In spite of great advances in cancer management, the outlook for lung cancer patients remains very bleak. This means that changes in mortality rates reflect changes in cancer incidence to a greater extent than many other cancers.

The age effect meant that the crude mortality rate could not be used to establish trends, as people progressively lived longer; statistical methods were developed to correct for this effect (age standardization).

Evidence for the link

In the 1950s, smoking histories began to be systematically recorded, in patients with many diseases; it was recognized that non-smokers did not contract lung cancer. It was realized that a link between smoking and cancer would only be revealed by large, prospective studies, in which smoking histories were obtained in apparently healthy people who were then followed over several years. A problem in such studies was the reliability of self reported smoking habits. However, the first study to establish a causative link between cancer and smoking was carried out in doctors, who were felt to be more reliable than the general population in this regard. Recruited into the study by Richard Doll and Austin Bradford Hill in the 1950s, 40,000 British doctors were followed over the succeeding 25 years [4]. Because they were followed regularly, their smoking history was more reliable than other surveys, and the effects of changes in smoking habits could be studied.

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The initial results of Doll and Hill's study, standardized for age distribution, showed that lung cancer was 10-15 times commoner in moderate smokers and 30-40 times commoner in heavy smokers than in lifelong non-smokers; cancer incidence in previous smokers who had quit before the study were 3-4 times commoner. Rates were lower in women than men, but women tended to start smoking later, to use filter tips more often and to inhale less. However, in females who were heavy smokers (40 cigarettes/day), rates were similar to their male counterparts.

Much larger studies in the US, by the American Cancer Society, in Japan and in Sweden, showed essentially similar results. However, among these studies there is considerable variation in the relationship between the quantity smoked and relative risk of cancer development (see Table 1) [2]. There are many possible reasons for the variability, which have to be kept in mind before ascribing a relative risk based on an individual history of smoking. These reasons include variability in recall, cultural differences in smoking perception, different smoking habits, and race-related effects.

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Table 1. Risk ratios for death from lung cancer in men and women, by quantity smoked in six prospective studies.

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Study	Women		Men	
	Smoking Status	Relative Risk	Smoking Status	Relative Risk
British doctors' study 1951-1973	Nonsmokers	1.0	Nonsmokers	1.0
	Current smokers	5.0	Current smokers	14.0
	1-14 cigarettes/d	1.3	1-14 cigarettes/d	7.8
	15-24 cigarettes/d	6.4	15-24 cigarettes/d	12.7
	≥ 25 cigarettes/d	29.7	≥ 25 cigarettes/d	25.1
Cancer Prevention Study I (CPS-I) 1959-1972	Never smoked	1.0	Never smoked	1.0
	Current smokers	3.6	Current smokers	8.5
	1-9 cigarettes/d	1.3	1-9 cigarettes/d	4.6
	10-19 cigarettes/d	2.4	10-19 cigarettes/d	8.6
	20-39 cigarettes/d	4.9	20-39 cigarettes/d	14.7
	≥ 40 cigarettes/d	7.5	≥ 40 cigarettes/d	18.7
Swedish study 1963-1979	Nonsmokers	1.0	Nonsmokers	1.0
	Current smokers	4.5	Current smokers	14.0
	1-7 cigarettes/d	1.8	1-7 cigarettes/d	7.8
	8-15 cigarettes/d	11.3	8-15 cigarettes/d	8.8
			≥ 16 cigarettes/d	13.7
Japanese study of 29 health districts 1966-1982	Nonsmokers	1.0	Nonsmokers	1.0
	Current smokers	2.0	Current smokers	3.8
	< 20 cigarettes/d	1.9	< 20 cigarettes/d	3.5
	20-29 cigarettes/d	4.2	20-39 cigarettes/d	5.7
			≥ 40 cigarettes/d	6.5
Kaiser Permanente Medical Care Program Study 1979-1987	Nonsmokers	1.0	Nonsmokers	1.0
	Current smokers	15.1	Current smokers	8.1
	1-19 cigarettes/d	8.5	1-19 cigarettes/d	4.7
	≥ 20 cigarettes/d	21.7	≥ 20 cigarettes/d	10.4
Cancer Prevention Study II (CPS-II) 1982-1988	Never smoked	1.0	Never smoked	1.0
	Former smokers	4.7	Former smokers	9.4
	Current smokers	11.9	Current smokers	20.3
	1-9 cigarettes/d	3.9	1-9 cigarettes/d	12.2
	10-19 cigarettes/d	8.3	10-19 cigarettes/d	14.6
	20 cigarettes/d	14.2	20 cigarettes/d	21.7
	21-39 cigarettes/d	21.4	21-39 cigarettes/d	22.8
	40 cigarettes/d	19.3	40 cigarettes/d	24.2
	≥ 41 cigarettes/d	18.2	≥ 41 cigarettes/d	45.7

From US Department of Health and Human Services: Women and Smoking: A Report of the Surgeon General, US Department of Health and Human Services, Centers for Disease Control and Prevention, Office on Smoking and Health, 2001.

Duration and intensity of smoking

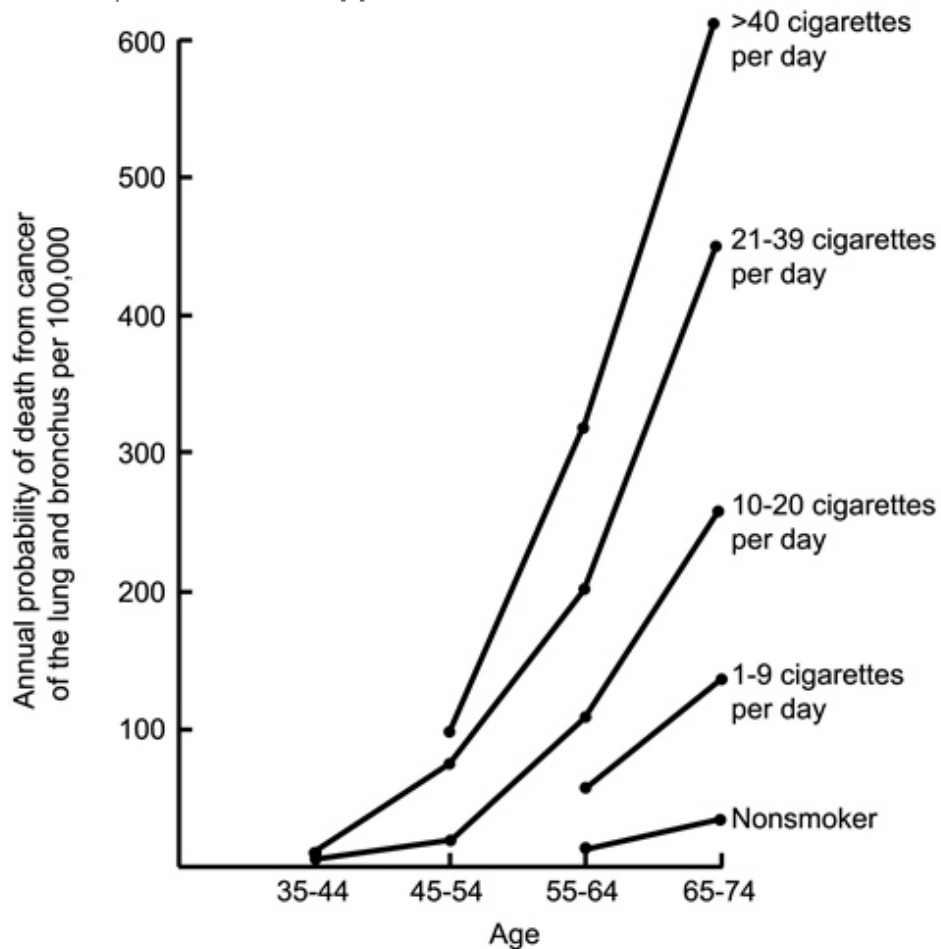
All large prospective studies have shown that lung cancer incidence and mortality increase with increasing duration and number of cigarettes smoked. This is impressively shown by data obtained in a study of US veterans (Figure 1), published by Kahn [8]. This led to the concept of “pack-years” of smoking, in which average cigarette usage in packs of cigarettes per day is multiplied by the total duration in years. Whilst this index is used extensively in clinical assessment, it seldom appears in epidemiological studies, mainly because of the unreliability in subjects’ recall of their past cigarette usage. Most prospective surveys have used current smoking at enrolment as the index of smoking intensity, and in the best studies the smoking habits were documented regularly at follow-up. **We do not have the information to quantify the difference in risk between, say, smokers with a 50 or 100 pack-year history, nor whether a 50 pack-year made up of 1 pack smoked for 50 years is equivalent to 2 packs smoked for 25 years.** Recent studies have shown that for a given pack-years value, lower intensity smokers (<20/day) have a higher risk ratio than higher intensity smokers (>20/day) [16]. Duration is more important than intensity. The finding is consistent with experimental carcinogen studies in animals.

The effect of quitting smoking could be studied in Doll and Hill’s study of British doctors; the incidence of lung cancer fell 5 years after quitting, but never reached the rate in life-long non-smokers. Fifteen years after stopping the rate had dropped from 16 times to twice the rate of non-smokers [4].

Finally surveys have shown that less than 2% of lung cancer deaths occur in lifelong non-smokers; however, women non-smokers have a much higher relative risk than their male counterparts (see below).

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Figure 1.
Reproduced with permission. From ref [8]



Death rates from cancer of the lung and bronchus in nonsmokers and smokers of various numbers of cigarettes per day.

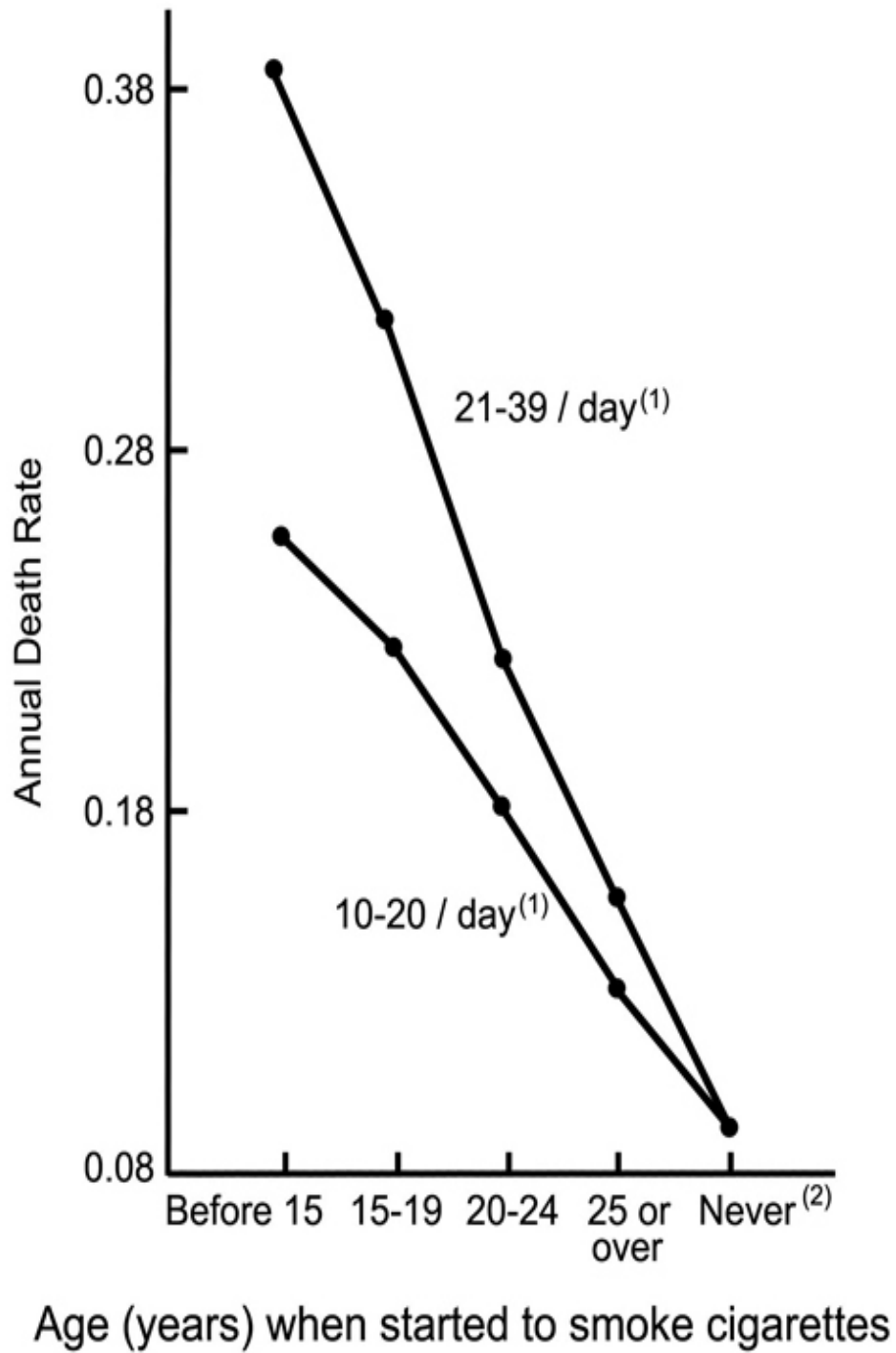
Source: Kahn (1966).

Age at which smoking started

The US veterans study revealed a large effect of age at which smoking commenced, steadily increasing in age below 25 years, in both moderate (10-20 per day) and heavy (21-30 per day) smokers; smokers who began before the age of 15, had a 3-4 times higher death rate at age 60 than those who began at 25 or over (Figure 2). This finding also has been supported by animal experiments in which age influences the effects of carcinogens on DNA damage [16].

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Figure 2. Annual death rate at age 60 related to age at which smoking began, for moderate and heavy cigarette consumption
Reproduced with permission. From ref [8]



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Type of cigarette smoked.

So-called low-tar and filter cigarettes were introduced in the 1940s, and now comprise close to 100% of cigarettes sold in North America. Prospective surveys have shown a significant reduction in risk, associated with a reduction in tar exposure, and the increasing use of filter cigarettes has been considered the cause for a gradual change in lung cancer type, from mainly squamous cell carcinoma to mainly adenocarcinoma. Against these effects has been the finding that smokers change their habits when switching from non-filter to filters- more cigarettes, more puffs, deeper inhalation, etc.

The prevalence of cigar and cigarillo smoking has steadily increased in the past two decades, probably related to the perception that they are “safer” than cigarettes; also, they do not have to carry a health warning. However, large studies have shown that cigar smokers have a risk of lung cancer development that is 5-9 times greater than non-smokers.

Smoking habits.

Heavy smokers (> 20/day) tend to inhale more deeply than lighter smokers, and prospective studies have demonstrated a greater mortality ratio for them, approaching double [5].

Environmental (“second-hand”) smoke exposure.

In 1991 the Edinburgh Lung Cancer Group reported that only 2% of lung cancers occurred in non-smokers, but that cancer in women non-smokers was more common than in males; 6.7% of lung cancers occurred in women non-smokers vs. 0.7% in men [9]. In the 1970s suggestions were made that exposure to smoke from family members posed a risk for cancer development, and a number of studies followed. In a meta-analysis of 37 studies (containing over 4000 incidences of cancer), a 24% excess risk for lung cancer in non-smokers living with a smoker [16], with a dose-response relationship being evident. Not surprisingly, it was later shown that the risk was highest in subjects exposed to tobacco smoke from a young age. There may be a genetic predisposition involved.

Gender

Several differences between males and females in cigarette usage and in tobacco related lung cancer have already been mentioned, and this section is merely to summarize findings and conclusions [12, 14]. Cigarette consumption in women lagged behind that of men by several decades, leading to the present situation where lung cancer mortality is declining in men, but still increasing in women, in whom the increase in lung cancer mortality has been over 600% during the past 50 years. Although it was felt initially that women were less prone to develop lung cancer, this seems to be

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explained by different smoking habits, such as greater use of filters and less inhaling. However, in the landmark studies of British doctors, it is noteworthy that women who smoked heavily (> 25/day) had the same mortality ratio as in comparable men (29.7 vs 25.1). Subsequent studies have confirmed this conclusion; for a given life-long smoking history, women are 1.2 to 1.7 times as likely as men to develop the disease. It has been argued that greater susceptibility to develop cancer in women may be related to ovarian hormones; evidence for this view comes from a case control study in which women undergoing estrogen replacement therapy were more likely to develop adenocarcinoma of the lung than controls; also, women who had experienced early menopause were at lower risk.

Review of the different histological types of lung cancer is outside the scope of the present review. Whilst all types are more common in smokers, adenocarcinoma occurs more often in females than males, in whom the squamous cell type predominates; the incidence of small cell cancer is consistently 2-3 times more common in females than males.

Occupation

The interaction between smoking and occupation has been a contentious issue for several decades. One report, anonymously authored but usually known as the "OSHA paper", drew conclusions from previous studies of cancer trends that up to 40% of cancers might be due to occupational exposures. However, these conclusions were dismissed on the grounds of faulty epidemiological methods by Doll and Peto in their authoritative report published in 1981- "The causes of cancer" [5]. Their conclusion was that up to 5% of lung cancers in women and up to 15% in men could be attributable to occupational exposure to carcinogens. Doll and Peto pointed out that conclusions drawn from population studies depended on the statistical model of causation that was assumed, for example whether smoking and occupational exposures acted additively, synergistically or in a multiplying fashion. In order to take account of such factors as those outlined above, the studies needed to be large and prospective. These factors have been extensively reviewed in a report edited by Peto and Schneiderman "The Banbury Report" [1]. In a cohort study from the Netherlands of nearly 60,000 men and women, it was possible to correct for age, gender and smoking; 11.5% of lung cancer cases were ascribed to asbestos exposure [15]. Among non-smoking subjects who worked with known carcinogens ("List-A" containing asbestos, arsenic, chromium, nickel and vinyl chloride) the odds ratio for lung cancer was 1.5 in both men and women. A meta-analysis of 29 studies that examined the risk of lung cancer in workers with silicosis, showed a relative risk of 2.2, suggesting that exposure to silica did constitute a causal association [10] Because few women work in high risk occupations, associations between exposure and lung cancer in women have been difficult to establish.

By far the best studied exposure has been asbestos; non- smoking asbestos workers have a mortality ratio of 5.15 compared to non-smokers who are not exposed(1.0) and of 10.55 in smokers who have not worked with asbestos; smoking asbestos workers have a ratio of 53.24 [7]. Exposure to radon gas in uranium miners carries an established risk for lung cancer

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Apart from asbestos and radon, the risks associated with occupational dust exposure are small compared to smoking, and the additive effects are much less marked.

Quantitative apportionment of risk

Over the past 50 years there have been many studies of contributory factors in lung cancer, and a number of recent publications have attempted to quantify the relative roles of smoking, environmental pollution, family history of cancer and occupation. Several statistical approaches have been presented, based on previous surveys [11], but have been hampered by variable selection criteria and confounders. However, they point the way to assessing risk so as to reduce what is essentially a preventable disease.

Smoking and other cancers

Doll and Peto have reviewed evidence for a role of smoking in causing cancer, concluding that the evidence was strong for cancer of the oesophagus, pancreas, and bladder [6].

Conclusions

“A custome lothsome to the eye, hatefull to the nose, harmfull to the braine, dangerous to the lungs, and in the blacke stinking fume thereof neerest resembling the horrible Stigian smoake of the pit that is bottomlesse.”¹

In his “Counterblaste to tobacco” James I of England, Jamie the Saxt (sixth) to the Scots, got it right. Subsequent events have shown that tobacco smoking accounts for 30% of all cancers, and over 80% of lung cancer. The evidence meets all the epidemiological criteria for causation. Thus, the risks of even mild smoking outweigh the known risks of working in a hazardous environment, even if this contains asbestos fibres. The risk of smoking is shown to increase by a number of factors that can be taken into account when assessing workers with lung cancer.

1. Duration of smoking; in a current smoker, the risk increases exponentially with the length of time they have smoked (Fig 1).
2. The age at which smoking began is independently important and may usually be obtained (Fig 2).

¹ King James the First, 1604

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3. In the case of a former smoker, the risk declines gradually, but takes 15 years before reaching its minimum.
4. Amount smoked will often be under estimated by workers and has been shown unreliable, unless obtained prospectively; however it is usually possible to judge if the maximum amount smoked per day exceeds 20 cigarettes or not, to define heavy consumption. The use of pack-years is not recommended. Information regarding smoking habits (type of cigarette, depth of inhalation) is unreliable.
5. Smoking in women should be assessed equally to men.
6. A family history of cancer is statistically associated with elevated risk.

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