

Uncovering the effects of smoking: historical perspective

Richard Doll ICRF/MRC/BHF Clinical Trial Service Unit, Radcliffe Infirmary, Oxford, UK

Tobacco was introduced into Europe from America at the end of the fifteenth century. At first used primarily for medicinal purposes it came to be burnt in pipes for pleasure on a large scale nearly 100 years later, at first in England and subsequently in Europe and throughout the world. Pipe smoking gave way to the use of tobacco as snuff and, in turn, to cigars and cigarettes at different times in different countries until cigarette smoking became the dominant form in most of the developed world between the two world wars. Societies were formed to discourage smoking at the beginning of the century in several countries, but they had little success except in Germany where they were officially supported by the government after the Nazis seized power.

In retrospect it can now be seen that medical evidence of the harm done by smoking has been accumulating for 200 years, at first in relation to cancers of the lip and mouth, and then in relation to vascular disease and cancer of the lung. The evidence was generally ignored until five case-control studies relating smoking to the development of lung cancer were published in 1950. These stimulated much research, including the conduct of cohort studies, which, by the late 1950s, were beginning to show that smoking was associated with the development of many other diseases as well. The interpretation that smoking caused these various diseases was vigorously debated for some years but came to be generally accepted in respect of lung cancer by the late 1950s and of many other diseases in the subsequent two decades.

Cigarette smoking has now been found to be positively associated with nearly 40 diseases or causes of death and to be negatively associated with eight or nine more. In some instances the positive associations are largely or wholly due to confounding, but the great majority have been shown to be causal in character. The few diseases negatively associated with smoking are for the most part rare or nonfatal and their impact on disease incidence and mortality as a result of smoking is less than 1% of the excess of other diseases that are caused by smoking. The most recent observations show that continued cigarette smoking throughout adult life doubles age-specific mortality rates, nearly trebling them in late middle age.

All the diseases related to smoking that cause large numbers of deaths should now have been discovered, but further nonfatal diseases may remain to be revealed by cohort studies that are able to link individuals' morbidity data with their personal characteristics.

1 Introduction

Tobacco grows naturally in Central America and the custom of burning the leaves and inhaling the smoke was adopted by the Mayans at least 2500 years ago. At first, the leaves were burnt in religious ceremonies and the priests, who were also the physicians, credited the plant with powers of healing. Later, tobacco came also to be burnt and the smoke inhaled for pleasure. The use of tobacco for these purposes spread north and south in America and east to the Caribbean islands, where leaves were presented to Spaniards when they invaded the continent at the end of the fifteenth century. Within a few years, tobacco was brought to Spain and Portugal and

Address for correspondence: Sir Richard Doll, ICRF/MRC/BHF Clinical Trial Service Unit and Epidemiological Studies Unit, Harkness Building, Radcliffe Infirmary, Oxford OX2 6HE, UK.

was claimed to have medicinal value. Its use for medical purposes spread through Europe, where it was chewed, taken nasally as a powder, or applied locally in the treatment of cough, asthma, headaches, stomach cramps, gout, diseases of women, intestinal worms, open wounds, and malignant tumours. Although the plant was named after Jean Nicot, he did not encounter it until 1559 in Lisbon, where he had been sent on a diplomatic mission. While there he became enthused by the reports of its healing powers, wrote about it to the Cardinal of Lorraine, and gave some seeds to a visiting dignitary from the French Court.¹

Smoking tobacco in pipes for pleasure became a common habit only in the last quarter of the sixteenth century, initially in Britain, where it had been introduced by the mathematician Thomas Harriot and was made socially acceptable by Sir Walter Raleigh. Many, however, thought it disgusting and the use of tobacco in this way was virulently attacked. The opposition was led by James VI of Scotland, when he succeeded to the throne of the United Kingdom (as James I) in 1603, and he published a pamphlet against it in Latin in the same year and in English anonymously, under the title of *A counterblaste to tobacco*, a year later.² The pamphlet was read widely, dutifully praised, and generally ignored. His attempt to persuade Parliament to increase taxation on tobacco failed and the main effect of his opposition was to diminish imports from Virginia and increase the amount grown at home.

At the beginning of the seventeenth century, the habit spread to the Netherlands and subsequently, in the course of the Thirty Years War, throughout Europe. Attempts were made to ban it in Japan, Russia, Switzerland and parts of Austria and Germany, but the prohibition was invariably flouted and control by taxation came to be preferred. This eventually proved to be such an important source of revenue that in 1851 Cardinal Antonelli, Secretary to the Papal States, issued an order that the dissemination of anti-tobacco literature would be punished by imprisonment.¹

The use of tobacco as snuff instead of in pipes became popular at the end of the seventeenth century and was common until cigars, which had been smoked in a primitive form in Spain and Portugal from the beginning, began to replace it a century later. By then, cigarettes had begun to be made in South America and their use had spread to Spain; but it was not until after the Crimean War that they were widely adopted. They were made fashionable in Britain by officers returning from the Crimea and by the end of the nineteenth century had begun to replace cigars. Cigarette consumption increased rapidly in the First World War, particularly in Britain, and by the end of the Second World War, cigarettes had largely replaced other tobacco products in most developed countries. By this time, smoking had become so much the norm for men, that in Britain 80% were regular smokers and some doctors offered a cigarette to patients, when they came to consult them, to put them at ease. Women began to smoke in large numbers much later and at different times in different countries: at first in the Maori population of New Zealand at the end of the nineteenth century, then in the USA and Britain in the 1920s, and especially in Britain during the Second World War when an increasing proportion worked outside the home and had an independent income. It was later still in many other countries, in France and Spain, for example, women began to smoke in any numbers only in the last few decades. Such

quantitative data, as is available for the sale of different tobacco products in different countries this century have been published by Wald *et al.*³ and Nicolaides-Bouman *et al.*⁴

2 Attitude to smoking in the first half of the twentieth century

2.1 Anti-tobacco movements

The idea that the use of tobacco might be beneficial had been largely abandoned by the beginning of the twentieth century, except in so far as it was claimed that nicotine might improve some aspects of cerebral function. Opposition to tobacco, in contrast, had been formalized in the activities of societies that sought to discourage smoking on the grounds that nicotine was an addictive drug. Tobacco was consequently classified with alcohol and the anti-tobacco societies, like the temperance movement, tended to be associated with the nonconformist churches.

These societies had little impact in the UK, but the idea that smoking stunted the growth of children impressed the Interdepartmental Committee on Physical Deterioration, which had been appointed to enquire into the reasons for the poor health of recruits at the time of the Boer war, and their findings contributed to the introduction of a law in 1908 prohibiting the sale of tobacco to children under 16 years of age and empowering the police to seize cigarettes from any child seen smoking in public.⁵ In the USA, the societies succeeded in getting the sale of tobacco prohibited in 12 states, but the prohibition was short-lived. In 1919, the temperance movement got the sale of alcohol prohibited nationally. The law was not, however, respected and criminal activity mushroomed, illicit sales were widespread, and the prohibition of alcohol was, in consequence, abandoned in 1933. The anti-tobacco movement lost credibility as a result of the backlash against the temperance movement with which it was associated and prohibition of the sale of tobacco was rescinded in the last state (Kansas) in 1927.

In Germany, the situation was different. Starting with the formation of the 'Deutscher Tabakgegnerverein zum Schutze für Nichtraucher' (German Association against Tobacco for the Protection of Nonsmokers) in 1904, the anti-tobacco movement, which was also committed to opposition to alcohol, had a chequered career until the rise of the National Socialist party in the 1930s.^{6,7} Hitler was personally opposed to the use of tobacco and alcohol, both of which were addictive and, he thought, weakened the national will and harmed the national 'germ plasm'. When the party came to power in 1933, elementary schools were required to discuss the dangers of tobacco, government pamphlets were published warning people against it, and mass meetings were addressed by the President of the National Health Office and by Nazi medical leaders, in which tobacco and alcohol were attacked as reproductive poisons and drains on the economy. The National Institute for Tobacco Research developed tobacco with very low levels of nicotine in its products (less than 0.1%); but they never captured more than a small percentage of the market. Beginning in 1938, smoking began to be forbidden in more and more situations, for example, by uniformed police and SS officers on duty, by soldiers in the streets, by young people under 18 years of age in public, and by anyone in air-raid shelters and city trains and buses. In 1941, a special institute was established in the medical school of Jena

University for investigation of the hazards of smoking (Wissenschaftliches Institut zur Erforschung der Tabakgefahren). The Institute was directed by Karl Astel, rector of the University and President of Thuringia's Office of Racial Affairs, and received an initial grant of 100 000 RM from Hitler's personal office. It was the first such institute in the world and its establishment reflected the integration of the anti-tobacco movement into German national health policy. The campaign does not, however, seem to have had much impact on the public as the daily consumption of tobacco increased annually after the party came to power to become 18% higher in 1938 before the outbreak of war stopped the publication of sales figures.⁴

2.2 Evidence of harmful effects before 1950

The anti-tobacco movements were, in general, not acting on sound medical evidence of substantial harm, for little such evidence was available to them. In retrospect, however, it can be seen that evidence had been accumulating since the end of the eighteenth century. It was of four types, namely clinical observations on patients, ecological observations of national trends, comparative studies of the smoking habits of patients with different diseases or no disease at all, and laboratory experiments.

Cancer

Most evidence related to cancer. Clinical observations, that is, observations on patients with a particular disease, without any comparable observations on what would now be regarded as a worthwhile control group, led Sömmering to write in a prize treatise in Germany in 1795⁸ that, from Clemmesen's translation,⁹ 'Carcinoma of the lip is most frequent when people indulge in tobacco pipes. For the lower lip is particularly attacked by carcinoma because it is compressed between the pipe and the teeth'. Holland¹⁰ is sometimes cited as the first to have noted an association of smoking with carcinoma of the lip, but Clemmesen⁹ makes a good case for doubting the justification of this attribution.

In the next 100 years, pipe smoking, and specially the smoking of clay pipes, came to be widely accepted as contributing to the development of cancers of the lip and tongue, and of other parts of the mouth. For review see Bouisson,¹¹ Anon,¹² and see Clemmesen.⁹ In the first half of this century, the same diseases were also found to be characteristically associated with 'heavy' smoking in patients attending cancer clinics in the USA, without reference to the method of smoking, by Hoffman,¹³ Lombard and Doering,¹⁴ and Potter and Tulley.¹⁵ Comparisons were made between patients with different types of cancer (Tables 1 and 2), and in the Lombard and Doering's study, with controls of the same sex and approximately the same age. The associations observed were not, however, taken very seriously and, in so far as pipe-smoking was thought to be a cause of cancers of the lip and mouth, the risk was commonly attributed to the heat of the pipe stem rather than to any component of the smoke.

Potter and Tulley¹⁵ also noted the possibility of an association between moderate and excessive smoking and cancer of the respiratory tract (Table 2) which had been considered periodically since 1898, when Rottmann¹⁶ suggested that a small cluster of cases of lung cancer in tobacco workers in Leipzig might point to an occupational hazard, possibly from tobacco dust. At that time, lung cancer was a rare disease, but it came to be diagnosed progressively more often in the next five decades and several

Table 1 Proportion of heavy smokers in US populations in the late 1920s

| Population | Hoffman ¹³ | | Lombard and Doering ¹⁴ | |
|---|-----------------------|-------|-----------------------------------|------|
| | Proportion | (%) | Proportion | (%) |
| Patients attending cancer clinics with: | | | | |
| cancers supposed to be affected by smoking ^a | 34/35 | (97) | 9/17 | (53) |
| lung cancer ^b | 5/5 | (100) | 17/38 | (45) |
| other cancer | 106/144 | (74) | | |
| Controls | – | – | 43 ^c /217 | (20) |

^aCancers of lip, tongue, and other parts of mouth.

^bIncluded with other cancers in original analysis.

^cNumerator calculated, not given in the paper.

clinicians and statisticians in Britain,¹⁷ Germany,^{18,19} and the USA^{20–22} suggested that cigarette smoking might be a cause, based on the smoking habits of affected patients and the crude correlation between the increase in the incidence of the disease and the consumption of cigarettes. Ochsner and DeBakey, however, who had made a similar suggestion in the USA²³ retracted it six years later when they found that 24% of 147 patients in whom pulmonary resection had been performed were nonsmokers.²⁴

Pathologists argued for many years about the reality of the increase, but some were sufficiently impressed to try to produce cancer with tobacco tar experimentally in laboratory animals. In the UK, Leitch²⁵ and Passey²⁶ reported negative results, while Cooper *et al.*²⁷ reported the production of one squamous carcinoma of the skin in 50 animals. As, however, similar procedures with coal tar had produced a high incidence of tumours, Cooper *et al.* concluded that ‘tobacco tar is relatively unimportant in the causation of cancers’. In their report, they pointed out that the temperature at which tobacco was burnt in pipes was normally between 370 and 590°C, with temperatures up to 700°C only on vigorous smoking and that Kennaway²⁸ had found that carcinogenic chemicals were not produced in coal tar in any appreciable quantity below 550°C. Roffo’s experiments in the Argentine in 1931,²⁹ in which he had produced cancer on the skin of rabbits with tars from tobacco burnt at uncontrolled temperatures, and in which he later identified a chemical with the characteristics of benzpyrene,³⁰ were consequently considered irrelevant. Other investigators reported the production of only occasional tumours^{31,32} and in 1950 the laboratory evidence was still not thought to support a significant role for smoking in cancer in either Britain or the USA.

Table 2 Percentage of men attending Massachusetts cancer clinics with different cancers, by smoking habit¹⁵

| Use of tobacco (number of men) | Type of cancer | | |
|-----------------------------------|------------------|----------------------|----------------|
| | Buccal cavity | Respiratory tract | Other sites |
| None (655) | 3.7 | 0.5 | 22.4 |
| Slight (357) | 8.1 | 1.1 | 25.1 |
| Moderate (1155) | 11.5 | 2.0 | 26.0 |
| Excessive (760) | 17.9 | 1.7 | 23.4 |

Müller³³ has the credit for the first case-control study of lung cancer and smoking, which was reported in 1939 even though the technique he employed was, by modern standards, crude. Questionnaires were sent to the relatives of people in whom lung cancer had been diagnosed at autopsy in the University Hospital in Cologne, asking about the subjects' smoking habits and previous exposure to respiratory irritants. Replies were received relating to 86 men and 10 women, but we are not told what proportion of the questionnaires were completed. Not all the respondents gave quantitative details of the amounts smoked and smokers were classed together in categories based on either quantitative or qualitative descriptions. The findings for the 86 men are shown in Table 3, in comparison with those obtained from 'the same number of healthy men of the same ages', but how the healthy men were selected and how the information was obtained from them is again not described. The findings, in combination with knowledge that the use of tobacco in Germany had increased fivefold since 1907 and the results of Roffo's experiments, led Müller to conclude that tobacco was an important cause of lung cancer and the single most important cause of the rising incidence of the disease. The weakness of the epidemiological method is evident and the conclusion was hardly justified, but the results should certainly have served to stimulate urgent research and might have done so in countries such as Britain (which, at that time, had the highest lung cancer rates in the world) had the war not intervened.

Further research was, however, carried out in Germany during the war and in the Netherlands shortly after. Schairer and Schöniger³⁴ reported a case-control study from Astel's Institute in Jena in 1943 and Wassink³⁵ reported the results of a Dutch study in 1948. Their findings are summarized with Müller's in Table 4. The similarity of the findings is impressive. Schairer and Schöniger's work was more convincing than Müller's, not only because they gave more details of their methodology – 93 questionnaires were completed by the families of the lung cancer patients out of 195 sent out, and 270 were completed by the controls out of 770 sent to male residents of Jena aged 53–54 years (the average age at death of the lung cancer patients) – but also because they had an additional control group of men who had died from stomach cancer. They considered bias and thought it was an unlikely explanation of their findings. Other common explanations for the rise in lung cancer mortality could be excluded and smoking, they thought, was very likely to be a cause of the disease.

Table 3 Use of tobacco by disease category: 86 men with and 86 men without lung cancer (after Müller³³)

| Type of smoker | Number of men | |
|--------------------------------|------------------|------------------|
| | with lung cancer | healthy controls |
| Extreme smoker ^a | 25 | 4 |
| Very heavy smoker ^b | 18 | 5 |
| Heavy smoker ^c | 13 | 22 |
| Moderate smoker ^d | 27 | 41 |
| Nonsmoker | 3 | 14 |

^a10–15 cigars, >35 cigarettes, or >50 g pipe tobacco/day.

^b7–9 cigars, 26–35 cigarettes, or 36–50 g pipe tobacco/day.

^c4–6 cigars, 16–25 cigarettes, or 21–35 g pipe tobacco/day.

^d1–3 cigars, 1–15 cigarettes, or 1–20 g pipe tobacco/day.

Table 4 Smoking and lung cancer case-control studies before 1950

| Reference (country) | Number of men | | Percentage of | | | |
|---|---------------|----------|---------------------------|------------------------|------------------------------|---------------------------|
| | Lung cancer | Controls | Nonsmokers Lung cancer | Nonsmokers Controls | Heavy smokers Lung cancer | Heavy smokers Controls |
| Müller ³³ (Germany) | 86 | 86 | 3.5 | 16.3 | 65 | 36 |
| Schairer and Schöniger ³⁴ (Germany) | 93 | 270 | 3.2 | 15.9 | 52 | 27 |
| Wassink ³⁵ (Holland) | 134 | 100 | 4.5 | 19.0 | 55 | 19 |

Vascular disease

The idea that smoking might be a cause of vascular disease dates from the end of the last century, when Huchard³⁶ wrote that ‘The [unfavourable] influences of nicotinism on the development of arteriosclerosis appears to have been demonstrated, and this is not surprising since nicotine produces most often arterial hypertension by vasoconstriction, as the experiments of Claude Bernard proved’. Eleven years later Erb³⁷ found that 25 out of 45 patients with intermittent claudication were heavy smokers and shortly after that Buerger³⁸ described a rare form of peripheral vascular disease in relatively young people (thromboangiitis obliterans) that was subsequently named after him and noted that it seldom occurred in nonsmokers. Buerger’s findings were repeatedly confirmed^{39–41} and Silbert,⁴² who reported a large series of cases from New York, stated that he had never seen a case in a nonsmoker. Others, however, said that they had⁴³ and the occasional occurrence of the disease in nonsmokers showed, as I was told in the mid-1930s when a medical student, that smoking was not the cause. The idea that smoking might increase the risk of developing the disease without being a necessary cause was apparently not given serious attention.

Coronary thrombosis, in contrast, was being reported progressively more often every year, after it was first diagnosed in life by Herrick⁴⁴ in 1912. Several clinical studies of the relationship with smoking were published and the suggestion was made as early as 1934 that smoking might be responsible for the increase,⁴⁵ but the findings were confused and no substantial evidence was obtained until 1940 when English, Willius and Berkson reported an association in the records of the Mayo clinic.⁴⁶ First, they compared the recorded habits of 1000 patients with the disease with those of 1000 other patients matched for sex and for age in three broad groups. Secondly, the frequency of the diagnosis of coronary disease in 1000 consecutive smokers was compared with that in 1000 nonsmokers, similarly matched for sex and age. The results are shown in Tables 5 and 6 and led them to conclude conservatively that the smoking of tobacco probably had ‘a more profound effect on younger individuals owing to the existence of relatively normal cardiovascular systems, influencing perhaps the earlier development of coronary disease’. They eschewed reference to causation, because they were aware that the subject would be controversial and that ‘physicians are not yet ready to agree on this important subject’.⁴⁷

Angina was occasionally attributed to smoking when attacks were precipitated by it, but they must have been very uncommon, as in 1945 Pickering and Sanderson thought it worthwhile to report three cases.⁴⁸

Table 5 Tobacco and coronary disease⁴⁶

| Men aged (years) | Percentage of smokers | | p^a |
|------------------|-----------------------|-----------------|--------|
| | Coronary disease | Others | |
| 40–49 | 79.7 (149/187) | 61.9 (187/302) | <0.001 |
| 50–59 | 71.7 (274/382) | 73.9 (274/371) | – |
| 60+ | 63.8 (275/431) | 61.8 (202/327) | 0.28 |
| 40+ | 69.8 (698/1000) | 66.3 (663/1000) | 0.05 |

^aAs published, described as ‘the probability that as large a difference in the direction found would occur by chance in random samples, if actually there was no difference’.

Table 6 Tobacco and coronary disease⁴⁶

| Men aged (years) | Percentage coronary disease in: | | p^a |
|------------------|---------------------------------|---------------|-------|
| | Smokers | Nonsmokers | |
| 40–49 | 4.8 (10/208) | 1.0 (2/208) | 0.01 |
| 50–59 | 6.2 (24/388) | 2.6 (10/388) | 0.01 |
| 60+ | 5.0 (20/404) | 6.4 (26/404) | – |
| 40+ | 5.4 (54/1000) | 3.8 (38/1000) | 0.04 |

^aSee footnote to Table 5.

Other conditions

A characteristic type of blindness, tobacco amblyopia, was first described by Beer in 1817.⁴⁹ It occurred principally in heavy pipe smokers in association with malnutrition and was probably caused by the cyanide in the smoke, when the ability to detoxify it was reduced.^{50,51} The disease is much less common in cigarette smokers than in pipe smokers and has now become extremely rare in developed countries.

Peptic ulcers were commonly thought to be aggravated by smoking, possibly as a result of the action of nicotine on gastric motility, but the physiological evidence for this and other mechanisms was inconsistent and was not, at the time, wholly convincing.

Extraordinarily, there was little reference to smoking as a cause of respiratory disease. Lickint⁵² described clinical or pathological series relating smoking to emphysema, pneumonia, and tuberculosis in his 1200-page tome on tobacco and the organism, but the cough that was so prevalent in smokers was generally dismissed in the UK as a benign ‘smokers’ cough’.

In retrospect, the most important evidence of the harmful effects of smoking was Pearl’s observation in 1938 from a study of the family history records of the Johns Hopkins School of Hygiene and Public Health that ‘The smoking of tobacco was statistically associated with the impairment of life duration and the amount or degree of this impairment increased as the habitual amount of smoking increased’.⁵³ Pearl’s unwelcome finding, illustrated by his original figure in Figure 1, was either ignored or dismissed as due to confounding with some hypothetical other feature.

2.3 Medical teaching

Despite the accumulating evidence, academic departments in general paid no attention to smoking and references to it in text books during and shortly after the war were scarce and brief. In the UK, smoking was mentioned as a cause of retrobulbar

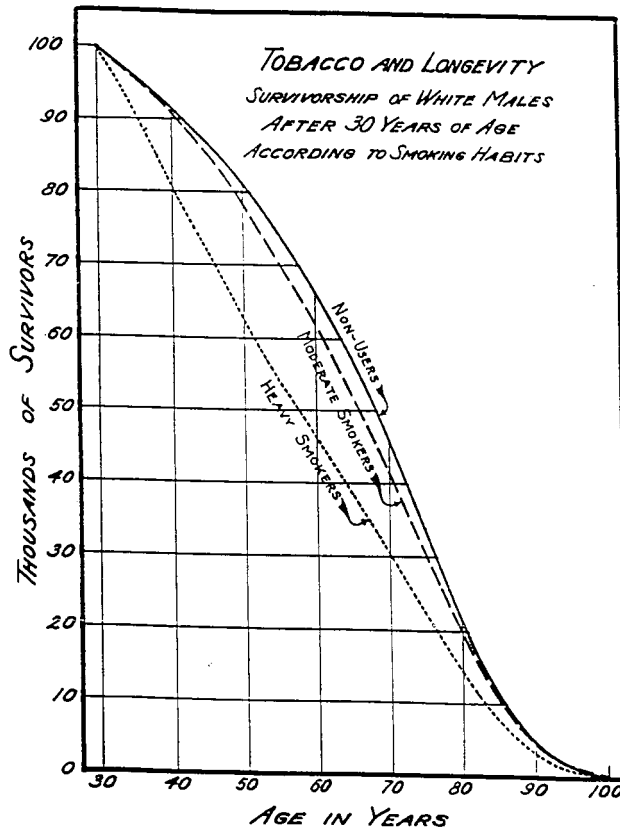


Figure 1 Survival curves for white males by tobacco use: nonusers (solid line), moderate smokers (dashed line), heavy smokers (dotted line)⁵³

neuritis,⁵⁴ chronic pharyngitis, tracheitis, and ptyalism (excessive secretion of saliva), as an 'exciting cause' of emphysema along with many other factors that gave rise to strain from coughing, and, when excessive, as predisposing to peptic ulcer.⁵⁵ Smoking a hot, short clay pipe was described as a cause of cancers of the lip and tongue.^{56,57} All mentioned excessive smoking in relation to thromboangiitis obliterans (Buerger's disease). None mentioned it in relation to cancer of the lung.

In the USA, two medical textbooks listed neither smoking nor tobacco in their indexes;^{58,59} one devoted five lines to tobacco amblyopia and mentioned tobacco as contributing to thromboangiitis obliterans and as aggravating but not as causing peptic ulcers;⁴³ another mentioned cigarette smoking only in relation to the treatment of angina pectoris, advising that it should be stopped, because it increased the heart rate and the amount of carbon monoxide in the blood;⁶⁰ while a fifth mentioned the importance of stopping smoking in the treatment of thromboangiitis obliterans, but stated that the cause of the disease was unknown.⁶¹ In a monograph on heart disease, White⁶² gave tobacco a whole paragraph, in which he stated that it caused no actual heart disease, but might, in large amounts or in susceptible people, excite tachycardia

and premature contractions and, in extreme cases, paroxysmal auricular fibrillation. Tobacco, he noted, had been suggested as a factor in causing thromboangiitis obliterans, but its chief disadvantage was that it could induce cardiospasm and even gastritis.

More attention was paid to tobacco in Germany, principally in relation to vascular disease. Nicotine was said to be a cause of hypertension in susceptible people⁶³ and a major cause of angina^{64,65} and atherosclerosis^{66,67} and it was also thought to aggravate peptic ulcers.⁶⁵ Dennig⁶³ and Wolf⁶⁶ described chronic nicotine poisoning from the misuse of tobacco and attributed to it effects in nearly every system – including, according to Wolf⁶⁶ an increased risk of abortion and female sterility. Smoking was mentioned as contributing to the production of cancers of the mouth,⁶⁷ tongue, and larynx⁶⁸ but, with rare exceptions, not in relation to cancer of the lung. Fischer⁶⁹ made no mention of tobacco in his inaugural address at the University of Jena in 1946, on cancer research in the last 100 years, influenced perhaps by memory of the distasteful activities of Karl Aslet in the university a few years earlier, but Bauer⁷⁰ noted in his textbook on cancer that both Müller's,³³ and Schairer and Schöniger's,³⁴ epidemiological work on lung cancer and Roffo's³⁰ experimental and chemical findings. Tobacco alone, he thought, could not account for the increase in the frequency of the disease but it might cause a precancerous condition in the bronchi that other agents converted into cancer.

3 The 1950 watershed

In 1950, the situation was radically changed by the publication of five papers – four in the USA and one in Britain. All were case-control studies in which a comparison was made between the past histories of patients with lung cancer and of patients with other diseases or, in one instance, members of a local population. All allowed for the effect of age by matching or standardization or, in one instance, by showing that similar differences were observed in each broad age group. Outline results are shown for men in Table 7 and are similar to those shown for the three pre-1950 studies in Table 4. All showed a close association with smoking.

Table 7 Smoking and lung cancer case-control studies published in 1950

| Reference (country) | Number of men | | Percentage of | | | |
|---|---------------|----------|------------------|-------------------|---------------|----------|
| | Lung cancer | Controls | Nonsmokers | | Heavy smokers | |
| | | | Lung cancer | Controls | Lung cancer | Controls |
| Schrek <i>et al.</i> ⁷² (USA) | 82 | 522 | 14.6 | 23.9 | 18 | 9 |
| Levin <i>et al.</i> ⁷³ (USA) | 236 | 481 | 15.3 | 21.7 | – | – |
| Mills and Porter ⁷¹ (USA) | 444 | 430 | 7 | 31 | – | – |
| Wynder and Graham ⁷⁴ (USA) | 605 | 780 | 1.3 ^a | 14.6 ^a | 51 | 19 |
| Doll and Hill ⁷⁵ (UK) | 649 | 649 | 0.3 ^a | 4.2 ^a | 26 | 13 |

^aLifelong nonsmokers, with ex-smokers carefully excluded.

Two studies stood out because of their size, the elimination of bias due to low response rates, the detailed information about the method and amount of smoking, the ages at which smoking had been started and stopped, the precision with which lifelong nonsmokers were defined, and the logic that led to their conclusion. One had been initiated by Ernst Wynder in 1948,⁷⁶ while a summer student at New York University, on the basis of knowledge 'that the burning of tobacco in pipes or as cigars or cigarettes, would lead to the formation of cancer-causing chemical compounds'. The results that he obtained from interviewing a few patients so impressed Evarts Graham, the Chief of Surgery at Washington University School of Medicine, that the study was continued in his surgical service and a grant for expansion obtained from the American Cancer Society in the spring of 1949. Analysis led to the conclusion that 'excessive and prolonged use of tobacco, especially of cigarettes, seems to be an important factor in the induction of bronchogenic cancer'.⁷⁴

The other had been initiated by the British Medical Research Council as a result of a conference held in 1947 to discuss the reasons for the increase in the mortality attributed to lung cancer.⁷⁵ Neither of the two German case-control studies were referred to at the conference and the Dutch paper had not then been published. One possible reason for the increase, that it was due to the increased consumption of cigarettes, was supported by Kennaway because of the probability that the combustion of the tobacco would produce carcinogens and this idea appealed to Sir Edward Mellanby, then Secretary of the Medical Research Council, because Stocks had shown that the mortality from lung cancer in men was substantially higher in Nottingham, a centre of the British tobacco industry, than in nearby Leicester.⁷⁷ Stocks, however, was convinced that atmospheric pollution was responsible. Bradford Hill was consequently asked to conduct a case-control study to test the various hypotheses that had been suggested. The study was completed and the results published within three years.⁷⁵ Detailed examination of the findings led the authors to exclude bias and confounding as possible explanations and they concluded, from the consistency of the findings in different studies, the biological relationships with the amount and duration of smoking, the size of the estimated relative risk, and the variation in the mortality from the disease over time and place and in each sex that 'cigarette smoking is a factor, and an important factor, in the production of carcinoma of the lung'.

This conclusion was accepted by Sir Harold Himsworth, then secretary of the Medical Research Council, but not generally by either medical or statistical scientists and certainly not by the British Department of Health's Standing Advisory Committee on Cancer and Radiotherapy.⁵ Most accepted that an association had been shown, but not that the association implied cause and effect. Some, however, were even more sceptical, citing Berkson's fallacy that the results of a case-control study using patients in hospital as a source of both cases and controls could be an artefact due to the combination of the disease and the agent of interest leading to a greater chance of a patient's admission to hospital than the disease would alone.⁷⁸ In retrospect, the critics had not paid sufficient attention to the strength of the association, but their scepticism had considerable influence during the early 1950s on both the public and professional perceptions of the evidence. The idea that smoking might be an important cause of disease had, however, been raised as a serious possibility and a great deal of research into its effects was initiated in many countries.

4 The evidence that led to general acceptance of major harm from smoking

4.1 The early cohort studies

To Doll and Hill, it seemed clear that evidence of a different type would have to be obtained, if reactions to the findings in the case-control studies were to be changed. This, Hill thought, might be achieved if the smoking habits of large numbers of people could be recorded and they were then followed up to see if the risk of lung cancer could be predicted from the information about the individual's level of smoking. The idea that doctors would make a suitable population to study is said to have come to Bradford Hill one Sunday morning when playing golf. This, at any rate, was believed by Dr Wynne Griffith (personal communication) who wrote some 25 years later 'I don't know what kind of a golfer he [is] but that was a stroke of genius'. It was indeed, for when Doll and Hill wrote to all the doctors on the British Medical Register in October 1951, over 40 000 (two-thirds) gave details of their smoking habits, and they have proved so easy to trace that nearly all the men who provided the details, and were not known to have died, could be traced 40 years later.⁷⁹ Sadly, however, the golfing part of Wynne Griffith's story is apocryphal, for Sir Austin told me that the idea actually came to him, in the classical manner, in his bath.

The evidence from the prospective 'cohort' study of British doctors mounted quickly, and within two and a half years the findings with regard to lung cancer had confirmed those predicted from the retrospective case-control studies. This is shown in Table 8, which gives the relative mortality rates for different levels of smoking, as estimated from the final results of the British case-control study based on 1357 deaths from lung cancer in men,⁸⁰ and the first results of the prospective study based on only 36 lung cancer deaths.⁸¹ With so few deaths in the second study, the confidence limits of the mortality rates were wide, but even so the trend in mortality with smoking was significant ($p < 0.01$).

Altogether, 789 deaths had been recorded in the cohort and it was possible to examine the relationship between smoking and several other diseases. With 235 deaths attributed to coronary thrombosis, the mortality (standardized for age) increased from 3.9 per 1000 men per year in lifelong nonsmokers, to 5.2 per 1000 in men smoking an average of 25 g of tobacco or more per day, including pipe and cigar smokers with cigarette smokers. The increase was small (33%) but the trend with the amount smoked was statistically significant and it was concluded that there was a subgroup of coronary cases in which 'tobacco has a significant adjuvant effect'.

Table 8 Relative death rates from lung cancer standardized for age by the amount smoked in case-control and cohort studies: men aged 45–74 years

| Study | Rate as a percentage for all men | | | |
|----------------------------|----------------------------------|----------------------|---------|--------------|
| | Nonsmokers | Smokers of (per day) | | |
| | | 1–14 g | 15–24 g | 25 g or more |
| Case-control ⁸⁰ | 6 | 79 | 112 | 201 |
| Cohort ⁸¹ | 0 | 68 | 133 | 199 |

Two years later these results were confirmed with larger numbers.⁸² More importantly, they were also confirmed in the much larger study that the American Cancer Society had begun in 1952 specifically, as the principal investigator told me, to disprove the relationship between smoking and lung cancer that had been observed in the case-control studies (Hammond, personal communication). The results, based on nearly 5000 deaths in 190 000 American men followed for two years, are shown in Table 9 for lung cancer and, in four age groups, for coronary disease.⁸³ The investigators were impressed by the correlations between national data for cigarette smoking and the mortality from coronary thrombosis in men and women, in urban and rural areas, and over time. The previous reports that cigarette smoking caused vasoconstriction and increased heart rate and blood pressure were supported and they concluded that ‘regular cigarette smoking causes an increase in death rates from these two diseases’ (that is, from coronary thrombosis and cancer of the lung) adding that ‘probably nicotine is at least partially responsible for the findings in relation to diseases of the coronary arteries’.

4.2 Statistical criticisms

With the publication of the results of these two prospective studies, scientific opinion rapidly changed. Two leading statisticians, however, remained unconvinced. Berkson⁸⁴ in the USA, had initially suggested that the first results of the two studies might be biased by the self-exclusion of seriously ill people who would tend not to have responded to the questionnaires and that the results might be differentially biased if healthy nonsmokers responded to the questionnaire more readily than healthy smokers, because answering the questionnaire was easier for them, while men who were seriously ill would be disinclined to answer the questionnaire equally, whatever their smoking habits might have been. A bias of this sort would, however, have worn off in the course of the first few months of follow-up, as those seriously ill from lung cancer died, and Doll and Hill’s 1956 results showed that this had not occurred.⁸²

Berkson was consequently left with only his second objection,⁸⁵ that the relationship with smoking held to some extent across the board with a variety of conditions, an objection which, he thought, was strengthened when the later results of the two studies were published.^{82,86} In the cohort of British doctors, the death rate for heavy smokers was higher than that for nonsmokers in 12 of the 15 categories of cause of death for

Table 9 Mortality by amount smoked relative to that in nonsmoker (after Hammond and Horn⁸³)

| Age (years) | Number of deaths | Regular cigarette smokers smoking (per day) | | | Cause of death |
|-------------|------------------|---|-------|------------|--------------------------|
| | | less than 10 | 10–19 | 20 or more | |
| 50–69 | 167 | 4.2 | | 8.8 | Lung cancer |
| 50–54 | 377 | 1.7 | 2.1 | 2.5 | } Coronary heart disease |
| 55–59 | 571 | 1.1 | 1.9 | 2.1 | |
| 60–64 | 594 | 1.5 | 2.2 | 2.0 | |
| 65–69 | 605 | 1.0 | 1.3 | 1.1 | |

which data were given, while in the larger American cohort the mortality in regular cigarette smokers was higher than that in nonsmokers in all the nine broad categories examined and in Berkson's view 'even more to the point' in many of the individual causes of death for which personal information had been provided.

If an investigation set up to test the theory that smoking caused lung cancer, turned out to indicate that smoking caused or provoked a whole gamut of diseases, it inevitably raised the suspicion, in Berkson's opinion, that something was amiss. A scientist, he thought, would say, 'There must be something wrong with the method of investigation' and he offered two noncausal explanations for the associations observed. First, that they were the result of the interplay of various subtle and complicated biases, which, he thought, was possible because the two definitive variables (a history of smoking and the cause of death) were both subject to considerable error, while the samples of subjects studied were 'selected' and not obtained by rigid sampling methods. Secondly, that the associations observed had a constitutional basis, persons who are nonsmokers, or relatively light smokers, being the kind of people who were biologically self-protective and that this 'correlated with robustness in meeting mortal stress from disease generally'.

In making his criticism,⁸⁵ Berkson took no account of the great difference in the relative risks of different diseases among heavy cigarette smokers compared to nonsmokers, varying in Doll and Hill's study⁸² from 24:1 for lung cancer to 1.01:1 for a residual group of cardiovascular diseases, nor of the fact that tobacco smoke was not a pure chemical entity, but a mixture of many chemicals, subsequently shown to number more than 4000. It was, as Hill pointed out,⁸⁷ as if he had said that milk could not be a cause of any disease because it spread tuberculosis, diphtheria, scarlet fever, undulant fever, dysentery, and typhoid and, Hill might have added, contributed to the production of a range of vascular diseases and prevented osteoporosis.

Fisher, in the UK, was the other outstanding statistician who questioned a causal interpretation. In his view,⁸⁸ Doll and Hill's original finding that reports of inhaling by smokers with lung cancer (62% of whom reported inhaling) were less common than by smokers without lung cancer (67% of whom did so)⁷⁵ weighed heavily against causation, unless it were also concluded that 'inhaling cigarette smoke was a practice of considerable prophylactic value in preventing the disease'. He preferred instead the idea that there was some common factor that was responsible both for the individual's smoking habits and his risks of developing the disease, which Fisher postulated was genetic, and he supported his hypothesis by showing that the smoking habits of monozygous pairs of twins were more similar than those of dizygous pairs and (on small numbers) appeared to be similar irrespective of whether they had been raised together or apart.^{88,89} He also argued that secular changes in smoking habits could not be related to the increase in lung cancer since 'lung cancer has been increasing more rapidly in men relatively to women' and that 'it is notorious, and conspicuous in the memory of most of us, that over the last 50 years the increase of smoking among women has been great, and that among men (even if positive) certainly small'.⁹⁰

Neither objection was, in fact, valid. The effects of reported inhaling were impossible to interpret without knowledge of where the smoke droplets would be deposited and this could not be predicted without direct observation, because tobacco aerosols swell under the warm and moist conditions of the lungs and might, if inhaled

deeply, deposit in the alveoli rather than on the bronchi.⁹¹ When their study was completed, Doll and Hill, moreover, found that while inhaling was associated with a diminished risk of cancer in the large bronchi, it was associated with an increased risk of developing cancer in the periphery of the lung, which made biological sense.⁸⁰ As for the ecological evidence, Fisher was wrong⁹⁰ for he had ignored the generation effects, whereby the risks among successive generations are directly determined not only by their recent smoking history but also by the predisposition to lung cancer imprinted on them by their smoking habits in the distant past. When this is allowed for and mortality rates and smoking habits are compared at appropriate ages, the trends in the sex ratio are not discrepant with the trends in cigarette consumption by gender over the relevant periods.⁹²

Fisher's genetic hypothesis left the increase in mortality from lung cancer unexplained and was later shown to be untenable on two counts. First, when a substantial proportion of British doctors gave up smoking, the mortality from lung cancer in the whole cohort of doctors was progressively reduced relative to that in the general population,⁹³ whereas, according to Fisher,⁹⁴ the change in habits should have had no effect on the mortality of the group as a whole, as those who gave up would have been those not susceptible to the disease. Secondly, three studies of monozygous twins with different smoking habits showed that the risk of lung cancer was associated with the individual's smoking habits rather than his or her genetic constitution.⁹⁵⁻⁹⁷ According to Sir Walter Bodmer, who had been a graduate student of Fisher's and met him a few months before he died, Fisher had come to accept, in the last year or two of his life, that smoking was probably a 'cofactor' in the production of lung cancer and had intended to make a public statement of his revised position (W Bodmer, personal communication).

4.3 Proof of causation

The conclusion that cigarette smoking was a major cause of disease had not been easy for some to accept, as the human evidence was observational rather than experimental and it was not practicable to produce comparable disease experimentally in animals. Different people, moreover, gave different meanings to 'cause'. It was, therefore, not surprising that the conclusion was challenged, particularly as it had serious economic implications for a major industry.

In saying that a particular factor (such as cigarette smoking) is a cause of disease, epidemiologists have in mind the sort of situation in which, for example, prolonged cigarette smoking results in a rare disease becoming ten times as common as it would have been in the absence of smoking. Cigarette smoking is not then a necessary cause (as some nonsmokers develop the disease) nor is it a sufficient cause (as some smokers do not develop it). In populations in which prolonged cigarette smoking is common, smoking is then an important cause of the disease (as few people would have developed the disease if they had not smoked). Whether it is, in this sense, an important cause of the disease is not contingent on the biochemical mechanisms involved or on the absence of other important causes. If, for example, some rare genetic trait greatly reduces the carcinogenicity of tobacco smoke for the human lung then it could be said that the absence of this trait was a genetic cause of most lung cancer deaths, but it would not alter the fact that smoking was also a cause of most of

the same deaths. Thus, any one case of cancer can have had several causes, the absence or avoidance of any of which would have avoided the occurrence of that particular cancer.

The claim was not that cigarette smoking was either a necessary or a sufficient cause for any of the diseases with which it was connected, apart from tobacco amblyopia and tobacco angina, for which it was a necessary cause as, by definition, these conditions occurred only in smokers. It was claimed that for several diseases, causation, in the sense described, was proved beyond reasonable doubt. For most of these diseases, the evidence consisted chiefly of epidemiological observations and there was, consequently, an element of personal judgment in weighing it, at least in the early years when the evidence was not as extensive as it is now. The evidence then available for lung cancer was reviewed by Doll⁹⁸ and I note here only the extraordinary strength of the association with smoking, which led to an increased risk of more than 20-fold in heavy cigarette smokers and alone made the alternative explanation of confounding virtually impossible, the evidence for a progressive increase in risk with amount smoked, a diminution in risk with late age at starting to smoke and with time since smoking stopped, the consistency of the main findings with different methods of investigation and in different countries and different cultures, and the broad agreement between the amount smoked and the mortality from the disease in men and women, in different populations, and at different times.

4.4 Acceptance of causality

During the 1950s, this epidemiological evidence of carcinogenicity was complemented by the experimental demonstration in Denmark, France, Japan, and the USA that relevant tobacco tars were carcinogenic when applied regularly for a long time to the skin of laboratory animals⁹⁹⁻¹⁰⁴ and by the identification in Britain and the USA of known carcinogens in tobacco smoke.^{105,106} All the expert committees appointed to review the evidence consequently reached positive conclusions about causality. Between 1957 and 1959, the Netherlands Ministry of Social Affairs and Public Health,¹⁰⁷ the British Medical Research Council,¹⁰⁸ a study group appointed jointly by the US National Cancer and National Heart Institutes and the American Cancer Society,¹⁰⁹ the Swedish Medical Research Council,¹¹⁰ and the US Public Health Service¹¹² all reported that cigarette smoking was a cause of lung cancer. A year later an expert committee of the World Health Organization agreed.¹¹³

Despite their provenance these reports had little lasting impact on the general public and the situation did not change materially until after the widely publicised reports by the Royal College of Physicians of London in 1962¹¹⁴ and the Advisory Committee to the US Surgeon General in 1964.¹¹⁵ The first was relatively short and aimed at interested laymen as well as practising doctors. The second was long and detailed and was particularly newsworthy, because the members of the advisory committee had been individually vetted by the tobacco industry, which had been privileged to veto anyone who had publicly expressed any views about the subject at issue.

By the time of these reports, much additional epidemiological evidence had been obtained. Further case-control studies of lung cancer and smoking had been carried out in Australia,¹¹⁶ Finland,^{117,118} France,¹¹⁹ Germany,^{120,121} Japan,¹²² Norway¹²³ and

Switzerland¹²⁴ as well as in Britain and the USA, and all had given generally similar results for the effects of the prolonged use of cigarettes. Other studies had reported similar relationships between smoking and several other major diseases and four further cohort studies had been reported from the USA and one from Canada. The diseases implicated by these studies are listed in Table 10.

Both the 1962 and 1964 reports agreed that smoking was a major cause of lung cancer and was either a major cause or 'an important conditioning factor' for chronic bronchitis, but they were more cautious about its relationship to other diseases. The Royal College of Physicians¹¹⁴ concluded that it also had an adverse effect on the healing of peptic ulcers, that it probably increased the risk of dying from coronary heart disease, and that it might promote the development and progression of peripheral vascular disease and contribute to the production of cancers of the mouth, pharynx, oesophagus and bladder. The Surgeon General¹¹⁵ added only the conclusion that pipe smoking appeared to be established as a cause of cancer of the lip and cigarette smoking as a factor in the causation of laryngeal cancer in men and it suspended judgment about the interpretation of the increased mortality from coronary disease in cigarette smokers. Both reports agreed that the excess of cirrhosis of the liver among smokers might well be noncausal, reflecting the tendency for heavy drinkers also to smoke.

Following these reports, the idea that smoking was a major cause of lung cancer ceased to be seriously challenged, except by the tobacco industry outside the UK (where it had been quietly accepted) and by a few eccentric individuals such as Burch¹²⁵ who, however, raised no material objections.

Table 10 Causes of death observed relatively more often^a in cigarette smokers than in nonsmokers in seven cohort studies (after Advisory Committee to the Surgeon General¹¹⁵)

| Cause of death | Numbers of deaths | Mortality ratio: cigarette smokers to nonsmokers |
|----------------------------|-------------------|--|
| Cancer of lung | 1833 | 10.8 |
| Cancer of larynx | 75 | 5.4 |
| Cancer of mouth | 152 | 4.1 |
| Cancer of oesophagus | 113 | 3.4 |
| Cancer of bladder | 216 | 1.9 |
| Cancer of kidney | 120 | 1.5 |
| Bronchitis and emphysema | 546 | 6.1 |
| Coronary heart disease | 11 177 | 1.7 |
| Hypertensive heart disease | 631 | 1.5 |
| Other heart disease | 868 | 1.7 |
| Other circulatory disease | 649 | 2.6 |
| General arteriosclerosis | 310 | 1.5 |
| Peptic ulcer | 294 | 2.8 |
| Cirrhosis of liver | 379 | 2.2 |

^aMortality ratio 1.5 or greater.

5 Current knowledge of effects

In the three subsequent decades, cigarette smoking has been found to be positively associated with nearly 40 diseases or causes of death and to be negatively associated with eight or nine more. In a few instances, the associations are due to confounding with other factors that cause the conditions, but the great majority arise because tobacco smoke is a direct contributory cause. *Pace* Berkson, this is not as surprising as might at first appear, not only because of the complexity of tobacco smoke, but also because many of the diseases are different clinical manifestations of common underlying pathologies, such as DNA damage, cytotoxicity, vascular occlusion, and damage to the small airways. Most of the associations have been demonstrated in cohort studies, which have now been carried out in China,¹²⁶ Japan,¹²⁷ Norway,¹²⁸ and Sweden¹²⁹ as well as in Canada, the UK, and the USA and have been extended to cover the last two decades, when most smokers have been smoking cigarettes for nearly all their smoking lives.^{79,130} The results have all been broadly consistent, though they have differed in detail, depending on differences in past smoking habits and in exposure to other agents with which smoking has interacted.

5.1 Harmful effects

The principal harmful effects of prolonged cigarette smoking are illustrated by the results of the American Cancer Society's most recent study of a million people¹³⁰ and of the study initiated by the British Medical Research Council of 34 000 male British doctors.⁷⁹ The American cohort was followed for nine years from 1982, but the first two years' observations have been omitted to reduce the 'healthy responder effect', that is the tendency for healthy people to respond more readily to questionnaires than people who are sick, which biases observed mortality rates downwards. In the subsequent seven years, over 80 000 deaths were recorded (C Heath Jr and M Thun, personal communication). In the British study, the cohort was followed for 40 years from 1951 with changes in smoking habits recorded at intervals of five to 12 years throughout and over 20 000 deaths were recorded.

Table 11 shows the risk of death in continuing cigarette smokers relative to that in lifelong nonsmokers from 22 causes of death. In both studies, the risks are standardized for age in single years according to the age distribution of the populations at risk and, in the British study, also for year of observation. In a few instances, data are given only for one study, either because the number of deaths in the other study was too small to provide reliable results or because the relevant diagnostic code was not used. For each cause of death, a figure is given for the percentage of deaths attributed to it in England and Wales in 1993¹³¹ as an indication of its relative importance.

The relative risks, which vary from 1.3:1 to ∞ :1 (because no death occurred in a nonsmoker) are all statistically significant ($p < 0.01$) and qualitatively similar in both studies and in both sexes. The exceptionally high relative risk for cancers of the mouth, pharynx, and larynx in the British study, which have been grouped together because of paucity of numbers, has wide confidence limits because only two deaths from this group of cancers were observed in nonsmokers.

Table 11 Principal diseases caused in part by smoking: mortality rates in cigarette smokers compared to rates in lifelong nonsmokers⁷⁹ (C Heath Jr and M Thun, personal communication)

| Cause of death (percentage of deaths in England and Wales in 1993) | Ratio of mortality rates | | | |
|--|-----------------------------------|--------------------------|-------|--|
| | British doctors 1951–91 men | US population 1984–91 | | |
| | | men | women | |
| Cancers of mouth, pharynx and larynx | (0.4) 24.0 | 11.4 | 6.9 | |
| Cancer of oesophagus | (1.0) 7.5 | 5.6 | 9.8 | |
| Cancer of lung | (5.6) 14.9 | 23.9 | 14.0 | |
| Cancer of pancreas | (1.0) 2.2 | 2.0 | 2.3 | |
| Cancer of bladder | (0.8) 2.3 | 3.9 | 1.8 | |
| Ischaemic heart disease | (25.3) 1.6 | 1.9 | 2.0 | |
| Hypertension | (0.5) 1.4 | 2.4 | 2.6 | |
| Myocardial degeneration | (2.0) 2.0 | } | 2.1 | |
| Pulmonary heart disease ^a | (0.3) ∞ | | | |
| Other heart disease | (3.0) – | | | |
| Aortic aneurysm | (1.6) 4.1 | 6.3 | 8.2 | |
| Peripheral vascular disease | (0.1) – | 9.7 | 5.7 | |
| Arteriosclerosis | (0.5) 1.8 | 2.7 | 3.0 | |
| Cerebral vascular disease | (10.6) 1.5 | 1.9 | 2.2 | |
| Chronic bronchitis and emphysema | (4.5) 12.7 | 17.6 | 16.2 | |
| Pulmonary tuberculosis | (0.1) 2.8 | – | – | |
| Asthma ^b | (0.3) 2.2 | 1.3 | 1.4 | |
| Pneumonia | (9.4) 1.9 | } | 1.7 | |
| Other respiratory disease | (1.4) 1.6 | | | |
| Peptic ulcer | (0.7) 3.0 | 4.6 | 4.0 | |
| All causes | 1.8 | 2.5 | 2.1 | |

^aNo death was reported in nonsmoking doctors.

^bSmokers include ex-smokers, as asthma may itself cause cessation of smoking.

Table 12 shows the corresponding risks in the British study, for ex-smokers and current cigarette smokers and for light and heavy smokers (that is, for men smoking less than 15, or 25 or more cigarettes a day). With one exception, the risks for ex-smokers are all intermediate between those for nonsmokers and current smokers and are all higher in heavy smokers than in light. The exception relates to the mortality from asthma and is due to the effect of asthma on smoking habits, rather than the reverse, as sufferers from the disease tend to stop smoking or to reduce the amount smoked.

Other harmful effects caused by smoking are listed in Table 13. For these, evidence has often had to be obtained from case-control studies; for cancers of the pelvis and body of the kidney, because they are seldom identified separately in the certified causes of death used in most cohort studies; for cancers of the stomach and myeloid leukaemia because they are only weakly related to smoking so that large numbers and evidence to exclude confounding have been needed; for cancers of the lip and nose and for Crohn's disease because they are too uncommon for substantial numbers of deaths to be observed in even the largest cohort studies. Six of the other seven conditions are seldom, if ever fatal, and evidence has principally been obtained in case-control studies or surveys and only occasionally in few cohort studies in which special enquiries have been made about the condition of interest.

Table 12 Principal diseases caused in part by smoking: mortality rates in ex-cigarette smokers and in cigarette smokers of different amounts compared to rates in lifelong nonsmokers⁷⁹

| Cause of death | Ratio of mortality rates | | | |
|--------------------------------------|--------------------------|--|------|------------|
| | Ex-cigarette smokers | Current cigarette smokers, smoking per day | | |
| | | Any number | 1–14 | 25 or more |
| Cancer of mouth, pharynx, and larynx | 3.0 | 24.0 | 12.0 | 48.0 |
| Cancer of oesophagus | 4.8 | 7.5 | 4.3 | 11.3 |
| Cancer of lung | 4.1 | 14.9 | 7.5 | 25.4 |
| Cancer of pancreas | 1.4 | 2.2 | 1.9 | 3.1 |
| Cancer of bladder | 1.6 | 2.3 | 2.2 | 2.8 |
| Ischaemic heart disease | 1.2 | 1.6 | 1.4 | 1.8 |
| Hypertension | 1.03 | 1.4 | 0.9 | 1.9 |
| Myocardial degeneration | 1.4 | 2.0 | 2.0 | 2.8 |
| Pulmonary heart disease ^a | (7) | (10) | (5) | (21) |
| Aortic aneurysm | 2.2 | 4.1 | 2.5 | 5.4 |
| Arteriosclerosis | 0.8 | 1.8 | 1.4 | 3.1 |
| Cerebral vascular disease | 1.1 | 1.5 | 1.4 | 1.7 |
| Chronic bronchitis and emphysema | 5.7 | 12.7 | 8.6 | 22.5 |
| Pulmonary tuberculosis | 2.0 | 2.8 | 1.8 | 5.0 |
| Asthma | 2.8 | 1.8 | 1.5 | 1.6 |
| Pneumonia | 1.3 | 1.9 | 1.6 | 2.4 |
| Other respiratory disease | 1.5 | 1.6 | 1.4 | 1.7 |
| Peptic ulcer | 1.5 | 3.0 | 1.4 | 4.5 |
| All causes | 1.2 | 1.8 | 1.5 | 2.3 |

^aFor pulmonary heart disease mortality rates are given in place of mortality ratios as the rate in nonsmokers was zero.

An association between maternal smoking and premature delivery and a low infant birth weight was reported in the late 1950s.^{142,143} The association initially reported was weak and, in at least one study, was closer with paternal smoking than maternal, and confounding with socioeconomic status was difficult to eliminate.¹⁴⁴ Large studies, however, have eventually shown that both maternal smoking and socioeconomic status have independent effects, that the reduction in weight produced by maternal smoking is, on average, about 200 g, and that smoking is associated with an increase in perinatal mortality of about a quarter.^{145,146}

Evidence that all these effects can be caused by smoking varies in strength. It includes, in nearly all cases, increases in risk with the amount smoked, decreases in risk since smoking stopped, qualitatively similar findings in different populations in

Table 13 Other harmful effects caused in part by smoking

| | |
|---|---|
| Cancer of lip ¹³² | Crohn's disease ¹³⁴ |
| Cancer of nose ¹³² | Osteoporosis ^{135,136} |
| Cancer of stomach ¹³² | Periodontitis ¹³⁷ |
| Cancer of pelvis of kidney ¹³² | Tobacco amblyopia ⁵¹ |
| Cancer of body of the kidney ¹³² | Age-related macular degeneration ^{138–140} |
| Myeloid leukaemia ¹³² | Reduced fecundity ¹⁴¹ |
| Reduced growth of fetus ^a | |

^aSee text.

which cigarette smoking has been prolonged, and biologically plausible mechanisms by which the risk of developing the disease could be affected. For some the evidence is very strong. For chronic obstructive lung disease (the term now preferred for chronic bronchitis and emphysema), it includes observations on a cohort of workers in whom the rate of deterioration of lung function in smokers slowed down to that in nonsmokers when smoking was stopped.^{147,148} For gastric ulcers, it includes a randomized controlled trial in which the rate of healing was greater in patients advised to stop smoking (and greatest in those who accepted the advice) than in those not so advised.¹⁴⁹ For ischaemic heart disease, it includes the evidence that smoking increases the level of plasma fibrinogen¹⁵⁰ and serum apolipoprotein B¹⁵¹ and decreases serum high density lipoprotein and apolipoprotein A1,¹⁵² all of which would increase the risk of the disease. For cancer of the bladder and myeloid leukaemia, it includes the identification in tobacco smoke of chemicals known to cause the disease occupationally in humans (2-naphthylamine, benzene), while for cancer of the lung it includes the identification of benzo(a)pyrene which has been shown to form adducts in bronchial DNA that lead to mutations of the type that are sometimes found in lung cancer, particularly in the p53 gene.¹⁵³ For some other conditions, the conclusion about causality is largely based on analogy with other diseases that have been studied more intensively.

5.2 Possibly harmful effects

Even these diseases may not constitute all the conditions produced by smoking, as there is some evidence of an increased risk of cataracts,¹⁵⁴ impotence,¹⁵⁵ reduced production of sperm,¹⁵⁶ and a small increase in the risk of cancer in children as a result of mutations produced in the fathers' gonads.¹⁵⁷ Some other major diseases or causes of death may also be partly due to smoking, though much, if not all, of the associated increase in risk is due to confounding with other aetiological agents. These are listed in Table 14. Confounding with the consumption of alcohol and with a certain personality, probably explains most or all of the association with suicide and poisoning and confounding with alcohol must account for much of the association with cancer of the liver in Western populations; but it cannot account for much of it in many Asian populations where alcohol is not an important cause of the disease.¹³² How far the associations with cancer of the cervix and cancer of the large bowel can be explained by confounding with sexual activity and diet, respectively, is still uncertain.

5.3 Beneficial effects

Lastly, there are some diseases that occur less often than expected in smokers and may be alleviated or prevented by some of the chemicals in tobacco smoke. These are listed in Table 15. In several, the reduction in risk suggests that smoking may have, at

Table 14 Causes of death associated with smoking that may be largely or wholly due to confounding with other factors

| | |
|------------------------|--------------------|
| Cancer of liver | Cirrhosis of liver |
| Cancer of cervix uteri | Suicide |
| Cancer of large bowel | Poisoning |

Table 15 Diseases negatively associated with smoking

| | |
|-----------------------|--------------------------------------|
| Parkinson's disease | Cancer of body of uterus |
| Ulcerative colitis | Fibroids |
| Aphthous ulcers | Nausea and vomiting during pregnancy |
| Allergic alveolitis | Pre-eclampsia |
| ? Alzheimer's disease | |

least indirectly, an anti-oestrogenic effect.^{158,159} Most of the conditions reduced in incidence are uncommon or seldom fatal and the combined impact on mortality of their reduction in incidence as a result of smoking is less than 1% of that due to the increased incidence of the diseases caused by smoking that have been listed earlier. Whether the risk of Alzheimer's disease is reduced by smoking is uncertain; if it were it might provide a useful clue to chemoprevention. The benefit obtained, however, be counterbalanced by an increased risk of tobacco-induced vascular dementia or dementia due to stroke and, in the study of British doctors, the mortality attributed to dementia as a whole was slightly higher in smokers than in lifelong nonsmokers.⁷⁹

5.4 Total effect on individual's risk of death

The sum of all these effects on mortality, which was shown in Table 11 to approximately double the risk in cigarette smokers compared to nonsmokers, varies with age, increasing up to 45 years of age, because of the long exposure needed to produce a large increase in the risk of cancer and chronic obstructive lung disease, and decreasing from 65 years of age, due partly to a reduction in the amount smoked, partly to a reduction in the proportion of deaths from cancer, and partly to a reduction in the relative risk of cardiovascular disease in smokers with age that has been seen in all cohort studies, from about 4:1 under 55 years of age, to about 1.2:1 at 85 years and over.

In the British doctors' study, which covered a 40-year period of observation from 1951 to 1991, the effect on mortality was greater in the second half of the period than in the first, as is shown in Figure 2. The greater excess risk of 200% in middle age that is seen in the second 20-year period, corresponding to a threefold relative risk, is paralleled by the greater relative risk observed in the second of the two studies of a million men and women carried out by the American Cancer Society in the early 1960s and mid-1980s. When those smoking at the start of the study are compared with those who never smoked regularly the relative risk in men, standardized for age, rose from 1.7 to 2.3 and the relative risk in women, standardized similarly, rose from 1.2 to 1.9.¹³⁰ The relative risks in the second period differ slightly from those shown in Table 11, as they relate to different years of observation and are standardized to a population with a different age distribution. These increases have occurred despite the slightly lower risks associated with the modern low tar/low nicotine cigarettes. They are not the result of increased absolute risks, so much as of a failure to benefit from the decreased risks of, in particular, cardiovascular disease that has occurred in nonsmokers as a result of improved therapy and prophylaxis. They can be attributed principally to a 'maturing' of the smoking epidemic in both countries, that is to say, longer durations of regular cigarette smoking by smokers of both sexes in the more

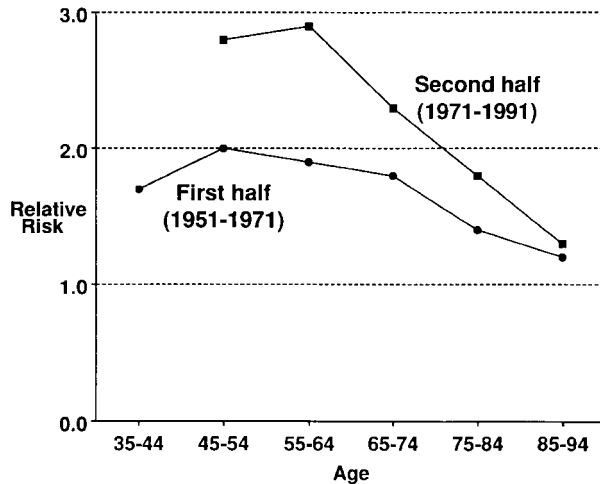


Figure 2 Excess at different ages in cigarette smokers compared to nonsmokers in 1951–71 (lower line) and 1971–91 (upper line). Bars indicate SD.⁷⁹ (Reproduced with permission of the BMJ Publishing Group.)

recent periods and possibly, in part, to the more intensive smoking of each cigarette in those who have persisted in the habit, when so many smokers in both countries have stopped.

As the British doctors have been followed for such a long time, it is possible to calculate ‘actuarial’ survival curves for different categories of smokers into the eleventh decade of life – 22 having survived to over 100 years – with results that are reasonably reliable up to at least 85 years of age. These are shown for nonsmokers and three categories of continuing smokers in Figure 3. Eighty per cent of nonsmokers survived to 70 years of age against 50% of heavy cigarette smokers and 33% of nonsmokers survived to 85 years of age against only 8% of heavy smokers. The loss of expectation of life shown by these data is substantial, for the age by which half the men have died is 7.5 years less for cigarette smokers than for nonsmokers and 10 years less for heavy cigarette smokers than for nonsmokers. Half of the deaths occurred in the second half of the follow-up and the differences are increased slightly by limiting the calculation to this period, when the loss of expectation of life for all cigarette smokers becomes eight years.

Allowance for confounding

These crude figures do not allow for the fact that some of the loss of life of cigarette smokers is due to characteristics confounded with smoking, such as personality, the consumption of alcohol, and, to a small extent, a less healthy diet. Such characteristics contributed to the increased mortality from the conditions that were listed in Table 14, which in total accounted for 6% of the excess mortality in cigarette smokers. Confounding can, however, diminish the apparent effect of an agent as well as increase it. This is particularly important in the case of alcohol, as small or moderate amounts reduce the risk of vascular disease. The possibility that alcohol might have such an effect has been suspected for many years; but the evidence that moderate consumption

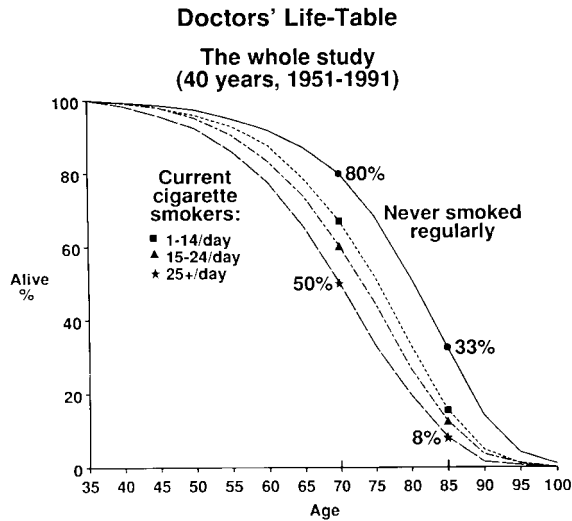


Figure 3 Survival after age 35 years among nonsmokers and cigarette smokers smoking different amounts at the time their last questionnaire was returned.⁷⁹ (Reproduced with permission of the BMJ Publishing Group.)

really has such an effect is now compelling. For a negative association between alcohol and the risk of vascular disease has been observed in nearly all large case-control and cohort studies that have investigated it and it is biologically plausible, because alcohol tends to reduce platelet aggregability and plasma fibrinogen and to increase the concentration of plasma high density lipoprotein, while it does not increase blood pressure until fairly large amounts are consumed (for a review see Doll¹⁶⁰). The beneficial effect is substantial, as is shown by the observations on British doctors.¹⁶¹ Precisely what effect standardization for alcohol has on the estimated relative risk for cigarette smokers will vary from one population to another, depending on the age distribution of the population, the background incidence of thrombotic vascular disease, and the extent of alcohol use and abuse. In many developed countries, the total effect of confounding with alcohol will cause the relative risk of cigarette smoking in the middle aged and elderly to be underestimated rather than overestimated, because vascular disease is responsible for such a high proportion of all deaths.

5.5 Indirect effects

With the recognition that tobacco smoke had such serious effects on the smoker, the possibility has had to be considered that it might have some weak effect on the nonsmoker who was exposed to it in the environment. Such a possibility was considered by Schönher¹⁶² as early as 1928, as an explanation for the lung cancers observed in nonsmoking women, but it did not begin to be investigated as a serious possibility until 1971 when Colley found an increased risk of bronchitis and pneumonia in children in their first year of life if the parents smoked.¹⁶³ Review of the many subsequent studies by the US Environmental Protection Agency¹⁶⁴ confirmed Colley's findings, extended them to all pre-school children, and added

effects on the incidence and severity of asthma, of middle-ear infections, and the incidence of the sudden infant death syndrome. For all these conditions, increases of the order of 50–100% have been attributed to the exposure.

The effects on adults have been more difficult to assess, perhaps because such long exposure is required to produce substantial increases in risk. They began to be reported only in 1981, when Hirayama¹⁶⁵ and Trichopoulos *et al.*¹⁶⁶ independently reported an increased risk of lung cancer in nonsmokers if their spouses smoked. An increased risk of chronic respiratory disease under similar circumstances was also reported by Hirayama¹⁶⁵ and similarly increased risks of myocardial infarction have been reported subsequently by others. The findings have been reviewed by Law and Hackshaw¹⁶⁷ but are not considered further here, as they present the problems of interpretation that are discussed in detail later in relation to lung cancer by Lee and by Hackshaw.

6 Envoi

In this review I have limited myself to the discovery of the effects of smoking and the scientific arguments to which it gave rise. I have said nothing about the reaction to that discovery of the public, governments, or the tobacco industry, to do so would require another long article. Nor have I attempted to assess the current contribution of smoking to total mortality in the developed and developing world. This has been plausibly estimated by Peto *et al.*^{168,169} to be about 3 million deaths per year (rising to about 10 million a year in a few decades) including about 30% of all cancer deaths in developed countries, while Parkin *et al.*¹⁷⁰ have estimated that world-wide about 15% of all cases of cancer were attributable to tobacco.

In retrospect, it may be surprising that resistance to the idea that smoking was a major cause of lung cancer was initially so strong. Three factors, at least, contributed to it. One was the ubiquity of the habit, which was as entrenched among male doctors and scientists as among the rest of the adult male population and had dulled the collective sense that tobacco might be a major threat to health. Another was the novelty of the epidemiological techniques, which had not previously been much used in the study of noninfectious disease. The epidemiological results were consequently undervalued as a source of scientific evidence. A third, was the primacy given to Koch's postulates in determining causation. The evidence that lung cancer occurred in nonsmokers was consequently taken to show that smoking could not be the cause and the possibility that it might be a cause was inappropriately doubted. The manner in which lung cancer was linked to smoking was not, however, unique. All the other major diseases related to smoking were found to be so by epidemiological enquiry and laboratory evidence of physiological effects that provided plausible mechanisms by which smoking might cause them was obtained only subsequently and, in some instances, is still unclear.

All the diseases related to smoking that cause large numbers of deaths should by now have been discovered, but further effects like age-related macular degeneration, which was firmly linked to smoking only in 1996,^{138–140} may well remain to be revealed by cohort studies that are able to link individuals' morbidity data with their personal

characteristics through personal identity numbers. That so many diseases – major and minor – should be related to smoking is one of the most remarkable medical research findings of the present century.

Acknowledgements

I am grateful to Professor Richard Peto for many helpful comments in the preparation of this paper, Professor Proctor for a preprint of his paper on the Nazi war on tobacco, colleagues in Germany (Professor Herman Heimpel, Professor Helmut Kohl, Professor Harald zur Hausen, Dr G Posner, and Mrs Roedler-Vogelsang) for assistance in the review of the early German literature, Professor Gunnar Steineck for a copy and a translation of the Swedish Medical Research Council's letter to the King, Professor Charles Hennekens and Ms Ina Smith for information about references to tobacco in American medical texts in the 1940s. I am grateful to Mrs Catherine Harwood for typing innumerable copies of the developing text, and the *British Medical Journal* for permission to reproduce Figures 2 and 3.

References

- 1 Corti E. *A history of smoking*. (Translated by Paul England.) London: George Harrap, 1931.
- 2 James I. *Misocapnus sive de abusu tobacci lusii regius*. London: 1603; also Anon. *A Counterblaste to tobacco*. London: 1604. See Jack RDS ed. *Scottish proses 1550–1700*. London: Calder and Boyars, 1971.
- 3 Wald N, Kiryuk S, Darby S, Doll R, Pike M, Peto R. *UK Smoking statistics*. Oxford: Oxford University Press, 1988.
- 4 Nicolaidis-Bouman A, Wald N, Forey B, Lee P. *International smoking statistics*. Oxford: Oxford University Press, 1993.
- 5 Webster C. Tobacco smoking addiction: a challenge to the National Health Service. *British Journal of Addiction* 1984; **79**: 7–16.
- 6 Proctor RN. The anti-tobacco campaign of the Nazis: a little known aspect of public health in Germany, 1933–45. *British Medical Journal* 1996; **313**: 1450–53.
- 7 Proctor RN. The Nazi war on tobacco: ideology, evidence, and possible cancer consequences. *Bulletin of History and Medicine* 1997; **71**: 435–88.
- 8 Sömmering ST. *De morbis vasorum absorbentium corporis humani*. Frankfurt: Varrentrapp & Wenner, 1795.
- 9 Clemmesen J. *Statistical studies in malignant neoplasms. I. Review and results*. København: Munksgaard, 1965: 59–116.
- 10 Holland JJ. *Dissertatio inaugur med chir sistens Carcinoma labii inferioris absque sectione persenatum*. Rinteln, 1739.
- 11 Bouisson EF. Du cancer buccal chez les fumeurs. *Montpellier Medical Journal* 1859; **2**: 539–99 and 1859; **3**: 19–41.
- 12 Anon. Cancer and smoking. *British Medical Journal* 1890; **1**: 748.
- 13 Hoffman F. *Cancer and overnutrition*. Prudential Press, 1927 (cited by Lombard and Doering, 1928).
- 14 Lombard HL, Doering CR. Cancer studies in Massachusetts. 2. Habits, characteristics and environment of individuals with and without cancer. *New England Journal of Medicine* 1928; **198**: 481–87.
- 15 Potter EA, Tulley MR. The statistical approach to the cancer problem in Massachusetts. *American Journal of Public Health* 1945; **35**: 485–90.
- 16 Rottmann H. *Über primäre lungencarcinoma*. Inaugural-dissertation. Würzburg: Universität Würzburg, 1898.
- 17 Tylecote FE. Cancer of the lung. *Lancet* 1927; **2**: 256–57.
- 18 Lickint F. Tabak und Tabakrauch als ätiologischer Faktor des Carcinoms. *Zeitschrift für Krebsforschung* 1929; **30**: 349–65.
- 19 Fleckseder R. Ueber den Bronchialkrebs und einiger seiner Entstehungsbedingungen. *Münchener Medizinische Wochenschrift* 1936; **83**: 1585–88.
- 20 Adler I. *Primary malignant growths of the lung and bronchi*. London: Longmans Green, 1912.
- 21 Hoffman FL. Cancer and smoking habits. *Annals of Surgery* 1931; **93**: 50–67.

- 22 Arkin A, Wagner DH. Primary carcinoma of the lung. *Journal of the American Medical Association* 1936; **106**: 587–91.
- 23 Ochsner A, de Bakey M. Carcinoma of the lung. *Archives of Surgery* 1941; **42**: 209–58.
- 24 Ochsner A, de Bakey M, Dixon JL. Primary cancer of the lung. *Journal of the American Medical Association* 1947; **135**: 321–27.
- 25 Leitch A. Experimental production of tumours by other methods. *Fifth annual report of the British Empire Cancer Campaign*. London: British Empire Cancer Campaign, 1928: 26.
- 26 Passey RD. Cancer of the lung. *Sixth report of British Empire Cancer Research Campaign*. London: British Empire Cancer Campaign, 1929: 85.
- 27 Cooper EA, Lamb FWM, Sanders E, Hirst EL. The role of tobacco-smoking in the production of cancer. *Journal of Hygiene London* 1932; **32**: 293–300.
- 28 Kennaway E. On cancer producing tars and tar fractions. *Journal of Industrial Hygiene* 1924; **5**: 462–88.
- 29 Roffo AH. Durch Tabak beim Kaninchen entwickeltes Carcinom. *Zeitschrift für Krebsforschung* 1931; **33**: 321–32.
- 30 Roffo AH. Krebserzeugendes Benzpyren, gewonnen aus Tabaktee. *Zeitschrift für Krebsforschung* 1940; **49**: 588–97.
- 31 Sugiura K. Observations on animals painted with tobacco tars. *American Journal of Cancer* 1940; **38**: 41–49.
- 32 Flory CM. Production of tumors by tobacco tars. *Cancer Research* 1941; **1**: 262–76.
- 33 Müller FH. Tabakmissbrauch und lungencarcinoma. *Zeitschrift für Krebsforschung* 1939; **49**: 57–85.
- 34 Schairer E, Schöniger E. Lungenkrebs und Tabakverbrauch. *Zeitschrift für Krebsforschung* 1943; **54**: 261–69.
- 35 Wassink WF. 'Onstaansvoorwarden voor Longkanker'. *Nederlands Tijdschrift voor Geneeskunde (Amsterdam)*, 1948; **92**: 3732–47.
- 36 Huchard H. *Traité clinique des maladies du coeur et des vaisseaux*, 2nd ed. Paris: Doin, 1893: 125–26.
- 37 Erb W. Ueber dysbasia angiosclerotica ('intermittierendes Hinken'). *Münchener med Woch* 1904; **51**: 905–908.
- 38 Buerger L. Thromboangiitis obliterans: a study of the vascular lesions leading to presenile spontaneous gangrene. *American Journal of Medical Science* 1908; **136**: 567–80.
- 39 Weber JB. Thromboangiitis obliterans. *Quarterly Journal of Medicine* 1916; **5**: 289–300.
- 40 Brown GE, Allen EV. *Thrombo-angiitis obliterans*. Philadelphia: WB Saunders, 1928: 141.
- 41 Allen EV, Barker NW, Hines EA Jr. *Peripheral vascular disease*. Philadelphia: WB Saunders, 1946: 390.
- 42 Silbert S. Thrombo-angiitis obliterans (Buerger): treatment of 524 cases by repeated intravenous injections of hypertonic salt solution: experience of 10 years. *Surgery Gynaecology and Obstetrics* 1935; **51**: 214–22.
- 43 Christian HA. *The principles and practice of medicine*, 16th edn. New York: Appleton–Century, 1947.
- 44 Herrick JB. Clinical features of sudden obstruction of the coronary arteries. *Journal of American Medical Association* 1912; **59**: 2015–20.
- 45 Howard T. Coronary occlusion: based on the study of 165 cases. *Medical Times Long Island Medical Journal* 1934; **68**: 337–41.
- 46 English JP, Willius FA, Berkson J. Tobacco and coronary disease. *Journal of the American Medical Association* 1940; **115**: 1327–29.
- 47 Willius FA. Tobacco and coronary disease (Discussion). *Journal of the American Medical Association* 1940; **115**: 1329.
- 48 Pickering GW, Sanderson PH. Angina pectoris and tobacco. *Clinical Science* 1945; **5**: 275–88.
- 49 Beer GJ. *Lehre von den Augenkrankheiten, vol II*. Vienna: 1817. (Cited by Duke-Elder WSD, *Textbook of Ophthalmology*, vol 3. London: Henry Kimpton, 1817: 3009.)
- 50 Heaton JM, McCormick AJA, Freeman AG. Tobacco amblyopia. A clinical manifestation of vitamin B₁₂ deficiency. *Lancet* 1958; **2**: 286–90.
- 51 Freeman AG. Optic neuropathy and chronic cyanide intoxication: a review. *Journal of the Royal Society of Medicine* 1988; **81**: 103–106.
- 52 Lickint F. *Tabak und Organismus. Handbuch der gesamten Tabakkunde*. Stuttgart: Hippokrates, 1939.
- 53 Pearl R. Tobacco smoking and longevity. *Science* 1938; **87**: 216–17.
- 54 Conybeare JJ. *Textbook of medicine*, 8th edn. Edinburgh: Livingstone, 1946.
- 55 Price FW. *A textbook of the practice of medicine by various authors*, 8th edn. London: Oxford University Press, 1950.
- 56 Romanes WHC, Mitchiner PH. *The science and practice of surgery*, 8th edn. London: Churchill, 1948.
- 57 Aird I. *A companion in surgical studies*. Edinburgh: Livingstone, 1949.

- 58 Yater WM. *Fundamentals of internal medicine*. New York: Appleton-Century, 1944.
- 59 Emerson CP, Taylor JE. *Essentials of medicine*, 15th edn. Philadelphia: JB Lippincott, 1946.
- 60 Cecil RL. *Textbook of medicine: by American authors*, 7th edn. Philadelphia: WB Saunders, 1949.
- 61 Harrison TR. *Principles of internal medicine*. Philadelphia: The Blakiston Company, 1950.
- 62 White PD. *Heart disease*, 3rd edn. New York: Macmillan, 1948.
- 63 Dennig H. *Lehrbuch der inneren Medizin*. Stuttgart: Georg Thieme, 1950.
- 64 Curschmann H, Jores A. *Lehrbuch der speziellen Therapie innsierer Krankheiten*. Berlin: Springer, 1947.
- 65 Hoff F. *Behandlung innerer Krankheiten*. Stuttgart: Georg Thieme, 1949.
- 66 Wolf HJ. *Einführung in die innere Medizin*. Stuttgart: Georg Thieme, 1948.
- 67 Lindemann A, Lorenz O. *Die Geschwülste der Mundhöhle, des Kiefers und des Gesichtes*. Stuttgart: Wissenschaftliche Verlagsgesellschaft MBH, 1950.
- 68 Stich R, Bauer KH. *Lehrbuch der Chirurgie*. Berlin: Springer, 1949.
- 69 Fischer W. *Die Krebsforschung in den letzten 100 Jahren*. Jena: Gustav Fischer, 1947
- 70 Bauer KH. *Das Krebsproblem*. Berlin: Springer, 1949.
- 71 Schrek R, Baker LA, Ballard GP, Dolgoff S. Tobacco smoking as an etiologic factor in disease. *Cancer Research* 1950; **10**: 49–58.
- 72 Levin ML, Goldstein H, Gerhardt PR. Cancer and tobacco smoking. *Journal of the American Medical Association* 1950; **143**: 336–38.
- 73 Mills CA, Porter MM. Tobacco smoking habits and cancer of the mouth and respiratory system. *Cancer Research* 1950; **10**: 539–42.
- 74 Wynder EL, Graham EA. Tobacco smoking as a possible etiologic factor in bronchogenic carcinoma. *Journal of the American Medical Association* 1950; **143**: 329–36.
- 75 Doll R, Hill AB. Smoking and carcinoma of the lung. Preliminary report. *British Medical Journal* 1950; **2**: 739–48.
- 76 Wynder EL. Tobacco and health: a review of the history and suggestions for public health policy. *Public Health Reports* 1988; **103**: 8–17.
- 77 Cuthbertson D. Historical notes on the origin of the association between lung cancer and smoking. *Journal of the Royal College of Physicians* 1967; **2**: 191–96.
- 78 Berkson J. Limitations of the application of fourfold table analysis to hospital data. *Biometrics* 1946; **2**: 47–53.
- 79 Doll R, Peto R, Wheatley K, Gray R, Sutherland I. Mortality in relation to smoking: 40 years' observations on male British doctors. *British Medical Journal* 1994; **309**: 901–11.
- 80 Doll R, Hill AB. A study of the aetiology of carcinoma of the lung. *British Medical Journal* 1952; **2**: 1271–86.
- 81 Doll R, Hill AB. The mortality of doctors in relation to their smoking habits. A preliminary report. *British Medical Journal* 1954; **1**: 1451–55.
- 82 Doll R, Hill AB. Lung cancer and other causes of death in relation to smoking. A second report on the mortality of British doctors. *British Medical Journal* 1956; **2**: 1071–76.
- 83 Hammond EC, Horn D. The relationship between human smoking habits and death rates: a follow-up study of 187 766 men. *Journal of the American Medical Association* 1954; **155**: 1316–28.
- 84 Berkson J. The statistical study of association between smoking and lung cancer. *Proceedings of the Staff Meetings of Mayo Clinic* 1955; **30**: 319–48.
- 85 Berkson J. Smoking and lung cancer: some observations on two recent reports. *Journal of the American Statistical Association* 1958; **53**: 28–38.
- 86 Hammond EC, Horn D. 1957 *Smoking in relation to death rates*. Manuscript distributed at the time of presentation at the meeting of the American Medical Association, New York, June 4 1957 and subsequently published as: Hammond EC, Horn D. Smoking and death rates: report on forty four months of follow-up of 187,783 men. *Journal of the American Medical Association* 1958; **166**: 1159–72, 1294–308.
- 87 Hill AB. *Principles of medical statistics*, 8th edn. London: Lancet, 1966: 305–13.
- 88 Fisher RA. Dangers of cigarette smoking. *British Medical Journal* 1957; **2**: 43.
- 89 Fisher RA. Cancer and smoking. *Nature* 1958a; **182**: 596.
- 90 Fisher RA. Lung cancer and cigarettes? *Nature* 1958b; **182**: 168.
- 91 Davies CN. Inhalation risk and particle size in dust and mist. *British Journal of Industrial Medicine* 1949; **6**: 245–53.
- 92 Doll R, Peto R. The causes of cancer: quantitative estimates of avoidable risks of cancer in the United States today. Appendix

- E. *Journal of the National Cancer Institute* 1981; **66**: 1191–308.
- 93 Doll R, Peto R. Mortality in relation to smoking: 20 years' observations on male British doctors. *British Medical Journal* 1976; **2**: 1525–36.
- 94 Fisher RA. *Smoking: the cancer controversy. Some attempts to assess the evidence*. Edinburgh: Oliver & Boyd, 1959.
- 95 Floderus B, Cederlöf R, Friberg L. Smoking and mortality: a 21 year follow-up based on the Swedish Twin Registry. *International Journal of Epidemiology* 1988; **17**: 332–40.
- 96 Kaprio J, Koskenvuo M. Twins, smoking and mortality: a 12 year prospective study of smoking discordant pairs. *Social Science and Medicine* 1985; **29**: 1083–89.
- 97 Carmelli D, Page WF. Twenty-four year mortality in World War II male veteran twins discordant for cigarette smoking. *International Journal of Epidemiology* 1996; **25**: 554–59.
- 98 Doll R. Etiology of lung cancer. In: *Advances in cancer research*, vol 3. Greenstein JP, Haddow A eds. New York: Academic Press, 1955: 1–50.
- 99 Engelbreth-Holm J, Ahlmann J. Production of carcinoma in St/Eh mice with cigarette tar. *Acta Pathological Microbiology Scandinavia* 1957; **41**: 267–72.
- 100 Guérin M, Cuzin JL. Action carcinogène du goudron de fumée de cigarette sur le peau de souris. *Bulletin of the Association of France Cancer*, 1957; **44**: 387–408.
- 101 Sugiura K. Experimental production of carcinoma in mice with cigarette smoke tar. *Gann* 1956; **47**: 243–44.
- 102 Wynder EL, Graham EA, Croninger AB. Experimental production of carcinoma with cigarette tar. Part I. *Cancer Research* 1953; **13**: 855–64.
- 103 Wynder EL, Graham EA, Croninger AB. Experimental production of carcinoma with cigarette tar. Part II. *Cancer Research* 1955; **15**: 445–48.
- 104 Croninger AB, Graham EA, Wynder EL. Experimental production of carcinoma with cigarette tar. Part V. *Cancer Research* 1958; **18**: 1263–71.
- 105 Cooper RL, Lindsay AJ. 3-4 benzpyrene and other polycyclic hydrocarbons in cigarette smoke. *British Journal of Cancer* 1955; **9**: 442–44.
- 106 Van Duuren BL. Identification of some polynuclear aromatic hydrocarbons in cigarette smoke condensate. *Journal of the National Cancer Institute* 1958; **21**: 1–16.
- 107 Netherlands Ministry of Social Affairs and Public Health. Roken en longkanker. *Nederlands Tijdschrift voor Geneeskunde (Amsterdam)* 1957; **101**: 459–64.
- 108 Medical Research Council. Tobacco smoking and cancer of the lung. *British Medical Journal* 1957; **1**: 1523.
- 109 Study Group on Smoking and Health. Joint report of study group on smoking and health. *Science* 1957; **125**: 1129–33.
- 110 Swedish Medical Research Council. Statement to the King, May 12 1958.
- 111 National Cancer Institute of Canada. Lung cancer and smoking. *Canadian Medical Association Journal* 1958; **79**: 566–68.
- 112 Burney LE. Smoking and lung cancer: a statement of the Public Health Service. *Journal of the American Medical Association* 1959; **171**: 1829–37.
- 113 World Health Organization. *Epidemiology of cancer of the lung. Report of a study group. World Health Organization technical report series 192*. Geneva: World Health Organization, 1960.
- 114 Royal College of Physicians of London. *Smoking and health*. London: Pitman Medical, 1962.
- 115 Advisory Committee to the Surgeon General of the Public Health Service. *Smoking and Health. Public Health Service Publication No. 1103*. Washington: US Government Printing Office, 1964.
- 116 Lancaster HO. Cancer statistics in Australia. Part II. Respiratory system. *Medical Journal of Australia* 1962; **1**: 1006–11.
- 117 Kouloumies M. Smoking and pulmonary carcinoma. *Acta Radiology (Stockholm)* 1953; **30**: 255–60.
- 118 Pernu J. An epidemiological study on cancer of the digestive organs and respiratory system. A study based on 7078 cases. *Annals Med intern Fenn* 1960; **49**: 1–117.
- 119 Schwartz D, Denoix PF. L'enquête Française sur l'étiologie du cancer broncho-pulmonaire. Rôle du tabac. *Semaine des Hopitaux de Paris* 1957; **33**: 3630–43.
- 120 Lickint F. *Ätiologie und Prophylaxe des Lungenkrebses. 2. Statistische Voraussetzungen zur Klärung der Tabakrauchätiologie des Lungenkrebses*. Leipzig: Theodor Steinkopff, 1953: 76–102.
- 121 Randig K. Untersuchungen zur Ätiologie des Bronchialkarzinoms. *Öff Gesundheitsdienst* 1954; **16**: 305–13.
- 122 Segi M, Fukushima L, Fujisako S, Kurihara M, Saito S, Atano K, Kamoi M. An

- epidemiological study on cancer in Japan. *Gann* 1957; **48**: 1–63.
- 123 Kreyberg L. Lung cancer and tobacco smoking in Norway. *British Journal of Cancer* 1955; **9**: 495–510.
- 124 Gsell O. Carcinome bronchique et tabac. *Medical Hygiene* 1954; **12**: 429–31.
- 125 Burch PRJ. The Surgeon General's 'Epidemiologic criteria for causality'. A critique. *Journal of Chronic Disease* 1983; **36**: 821–36.
- 126 Chen Z, Xu Z, Collins R, Li W-X, Peto R. The early effects of the emerging tobacco epidemic in China: 16-year prospective study of 9351 middle-age adults in Shanghai. *Journal of the American Medical Association* (in press).
- 127 Akiba S, Hirayama T. Cigarette smoking and cancer mortality: risk in Japanese men and women – results from reanalyses of the six-prefecture cohort study data. *Environmental Health Perspectives* 1990; **87**: 19–26.
- 128 Lund E, Zeiner-Henriksen T. Smoking as a risk factor for cancer among 26 000 Norwegian males and females (in Norwegian) *Tidsskr nor laegeforen* 1981; **101**: 1937–40.
- 129 Cederlöf R, Friberg, L, Hrubec Z, Lorich U. *The relationship of smoking and some social covariables to mortality and cancer morbidity*. Stockholm: The Karolinska Institute, 1975.
- 130 Thun MJ, Day-Lalley CA, Calle EE, Flanders WD, Heath CA. Excess mortality among cigarette smokers: changes in a 20-year interval. *American Journal of Public Health* 1995; **85**: 1223–30.
- 131 Office of Population Censuses and Surveys. *1993 Mortality statistics, cause. Series DH2 no. 20*. London: HMSO, 1995
- 132 Doll R. Cancers weakly associated with smoking. *British Medical Bulletin* (in press).
- 133 International Agency for Research on Cancer. *IARC Monographs on the evaluation of the carcinogenic risk of chemicals to humans: Tobacco smoking. Vol. 38*. Lyon: International Agency for Research on Cancer, 1986.
- 134 Logan RFA. Smoking and inflammatory bowel disease. In: Wald N, Baron J ed. *Smoking and hormone related disorders*. Oxford: Oxford University Press, 1990: 122–34.
- 135 Law M. Smoking and osteoporosis. In: Wald N, Baron J ed. *Smoking and hormone-related disorders*. Oxford: Oxford University Press, 1990: 83–92.
- 136 Egger P, Duggleby S, Hobbs R, Fall C, Cooper C. Cigarette smoking and bone mineral density in the elderly. *Journal of Epidemiology and Community Health* 1996; **50**: 47–50.
- 137 Haber J. Smoking is a major risk factor for periodontitis. *Current Opinion in Periodontology* 1994; 12–18.
- 138 Christen WG, Glynn RJ, Manson JE, Ajani UA, Buring JE. A prospective study of cigarette smoking and risk of age-related macular degeneration in men. *Journal of the American Medical Association* 1996; **276**: 1147–51.
- 139 Seddon JM, Willett WC, Speizer FE, Hankinson SE. A prospective study of cigarette smoking and age-related macular degeneration in women. *Journal of the American Medical Association* 1996; **276**: 1141–46.
- 140 Vingerling JR, Hofman A, Grobee DE, de Jong PTVM. Age-related macular degeneration and smoking. *Archives of Ophthalmology* 1996; **114**: 1193–96.
- 141 Hughes EF, Brennan BG. Does cigarette smoking impair natural and assisted fecundity? *Fertility Sterility* 1996; **66**: 679–89.
- 142 Simpson WJ. A preliminary report on cigarette smoking and the incidence of prematurity. *American Journal of Obstetrics and Gynecology* 1957; **73**: 808–15.
- 143 Lowe CR. Effect of mothers' smoking habits on birth weight of their children. *British Medical Journal* 1958; **2**: 673–6.
- 144 Yerushalmy J. The relationship of parents' cigarette smoking to outcome of pregnancy – implications as to the problem of inferring causation from observed associations. *American Journal of Epidemiology* 1971; **93**: 443–56.
- 145 Independent Scientific Committee on Smoking and Health. *Fourth report of the independent scientific committee on smoking and health*. London: HMSO, 1988.
- 146 Cnattingius S, Haglund B, Meirik O. Cigarette smoking as a risk factor for late fetal and early neonatal death. *British Medical Journal* 1988; **297**: 258–61.
- 147 Fletcher C, Peto R, Tinker C, Speizer FE. *The natural history of chronic bronchitis and emphysema*. Oxford: Oxford University Press, 1976.
- 148 Fletcher CM, Peto R. The natural history of chronic airflow obstruction. *British Medical Journal* 1977; **1**, 1645–48.
- 149 Doll R, Jones FA, Pygott F. Effect of smoking on production and maintenance of gastric and duodenal ulcer. *Lancet* 1958; **1**: 657–62.
- 150 Meade JW, Imeson J, Stirling Y. Effects of changes in smoking and other characteristics

- on clotting factors and the risk of ischaemic heart disease. *Lancet* 1987; **ii**: 986–88.
- 151 Parish S, Collins R, Peto R, Youngman L, Barton J, Jayne K, Clarke R, Appleby P, Lyon V, Cederholm-Williams S, Marshall J, Sleight P. For the International Studies of Infarct Survival (ISIS) Collaborators. Cigarette smoking, tar yields, and non-fatal myocardial infarction: 14 000 cases and 32 000 controls in the United Kingdom. *British Medical Journal* 1995; **311**: 471–77.
- 152 Craig WY, Palomaki GE, Maddow JE. Cigarette smoking and serum lipid and lipoprotein concentrations: an analysis of published data. *British Medical Journal* 1989; **298**: 784–88.
- 153 Denisenko MF, Pao A, Tang M, Pfeifer GP. Preferential formation of benzo(a)pyrene adducts at lung cancer mutational hot spots in P53. *Science* 1996; **274**: 430–32.
- 154 Christen WG, Manson JE, Seddon SM, Glynn RJ, Buring JE, Rosner B, Hennekens CH. A prospective study of cigarette smoking and risk of cataract in men. *Journal of the American Medical Association* 1992; **268**: 989–93.
- 155 Manino DM, Klevers M, Flanders DW. Cigarette smoking: an independent risk factor for impotence? *American Journal of Epidemiology* 1994; **140**: 1003–1008.
- 156 Nagler HM. Smoking and urology: male fertility and sexuality dysfunctions. In: London WM, Whelan EM, Case AG eds. *Cigarettes: what the warning label doesn't tell you*. New York: American Council on Science and Health, 1996: 96–100.
- 157 Sorahan T, Lancashire RJ, Hulten MA, Peck I, Stewart AM. Childhood cancer and parental use of tobacco: deaths from 1953 to 1955. *British Journal of Cancer* 1997; **75**: 134–38.
- 158 Barrett-Connor E. Smoking and endogenous sex hormones in men and women. In: Wald N, Baron J ed. *Smoking and hormone-related diseases*. Oxford: Oxford University Press, 1990: 183–96.
- 159 Michnovitz JJ, Fishman J. Increased oxidative metabolism of oestrogens in male and female smokers. In: Wald N, Baron J eds. *Smoking and hormone-related disorders*. Oxford: Oxford University Press, 1990: 197–207.
- 160 Doll R. Cochrane and the benefits of wine. In: Maynard A, Chalmers I eds. *Non-random reflections on health services research*. London: Nuffield Provincial Hospitals Trust, 1997.
- 161 Doll R, Peto R, Hall E, Wheatley K, Gray R. Mortality in relation to consumption of alcohol: 13 years' observations on male British doctors. *British Medical Journal* 1994; **309**: 911–18.
- 162 Schönherr E. Beitrag zur Statistik und Klinik der Lungentumoren. *Zeitschrift für Krebsforschung* 1928; **27**: 446–50.
- 163 Colley JRT. Respiratory disease in childhood. *British Medical Bulletin* 1971; **27**: 9–14.
- 164 Environmental Protection Agency. *Respiratory health effects of passive smoking. Lung cancer and other disorders*. Washington: US Environmental Protection Agency, 1992.
- 165 Hirayama T. Non-smoking wives of heavy smokers have a higher risk of lung cancer: a study from Japan. *British Medical Journal* 1981; **282**: 183–85.
- 166 Trichopoulos D, Kalandida A, Sparros L, MacMahon B. Lung cancer and passive smoking. *International Journal of Cancer* 1981; **23**: 803–807.
- 167 Law MR, Hackshaw AK. Environmental tobacco smoke. *British Medical Bulletin* 1996; **52**: 22–34.
- 168 Peto R, Lopez AD, Boreham J, Thun M, Heath C Jr., Doll R. Mortality from smoking worldwide. *British Medical Bulletin* 1996; **52**: 12–21.
- 169 Peto R, Lopez AD, Boreham J, Thun M, Heath C. *Mortality from smoking in developed countries*. Oxford: Oxford University Press, 1994: A7–A18.
- 170 Parkin DM, Pisani P, Lopez AD, Masuyer E. At least one in seven cases of cancer worldwide is caused by smoking. Global estimates for 1985. *International Journal of Cancer* 1994; **59**: 491–93.

Copyright of Statistical Methods in Medical Research is the property of Arnold Publishers and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.