



DEPARTMENT OF HEALTH
DEPARTMENT OF HEALTH AND SOCIAL SERVICES, NORTHERN IRELAND
THE SCOTTISH OFFICE DEPARTMENT OF HEALTH
WELSH OFFICE

REPORT OF THE SCIENTIFIC COMMITTEE ON TOBACCO AND HEALTH

CHAIRMAN:
PROFESSOR DAVID POSWILLO

London: The Stationery Office

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ISBN 0 11 322124 X

DISEASES WITH LOWER RISKS IN SMOKERS

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Introduction

When tobacco was first introduced into Europe its use was advocated as a cure and castigated as a cause of many diseases. Little scientific evidence of either was, however, adduced until the 1930s, when serious evidence of the harmful effect of smoking began to accumulate. At first this pointed to the production of cancer, primarily in the lung, but also, to some extent, in the upper respiratory and digestive tracts as a whole. Later, when cohort studies were undertaken, it became clear that smoking was also associated with an increased mortality from many diseases in many different organs. This was at first surprising, but it ceased to be so when it was realized that tobacco smoke contained more than 4000 different chemicals, many of which were readily absorbed from the alveoli and were noxious in animal experiments. That some of them might also be beneficial in counteracting the harmful effects of other agents, or perhaps by making up for physiological deficiencies, should have been equally evident, but it is only in recent years that this possibility has come to be seriously considered. Now, however, there is good evidence that smoking does alleviate or reduce the risk of a few diseases and this needs to be put into balance and weighed against the risk of harm, when attempts are made to assess the total effects of smoking on the public health.

Parkinsonism

Parkinsonism was the first condition that was found to be less common (or less fatal) in smokers than in non-smokers. It was found by Kahn (1966)¹ after following 200,000 US veterans with known smoking habits for 8 years and quickly confirmed in cohort studies of a million American men and women (Hammond, 1966)² and 34,000 male British doctors (Doll, personal communication). Kahn's and Hammond's data and later data for 280,000 Japanese followed by Hirayama (1985)³ and for the British doctors who have now been followed for 40 years (Doll et al., 1994)⁴ are summarised in Table 1. All show relative risks for ever smokers less than 1.0 ranging from 0.4 to 0.8.

Further information has been provided in 14 case-control studies, including 12 reviewed by Marmot (1990)⁶ and 2 published subsequently (Sasco and Paffenbarger, 1990;⁷ Stern et al., 1991⁸). The estimated relative risks ranged from 0.2 to 0.7, 13 were significantly less than 1.0 out of 18 (including some separate estimates for men and women) and the mean was 0.5.

The totality of these observations cannot be due to chance nor to bias nor can the relationship be dismissed as an artefact, as Riggs (1992)⁹ has suggested on the grounds that the increased mortality of smokers early in life leaves a higher proportion of non-smokers in old age when Parkinson's disease characteristically occurs. The mathematical models that Riggs employs to bolster his argument are themselves unrealistic and the possibility that he suggests is excluded by the

fact that the epidemiological findings are all obtained from studies in which cases and controls have been matched for age.

Table 1: Mortality from Parkinson's Disease by Smoking Habit: Observations in Cohort Studies

Author	Comparison	Relative Risk
Kahn, 1966 ¹	Men who had ever smoked cigarettes compared with men who never smoked or smoked very occasionally	0.36 ⁽ⁱ⁾
Hammond, 1966 ²	Men with history of "only cigarette smoking" compared with men who had never smoked regularly ages 45-64 years ages 65-79 years	0.76 ⁽ⁱⁱ⁾ 0.81 ⁽ⁱⁱ⁾
Hirayama, 1985 ³	Smokers compared with non smokers	0.6 ⁽ⁱⁱⁱ⁾
Doll et al., 1994 ⁴	Men who had ever smoked compared with lifelong non-smokers	0.80 ^(iv)

- (i) "40 deaths compared with 112.3 expected".
- (ii) "These rates are unstable statistically due to small numbers observed". (Total Parkinsonism deaths, all habits, 51 underlying cause and 72 contributory cause.)
- (iii) Cited by Baron (1986).⁵
- (iv) $p < 0.01$ for trend non-smokers, ex-smokers, current smokers

That smoking should protect against the disease is biologically plausible, as nicotine stimulates the dopaminergic pathways that are characteristically damaged in affected subjects. It should, therefore, be concluded, on the present evidence, that smoking either diminishes the risk of developing the disease or reduces its fatality and that it does so, in either case by between 20 and 50 per cent.

Endometrial Cancer

The idea that the risk of endometrial cancer might be reduced by smoking arose partly because of the knowledge that it reduced the age at menopause and partly because of the findings in case-control studies initially undertaken to test the effect of oestrogens on the risk of the disease. Evidence that smoking does have this effect is compelling. The principal epidemiological evidence from three cohort studies^{10,11,12} is summarised in Table 2. The three studies that showed a reduced risk related entirely (Ross et al., 1990)¹² or almost entirely to postmenopausal women, while nearly half the cases in the one study that did not (70 out of 150) related to premenopausal women.

TABLE 2: Risk of Endometrial Cancer by Smoking Habit: Observations in Cohort Studies

Risk relative to that in women who never smoked cigarettes.			
Author	Current smoker	Ex-smoker	No. of cases
Garfinkel, Boffeta (1990)* ¹⁰	0.9	1.1	68
1960-72	0.6	0.7	44
1982-86			
Stampfer et al (1990)† ¹¹	1.0	1.0	150
Ross et al (1990)† ¹²	0.7	0.7	55

* Mortality data. The numbers of cases include only smokers and ex-smokers; number of non smokers not given

† Incidence data

Further evidence has been provided in 16 case-control studies, including nine reviewed by Weiss (1990)¹³ and seven published subsequently (Koumantaki et al., 1989;¹⁴ Lawrence et al., 1989;¹⁵ Elliott et al., 1990;¹⁶ Dahlgren et al., 1991;¹⁷ Shu et al., 1991;¹⁸ Brinton et al., 1993;¹⁹ Austin et al., 1993²⁰). With one exception the relative risks ranged from 0.5 to 0.8, the exception being a study of 268 affected women in Shanghai in whom the relative risk was 1.7 with 95 per cent confidence limits of 0.9 and 3.0¹⁸. Other evidence, summarised by Weiss¹³ showed that the risk diminished with the amount smoked, and was greater in post-menopausal women than in premenopausal and in oestrogen users than in non-users. Several studies showed that the reduction in risk was not due to confounding with the use of oral contraceptives.

In this case, there is a clear mechanism by which smoking might be expected to have such an effect. The risk of endometrial cancer is directly related to the extent to which the endometrium is exposed to unopposed oestrogen and there is evidence that smoking has a generally anti-oestrogenic effect. It is, for example, associated with increased risks of osteoporosis postmenopausally (Law, 1990)²¹ and with decreased risks of fibroids, vomiting in pregnancy, and endometriosis (Ross et al., 1990).¹² Smoking does not materially affect the level of oestrogen in the blood (Barrett-Connor, 1990)²² but there are other ways in which it might have an anti-oestrogenic effect. One is a modification of the normal metabolism of oestrogen in the blood, in particular by enhancing the hydroxylation of oestrone at the C-2 position rather than the C-16c position, leading to the production of metabolites that are virtually devoid of peripheral oestrogenic activity and are rapidly

cleared from the circulation (Michnovitz and Fishman, 1990;²³ Black et al., 1990²⁴). Another way is by increasing the secretion of androgens (see Barrett-Connor²² for review).

On present evidence it should be concluded that smoking reduces the risk of endometrial cancer by about 50 per cent.

Ulcerative Colitis

The idea that smoking might reduce the risk of ulcerative colitis was more surprising. It arose when Harries and his colleagues noticed that very few of their patients with the disease were smokers and sent a questionnaire to 230 patients.²⁵ Only 8 per cent proved to be current smokers against 44 per cent of the same number of men and women attending a fracture clinic, matched for sex and age. By 1993, the results had been reported of thirteen case-control studies in Britain, Germany, Italy, Sweden, the United States, and Yugoslavia and of two cohort studies in Britain (see Logan, 1990²⁶ for review and Lorusso et al., 1989;²⁷ Vucelic et al., 1990;²⁸ Persson et al., 1990;²⁹ Samuelsson et al., 1991;³⁰ Katschinski 1993³¹). All gave odds ratios of less than 1.0 for current smokers, varying from 0.18 to 0.96 in the case-control studies and almost identical ratios of 0.68 and 0.65 in the two cohort studies. The ratios in ex-smokers were, in contrast, consistently greater than 1.0 so that in Logan's review²⁶ the ratios for men and women who had ever smoked were nearer to 1.0 and led to an estimate of 0.82 with 95% confidence limits of 0.71 and 0.85 for the combined data from eight studies.

Smoking, in contrast is found to be associated with an increased risk of Crohn's disease, which is thought to share a common genetic susceptibility with ulcerative colitis and the interpretation of these findings is obscure. It could be that smoking promotes Crohn's disease in the susceptible population, leaving the non-smokers to develop ulcerative colitis; but why then should the risk in ex-smokers be increased? A direct protective effect seems more likely with the disease relapsing or appearing for the first time when the protective effect is withdrawn. In this case, the benefit is relatively small, the overall reduction in risk from smoking being of the order of 20 per cent.

Other Conditions

No other condition that carries a material risk of death has been shown to be less common in smokers than in non-smokers and, with one possible exception referred to below, it is unlikely that any is likely to be found. In particular, smokers do not have a reduced risk of breast cancer, although one might have been expected because of the anti-oestrogenic effect of smoking (MacMahon, 1990)³² and Parkinson's disease was the only disease that was negatively related to smoking among the 54 causes or groups of causes of death that were individually responsible for more than 50 deaths in a 40 year follow-up of British doctors with known smoking habits (Doll et al., 1994)⁴. If any other diseases are similarly related, they would not, in that study, have accounted individually for more than 0.25 per cent of the total mortality.

Alzheimer's Disease

The exception that still has to be considered in Alzheimer's disease. A review of eight case-control studies in Australia, Italy, the Netherlands, and the USA (Graves et al., 1991)³³ found a reduced relative risk in seven with an estimated risk from the pooled results of 0.78 that was marginally significant (95% confidence limits 0.62, 0.98), a non significant decreasing risk with amount smoked ($p=0.11$), and a significantly decreasing risk with the product of duration of smoking and amount smoked ($p=0.0003$). Information was obtained in all studies from next of kin or other informants in the same way for both cases and controls, but even so there are several opportunities for bias in such studies that make it difficult to accept the results at face value. The differ-

ence between cases and controls was more marked in the older group (70 years of age and older) in which alone it was statistically significant and it is possible that older patients with Alzheimer's disease who smoked were differentially screened out, as a result of the presence of morbid conditions associated with smoking (through for example, early death or differential hospitalisation). A similar result was obtained in a study of 31 pairs of monozygous and 10 pairs of dizygous twins, discordant for Alzheimer's disease (Bharucha et al., 1986)³⁴ and when data from both sets were combined, the relative risk in cigarette smokers was 0.4 (p , one sided, <0.05). Here again, however, there is the possibility that the result was an artefact, as information about deceased twins was obtained from relatives and the comparison was apparently not limited, as it should have been, to unaffected twins that were known to have been alive at the time the affected twin's disease was diagnosed.

Neuropharmacological mechanisms exist by which smoking might be thought to delay the onset of the disease, as in the case of Parkinsonism, but it cannot be concluded that smoking reduces the risk until a reduction is also seen in cohort studies, based on smoking histories given by the subjects themselves before the disease appeared. One such study has been reported from the USA. Herbert et al., (1992)³⁵ took advantage of the data collected for one of the four Established Populations for Epidemiologic Study of the Elderly that had been sponsored by the National Institute on Aging. Participants had been interviewed twice, with an interval of three years between interviews, which enabled them to be classified by degree of memory loss. Herbert and his colleagues were, therefore, able to select a stratified random sample of 690 individuals, weighted to provide a high proportion with some degree of memory loss. Thirty two died before the study could be completed and 513 (78 per cent of the remainder) had a thorough neuropsychiatric examination. Probable Alzheimer's disease was diagnosed in 76. After allowance for sex, age, use of alcohol, and education, the odds ratio for ever smoked cigarettes was 0.7 with 95 per cent confidence limits of 0.3 and 1.4.

Much more information is likely to be obtained about Alzheimer's disease in the next few years. It will not be easy to interpret, partly for the reasons given above (it is derived from case-control studies) and partly because the death rate at old ages is so high that the difference between the rates in cigarette smokers and non-smokers may require age-standardisation to be carried out by single years of age. If it proves, as it may do, that cigarette smoking helps to delay the onset of Alzheimer's disease, this may be of some practical assistance to research into the mechanism by which the disease is produced and into methods by which the disease can be treated. If, however, other forms of dementia (due, for example, to microvascular disease) are made more common by smoking (as they may be too), there may be no overall benefit in relation to dementia to put into scales against the harmful effects of smoking. That such may be the case is suggested by the results of a 40 year follow-up of British doctors with known smoking habits (Doll et al.,)⁴ Too few deaths (19) were certified as due to Alzheimer's disease to provide useful information specifically for that disease, but it is notable that the annual age standardized mortality attributed to dementia, based on 100 deaths, about half of which are likely to have been due to Alzheimer's disease, was slightly higher in those who had ever smoked (11 per 100,000 per year) than in those who had never smoked (9 per 100,000 per year).

Premature Deaths Avoided By Smoking

No precise estimate can be made of the number of premature deaths that have been avoided in this country as a result of smoking, but an approximate estimate can be made from the figures cited above for the effect of smoking on the risks of Parkinson's disease (reduced by 20-50 per cent), endometrial cancer (reduced by 50 per cent), and ulcerative colitis (reduced by 20 per cent). In Britain, in 1990 these diseases accounted, respectively, for 4401, 1587 and 199 deaths (including all deaths attributed to cancer of the uterus unspecified with cancer of the corpus uteri). If

we assume that 50 per cent of the population had been smokers, the number of premature deaths avoided by smoking could have been between 1000 and 2000. This compares with 138,000 deaths which, according to Peto et al., (1994),³⁶ were attributable to smoking in the UK in the same year.

Acknowledgement

The author is grateful to Professor Richard Peto for his help in preparing this paper.

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