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Black Tobacco and Cancer: Introducing an Epidemiological Review

MANY EPIDEMIOLOGICAL studies have been carried out since the 1950s on the carcinogenic effect of tobacco smoking. Most of these have shown a strong association between smoking cigarettes and the risk of developing cancer of the lung, larynx, oral cavity and pharynx, oesophagus, pancreas, renal pelvis and bladder; some evidence also exists for cancer of the cervix uteri and perhaps for cancer of the liver [1].

Several studies have allowed the quantitative and qualitative evaluation of the risk as a function of the characteristics of smoking history (such as age at start of smoking, duration of exposure and smoking cessation). Substantial information also exists on the increased risk linked to specific smoking practices such as smoke inhalation and use of smokeless tobacco, and evidence is accumulating on the effects of changes introduced in marketed tobacco products (use of filters and changes in the composition of cigarettes, in particular the availability of low tar, low nicotine cigarettes).

The majority of epidemiological studies have been conducted in countries where the predominant or even the sole type of tobacco consumed in past decades is blond (flue-cured), and it has been estimated that in these countries, 30–40% of all cancers are attributable to smoking. In contrast, relatively little information is available on the public health impact of black (air-cured) tobacco in spite of growing epidemiological evidence suggesting that the carcinogenic potency of black tobacco products is two to three fold greater.

Black tobacco has traditionally been used in Latin America and in parts of Europe including most of the Mediterranean countries, although the relative proportion of smokers of black and blond tobacco varies from country to country (Table 1). Analyses of recent trends in tobacco consumption in southern Europe indicate that blond tobacco consumption is increasing in these countries relative to black tobacco, but that the rate and magnitude of this change is also country dependent [2]. A

Table 1. Proportion of smokers in samples of the general population and of types of tobacco currently used

Country (city)	Ref.	% of current smokers	Type of tobacco: Black (%)	Type of tobacco: Blond (%)
Colombia (Bogota)	PAHO, 1977* [32]	52	59	30
Venezuela (Caracas)	PAHO, 1977* [32]	49	4	93
Guatemala (Guatemala City)	PAHO, 1977* [32]	36	13	74
Argentina (La Plata)	PAHO, 1977* [32]	58	26	65
Peru (Lima)	PAHO, 1977* [32]	34	17	76
Mexico (Mexico City)	PAHO, 1977* [32]	45	14	75
Chile (Santiago)	PAHO, 1977* [32]	47	34	59
Brazil (Sao Paulo)	PAHO, 1977* [32]	54	2	96
Uruguay (Montevideo)	de Stefani, 1990† [20]	64	45	25
Spain (Navarra)	Berrino *et al.*, 1988† [2]	41 (73)‡	88	—
Spain (Zaragoza)	Berrino *et al.*, 1988† [2]	25 (60)	82	—
Italy (Varese)	Berrino *et al.*, 1988† [2]	50 (95)	28	—
Italy (Torino)	Berrino *et al.*, 1988† [2]	24 (87)	35	—
France (Calvados)	Berrino *et al.*, 1988† [2]	46 (79)	93	—
Switzerland (Geneva)	Berrino *et al.*, 1988† [2]	33 (74)	74	—

*Men 15–74 years of age; tobacco survey.
†Men; hospital controls in Uruguay; population controls aged 25–85 in Europe.
‡Proportion of ever smoked cigarettes.
— = Not reported.

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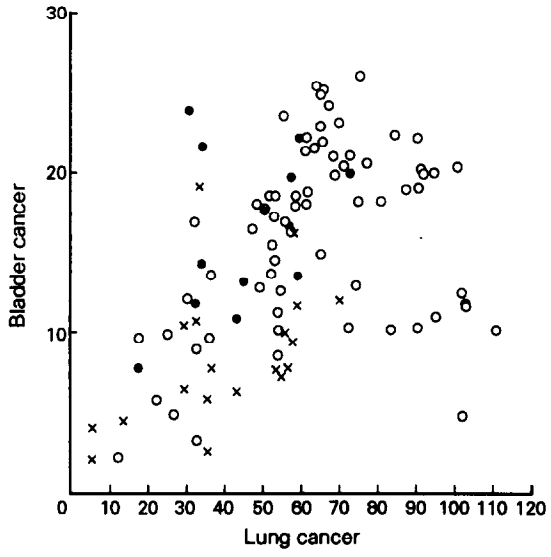

Fig. 1. Joint distribution of the incidences of lung and bladder cancers in men, by predominant type of tobacco used in the country, based on data from cancer registries around the world. ○ = Blond tobacco, ● = black tobacco, x = unspecified.

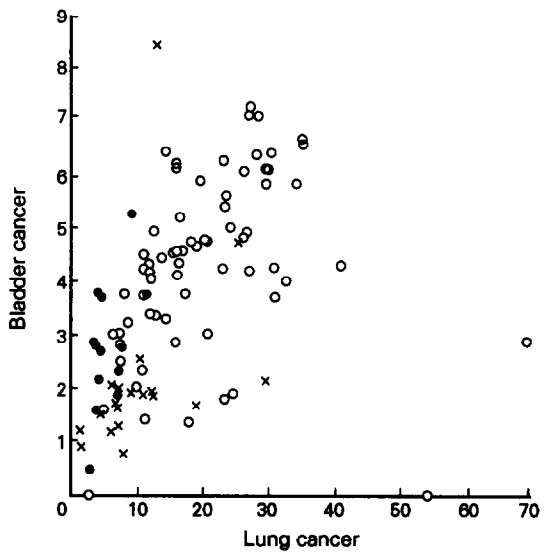

Fig. 2. Joint distribution of the incidences of lung and bladder cancers in women, by predominant type of tobacco used in the country, based on data from cancer registries around the world. ○ = Blond tobacco, ● = black tobacco, x = unspecified.

global prediction about the public health impact of tobacco smoking in these countries is therefore not straightforward.

DESCRIPTIVE STUDIES

Geographical data on cancer incidence and mortality have suggested that the relative frequency of several tobacco-related cancers may differ in countries where different tobacco types are used. In Europe in particular, a very clear north–south pattern has been repeatedly described: very high rates of lung cancer, accompanied by low rates of larynx and intermediate rates of bladder cancers, are observed in the UK, while high rates of larynx and bladder cancers and relatively lower rates of lung cancer are observed in Spain and certain parts of Italy [3, 4]. These striking differences should be considered in the light of the geographical variation in exposures to established risk factors for these cancer sites. For example, the control and regulation of occupational exposures linked to bladder cancer is likely to have been differently implemented in the last decades in northern and southern European countries. Alcohol consumption, a major risk factor for oropharyngeal and laryngeal cancers is also known to vary between the north and the south of Europe. On a more global scale, we have used the data on age-standardised incidence of cancer of the bladder and lung in 135 registries around the world from volume 5 of *Cancer Incidence in Five Continents* [5], and devised a crude classification of countries by estimates of the predominant type of tobacco smoked in the past. This classification was based on previous surveys as shown in Table 1 and *ad hoc* compilation of existing information.

Figures 1 and 2 show the correlation between incidence rates of lung and bladder cancers by type of tobacco and by sex. Registries where black tobacco consumption is, or has been, common tend to exhibit higher levels of bladder cancer incidence at equal level of lung cancer incidence than do registries where blond tobacco is predominantly consumed. This may be interpreted as a difference in the relative carcinogenic potencies of black and blond tobacco in these two organs. Additionally, these findings may indicate a difference in the average latency period for the induction of these two types of cancer: registries where black tobacco is consumed predominantly are located in countries where heavy tobacco consumption is a relatively recent phenomenon, compared for example with the USA or the UK, and where the rising incidence of lung cancer has presumably not yet reached its maximum.

Observations based on the results of geographical correlation studies are difficult to interpret due to the inevitable weaknesses of such studies, which include possible differences between populations in disease and exposure ascertainment and difficulties in taking into account potential confounding factors [6]. It is also important to consider the time interval between heavy population exposure to cigarettes and subsequent increases in cancer incidence. As an illustration, in 1950, the average number of cigarettes consumed per capita in the UK was more than double that consumed in France or in Spain [7] and these differences in exposure should largely explain the differences in tobacco-related cancer incidence rates observed in the 1970s and 1980s. Comparisons of incidence and mortality between countries at a fixed point in time may therefore be misleading if they do not take into account relevant (i.e. past, often several decades previously) exposure levels.

ANALYTICAL STUDIES

The first suggestion from analytical studies that black and blond tobacco may have different carcinogenic potencies arose from the observation, in case-control studies carried out in populations exposed mainly to black tobacco, of very large relative risks compared with those observed in populations exposed predominantly to blond tobacco. For bladder cancer, for example, Vineis *et al.* [8] reported a relative risk of 9.0 for smokers of 20 cigarettes or more per day, compared with relative risks of the order of 2.0 or 3.0 in studies carried out in the US, UK, Japan or, Canada [1]. These differences held even when taking into account the effects of occupational exposures and were subsequently confirmed by other studies [9].

In 1983, a lung cancer case-control study carried out in Cuba specifically addressed the effect of tobacco type on cancer risk within a single population [10]. Compared with that in non-smokers, the relative risk of lung cancer was higher for black

tobacco smokers than for blond tobacco smokers (relative risks of 8.6 and 4.6, respectively, in women and 14.3 and 11.3 in men). When taking into account duration of smoking these differences were no longer statistically significant, but the number of subjects having smoked blond tobacco exclusively (3% of the cases and 2.3% of the controls) or in combination with black tobacco was very small. The authors concluded that further studies of the effects of black tobacco were necessary.

Soon after, a review of the analytical studies on tobacco-related cancers available from France, Italy, Spain and Switzerland was published [6]. These countries include substantial proportions of smokers of black tobacco products exclusively (18–66% of the individuals interviewed) as well as of subjects having smoked both black and blond tobacco (3–32%). The review included data on cancers of the lung, larynx, oesophagus and urinary bladder and concluded that there was at that time "little convincing epidemiological evidence that air-cured tobacco is more or less carcinogenic than flue-cured tobacco. There is some indication that the risk difference, if any, might be greater for bladder cancer".

The effect of type of tobacco on cancer risk was subsequently addressed in an increasing number of analytical studies that consistently documented an increased risk among black tobacco smokers. The reported increase was about 2-fold for cancer of the lung in France [11] and in Uruguay (de Stefani *et al.*, Oncology Institute, Montevideo, Uruguay). For cancers of the urinary bladder, the increase was 2 to 3-fold in Italy [12, 13], in Argentina [14], in France [15] and in Uruguay [16]. In the study in Italy, the relative risk for smokers of blond tobacco exclusively was similar to the risk observed among smokers in countries where blond tobacco is the predominant type [13]. Other results indicate that the risk associated with specific tobacco types may vary between different parts of Italy [17].

For cancer of the larynx, a 2 to 2.5-fold increase among black tobacco users compared with blond tobacco smokers has been documented in four southern European countries [18] and in Uruguay [19]. Increases in risk were also reported in Uruguay [20] and Argentina for oesophageal cancer (R. Castelletto *et al.*, Medical School, La Plata, Argentina, and ref. 20), for cancers of the mouth in Brazil [21], and of the oropharynx in Uruguay [22]. In contrast, no excess risk among black tobacco smokers was found in a study in northern Italy, which included cancers of the mouth and oropharynx [23]. The results of some of these studies also suggest that the reduction in risk following smoking cessation may be delayed among smokers of black tobacco compared with blond tobacco smokers [21]. Overall, these studies are fairly consistent in showing that, for all cancer sites so far studied, black tobacco may be substantially more carcinogenic than blond tobacco.

The question is still open, however, as to the nature of the difference in carcinogenic potencies between the two types of tobacco: it could be due to the fact that black tobacco smoke contains higher concentrations of carcinogens common to both types, or to the presence, in black tobacco smoke, of specific carcinogens not found in blond tobacco smoke.

LABORATORY EVIDENCE

A number of biochemical and molecular studies of the effects of tobacco type have been carried out which appear to confirm the epidemiological observations. Higher levels of N-nitrosamines and of aromatic amines have been reported in smoke produced by black tobacco compared with blond tobacco brands [24, 25].

Mutagenicity tests in experimental systems have indicated that the urine of black tobacco smokers contains substances that are twice as mutagenic compared with the urine of blond tobacco smokers [26, 27] and analyses of the mutagens in the urine of smokers of black tobacco have identified the aromatic amine, 2-amino-1-methyl-6-phenylimidazol [4–5 b] pyridine (-PhIP-) as a mutagen possibly linked to black tobacco [28]. Haemoglobin adducts of other aromatic amines (4-aminobiphenyl) are also increased among smokers of black tobacco compared with smokers of blond tobacco [29]. Aromatic amines are known bladder carcinogens and these findings could account for the increased risk for bladder cancer among smokers of black tobacco products.

Relatively few animal experiments have been carried out. Muñoz *et al.* [30] reported an increased rate of skin tumours in mice obtained after painting with 4% dilutions of refined tar from black tobacco, as compared with similar extracts of blond tobacco. On the other hand, based on one inhalation experiment, Passey *et al.* [31] concluded that the smoke of air-cured cigar tobacco is less damaging to the respiratory system than that of flue-cured commercial British cigarettes.

In view of the potential implications of an increased risk attributable to the consumption of black tobacco, it appears timely to review the existing epidemiological evidence on the subject and to reassess the likely public health impact of tobacco smoking in cancer risk in extensive areas of the world.

This commentary introduces a series of papers on this topic, to be published in forthcoming issues of the *European Journal of Cancer*. This series will include a review of site-specific epidemiological evidence for the bladder (p. 1491), the lung, the oesophagus, the larynx and the pharynx, and the buccal cavity, as well as a summary paper discussing the public health consequences of black tobacco consumption.

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Smoking and Commercial Airline Flights in Europe

THE REVIEW of smoking and cancer in Europe by La Vecchia and his colleagues in a recent issue of the *EJC* affords us no respite in efforts to control what is "unquestionably the single most important cause of cancer" [1]. If the current burden of smoking-related illness is not sufficient stimulus for appropriate action, we can always consider what lies ahead. Given the long induction period for lung cancer, future high-risk groups can be identified from past and current habits [2]. Particular problems cited by La Vecchia *et al.* are the upward trends in the incidence and mortality from lung cancer in females, and the increases in smoking-related neoplasms expected within the next 2 decades in southern and eastern Europe, areas of high smoking prevalence and high-tar cigarettes.

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The effect of direct exposure to tobacco smoke is not the only concern. Illness caused by environmental tobacco smoke (ETS)—passive smoking—is steadily moving up the agenda of problems faced by health professionals, employers and employees, and governments. In this issue of the Journal, Woodward and McMichael (p. 1472) consider the epidemiological evidence for the carcinogenicity of ETS, and discuss the nature of "proof" and its use by scientists, public health bodies and the judiciary. Any intervention at either the individual, clinical level or at the population-wide, public health level must be based on good science and reasonable expectation of benefit over cost. But, as Greenland states: "Public health decisions must (also) consider the cost of inaction if the substance at issue is indeed harmful. . . " [3]. The parallels of the situation with passive smoking in the 1990s and that of direct exposure to