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Black (Air-cured) and Blond (Flue-cured) Tobacco and Cancer Risk I: Bladder Cancer

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Four case-control studies in different Latin countries have reported risks of bladder cancer 2–3 times higher for smokers of black (air-cured) than for smokers of blond (flue-cured) tobacco. This observation is interesting in the light of a higher concentration of arylamines in black tobacco. The relative risk dropped very rapidly after discontinuation of smoking, and there was also an effect of age at start, with higher risks associated with earlier onset of the habit. Overall, black tobacco seems to act both on early and late stages of bladder carcinogenesis.
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THE HYPOTHESIS that the risk of bladder cancer is stronger among smokers of black (air-cured) tobacco than among smokers of blond (flue-cured) tobacco was generated several years ago on the basis of geographic patterns. It was noted, in fact, that the ratio of lung to bladder cancer mortality was highest in countries, such as England and Wales and the USA, where virtually no use of black tobacco had been made in the previous decades, while the ratio was lowest in Italy and France, where black tobacco has been smoked until very recently [1].

The hypothesis has been confirmed independently by four hospital-based case-control studies. The first investigation was conducted in Torino, Italy, and was based on interviews of 512 male bladder cases and 596 male hospital controls [2]. Detailed information was collected on the whole smoking history, including cigarette brands, date started and date of cessation, number of cigarettes smoked, and use of filters. Brands were classified as to the type of tobacco (black/blond/mixed/unknown) on the basis of information collected from the Italian monopoly of tobacco producers and from private tobacconists. The study was conducted between 1977 and 1983, i.e. a period in which the prevalence of black tobacco smoking was still high in the Italian population (18% of the controls interviewed). Table 1 shows the results concerning the effects of the two varieties of tobacco: the risk associated with black tobacco is clearly higher than the risk for the blond variety. Multivariate models were also fitted, including potential confounders; in fact, several smoking characteristics are associated with the use of black tobacco (duration, amount, filter, time since cessation) and modulate the risk of bladder cancer. The odds ratio for bladder cancer for smokers of blond tobacco, compared with that of smokers of black tobacco, was 0.4, a result comparable to that of univariate analysis. Although no clear confounding phenomenon was noted, interesting effect modifications were observed. When age at start was considered separately among smokers of the two types of tobacco [3], a decreasing trend with increasing age was noted among smokers of black but not of blond tobacco. In addition, among both types of smokers cessation was associated with a rapid decrease of the relative risk, although among black tobacco smokers after 10 years since quitting the risk reached a plateau well above the level of risk of non-smokers. An in-depth analysis of smokers of black tobacco, considering duration, cessation and switching from the black to the blond form was reported (Table 2). If one makes a broad distinction between those who stopped smoking and those who did not, apparently the relative risk is the same for smokers of black tobacco throughout life and the subjects who switched to blond tobacco (none had switched from blond to black). The main effects of black tobacco, therefore, seem to be exerted early in life, whereas later continuation of this habit or switching to blond tobacco might have similar effects. The use of filters was not associated with protection among black tobacco smokers [3].

The second study was in Argentina and included 117 cases, 117 hospital controls and 117 neighbourhood controls [4]. Smoking histories were collected in a way similar to that described for the Italian study. The proportion of lifelong smokers of black tobacco among the controls was 37%. Overall, a clear association between the use of black tobacco and the risk of bladder cancer was reported (Table 3), with a relative risk 2–3 times higher than for smokers of the flue-cured type.

The third study, in France, was based on 477 male cases and an equal number of controls [5]. Detailed smoking histories allowed the researchers to classify the brands into the groups of black/blond/mixed tobacco, on the basis of information provided by the French state monopoly. The proportion of black tobacco

Table 1. Types of tobacco: relative risk (RR) for smokers of black cigarettes only and blond cigarettes only [2]

Age group	Cases/controls	RR	95% CI
< 50			
Non-smokers	3/34	1.0	–
Black tobacco	15/24	7.1	2.1–24.5
Blond tobacco	6/41	1.7	0.4– 7.1
50–59			
Non-smokers	3/28	1.0	–
Black tobacco	28/32	8.2	2.5–26.4
Blond tobacco	3/10	2.8	0.5–15.8
60+			
Non-smokers	13/35	1.0	–
Black tobacco	47/54	2.3	1.1– 4.9
Blond tobacco	10/16	1.7	0.6– 4.7

Reference category: non-smokers.

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Table 2. Duration and cessation among smokers of black tobacco only and among smokers switching from black to blond tobacco, males [3]

	Black only		Black then blond*	
Duration	Current	Former	Former black current blond	Former black, later blond, then quitting
1–19	2.1 (0.2–22.9)	0.8 (0.2–3.0)	3.3 (1.0–10.3)	1.3 (0.1–12.6)
20+	6.6 (3.5–12.6)	2.2 (1.0–4.9)	5.7 (3.3–10.0)	2.6 (1.2– 5.6)
All durations	6.2 (3.3–11.7)	2.1 (1.1–4.0)	5.5 (3.2– 9.5)	2.5 (1.3– 5.0)
Cases/controls	65/47	22/62	151/127	30/45

Odds ratios and 95% confidence intervals. All odds ratios are age-adjusted. Reference category: non-smokers.
* Including 68/42 subjects smoking mostly black, 13/14 smoking mostly blond tobacco, and 100/116 mostly mixed smokers.

smokers among the controls was as high as 55%. Univariate analysis revealed a relative risk of 1.9 (95% CI 1.2–2.9) for blond tobacco and of 4.4 (2.3–8.3) for black tobacco. The risk remained more elevated among black tobacco smokers even when allowing for potential confounders. The relative risk declined after stopping smoking, and in the case of black tobacco it seemed to reach a plateau after 15 years since quitting; this was not observed for blond tobacco. The most peculiar observation of the French investigation was that the effect of black tobacco was noted only in inhalers. Overall, increasing age at start was associated with decreasing relative risks, but this analysis was not reported separately for the two tobacco types.

The fourth study was conducted in Uruguay on 111 incident cases and 222 controls [6]. Among men, the risk of bladder cancer was 2.7 times higher for smokers of black tobacco than for smokers of blond tobacco. Also in this investigation the effect of stopping was immediate and a younger age at start (< 20) was associated with an increased risk of bladder cancer, but the information was not given separately for the two types of tobacco.

MECHANISMS OF ACTION

Four case-control studies, conducted with similar methods in countries with a high prevalence of black tobacco smokers, have

Table 3. Relative risk for bladder cancer according to duration of cigarette smoking and type of tobacco [4]

Duration of black cigarette smoking (years)	Duration of all cigarette smoking (years)			
	1–24	25–39	40+	RR
0–24	1.0	3.95	6.47	1.0
25+	–	10.60	10.80	2.04
RR	1.0	4.47	5.69	

Estimates adjusted for age and average consumption of cigarettes per day.

Table 4. Dose-response relationship between the number of cigarettes smoked and the risk of bladder cancer in men [5, 7, 8]

	Cigarettes /day	RR	No. of cases or 95% CI
Case-control studies			
Wynder and Goldsmith, 1977	0	1.0	–
	1–10	1.4	(0.9– 2.2)
	11–20	2.4	(1.7– 3.3)
	21–30	2.7	(1.8– 4.1)
	31–40	2.3	(1.5– 3.4)
	41+	3.3	(2.1– 5.3)
Howe *et al.*, 1980	0	1.0	–
	< 10	2.6	(1.7– 4.4)
	10–20	3.8	(2.6– 6.0)
	> 20	5.1	(3.5– 8.6)
Moller-Jensen *et al.*, 1983	0	1.0	9
	1–14	4.2	82
	15–24	4.9	112
	25+	4.3	54
Vineis *et al.*, 1984	0	1.0	–
	1–14	4.0	(2.4– 6.8)
	15–29	5.7	(3.5– 9.3)
	30+	10.1	(4.9–20.7)
Morrison *et al.*, 1984			
Boston current smokers	0	1.0	53
	< 20	1.4	25
	20–39	3.2	91
	40+	4.7	67
Manchester current smokers	0	1.0	28
	< 20	1.9	85
	20–39	3.2	104
	40+	4.0	31
Nagoya current smokers	0	1.0	24
	< 20	1.6	47
	20–39	2.1	92
	20+	2.8	33
Hartge *et al.*, 1987	0	1.0	657
	< 20	1.8	568
	20–39	2.6	1102
	40+	2.6	392
Clavel *et al.*, 1989	0	1.0	35
	1–19	3.3	200
	20–39	4.4	186
	40+	6.9	52
Cohort studies			
Hamond and Horn, 1958	0	1.0	38
	< 10	2.0	14
	< –20	2.0	42
	> 20	3.4	41
Kahn, 1966	0	1.0	52
	< 10	1.0	11
	10–20	2.3	71
	21–39	3.1	51
	40+	3.0	9
Doll and Peto, 1976 (total deaths 80)	0	1.0	
	1–14	2.2	
	15–24	2.2	
	25+	1.4	

reported relative risks 2–3 times higher among smokers of black tobacco than of blond tobacco cigarettes. The greater effect of the black variety was not explained by potential confounders. It is also interesting to note that the relative risk for blond tobacco smokers was around 2.0, i.e. similar to the estimates found for smoking in countries where black tobacco has not been used in the last decades [7].

Some effect modifications were noted for other smoking characteristics. Increasing age at start seemed to be associated with decreasing relative risks in a few investigations [5, 6, 8], irrespective of type of tobacoo. In the Italian study, this pattern was evident for smokers of black tobacco but not for smokers of blond tobacco, after allowing for time since quitting. In addition, switching from black to blond tobacco did not change the risk substantially in comparison with smoking black tobacco throughout life, indicating a more important effect of the black variety early in life.

Quitting smoking is associated with a dramatic drop in the risks of bladder cancer [7], irrespective of the type of tobacco. In the two studies which considered the effect of quitting separately by type, the relative risk remained well above the level of non-smokers only for smokers of black tobacco.

The study of time-related variables is complex, since they are strictly correlated. Only if a large proportion of the subjects stopped smoking and then started again several times, a distinction between duration, age started and time since quitting can be made on statistical grounds; usually, however, such a distinction cannot be made [9]. The overall picture concerning the type of tobacco and bladder cancer, as far as time-related variables are concerned, seems to be the following: in general, tobacco smoking mainly exerts a "late stage" action, as is clearly indicated by the rapid drop in risks after discontinuation. Black tobacco, however, seems to have also an "early stage" action, as suggested by the stronger association with age at start, the fact that the relative risks remain high after 10 or 15 years since quitting and the fact that switching to blond tobacco does not seem to be different from continuing to smoke black tobacco.

Other observations are interesting, including the lack of protection from the use of filters among black tobacco smokers. This seems to indicate that bladder carcinogens belong to the highly volatile fraction of smoke, possibly aromatic amines. In addition, such carcinogens seem to be affected by the level of inhalation, as the French study suggests. Finally, the dose-response relation between the number of cigarettes smoked and the risk of bladder cancer (Table 4) is worth mentioning. In most of the studies there is a less than linear relation, with a steep increase at low doses and a plateau at high doses. This observation might indicate that metabolic pathways of activation/deactivation of bladder carcinogens are of importance in the carcinogenic process. All these hypotheses have to be verified in biochemical epidemiology investigations.

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Emerging Clinical Uses for GM-CSF

J. Howard Scarffe

INTRODUCTION

GRANULOCYTE–MACROPHAGE colony-stimulating factor (GM-CSF), like interleukin-3 (IL-3), displays a broader range of haematopoietic activities than the more lineage-restricted factors such as granulocyte colony-stimulating factor (G-CSF), macrophage stimulating factor (M-CSF) and erythropoietin. GM-CSF interacts with early, multipotent progenitor cells, promoting the growth and differentiation of burst and colony-forming units. GM-CSF is not as effective as IL-3 at supporting primitive blast cells, erythroid and megakaryocyte colony formation [1] although the effects of both these factors are enhanced by other CSFs such as IL-1 and IL-6 [2–6].

The actions of GM-CSF further down the cascade are more restricted, with predominant effects on the maturation of monocytes and granulocytes. Evidence from both murine and human systems suggests GM-CSF can promote the growth of megakaryocytes and eosinophil colonies and assist the growth of erythrocyte progenitors [7–15]. These effects are primarily seen when acting in concert with the later-acting growth factors such as erythropoietin, M-CSF and G-CSF. Both GM-CSF and M-CSF

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