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Feature Articles

Black (Air-cured) and Blond (Flue-cured) Tobacco and Cancer Risk III: Oesophageal Cancer

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Relative risks of oesophageal cancer for smoking were higher in communities smoking mainly black tobacco, when compared with results from populations comprising mainly users of blond tobacco. Also, hand-rolled cigarette smoking, which could be considered as a proxy indicator of black tobacco smoking, was also associated with higher risk of oesophageal cancer, in comparison with the use of commercial (manufactured) cigarettes. Finally, the use of pipes and cigars showed odds ratios of higher magnitude than those associated with cigarettes. This indirect evidence of a higher risk of oesophageal cancer due to the use of black products was confirmed in three recent hospital-based case–control studies. These investigations were able to compare the effect of both types of tobacco; relative risks for black tobacco were two to three times higher than risks associated with blond tobacco smoking, after controlling for major potential confounders. Laboratory evidence suggests that swallowing tobacco condensates could be a major risk factor for oesophageal cancer. Also, the higher content of tobacco-specific *N*-nitroso compounds in black tobacco, including organospecific substances, could explain its higher carcinogenic effect on the oesophageal mucosa.
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INTRODUCTION

Oesophageal cancer has been classified aetiologically into two broad categories: (1) oesophageal cancer associated with tobacco and alcohol consumption, and (2) oesophageal cancer unrelated (or weakly related) to these exposures [1]. The first pattern is mainly observed in Western developed countries, South America and South Africa, whereas in high risk countries, like China and Iran, the aetiological fraction for tobacco is of small magnitude. The first case–control study showing a significant association between tobacco use and oesophageal cancer risk was performed by Wynder and Bross [2]; they provided estimates for tobacco smoking after adjusting for alcohol consumption, calling attention to the fact that both exposures are highly correlated and confound the estimates of each other.

In studies performed in western and South American countries, the relative risks (RR) associated with smoking have been of higher magnitude in populations smoking a sizeable proportion of black tobacco [3–8], compared with those smoking mainly blond tobacco [2, 9–12] (Table 1).

As is well known, hand-rolled cigarettes are mainly filled with air-cured (black) tobacco [13]; according to this, odds ratios (OR) associated with smoking this type of cigarettes could be considered as a proxy indicator of the black tobacco effect. Several studies have addressed the relationship between hand-rolling and oesophageal cancer risk [6, 7, 14, 15]. RR of oesophageal cancer have been higher among smokers of hand-rolled cigarettes when compared with those observed for smokers of commercial cigarettes (Table 2).

Since the early study of Wynder and Bross [2], it has been repeatedly suggested that cigar and pipe smoking could be associated with higher risks of oesophageal cancer than smoking manufactured cigarettes [14, 15]. Furthermore, it has been proposed that pipe tobacco condensates are swallowed into the oesophagus, allowing close contact of the tobacco carcinogens with the oesophageal mucosa [1, 14]. Case–control studies, performed in the U.S.A. [2], Italy [5], France [14] and South Africa [15, 16] apparently support the suggestion that pipe smoking carries a higher risk of oesophageal cancer than commercial cigarette smoking (Table 3).

The previous evidence suggesting that the risk of oesophageal cancer is stronger among smokers of black tobacco than among smokers of blond tobacco, has been confirmed by three hospital-based case-control studies. The first investigation was carried out in Uruguay and followed a matched design, involving 261 cases and 522 controls [6]. The questionnaire used included a detailed smoking history section requesting information on brands of tobacco smoked. The prevalence of black tobacco smoking is still high in Uruguay (38.9% of controls). After logistic regression analysis, the risk associated with black tobacco smoking was 2.6 higher than the risk of blond tobacco smoking, while controlling for important factors such as age, residence, smoking duration and alcohol ingestion (Table 4). Furthermore, the effect of type of tobacco combined multiplicatively with duration of smoking. When the estimates were analysed separately by sex, females showed a RR of 3.2 for black tobacco smoking; no difference between sexes was observed.

The second study was also performed in Uruguay [7]. In the period 1988–1990, 136 newly diagnosed cases of oesophageal cancer (104 males and 32 females), were matched with respect

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Table 1. Relative risk of oesophageal cancer with smoking. Case–control studies carried out in populations smoking mainly blond cigarettes

Reference	Amount (cigarettes/day*)	RR	95% confidence interval
Wynder and Bross (1961)	1–9	2.3	—
	10–20	2.7	—
	21–34	4.1	—
	35+	4.6	—
Pottern *et al.* (1982)	1–10	1.0	—
	11–39	1.2	—
	40+	2.1	—
Victora *et al.* (1987)	1–14	4.3	—
	15–29	4.0	—
	30+	3.1	—
Yu *et al.* (1988)	1–7	1.2	—
	8–14	1.4	—
	15–24	1.8	—
	25+	2.3	—
Graham *et al.* (1990)	1–27 (packs/year)	1.4	0.7–2.6
	28–47	1.7	0.9–3.2
	48–124	2.1	1.1–3.9
Tuyns *et al.* (1977)	10–19	1.5	—
	20–29	1.6	—
	30+	8.1	—
Vassallo *et al.* (1985)	1–9	1.0	0.3–2.8
	10–19	4.7	2.5–8.9
	20+	10.8	6.4–19.1
La Vecchia *et al.* (1986)	1–14	2.7	1.5–4.9
	15+	4.6	2.6–7.4
De Stefani *et al.* (1990)	1–7	1.9	0.7–5.4
	8–14	2.7	1.1–6.8
	15–24	4.3	1.7–10.4
	25+	4.6	1.9–11.1

*Unless stated otherwise.

to age (± 2 years), sex, residence and urban/rural condition, to 272 controls. All patients were admitted to the Instituto Nacional de Oncologia and were requested to complete a structured questionnaire, which included a detailed section on tobacco and alcohol history. Again, the type of tobacco was classified by brand, according to the information submitted by the Uruguayan Association of Tobacconists. The analysis was performed through conditional logistic regression and the odds ratio (OR) for black tobacco smokers was 3.6 higher than that observed for blond tobacco smokers. Mixed smokers also carried an increased risk of 2.5, when compared with blond tobacco smokers (Table 5). These estimates were obtained after adjusting for smoking intensity, total alcohol consumption, maté consumption (folk name for a local infusion which is drunk at high temperature), vegetable intake, birthplace and socioeconomic status, all of which constitute important potential confounders in oesophageal cancer. The findings replicate those observed in the first study, clearly showing the important role of black tobacco in the aetiology of oesophageal cancer.

The third study was performed in southern Thailand and included 154 cases with the same elegibility criteria as the Uruguayan study [8]. 296 controls were selected among patients

*Table 2. Relative risk of oesophageal cancer for type of cigarette. The effect of hand-rolled cigarettes**

Reference	Type of cigarette	RR	95% confidence interval
Tuyns and Esteve (1983)			
	Commercial	6.2	—
	≤ 19 g/day	4.8	2.1–11.0
	20+ g/day	9.0	3.8–21.2
	Hand-rolled	7.5	—
	≤19 g/day	7.0	3.2–15.2
	20+ g/day	9.9	3.8–25.8
Segal *et al.* (1988)			
	Commercial	1.1	0.6–1.8
	Hand-rolled	2.8	1.1–8.0
	Both	6.6	3.5–12.4
De Stefani *et al.* (1990)			
Blond tobacco			
	Commercial	1.3	0.7–2.5
	Hand-rolled	1.5	0.7–3.1
Black tobacco			
	Commercial	2.1	1.0–4.4
	Hand-rolled	4.2	2.3–7.7
De Stefani *et al.* (1991)			
	Commercial	1.0	—
	Hand-rolled	2.5	0.9–6.5

*All estimates are relative to non-smokers, with the exception of the last study, in which the referent category corresponds to commercial cigarette smokers.

Table 3. Relative risks of oesophageal cancer for cigars and pipe use

Reference	Dose	RR	95% confidence interval
Wynder and Bross (1961)			
	Cigarettes	2.8	—
	Cigar/pipe	6.0	—
	Pipe only	9.0	—
Brandshaw and Schonland (1974)			
	Cigarettes	4.3	—
	Pipe only	6.0	—
Tuyns and Esteve (1983)			
	Cigarettes	6.2	—
	Pipe only	10.7	—
	1–19 g/day	9.4	1.8–48.0
	20+ g/day	18.0	1.0–317.0
La Vecchia *et al.* (1986)			
	Cigarettes	4.6	2.8–7.7
	Cigar/pipe	6.2	2.6–15.0
Segal *et al.* (1988)			
	Cigarettes	3.4	2.4–5.0
	Pipe	4.9	2.2–10.9

Table 4. Age, residence and alcohol adjusted RR (95% confidence interval for duration of smoking and type of tobacco (males only)

Duration (yrs)	Type of tobacco Blond	Black	Type adjusted
Wynder and Bross (1961)			
1–24	1.0	3.2	1.0
25–44	2.5	8.1	2.5 (1.1–5.7)
45+	4.4	9.0	3.3 (1.5–7.3)
Duration adjusted	1.0	2.6 (1.7–3.9)	

Table 5. RR of oesophageal cancer for type of tobacco

Type of tobacco	Cases/ controls	OR	95% confidence interval
De Stefani *et al.* (1991)			
Blond	26/95	1.0	—
Mixed	18/26	2.5	0.9–6.6
Black	63/70	3.6	1.7–7.6

Adjusted for birthplace, income, smoking intensity, total alcohol ingestion, maté ingestion and vegetable intake.

without smoking-related diseases and they were matched to the cases on age, sex and hospital. This investigation was designed in order to compare two types of cigarettes: the Thai commercial cigarettes, which are flue-cured and filled with Virginia type tobacco, and hand-rolled cigarettes, filled with air-cured local tobacco (black coloured). Odds ratio obtained through conditional logistic regression, after controlling for alcohol ingestion, betel chewing, diet and socioeconomic status showed a 3.6 increased risk for pure smokers of air-cured tobacco products, compared with smokers of commercial cigarettes (Table 6). Mixed smokers (Thai plus hand-rolled) displayed a 6.7 increased risk taking the same referent category. The high risk associated with mixed smoking was also observed in a previous study on lung cancer [17], but not in the Uruguayan studies on oesophageal cancer [6, 7]. This finding deserves further investigation. The risk associated with smoking intensity and duration was significantly higher in smokers of black cigarettes, and deep inhalation was associated with a RR of 6.9, agreeing with the findings of a recent French study on black tobacco and bladder cancer [18].

Table 6. Relative risks of oesophageal cancer for type of tobacco in southern Thailand

Type of tobacco	Cases/ controls	OR	95% confidence interval
Geater *et al.* Personal communication			
Non-smokers	4/46	1.0	—
Thai commercial (blond)	14/74	2.6	0.9–13.1
Mixed	34/27	16.4	3.2–84.9
Hand rolled (black)	99/132	9.3	2.4–36.5

Adjusted for alcohol, betel chewing, local dietary components and socioeconomic status.

MECHANISMS OF ACTION

Three case–control studies, performed in Uruguay and Thailand, countries with high prevalence of black tobacco smokers have reported RR 2–3 times higher among smokers of black tobacco, taking as referents smokers of blond tobacco. Detailed study of time-related variables revealed a more pronounced decrease in the OR associated with increasing age at start among black tobacco users, in comparison with blond tobacco smokers (0.65 for black tobacco vs. 0.79 for blond tobacco). Also, long-term abstainers (10 or more years) who smoked black tobacco showed a RR of 3.6, compared with a RR of 1.4 for previous blond tobacco users. These findings suggests that black tobacco exerts both an early and late stage action in oesophageal carcinogenesis, similar to that shown by Vineis in bladder cancer [19]. The high risk associated with deep inhalation of hand-rolled black tobacco cigarettes in the study from Thailand [8], suggests that the active carcinogens present in black tobacco could act both by the swallowing mechanism [1, 14] and systemically.

LABORATORY EVIDENCE

Black (air-cured) tobacco contains lower levels of polycyclic aromatic hydrocarbon (PAH) and higher levels of *N*-nitroso compounds than blond (flue-cured) tobacco. In experimental studies, *N*-nitroso compounds are potent carcinogens for the oesophageal mucosa [20] and chemical analyses of black tobacco have disclosed higher concentrations of tobacco-specific nitrosamines (TSNA), mainly *NNK* and *NNN*, when compared with blond (flue-cured) tobacco. These compounds have been proved to induce oesophageal cancer in rodents under experimental conditions [21, 22]. Tar delivery, which is widely considered to reflect the carcinogenic potential of cigarette smoke, did not correlate with the amounts of the strong carcinogens NNN (r^2=0.18) and NNK (r^2=0.14) in the mainstream smoke [23]. Black tobacco cigarettes, which are high in nitrate, show the highest TSNA concentrations [23]. Nitrosamines are the only components of cigarette smoke with organospecific activity for the oesophagus, and metabolic activation of NNN has been observed in cultured human oesophageal cells [24]. Although further studies are needed to define the role of nitrosamines as causative factors for oesophageal cancer in smokers, the available evidence is suggestive and more compelling than for any other tobacco smoke substances [25].

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Economic Evaluation and Quality of Life Assessments in Cancer Clinical Trials: The CHART Trial

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Arguments are being made more frequently to incorporate economic evaluations and quality of life assessments into clinical trials. Using a randomised, multicentre, phase 3 cancer clinical trial as an example, this paper outlines the importance of including such assessments; the practical considerations associated with the design of such trials; the methods for collecting such data; and, how such data can be used. Finally, it is emphasised that the anticipated benefits of collecting data relating to resource use and quality of life should outweigh the associated costs to research funding organisations.
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INTRODUCTION

IN RECENT years there has been considerable growth in the number of economic evaluations being integrated into clinical trials, especially phase 3 trials. Perhaps one of the most important reasons for such development is the recognition that the diffusion of many medical interventions takes place rapidly, prior to the assessment of associated costs and benefits [1]. The incorporation of economic analysis at an early stage can provide useful information to assist in the rational diffusion of technologies in the health care system [2]. Resources for health care can be used more efficiently, providing maximum patient benefit at minimum cost to the health service only if systematic evidence relating to the costs and benefits of interventions is available.

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