Table 2. Side-effects in 21 evaluable patients

Side-effect	WHO grade 1	2	3	4
Leucopenia	2	2	0	0
Thrombocytopenia	1	3	0	0
Anaemia	0	1	0	0
Nausea/vomiting	2	5	1	0
Fever	0	1	0	0

moderate). Myelosuppression delayed 10/66 cycles (15%) but there was no WHO grade 3–4 toxicity. The other toxic events were limited.

CONCLUSION

There is no active medical treatment for advanced colorectal cancers refractory to fluoropyrimidines, although published phase II studies report the therapeutic efficacy of CBDCA in previously untreated patients [9–12].

The present study evaluated the role of CBDCA as a single drug in pretreated cases, and the results demonstrate its inefficacy in this subset of patients; the most important toxicity was myelosuppression.

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Feature Articles

Black (Air-cured) and Blond (Flue-cured) Tobacco and Cancer Risk V: Oral Cavity Cancer

Paolo Boffetta

INTRODUCTION

BLACK TOBACCO has traditionally been used in Latin American and Mediterranean European countries. A stronger carcinogenic effect of black tobacco as compared with blond tobacco has been shown on four sites: larynx, lung, oesophagus and urinary bladder. They are the object of other reviews in the same series [1–4]. The difference in effect has been related to higher levels of *N*-nitrosamines and of aromatic amines in black tobacco smoke [5, 6].

Tobacco smoking is probably the most important risk factor for cancer of the oral cavity [7, 8]. Some aspects of tobacco smoking, such as average consumption, duration of exposure, quitting smoking, use of filter cigarettes and smoking of cigar and pipe, have been studied in detail with respect to risk of oral cancer [8]. In general, the association between various aspects of cigarette smoking and cancer risk closely resembles that found for other cancer sites, such as larynx and lung, although the relative risks are somewhat lower for oral cancer than for low respiratory tract. Cigar and pipe smoking, on the other hand, seem to exert a stronger carcinogenic effect in the oral cavity than in other sites [8]. Furthermore, a synergistic effect in the causation of oral cancer has been shown between tobacco smoking and alcohol drinking [8, 9].

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In some European countries during the past decades there has been an important shift from black to blond cigarettes [10]: it would be important from a public health perspective to predict its effect on the occurrence of oral cancer. This paper will review in detail the data available on the risk of cancer of the oral cavity according to the type of tobacco products.

DESCRIPTIVE EPIDEMIOLOGY

Information on type of tobacco smoking, expressed as a proportion of smokers of black tobacco in samples of the general population, was available for seven areas covered by cancer registries: Cali (Colombia), Sao Paulo (Brazil), Navarra and Zaragoza (Spain), Varese (Italy), Calvados (France), Geneva (Switzerland) [10, 11]. Cancer incidence data were derived from Vol. V of Cancer Incidence in Five Continents [12]. Figure 1 shows the relationship between age-standardised incidence rate of tongue (ICD-9, 141) and mouth (ICD-9, 143–145) cancer and proportion of black tobacco smokers among males: rates in Sao Paulo are different from those in the remaining centres, but even after excluding that centre, only a very weak relationship is suggested between proportion of black tobacco smokers and both cancers (P value for linear regression, after exclusion of Sao Paulo, 0.30 for tongue and 0.59 for mouth cancer). In the five European population samples, data on average cigarette consumption and alcohol drinking were also available [10, 13]. Amounts of cigarettes were similar in the five centres, ranging from 15.4 to 19.2 cigarettes per day. Median alcohol intake varied from 41.8 to 47.9 g/day in four centres, and was higher (60.1 g/day) in Navarra.

ANALYTICAL STUDIES

To date, three epidemiological studies [14–16] have presented risk estimates according to type of tobacco. The paucity of data might be due to the fact that most epidemiological studies on risk factors of oral and pharyngeal cancers have been conducted in areas like the U.S.A. and India, where basically only one type of tobacco is used. A fourth study [17] provided some information relevant to type of tobacoo.

A case–control study of oral and pharyngeal cancer included 108 male cases admitted during 1985–1986 to the University Hospital in Montevideo, Uruguay [14]. 286 hospital patients without alcohol- or tobacco-related diseases were chosen as controls. Histories of tobacco smoking (including information on type of tobacco), alcohol and maté drinking, and diet were collected. It was not stated whether the classification of type of tobacco was based on reports by the study subjects or was derived by the investigators on the basis of cigarette brand. Tobacco products other than cigarettes were not considered in the study: however, the prevalence of this habit is low in the region [11]. Analysis was carried out via logistic regression.

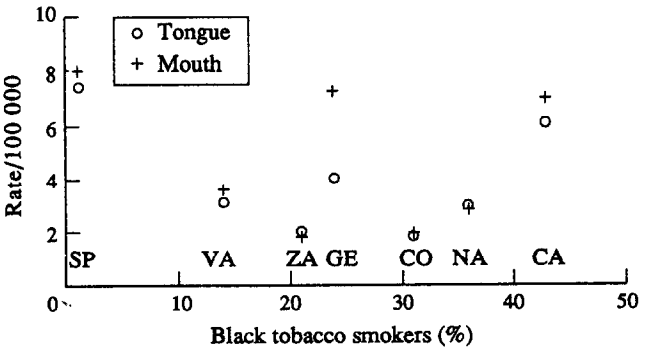

Fig. 1. Incidence rate of tongue (ICD-9, 141) and mouth (ICD-9, 143–145) cancer and proportion of black tobacco smokers among males in seven areas [10–12]. SP: Sao Paulo, Brazil; VA: Varese, Italy; ZA: Zaragoza, Spain; GE: Geneva, Switzerland; CO: Cali, Colombia; NA: Navarra, Spain; CA: Calvados, France.

After controlling for age- and tobacco-related variables (age at start, duration, years since quitting and filter use), dark tobacco smokers had an odds ratio (OR) of 3.4 as compared with blond tobacco smokers [95% confidence interval (CI), 1.8–6.5]. The OR for level of consumption of black and blond tobacco are reported in Table 1: tests for linear trend were highly significant for both types of tobacco. The study also investigated the interaction of type of tobacco with wine, hard liquor and maté exposure. In all three analyses, black tobacco smokers had higher OR than blond tobacco smokers: the combined effects of type of tobacco and wine, hard liquor or maté drinking were consistent with a multiplicative model of interaction. When all major exposure variables were fitted into a stepwise logistic regression model, dark tobacco consumption was the first variable to be entered in the model ($P < 0.001$). After the inclusion of black tobacco, the index of total tobacco intake had a P value of 0.05, and the index of blond tobacco did not reach the level of statistical significance. Among the remaining exposures, consumption of wine, hard liquor and maté, but not indicators of fruit or vegetable consumption, were statistically significant predictors of oral cancer risk. It should be noted that no adjustment was carried out for socioeconomic status or occupational exposures.

A population-based case–control study was conducted in Torino, northern Italy, between 1982 and 1984 [15]. 143 cases of oral cavity and oropharynx (ICD-9, 140.3–140.5, 141, 143–146) were identified and 122 were interviewed (86 men and 36 women). Controls were a random sample of the population of the city: out of 679 men and 425 women, interviews were performed for 385 and 221, respectively. Younger and more educated controls were more likely to be interviewed. Information was collected on tobacco smoking, alcohol drinking, diet and occupational history, as well as demographic variables. Brands of cigarettes, cigars and tobacco smoked in pipes were classifed as black or blond tobacco on the basis of information from the State Monopoly. Cigarette smokers were then classified according to the proportion of tobacco type smoked. Analysis was carried out via Mantel–Haenszel stratification and logistic regression.

In the age-stratified analysis, black tobacco smokers of both sexes had a higher risk of oral and oropharyngeal cancer than blond tobacco smokers: OR among males were 4.8 (95% CI, 1.9–12.1), and 2.4 (95% CI, 0.8–7.2) for smokers of > 66% of black and blond tobacco, respectively (reference category, never

Table 1. Risk of oral and pharyngeal cancer by amount of cigarette smoking and type of tobacco in the case–control study from Montevideo, Uruguay [14]

Amount of cigarette smoking (cigarettes/day)	Black tobacco OR*	Black tobacco 95% CI	Blond tobacco OR*	Blond tobacco 95% CI
0–10†	1	—	1	—
11–20	26.7	7.9–89.9	4.6	0.6–34.9
⩾ 21	31.6	10.6–93.6	21.5	4.4–10.2

* Odds ratio estimated via logistic regression. No details were given on the variables entered in the model. † Reference category.

Table 2. Risk of oral and oropharyngeal cancer by type of tobacco and sex in the case–control study from Torino, Italy [15]

Type of tobacco* (% of total tobacco)	Men		Women	
	OR†	95% CI	OR†	95% CI
> 66% blond‡	1.0	—	1.0	—
Both types ≤ 66%	0.7	0.2–2.7	2.0	0.1–25.9
> black	1.0	0.4–2.6	2.3	0.3–15.2

* Analysis restricted to cigarette smokers.
† Odds ratio estimated via logistic regression, controlling for age, education, area of birth, tobacco variables (consumption, duration, time since quitting, percentage of filter), alcohol drinking and type of alcoholic beverage.
‡ Reference category.

smokers). Corresponding figures for women were 6.9 (95% CI, 2.5–19.1) and 6.0 (95% CI, 2.2–16.1), respectively. When the effect of type of tobacco was adjusted for education, area of birth, alcohol drinking, type of alcoholic beverage, as well as several tobacco variables (consumption, duration, time since quitting, filter), no extra risk due to black tobacco was found among males, whereas among females the effect was still present, although smaller (Table 2). No results were presented on the interaction between type of tobacco and other exposure variables, such as alcohol drinking.

A case–control study was conducted between 1986 and 1988 in three Brazilian metropolitan areas [16]. 232 oral cavity cancer cases (ICD-9, 141, 143–145) and a double number of hospital (excluding neoplastic and mental diseases) controls, matched to cases on sex, age and period of hospital admission were included in the study. Among cases, there were 193 whites and 201 males. 106 cases had a cancer of the tongue (ICD-9, 141), and results were presented separately for this site and for the remaining regions of the oral cavity. Information was collected on socioeconomic and demographic variables, occupational and environmental exposures, tobacco smoking, alcohol drinking, diet and oral hygiene. Separate information was collected on manufactured cigarettes and hand-rolled, black tobacco cigarettes. All hand-rolled cigarettes in the study areas are made of black tobacco, whereas practically all manufactured cigarettes from the early 1960s are made of blond tobacco (Dr Franco, personal communication). Analysis was based on conditional logistic regression models, including matching variables.

OR of oral cancer by type of cigarettes are reported in Table 3: these results are adjusted for other smoking variables: smokers of hand-rolled cigarettes had OR which were only slightly increased as compared with smokers of manufactured cigarettes. Risks were consistently higher among tongue cancer cases than among cases with a lesion from other sites (e.g. OR of tongue and other site cancer were 16.3 and 4.2 for never hand-rolled cigarette smokers, and 16.9 and 4.5 for ever hand-rolled cigarette smokers, respectively).

A case–control study was carried out in two areas of northern Italy between 1984 and 1989 [17]. 291 male cases of cancer of the oral cavity and pharynx below the age of 75 and 1272 hospital controls (patients admitted for acute conditions not related to alcohol and tobacco) were interviewed with respect to their history of tobacco smoking, alcohol and coffee drinking, and drug intake. Among the information on smoking, cigarette brands smoked for the longest time were recorded and classified according to tar yield. A cut-off point of 22 mg of tar was chosen for the analysis, for this value allows a distinction between filter and non-filter as well as between blond and black tobacco cigarettes. Logistic regression models were used in the analysis, taking into account age, education, area of residence and alcohol drinking.

Results according to tar yield of cigarettes smoked are presented in Table 4: both ever and current smokers of high tar cigarettes had a higher risk of oral and pharyngeal cancer than smokers of low and medium tar cigarettes. When amount and duration of smoking were also controlled for, smokers of high tar cigarettes still had a significantly increased risk of oral and pharyngeal cancer (OR, 2.3; 95% CI, 1.6–3.2). This effect was present among younger and older subjects (cut-off point at 60 years of age). However, a negative interaction was suggested between tar yield and alcohol drinking, even if in all alcohol strata high tar smokers had higher risks than low/medium tar smokers. No attempt was made to separate the effect of filter from the effect of type of tobacco.

DISCUSSION

Although the studies included in this review differ in some aspects of the design, they are consistent in showing an effect of tobacco smoking and alcohol drinking on oral cancer risk. In fact, three studies provided risk estimates according to amount of total tobacco smoked, and the OR were fairly similar [15–17]. Even if these studies are not without problems in the design, conduction or analysis, they can be considered of good epidemiological quality.

The results of these studies with respect to colour of tobacco are not consistent: little or no difference in risk between black and blond tobacco smokers was found in the studies from Brazil and from Torino, Italy, whereas the study from Uruguay found a stronger carcinogenic effect of black tobacco cigarettes as

Table 3. Risk of oral cancer by type of smoker and type of cigarettes in the case–control study from three Brazilian areas [16]

Type of smoker	Manufactured cigarettes		Hand-rolled cigarettes	
	OR*	95% CI	OR*	95% CI
Current smoker	9.3	3.4–25.9	14.4	5.2–40.0
Ex-smoker, 1–10 years	2.9	0.9–9.2	4.9	1.6–14.8
Ex-smoker, > 10 years	0.6	0.1–2.8	2.3	0.8–7.1

* Odds ratio estimated via conditional logistic regression, controlling for age, sex, study area and admission period. Reference category: never smokers.

Table 4. Risk of oral and pharyngeal cancer by type of smoker and tar yield of cigarettes in the case–control study from two Italian areas [17]

Type of smoker	Tar yield of cigarettes			
	< 22 mg		≥ 22 mg	
	OR*	95% CI	OR*	95% CI
Ever cigarette smoker	8.5	3.7–19.4	16.4	7.1–38.2
Current cigarette smoker	10.9	4.7–25.0	30.0	12.7–71.2

* Odds ratio estimated via logistic regression, controlling for age, area of residence, education, alcohol drinking. Reference category: never smokers.

Table 5. Risk of oral and oropharyngeal cancer by type of tobacco and regression model among male cigarette smokers in the case–control study from Torino, Italy (Dr Merletti, personal communication)

Covariates in the regression model	Type of tobacco: Both types < 66% OR*	95% CI	Black > 66% OR*	95% CI
None	1.2	0.5–3.3	2.2	1.1–4.3
Age	1.2	0.4–3.4	2.0	1.0–3.9
Age, education and area of birth	1.0	0.3–2.9	1.5	0.7–3.2
Age, education, area of birth and smoking variables†	0.9	0.3–3.0	1.0	0.4–2.4
Age, education, area of birth, smoking variables, alcohol drinking and type of alcoholic beverage	0.7	0.2–2.7	1.0	0.4–2.6

* Odds ratio estimated via logistic regression. Reference category: smokers of > 66% blond tobacco.
† Smoking variables include amount of tobacco, duration, years since quitting, percentage of filter cigarettes.

compared with blond tobacco cigarettes, as did the study from the two Italian areas, in which high and low/medium tar cigarettes were compared.

A careful analysis of the results of these studies, however, might offer some clues in their interpretation. The two clearly "positive" studies [14, 17] also included cases of pharyngeal cancer, and did not provide specific estimates of cancer risk according to site. It is possible, therefore, that the excess risk found in these studies is restricted to pharyngeal cancer cases [1]. The study by Merletti *et al.* [15] found an effect of black tobacco when only age was taken into account: when other exposure variables were controlled for, however, this effect disappeared. Table 5, which was provided by Dr Merletti, shows the details of the adjustment process: the inclusion of education and area of birth variables in the regression model reduced the risk of black tobacco; the latter practically disappeared when other tobacco variables (quantity, duration, filter, time since quitting, filter) were also included, whereas the further inclusion of drinking variables did not substantially alter the picture. In the study from Uruguay [14], socioeconomic factors were not controlled for: the effect of black tobacco in that study could, therefore, be the result of a confounding effect. The positive result of the study by La Vecchia *et al.* [17], on the other hand, could be explained by the fact that their exposure variable was an indirect indicator of tobacco colour: the effect could be due to other characteristics of high tar cigarettes, including lack of filter and tar content itself, independently of type of tobacco.

On the other hand, one should bear in mind that non-differential misclassification, leading to false negative results, is in general more frequent in epidemiology than differential misclassification, which may cause false positive results. It is also important to note that the two "negative" studies [15, 16] were not without pitfalls: in the study by Merletti *et al.* [15], there was a low response rate among controls, and response was associated with socioeconomic status and, therefore, most probably, with black tobacco exposure (it is more likely, however, that such a bias lead to a false positive result). In the Brazilian study [16], classification of type of tobacco was based on a proxy variable (manufactured vs. hand-rolled), which might obscure a true association between black tobacco smoking and cancer risk.

A number of important issues have not been adequately studied. The interaction between tobacco type and alcohol drinking has been addressed only by De Stefani *et al.* [14]: if alcohol drinking is indeed a modifier of the effect of type of tobacco, this might contribute towards explaining the inconsistencies of results according to type of tobacco. Similarly, it is not known whether the different effect of black tobacco in men and women, found by Merletti *et al.* [15], reflects a true biological effect or is due to chance or bias. The effect of type of tobacco on different sites within the oral cavity and the oropharynx, such as floor of the mouth, oral tongue, soft palate (the three most common sites in European and American populations), has been partially addressed only by Franco *et al.* [16], who found no effect of type of tobacco on the oral tongue as well as on the other sites.

On the basis of the available data it can be concluded that a clear effect of type of tobacco has not yet been shown for oral cancer. If anything, the current evidence points towards a lack of effect. If this is the case, an implication would be the fact that carcinogens present at higher concentration in black tobacco, such as *N*-nitrosamines, do not exert an important role in the carcinogenicity of tobacco on the oral mucosa, and that, in general, the carcinogenic effect of tobacco in the oral cavity is not identical to the effect on sites such as larynx and lung.

More studies are needed to reach a final conclusion: two examples are the case–control studies currently carried out in Villejuif, France (Dr S. Benhamou, personal communication) and Ragusa, Italy (Prof. L. Gafá, personal communication). Other populations suitable for such studies include Spain, Portugal, southern Italy, southern France, Switzerland, Cuba, Argentina and other Latin American countries [18]. Furthermore, studies with information on cigarette brands, such as the one by La Vecchia *et al.*, could be reanalysed with a better characterisation of type of tobacco. A final answer to the problem of the action of black and blond tobacco on the oral mucosa would be important for preventive purposes as well as to advance the knowledge on the carcinogenic mechanism of tobacco smoke on the upper aerodigestive tract.

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Carotenoids and Cancer: An Update with Emphasis on Human Intervention Studies

Geert van Poppel

This article gives an overview of the current state of knowledge on the cancer preventive potential of carotenoids. Numerous retrospective and prospective epidemiological studies have shown that a high intake of carotenoid-rich fruits and vegetables is associated with a decreased risk of cancer at a number of common sites. For several other cancer sites, however, the epidemiological evidence is not very consistent. A number of mechanisms for the cancer preventive properties of carotenoids have been proposed. Conversion to retinol, possibly in posthepatic tissues, would allow an effect on cellular differentiation and proliferation, and on cell-to-cell communication. Antioxidant functions could prevent free radical-induced damage to cellular DNA and other macromolecules. Immunomodulatory effects could enhance immune surveillance in tumorigenesis. In addition, non-retinol-mediated effects of carotenoids on metabolism of carcinogens and cell-to-cell communication have been shown. Observational epidemiology cannot resolve whether associations are due to a specific carotenoid, or to an associated factor in fruits and vegetables, whereas interpretation of animal studies is hampered by uncertainties in extrapolation between species, more so because the metabolism of carotenoids in most animals differs notably from that in humans. Human intervention studies on biomarkers related to cancer risk and on cancer incidence are, therefore, necessary. Human intervention studies performed so far suggest that β-carotene can affect carcinogenesis, though not at all stages and not at all cancer sites. Implications for future human intervention research are discussed.
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INTRODUCTION

In 1981, Peto *et al.* [1] hypothesised that dietary carotenoids may reduce human cancer rates. Since then, a large number of epidemiological studies have addressed this topic, and a flurry of experimental work has been aimed at unravelling the possible mechanisms of chemoprevention by carotenoids. This article will give an overview of the current state of knowledge regarding the cancer preventive potential of carotenoids. Firstly, an update on epidemiological studies regarding carotenoids and cancer will be given. Subsequently, the current concepts on mechanisms of carcinogenesis will be addressed and possible mechanisms of action of carotenoids will be discussed. Finally, results of human intervention studies that have so far been performed will be addressed with implications for future research.

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EPIDEMIOLOGICAL STUDIES ON CAROTENOIDS AND CANCER

A large number of case–control studies have evaluated the association between intake of fruits and vegetables containing carotenoids and cancer. Likewise, prospective cohort studies have evaluated the relation between prediagnostic consumption or blood levels of carotenoids and subsequent risk of cancer. Tables 1 and 2 summarise the results for the retrospective and prospective studies. Several points should be considered when