

In conclusion, our data demonstrate that VER can modulate *in vitro* DOX cytotoxicity in HCOC cells expressing levels of *mdr1* products comparable to those expressed by non-drug-treated primary HCOC and that drug cytotoxic enhancement is a schedule-dependent phenomenon.

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## Feature Articles

# Black (Air-cured) and Blond (Flue-cured) Tobacco and Cancer Risk VI : Lung Cancer

Ellen Benhamou and Simone Benhamou

FEW STUDIES have compared the risk of lung cancer incurred by smokers of black tobacco to the risk incurred by smokers of light tobacco. The small number of studies can be explained by the geographical distribution of black and light tobacco use all over the world: most studies on lung cancer and cigarette smoking have been conducted in countries where light tobacco has been mainly used, such as the U.S.A. or U.K., whereas black tobacco is common mainly in southern Europe and Latin America.

Between 1983 and 1989, four case-control studies addressing

the differential role of light and black tobacco on lung cancer risk were performed in Cuba, France, Uruguay and Italy [1–4]. The main characteristics of these studies are summarised in Table 1. They were hospital-based studies and the controls were without tobacco-related diseases. All cases had a histologically verified diagnosis. The data were recorded from a face-to-face interview except in [3] in which 75% of cases and 60% of controls were interviewed through a next of kin. In all studies but [3], controls were matched to cases on sex and age. The total number of male manufactured or hand-rolled cigarette smokers ranges from 1253 in [3] to 3019 in [4].

Because of the small number of women enrolled in these studies, only the analysis on males will be presented here. Analyses were conducted on squamous cell type cancers in [3], on Kreyberg I type (squamous, small and large cell) in [2], and all histological types in [1, 4]. Table 2 shows the number of male

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Table 1. Main characteristics of data included in the review of the four case-control studies of lung cancer in males

Ref.	Authors, country and year of study	Number of male cigarette smokers		Origin		Histology of lung cancer	Criteria for matching
		Cases	Controls	Cases	Controls		
1	Joly, <i>et al.</i> Cuba, 1978-1980	552	709	Hospital	Hospital and neighbours	All histological types	Age, sex, hospital, date of admission (place of residence for matched neighbourhood controls)
2	Benhamou, <i>et al.</i> France, 1976-1980	1074	1249	Hospital	Hospital	Kreyberg I type	Age, sex, hospital, interviewer and date of diagnosis
3	De Stefani, <i>et al.</i> Uruguay, 1984-1988	531	722	Hospital	Hospital	Squamous type	No matching
4	Berrino. Italy, 1977-1980	1101	1918	Hospital	Hospital	All histological types	Age, sex, date of diagnosis and residence

cigarette smokers according to the type of tobacco (light, mixed, dark). Exclusive light tobacco smokers are defined as people having smoked light tobacco for 100% of their smoking lifetime in [1, 2, 4], and for at least 80% of their smoking lifetime in [3]. Among cigarette smokers, the percentage of exclusive light cigarette smokers is very low in Cuba, in France and in Italy (2, 3 and 9%, respectively); in Uruguay (3), this proportion is much higher (42%) but the definition of exclusive light tobacco smokers is less stringent in this study. When people having smoked light tobacco for at least 1 year of their smoking lifetime are considered, these figures are 5% in Cuba, 12% in France, 63% in Italy and 53% in Uruguay.

Relative risks of lung cancer according to characteristics of tobacco exposure, such as age at first cigarette, age at cessation, duration of smoking, daily consumption and inhalation, showed dose-responses as expected in all four studies (data not shown); however, the risks were much higher in the Uruguayan study than in the other studies.

The risks associated with the type of tobacco are presented in Tables 3 and 4. When crude risks are considered, all four studies show a higher risk for smokers of mixed and black tobacco as compared to smokers of light tobacco. Risks associated with dark tobacco computed for Kreyberg I [2] or squamous cell cancers only [3] are higher than those for all histological types [1, 4]. The relative risk of black versus light tobacco is 2.1 in [3]

Table 2. Distribution of male cigarette smokers according to type of tobacco\*

Ref.	Histology of lung cancer		Light tobacco	Mixed tobacco	Dark tobacco
1	All histological types	Cases (n = 552)	1.8%	2.4%	95.8%
		Controls (n = 709)	2.2%	2.7%	95.1%
2	Kreyberg I type	Cases (n = 1074)	1.4%	7.7%	90.0%
		Controls (n = 1249)	4.9%	8.8%	86.3%
3	Squamous type	Cases (n = 531)	32.4%	11.5%	56.1%
		Controls (n = 722)	49.7%	9.7%	40.6%
4	All histological types	Cases (n = 1101)	6.5%	54.1%	39.3%
		Controls (n = 1918)	10.4%	53.6%	36.0%

\*100% lifetime light tobacco except in [3]:  $\geq 80\%$  of lifetime light tobacco.

Table 3. Relative risks of lung cancer (95% confidence interval) according to type of tobacco\* among male cigarette smokers as compared to non-smokers

Ref.	Histology of lung cancer	Light tobacco	Mixed tobacco	Dark tobacco
1	All histological types	11.3 (3.8-33.9)	12.4 (4.6-34.3)	14.3 (7.7-27.9)
2	Kreyberg I type	4.9 (2.3-10.4)	15.1 (8.9-25.7)	18.1 (11.7-28.3)
3	Squamous type	24.4 (8.0-18.5)	44.4 (14.8-149.5)	51.9 (18.3-166.0)
4	All histological types	5.3 (3.3-8.4)	8.4 (5.7-12.4)	9.1 (6.2-13.4)

\*100% lifetime light tobacco except in [3]:  $\geq 80\%$  of lifetime light tobacco.

Table 4. Adjusted relative risks of lung cancer (95% confidence interval) according to type of tobacco among male cigarette smokers as compared to light cigarette smokers\*

Ref.	Histology of lung cancer	Light tobacco	Mixed tobacco	Dark tobacco
1	All histological types†	1.0	1.2 (0.4-3.6)	1.3 (0.6-3.0)
2	Kreyberg I type‡	1.0	1.6 (0.7-3.4)	1.9 (1.0-4.0)
3	Squamous type§	1.0	1.6 (1.1-2.4)	1.6 (1.2-2.2)
4	All histological types	1.0	1.1-1.2 P < 0.05	1.6 P < 0.05

\*100% lifetime light tobacco except in [3];  $> 80\%$  of lifetime light tobacco. †These figures adjusted for daily consumption were computed from a separate analysis for light and dark tobacco. ‡Matched model adjusted for duration of consumption, daily consumption, social class, use of filter, current smoking, use of hand-rolled cigarettes and inhalation. §Adjusted for age, county, socio-economic status, hospital, respondent status, daily consumption, duration, years since cessation, use of filter and use of hand-rolled cigarettes. ||Adjusted for age, residence, daily consumption, use of filter, years since cessation.

Table 5. Adjusted relative risks for lung cancer (95% confidence interval) according to filtered cigarettes use among male cigarette smokers

Ref.	Histology of lung cancer	Always filtered	≥ 50% filtered	< 50% filtered	Always unfiltered
2	Kreyberg I type*	1.0		1.1 (0.7–1.6)	1.2 (0.9–1.7)
3	Squamous type†	1.0			1.7
4	All histological types‡	1.0	1.4 NS	1.3 NS	1.1 NS

\*Matched model adjusted for duration of consumption, daily consumption, social class, type of tobacco, current smoking, use of hand-rolled cigarettes and inhalation. †Adjusted for age, county, socio-economic status, hospital, respondent status, daily consumption, duration, years since cessation, type of tobacco and use of hand-rolled cigarettes. ‡Adjusted for age, residence, daily consumption, current smoking, type of tobacco.

and 3.7 in [2]; the lower risk observed in [3] may be due to the different definition of dark tobacco in the two studies (100% lifetime dark tobacco vs. ≥ 80% lifetime dark tobacco). Adjusted risks (Table 4), although obviously lower, show similar patterns with a risk for smokers of black tobacco about twice the risk for smokers of light tobacco in Kreyberg I.

The comparisons of the adjusted risks observed in different studies are difficult to interpret because different cofactors were taken into account. To study the effect of the type of tobacco, not only daily consumption, duration of smoking, age at first cigarette, depth of inhalation, and years since cessation should be considered; one should consider also the characteristics of the cigarettes smoked, i.e. filter use or not, tar content, and whether the cigarettes were manufactured or hand-rolled because these three characteristics are strongly associated with the type of tobacco. Three studies [2–4] have analysed the role of the type of tobacco together with the use of a filter (Table 5) and two studies [2, 3] with the hand-rolling habit (Table 6). In all three, the significant excess of risk found in the univariate analysis for non-filter cigarettes as compared to filter cigarettes disappeared when type of tobacco was introduced in the logistic regression. No analysis of both type of tobacco and use of a filter was performed in [1] since only less than 5% of smokers used filtered cigarettes. Adjusted risk associated with hand-rolling was significantly increased in [3] (RR = 2.8).

Tar exposure was studied in [1] only; tar levels were measured for the four most popular cigarette brands currently smoked. Only persons consuming exclusively the four brands tested were studied, which reduced the number of subjects available for the investigation to 29% of the cases and 18% of the controls. Three

Table 6. Adjusted risks according to hand-rolled cigarettes use among male cigarette smokers

Ref.	Histology of lung cancer	Never hand-rolled	Always hand-rolled
2	Kreyberg I type*	1.0	1.2 (0.8–1.8)
3	Squamous type†	1.0	2.8 (2.0–4.0)

\*Matched model adjusted for duration of consumption, daily consumption, social class, type of tobacco, current smoking, use of filter and inhalation. †Adjusted for age, county, socio-economic status, hospital, respondent status, daily consumption, duration, years since cessation, use of filter and type of tobacco.

categories of lifetime tar exposure were constituted: less than 16 g; 16–24 g and more than 24 g. The increase of risks with tar intake as compared to non-smokers (RR = 12.9, 16.5 and 21.8) was statistically significant ( $P < 0.001$ ) in a univariate analysis; however, trend tests were not significant when an adjustment for either daily consumption (RR = 1.0, 1.3 and 1.2) or duration of smoking (RR = 1.0, 1.1 and 1.2) was performed. No analysis taking simultaneously tar and type of tobacco and/or use of filter into account was performed.

In conclusion, all studies of the relation between lung cancer risk and type of tobacco have found an increased risk for smokers of black tobacco as compared to smokers of light tobacco. However, to conclude that there is a real effect of type of tobacco, tar content should be taken into account together with type of tobacco, use of filter or not and use of manufactured or hand-rolled cigarettes. Such an analysis may be difficult to perform, because of the strong associations between these covariates; for instance, in France, non-filter cigarette smokers are mainly dark tobacco smokers. Moreover, in all studies realised, the number of smokers of light cigarette was very small as compared with smokers of dark tobacco. In the future, the role of the type of tobacco should be easier to study because of the increasing proportion of light cigarette smokers in southern Europe and Latin America; however, the spreading use of filtered, low-tar content light cigarettes may limit further studies.

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