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Cigarette tar yield and risk of upper digestive tract cancers: case–control studies from Italy and Switzerland

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Background: Tobacco smoking is one of the main risk factors for oral, pharyngeal and oesophageal cancers in developed countries. Information on the role of the tar yield of cigarettes in upper digestive tract carcinogenesis is sparse and needs to be updated because the tar yield of cigarettes has steadily decreased over the last few decades.

Patients and methods: We analysed two case–control studies, from Italy and Switzerland, conducted between 1992 and 1999, involving 749 cases of oral and pharyngeal cancer and 1770 controls, and 395 cases of squamous-cell oesophageal carcinoma and 1066 matched controls. Odds ratios (ORs) were estimated by unconditional multiple logistic regression models, including terms for age, sex, study centre, education and alcohol consumption.

Results: Based on the brand of cigarettes smoked for the longest time, the multivariate ORs for current smokers compared with never smokers were 6.1 for <20 mg and 9.8 for ≥20 mg tar for oral and pharyngeal neoplasms, and 4.8 and 5.4 for oesophageal cancer, respectively. For the cigarette brand smoked in the previous six months, the ORs for ≥10 mg compared with <10 mg were 1.9 for cancer of the oral cavity and pharynx and 1.8 for oesophageal cancer, after allowance for number of cigarettes and duration of smoking.

Conclusions: The present study confirms the direct relationship between the tar yield of cigarettes and upper digestive tract neoplasms, and provides innovative information on lower tar cigarettes, which imply reduced risks compared with higher tar ones. However, significant excess risks were observed even in the lower tar category, thus giving unequivocal indications for stopping smoking as a priority for prevention of upper digestive tract neoplasms.

Key words: case–control studies, oesophageal cancer, oral cancer, risk factor, tar yield, tobacco smoking

Introduction

Tobacco smoking is, together with drinking alcohol, the major risk factor for oral, pharyngeal and oesophageal cancer in developed countries [1–9]. Different types of tobacco products (cigarettes, cigars, pipes, betel chewing and snuff) increase the risk of upper digestive tract neoplasms [5, 10–15], although precise quantification of their risk is still open to discussion.

With reference to the role of type or tar yield of cigarettes, a case–control study conducted in Northern Italy, based on 291 males with cancer of the oral cavity and pharynx and 288 with cancer of the oesophagus, reported odds ratios (ORs) of 2.3 for oral and pharyngeal cancer in high-tar cigarette smokers compared with low-tar ones, and 2.8 for oesophageal cancer [3, 4]. A case–control study from the USA, based on 1009 oral cavity and pharyngeal cancer cases, found ORs of 2.1 for men and 4.6 for women for the highest category of cumulative lifetime exposure to cigarette tar compared with never smokers [16]. A multicentre case–control study on cancers of the hypopharynx and larynx, from France, Switzerland, Italy and Spain, found a relative risk for hypopharyngeal cancer of 2.2 among smokers of black tobacco (which tends to have higher tar yield) compared with blond [17]. A case–control study from France found that black/dark tobacco and non filter-tipped cigarettes were associated with an increased risk of oesophageal cancer compared with light filter-tipped cigarettes and mild tobacco [12]. Furthermore, an investigation based on 830 subjects with oesophageal cancer, from five hospital-based case–control studies conducted in South America, found an increased risk in black tobacco-type cigarette smokers compared to smokers of the blond type, with ORs of 2.0 for men and 3.4 for women [7]. As yet no information is available on the risks associated with newer very low tar yield cigarettes.

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The tar yield of cigarettes has steadily decreased over the last few decades [18], and this may have influenced recent favourable trends in mortality from upper digestive tract neoplasms in males from several western European countries, following earlier rises [19–22]. The average tar yield of Italian cigarettes was ~25 mg in the 1960s, ~17 mg in 1983–1984 [23] and declined to ~12 mg in the late 1990s. To provide further information on the role of the most recent cigarettes in relation to the risk of upper digestive tract cancers, we analysed data from two multicentre case–control studies conducted in Northern Italy and Switzerland.

Patients and methods

This analysis is based on data from two case–control studies on the upper digestive tract cancer. The first one, on cancer of the oral cavity and pharynx, was conducted between 1992 and 1997 in two Italian areas (the province of Pordenone, Northern Italy, and those of Rome and Latina, Central Italy) and in the Swiss Canton of Vaud [24, 25]. The second one, on squamous-cell oesophageal cancer, was conducted between 1992 and 1999 in the provinces of Pordenone, Padua and Milan, Northern Italy [26], and in the Swiss Canton of Vaud [25, 27].

The first study included 749 cases (634 men, 115 women) aged <77 years (median 58 years) with incident, histologically confirmed cancers of the oral cavity and pharynx, and 1770 hospital controls (1252 men, 518 women) <78 years of age (median 58 years). Twenty-eight percent of controls were admitted to hospital for traumas, 25% for non-traumatic orthopaedic conditions, 24% for acute surgical disorders and 23% for miscellaneous other illnesses (including skin, eye or ear disorders).

The second study included 395 cases (351 men, 44 women) <77 years of age (median 60 years) with incident, histologically confirmed squamous-cell oesophageal cancer, and 1066 hospital controls (875 men, 191 women) aged <75 years (median 60 years). Controls were matched with cases by age (within 5 year intervals), sex and study centre, with a control:case ratio of ~5 for women and ~2 for men. Twenty-nine percent of controls were admitted for traumas, 36% for non-traumatic orthopaedic conditions, 12% for acute surgical disorders and 23% for miscellaneous other illnesses. In both studies, the response rate was >95% for cases and controls.

Trained interviewers collected data using structured questionnaires, including information on sociodemographic characteristics, anthropometric measures and lifestyle habits, such as smoking and alcohol consumption. The questions on tobacco smoking included smoking status (never, ex, current smoker), number of cigarettes or cigars and grams of tobacco for pipe smoked per day, the age at starting and (for ex-smokers) the time since stopping smoking, and brands of cigarette smoked. Each subject could indicate the brands smoked for up to three periods of their life and, for current smokers, the brand smoked during the previous 6 months. Reproducibility of the information on tobacco smoking was satisfactory [28]. Tar yields of more than 100 kinds of cigarette, i.e. the most common Italian and international brands, were determined by the Laboratory of the British Government Chemist for cigarettes smoked before 1983 [29], and obtained from published sources by the Italian Government for dates thereafter [30]. Tar yield of Swiss cigarettes was obtained from cigarette packets.

The cigarette brands were classified into three categories according to their tar yield: high tar (≥20 mg), including older, mostly unfiltered cigarettes; intermediate tar (10–19 mg); and low tar (<10 mg), including vented filter cigarettes.

Odds ratios and corresponding 95% confidence intervals (CI) were estimated by unconditional multiple logistic regression models [31], including terms for age, sex, study centre, years of education and alcohol consumption. For the comparison of high versus low tar yield categories the analyses were restricted to ever and current smokers, and further terms for smoking status (when required), the number of cigarettes smoked and the duration of the habit were included in the models.

Results

Table 1 shows the multivariate ORs for cancers of the oral cavity and pharynx and oesophagus according to selected measures of tobacco smoking. Cigarette smoking was strongly associated to the risk for both cancer sites; comparing current to never smokers, the ORs were 6.8 for oral and pharyngeal cancer, and 5.1 for oesophageal cancer (the ORs for ex-smokers were ~2 for both these cancers). The ORs increased with the number of cigarettes smoked to 12.3 for oral and pharyngeal cancer, and 7.9 for oesophageal cancer, for current smokers of ≥25 cigarettes per day. For pipe and cigar smoking, the ORs were 6.6 for oral and pharyngeal cancer, and 12.6 for oesophageal cancer. Increasing risks were observed in relation to duration of smoking, with ORs of 7.7 for oral and pharyngeal cancer, and of 5.5 for oesophageal cancer, for current smokers for ≥30 years. Consistent patterns of risk with dose and duration were also observed for ex-smokers.

The effect of tar yield among ever and current smokers is presented in Table 2. When compared with never smokers, the multivariate ORs for oral and pharyngeal cancer for ever smokers were 4.2 for low/medium tar yield (<20 mg) and 5.9 for high tar (≥20 mg). For oesophageal cancer, the OR was 3.5 in both strata. A similar effect of tar yield was observed when considering current smokers only: compared with never smokers, the multivariate ORs of oral and pharyngeal cancer were 6.1 for low/intermediate tar yield and 9.8 for high tar, and those for oesophageal cancer were 4.8 and 5.4, respectively. When considering the cigarettes smoked in the last 6 months, the ORs for oral and pharyngeal cancer were 3.8 for low (<10 mg) and 7.1 for intermediate/high tar yield (≥10 mg). A similar pattern of risk was found for oesophageal cancer, the ORs being 2.4 and 5.4 for low and intermediate/high tar, respectively.

In Table 3, lower and higher tar yield cigarettes were compared among ever and current smokers, after further allowance for smoking status (when considering ever smokers), number of cigarettes smoked and duration of habit. In ever smokers, the ORs for ≥20 mg compared to <20 mg tar yield were 1.6 for cancer of the oral cavity and pharynx, and 1.1 for cancer of the oesophagus. Corresponding values in current smokers were 1.6 for oral and pharyngeal cancer, and 1.3 for oesophageal cancer. When considering the cigarette brand smoked in the previous 6 months, the ORs for ≥10 mg compared with <10 mg were 1.9 (95% CI 1.1–3.3) for cancer of the oral cavity and pharynx, and 1.8 (95% CI 0.8–4.1) for oesophageal cancer.

Discussion

The present study confirms and extends previous findings of a relationship between the tar yield of cigarettes and upper digestive tract neoplasms [3, 4, 7, 12, 16, 17].

Table 1. Distribution of 749 cases of cancers of the oral cavity and pharynx and 1770 controls, and 395 cases of squamous-cell oesophageal cancer and 1066 controls according to selected tobacco variables, with corresponding odds ratios (OR) and 95% confidence intervals (CI). Northern Italy and Switzerland, 1992–1999.

Smoking habit[a]	Oral cavity and pharynx			Oesophagus		
	Cases	Controls	OR[b] (95% CI)	Cases	Controls	OR[b] (95% CI)
Never smokers	60	692	1[c]	37	376	1[c]
Current smokers	517	521	6.8 (4.9–9.4)	234	318	5.1 (3.3–7.7)
Cigarettes per day						
<15	108	205	4.6 (3.1–6.7)	40	109	2.7 (1.6–4.7)
15–24	244	225	7.7 (5.3–11.0)	110	135	5.7 (3.5–9.1)
≥25	157	82	12.3 (7.9–19.0)	77	63	7.9 (4.5–13.8)
Pipe/cigar only	8	9	6.6 (2.0–21.3)	6	11	12.6 (3.6–43.6)
Total duration of smoking (years)						
<30	126	214	5.1 (3.4–7.8)	32	83	3.3 (1.7–6.4)
≥30	391	307	7.7 (5.5–10.9)	202	234	5.5 (3.6–8.5)
Ex-smokers	172	557	2.1 (1.5–3.1)	124	372	2.2 (1.4–3.4)
Cigarettes per day						
<15	41	200	1.7 (1.0–2.7)	31	132	1.7 (1.0–3.0)
≥15	125	347	2.3 (1.6–3.4)	90	230	2.5 (1.5–4.0)
Pipe/cigar only	4	6	4.4 (1.0–18.9)	2	7	1.9 (0.3–13.2)
Total duration of smoking (years)						
<30	67	344	1.5 (1.0–2.3)	39	216	1.4 (0.8–2.4)
≥30	105	213	3.1 (2.1–4.6)	85	156	3.3 (2.0–5.3)
Time since smoking cessation (years)						
<10	101	202	3.6 (2.4–5.4)	64	107	4.1 (2.5–7.0)
≥10	71	355	1.3 (0.9–2.0)	60	265	1.4 (0.9–2.3)

[a]In some strata the sum does not add up to the total due to some missing values.
[b]Estimates from unconditional multiple logistic regression models, including terms for age, sex, study centre, education and alcohol consumption.
[c]Reference category.

The most innovative findings of our investigation concern very low tar (<10 mg) cigarettes. The large number of current smokers allowed us to compare recent smokers of cigarettes with <10 mg tar yield to higher tar ones. The ORs for current smokers of ≥10 mg tar cigarettes compared with <10 mg were almost 2-fold for oral and oesophageal cancers. These results are of particular relevance because they were obtained after allowance for duration and number of cigarettes. It is possible that low-tar smokers tend to compensate in terms of number of cigarettes smoked. In fact, in our data, current smokers of low yield cigarettes had an average consumption of about one cigarette per day more than high tar ones. Furthermore, smokers who switch from higher tar yield cigarettes to lower ones tend to compensate for reduced tar yields by taking larger puffs, puffing more frequently, and leaving a shorter butt [19, 32].

The choice of considering the cigarette brand smoked for the longest time could introduce some bias, since information on the distant past is often imprecise and influenced by current or more recent habits [3]. To avoid these possible misclassifications or bias, we considered cases and controls who had smoked only one cigarette brand lifelong (or brands of the same category of tar yield) and found similar risks. The OR for oral and pharyngeal cancers among current smokers with continual tar yield ≥20 mg compared with never smokers was 10.6 (95% CI 6.1–18.4), and that for oesophageal cancer was 9.6 (95% CI 4.6–20.1). However, current smokers who had smoked only high tar yield cigarettes had a longer duration of the habit than those smoking only low tar ones, since intermediate and low tar cigarettes have become widespread in Southern Europe just over the last two to three decades [29, 30].

To avoid possible sources of bias, cases and controls were drawn from comparable catchment areas and participation was almost complete. The results were not substantially modified by allowance for potential major confounding factors, including socioeconomic characteristics, alcohol consumption, duration and amount of smoking. Information on cigarette smoking was satisfactorily reproducible [28], and there is no reason to suppose differential recall of brand type in cases and controls.

These results have important public health implications [33], together with the evidence of lower excess risk for low tar

Table 2. Distribution of 749 cases of cancers of the oral cavity and pharynx and 1770 controls, and 395 cases of squamous-cell oesophageal cancer and 1066 controls, according to tar yield of cigarettes smoked, and corresponding odds ratios (ORs) and 95% confidence intervals (CI). Northern Italy and Switzerland, 1992–1999.

Tar yield[a]	Oral cavity and pharynx			Oesophagus		
	Cases	Controls	OR[b] (95% CI)	Cases	Controls	OR[b] (95% CI)
Never smokers	60	692	1[c]	37	376	1[c]
Ever smokers (mg)[d]						
<20	396	708	4.2 (3.0–5.8)	205	430	3.5 (2.3–5.3)
≥20	241	256	5.9 (4.1–8.5)	116	185	3.5 (2.2–5.6)
Current smokers (mg)[d]						
<20	318	382	6.1 (4.4–8.6)	146	215	4.8 (3.1–7.6)
≥20	163	90	9.8 (6.5–14.8)	67	67	5.4 (3.2–9.3)
Cigarettes smoked in the previous 6 months (mg)						
<10	31	63	3.8 (2.2–6.8)	11	37	2.4 (1.0–5.4)
≥10	462	434	7.1 (5.1–9.9)	210	264	5.4 (3.5–8.3)

[a]In some strata the sum does not add up to the total because of some missing values.
[b]Estimates from unconditional multiple logistic regression models, including terms for age, sex, study centre, education level and alcohol consumption.
[c]Reference category.
[d]Tar yield of cigarettes smoked for the longest time.

cigarettes compared to high tar ones on lung [19, 32, 34] and laryngeal cancers [3], and coronary heart diseases [19, 35]. Nevertheless, significant and substantial excess risks for the oral cavity and pharynx and oesophagus were observed even in the lower tar category, providing unequivocal indications for stopping smoking as a priority for prevention of upper digestive tract neoplasms.

Table 3. Odds ratios (ORs) and 95% confidence intervals (CI) of oral, pharyngeal and oesophageal cancers, according to tar yield of cigarettes smoked, in ever/current smokers. Northern Italy and Switzerland, 1992–1999.

Tar yield	Oral cavity and pharynx OR[a] (95% CI)	Oesophagus OR[a] (95% CI)
Ever smokers (mg)[b]		
<20	1[c]	1[c]
≥20	1.6 (1.2–2.1)	1.1 (0.8–1.6)
Current smokers (mg)[b]		
<20	1[c]	1[c]
≥20	1.6 (1.1–2.4)	1.3 (0.8–2.1)
Cigarettes smoked in the previous 6 months (mg)		
<10	1[c]	1[c]
≥10	1.9 (1.1–3.3)	1.8 (0.8–4.1)

[a]Estimates from unconditional multiple logistic regression models, including terms for age, sex, study centre, education level, alcohol consumption, smoking status (when required), number of cigarettes and duration of habit.
[b]Tar yield of cigarettes smoked for the longest time.
[c]Reference category.

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