

# Fried foods: a risk factor for laryngeal cancer?

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The role of fried foods on laryngeal cancer risk was investigated in a case–control study from Italy and Switzerland on 527 cases and 1297 hospital controls. A significant increased risk was found for high consumption of fried meat, fish, eggs and potatoes, with odds ratios of 1.6, 3.1, 1.9 and 1.9, respectively.

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The relation between cooking methods such as frying, boiling and barbecuing and cancer risk has been inadequately investigated in epidemiological studies (Archer, 1988; Steineck *et al*, 1993). Among the few studies considering this issue, some investigations reported an increased risk of cancer of the colon, rectum and stomach in relation to consumption of fried foods (mostly meat) (IARC, 1993; Steineck *et al*, 1993), and a few others found a positive association with other common non digestive neoplasms, including breast (Phillips, 1975; Knekt *et al*, 1994; De Stefani *et al*, 1997a), oesophageal (Ward *et al*, 1997), lung (Sinha *et al*, 1998a), pancreatic cancer (Norell *et al*, 1986) and low urinary tract (Steineck *et al*, 1990).

During the process of frying protein-rich foods, such as meat and fish, various kinds of mutagenic and carcinogenic heterocyclic amines (HA) are produced, particularly when cooking temperature is very high (Övervik and Gustafsson, 1990; Layton *et al*, 1995; Skog *et al*, 1998). The fats used for frying seem to further increase the mutagenic activity of HA, probably enhancing heat conduction (Övervik and Gustafsson, 1990; Skog *et al*, 1998). Heterocyclic amines have been shown to cause malignant tumours in the colon and breast of mice and rats, and are possible or probable carcinogens for humans (IARC, 1993). Fried foods other than meat or fish contain only small amounts of HA and have therefore low mutagenic activity (Bjeldand *et al*, 1982a,b). However, some epidemiological studies have reported an increased risk of cancer with consumption of fried eggs and potatoes as well (Phillips, 1975; Demiret *et al*, 1990; Steineck *et al*, 1990).

The larynx is directly exposed to volatile carcinogens in tobacco smoking. Besides tobacco and alcohol consumption, which are the main recognised risk factors, diet has been associated with laryngeal cancer risk (World Cancer Research Fund, 1997). However, scanty data exists on the potential role of carcinogens present in fried meat or other foods with specific reference to laryngeal cancer. A case–control study in China on 201 incident cases and 414 controls, reported that consuming deep-fried foods 'daily', as opposed to 'never/occasionally', increased the risk of laryngeal cancer (odds ratio (OR)=2.5, 95% confidence interval (CI)=1.0–

6.1), although no clear dose-response relation was observed (Zheng *et al*, 1992). A case–control study in Uruguay on cancers of the upper aerodigestive tract found no association with consumption of fried meat, but reported an increased risk in relation to total HA intake whose effect was similar for different cancer sites (De Stefani *et al*, 1997b).

We have therefore investigated the possible relation between fried food intake and laryngeal cancer risk using data from a large case–control study conducted in Italy and Switzerland, which reported a protective effect of vegetables, fruit, and olive oil and a detrimental effect of meat and other protein rich foods (Bosetti *et al*, 2002).

## MATERIALS AND METHODS

The present study is based on data of a case–control study of laryngeal cancer conducted between 1992 and 2000 in two Italian areas (the provinces of Pordenone and the greater Milan area) and in the Swiss Canton of Vaud (Bosetti *et al*, 2002). Cases were 527 patients (478 men and 49 women, median age 61 years, range 30–79) admitted to teaching and general hospitals in the areas under study with incident, histologically confirmed squamous-cell carcinoma of the larynx, diagnosed no longer than 1 year before the interview. These included 271 glottis, 117 supraglottis, 4 subglottis and 135 other or unspecified laryngeal cancers. Controls were 1297 subjects (1052 men and 245 women, median age 61 years, range 31–79) selected among patients admitted to the same hospitals for a wide spectrum of acute, non-neoplastic conditions, not related to smoking, alcohol consumption and long-term modification of diet. These were frequency-matched to cases by 5-year groups, sex and area of residence; to compensate for the rarity of laryngeal cancer in women, a control-to-case ratio of about five was chosen for females, as apposed to two for males. Among the controls, 27% were admitted for traumas, 22% for other orthopaedic disorders, 29% for acute surgical conditions, and 23% for miscellaneous other illnesses, including eye, nose, ear, skin or dental disorders.

Cases and controls were interviewed during their hospital stay using a structured questionnaire, including information on socio-demographic characteristics, anthropometric measures, life-style habits, such as tobacco smoking and alcohol drinking, a personal

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medical history and family history of cancer in first-degree relatives.

The subjects' usual diet during the 2 years prior to cancer diagnosis or hospital admission (for controls) was investigated through an interview-administered food frequency questionnaire (FFQ), previously tested for validity (Decarli *et al*, 1996) and reproducibility (Franceschi *et al*, 1993). The FFQ included 78 foods and beverages, as well as a range of recipes, grouped into seven sections: (i) bread and cereal dishes (first courses); (ii) meat and other main dishes (second courses); (iii) vegetables (side dishes); (iv) fruit; (v) sweets, desserts and soft drinks; (vi) milk, hot beverages and sweeteners; (vii) alcoholic beverages. Specific questions referred to fried foods, such as beef or veal, fish or shellfish, eggs or omelette and potatoes. No information was available on how long the meat was cooked. Subjects were asked to indicate the average weekly frequency of consumption of each dietary item; intakes lower than once a week, but at least once a month, were coded as 0.5 per week. To estimate total energy intake an Italian food composition database was used (Salvini *et al*, 1996). Further questions aimed to assess the fat intake pattern were also included in the questionnaire, and used to derive quantitative estimates of intake of various seasoning fats.

Odds ratios (OR) and the corresponding 95% confidence intervals (CI) for each category of intake of fried foods (low, medium, high) were estimated using unconditional multiple logistic regression models (Breslow and Day, 1980). All models were adjusted for age, sex, area of residence, years of education, tobacco smoking, alcohol drinking, and non-alcohol energy intake (Willett and Stampfer, 1986). Tests for trend were based on the likelihood ratio test between models with and without a linear term for each food group.

## RESULTS

Table 1 gives the distribution of 527 laryngeal cancer cases and 1297 controls, and the corresponding ORs according to level of intake of fried foods. A significantly increased risk of laryngeal

cancer was found for all the fried foods examined: the ORs for the highest level of consumption compared to the lowest one was 1.63 for beef or veal, 3.06 for fish or shellfish, 1.85 for eggs or omelette and 1.86 for potatoes. The trends in risk were highly significant for all the food items considered, with the exception of potatoes. Since a high intake of fried foods may simply be a marker of a low vegetable and fruit consumption – found to be strongly inversely related to laryngeal cancer risk in our dataset – the association of fried foods and laryngeal cancer was also evaluated after further adjustment for vegetable and fruit intake. The risk estimates were however not meaningfully modified. The associations between fried foods and laryngeal cancer risk was similar in various subsites, although higher ORs were observed for supraglottis than for glottis and others or unspecified sites.

Table 2 shows the ORs for an increment of 1 weekly portion of fried meat or fish in strata of selected covariates. A consistent increased risk was observed in each stratum of age, alcohol drinking, tobacco smoking and body mass index. However, the association between the consumption of fried meat or fish was apparently stronger in older subjects ( $\geq 60$  years) in those with higher alcohol consumption ( $\geq 28$  drinks/week), in smokers or ex-smokers of less than 20 years, and subjects with a higher body mass index ( $\geq 26$  kg m<sup>-2</sup>).

## DISCUSSION

Our study suggests that consumption of fried foods is directly related to the risk of laryngeal cancer. A similar finding has been reported in another study which considered fried meat in relation to cancer of the larynx (Zheng *et al*, 1992), although there is evidence of a positive association between fried foods and cancer of the colorectum, stomach, as well as other neoplasms (IARC, 1993; Steineck *et al*, 1993). The associations between fried protein-rich foods and digestive tract cancers have been mainly attributed to the presence of genotoxic and mutagenic HA produced in cooked foods, particularly when a high temperature is reached, as in the case of frying (Övervik and Gustafsson,

**Table 1** Odds ratios<sup>a</sup> (OR) and corresponding 95% confidence intervals (CI) according to fried food consumption, among 527 laryngeal cancer cases and 1297 controls. Italy and Switzerland, 1992–2000

Fried food (servings per week)	Level of intake			$\chi^2$ trend (P value)
	Low <sup>b</sup>	Medium	High	
<b>Beef/veal</b>				
Upper limit	0.4	0.9	2.5	
Cases/Controls	252/815	153/304	122/178	
OR	1	1.89	1.63	13.25
(95% CI)		(1.40–2.55)	(1.17–2.28)	(0.003)
<b>Fish/shellfish</b>				
Upper limit	0.4	0.9	2	
Cases/Controls	196/800	189/314	142/183	
OR	1	2.39	3.06	51.90
(95% CI)		(1.79–3.20)	(2.19–4.27)	(<0.0001)
<b>Eggs/Omelette</b>				
Upper limit	0.4	0.9	7	
Cases/Controls	138/543	135/269	254/485	
OR	1	1.96	1.85	15.63
(95% CI)		(1.40–2.75)	(1.38–2.49)	(<0.0001)
<b>Potatoes</b>				
Upper limit	0.9	1.9	4	
Cases/Controls	269/747	148/377	110/173	
OR	1	0.86	1.86	5.54
(95% CI)		(0.64–1.14)	(1.29–2.68)	(0.019)

<sup>a</sup>Estimates from unconditional logistic regression adjusted for sex, age (5-year groups), centre, years of education (<7, 7–11,  $\geq 12$ ), tobacco smoking (never, ex-smoker, current smokers of <15, 15–24,  $\geq 25$  cigarettes/day), alcohol drinking (<14, 14–27, 28–55,  $\geq 56$  drinks/day) and non-alcohol energy intake (quintiles). <sup>b</sup>Reference category.

**Table 2** Odds ratios<sup>a</sup> (OR) and corresponding 95% confidence intervals (CI) according to selected fried food consumption in strata of covariates, among 527 laryngeal cancer cases and 1297 controls. Italy and Switzerland, 1992–2000.

Fried food	OR <sup>a</sup> (95% CI)							
	Age (years)		Alcohol (drinks/week)		Tobacco smoking		Body mass index (kg m <sup>-2</sup> )	
	< 60	≥ 60	< 28	≥ 28	Non-smoker <sup>b</sup>	Smoker <sup>c</sup>	< 26	≥ 26
Beef/veal	1.52 (1.03–2.24)	1.53 (1.08–2.17)	1.26 (0.80–1.98)	1.68 (1.21–2.33)	1.15 (0.66–2.01)	1.67 (1.23–2.26)	1.64 (1.15–2.34)	1.40 (0.94–2.07)
Fish/shellfish	2.22 (1.47–3.36)	3.10 (2.11–4.55)	2.05 (1.27–3.29)	3.07 (2.14–4.39)	1.74 (0.96–3.20)	3.05 (2.20–4.23)	3.22 (2.15–4.82)	2.31 (1.56–3.43)

<sup>a</sup>For an intake increase of one serving per week; estimates from unconditional logistic regression adjusted for sex, age (5-year groups), centre, years of education (<7, 7–11, 12), tobacco smoking (never, ex-smoker, current smokers of <15, 15–24, ≥25 cigarettes/day), alcohol drinking (<14, 14–27, 28–55, ≥56 drinks/day) and non-alcohol energy intake (quintiles). <sup>b</sup>Including never smokers and ex-smokers for 20 or more years. <sup>c</sup>Including smokers and ex-smokers for less than 20 years.

1990; Layton *et al*, 1995; Skog *et al*, 1998; Sinha *et al*, 1998b). How these compounds could be involved in laryngeal carcinogenesis is less clear, although they may exert a particular effect on the tissues lining the upper aerodigestive tract, which enters in direct contact with them. Similar increased risks in relation to fried foods has also been observed in a companion case–control study of oral cancer (Franceschi *et al*, 1999), where the ORs for the highest level of consumption were 1.3 for meat, 1.2 for fish, 1.7 for eggs, and 1.4 for potatoes. Along the same line, there is the evidence of an excess lung cancer risk for exposure to HA from meats in rodents (Ohgaki *et al*, 1987) and humans (Sinha *et al*, 2000).

The role of HA could not explain the association found for fried potatoes, since they are produced essentially in the presence of protein. Fried potatoes, however, has been found to contain appreciable amounts of acrylamide, a chemical classified as a probable human carcinogen (IARC, 1994).

Factors other than the mutagenic activity of HA could also explain or confound the positive association of fried foods and laryngeal cancer. Meat and eggs themselves, irrespective of cooking methods, could be related to laryngeal cancer risk. In our data, however, the association of laryngeal cancer risk with meat or egg items consumed boiled was less strong than that with fried items, whereas no association was found for boiled fish or shellfish (Bosetti *et al*, 2002).

The role of fat for frying is a possible explanation of the increased risk observed. In particular mixed (unspecified) seed oils, frequently used for frying, have been shown in our dataset to be positively related to laryngeal cancer risk (Bosetti *et al*, 2002), and they could, at least in part, explain the positive association of fried foods. Furthermore, oils rich in n-6 polyunsaturated fats could be directly involved in the mutagenic activity of HA, enhancing their action through a promoting effect, more than other monounsaturated fats such as olive oil (Weisburger, 2000). However, the estimates for fried food consumption were only attenuated, but not materially modified, after further adjustment for consumption of mixed seed oils.

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The hospital-based setting is a potential limitation of our study, since hospital controls may not be comparable with cases. However, controls were selected among patients with admission diagnosis not related to tobacco smoking, alcohol drinking and diet modifications. Moreover, in order to reduce any information bias, the questionnaire was administered to both cases and controls by the same interviewers and under similar conditions, and the food frequency intake for subjects interviewed at home was well comparable with that obtained at hospital (D'Avanzo *et al*, 1997).

The high participation rate of cases and controls, the comparable catchment areas of study subjects, the careful adjustment for tobacco and alcohol, as well as other potential confounding factors, are among the strengths of the study. Moreover, the use of FFQ, reported to be satisfactorily valid (Decarli *et al*, 1996) and reproducible (Franceschi *et al*, 1993), allowed to take into account the full dietary pattern, and to adjust for total energy intake (Willett and Stampfer, 1986).

In conclusion, our analysis suggests that the consumption of fried foods, irrespective of the content of foods, might be associated with an excess in laryngeal cancer risk. Selection, information bias or confounding are unlikely to explain this association, and its strength indicates that it is unlikely to be due to chance alone. In the absence of simple biological mechanisms, it is however unclear whether this implies causation, or a non-specific association with a poorer diet (La Vecchia *et al*, 1990).

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