

## Short Communication

# Oesophageal cancer in women: tobacco, alcohol, nutritional and hormonal factors

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**Summary** We analysed 3 case–control studies from Italy and Switzerland including 114 women with squamous cell oesophageal cancer and 425 controls. The multivariate odds ratio was 4.5 for heavy smoking and 5.4 for heavy alcohol drinking. Fruit intake, vegetable intake, oral contraceptive and HRT use were inversely related to oesophageal cancer. © 2001 Cancer Research Campaign <http://www.bjcancer.com>

**Keywords:** oesophageal cancer; female; alcohol drinking; smoking; diet; case–control studies

Squamous cell oesophageal cancer is relatively rare in women in developed countries, so, not surprisingly, most published data relate to men. In several countries, however, oesophageal cancer rates in women have tended to increase over the last few decades (Launoy et al, 1994; Negri et al, 1996; Desoubreaux et al, 1999; Levi et al, 1999). Among studies providing data on women, one from Italy (Tavani et al, 1993) and another from South America (Castellsagué et al, 1999), showed strong associations with alcohol and tobacco consumption. The relative risks for the highest level of alcohol consumption were around 2, and those for the highest level of tobacco consumption between 3 and 5 in both studies, apparently lower than those reported for men (Franceschi et al, 1990; Castellsagué et al, 1999). A case–control study from Shanghai, China, estimated that cigarette smoking accounted for 50% of oesophageal cancers in men, but only 14% in women (Gao et al, 1994). Among other factors investigated, hot mate drinking was strongly associated with oesophageal cancer in women in South America (Castellsagué et al, 2000), and a diet poor in fresh fruit or vegetables was directly related to risk in an Italian study (Tavani et al, 1993).

A role of female hormones has been suggested for several digestive tract cancers, including oral cavity (Bosetti et al, 2000a), stomach (La Vecchia et al, 1994) and colo-rectum (Fernandez et al, 2000). Little information, however, is available on any potential effect of female hormones on oesophageal carcinogenesis (IARC, 1999).

## SUBJECTS AND METHODS

The current analysis is based on data from 3 case–control studies of squamous cell oesophageal cancer, the first conducted in

1984–93 in the provinces of Milan and Pordenone (Fioretti et al, 1997), the second in 1992–97 in the provinces of Padua and Pordenone, and the greater Milan area, northern Italy (Franceschi et al, 2000), and the third, in 1992–99, in the Swiss Canton of Vaud (Levi et al, 2000). Data collected in Italy before 1991 have already been published (Tavani et al, 1993).

Cases considered in the present report were 114 women under 79 years (median age 63 years), with newly diagnosed histologically confirmed squamous cell oesophageal cancer, admitted to the major hospitals in the areas under study. Controls were 425 women (median age 62 years), admitted for acute, non-neoplastic conditions to the same hospitals. 40% of the controls were admitted for trauma, 21% for non-traumatic orthopaedic conditions, 24% for acute surgical disorders and 15% for miscellaneous other illnesses (including skin, eye, or ear disorders). Controls were frequency matched to cases by quinquennia of age and study centre, with a control-to-case ratio of 4, whenever possible.

Trained interviewers collected data using structured questionnaires, including information on socio-demographic characteristics, lifestyle habits, such as smoking and alcohol consumption, frequency of intake of selected food items, including major sources of carotene and retinol, menstrual, reproductive and hormonal factors, including lifelong use of oral contraceptives (OC) and hormone replacement therapy (HRT) during menopause. Reproducibility of the questionnaires was satisfactory (D'Avanzo et al, 1996, 1997). The questionnaire of the most recent study included more detailed and validated information about diet, in order to obtain estimates of the intake of several other nutrients (Franceschi et al, 1995; Decarli et al, 1996).

Cut-off points of the tertiles, based on discrete distributions of various foods and nutrients, were computed separately for the 3 studies. Odds ratios (ORs), and corresponding 95% confidence intervals (CI), were estimated using multiple logistic regression models (Breslow and Day, 1980) conditioned for age and study centre, and including terms for education, body mass index (BMI), non alcohol energy intake, tobacco and alcohol consumption.

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**Table 1** Distribution of 114 female cases of oesophageal cancer and 425 controls according to age, education, and selected variables and corresponding odds ratios (OR) and 95% confidence intervals (CI), 1984–1999

	Cases n (%)	Controls n (%)	OR <sup>a</sup> (95% CI)
Age			
<50	17 (14.9)	60 (14.1)	
50–54	12 (10.5)	41 (9.7)	
55–59	16 (14.0)	62 (14.6)	
60–64	28 (24.6)	108 (25.4)	
65–69	14 (12.3)	59 (13.9)	
≥70	27 (23.7)	95 (22.4)	
Education (years)			
<7	66 (57.9)	234 (55.1)	1 <sup>b</sup>
7–11	33 (29.0)	123 (28.9)	0.49 (0.26–0.92)
≥12	15 (13.2)	68 (16.0)	0.36 (0.16–0.80)
χ <sup>2</sup> trend			7.89 ( <i>P</i> = 0.005)
Smoking habit			
Never smoker	52 (45.6)	295 (69.4)	1 <sup>b</sup>
Ex-smoker	9 (7.9)	45 (10.6)	0.86 (0.35–2.09)
Current smoker (cigarettes/day)			
<15	16 (14.0)	45 (10.6)	1.74 (0.88–3.44)
15–24	25 (21.9)	32 (7.5)	3.51 (1.76–7.01)
≥25	12 (10.5)	8 (1.9)	4.54 (1.40–14.74)
χ <sup>2</sup> trend <sup>c</sup>			15.45 ( <i>P</i> < 0.001)
Alcohol intake (drinks/day)			
<1	29 (25.4)	204 (48.0)	1 <sup>b</sup>
1–2	50 (43.9)	181 (42.6)	1.99 (1.15–3.44)
≥3	35 (30.7)	40 (9.4)	5.40 (2.70–10.80)
χ <sup>2</sup> trend			22.01 ( <i>P</i> < 0.001)
Body mass index (kg/m <sup>2</sup> ) <sup>d</sup>			
<23	71 (62.3)	145 (34.4)	1 <sup>b</sup>
23–<26	20 (17.5)	120 (28.5)	0.25 (0.13–0.48)
≥26	23 (20.2)	156 (37.1)	0.28 (0.15–0.51)
χ <sup>2</sup> trend			19.97 ( <i>P</i> < 0.001)

<sup>a</sup>Estimates from multiple logistic regression models, conditioned for quinquennia of age and study centre, and including terms for education, body mass index, non-alcohol energy intake, tobacco and alcohol consumption. <sup>b</sup>Reference category. <sup>c</sup>Omitting ex-smokers. <sup>d</sup>The sum does not add up to the total because of some missing values.

## RESULTS

Table 1 shows the distribution of cases of squamous cell oesophageal cancer and controls according to age, education and selected characteristics. Cases were significantly less educated than controls (OR 0.36 for education ≥ 12 years compared to < 7 years), more frequently current smokers (OR 4.5 for ≥ 25 cigarettes per day), and heavy alcohol drinkers (OR 5.4 for ≥ 3 drinks per day). An inverse relation was observed with BMI (for the highest level, OR 0.28).

Table 2 gives the distribution of cases and controls by approximate tertiles of consumption of selected foods and micronutrients. Green vegetables, fresh fruit and carotene showed an inverse relation. For the highest tertile of intake compared to the lowest, the ORs were 0.45 for vegetables, 0.43 for fruit and 0.45 for carotene. There was no association with retinol intake.

Table 3 shows the distribution of cases and controls interviewed after 1992 by tertiles of olive oil and butter consumption and of several other nutrients. Most nutrients considered tended to be inversely related to the risk of oesophageal cancer, and the OR for the highest tertile of intake was 0.80 for lycopene, 0.85 for vitamin C, 0.59 for vitamin E, 0.11 for vitamin B6, 0.32 for folic acid, 0.34 for niacin and 0.57 for monounsaturated fatty acids, though the trend

in risk was significant only for vitamin B6, possibly because of the small numbers. Olive oil consumption showed a non-significant inverse relation (OR = 0.67), while butter consumption showed a positive but also non-significant relation (OR = 2.2).

The relation between oesophageal cancer risk and selected menstrual, reproductive and hormonal factors is shown in Table 4. The OR was higher for parous than for nulliparous women, but there was no significant trend in risk with parity. No association was observed with age at menarche, menopausal status and number of abortions. Cases reported earlier age at menopause (*P* for trend, 0.01). OC and HRT use were inversely associated to oesophageal cancer risk; for ever OC users the OR was 0.24, and for ever HRT users 0.32.

Table 5 shows the combined effect of alcohol intake and certain other factors. For the combined exposure of heavy drinking with heavy smoking the OR was 12.8, with low BMI was 10.1, with low vegetable intake was 8.9, and with low fruit intake was 13.9.

## DISCUSSION

This study, based on one of the largest datasets on squamous cell oesophageal cancer in women, confirms that in northern Italy and Switzerland tobacco smoking and alcohol drinking are the most

**Table 2** Odds ratios (OR) and 95% confidence intervals (CI) of oesophageal cancer according to intake of green vegetables, fresh fruit, retinol, and carotene, 1984–1999

	Tertiles, cases: controls, OR <sup>a</sup> (95% CI)			$\chi^2$ trend (P)
	1 (low)	2	3 (high)	
Green vegetables <sup>b</sup>	41 : 84 1 <sup>c</sup>	21 : 90 0.61 (0.30–1.25)	49 : 237 0.45 (0.24–0.85)	5.93 (0.01)
Fresh fruit	40 : 92 1 <sup>c</sup>	42 : 145 0.81 (0.44–1.51)	32 : 188 0.43 (0.22–0.85)	6.23 (0.01)
Retinol	30 : 150 1 <sup>c</sup>	43 : 137 1.53 (0.84–2.78)	41 : 138 1.40 (0.75–2.62)	1.03 (0.31)
Carotene	50 : 139 1 <sup>c</sup>	38 : 134 0.83 (0.45–1.53)	26 : 152 0.45 (0.22–0.91)	4.83 (0.03)

<sup>a</sup>Estimates from multiple logistic regression models, conditioned by age and study centre, including terms for education, body mass index, non alcohol energy intake, tobacco and alcohol consumption. <sup>b</sup>The sum does not add up to the total because of some missing values.

<sup>c</sup>Reference category.

**Table 3** Odds ratios (OR) and 95% confidence intervals (CI) of 47 female cases of oesophageal cancer and 157 controls, according to intake of selected nutrients, olive oil and butter, 1992–1999

	Tertiles, cases: controls, OR <sup>a</sup> (95% CI)			$\chi^2$ trend (P)
	1 (low)	2	3 (high)	
Lycopene	18 : 50 1 <sup>b</sup>	13 : 55 1.05 (0.35–3.10)	16 : 52 0.80 (0.25–2.57)	0.15 (0.70)
Vitamin C	19 : 48 1 <sup>b</sup>	14 : 54 0.65 (0.23–1.84)	14 : 55 0.85 (0.29–2.54)	0.10 (0.75)
Vitamin E	15 : 53 1 <sup>b</sup>	15 : 53 0.85 (0.26–2.71)	17 : 51 0.59 (0.16–2.21)	0.65 (0.42)
Vitamin B6	18 : 52 1 <sup>b</sup>	14 : 52 0.26 (0.07–0.95)	15 : 53 0.11 (0.02–0.54)	7.32 (< 0.01)
Folic acid	17 : 50 1 <sup>b</sup>	12 : 56 0.43 (0.13–1.44)	18 : 51 0.32 (0.07–1.43)	2.10 (0.15)
Niacin	17 : 50 1 <sup>b</sup>	14 : 56 0.34 (0.10–1.09)	16 : 51 0.34 (0.10–1.16)	2.94 (0.09)
Monounsaturated fatty acids	14 : 53 1 <sup>b</sup>	15 : 53 0.47 (0.12–1.90)	18 : 51 0.57 (0.12–2.81)	0.20 (0.65)
Olive oil	19 : 49 1 <sup>b</sup>	12 : 53 0.41 (0.13–1.26)	16 : 55 0.67 (0.23–1.95)	0.63 (0.43)
Butter	10 : 58 1 <sup>b</sup>	17 : 54 1.34 (0.47–3.80)	20 : 45 2.20 (0.73–6.65)	1.93 (0.17)

<sup>a</sup>Estimates from multiple logistic regression models, conditioned by age and study centre, and including terms for education, body mass index, non alcohol energy intake, tobacco and alcohol consumption. <sup>b</sup>Reference category.

important risk factors for this neoplasm in women as they are for men (Negri et al, 1992). In a study from northern Italy, the OR for men was 4.7 for heavy smokers and 6.0 for heavy drinkers (Franceschi et al, 1990). Although reported levels of alcohol consumption differ between men and women, our investigation indicates that, for highest levels of alcohol and tobacco consumption, the relative risks of oesophageal cancer are comparable in women and in men, as with smoking and lung and other tobacco-related neoplasms (Doll et al, 1980). This study confirms that women with oesophageal cancer tend to be less educated than controls (Tavani et al, 1993). Further, the present data indicate that cases have a lower BMI, though this could be partly a consequence of the cancer. Low BMI in the few years before diagnosis may be associated with decreased intake of protective nutrients. However,

allowance for selected dietary indicators did not appreciably modify the association (Gallus et al, 2001). Our investigation also provides additional evidence that green vegetables, fresh fruit (Tavani et al, 1993; Castellsagué et al, 2000) and, consequently, carotene (Tavani et al, 1993) have a favourable effect on oesophageal cancer. The simultaneous exposure to alcohol and BMI, green vegetables or fruit seems to have an additive effect on oesophageal cancer (Breslow and Day, 1980). In contrast, simultaneous exposure to alcohol and tobacco has a multiplicative effect on oesophageal cancer, for women, as for men (Tuyns et al, 1977; Castellsagué et al, 1999). According to the multistage theory of carcinogenesis (Day and Brown, 1980), therefore, alcohol and tobacco would appear to act on different stages of the process, whereas alcohol and nutritional factors may act on the same

**Table 4** Distribution of 114 women with oesophageal cancer and 425 controls according to gynecologic and hormonal factors, and corresponding odds ratio (OR) and 95% confidence interval (CI), 1984–1999

	Cases	Controls	OR <sup>a</sup> (95% CI)
Age at menarche <sup>b</sup>			
<12	17	65	1 <sup>c</sup>
12–13	52	162	0.84 (0.40–1.73)
≥14	44	198	0.60 (0.29–1.23)
χ <sup>2</sup> trend			2.51 (P = 0.11)
Menopausal status <sup>b</sup>			
Pre + peri	19	76	1 <sup>c</sup>
Post	93	349	1.78 (0.56–5.67)
Age at menopause <sup>b,d</sup>			
<45	29	67	1 <sup>c</sup>
45–49	27	80	0.75 (0.36–1.58)
≥50	37	201	0.43 (0.22–0.83)
χ <sup>2</sup> trend			6.61 (P = 0.01)
Number of births <sup>b</sup>			
0	18	88	1 <sup>c</sup>
1	32	86	2.26 (1.03–4.96)
2	39	133	2.22 (1.03–4.79)
≥3	24	115	1.84 (0.82–4.16)
χ <sup>2</sup> trend			1.41 (P = 0.24)
Number of abortions <sup>b</sup>			
0	90	305	1 <sup>c</sup>
≥1	23	117	0.60 (0.33–1.07)
Oral contraceptive use			
Never	110	392	1 <sup>c</sup>
Ever	4	33	0.24 (0.06–0.96)
Hormone replacement therapy use <sup>d</sup>			
Never	89	308	1 <sup>c</sup>
Ever	4	41	0.32 (0.09–1.13)

<sup>a</sup>Estimates from multiple logistic regression models, conditioned by age and study centre, and including terms for age (continuous term), education, body mass index, non alcohol energy intake, tobacco and alcohol consumption. <sup>b</sup>The sum does not add up to the total because of some missing values. <sup>c</sup>Reference category.

<sup>d</sup>Post menopausal women only.

**Table 5** Odds ratios (OR) of oesophageal cancer in women and corresponding 95% confidence intervals (CI) according to the combined effect of alcohol drinking and smoking, BMI, vegetable and fruit intake, 1984–1999

	Drinks/day, cases : controls, OR <sup>a</sup> (95% CI)		
	< 1 drink	1–2 drinks	≥ 3 drinks
Smoking habit			
Never and ex smokers	18 : 165 1 <sup>b</sup>	27:147 1.66 (0.85–3.25)	16 : 28 5.79 (2.48–13.50)
Current smokers	11 : 39 2.25 (0.95–5.33)	23:34 5.52 (2.57–11.85)	19 : 12 12.75 (5.09–31.96)
Body mass index <sup>c</sup>			
≥25 kg/m <sup>2</sup>	8 : 106 1 <sup>b</sup>	8 : 81 1.40 (0.49–4.03)	9 : 15 7.82 (2.44–25.03)
<25 kg/m <sup>2</sup>	21 : 95 3.06 (1.26–7.44)	42 : 99 6.11 (2.62–14.26)	26 : 25 10.12 (3.84–26.72)
Vegetable intake <sup>c</sup>			
High	11 : 116 1 <sup>b</sup>	26 : 115 2.40 (1.08–5.33)	17 : 23 7.50 (2.76–20.37)
Low	17 : 76 2.35 (0.96–5.75)	23 : 64 3.84 (1.59–9.26)	17 : 17 8.94 (3.03–26.38)
Fruit intake			
High	10 : 119 1 <sup>b</sup>	24 : 103 2.95 (1.28–6.79)	10 : 17 5.74 (1.84–17.89)
Low	19 : 85 2.92 (1.20–7.13)	26 : 78 4.00 (1.68–9.55)	25 : 23 13.89 (5.07–38.04)

<sup>a</sup>Estimates from multiple logistic regression models, conditioned by age and study centre, and including terms for education, body mass index, non alcohol energy intake and tobacco consumption. <sup>b</sup>Reference category. <sup>c</sup>The sum does not add up to the total because of some missing values.

stage(s). This again confirms the observations in males (Bosetti et al, 2000b; Franceschi et al, 2000), indicating that similar (dietary) patterns influence the risk of oesophageal cancer in women and men.

This study provides evidence of a potential favourable effect of female exogenous hormones (OC and HRT) (IARC, 1999), and suggests that age at menopause is inversely associated to squamous cell oesophageal cancer risk. This may be related to cigarette smoking, since smokers have earlier menopause (Baron et al, 1990). In contrast with oesophageal adenocarcinoma (Cheng et al, 2000), women with squamous cell oesophageal cancer were more frequently parous. This apparent association may be due to residual confounding by social class, although the social class correlates of oesophageal cancer seem to be changing (Bosetti et al, 2001).

In terms of population attributable risk (PAR) (Bruzzi et al, 1985; Mezzetti et al, 1996), tobacco smoking accounted for 31% of oesophageal cancer in women, alcohol drinking for 46%, and the combination of the 2 factors for 56%. The estimated PARs were 26% for low vegetable intake, 37% for low fruit, and 40% for vegetable and fruit combined. The PAR for the combination of alcohol, tobacco and vegetables was 75% (95% CI: 56–94%).

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