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Attributable Risks for Oesophageal Cancer in Northern Italy

Eva Negri, Carlo La Vecchia, Silvia Franceschi, Adriano Decarli and Paolo Bruzzi

The population attributable risk for oesophageal cancer in relation to cigarette smoking, elevated alcohol use and low beta-carotene intake has been estimated with 300 cases and 1203 controls in Greater Milan. In males 71% of oesophageal cancers were attributable to smoking, 45% to elevated alcohol use and 40% to low beta-carotene consumption. The corresponding figures were 32%, 10% and 29% in females and 61%, 39% and 38% in total. The overall estimate, including the joint effect of the three factors, was 90% in males, 58% in females and 83% in total. The discrepancies between the sums are due to the assumption of a multiplicative model and to the great percentage of oesophageal cancers attributable to each single factor. Cigarette smoking is the major known cause of oesophageal cancer and the three factors account for practically all the difference between male and female mortality rates. Elimination of smoking, reduction of alcohol consumption and enrichment of diet with fruit and vegetables would make oesophageal cancer a rare disease in Italians of both sexes.
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INTRODUCTION

AMONG COMMON neoplasms, oesophageal cancer is the one showing the largest geographical variation, with a several hundred times difference between high risk areas in Iran and low risk ones in north Africa, and also within Europe there is a 25-fold ratio between the highest risk areas in France and the lowest ones in Scandinavia and Eastern Europe [1, 2].

Elevated alcohol and tobacco consumption can explain most of the excess risk in Europe or North America [3]. A study conducted in the French department of Ille-et-Vilaine, for instance, found that over 87% of the cases could be explained by alcohol and tobacco [4]. However, alcohol and tobacco cannot explain the high risk areas in Asia or South Africa [3, 5], and have a quantitatively different role in developed countries, too. Thus, factors other than alcohol and tobacco, such as, for instance, a diet poor in fresh fruit and vegetables, may influence—to a variable degree—oesophageal cancer risk in Europe [6, 7].

We have therefore tried to quantify the role of tobacco, alcohol and dietary deficiencies on oesophageal cancer risk in males and females in a northern Italian population, using data from a large case-control study.

SUBJECTS AND METHODS

Since January 1984 we have been conducting a case-control study of oesophageal cancer in the greater Milan area, whose

general design and methods have been previously described [7, 8]. Briefly, trained interviewers identified and questioned cases and controls using a structured questionnaire. Less than 3% of eligible subjects (cases and controls) refused to be interviewed. The present report is based on data collected before December 1990.

Cases

The cases studied were patients below age 75, residing in the greater Milan area with histologically confirmed newly diagnosed cancer of the oesophagus, admitted to the National Cancer Institute, several university clinics (chiefly of surgery) and the Ospedale Maggiore, which includes the four largest teaching and general hospitals in Milan. A total of 300 cases (244 males, 56 females, aged 29 to 74, median age 60 years) were interviewed.

Controls

Patients residing in the greater Milan area who were admitted for acute conditions to several specialised university clinics or to the Ospedale Maggiore of Milan were eligible as controls. They had diseases other than malignant or digestive, and unrelated to alcohol or tobacco. Among 1203 control subjects (901 males, 302 females, aged 25 to 74, median age 55 years), 34% were admitted for traumas, 26% for non-traumatic orthopaedic conditions, 28% had acute surgical disease (including plastic surgery), and 12% various other diseases (acute infections, diseases of the skin, eye, etc.).

Information was collected on socio-demographic factors, personal characteristics and habits, related medical history, use of tobacco, alcohol, and ten indicator foods, including the major sources of beta-carotene (pro-vitamin A) in the Italian diet. From these data, total alcohol consumption was computed as the mean number of alcoholic beverages (wine, beer and spirits) per day, almost 90% of all alcohol intake being accounted for by wine alone. An index of beta-carotene intake was computed using tables from the Italian Department of Agriculture [9]. This index can however be simply viewed as a weighted measure of vegetable and fruit intake.

Relative risks of oesophageal cancer in relation to tobacco, alcohol and beta-carotene intake were computed after allowance for (i) quinquennia of age, sex (when required) and education as a measure of social class, and (ii) the above mentioned variables plus simultaneously the three factors considered, using unconditional multiple logistic regression, fitted by the method of maximum likelihood [10, 11].

On the basis of these logistic models, the population attributable risk percentage (aetiological fraction, attributable fraction) was obtained. This measure represents the fraction of total disease experienced in this population that would not have occurred if the effect(s) associated with the risk factor(s) of interest were absent, and is a useful measure of public health and prevention relevance. Under a multiplicative model of disease aetiology, attributable risk for any given set of risk factors can be computed using the multivariate relative risk (RR) estimates and the distribution of this factors among cases only. In the absence of statistically significant deviations from a multiplicative model, the RR's for combined exposures were computed by simply multiplying the estimated risks of the main effects. Thus, using the multivariate relative risks, population attributable risks were computed for each separate factor, and for various combinations of them, after allowance for confounding [12]. The method requires information only on the joint distribution of the risk factors among cases and on the adjusted relative risk associated with each risk factor. Provided that

Table 1. Distribution of 300 cases of oesophageal cancer and 1203 controls according to sex, age and education. Milan, Italy, 1984–1990

	Males		Females	
	Cases	Controls	Cases	Controls
Age group (years)				
<50	31 (12.7)	317 (35.2)	10 (17.9)	79 (26.2)
50–59	92 (37.7)	293 (32.5)	12 (21.4)	79 (26.2)
60–69	98 (40.2)	207 (23.0)	21 (37.5)	91 (30.1)
70–74	23 (9.4)	84 (9.3)	13 (23.2)	53 (17.5)
Education (years)				
<7	169 (69.3)	407 (45.2)	36 (64.3)	162 (53.6)
7–11	44 (18.0)	275 (30.5)	11 (19.6)	85 (28.1)
≥12	29 (11.9)	213 (23.6)	9 (16.1)	53 (17.5)
Undefined	2 (0.8)	6 (0.7)	—	2 (0.7)
Total	244	901	56	302

No. (%).

Table 2. Distribution of 300 cases of oesophageal cancer and 1203 controls according to sex, tobacco, alcohol and beta-carotene consumption. Milan, Italy, 1984–1990

	Males		Females	
	Cases	Controls	Cases	Controls
Tobacco consumption				
Never smokers	16 (6.6)	228 (25.3)	28 (50.0)	207 (68.5)
Ex/moderate smokers (<15 cigarettes/day)	96 (39.3)	361 (40.1)	12 (21.4)	63 (20.9)
Heavy smokers	132 (54.1)	312 (34.6)	16 (28.6)	32 (10.6)
Alcohol consumption (drinks per day)				
<4	63 (25.8)	475 (52.7)	48 (85.7)	285 (94.4)
4–6	50 (20.5)	229 (25.4)	8 (14.3)	17 (5.6)
>6	131 (53.7)	197 (21.9)		
Beta-carotene (tertile of intake)				
1 (High)*	47 (19.3)	318 (35.3)	15 (26.8)	123 (40.7)
2	66 (27.0)	314 (34.9)	18 (32.1)	105 (34.8)
3 (Low)	131 (53.7)	269 (29.9)	23 (41.1)	74 (24.5)

*Cut-off points, in thousand international units 104, 156, intake per month.
No. (%).

Correspondence to E. Negri.
E. Negri and C. La Vecchia are at the Istituto di Ricerche Farmacologiche "Mario Negri", Via Eritrea 62, 20157 Milano, Italy; C. La Vecchia is also at the Institute of Social and Preventative Medicine, University of Lausanne, 1005 Lausanne, Switzerland; S. Franceschi is at the Servizio di Epidemiologia, Centro Riferimento Oncologico, 33081 Aviano (PN), Italy; A. Decarli is at the Istituto di Biometria e Statistica Medica, Università di Milano, 20133 Milano, and Istituto di Statistica, Università di Trento, 38100 Trento, Italy; and P. Bruzzi is at the Istituto Nazionale per la Ricerca sul Cancro, Genova, Italy.
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Table 3. Relative risk estimates (and 95% confidence intervals) of oesophageal cancer in relation to tobacco, alcohol, and beta-carotene consumption. Milan, Italy, 1984–1990

	Males		Females		Total	
	RR*	RR†	RR*	RR†	RR*	RR†
Tobacco consumption						
Never smokers	1‡	1‡	1‡	1‡	1‡	1‡
Ex/moderate smokers	3.4	3.5	1.8	1.8	2.8	2.8
(<15 cigarettes/day)	(1.9–6.0)	(1.9–6.3)	(0.8–3.9)	(0.8–4.0)	(1.8–4.2)	(1.8–4.3)
Heavy smokers	6.2	5.1	5.2	4.8	5.4	4.3
	(3.5–10.9)	(2.9–9.0)	(2.4–11.5)	(2.1–10.7)	(3.6–9.2)	(2.8–6.6)
χ^2_1 (trend)	52.94	32.63	15.98	13.83	71.17	45.77
	($P < 0.001$)	($P < 0.001$)	($P < 0.001$)	($P < 0.001$)	($P < 0.001$)	($P < 0.001$)
Alcohol consumption (drinks per day)						
<4	1‡	1‡	1‡	1‡	1‡	1‡
4–6	1.6	1.5	2.2	2.2	1.7	1.6
	(1.0–2.4)	(0.9–2.2)	(1.1–4.3)	(1.0–4.3)	(1.2–2.6)	(1.1–2.4)
>6	4.2	3.5			4.4	3.5
	(3.0–6.1)	(2.4–5.1)			(3.1–6.2)	(2.5–5.1)
χ^2_1 (trend)	65.66	44.27	4.53	3.76	71.08	48.37
	($P < 0.001$)	($P < 0.001$)	($P = 0.04$)	($P = 0.05$)	($P < 0.001$)	($P < 0.001$)
Beta-carotene intake (tertile)						
1 (high)	1‡	1‡	1‡	1‡	1‡	1‡
2	1.4	1.3	1.4	1.3	1.4	1.3
	(0.9–2.0)	(0.8–2.1)	(0.7–3.0)	(0.5–2.7)	(1.0–2.0)	(0.9–2.9)
3	3.1	2.6	2.7	2.2	3.1	2.5
	(2.1–4.6)	(1.7–3.9)	(1.3–5.6)	(1.0–4.8)	(2.2–4.3)	(1.8–2.5)
χ^2_1 (trend)	39.46	24.35	7.17	4.42	48.73	29.20
	($P < 0.001$)	($P < 0.001$)	($P < 0.01$)	($P = 0.04$)	($P < 0.001$)	($P < 0.001$)

*Adjusted for age, sex (when required) and education.
†Adjusted for age, sex (when required), education, plus the above listed variables.
‡Reference category.

unbiased relative risk estimates are obtained and that the cases can be assumed to be representative of cases in the population in terms of exposure distribution, this method can be applied to data from hospital-based case-control studies.

RESULTS

Table 1 gives the distribution of oesophageal cancer cases according to sex, age group and education. In both sexes, cases were older than the comparison group, and significantly less educated. Thus, allowance for these variables was made in all analyses.

Tobacco, alcohol and beta-carotene consumption are considered in Table 2 in terms of distribution of cases and controls for each sex, and in Table 3 in terms of relative risk estimates. Compared with never smokers, the relative risk was about 3 in both sexes combined for moderate (<15 cigarettes/day) or ex-smokers, and around 5 for heavy smokers (≥15 cigarettes, pipe or cigar). Heavy alcohol consumption (over 6 drinks per day) was reported by 54% of male cases and 22% of male controls, but was very rare among females. In males, the relative risk was 1.6 for intermediate as compared with abstainers or moderate alcohol drinkers, and 4.2 for heavy drinkers. Among females, the two highest categories were combined, giving a relative risk of 2.2 as compared with the lowest one. In relation to the index of beta-carotene intake, compared with the highest tertile the relative risk was around 1.4 in both sexes for the intermediate, and around 3 for the lowest one. Since the three risk factors considered were correlated, the estimates from the model including simultaneously terms for all these factors were somewhat lower than the ones adjusted for age and education only, but all the trends in risk remained statistically significant.

Table 4 gives the number of cases and the estimated relative risks in all combinations of level of consumption of alcohol, tobacco and beta-carotene, assuming that these factors act multiplicatively on the relative risk. Compared with the lowest risk category (non-smokers, moderate alcohol drinkers and high beta-carotene consumers) the relative risk rose up to 45.9 for males and to 36.4 for females who were heavy drinkers, heavy smokers and had a diet poor in beta-carotene. There were 45 cases (15.0%) in this category.

Only 1 male (0.4%) and 6 female (10.7%) cases were in the lowest risk category for all the three factors considered.

The estimated attributable risks for the three factors and their combinations are presented in Table 5. Tobacco was the single cause with the highest percentage of attributable cases in each sex (71% in males and 32% in females) and, hence, in both sexes combined (61%). The highest percentage of attributable cases for two factors was attributable to tobacco and and alcohol in males (84%) and to tobacco and beta-carotene in women (53%). Together the three factors accounted for 83% of the cases (90% for males and 58% for females).

DISCUSSION

In this study from a northern Italian population, smoking, high alcohol consumption and a diet poor in beta-carotene (i.e.

Table 4. Estimated relative risks, assuming a multiplicative model, for various combinations of consumption of alcohol, tobacco and beta-carotene. Milan, Italy 1984–1990*

Risk level for†			Relative risk (no. of cases)		
Alcohol	Tobacco	Beta-carotene	Males	Females	Total
–	–	–	1 ‡(1)	1 ‡(6)	1 ‡(7)
+	–	–	1.5 (0)		1.6 (2)
				3.9 (2)	
++	–	–	3.5 (1)		3.5 (1)
–	+	–	3.5 (8)	1.8 (2)	2.8(10)
+	+	–	5.1 (4)		4.5 (4)
				6.1 (0)	
++	+	–	12.2 (9)		3.8 (9)
–	++	–	5.1 (6)	4.8 (5)	4.3(11)
+	++	–	7.4 (6)		6.9 (6)
				16.2 (0)	
++	++	–	17.7(12)		15.3(12)
–	–	+	1.3 (2)	1.3 (7)	1.3 (9)
+	–	+	2.0 (1)		2.1 (1)
				4.3 (0)	
++	–	+	4.6 (3)		4.7 (3)
–	+	+	4.7 (7)	2.3 (4)	3.6(11)
+	+	+	6.8 (7)		5.9 (7)
				7.8 (1)	
++	+	+	16.2(15)		12.9(16)
–	++	+	6.7(11)	6.0 (5)	5.7(16)
+	++	+	9.9 (2)		9.1 (3)
				20.40(1)	
++	++	+	23.5(18)		20.1(18)
–	–	++	2.6 (2)	2.3(10)	2.5(12)
+	–	++	3.8 (3)		4.1 (5)
				7.6 (3)	
++	–	++	9.1 (3)		9.0 (4)
–	+	++	9.1 (8)	4.1 (4)	7.0(12)
+	+	++	13.3(13)		11.3(14)
				13.8 (1)	
++	+	++	31.7(25)		24.8(25)
–	++	++	13.2(18)	10.7 (5)	10.9(23)
+	++	++	19.2(14)		17.5(14)
				36.4 (0)	
++	++	++	45.9(45)		38.5(45)

*See Subjects and Methods for the description of the model used.
†Represents the category with lowest risk, + the medium risk and ++ the highest risk category (See Table 3 for the cutpoints).
‡Reference category.

Table 5. Attributable risk percentages of oesophageal cancer in relation to selected risk factors and their combination. Milan, Italy 1984–1990

Factor	Attributable risk percentage		
	Males	Females	Total
Smoking	71	32	61
Alcohol	45	10	39
Beta-carotene	40	29	38
Smoking + beta-carotene	83	53	75
Smoking + alcohol	84	40	74
Alcohol + beta-carotene	66	36	61
Smoking + alcohol + beta-carotene	90	58	83

an indicator of low intake of vegetables and fruit) are responsible of 83% of oesophageal cancer cases (90% of male and 58% of female cases). 71% of cancers of the oesophagus in males and 32% in females are attributable to tobacco consumption alone.

With reference to the limitations of this study, the use of hospital controls in order to study smoking can be criticised, since smokers tend to be admitted to hospital more frequently than the general population. In the present investigation, however, great attention was paid to excluding patients admitted for diseases related to smoking from the control group, as well as to alcohol consumption and potentially inducing dietary changes.

As concerns recall bias, there is no reason to believe that cases and controls should have reported their consumption of tobacco, alcohol, vegetables and fruit in a different way, since smoking and alcohol drinking are socially acceptable in Italy and the protective effect of fruit and vegetables had not gained a wide popularity at the time of the present data collection. Thus, differential misclassification cannot explain the observed associations. Furthermore, the associations of oesophageal cancer with alcohol and smoking, as they emerge from the present study, have been reported in most previous works [4, 8, 13–24] and can be considered as well established.

Finally, as concerns the representativeness of cases of oesophageal cancer, for the purpose of computing attributable risks, some concern may come from the fact that the Milan area is not covered by a cancer registry and therefore, the proportion of cases collected among all oesophageal cancers is not known. The hospitals included in the present study, however, included the majority of diagnostic and therapeutic facilities in the area under examination and there is no reason to suspect that cancer cases had been differently included in the present investigation according to their smoking, drinking or eating pattern.

Most studies found association of some index of fruit and vegetable consumption and oesophageal cancer risk [6, 7, 14, 18, 19, 22, 25–27] although the evidence is less clear in other investigations [17, 28].

The attribution of this protection to any specific micronutrient is at the present state of knowledge impossible: beta-carotene and vitamin C have been proposed (as well as riboflavin) [6, 7, 29], but there is by now no clear evidence on the matter. For the above mentioned reason, and for the small number of food items considered in this study, our index of beta-carotene should be considered with caution, and viewed merely as an indicator of a diet rich in fruit and vegetables.

Smoking was the risk factor with the highest attributable risk for both sexes, although for males the attributable risk was much higher than for females, reflecting the higher prevalence of tobacco consumption in men.

Alcohol was a major cause of oesophageal cancer in men, but for women the estimated attributable risk was only 10%. The relative small proportion of female cases attributable to alcohol reflects the low prevalence of women reporting to drink four or more drinks per day. This proportion could however be underestimated, since there is some evidence that women tend to under-report their alcohol consumption [24].

The sum of the three single-factor attributable risks is 156% in males and 71% in females, which is substantially higher than the risk attributable jointly to the three factors. This is not surprising since, under a multiplicative model, whenever risk factors are not mutally exclusive, their combined attributable risk will differ from the simple sum of the attributable risks for each factor. This discrepancy is more evident when the risks attributable to each single factor are greater.

In a case-control study of oesophageal cancer in males, conducted in the French Department of Ille-et-Vilaine [4], the risk attributable to consumption of more than 9 g of tobacco per day was 25% and the one attributable to consumption of more than 40 g of alcohol per day was 69%. The risk attributable jointly to the two exposures was 87%. Thus, in our study smoking was more important than alcohol, while in Ille-et-Vilaine the opposite was true. This might be explained by the different prevalence of the two exposures in the two areas. Nevertheless, the attributable risk of the combination of alcohol and tobacco in males was between 84 and 87% in both studies.

It is worth noting that for a few other cancer sites such a high proportion of cases is attributable to well established causes as it seems to be for oesophageal cancer in these investigations.

Although our estimates should be considered approximate and restricted to the area under surveillance, there is some evidence that the observed pattern of alcohol and tobacco consumption may be shared by other northern Italian areas [30].

The number of deaths from oesophageal cancer per year in Italy is about 1800 males and 450 females and the corresponding death rates standardised for age on the European population are 7.0 and 1.2 [31].

Thus, in this study not only the risk factors under examination show very consistent effects in the two sexes, but the number of deaths due to cancer of the oesophagus which cannot be explained by the three factors considered are extremely similar, i.e. approximately 180 males and 190 females. The corresponding rates would be 0.7 and 0.5. Thus, these three factors, besides accounting for 83% of oesophageal cancer overall, seem to account for materially all the observed difference between males and females in Italy.

The elimination of smoking, the reduction of alcohol consumption and the enrichment of diet with fruit and vegetables would make oesophageal cancer a rare disease in Italians of both sexes.

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