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Original article

Leanness and squamous cell oesophageal cancer

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Summary

Background: Squamous cell oesophageal cancer is one of the few neoplasms inversely related to body mass index (BMI). However, it is not clear whether this is due to cancer-related weight loss or to other correlates of leanness.

Patients and methods: 395 incident, histologically confirmed cases of squamous cell oesophageal cancer and 1,066 controls, admitted for acute, non-neoplastic diseases, in Italy and Switzerland. Odds ratios (ORs) were derived from multiple logistic regression, including terms for education, tobacco, alcohol, non-alcohol energy, fruit and vegetable intake.

Results: The ORs for the lowest vs. the highest quartile of BMI in the year before diagnosis were 2.0 in men, 1.6 in women, and 1.9 (95% confidence interval: 1.3–2.9) in both sexes combined. The association with leanness was stronger in heavy smokers, but was not accounted for by smoking and drinking, nor by differences in diet. Weight change in the decade prior to diagnosis showed no linear association with risk. However, cases were not leaner than controls at age 30 (OR = 0.6 for the lowest BMI quartile) and 50 (OR = 1.1).

Conclusions: Leanness appears to be an indicator of squamous cell oesophageal carcinogenesis. However, low BMI in the distant past was unrelated to oesophageal cancer risk.

Key words: body mass index, drinking, oral cancer, oesophageal cancer, smoking

Introduction

Tobacco smoking and alcohol drinking account for over 80% of oesophageal cancers in developed countries. However, dietary and nutritional factors (including a diet low in fruit and vegetables, and high in saturated fats) have also been related to squamous cell oesophageal cancer [1, 2].

Among nutritional aspects, leanness has been associated with increased oesophageal cancer risk in studies from North America [3, 4] and in a case-control study conducted in the 1980's in northern Italy [5]. Similar inverse relations with measures of body mass have been observed for oral and pharyngeal cancer or oral leukoplakias in studies from the US [6], Europe [5], China [7], and India [8].

In the present paper, we were able to consider data on body weight at various ages and subsequent oesophageal cancer risk using data from a case-control study conducted in Italy and Switzerland, and thus addressing the question of leanness as a potential early indicator of squamous cell oesophageal carcinogenesis. This is of specific interest, since oesophageal adenocarcinoma, in contrast, has been directly related to overweight and obesity [4, 9, 10].

Patients and methods

Between 1992 and 1997, a case-control study of oesophageal cancer was conducted in the provinces of Pordenone, Milan, and Padova in northern Italy, and (up to 1999) in the Swiss Canton of Vaud [2, 11].

Cases considered in the present report were individuals admitted to the major teaching and general hospitals in the areas under study with incident, histologically confirmed squamous cell cancer of the oesophagus, diagnosed no longer than one year before the interview and with no history of cancer of other sites. A total of 395 individuals were enrolled, 351 men and 44 women, whose median age was 60 years (range from 34 to 77). Response rate for the cases was over 95%. Thirty-one additional cases of adenocarcinoma of the oesophagus were not considered in the main analyses.

Controls were patients admitted to the same hospitals as the above cases for a wide spectrum of acute, non-neoplastic conditions, not related to smoking or alcohol consumption and long-term modification of diet. Controls were frequency-matched with cases on quinquennia of age, sex and study center. To compensate for the rarity of oesophageal cancer in women, a control-to-case ratio of about five was chosen for females, as opposed to about two for males. Less than 5% of the identified controls refused or were unable to participate. The control group comprised 1,066 subjects, 875 men and 191 women, whose median age was 60 years, ranging from 30 to 77. Twenty-nine percent of controls were admitted for traumas, 36% for other non-traumatic orthopedic conditions, 12% for acute surgical conditions and 23% for other miscellaneous illnesses, including eye, nose, ear, skin or dental disorders.

Similar structured questionnaires and coding manuals were used in each center, and all interviewers were centrally trained and routinely supervised. The questionnaires included information on socio-demographic characteristics, such as education and occupation, lifetime

Table I. Distribution of 395 cases of squamous cell oesophageal cancer and 1,066 controls, odds ratios (ORs) and corresponding 95% confidence intervals (CI) according to various anthropometric factors and gender; Italy and Switzerland, 1992–1999.

Approximate quartiles[a]	Males		Females		Total	
	Ca:Co[b]	OR[c] (95% CI)	Ca:Co[b]	OR[c] (95% CI)	Ca:Co[b]	OR[c] (95% CI)
Height						
1 (high)	63:220	1[d]	13.53	1[d]	86:284	1[d]
2	101:284	1.17 (0.75–1 81)	7:46	1.23 (0.30–5.10)	89:261	1.12 (0.74–1.71)
3	77:154	1.69 (1.04–2.75)	15:45	2.33 (0.65–8.34)	122:257	1.38 (0.92–2.07)
4 (low)	106:217	1.33 (0 85–2.09)	9:47	1.41 (0.38–5.25)	94:264	1.40 (0.88–2.22)
χ^2 trend	2 30 (P = 0 129)		0.61 (P = 0.435)		2.82 (P = 0.093)	
Weight						
1 (high)	59:236	1[d]	6:50	1[d]	66:275	1[d]
2	84.224	1.29 (0.82–2.03)	9:52	1.07 (0.26–4.42)	93:273	1 37 (0.89–2.10)
3	66:204	1 07 (0.66–1.74)	12.46	1.51 (0.36–6.26)	95·261	1 58 (1.03–2.44)
4 (low)	140:210	2.29 (1.47–3.56)	17:43	2.71(0.70–10 51)	139:256	2.53 (1.63–3.94)
χ^2 trend	12.28 (P = 0.0005)		2.63 (P = 0.105)		17.06 (P = 0.0001)	
Body mass index, kg/m^2						
⩾28.1	76:218	1[d]	8:50	1[d]	84:268	1[d]
25.9–28 0	62:231	0 81 (0.51–1.28)	4.36	0.32 (0.06–1.88)	66.267	0.79 (0.51–1.22)
23.9-25.8	80:228	1.18 (0.75–1.85)	7:36	0.83 (0.21–3.25)	87:264	1.15 (0.75–1.76)
<23.9	127:197	1.98 (1.29–3.06)	25:69	1.59 (0 47–5.38)	152:266	1.93 (1.30–2.88)
χ^2 trend	11.89 (P = 0.0006)		1.19 (P = 0.275)		13.31 (P = 0.0003)	

[a] Quartiles cutpoints for height were 178, 172, 169 cm in males; 166, 162, 158 cm in females; 176, 171, 166 cm in the overall dataset. For weight 85, 78, 71 kg in males; 74, 67, 59 kg in females; 84, 76, 69 kg in the overall dataset.

[b] The sum does not add up to the total because of some missing values.

[c] Estimates from logistic regression, conditioned for age, center and, when indicated, sex, and including terms for education, tobacco, alcohol, non alcohol energy, fruit and vegetable intake.

[d] Reference category.

smoking and alcohol-drinking habits, and a validated food frequency section. Study subjects were asked to report their height and weight in the year before cancer diagnosis or interview (in controls). Self-reported values were validated by means of available medical records

For the Italian centers, additional measures were elicited: weight at 30 and 50 years and highest (outside pregnancy) and lowest weight in adult life, perceived body size at 12 years of age (i.e., thinner than, same as, heavier than peers), the circumferences of waist, measured 2 cm above the umbilicus, and hip, measured at the maximal protrusion. Waist-to hip ratio (WHR) was derived from these measures.

Body mass index (BMI) was computed as weight in kilograms divided by height in square meters. Change in weight was computed as the differences between weight at diagnosis or interview (for controls) and weight at age 30 for subjects with age at diagnosis less than 55, and at age 50 for subjects with age at diagnosis 55 years or above.

Approximate quartiles of height, weight, and WHR were defined on the distribution of controls, and separately for men and women The distribution of BMI was similar in men and women, and the same cut-off points were used for the two genders Odds ratio (OR) and 95% confidence interval (CI) were computed using conditional multiple logistic regression models [12]. A marked excess of current smokers, especially heavy smokers, and heavy alcohol drinkers was found in cases of oesophageal cancer as compared to controls [13]. All the regression models were conditioned for quinquennia of age, study center and sex, and included terms for non alcohol energy intake, alcohol drinking (<21, 21–48, ⩾49 drinks/week), tobacco smoking (never smoker, ex-smoker, smoker of 1–14, 15–24, ⩾25 cigarettes/day), vegetable and fruit intake.

Results

Table 1 shows the distribution of 395 cases of squamous cell oesophageal cancer and 1,066 control subjects according to height, weight, and BMI, in separate strata of sex, and the corresponding ORs. Cases tended to be shorter than controls, but the inverse association with height was not significant. The ORs for the lowest quartile of height compared to the highest one were 1.3 for men, 1.4 for women, and 1.4 (95% CI: 0.9–2.2) for both sexes combined. An inverse association between weight, or BMI, and oesophageal cancer risk emerged for both men and women. The ORs for the lowest quartile of weight compared to the highest one were 2.3 for men, 2.7 for women, and 2.5 for both sexes combined. The corresponding values for BMI were 2.0 for men, 1.6 for women, and 1.9 for both sexes combined. In the absence of allowance of vegetables and fruits, the OR for the lowest quartile of BMI was 2.1 (95% CI: 1.4–3.1). The trends in risk were significant for weight and BMI in men only and in the overall dataset. The OR for the lowest vs. highest quartile (i.e., <0.90 vs. ⩾0.97) of WHR in both sexes combined was 2.1 (95% CI: 1.2–3.8). With reference to the 31 adenocarcinomas, the OR for subjects with BMI <25.9 vs. ⩾25.9 was 0.81 (95% CI: 0.39–1.66).

The effect of BMI at diagnosis or interview in separate strata of cigarette smoking and alcohol drinking is examined in Table 2, in men and women combined. Among never and ex smokers, and moderate smokers, BMI was not significantly related to cancer risk (OR for the lowest quartile = 1.3 and 1.5 respectively). Conversely, a strong inverse association emerged among heavy smokers (OR = 7.7; 95% CI: 3.0–19.3). Alcohol

Table 2. Odds ratios (ORs)[a] and corresponding 95% confidence intervals (95% CI) of squamous cell oesophageal cancer according to body mass index (BMI) in separate strata of alcohol drinking and smoking. Italy and Switzerland, 1992–1999.

	BMI quartiles[b]								
	⩾28 1		25.9–28.0		23.9–25.8		<23.9		χ^2 trend
	Ca·Co	OR	Ca:Co	OR (95% CI)	Ca:Co	OR (95% CI)	Ca Co	OR (95% CI)	
Smoking habits									
Never/ex smokers	47.197	1[c]	33:204	0.65 (0.37–1 15)	39:178	1.12 (0.63–1 98)	40 168	1 30 (0.73–2.29)	1.60 $P = 0.205$
<20 cigarettes/day	13:29	1[c]	8 38	0.57 (0.18–1.86)	16.38	1.09 (0 34–3 46)	28:53	1.49 (0.53–4.18)	1.79 $P = 0.181$
⩾20 cigarettes/day	24:42	1[c]	25:25	1.57 (0.56–4.42)	32:48	1.31 (0.53–3.24)	84:45	7.65 (3 03–19.32)	17.51 $P = 0.0001$
Alcohol drinking (drinks/week)									
<21	5:126	1[c]	6:131	0.90 (0.24–3 31)	7:152	0.97 (0.26–3.56)	28.161	3.00 (0 99–9 04)	6.29 $P = 0.012$
21–48	28:91	1[c]	20:85	0 98 (0.47–2.05)	29:82	1 28 (0.64–2.57)	54:77	1.67 (0.88–3.18)	3.00 $P = 0.083$
⩾49	51:50	1[c]	40:50	0.78 (0.40–1 50)	50:29	0.96 (0.48–1.92)	70 27	2 19 (1.08–4.45)	4.64 $P = 0.031$

[a] Estimate from logistic regression, conditioned for age, center and sex, and including terms for education, non alcohol energy, fruit and vegetable intake, and, in turn, alcohol and tobacco.
[b] In some strata the sum does not add up to the total because of a few missing values.
[c] Reference category.

drinking, however, did not consistently nor significantly modify the relation between BMI and risk of squamous cell oesophageal cancer: the ORs for the lowest BMI quartile were 3.0 in subjects reporting <21 drinks per week, 1.7 in those reporting 21 to 48, and 2.2 in those reporting ⩾49 drinks per week.

In Table 3 the relation between the risk of squamous cell oesophageal cancer, BMI at different ages, and weight change is examined in the Italian data-set only. Cases were not thinner than controls at ages 12, 30, and 50; ORs for the lowest vs. the highest BMI level were 0.9 (95% CI: 0.6–1.4), 0.6 (0.4–1.0), and 1.1 (0.7–1.8) respectively. Weight change in the decade prior to diagnosis showed no linear association with oesophageal cancer risk, since the ORs were below unity both for weight loss (OR = 0.6) and for weight gain (OR = 0.5).

Discussion

The present findings support the observation that leanness is an indicator of squamous cell oesophageal cancer risk, independently from major recognised risk factors for oesophageal cancer, including tobacco, alcohol and related dietary factors [3–5]. The inverse relation was of similar magnitude when weight, BMI or WHR were considered. No significant association with BMI was observed in the few cases of adenocarcinoma although the point estimate was below unity in leaner subjects, confirming previous observations [4, 9, 14, 15].

The strength of this study lies in the availability of a measure of (non alcohol) energy intake, which indicates that the lower BMI in cases could not be explained by reduced energy intake in the few years before diagnosis [16]. It is, therefore, unlikely that the association is explained by decreased food intake prior to oesophageal cancer diagnosis. Nor it can be explained in terms of obvious confounding effects of social class or dietary

Table 3 Distribution of 303 cases of squamous cell oesophageal cancer and 739 controls according to measures of body mass index (BMI) at various ages, and corresponding odds ratios (ORs) with 95% confidence intervals (CI). Italy, 1992–1997.

Variable	Oesophageal cancer	Controls	OR[a] (95% CI)
Perceived body size at age 12			
Heavier than peers	77	190	1[b]
Same	125	290	1.05 (0.70–1.57)
Thinner than peers	101	259	0 92 (0.60–1.41)
χ^2 trend			0.17 ($P = 0.683$)
BMI at age 30, kg/m^2[c]			
⩾25 1	77	180	1[b]
23 4–25.0	67	183	0.73 (0.46–1.16)
21–23 3	69	171	0.83 (0.52–1 33)
<21 8	59	188	0.63 (0.39–1.03)
χ^2 trend			2.55 ($P = 0.111$)
BMI at age 50, kg/m^2[d]			
⩾27.4	58	170	1[b]
25.2–27.3	64	160	1.23 (0.74–2.03)
23.2–25.1	64	160	1.10 (0.66–1.84)
<23.2	76	163	1.10 (0.67–1.82)
χ^2 trend			0.05 ($P = 0.822$)
Weight change[e]			
Decrease	64	154	0.61 (0.37–1 01)
Equal	79	109	1[b]
Increase	150	464	0.49 (0.32–0.74)
χ^2 trend			2.97 ($P = 0 085$)

[a] Estimates from logistic regression, conditioned for age, sex and center, and including terms for education, tobacco, alcohol, non alcohol energy, fruit and vegetable intake
[b] Reference category.
[c] Subjects aged 30 years or more.
[d] Subjects aged 50 years or more.
[e] In the decade before diagnosis/interview. The sum does not add up to the total because of missing values.

factors, since all these covariates had only a modest influence on multivariate risk estimates.

A potential source of selection bias was the use of hospital controls. However, when asking about body weight, our interviewers specifically investigated cases and controls about their weight in the year before hospital admission, and medical records were checked for this purpose. Some of the diagnoses of controls have been associated with either reduced (e.g., fractures) or increased BMI (e.g., arthritis, cataract) [17, 18]. However, the association was observed at separate analysis across various diagnostic categories of controls, and the distributions of height and weight in the comparison group were similar to those from population surveys in Italy [19] and Switzerland [20].

The inverse association between BMI and oesophageal cancer was observed in smokers and drinkers and was stronger in heavy smokers, confirming previous observations on oral and pharyngeal as well as oesophageal cancer [5, 21]. Alcohol drinking and tobacco smoking, in fact, can contribute to lowering weight in oesophageal cancer cases, and several studies showed reduced body weight – but increased energy intake – in drinkers as compared to nondrinkers [22–24].

Leanness in the few years before diagnosis may be associated with decreased intake of protective nutrients or with increased intake of unfavourable ones [2, 25]. However, intake of vegetable and fruit was not appreciably correlated with measure of BMI (correlation coefficient, $r = 0.10$ for vegetables and $r = 0.14$ for fruit). Further allowance for total energy (a possible correlate of leanness) or vegetables and fruit (two of the major favourable indicators of oesophageal cancer risk in this population [25]) did not appreciably modify the association observed, and inclusion of all these factors in the logistic models may well represent an overadjustment.

Weight change in the decade before diagnosis was not consistently related to oesophageal cancer risk. Leanness, however, appears to be an indicator rather than a determinant of the process of oesophageal carcinogenesis [26], since this study included information on lifetime history of body mass, and BMI was not related to risk several years before diagnosis of oesophageal cancer. This apparently contrasts with the results of a companion study on oral and pharyngeal cancer [21], for which leanness in the distant past remained a strong determinant of risk.

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