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Original article

Leanness as early marker of cancer of the oral cavity and pharynx

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Summary

Background: It is not clear whether the purported association of leanness with cancer of the oral cavity and pharynx was due to cancer-related weight loss or to the influence of factors associated with leanness.

Patients and methods: Seven hundred fifty-four incident cases of cancers of the oral cavity and pharynx and 1775 controls, admitted to hospital for acute, non-neoplastic diseases, in Italy and Switzerland. Questionnaire included height, lifetime history of weight and of physical activity, waist and hip measurements, and a validated food-frequency section.

Results: Leanness at diagnosis was associated with elevated risk in men (adjusted odds ratio, OR for 5-unit decrease in body-mass index, BMI = 1.9; 95% confidence interval (CI): 1.6–2.2 in men). Male cases were significantly leaner than control subjects at the age of 30 and of 50. Thinner women also had an increased risk, but the inverse association with BMI was non linear. In both sexes, the association with leanness was restricted to smokers and moderate/heavy drinkers, but was not accounted for by drinking and smoking habits, nor by differences in physical activity or dietary habits.

Conclusions: Leanness appears to be an early marker of some unknown biological effect of smoking and/or of alcohol abuse, which may contribute to the prediction of cancers of the oral cavity and pharynx. Cessation of smoking and substantial reduction of alcohol intake may improve nutritional status, besides stopping carcinogen exposure.

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

Introduction

Tobacco smoking and alcohol drinking account for over 90% of cancers of the oral cavity and pharynx in developed countries [1, 2]. Dietary factors (i.e., low fruit and vegetable consumption, and high intake of saturated fat) [2–5] have also been related to risk.

Leanness seems, according to a few case-control studies, another characteristic of subjects at high risk for cancers of the oral cavity and pharynx. An inverse association between body mass index (BMI) and oral cancer risk has been shown in a study from Western New York (odds ratio, OR for BMI $\geqslant 28$ vs. $\leqslant 23 = 0.4$, 95% confidence interval (CI): 0.2–0.6) [6] and in one from Beijing, China (OR for BMI $\geqslant 26$ vs. $\leqslant 23 = 0.4$, 95% CI: 0.3–0.7) [7]. A high BMI was related to decreased risk of cancer of the oral cavity and pharynx in both Whites (OR for highest quartile = 0.6) and Blacks (OR = 0.3) in the US [8]. In two additional case-control studies from the US [9, 10] and one from Italy [11], individuals in the lowest BMI quartile showed two- to four-fold increased risks. D'Avanzo et al. [11] also reported a significant inverse association with height. Allowance for tobacco smoking and alcohol drinking was made in all the studies above. In some instances [7, 11], poor dentition, education, selected dietary factors, and total energy intake were also taken into account. In no study was it possible, however, to assess lifetime weight history.

In order to examine in greater detail the influence of different body size indices, we took advantage of a new case-control study on cancers of the oral cavity and pharynx carried out in Italy [4] and the Swiss Canton of Vaud [12]. In addition to detailed information on a wide range of possible confounding factors (e.g., dietary habits, physical activity, etc.), this study included information on weight at different ages and the distribution of body fat.

Patients and methods

Between January 1992 and November 1997, a case-control study of cancer of the oral cavity and pharynx was conducted in two Italian areas (the province of Pordenone, in northeast Italy, and the ones of Rome and Latina, in central Italy) and in the Swiss Canton of Vaud. Cases had a first histologically confirmed cancer of the oral cavity or pharynx diagnosed no longer than one year prior to the interview: 344 subjects with cancer of the oral cavity (274 men and 70 women, median age 58, range 22–77 years) and 410 with cancer of the pharynx (364 men and 46 women, median age 57, range 32–76 years) were interviewed. Cancer of the lip, salivary glands, and nasopharynx were not included.

Patients admitted for acute illnesses to major hospitals in the areas where they lived were eligible as controls. None of these patients had

been admitted for malignant tumours. In order not to overrepresent smokers and heavy drinkers as compared to source population, hospital admissions due to diseases related to tobacco smoking (e.g., chronic obstructive bronchitis and cardiovascular diseases), or alcohol abuse (e.g., liver cirrhosis and pancreatitis) were excluded. By and large, all chronic conditions which may have led to lifestyle modifications (e.g., diabetes mellitus) were not eligible as causes of hospital admission. Conversely comorbidity from the above conditions did not represent an exclusion criterion. A total of 1254 male controls and 521 female controls (age range 20–78, median age 57 years) frequency-matched with cases by five-year age group and area of residence were interviewed. They belonged to the following diagnostic categories: traumas, mostly fractures and sprains (28%); other orthopedic disorders, such as low back pain and disc disorders (25%); acute surgical conditions (24%); eye diseases (14%); and other miscellaneous diseases, such as skin and dental conditions (9%). In order to compensate for the rarity of cancer of the oral cavity and pharynx in women, a control-to-case ratio of about five was chosen for females, as opposed to two for males. All interviews were carried out in a hospital setting. The nurses who conducted the interviews were introduced to patients by the attending clinical staff, in order to encourage a high participation rate (about 95% in either cases or controls).

The same structured questionnaire and coding manual were used in each center, and all interviewers were centrally trained and routinely supervised. The questionnaire included information on socio-demographic characteristics, such as education and occupation, lifetime smoking and alcohol-drinking habits, and physical activity. Study subjects were asked to report their habitual height and weight in the year before cancer diagnosis or interview (in controls). Self-reported values were validated by means of medical records.

For the Italian centers some additional measures were elicited: weight at 30 and 50 years of age, 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) and waist-to-hip ratio (WHR), i.e., the ratio between the circumferences of waist, measured 2 cm. above the umbilicus, and hip, measured at the maximal protrusion. The BMI was computed as weight in kilograms divided by height in square meters.

Approximate quantiles of height, weight, and WHR were separately defined for men and women from the joint distribution of cases and controls. The distribution of BMI was similar in men and women, and the same cut-off points were used for the two genders. OR and 95% CI were computed using unconditional multiple-logistic regression models [13]. Regression equations, therefore, included terms for age (in quinquennia); study center, occupational physical activity (since recreational physical activity was rarely reported); intake of total energy, vegetables and fruit; alcohol drinking (never, former, and current drinker, and weekly drinks, as a continuous variable), tobacco smoking (never smoker, former, and current smoker, and number of daily cigarettes and duration of the habit as continuous variables). The interaction between BMI and other variables was assessed by means of the Wald chi-square on the product of the variables considered as categorical.

Table 1. Distribution of 754 cases of cancers of the oral cavity and pharynx and 1775 controls[a] according to selected characteristics in Italy and Switzerland 1992–1997.

Characteristic	Number of cases (%)	Number of controls (%)
Sex		
Male	638 (85)	1254 (71)
Female	116 (15)	521 (29)
Age group (years)		
<40	28 (4)	151 (9)
40–49	141 (19)	337 (19)
50–59	274 (36)	534 (30)
60–69	254 (34)	574 (32)
$\geqslant 70$	57 (8)	179 (10)
Education (years)		
<7	411 (55)	903 (51)
7–11	197 (26)	534 (30)
$\geqslant 12$	141 (19)	337 (19)
χ^2_1 (trend)[a]		0.65 ($P = 0.42$)
Smoking habits[b]		
Never	60 (8)	694 (39)
Former	107 (14)	196 (11)
Current		
$\leqslant 14$	239 (32)	220 (12)
15–24	175 (23)	106 (6)
$\geqslant 25$	173 (23)	559 (31)
χ^2_1 (trend)[a, b]		76.9 ($P < 0.01$)
Alcohol drinking (drinks/week)		
0–20	114 (15)	970 (55)
21–48	177 (23)	505 (28)
49–76	179 (24)	140 (8)
$\geqslant 77$	161 (21)	50 (3)
Former	123 (16)	110 (6)
χ^2_1 (trend)[a, b]		182.7 ($P < 0.01$)

[a] Some strata do not add up to the total because of a few missing values.

[b] Adjusted for age, centre, sex, and smoking and drinking habits (as appropriate).

Results

Cases of cancer of the oral cavity and pharynx were similar to control subjects according to age. However, lower years of education, and a strong excess of smokers and heavy alcohol drinkers were reported by cases (Table 1). After adjustment for smoking and drinking the difference in education was not significant ($\chi^2_{1,\text{trend}} = 0.65$, $P = 0.42$).

Table 2 shows the distribution of cases of cancers of the oral cavity and pharynx and control subjects by height, weight, BMI, and gender, and the corresponding ORs. Cases tended to be shorter than controls, but the inverse association with height was not significant (OR for 5 cm decrease in height = 1.1, 95% CI: 1.0–1.2 in men, and 1.1, 95% CI: 0.9–1.3 in women). An inverse association between weight, or BMI, and cancer risk emerged for either men or women. A 5 kg decrease in weight was associated with a 19% and 15% risk increase, in men and women, respectively. The ORs for BMI lower than 22.7, compared to equal to or greater than 28.5, were 3.8 (95% CI: 2.5–5.7) in men and 2.0 (95% CI: 0.9–4.4) in women. Risk trend was significant in men, but not women, where the association with BMI was non linear.

In Table 3 the relation between the risk of cancers of the oral cavity and pharynx, BMI at different ages, and WHR is examined in the Italian sub-data-set. While cases were not more often thinner than their peer control subjects at age 12, an inverse association emerged for men between cancer risk and BMI at ages 30 and 50 (OR for lowest *versus* highest BMI quintile: 2.2, 95% CI: 1.3–3.5; and 2.0; 95% CI: 1.2–3.2, respectively). WHR was positively correlated to BMI (correlation coefficient, $r = 0.38$ in men and 0.28 in women). After allowance for

Table 2. Distribution of 754 cases of cancers of the oral cavity and pharynx and 1775 controls[a], odds ratio (OR) and corresponding 95% confidence interval (CI)[b] by various body size measurements and sex. Italy and Switzerland, 1992–1997.

Variable	Approximate quintile	Males		Females	
		Ca : Co	OR (95% CI)	Ca : Co	OR (95% CI)
Height[c]	1 (high)	92 : 213	1	14 : 84	1
	2	125 : 255	0.95 (0.63–1.41)	27 : 134	1.09 (0.49–2.45)
	3	109 : 264	0.87 (0.58–1.32)	22 : 78	1.30 (0.55–3.09)
	4	164 : 296	1.05 (0.72–1.55)	24 : 117	1.16 (0.50–2.66)
	5 (low)	148 : 226	1.30 (0.86–1.96)	29 : 105	1.32 (0.58–2.98)
χ^2_1 (trend)			2.16; $P = 0.14$		0.44; $P = 0.51$
5 cm decrease (continuous)			1.06 (0.96–1.16)		1.11 (0.92–1.34)
Weight[d]	1 (high)	81 : 275	1	13 : 109	1
	2	88 : 309	0.99 (0.66–1.48)	18 : 105	1.66 (0.71–3.88)
	3	104 : 240	1.26 (0.84–1.89)	18 : 103	1.40 (0.59–3.28)
	4	141 : 253	1.60 (1.08–2.36)	24 : 109	1.70 (0.75–3.85)
	5 (low)	219 : 173	3.13 (2.12–4.63)	42 : 93	2.63 (1.18–5.87)
χ^2_1 (trend)			40.4; $P < 0.01$		4.87; $P = 0.03$
5 kg decrease (continuous)			1.19 (1.13–1.26)		1.15 (1.02–1.29)
Body mass index (BMI) (kg/m^2)	⩾ 28.5	83 : 293	1	13 : 113	1
	26.2–28.4	96 : 294	1.25 (0.84–1.86)	25 : 85	2.57 (1.14–5.80)
	24.5–26.1	117 : 286	1.54 (1.04–2.28)	16 : 88	1.61 (0.66–3.95)
	22.7–24.4	138 : 243	1.86 (1.25–2.76)	18 : 105	1.32 (0.55–3.18)
	< 22.7	199 : 134	3.78 (2.52–5.67)	43 : 125	1.99 (0.89–4.44)
χ^2_1 (trend)			44.4; $P < 0.01$		0.58; $P = 0.45$
5 unit decrease (continuous)			1.87 (1.55–2.24)		1.37 (1.00–1.88)

[a] Some strata do not add up to the total because of a few missing values.
[b] Estimates from multiple logistic regression models including terms for age, center, physical activity, alcohol drinking and smoking habit, and total intake of energy, vegetables and fruit.
[c] Lower quintile limits were 179, 175, 171, and 167 cm for males and 169, 165, 161, and 158 cm for females.
[d] Lower quintile limits were 86, 79, 74, and 67 kg for males and 76, 69, 64, and 58 kg for females.

Table 3. Distribution of 598 cases of cancers of the oral cavity and pharynx and 1491 controls[a], odds ratio (OR) and corresponding 95% confidence interval (CI)[b] by body mass index (BMI) at various ages, waist-to-hip ratio, and sex. Italy, 1992–1997.

Variable	Approximate quintile	Males		Females	
		Ca : Co	OR (95% CI)	Ca : Co	OR (95% CI)
Perceived body size at age 12	Heavier	88 : 236	1	28 : 108	1
	Same	268 : 432	1.48 (1.03–2.11)	31 : 214	0.67 (0.35–1.27)
	Thinner	151 : 333	1.26 (0.86–1.84)	25 : 158	0.83 (0.42–1.64)
χ^2_1 (trend)			0.69; $P = 0.41$		0.27; $P = 0.61$
BMI at age 30	⩾ 26.1	77 : 220	1	14 : 84	1
	24.2–26.0	110 : 236	1.27 (0.83–1.92)	9 : 55	0.88 (0.30–2.57)
	23.0–24.2	102 : 215	1.33 (0.86–2.04)	13 : 61	1.60 (0.63–4.08)
	21.2–22.9	114 : 189	1.58 (1.03–2.43)	12 : 92	0.71 (0.27–1.84)
	< 21.2	89 : 120	2.15 (1.34–3.45)	33 : 166	1.21 (0.55–2.64)
χ^2_1 (trend)			10.8; $P < 0.01$		0.13; $P = 0.71$
BMI at age 50	⩾ 27.9	63 : 174	1	6 : 70	1
	25.8–27.8	60 : 192	0.92 (0.57–1.50)	12 : 55	2.48 (0.79–7.78)
	24.3–25.7	82 : 175	1.37 (0.85–2.20)	11 : 49	3.10 (0.92–10.43)
	22.6–24.2	102 : 121	2.26 (1.39–3.69)	11 : 67	1.79 (0.55–5.79)
	< 22.6	98 : 106	2.00 (1.24–3.24)	19 : 89	1.81 (0.62–5.31)
χ^2_1 (trend)			17.3; $P < 0.01$		0.20; $P = 0.66$
Waist-to-hip ratio[c]	1 (low)	205 : 258	1	12 : 160	1
	2	150 : 303	0.70 (0.49–1.00)	35 : 138	2.87 (1.29–6.41)
	3 (high)	137 : 325	0.72 (0.50–1.04)	37 : 138	2.66 (1.15–6.18)
χ^2_1 (trend)			3.03; $P = 0.08$		4.39; $P = 0.04$

[a] Some strata do not add up to the total because of a few missing values.
[b] Estimates from multiple logistic regression models including terms for age, center, physical activity, alcohol drinking and smoking habit, and total intake of energy, vegetables and fruit.
[c] Adjusted for BMI at diagnosis in addition to the variables indicated above.

Table 4. Odds ratio (OR) and corresponding 95% confidence interval (CI)[a] of cancers of the oral cavity and pharynx by body mass index (BMI) in separate strata of alcohol drinking and smoking. Italy and Switzerland, 1992–1997.

	BMI tertile[b]						Trend chi-square
	⩾ 26.9[c]		23.9–26.8		⩽ 23.8		
	Ca : Co	OR	Ca : Co	OR (95% CI)	Ca : Co	OR (95% CI)	
Smoking habit							
Never smoker	19 : 254	1	23 : 233	1.51 (0.78–2.94)	18 : 200	1.26 (0.62–2.53)	0.46
Ex-smoker	63 : 252	1	51 : 197	1.22 (0.77–1.95)	56 : 110	2.23 (1.38–3.62)	10.00[d]
Smoker (cigs/day)							
< 20	43 : 90	1	64 : 98	1.60 (0.86–2.98)	106 : 98	2.35 (1.29–4.27)	7.92[d]
⩾ 20	47 : 69	1	84 : 88	1.09 (0.62–1.92)	174 : 75	2.98 (1.72–5.16)	18.44[d]
Alcohol drinking (drinks/week)							
< 21	34 : 328	1	32 : 334	0.89 (0.52–1.49)	48 : 306	1.45 (0.88–2.36)	2.29
21–48	35 : 211	1	43 : 187	1.38 (0.80–2.38)	99 : 106	3.32 (1.97–5.60)	20.80[d]
⩾ 49	82 : 93	1	109 : 56	1.59 (0.94–2.67)	146 : 37	2.53 (1.47–4.36)	11.17[d]
Ex-drinkers	21 : 34	1	38 : 39	1.59 (0.67–3.77)	61 : 35	1.91 (0.80–4.52)	2.03
Current smoker of ⩾ 20 cigarettes/day and drinker of ⩾ 21 drinks/week	34 : 37	1	67 : 42	1.47 (0.72–3.00)	137 : 31	4.48 (2.16–9.28)	18.36[d]

[a] Estimates from multiple logistic regression models including terms for age, gender, center, physical activity, alcohol drinking and smoking habit, and total intake of energy, vegetables and fruit.
[b] Some strata do not add up to the total because of a few missing values.
[c] Reference category.
[d] $P < 0.01$.

BMI, women, but not men, with cancers of the oral cavity and pharynx tended to have higher WHR than control subjects of the same gender (OR = 2.7; 95% CI: 1.2–6.2) (Table 3).

The effect of BMI at diagnosis or interview in separate strata of cigarette smoking and alcohol drinking is examined in Table 4, in men and women combined. Among never smokers, BMI was unrelated to cancer risk. Conversely, an inverse association emerged for former and current smokers, most notably heavy smokers (OR for BMI ⩽ 23.8 vs. ⩾ 26.9 in heavy smokers = 3.0; 95% CI: 1.7–5.2) (Wald chi-square for interaction, never *versus* ever smokers = 4.10; $P = 0.04$). Also alcohol drinking seemed to modify significantly the relation between BMI and risk of cancer of the oral cavity and pharynx (Wald chi-square for interaction = 6.14; $P = 0.01$). The inverse association was weak and not significant among subjects whose current alcohol intake was below 21 drinks per week. For drinkers of 21–48 and 49 drinks or more per week, the lowest BMI tertile showed ORs of 3.3 (95% CI: 2.0–5.6) and 2.5 (95% CI: 1.5–4.4), respectively (Table 4). The strongest association with leanness was found in individuals who were current heavy smokers and heavy drinkers (OR = 4.5; 95% CI: 2.2–9.3).

The effect of BMI was similar in different strata of gender, age, center, physical activity, and intake of total energy, fat, and vegetables and fruit. Separate analyses of oral and pharyngeal cancer did not reveal differences between the two sites with respect to the influence of height, weight, or BMI. Findings were consistent when the comparison was restricted to each major control category, i.e., trauma (OR for lowest *versus* highest BMI quintile = 2.5; 95% CI: 1.6–4.0); orthopedic diseases (OR = 3.7; 95% CI: 2.3–6.0); surgical conditions (OR = 3.3; 95% CI: 1.9–5.7); and other diseases (OR = 3.1; 95% CI: 1.9–5.1).

Discussion

For several cancer sites, incidence and mortality increase with excess body weight [14]. However, lean individuals are at increased risk for cancer of the lung [15, 16], bladder [14], and, as in our present report, upper aerodigestive tract [9–11, 17], i.e., smoking-related sites. Although self-reported height tends to be overestimated and weight underestimated [18], such misclassification is unlikely to be different between cases and controls, particularly since all interviews were performed in a hospital setting. Misclassification should not, therefore, account for the consistent inverse association between BMI and the risk of smoking-related tumors.

Our study is the first to allow the assessment of risk pattern of cancers of the oral cavity and pharynx in relation to lifetime history of BMI, body fat distribution, and smoking and drinking habits. We have, therefore, been able to show that the association with leanness substantially antedates cancer diagnosis, at least among men. It is, thus, unlikely that this association is due exclusively to weight loss secondary to dysphagia or other early cancer symptoms. Nor can it be explained in terms of confounding effects of socio-cultural indicators, or physical activity, since all these variables had a negligible influence on risk estimates.

Leanness may be associated with either decreased levels of protective nutrients or with increased levels of detrimental ones. Our data did not suggest, however,

that intakes of total energy (a possible correlate of leanness), fat, or vegetables and fruit (i.e., major dietary risk factors in our study) [4, 13] exert a substantial confounding influence or effect modification on the association with leanness. Conversely, cigarette smoking and alcohol drinking were important effect modifiers with respect to body mass. The association between leanness and risk of cancers of the oral cavity and pharynx was weak, if any, in never-smokers or abstainers/light drinkers.

Smokers tend to weigh less than non-smokers and gain weight after they stop smoking [19]. The failure to explain such differences in weight by differences between smokers and non-smokers in energy intake or physical activity has induced speculation that smoking, probably nicotine, may affect the energy balance by increasing the metabolic rate (i.e., at rest, approximately 70% of total daily energy expenditure) [19, 20]. In fact, in our study, as well as in a few previous ones [9, 16], there was a decreasing gradient in the influence of BMI from current smokers to former smokers to never smokers. A few previous reports [21, 22] have also suggested that the redistribution of body fat associated with smoking results in a more android (higher) WHR. Our data showed that women, albeit not men, with cancers of the oral cavity and pharynx had higher WHR than controls. While an anti-estrogenic effect of smoking is well-documented [23], our findings await confirmation from larger studies.

Alcohol drinking can contribute with smoking to weight reduction in cases of cancers of the oral cavity and pharynx. Several studies showed lower than expected body weight – but greater than expected energy intake – in drinkers compared to non-drinkers [24, 25]. In experimental studies of high alcohol intake (i.e., about 20%–50% of total energy, close to the percentage of many of our oral cancer cases) [26–28], it was not possible to keep body weight constant. In our present report, the inverse association between oral cancer risk and BMI was significantly stronger in moderate or heavy drinkers than in abstainers or light drinkers, suggesting a similar modification of BMI effect by alcohol as by cigarette smoking. For both factors, former smokers and drinkers showed ORs for different BMI tertiles which were intermediate between those in never and current smokers and drinkers.

A potential source of bias was the use of hospitalized controls in our study, because people who are sick generally cannot be expected to be representative of a healthy population in respect to weight [29]. When asking about body weight during the patient interviews, however, our interviewers specifically asked cases and controls for their average weight in the two years before admission to the hospital, and medical records could be checked for this purpose. Some of the eligible diseases for control subjects have been reported to be associated with either lowered (e.g., fractures, vertebral disk problems, hernia) or increased BMI (e.g., arthritis, cataract) [29]. However, leanness was consistently related to increased oral cancer risk in all major control categories and after allowance for a number of lifestyle factors. Finally, distributions by height and weight in our control group were similar to those from population surveys in Italy [30] and the Swiss Canton of Vaud [31].

In conclusion, it appears that smokers and/or heavy drinkers, in addition to being exposed to high levels of carcinogens, suffer from weight loss and, possibly, from an as yet ill-defined nutritional deficiency [19, 24]. Thus, leanness appears to contribute to the prediction of cancers of the oral cavity and pharynx. Since the assessment of weight in case-control studies can be affected by bias, our present findings should be confirmed in cohort studies and programs of smoking and drinking cessation.

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