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Short Communication

Lifetime body mass index and risk of oral cavity and oropharyngeal cancer by smoking and drinking habits

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The influence of body mass index (BMI) on oral cancer risk was evaluated in 375 incident cases and 375 age–gender-matched hospital-based controls. Low BMIs at diagnosis and 2 years before diagnosis were associated with significantly elevated odds ratios (OR for BMI $\leqslant 22$ *vs* $>26\,kg\,m^{-2}$; 3.64; 95% confidence interval, CI: 2.27–5.82 and 3.31; 95% CI: 2.04–5.39, respectively). The association with low BMI, however, tended to be weaker and nonsignificant among never smokers and never drinkers.
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Epidemiology

Mortality and incidence of cancers of the oral cavity and oropharynx (oral cancer) have been increasing in many areas of the world in recent decades (Parkin *et al*, 1999; Pisani *et al*, 1999), most notably in young adults (Levi *et al*, 1999; Mackenzie *et al*, 2000; Llewellyn *et al* (2001)).

Risk factors for oral cancer include tobacco smoking and alcohol consumption (Blot *et al*, 1988) and low intake of fruit and vegetables (Bosetti *et al*, 2000; Tavani *et al*, 2001). Recently, the role of other factors, such as poor oral hygiene and dentition (Talamini *et al*, 2000), genetic susceptibility (Warnakulasuriya *et al*, 1998), sexual habits (Garrote *et al*, 2001) and infection by human papillomavirus (Mork *et al*, 2001), has been investigated.

The aim of this report is to assess whether body mass index (BMI) estimated at various points in life is related to oral cancer after taking into account the influence of established aetiological factors.

MATERIAL AND METHODS

The present case–control study is part of an international study on oral cancer and human papillomavirus coordinated by the International Agency for Research on Cancer (IARC) (Herrero *et al*, in press) and carried out simultaneously in Spain, Italy, Ireland, Poland, Cuba, Canada, India, Sudan and Australia. The project was approved by the Ethical Committee of IARC and local research and ethical committees. Informed consent was obtained from each participant in the study.

Eligible cases were incident, histologically confirmed and consecutively diagnosed (between 1996 and 1999) invasive cancers of the oral cavity and oropharynx, codes C 01–C 10 of the second edition of the International Classification of Diseases for Oncology (Percy *et al*, 1990) from four hospitals: two in Barcelona, one in Granada and one in Seville. The overall participation among eligible cases was 76.5% (375 out of 490): 70.6% in Barcelona, 78.2% in Granada and 90.5% in Seville.

Controls were in-patients or outpatients in the same hospitals with conditions unrelated to smoking, alcohol or long-term modification of diet. They were frequency-matched with cases by age (in 5-year periods), gender and hospital. One control was selected for each case in the 3-month time interval after the recruitment of the case. The overall participation among controls was 91% (375 out of 412): 91.1% in Barcelona, 91.2% in Granada and 90.5% in Seville. Exfoliated cells from oral cavity, blood samples and tissue biopsies were also collected from cases and controls.

Identical questionnaires and coding manuals were used in each centre, and all interviewers received the same training and were routinely supervised. Body mass indexes were calculated from self-reported height and weight at diagnosis, 2 years before diagnosis, and in young adulthood, as weight in kilograms divided by the square of height in metres. A difference between the questionnaires used in the three centres was that participants in Barcelona were asked to report their weight at the age of 30 years, while in Granada and Sevilla they reported their weight at the age of 20 years; both are referred to herein as weight in young adulthood. Height, weight and BMI distributions were categorised into approximate tertiles (based on the whole distribution of participants) using the highest tertile as the reference category.

Smoking was defined as having smoked at least one cigarette (or the equivalent) daily for at least 1 year. Subjects were also asked about duration of the habit and amount of tobacco smoked. Drinking was defined as having drunk alcoholic beverages at least once a month, and details on amount and duration were obtained.

Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were calculated for the overall number of participants using

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unconditional multiple logistic regression models (Breslow and Day, 1980) that included as covariates the three design variables: age, gender and centre, and also years of schooling, as an indicator of social and economic status. Odds ratios were further adjusted for: average number of cigarettes smoked per day, average millilitres of ethanol consumed per day and weekly consumption of fruit and vegetables. All these variables were categorized in approximate quartiles of the whole distribution of participants.

Dose–response relationship with risk was evaluated by treating categorical ordinal variables as continuous in the logistic regression models. All *P*-values were derived from two-sided statistical tests.

RESULTS

Table 1 shows the distribution of study participants by gender and age, years of schooling, smoking and drinking habits, and intake of fruit and vegetables. A marked excess of current smokers and alcohol drinkers was found among cases compared to controls of each gender. After adjusting for smoking and drinking habits, there were no differences between cases and controls in years of schooling (data not shown).

Table 2 shows a significant association between oral cancer risk and low BMI ($\leqslant 22$ *vs* $\geqslant 26\,kg\,m^{-2}$) at diagnosis (OR: 3.64; 95% CI: 2.27–5.82), and 2 years before diagnosis (OR: 3.31; 95% CI: 2.04–5.39; $P<0.001$) after adjusting for smoking, drinking and the intake of fruit and vegetables. Conversely, low BMI in young adulthood ($\leqslant 22$ *vs* $\geqslant 25\,kg\,m^{-2}$) was not significantly related to oral cancer risk (OR: 1.32; 95% CI: 0.87–2.00).

Table 1 Sociodemographics characteristics, smoking and alcohol drinking status, fruit and vegetables intake in cases and controls, Spain, 1996–1999

	Males		Females	
	Cases[a] *N* (%)	Controls[a] *N* (%)	Cases[a] *N* (%)	Controls[a] *N* (%)
Age groups (years)				
20–51	77 (25.3)	76 (25.0)	21 (29.6)	18 (25.4)
52–59	76 (25.0)	78 (25.7)	9 (12.7)	10 (14.1)
60–69	91 (29.9)	90 (29.6)	12 (16.9)	13 (18.3)
⩾70	60 (19.8)	60 (19.7)	29 (40.8)	30 (42.2)
Years of schooling				
0	35 (11.5)	37 (12.2)	8 (11.3)	9 (12.7)
1–5	90 (29.6)	92 (30.3)	20 (28.2)	16 (22.5)
6–8	89 (29.3)	88 (28.9)	20 (28.2)	28 (39.4)
⩾9	89 (29.3)	87 (28.6)	22 (31.0)	18 (25.4)
Smoking status				
Never smokers	5 (1.6)	52 (17.1)	50 (70.4)	61 (85.9)
Exsmokers	76 (25.0)	130 (42.8)	6 (8.5)	3 (4.2)
Current smokers	223 (73.4)	122 (40.1)	15 (21.1)	7 (9.9)
Alcohol drinking status				
Nondrinkers	4 (1.3)	27 (8.9)	31 (43.7)	48 (67.6)
Exdrinkers	74 (24.3)	95 (31.2)	15 (21.1)	8 (11.3)
Current drinkers	226 (74.4)	182 (59.9)	25 (35.2)	15 (21.1)
Vegetables intake (portions)				
⩽3	124 (40.8)	93 (30.6)	19 (26.8)	27 (38.0)
4–7	129 (42.4)	127 (41.8)	35 (49.3)	23 (32.4)
⩾8	45 (14.8)	82 (27.0)	16 (22.5)	21 (29.6)
Fruits intake (pieces)				
⩽5	134 (44.1)	74 (24.3)	15 (21.1)	19 (26.8)
6–9	90 (29.6)	112 (36.8)	28 (39.4)	24 (33.8)
⩾10	75 (24.7)	116 (38.2)	27 (38.0)	28 (39.4)
Number of subjects	304 (100)	304 (100)	71 (100)	71 (100)

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

Table 2 Height, weight and body mass index: odds ratios (OR) and confidence intervals (95% CI) for oral cavity and oropharyngeal cancer, Spain 1996–1999

	Cases[a]	Controls[a]	OR[b]	95% CI
Height (cm)				
⩾170	101	124	1.0[c]	
169–163	113	116	1.19	0.78–1.82
⩽162	123	97	1.39	0.88–2.19
P-value for trend			0.103	
At diagnosis				
Weight (kg)				
⩾76	75	147	1.0[c]	
75–66	87	123	1.20	0.78–1.86
⩽65	179	75	3.57	2.32–5.51
P-value for trend			**<0.001**	
Body mass index ($kg\,m^{-2}$)				
⩾26	113	204	1.0[c]	
25–23	104	88	1.84	1.22–2.76
⩽22	112	40	3.64	2.27–5.82
P-value for trend			**<0.001**	
2 years before				
Weight (kg)				
⩾76	80	149	1.0[c]	
75–66	108	126	1.32	0.87–2.00
⩽65	159	79	2.96	1.93–4.53
P-value for trend			**<0.001**	
Body mass index ($kg\,m^{-2}$)				
⩾26	129	207	1.0[c]	
25–23	106	88	1.65	1.11–2.47
⩽22	96	36	3.31	2.04–5.39
P-value for trend			**<0.001**	
In young adulthood				
Weight (kg)				
⩾69	98	135	1.0[c]	
68–61	90	91	1.27	0.82–1.97
⩽60	155	125	1.49	0.99–2.26
P-value for trend			0.065	
Body mass index ($kg\,m^{-2}$)				
⩾25	100	118	1.0[c]	
24–23	85	94	0.98	0.63–1.53
⩽22	140	113	1.32	0.87–2.00
P-value for trend			0.211	

[a]Some strata do not add up to the total because of missing values. [b]Estimates from unconditional regression equations including terms for age, gender, centre, education, smoking and drinking habits, fruits and vegetables intakes. [c]Reference category.

The same variables are re-evaluated in Tables 3 and 4 in separate smoking and drinking strata. A significant association was found between risk and low BMI at diagnosis (OR: 4.12; 95% CI: 1.99–8.51; $P<0.001$) and 2 years before diagnosis (OR: 4.10; 95% CI: 1.97–8.55; $P<0.001$) among current smokers (Table 3). Low BMI in young adulthood was also associated with an increased risk of oral cancer in current smokers (OR: 2.13; 95% CI: 1.07–4.24; $P=0.041$). A similar relationship was observed in former smokers only for BMI at diagnosis (OR: 2.89; 95% CI: 1.07–7.80; $P=0.011$), but was not present in never smokers.

Low BMI at diagnosis (OR: 3.64; 95% CI: 2.18–6.05; $P<0.001$), and 2 years before diagnosis (OR: 3.39; 95% CI: 2.00–5.73; $P<0.001$) were related to an increased risk of oral cancer among ever-drinkers, but not among never drinkers (Table 4).

DISCUSSION

Our results are consistent with some previous studies in showing an inverse association between leanness and increased oral cancer risk (Kabat *et al*, 1994; Franceschi *et al*, 2001). Subjects were asked

Table 3 Height, weight and body mass index in never, former and current smokers: Odds ratios (OR) and confidence intervals (95% CI) for oral cavity and oropharyngeal cancer, Spain 1996–1999

	Never smokers			Former smokers			Current smokers		
	Ca/Co[a]	**OR[b]**	**95% CI**	**Ca/Co[a]**	**OR[c]**	**95% CI**	**Ca/Co[a]**	**OR[c]**	**95% CI**
Height (cm)									
⩾170	4/21	1.0[d]		22/52	1.0[d]		75/51	1.0[d]	
169–163	7/32	0.14	0.01–1.68	29/41	1.79	0.78–4.10	77/43	1.43	0.76–2.70
⩽162	29/41	0.24	0.02–3.12	20/34	1.73	0.69–4.33	74/22	1.88	0.91–3.86
P-value for trend		0.932			0.192			0.062	
At diagnosis									
Weight (kg)									
⩾76	12/40	1.0[d]		25/54	1.0[d]		38/53	1.0[d]	
66–75	11/31	1.44	0.46–4.49	20/50	0.70	0.28–1.74	56/42	1.67	0.85–3.27
⩽65	24/28	2.28	0.79–6.59	28/21	3.60	1.45–8.94	127/26	4.57	2.29–9.09
P-value for trend		0.096			**0.009**			**<0.001**	
Body mass index (kg m^{-2})									
⩾26	21/59	1.0[d]		31/81	1.0[d]		61/64	1.0[d]	
23–25	11/25	1.12	0.38–3.28	25/28	2.34	1.02–5.35	68/35	1.59	0.84–3.02
⩽22	7/9	3.45	0.85–14.1	15/15	2.89	1.07–7.80	90/16	4.12	1.99–8.51
P-value for trend		0.191			**0.011**			**<0.001**	
2 years before									
Weight (kg)									
⩾76	11/40	1.0[d]		24/59	1.0[d]		45/50	1.0[d]	
75–66	13/31	1.92	0.64–5.80	24/49	1.12	0.48–2.63	71/46	1.40	0.73–2.69
⩽65	25/32	2.71	0.94–7.85	22/21	2.54	1.02–6.35	112/26	3.51	1.77–6.96
P-value for trend		0.068			**0.047**			**<0.001**	
Body mass index (kg m^{-2})									
⩾26	20/59	1.0[d]		34/84	1.0[d]		75/64	1.0[d]	
25–23	14/24	2.23	0.76–6.40	25/30	1.69	0.78–3.69	67/34	1.31	0.69–2.48
⩽22	5/9	2.38	0.53–10.7	10/11	1.72	0.56–5.30	81/16	4.10	1.97–8.55
P-value for trend		0.134			0.163			**<0.001**	
In young adulthood									
Weight (kg)									
⩾69	12/32	1.0[d]		22/54	1.0[d]		64/49	1.0[d]	
68–61	8/17	1.11	0.27–4.56	23/33	2.15	0.88–5.27	59/41	1.15	0.59–2.24
⩽60	30/55	0.78	0.28–2.18	25/39	1.68	0.69–4.12	100/31	2.57	1.31–5.06
P-value for trend		0.569			0.229			**0.007**	
Body mass index (kg m^{-2})									
⩾25	14/34	1.0[d]		20/43	1.0[d]		66/41	1.0[d]	
24–23	7/18	1.26	0.33–4.76	20/39	1.20	0.49–2.94	58/37	1.00	0.51–1.98
⩽22	17/40	0.99	0.37–2.69	29/40	1.34	0.56–3.21	94/33	2.13	1.07–4.24
P-value for trend		0.922			0.514			**0.041**	

[a]Some strata do not add up to the total because of a few missing values. [b]Estimates from unconditional regression equations including terms for age, gender, centre, education, drinking habits, fruit and vegetables intake in never smokers. [c]Estimates from unconditional regression equations including terms for age, gender, centre, education, smoking and drinking habits, fruit and vegetables intakes in former and current smokers. [d]Reference category.

about their weight 2 years before diagnosis and in young adulthood in an attempt to evaluate weight before the diagnosis of cancer. Obviously the choice of any specific life period is somewhat arbitrary since the time at which oral cancer started is unknown (Hawkins *et al*, 1999).

As with most case–control studies, our study may be affected by bias and confounding. In particular, the selection of hospital controls is open to criticism. However, we chose as controls individuals who, in the event of a cancer diagnosis, would have been admitted to the same hospitals where the cases had been identified (Rothman, 2002). Another possible weakness is reliance on self-reported weight and height. The absence of a relationship between BMI in young adulthood and subsequent risk of oral cancer might have been influenced by this long time of recall.

We observed a gradual decrease in the magnitude of oral cancer risk from current smokers to former smokers and to nonsmokers. In fact, the influence of leanness on risk lacked significance in nonsmokers, and it was statistically significant in former smokers only at diagnosis, but not 2 years before diagnosis. In contrast, among current smokers, leanness was strongly associated with an increased risk at any one point in time, suggesting that smokers, in addition to being exposed to a high level of carcinogens, may suffer from weight loss as an expression of nutritional deficiency (Franceschi *et al*, 2001). Low BMI might therefore be a result of smoking. The Minnesota Lipid Research Clinic (LRC) Prevalence Study showed, however, that smokers of 15–29 cig/day generally consumed at least as many or more calories as those who had never smoked yet had lower weight (Jacobs and Gottenborg, 1981).

Similarly, it has been shown that ethanol may contribute to this effect by altering absorption and metabolism of many different nutrients (Clinton *et al*, 2000). High ethanol intake causes primary malnutrition by replacing nutrients in the diet and secondary

Table 4 Height, weight and body mass index in never and ever alcohol drinking: odds ratios (OR) and confidence intervals (95% CI) for oral cavity and oropharyngeal cancer, Spain 1996–1999

	Nondrinkers			Ever-drinkers		
	Ca/Co[a]	**OR[b]**	**95% CI**	**Ca/Co[a]**	**OR[c]**	**95% CI**
Height (cm)						
⩾170	2/14	1.0[d]		99/110	1.0[d]	
169–163	5/16	1.70	0.16–18.25	108/100	1.22	0.78–1.89
⩽162	16/28	2.50	0.18–34.54	107/69	1.43	0.88–2.33
P-value for trend		0.449			0.100	
At diagnosis						
Weight (kg)						
⩾76	6/25	1.0[d]		69/122	1.0[d]	
66–75	5/17	2.70	0.49–14.84	82/106	1.18	0.75–1.87
⩽65	15/19	3.74	0.92–15.19	164/56	3.54	2.21–5.66
P-value for trend		**0.047**			**<0.001**	
Body mass index (kg m^{-2})						
⩾26	10/33	1.0[d]		103/171	1.0[d]	
23–25	6/16	2.11	0.51–8.77	98/72	1.82	1.17–2.81
⩽22	6/8	2.06	0.42–10.22	106/32	3.64	2.18–6.05
P-value for trend		**0.495**			**<0.001**	
2 years before						
Weight (kg)						
⩾76	6/26	1.0[d]		74/123	1.0[d]	
75–66	8/19	2.97	0.61–14.49	100/107	1.22	0.78–1.92
⩽65	14//20	3.32	0.81–13.64	145/59	2.90	1.82–4.61
P-value for trend		**0.098**			**<0.001**	
Body mass index (kg m^{-2})						
⩾26	13/37	1.0[d]		116/170	1.0[d]	
25–23	6/12	4.06	0.89–18.49	100/76	1.59	1.04–2.43
⩽22	4/7	1.26	0.23–6.87	92/29	3.39	2.00–5.73
P-value for trend		**0.419**			**<0.001**	
In young adulthood						
Weight (kg)						
⩾69	5/24	1.0[d]		93/111	1.0[d]	
68–61	6/11	4.53	0.69–29.69	84/80	1.15	0.72–1.83
⩽60	19/30	3.89	0.80–18.77	136/95	1.45	0.93–2.27
P-value for trend		**0.238**			0.102	
Body mass index (kg m^{-2})						
⩾25	8/22	1.0[d]		92/96	1.0[d]	
24–23	5/15	1.98	0.38–10.39	80/79	0.90	0.56–1.46
⩽22	9/18	1.37	0.36–5.27	131/95	1.33	0.85–2.09
P-value for trend		**0.920**			0.237	

[a]Some strata do not add up to the total because of a few missing values. [b]Estimates from unconditional regression equations including terms for age, gender, centre, education, smoking habits, fruits and vegetables intake in nondrinkers. [c]Estimates from unconditional regression equations including terms for age, gender, centre, education, smoking and drinking habits, fruits and vegetables intakes in ever-drinkers. [d]Reference category.

malnutrition via malabsorption and cellular injury (Lieber, 1993). Additionally, excessive consumption of alcoholic beverages is often associated with poor dietary habits (Darmon *et al*, 2001). In our study, leanness at diagnosis and 2 years before diagnosis was significantly associated with an increased risk among drinkers, but not in nondrinkers. Overall, however, a strong effect of low BMI on oral cancer risk was confirmed after careful adjustment for smoking, alcohol and dietary habits.

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