Short Communication

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

A Nieto*,1, MJ Sánchez2, C Martínez2, X Castellsagué3, MJ Quintana3, X Bosch3, M Conde1, N Muñoz4, R Herrero5 and S Franceschi6

1Departamento de Ciencias Socio sanitarias, Facultad de Medicina, Universidad de Sevilla, Avda. Sánchez Pizjuán S/n, 41009 Sevilla, Spain; 2Escuela Andaluza de Salud Pública, Granada, Spain; 3Institut Català d’Oncologia, Barcelona, Spain; 4International Agency for Research on Cancer, Lyon, France; 5Proyecto Epidemiológico Guanacaste, Costa Rican Foundation for Health Sciences, San José, Costa Rica

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 ≤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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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 Seville 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
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 (≤ 22 vs ≥ 26 kg m−2) at diagnosis (OR: 3.64; 95% CI: 2.18–6.05), and 2 years before diagnosis (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 (≤ 22 vs ≥ 25 kg m−2) was not significantly related to oral cancer risk (OR: 1.32; 95% CI: 0.87–2.00).

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 (≤ 22 vs ≥ 25 kg m−2) 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...
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 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 | Current smokers | Former smokers |
|----------------------|---------------|-----------------|----------------|
|                      | Ca/Co | OR     | 95% CI | Ca/Co | OR     | 95% CI | Ca/Co | OR     | 95% CI |
| Height (cm)          |       |        |        |       |        |        |       |        |        |
| ≥170                 | 4/21  | 1.0d   |        | 22/52 | 1.0d   |        | 75/51 | 1.0d   |        |
| 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 | 1.0d   |        | 25/54 | 1.0d   |        | 38/53 | 1.0d   |        |
| 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    | 0.095 |        |        | 0.009 |        |        | 0.001 |        |        |
| Body mass index (kg m⁻²) |     |        |        |       |        |        |       |        |        |
| ≥26                  | 21/59 | 1.0d   |        | 31/81 | 1.0d   |        | 61/64 | 1.0d   |        |
| 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 |        |        | 0.001 |        |        | 0.001 |        |        |
| 2 years before       |       |        |        |       |        |        |       |        |        |
| Weight (kg)          |       |        |        |       |        |        |       |        |        |
| ≥76                  | 11/40 | 1.0d   |        | 24/59 | 1.0d   |        | 45/50 | 1.0d   |        |
| 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   | 1.02–6.33 | 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 | 1.0d   |        | 34/84 | 1.0d   |        | 75/64 | 1.0d   |        |
| 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 | 1.0d   |        | 22/54 | 1.0d   |        | 64/49 | 1.0d   |        |
| 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 | 1.0d   |        | 20/43 | 1.0d   |        | 66/41 | 1.0d   |        |
| 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 |        |        |

*Some strata do not add up to the total because of a few missing values. Estimates from unconditional regression equations including terms for age, gender, centre, education, drinking habits, fruit and vegetables intake in never smokers. 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. 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.

**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*      | ORa      | 95% CI  | Ca/Co*        | ORc      | 95% CI  |
| Height (cm)      |             |          |         |               |          |         |
| ≥ 170            | 2/14        | 1.0d     |         | 99/110        | 1.0d     |         |
| 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| 0.049       |          |         |               | 0.100    |         |
| At diagnosis     |             |          |         |               |          |         |
| Weight (kg)      |             |          |         |               |          |         |
| ≥ 76             | 6/25        | 1.0d     |         | 69/122        | 1.0d     |         |
| 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 | 2.54 | 2.21–5.66 |
| P-value for trend| 0.047       |          |         |               | <0.001   |         |
| Body mass index (kg·m⁻²) |             |          |         |               |          |         |
| ≥ 26             | 10/33       | 1.0d     |         | 103/171       | 1.0d     |         |
| 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        | 1.0d     |         | 74/123        | 1.0d     |         |
| 75–66            | 8/19        | 2.97     | 0.61–14.49 | 100/107 | 1.22 | 0.78–1.92 |
| ≤ 65             | 14/20       | 3.22     | 0.81–13.64 | 145/59 | 2.90 | 1.82–4.61 |
| P-value for trend| 0.088       |          |         |               | <0.001   |         |
| Body mass index (kg·m⁻²) |             |          |         |               |          |         |
| ≥ 26             | 13/37       | 1.0d     |         | 116/170       | 1.0d     |         |
| 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        | 1.0d     |         | 93/111        | 1.0d     |         |
| 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        | 1.0d     |         | 92/96        | 1.0d     |         |
| 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    |         |

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

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