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Chewing gum and risk of oesophageal adenocarcinoma: A new hypothesis tested in a population-based study

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ABSTRACT

The aim of this study was to test the hypothesis that chewing gum is associated with risk of oesophageal and cardia adenocarcinoma. A Swedish nationwide, population-based, case-control study was conducted in 1995–1997. All patients were prospectively and uniformly documented and classified shortly after diagnosis. In all, 189 and 262 patients with oesophageal and cardia adenocarcinoma, respectively, and 820 population-based control subjects were interviewed. These patients together constituted 85% of eligible cases occurring in Sweden. Odds ratios (OR) with 95% confidence intervals (CI) were calculated by multivariable logistic regression with adjustment for plausible confounders. Regular users of chewing gum (*P*3 times/week for *P*6 months) were not at increased risk of oesophageal adenocarcinoma (OR 1.0, 95% CI 0.6–2.2), and no duration-response relation was observed ($P = 0.38$). No association between regular gum chewing and cardia adenocarcinoma was found (OR 1.0, 95% CI 0.6–1.7), irrespective of duration of use ($P = 0.56$). In conclusion, with regard to risk of oesophageal or cardia adenocarcinoma, gum chewing seems harmless.

1. Introduction

The incidence of oesophageal adenocarcinoma is increasing more rapidly than virtually any other tumour in western populations.[1–4] Gastro-oesophageal reflux[5–7] and a high body mass[6,8–11] have been established as the strongest known risk factors for these tumours, but these factors cannot entirely explain the increasing incidence trend.[9] The rapidity and suddenness of the increase are more likely to be explained by one or more environmental factors introduced before the increase began in the mid-1970s.[1–3,9] We hypothesised that the increased use of chewing gum in western societies[12] might contribute to the rising incidence of oesophageal adenocarcinoma. Chewing gum meets several criteria of possibly being associated with the increased incidence of oesophageal and cardia adenocarcinoma in western populations: (i) it is an environmental factor; (ii) it was introduced before the increase in this tumour began; (iii) it is widely used in western societies; (iv) its use is increasing;[12] and (v) there are biologically plausible mechanisms for such an association. One such potential mechanism is based on the increased production of saliva due to chewing of gum.[13] Previous research has shown that when the high nitrite content of the saliva, derived from the enterosalivary recirculation of dietary nitrate, first meets the acidic gastric juice at the gastro-oesophageal junction (or above this junction when reflux is occurring), the nitrite is converted to carcinogenic compounds, such as nitrous acid, nitrosative species, and nitric oxide.[14,15] These potentially harmful compounds might act directly on the oesophagogastric mucosa. Alternatively, chewing gum might be linked with an increased risk of oesophageal adenocarcinoma through obesity, since chewing gum increases the appetite.[16] Because

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of the similarities between oesophageal and cardia adenocarcinoma regarding several epidemiological features, including risk factor profiles and incidence patterns,[2,4–8,10,11,17–19] and the close anatomical sites of these tumours, we included cardia adenocarcinoma in our study. The aim of this study was to test the hypothesis that use of chewing gum increases the risk of oesophageal or cardia adenocarcinoma.

2. Patients and methods

The general design of this Swedish nationwide, population-based case-control study has been described in detail elsewhere.[5] The study was based on all native Swedish residents of ages below 80 years, living in Sweden during the period 1995–1997. All newly diagnosed cases of oesophageal or cardia adenocarcinoma were eligible for the study. To reduce tumour misclassification, we introduced prospective, uniform and thorough documentation of the tumours at all 195 relevant collaborating hospital departments throughout Sweden, and finally, 1 pathologist reviewed the histological slides. Control persons were selected randomly from the complete and continuously up-dated population register in Sweden, and frequency-matched to the age and sex distribution of the oesophageal adenocarcinoma patients.

All cases and controls underwent computer-aided face-to-face interviews by professional interviewers from Statistics Sweden. The case patients were interviewed shortly after the histological diagnosis was confirmed. This computerised structured interview partly consisted of questions addressing the use of chewing gum, as well as factors that were considered as potential confounders for the present study, i.e. reflux symptoms (at least weekly heartburn or regurgitation, categorised as yes or no), body mass index (BMI) (grouped into quartiles among the control participants, referring to 20 years before the interview), tobacco smoking status (grouped into never, previous and current, referring to 2 years before the interview), alcohol use (in four groups of total alcohol consumed, referring to 20 years before the interview), socioeconomic status (in six groups, based on occupations of longest lifetime duration), and dietary intake of fruit and vegetables (in three categories based on frequency of average intake, referring to 20 years before the interview). Two variables were constructed regarding the use of chewing gum: (i) ever or never regular use of chewing gum; and (ii) the total lifetime duration in years of such use among regular ever users. Regular use was defined as gum chewing at least three times per week for at least 6 months. The duration variable was categorised into no exposure (0 years, reference category), low exposure (1–9 years), medium exposure (10–25 years), and high exposure (>25 years).

Relative risks were estimated by odds ratios (OR) with 95% confidence intervals (CI), using conditional logistic regression (SAS PHREG procedure). The effect of chewing gum was analysed in both crude and adjusted models. The crude model meant estimates from a conditional logistic model conditioning on the matching variables age and sex, but not adjusted for other variables. The multivariable models were adjusted for all covariates described above. Each exposure was evaluated using the Wald test, which considers all categories of the variable and not just pairwise comparisons with the reference category.

Individual informed consent was obtained from each study participant, and all regional ethics committees in Sweden approved the study.

3. Results

The 189 study patients with oesophageal adenocarcinoma (88% of all eligible patients) and 262 patients with cardia adenocarcinoma (84% of all eligible patients) were compared with 820 control persons (73% of all who had been primarily selected). The proportions of men among the cases of oesophageal adenocarcinoma and cardia adenocarcinoma were 87% and 85%, respectively, and among the control subjects 83%. The median ages in these groups were 69, 66, and 68 years, respectively. Reflux symptoms (occurring at least weekly) and obesity (>30 kg/m^2) were most common among patients with oesophageal adenocarcinoma, followed by cardia cancer patients, and least common among the controls (Table 1). There were more smokers among the cases of cardia adenocarcinoma than among those of oesophageal adenocarcinoma and the controls. No major differences between the groups of study participants were observed regarding high alcohol consumption (>70 g/week) (Table 1).

Data regarding the use of chewing gum and the risk of oesophageal and cardia adenocarcinoma are presented in Table 2. Regular users of chewing gum (least three times per week for at least 6 months) were not at increased risk of this cancer compared with never regular users (adjusted OR 1.0, 95% CI 0.59–2.2). Increasing duration of such use was not associated with a risk of this tumour ($P = 0.38$). The adjusted OR among highly exposed persons, i.e. those who had been regular users of chewing gum for more than 25 years, was 1.7 (95% CI 0.3–10.7) compared with never regular users. The ORs were generally similar in the crude and multivariably

Table 1 – Selected characteristics of the study participants

Variable	Controls ($n = 820$) n (%)	Oesophageal adenocarcinoma ($n = 189$) n (%)	Cardia adenocarcinoma ($n = 262$) n (%)
Reflux symptoms (at least weekly)			
No	685 (84)	76 (40)	187 (71)
Yes	135 (16)	113 (60)	75 (29)
Body mass index (kg/m^2)			
<30	791 (97)	167 (88)	238 (91)
>30	25 (3)	22 (12)	24 (9)
Missing	4 (–)		
Smoking status (2 years before interview)			
Never	325 (40)	57 (30)	43 (16)
Ever	495 (60)	132 (70)	219 (83)
Alcohol consumption			
Low or moderate (<70 g/week)	642 (78)	146 (77)	186 (71)
High (>70 g/week)	178 (22)	43 (23)	76 (29)

Table 2 – Use of chewing gum and risk of oesophageal and cardia adenocarcinoma

Regular use of chewing gum[a]	Controls[b]	Oesophageal adenocarcinoma[b]			Cardia adenocarcinoma[b]		
	n (%)	*n* (%)	Crude OR[c] (95% CI)	Adjusted OR[d] (95% CI)	*n* (%)	Crude OR[c] (95% CI)	Adjusted OR[d] (95% CI)
Never	725 (91)	168 (93)	(reference)	(reference)	231 (90)	(reference)	(reference)
Ever	74 (9)	12 (7)	0.8 (0.4–1.6)	1.0 (0.5–2.2)	25 (10)	1.0 (0.6–1.6)	1.0 (0.6–1.7)
			$P^e = 0.60$	$P = 0.93$		$P = 0.96$	$P = 0.94$
Duration (years)							
No exposure (0)	728 (92)	170 (95)			232 (91)		
Low exposure (1–9)	38 (5)	3 (2)	0.4 (0.1–1.2)	0.4 (0.1–1.6)	10 (4)	0.8 (0.4–1.6)	0.9 (0.4–1.9)
Medium exposure (10–25)	15 (2)	4 (2)	1.4 (0.4–4.4)	2.0 (0.5–7.4)	9 (4)	1.7 (0.7–4.1)	1.7 (0.7–4.3)
High exposure (>25)	11 (1)	2 (1)	1.1 (0.2–5.4)	1.7 (0.3–10.7)	3 (1)	0.7 (0.2–2.7)	0.5 (0.1–2.2)
			$P = 0.39^e$	$P = 0.38^e$		$P = 0.49^e$	$P = 0.56^e$

a Regular use defined as gum chewing at least three times/week for at least 6 months.
b Observations with missing data on any covariate included in the models were excluded from the analyses. Data were missing for 1 case of oesophageal adenocarcinoma regarding never/ever use of chewing gum, but no case of cardia adenocarcinoma or controls. There were 2 oesophageal adenocarcinoma cases, 3 cardia adenocarcinoma cases and 7 controls with missing data regarding duration of use of chewing gum.
c Crude ORs controlled for age and sex by matching.
d ORs controlled for age and sex by matching, and adjusted for reflux symptoms, body mass index, tobacco smoking status, alcohol use, socioeconomic status, and dietary intake of fruit and vegetables.
e Wald test of overall effect across all exposure strata.

adjusted model, indicating lack of strong confounding by the evaluated covariates, including BMI (Table 2).

No increased risk of cardia adenocarcinoma was found among regular users of chewing gum compared with never regular users (adjusted OR 1.0, 95% CI 0.6–1.7). There was no duration-response relation between regular use of chewing gum and risk of this cancer ($P = 0.56$). Persons who had used chewing gum for more than 25 years had an adjusted OR of 0.5 (95% CI 0.1–2.2) compared with never regular users.

4. Discussion

This study provided no evidence supporting our new hypothesis that regular, long-term use of chewing gum might be associated with an increased risk of oesophageal or cardia adenocarcinoma.

This study is, to our knowledge, the first that has addressed the possible role of chewing gum in the aetiology of oesophageal or cardia adenocarcinoma. Despite several well-fitting criteria and the plausible mechanisms that were defined before the initiation of any analyses regarding chewing gum and these tumours, our results indicate a lack of association. Although the sample size of the study was considerable, the relative number of participants reporting regular use of chewing gum was limited, a fact which hampered our precision. On the other hand, since the threshold for classification as a regular user was high, the users were generally highly exposed. The point estimates for ever users were very close to unity; a finding which strongly indicates that chewing gum seems not to increase the risk of oesophageal or cardia adenocarcinoma. The truly population-based design, with strict random sampling of control participants, and the prospective and rapid case ascertainment with high participation frequencies, are strengths of the present study that should have reduced any selection bias. Other advantages include the information available on all plausible confounding factors as well as the prospective and uniform tumour classification. Moreover, the face-to-face interviews conducted with all study participants facilitated valid exposure assessment. The lack of an association should not be explained by recall bias, since it is unlikely that case patients would report less use of chewing gum on account of their cancer than was actually consumed, compared with the reporting by control participants. Furthermore, the hypothesis that chewing gum might potentially affect the risk of these tumours was not known by the study participants, which is a further argument against recall bias.

Although this study did not identify any association between chewing gum and risk of oesophageal or cardia adenocarcinoma, and we found no obvious methodological flaws that could explain the negative results, the hypothesis deserves further attention in other studies before it can be dismissed. One single study cannot rule out a plausible hypothesis. Moreover, any relation, if existing, might occur in other populations, e.g. in other countries or in other birth cohorts.

In conclusion, this nationwide and population-based case-control study suggests that, with regard to risk of oesophageal or cardia adenocarcinoma, it seems harmless to use chewing gum. A continued and intensified search for environmental risk factors that can explain the rising incidence of these tumours is urgently warranted.

Conflict of interest statement

None declared.

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