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Oral disease and risk of oesophageal and gastric cancer in a nationwide nested case-control study in Sweden ☆

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ABSTRACT

The association between the exposure to oral disease and the outcomes of oesophageal and gastric cancer was examined in a Swedish nationwide inpatient register-based nested case-control study in 1964–2008. The study included 6,156 oesophageal squamous-cell carcinoma cases that were compared with 29,993 controls, 2684 oesophageal adenocarcinoma cases that were compared with 15,036 controls and 38,308 gastric cancer cases that were compared with 99,991 controls. For oesophageal squamous cell carcinoma, the age and sex adjusted odds ratio (OR) among patients with a history of oral disease was 1.3 (95% confidence interval (95% CI): 0.9,–1.9), and 1.1 (95% CI 0.8,–1.7) after adjustment for diseases related to alcohol consumption or tobacco smoking. For oesophageal adenocarcinoma, the age and sex adjusted OR was increased (OR 1.7, 95% CI 1.1–2.6), and remained increased (OR 1.6, 95% CI 1.0–2.4) after adjustment for diseases related to smoking or alcohol consumption, gastroesophageal reflux, obesity and ulcer disease. For gastric cancer, no statistically significantly increased risk was observed (age and sex adjusted OR 0.9, 95% CI 0.7–1.1, and fully adjusted OR 0.9, 95% CI 0.7–1.1). In conclusion, this study supports the hypothesis that oral disease increases the risk of oesophageal adenocarcinoma, but not for oesophageal squamous cell carcinoma or gastric cancer. Further investigations are warranted.

1. Introduction

In Europe, the incidence of oesophageal and gastric cancer is within the top twenty and the top five cancers, respectively, together representing about 200,000 persons diagnosed every year.[1] They share a poor prognosis, and they are within the top 15 and the top five among all types of cancer deaths. Use of tobacco and alcohol are the main risk factors for squamous cell carcinoma of the oesophagus, while gastroesophageal reflux and obesity are the main risk factors for the other main histological type of oesophageal cancer, i.e. adenocarcinoma. The main risk factor for gastric cancer (the main histological type is adenocarcinoma) is infection with the bacteria *Helicobacter pylori*, an infection that seems to be inversely associated with oesophageal adenocarcinoma. Also diseases of the oral cavity have been suggested to contribute to the aetiology of these tumours, particularly of oesophageal squamous cell carcinoma[2–8] and gastric cancer.[4,9–11] An increased production of nitrosamines due to an altered oral flora, mechanical injuries of the mucous membrane by undigested

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food, as well as systemic inflammation are among the hypothesised mechanisms behind a possible association between oral disease and cancer.[4,6,12] However, the biological role of nitrate and nitrite has recently been re-evaluated, and possible cytoprotective effects have been highlighted.[13,14] The role of oral disease in the aetiology of oesophageal and gastric tumours is not established. The findings are contradictory and more studies with consistent definition of oral disease together with rigorous control of confounding factors, foremost smoking, are warranted.[15] The aim of this study was to test the hypothesis that diseases of the oral cavity can cause oesophageal or gastric cancer in a large study with long and complete follow-up.

2. Material and methods

2.1. Study design

This was a case–control study, nested in the nationwide Swedish Patient Register during the study period from January 1, 1964 through December 31, 2008. All persons registered in the Patient Register during the study period constituted the cohort from which cases and controls were identified. The percentage of the Swedish population covered by this register was 60% in 1969 and 85% in 1983, and since 1987 it has been 100%. We used the unique personal identity number, assigned to each Swedish resident (about 9 million in total), to link information from three population-based registers of almost complete coverage and high quality. The Patient Register, the Cancer Register and the Cause of Death Register, all maintained by the Swedish National Board of Health and Welfare, were used to obtain information on exposures, outcomes and covariates.[16,17]

2.2. Identification of cases

All new cases of oesophageal squamous cell carcinoma (ICD7150, WHO/HS/CANC/24.1, histology code 146), oesophageal adenocarcinoma (International Classification of Disease (ICD) ICD7 150, WHO/HS/CANC/24.1, histology code 096) and gastric cancer (ICD7 151) diagnosed during the period from January 1, 1970 to December 31, 2008 with no prior other cancer (except non-melanoma skin cancer) were identified in the Cancer Register. To evaluate confounding by tobacco smoking, we also studied first incident lung cancer (ICD162, 163), a tumour strongly associated with smoking. The Swedish Cancer Register was started in 1958 and since that time every clinician, pathologist and cytologist in Sweden must notify each subject having been diagnosed with a new primary cancer. The Cancer Register documents all primary malignant tumours.[18] A comparison with death certificates revealed the non-reporting rate to the Cancer Registry to be less than 2%.[19] The completeness of the reporting of both oesophageal and gastric cancer to the Register has been found to be 98%.[20,21]

2.3. Identification of controls

Controls were randomly selected by frequency-based sampling on four variables: (1) calendar year of the incident cancer of the corresponding case in 5-year periods, (2) sex, (3) age in 5-year age groups and (4) year of the first record (deliveries excluded) in the Patient Register in 5-year periods. If for example the case was a women, aged 60, with a first incident gastric cancer in 2005 and the first record of an in-patient hospitalisation (excluding deliveries) was in 1990, the controls were sampled from women alive in 2005, aged 60, and with their first in-patient hospitalisation in 1990 (excluding deliveries). Such control sampling from the Patient Register would avoid including controls generally healthier than those not hospitalised. To optimise the frequency matching, controls were sampled separately for oesophageal squamous cell carcinoma, oesophageal adenocarcinoma and gastric cancer.

2.4. Definition of exposures

A main or secondary diagnosis of a defined disease of the oral cavity (ICD-10: K00–K14, ICD-8/9: 520–529) since the start of the Patient Register in 1964 represented the study exposure, and was studied with regard to latency time. A case or a control with an inpatient hospitalisation for any such oral disease five or more years prior to inclusion was regarded as exposed. A first record of oral disease less than five years before inclusion was not regarded as exposure.

2.5. Definition of covariates

For evaluation of confounding, we collected information about co-morbidities and known risk factors for oesophageal and gastric cancer by inpatient records in the Patient Register prior to inclusion. These covariates were: (1) *Alcohol related disease*: K85.2 or a history of excessive alcohol consumption recorded in Patient Register as F10, Y15, Y91 (ICD-10) or 291, 303, 980 (ICD-9) or liver disease due to alcohol K70 (ICD-10) or 571.0, 571.2 (ICD-9 and earlier), (2) *Tobacco use*: chronic obstructive pulmonary disease or bronchitis J40–J44 (ICD-10), 490–492 (ICD-9 and earlier), (3) *Obesity*: E65, E66 (ICD-10) 278A (ICD-9), (4) *Gastroesophageal reflux*: K21, (ICD-10), 530B, 530C (ICD-9), and (5) Infection with *H. pylori* assessed through the occurrence of gastric or duodenal ulcer: K25, K26, K27 (ICD-10) 531, 532 and 533 (ICD-9 and earlier).

2.6. Statistical analysis

Estimates of risk of oesophagus and gastric cancer were calculated as odds ratios (OR) with 95% confidence intervals (CI), using unconditional logistic regression analysis. The potential confounders and mediators were defined a priori, and were included in the multivariable adjusted models. The SAS statistical software package (SAS Institute, Cary, NC, USA) was used for the calculations.

3. Results

3.1. Study participants

The study included 6156 oesophageal squamous-cell carcinoma cases who were compared with 29,993 controls, 2684 oesophageal adenocarcinoma cases who were compared with 15,036 controls and 38,308 gastric cancer cases who were compared with 99,991 controls. Some characteristics of the

Table 1 – Characteristics of cases of oesophageal squamous cell carcinoma, oesophageal adenocarcinoma, and gastric cancer and their corresponding age and sex matched controls, Sweden, 1970–2008.

	Oesophageal squamous cell carcinoma				Oesophageal adenocarcinoma				Gastric cancer			
	Cases		Controls		Cases		Controls		Cases		Controls	
	N	%	N	%	N	%	N	%	N	%	N	%
Total	6156	100	29,993	100	2684	100	15,036	100	38,308	100	99,991	100
Sex												
Women	1843	299	8981	29.9	446	16.6	2521	16.8	14,155	37.0	36,944	36.9
Men	4313	701	21,012	70.1	2238	83.4	12,515	83.2	24,153	63.0	63,047	63.1
Age												
40–44	38	0.6	189	0.6	31	1.2	177	1.2	638	1.7	1660	1.7
45–49	134	2.2	660	2.2	85	3.2	481	3.2	1012	2.6	2644	2.6
50–54	284	4.6	1384	4.6	171	6.4	960	6.4	1614	4.2	4213	4.2
55–59	631	10.3	3073	10.2	260	9.7	1455	9.7	2600	6.8	6784	6.8
60–64	915	14.9	4457	14.9	382	14.2	2137	14.2	3990	10.4	10,414	10.4
65–69	1092	17.7	5316	17.7	436	16.2	2443	16.2	5683	14.8	14834	14.8
70–74	1199	19.5	5842	19.5	490	18.3	2738	18.2	7403	19.3	19,326	19.3
75–79	1121	18.2	5457	18.2	457	17.0	2558	17.0	8290	21.6	21,636	21.6
80–84	742	12.1	3615	12.1	372	13.9	2087	13.9	7078	18.5	18,480	18.5
Oral disease												
No	5456	99.5	28,882	99.6	2657	99.0	14,945	99.4	37,103	99.7	97,124	99.7
Yes	33	0.5	125	0.4	27	1.0	91	0.6	104	0.3	303	0.3

study participants are presented in Table 1. There was an expected male predominance for all three cancers. The gastric cancer patients were slightly older than the oesophageal cancer patients. The frequency-based sampling on age and sex provided similar age and sex distribution among cases and controls. The occurrence of disease of the oral cavity was more common among oesophageal adenocarcinoma cancer cases than that among controls, while this distribution was similar in cases of oesophageal squamous cell carcinoma and gastric cancer and their controls. Among covariates, gastroesophageal reflux was particularly more frequent among cases of oesophageal adenocarcinoma compared to the controls, while diseases related to alcohol consumption and chronic obstructive pulmonary disease were much more common among cases of oesophageal squamous cell carcinoma than among their controls (data not shown).

3.2. *Oral disease in relation to risk of oesophageal and gastric cancer*

Table 2 presents the relative risk estimates for the association between diseases of the oral cavity and the risk of oesophageal and gastric tumours. The first model presents the OR for diseases of the oral cavity in relation to cancer adjusted for age and sex only. In the second model we have also adjusted for previous in-patient care due to diseases related to alcohol consumption and to chronic obstructive pulmonary disease (as a marker for tobacco smoking). For oesophageal squamous cell carcinoma the OR in the first model showed a statistically non-significantly increased risk (OR 1.3, 95% CI: 0.9–1.9), which decreased (1.1, 95% CI: 0.8–1.7) after adjustment for diseases related to alcohol consumption and tobacco smoking.

For adenocarcinoma of the oesophagus, the age and sex adjusted risk estimates indicated an increased risk (OR 1.7, 95% CI: 1.1–2.6), and additional adjustment for alcohol and smoking related diseases, gastroesophageal reflux, obesity and ulcer disease did not change the estimate to any great extent (OR 1.6 95% CI: 1.0–2.4). There was no statistically significantly increased risk of gastric cancer among patients with oral disease in any of the adjustment models. The age and sex adjusted OR for lung cancer was 1.2 (1.0–1.4), and additional adjustment for alcohol and tobacco smoking related diseases, decreased the OR to 1.1 (1.0–1.3).

Table 2 – Disease of the oral cavity and the odds ratio (OR) with 95% confidence intervals (CI) of oesophageal squamous cell carcinoma, oesophageal adenocarcinoma, and gastric cancer, Sweden, 1970–2008.

Adjusted for:	Oesophageal squamous cell carcinoma OR (95% CI)	Oesophageal adenocarcinoma OR (95% CI)	Gastric cancer OR (95% CI)
Age and sex	1.3 (0.9–1.9)	1.7 (1.1–2.6)	0.9 (0.7–1.1)
Age, sex, alcohol and COPD*	1.1 (0.8–1.7)	1.6 (1.0–2.5)	0.9 (0.7–1.1)
Age, sex, alcohol, COPD*, reflux, ulcer and obesity	1.1 (0.8–1.7)	1.6 (1.0–2.4)	0.9 (0.7–1.1)

* COPD = chronic obstructive pulmonary disease.

4. Discussion

This study found no evidence of any association between diseases of the oral cavity and the risk of developing oesophageal squamous cell carcinoma, or gastric cancer. However, an increased risk for oesophageal adenocarcinoma remained after adjustment for relevant confounding factors.

The main strengths of the present study include the large sample size, the complete nationwide coverage of all hospitalisations for oral cavity disease and of all cancers of the oesophagus and of the stomach, and the possibility to adjust for confounding by relevant variables. The nationwide register-based design counteracts recall or selection bias. Moreover, by only evaluating oral disease that occurred at least five years before inclusion we reduced the problem with possible reverse causation. However, there are weaknesses that need a discussion. Since the design is based on in-hospital care we only capture the most severe forms of oral cavity disease, resulting in underestimation of the exposure and the covariates. Also, our definition of oral disease includes a broad range of diseases of the oral cavity resulting in a less specific exposure classification. However, all of the included diseases or consequences thereof could result in an altered oral flora, mechanical injury of the mucous membrane, as well as systemic inflammation – all among the hypothesised mechanisms behind a possible association between oral disease and cancer.[4,6,12] Another limitation is that we lack direct information on tobacco smoking, a risk factor for all studied cancers and the main risk factor for periodontal disease.[22] Instead we used hospitalisation for diseases related to smoking,[23,24] as has been done in a previous study of upper gastrointestinal cancer and comorbidity.[25] Although this might be a rather blunt measure of smoking status, the OR for hospitalisation for chronic obstructive pulmonary disorder and the risk of lung cancer was 3.0 (2.9–3.1) indicating that it does reflect smoking status. Similarly, gastroesophageal reflux and obesity showed strong effects for the association between oral disease and oesophageal adenocarcinoma (data not shown).

Several studies have indicated an association between oral disease and oesophageal squamous cell carcinoma,[2–8] whereas a few have found no clear association[9,26] Similarly, the findings regarding gastric cancer are contradictory.[4,6,9–11,26,27] A recent review exploring the evidence of an association between oral disease and, among others, oesophageal and gastric cancer found inconclusive results. A concern was that smoking appeared to be a confounder in several of the evaluated studies.[15] Our study is by far the largest so far evaluating the association between oral disease and oesophageal and gastric cancer. No previous large study has analysed the association between oral disease and oesophageal adenocarcinoma, and our findings of an increased risk deserves further attention. However, despite that we have a large study we only had 27 exposed cases of oesophageal adenocarcinoma.

In conclusion, this large and complete nationwide, nested, case–control study indicates that oral cavity disease does not cause oesophageal squamous cell carcinoma or gastric cancer after adjustment for confounding factors. The novel finding of an association between diseases of the oral cavity and oesophageal adenocarcinoma, mainly unaffected by adjustment for relevant confounders, deserves further attention.

Conflict of interest statement

None declared.

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REFERENCES

1. Ferlay J, Parkin DM, Steliarova-Foucher E. Estimates of cancer incidence and mortality in Europe in 2008. *Eur J Cancer* 2010;**46**(4):765–81.
2. Abnet CC, Kamangar F, Islami F, et al. Tooth loss and lack of regular oral hygiene are associated with higher risk of esophageal squamous cell carcinoma. *Cancer Epidemiol Biomarkers Prev* 2008;**17**(11):3062–8.
3. Abnet CC, Qiao YL, Dawsey SM, Dong ZW, Taylor PR, Mark SD. Tooth loss is associated with increased risk of total death and death from upper gastrointestinal cancer, heart disease, and stroke in a Chinese population-based cohort. *Int J Epidemiol* 2005;**34**(2):467–74.
4. Abnet CC, Qiao YL, Mark SD, Dong ZW, Taylor PR, Dawsey SM. Prospective study of tooth loss and incident esophageal and gastric cancers in China. *Cancer Causes Control* 2001;**12**(9):847–54.
5. Guha N, Boffetta P, Wunsch Filho V, et al. Oral health and risk of squamous cell carcinoma of the head and neck and esophagus: results of two multicentric case-control studies. *Am J Epidemiol* 2007;**166**(10):1159–73.
6. Hiraki A, Matsuo K, Suzuki T, Kawase T, Tajima K. Teeth loss and risk of cancer at 14 common sites in Japanese. *Cancer Epidemiol Biomarkers Prev* 2008;**17**(5):1222–7.
7. Sepehr A, Kamangar F, Fahimi S. Poor oral health as a risk factor for esophageal squamous dysplasia in northeastern Iran. *Anticancer Res*. 2005;**25**(1B):543–6.
8. Wei WQ, Abnet CC, Lu N, et al. Risk factors for oesophageal squamous dysplasia in adult inhabitants of a high risk region of China. *Gut* 2005;**54**(6):759–63.
9. Abnet CC, Kamangar F, Dawsey SM, et al. Tooth loss is associated with increased risk of gastric non-cardia adenocarcinoma in a cohort of Finnish smokers. *Scand J Gastroenterol* 2005;**40**(6):681–7.
10. Demirer T, Icli F, Uzunalimoglu O, Kucuk O. Diet and stomach cancer incidence. A case-control study in Turkey. *Cancer* 1990;**65**(10):2344–8.
11. Watabe K, Nishi M, Miyake H, Hirata K. Lifestyle and gastric cancer: a case-control study. *Oncol Rep* 1998;**5**(5):1191–4.
12. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. *Nature* 2008;**454**(7203):436–44.
13. Larsen FJ, Schiffer TA, Borniquel S, et al. Dietary inorganic nitrate improves mitochondrial efficiency in humans. *Cell Metab* 2011;**13**(2):149–59.

14. Lundberg JO, Weitzberg E. The biological role of nitrate and nitrite: the times they are a-changin'. *Nitric Oxide* 2010;**22**(2):61–3.
15. Fitzpatrick SG, Katz J. The association between periodontal disease and cancer: a review of the literature. *J Dent* 2010;**38**(2):83–95.
16. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekbom A. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. *Eur J Epidemiol* 2009;**24**(11):659–67.
17. Rosen M. National health data registers: a Nordic heritage to public health. *Scand J Public Health* 2002;**30**(2):81–5.
18. Cancer Incidence in Sweden 2007: Centre for Epidemiology. National Board of Health and Welfare. Official Statistics of Sweden 2008.
19. Mattsson B, Wallgren A. Completeness of the Swedish Cancer Register. Non-notified cancer cases recorded on death certificates in 1978. *Acta Radiol Oncol* 1984;**23**(5):305–13.
20. Ekstrom AM, Signorello LB, Hansson LE, Bergstrom R, Lindgren A, Nyren O. Evaluating gastric cancer misclassification: a potential explanation for the rise in cardia cancer incidence. *J Natl Cancer Inst* 1999;**91**(9):786–90.
21. Lindblad M, Ye W, Lindgren A, Lagergren J. Disparities in the classification of esophageal and cardia adenocarcinomas and their influence on reported incidence rates. *Ann Surg* 2006;**243**(4):479–85.
22. Bergstrom J. Tobacco smoking and chronic destructive periodontal disease. *Odontology* 2004;**92**(1):1–8.
23. Chapman KR, Mannino DM, Soriano JB, et al. Epidemiology and costs of chronic obstructive pulmonary disease. *Eur Respir J* 2006;**27**(1):188–207.
24. Dawson DA. Drinking as a risk factor for sustained smoking. *Drug Alcohol Depend* 2000;**59**(3):235–49.
25. Koppert LB, Janssen-Heijnen ML, Louwman MW, et al. Comparison of comorbidity prevalence in oesophageal and gastric carcinoma patients: a population-based study. *Eur J Gastroenterol Hepatol* 2004;**16**(7):681–8.
26. Michaud DS, Liu Y, Meyer M, Giovannucci E, Joshipura K. Periodontal disease, tooth loss, and cancer risk in male health professionals: a prospective cohort study. *Lancet Oncol* 2008;**9**(6):550–8.
27. Hujoel PP, Drangsholt M, Spiekerman C, Weiss NS. An exploration of the periodontitis-cancer association. *Ann Epidemiol* 2003;**13**(5):312–6.