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Reproductive factors and risk of oesophageal cancer, a population-based nested case–control study in Sweden

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BACKGROUND: The role of sex hormonal influence in explaining the strong male predominance in oesophageal adenocarcinoma (EA) needs attention.

METHODS: A nation-wide nested case–control study was initiated from the Swedish Multi-Generation Register with subjects born since 1932. The study exposures were the number of children and age at having the first child. Cases of EA, gastroesophageal junctional adenocarcinoma (EJA), and oesophageal squamous cell carcinoma (SCC) were identified. Ten age- and sex-matched controls were randomly selected for each case. Conditional logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs).

RESULTS: In women, 115 EA, 246 EJA, and 363 SCC were identified. Comparing parous with non-parous women, a decreased risk of EA was indicated (OR = 0.66, 95% CI 0.38–1.14), which became statistically significant when EA and EJA were combined (OR = 0.73, 95% CI 0.53–0.99). All these associations were, however, at least as strong in men. Age at first birth did not show significant risk in women, but showed risk in men. In addition, the results were similar for SCC in both sexes.

CONCLUSION: These findings indicate that associations between the reproductive factors parity and age at first birth, and risk of EA might not be explained by sex hormonal influence.

The incidence of oesophageal adenocarcinoma (EA) has increased rapidly in western populations, particularly in White men (Blot *et al*, 1991; Botterweck *et al*, 2000; Lepage *et al*, 2008; Voutilainen, 2008; Cook *et al*, 2009). Sex hormonal influence has been hypothesised to be involved in the aetiology of EA and gastroesophageal junctional adenocarcinoma (EJA). However, little evidence is currently available, except for a protective effect of breastfeeding in women (Cronin-Fenton *et al*, 2010). Adenocarcinoma and squamous cell carcinoma (SCC) are the main histological types of oesophageal cancer, and they have different risk factor profiles. The male to female ratio (2:1 to 3:1) in SCC is explained by different patterns in the use of the main risk factors, alcohol and tobacco smoking, in men and women (Castellsague *et al*, 1999), but the 5:1 to 7:1 male predominance in EA and junctional adenocarcinoma is not fully explained by the main risk factors, gastroesophageal reflux or obesity (Lofdahl *et al*, 2008; Whiteman *et al*, 2008). Previous studies evaluating endogenous or exogenous sex hormonal factors in relation to risk of EA or junctional adenocarcinoma have been hampered by small sample sizes and have provided contradictory results (Lagergren *et al*, 1998, 2005; Cheng *et al*, 2000; Freedman *et al*, 2010; Bodelon *et al*, 2011; Green *et al*, 2012a). The reproductive factors parity and age at first delivery are regarded as proxies for endogenous sex hormonal exposure in women (Hankinson *et al*, 1995) but because of the rarity of female adenocarcinoma, few cohort studies have

recruited more than 30 cases to examine the aetiologic role of such reproductive factors, except one recent study from the United Kingdom (Green *et al*, 2012b). Furthermore, the previous studies addressing reproductive factors as a proxy for sex hormonal influence did not consider men, but including an evaluation of men could provide a measure of confounding by non-hormonal factors, for example, education, socio-economic status, and lifestyle habits, which might influence the patterns of childbearing. The long history and nation-wide completeness of health registers in Sweden provide excellent opportunities for large and population-based cohort studies with long and complete follow-up. This study used such register data to test the hypothesis that reproductive factors have a role in the aetiology of EA and junctional adeno-carcinoma in women. For assessment of confounding and other biases, we also studied these exposures in men and in relation to oesophageal SCC.

METHODS

Study design

This was a population-based, Swedish nation-wide case–control study, nested within the Swedish Multi-Generation Register during the period 1 January 1932 to 31 December 2008. Subjects aged older than 15 years were included in the study cohort. The study exposures, that is, number of children and age at first childbirth, were assessed from the Multi-Generation Register. The cases comprised all cohort members with a first (no previous gastrointestinal cancer) EA, EJA, or SCC. Cases with cancer of the oesophagus

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or gastroesophageal junction diagnosed during 1960–2008 were identified from the Swedish Cancer Register. Malignancies found first at autopsy were not included. The International Classification of Diseases version seven (ICD7) codes for cancer of the oesophagus and gastroesophageal junction were '150' and '1511', respectively. The histological types were identified using WHO/HS/CANC/24.1 histology codes, in which the code '096' defined adenocarcinoma and '146' defined SCC. Cancer of the gastroesophageal junction was registered separately from 1970.

For each case, 10 control subjects were randomly selected from the source cohort, and matched for sex and age (the same calendar year) of the cases. To be eligible, a control had to be alive, have to had no previous diagnosis of any gastrointestinal cancer, and no history of emigration before the date of the diagnosis of the corresponding case. The number of births was assessed up to the date of the diagnosis of cancer for cases and the corresponding date for the controls. The study endpoints were any cancer, death, emigration, or end of the study period (31 December 2008), whichever occurred first. The study was approved by the Regional Ethical Review Board in Stockholm, Sweden.

Data sources

This study was based on data collected from four nation-wide Swedish population-based registers: the Multi-Generation Register, the Cancer Register, the Register of the Total Population, and the Education Register. The personal identity number, a unique 10-digit number assigned to each resident in Sweden upon birth or immigration, was used for the linkage of all participating individuals between these registers.

The Multi-Generation Register is based on index persons born in 1932 and later who have lived in Sweden since at least 1961. The parents, siblings, and children of each included individual are recorded, thus enabling retrieval of data on number of children and age at childbirths. All cohort members were included in this register.

The Swedish Cancer Register includes the date of diagnosis, site, and histological type of all malignant tumours diagnosed in Sweden since 1958. All newly diagnosed tumours in Sweden must be reported to the Cancer Register by the clinician, pathologist, or cytologist. All diagnosis codes are translated into ICD7. The Cancer Register is 98% complete regarding oesophageal cancer (Lindblad et al, 2006), and at least 96% complete regarding all cancers (Barlow et al, 2008).

The Register of the Total Population provides 100% complete and continuously updated information on dates of birth, death, emigration, and immigration, which were used to define some study endpoints.

The Swedish Education Register provides information on highest attained educational level (years of education) for virtually all Swedish residents. This register is updated yearly.

Statistical analyses

Multivariable conditional logistic regression, conditioned on age and sex, was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) as measures of the association between parity and age at first birth in relation to risk of oesophageal cancers. Parity and age at first birth were included in the same model to disentangle the separate effects of these variables following mutual adjustments (McKnight et al, 1999). Participants with at least one child were categorised as parous (has children for men), whereas those without any children were classified as non-parous (no children for men). Parity was further defined as the number of live births before the cohort member reached any of the endpoints, and was categorised into three groups as follows: 1, 2, or ⩾3 births. Age at first birth was categorised into three groups: <20, 20–29, or ⩾30 years. To identify potential differences in

effects in pre- and post-menopausal women, analyses were stratified into women older or younger than 50 years at diagnosis or index date, a cut-off well in agreement with the previous research (Gold et al, 2001; Rodstrom et al, 2003). Only results for subjects aged 50 years or older were reported because of the limited sample size for subjects younger than 50 years. All exposure variables were similarly categorised in male participants.

Potential confounding factors were considered in the analyses based on different causal hypothetical models for adenocarcinoma or SCC of the oesophagus or gastroesophageal junction: (1) education (categorised into ⩽9, 10–12, or ⩾13 years), (2) diabetes (yes or no, yes including ICD codes: 260 in ICD-8, 250 in ICD-9, and E10–E14 in ICD-10), (3) obesity (yes or no, yes including codes 277 99 in ICD-8, 278A in ICD-9, and E66 in ICD-10), (4) tobacco smoking (yes or no, yes included diagnoses known to be associated with smoking, i.e., chronic obstructive pulmonary disease or bronchitis with codes 501.99, 502, 527.10, or 527.11 in ICD-7, 490–492 in ICD-9 and ICD-8, and J41–J44 in ICD-10, or atherosclerosis or peripheral vascular disease with codes 450.00, 450.10, 453.33 in ICD-7, 440, 443.90 or 445 in ICD-8, 440, 443X in ICD-9, and I70, I73.9 in ICD-10), and (5) alcohol abuse (yes or no, yes including diagnoses known to be associated with over-consumption of alcohol, i.e., alcohol-related liver disease with codes 581.10 or 583.10 in ICD-7, 571.00 or 571.01 in ICD-8, 571.A or 571.C in ICD-9, and K70 in ICD-10, history of excessive alcohol consumption with code 307 or 322 in ICD-7, 291 or 303 in ICD-9 and ICD-8, and F10 in ICD-10, or vitamin-B deficiency associated with alcohol with codes 280–281 in ICD-7, 261.00–262.00 in ICD-8, 265 in ICD-9, or E51–52 G62.1 in ICD-10).

All tests were two-sided with the significance level of 0.05. Analyses were performed using SAS Statistical Package (version 9.0, SAS Institute Inc., Gary, NC, USA).

RESULTS

Study participants

During the follow-up of all women in the study cohort, 115 cases of EA, 246 cases of EJA, and 363 cases of SCC were identified. The corresponding numbers of male cases were 890, 1116, and 917, respectively. The numbers of controls were 10 times the number in each case group (Table 1). The average age at diagnosis in women was 59, 55, and 58 years for EA, EJA, and SCC, respectively. The corresponding ages in men were 59, 56, and 58 years for EA, EJA, and SCC, respectively. Some characteristics of the cases and controls are presented in Table 1. Both female and male cases had, in general, a shorter education. The frequency of people with no children was higher in the controls groups compared with each of the case groups.

Reproductive factors and risk of EA

As presented in Table 2, parous women were at a possibly decreased risk of EA compared with non-parous women, but there was no statistically significant effect (OR = 0.66, 95% CI 0.38–1.14). A decreased risk was also indicated among women with three or more children compared with women with one child, but it was not statistically significant (OR = 0.81, 95% CI 0.44–1.50). Older age at first birth suggested an increased risk compared with younger age, but it was not statistically significant (OR = 1.33, 95% CI 0.57–3.13). In analyses restricted to women aged at least 50 years, similar results were found (Table 3).

Men who had children were at a decreased risk of EA compared with men without children (OR = 0.76, 95% CI 0.65–0.90). However, the number of children did not influence the risk (Table 2). Unlike women, men having their first child at ages over

Table I Characteristics of cases of EA or/and EJA, SCC of the oesophagus, and controls in women and men in Sweden, 1932–2008

	EA				EJA				EA and EJA				SCC of the oesophagus			
	Cases		Controls		Cases		Controlss		Cases		Controls		Cases		Control	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Women																
Total	115		1150		246		2460		361		3610		363		3630	
Education (years)																
<9	50	43	388	34	72	29	693	28	122	34	1081	30	138	38	1215	33
9–12	47	41	470	41	95	39	941	38	142	39	1411	39	127	35	1321	36
>12	12	10	252	22	49	20	600	24	61	17	852	24	50	14	745	21
Missing	6	5	40	3	30	12	226	9	36	10	266	7	48	13	349	10
Number of children																
0	19	17	138	12	41	17	310	13	60	17	448	12	74	20	505	14
1	21	18	190	17	49	20	438	18	70	19	628	17	87	24	675	19
2	40	35	445	39	79	32	1038	42	119	33	1483	41	98	27	1419	39
≥3	35	30	377	33	77	31	674	27	112	31	1051	29	104	29	1031	28
Age at first birth (years)																
<20	19	20	196	19	39	19	341	16	58	19	537	17	62	21	552	18
20–29	66	69	704	70	142	69	1518	71	208	69	2222	70	206	71	2194	70
≥30	11	11	112	11	24	12	291	14	35	12	403	13	21	7	379	12
Men																
Total	890		8900		1116		11160		2006		20060		917		9170	
Education (years)																
<9	366	41	3112	35	387	35	3656	33	753	38	6768	34	365	40	3213	35
9–12	351	39	3426	38	422	38	4063	36	773	39	7489	37	315	34	3191	35
>12	110	12	1923	22	157	14	2277	20	267	13	4200	21	108	12	1810	20
Missing	63	7	439	5	150	13	1164	10	213	11	1603	8	129	14	956	10
Number of children																
0	211	24	1619	18	247	22	2102	19	458	23	3721	19	261	28	1628	18
1	154	17	1581	18	181	16	2070	19	335	17	3651	18	165	18	1737	19
2	290	33	3214	36	387	35	4059	36	677	34	7273	36	269	29	3323	36
≥3	235	26	2486	28	301	27	2929	26	536	27	5415	27	222	24	2482	27
Age at first birth (years)																
<20	42	6	267	4	52	6	318	4	94	6	585	4	55	8	325	04
20–29	472	70	5114	70	640	74	6305	70	1112	72	11419	70	475	72	5324	71
≥30	165	24	1900	26	177	20	2435	27	342	22	4335	27	126	19	1893	25

Abbreviations: EA = oesophageal adenocarcinoma; EJA = gastroesophageal junctional adenocarcinoma; SCC = squamous cell carcinoma.

30 years were at a decreased risk compared with men aged younger than 20 years (OR = 0.64, 95% CI 0.44–0.93), but no dose-response risk was found (*P*-value for trend = 0.34, Table 2).

Reproductive factors and risk of EJA

A possibly decreased risk EJA was found for parous women compared with non-parous women (OR = 0.76, 95% CI 0.52–1.11). Women with three or more children were at a similar risk compared with women with one child (OR = 0.97, 95% CI 0.65–1.46). Older age at first birth indicated a decreased risk (Table 2). When the analyses were restricted to women aged at least 50 years, similar results were found (Table 3).

Men with at least one child were at a decreased risk EJA compared with men without children (OR = 0.86, 95% CI 0.74–1.00), but no such association was found for those who reported to have more than one child (Table 2). Older age at first birth in men was followed by a decreased risk (*P*-value for trend <0.01).

Reproductive factors and risk of EA and EJA

When combining EA and EJA, parous women were at a significantly decreased risk compared with non-parous women (OR = 0.73, 95% CI 0 53–0.99). There was no further reduction in risk in women who had given birth to at least three children compared with those with one child (OR = 0.93, 95% CI 0.67–1.30).

Age at first birth did not influence the risk in women (Table 2). In analyses restricted to women aged at least 50 years, similar results were found (Table 3).

In men, the results were similar, exceptfor a decreased risk of EA and EJA with older age (*P* for trend <0.01).

Reproductive factors and risk of SCC

Women with at least one child showed a decreased risk of SCC compared with women with no children (OR = 0.65, 95% CI 0.48–0.88), but there were no trends for more than one child (*P* = 0.25) or for age at first birth (*P* = 0.15). When the analyses were restricted to women aged at least 50 years, similar results were found (Table 3).

Similar results were observed in men with children compared with men with no children, and in men with more than one child (Table 2). Older age at first birth indicated a decreased risk of SCC (*P*-value for trend = 0.03).

DISCUSSION

This study indicated that childlessness is followed by an increased risk of EA and EJA, whereas the results of having more than one child and age at first delivery were contradictory, regarding the hypotheses of the effects of sex hormone. The results were similar in men and also the risk estimates for SCC were similar.

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Table 2 OR and 95% CI for association among parity, age at first birth, and risk of EA or/and EJA, SCC of the oesophagus in women and men in Sweden, 1932–2008

	EA OR (95% CI)	EJA OR (95% CI)	EA and EJA OR (95% CI)	SCC of the oesophagus OR (95% CI)
Women				
Parity[a,b]				
Non-parous	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Parous	0.66 (0.38–1.14)	0.76 (0.52–1.11)	0.73 (0.53–0.99)	0.65 (0.48–0.88)
Number of children[a,c]				
1	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
2	0.89 (0.50–1.58)	0.69 (0.47–1.01)	0.74 (0.54–1.02)	0.49 (0.36–0.68)
⩾3	0.81 (0.44–1.50)	0.97 (0.65–1.46)	0.93 (0.67–1.30)	0.72 (0.51–1.00)
P-value for trend	0.43	0.54	0.94	0.25
Age at first birth (years)[a,c]				
<20	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
20–29	1.13 (0.64–1.99)	0.92 (0.63–1.36)	0.99 (0.73–1.37)	1.05 (0.75–1.45)
⩾30	1.33 (0.57–3.13)	0.80 (0.45–1.42)	0.95 (0.59–1.53)	0.61 (0.35–1.07)
P-value for trend	0.42	0.32	0.71	0.15
Men				
Parity[a,b]				
No children	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Has children	0.76 (0.65–0.90)	0.86 (0.74–1.00)	0.82 (0.73–0.91)	0.57 (0.49–0.67)
Number of children[a,c]				
1	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
2	0.97 (0.78–1.20)	1.04 (0.86–1.25)	1.01 (0.87–1.16)	0.91 (0.74–1.13)
⩾3	0.92 (0.74–1.16)	1.04 (0.85–1.27)	0.99 (0.85–1.15)	0.90 (0.71–1.13)
P-value for trend	0.75	0.69	0.60	0.21
Age at first birth (years)[a,c]				
<20	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
20–29	0.65 (0.46–0.91)	0.66 (0.49–0.90)	0.65 (0.52–0.82)	0.70 (0.51–0.98)
⩾30	0.64 (0.44–0.93)	0.49 (0.35–0.69)	0.55 (0.43–0.71)	0.60 (0.41–0.87)
P-value for trend	0.34	<0.01	<0.01	0.03

Abbreviations: CI = confidence interval; EA = oesophageal adenocarcinoma; EJA = gastroesophageal junctional adenocarcinoma; OR = odds ratio; SCC = squamous cell carcinoma. [a]ORs were estimated from conditional logistic regression models, conditioned on age and sex, and adjusted for education, diabetes, obesity, tobacco smoking and alcohol abuse, and when appropriate for parity and age at first birth. [b]'Non-parous' labelled women without children and 'parous' labelled women with children. The variable had the same categories for men but was named as 'no children' and 'has children'. [c]Men or women have children.

Strengths of the present study include the nation-wide, population-based design, large sample size, complete and long-term follow-up, and high validity of Swedish register data. Furthermore, the use of men for comparison made it possible to differentiate between sex hormonal exposure effects and confounding effects. However, a limitation was the inability to control for some specific potential confounders, that is, age at menarche and menopause, use of oral contraceptives, hormone replacement therapy (HRT), non-steroidal anti-inflammatory drugs, and dietary factors. Although there is a possibility to retrieve data on oral contraceptives and hormone replacement therapy from the Swedish Prescription Register, this registry was initiated only in July 2005, leaving a too short follow-up time to include enough number of cases, especially female cases. Moreover, education, place of residence, and diagnoses related to some other potential confounding factors were considered, that is, diabetes, obesity, tobacco smoking, and alcohol abuse. Selection and information biases were not an issue, as the study was nested within a well-defined cohort, and the exposure information was recorded independent of the outcome. Information on stillbirths was not available, but stillbirths constitute only a small proportion of all births in Sweden with a rate of 1.7% in 1955 that decreased to 0.4% in 1985 (2000).

The rarity of female cases of EA and EJA has prohibited studies addressing the association with reproductive factors. And the few available studies have provided inconsistent results. Compared with the present study, previous studies included substantially fewer female cases of EA, except a recent cohort study from the United Kingdom (Green *et al*, 2012b). Briefly, a case–control study from the United Kingdom, including 74 cases of EA, reported a statistically non-significant protective effect of having three or more children compared with no children (OR = 0.69, 95% CI 0.23–2.01). In the Women's Health Initiative clinical trials from the United States, which identified 23 EA and 34 SCC in post-menopausal women, non-significant results were observed (Bodelon *et al*, 2011). A pooled analysis including cases from Ireland, the United Kingdom, the United States, and Australia suggested that lower parity might be related to a higher risk of EA and EJA, but the results were not statistically significant (Cronin-Fenton *et al*, 2010). Our group conducted a case–control study of 63 female cases of EA and EJA in which no associations with parity or age at delivery were identified (Lagergren *et al*, 2005). The National Institutes of Health of the United States of the American Association of Retired Persons (NIH AARP diet and Health cohort) identified 25 EA and found a potentially decreased risk of high parity and older age at first birth, although not statistically significant (Freedman *et al*, 2010). However, similar results were observed for SCC, and they did not study the association in men (Freedman *et al*, 2010). Our study regarding parity is consistent with results from the Million Women Study Cohort conducted in United Kingdom, which included substantial female oesophageal cancer cases (Green *et al*, 2012b). Both studies found a protective association of parous women compared with non-parous women, although the role of age at first birth were not clear in the both studies. Furthermore, the evidence from men in our study indicated the possible confounding factors other than sex hormones. The previous results combined with the results of the present study do not strongly support association between reproductive factors and the risk of EA.

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Table 3 OR and 95% CI for association among parity, age at first birth, and risk of EA or/and EJA, SCC of the oesophagus in women and men aged equal or older than 50 years, Sweden, 1932–2008

	EA ≥50 OR (95% CI)	EJA ≥50 OR (95% CI)	EA and EJA ≥50 OR (95% CI)	SCC of the oesophagus ≥50 OR (95% CI)
Women				
Parity[a,b]				
Non-parous	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Parous	0.66 (0.37–1.17)	0.69 (0.45–1.06)	0.67 (0.47–0.94)	0.68 (0.50–0.94)
Number of children[a,c]				
1	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
2	0.81 (0.45–1.49)	0.75 (0.47–1.20)	0.77 (0.53–1.11)	0.53 (0.38–0.75)
≥3	0.72 (0.38–1.38)	1.21 (0.75–1.96)	1.01 (0.69–1.49)	0.68 (0.48–0.98)
P-value for trend	0.30	0.26	0.80	0.19
Age at first birth (years)[a,c]				
<20	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
20–29	1.11 (0.60–2.03)	0.83 (0.53–1.30)	0.94 (0.66–1.35)	0.99 (0.69–1.40)
≥30	1.01 (0.39–2.65)	0.80 (0.41–1.60)	0.89 (0.51–1.55)	0.54 (0.29–1.00)
P-value for trend	0.90	0.37	0.53	0.10
Men				
Parity[a,b]				
No children	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Has children	0.77 (0.64–0.93)	0.92 (0.76–1.10)	0.84 (0.74–0.96)	0.61 (0.52–0.72)
Number of children[a,c]				
1	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
2	1.05 (0.83–1.32)	1.10 (0.89–1.36)	1.07 (0.92–1.25)	0.99 (0.78–1.24)
≥3	0.99 (0.78–1.27)	1.09 (0.86–1.37)	1.04 (0.88–1.23)	0.91 (0.71–1.17)
P-value for trend	0.96	0.78	0.86	0.24
Age at first birth (years)[a,c]				
<20	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
20–29	0.65 (0.45–0.95)	0.76 (0.53–1.10)	0.71 (0.55–0.92)	0.66 (0.46–0.93)
≥30	0.66 (0.44–1.00)	0.57 (0.38–0.85)	0.61 (0.46–0.82)	0.55 (0.37–0.82)
P-value for trend	0.48	0.01	<0.01	0.01

Abbreviations: CI = confidence interval; EA = oesophageal adenocarcinoma; EJA = gastroesophageal junctional adenocarcinoma; OR = odds ratio; SCC = squamous cell carcinoma. [a]ORs were estimated from conditional logistic regression models, conditioned on age and sex, and adjusted for education, diabetes, obesity, tobacco smoking, and alcohol abuse, and when appropriate for parity and age at first birth. [b]'Non-parous' labelled women without children and 'parous' labelled women with children. The variable had the same categories for men but was named as 'no children' and 'has children'. [c]Men or women have children.

Other reproductive factors, that is, age at menarche, age at menopause, surgery with excision of genital organs, and breast-feeding, have also been studied in relation to risk of EA and EJA in women, although most of them did not reveal significant associations (Cronin-Fenton *et al*, 2010; Freedman *et al*, 2010; Bodelon *et al*, 2011). An exception is a decreased risk of these tumours related to an increased level of breastfeeding among women, which was first suggested in a case–control study from the United Kingdom (Cheng *et al*, 2000), and later confirmed in a pooled analysis of large population-based case–control studies (Cronin-Fenton *et al*, 2010). Exogenous hormone replacement treatment does not seem to substantially influence the risk of EA (Lofdahl *et al*, 2008; Bodelon *et al*, 2011); however, a nested case–control study from the United Kingdom recently identified a significant reduced risk of oesophageal cancer in women who prescribed hormone therapy. Our study restricted the analysis to women or men aged equal or older than 50 years, as the hypothesis is that endogenous hormone levels would fall at the time of menopause (Rannevik *et al*, 1995), and hormone therapy might involve supplementation with exogenous oestrogens. As there were too few cases of pre-menopause in this study, we only included a sub-analysis for the hypothetical post-menopausal population (age ≥50 years). The results of this subgroup were similar as in the overall analysis.

The finding of similar effects of reproductive factors in women and men on risk of EA or EJA in the present study highlights the possibility of confounding by non-hormonal exposures. In addition, the similar effects comparing adenocarcinomas with SCC suggest an influence of confounding rather than causality. Several factors unrelated to sex hormones might explain the inverse association between parity and these tumours, for example, education, socio-economic status, culture, religion, diet, and other lifestyle habits. Older age at first birth, for example, would be related to higher education level, which might explain the similar risk patterns in women and men in this study. Moreover, people with children might smoke less, use less alcohol, or lead a generally healthier life than those without children. In addition, women with a higher education level or socio-economic status would use hormone replacement treatment more often.

In conclusion, this large and population-based study suggests that reproductive factors are associated with risk of EA or EJA, but the similar findings in women and men, and the similar results in patients with SCC could not rule out factors other than sex hormones that explain these associations. However, the lack of information of age at menarche/menopause and HRT use in the present study could not counteract the hormonal hypothesis completely.

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