EUROPEAN JOURNAL OF CANCER 46 (2010) 2067–2076

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Reproductive and sex hormonal factors and oesophageal and gastric junction adenocarcinoma: A pooled analysis

Deirdre P. Cronin-Fenton [a,], Liam J. Murray [b], David C. Whiteman [c], Chris Cardwell [d], Penelope M. Webb [c], Susan J. Jordan [c,d], Douglas A. Corley [e], Linda Sharp [f], Jesper Lagergren [g], on behalf of the Barrett's Esophagus, Adenocarcinoma Consortium (BEACON) Investigators*

[a] *Department of Clinical Epidemiology, Aarhus University Hospital, Olof Palmes 43-45, 8200 Aarhus N, Denmark*
[b] *Centre for Clinical and Population Sciences, Queen's University Belfast, Northern Ireland*
[c] *Division of Population Studies and Human Genetics, Queensland Institute for Medical Research, Herston, Brisbane, Queensland, Australia*
[d] *School of Population Health, University of Queensland, Brisbane, Australia*
[e] *Division of Research, Kaiser Permanente, Oakland, CA, USA*
[f] *National Cancer Registry of Ireland, Cork, Ireland*
[g] *Upper Gastrointestinal Research, Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden*

ARTICLE INFO

Article history:
Received 14 January 2010
Received in revised form 22 March 2010
Accepted 24 March 2010
Available online 22 April 2010

Keywords:
Oesophageal cancer
Adenocarcinoma
Breastfeeding
Cancer epidemiology
Epidemiology

ABSTRACT

Background: The rapidly rising incidence and the striking male predominance are as yet unexplained features of oesophageal and gastric junction adenocarcinoma. Few and underpowered studies have examined the impact of female reproductive factors on risk of these adenocarcinomas in women. We therefore pooled data on women from four population-based case-control studies to examine the association of female reproductive and sex hormonal factors with oesophageal and gastric junction adenocarcinoma.

Methods: Data on women from case-control studies conducted in Ireland, the United Kingdom (UK), Australia and United States of America (USA) were pooled. Multivariable logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for a range of reproductive factors, adjusted for age, study and major risk factors for oesophageal and gastric junction adenocarcinoma.

Results: We included 218 cases and 862 controls. Among parous women, a reduced risk of oesophageal and gastric junction adenocarcinoma was found after breastfeeding (OR = 0.58, 95% CI = 0.37–0.92) and the risk decreased with increased duration of breastfeeding (>12 months OR = 0.42, 95% CI = 0.23–0.77). The endogenous reproductive factors such as parity, menstruation, history of pregnancy and the exogenous factors such as use of oral contraceptives and of hormone replacement therapy were not statistically significantly associated with oesophageal and gastric junction adenocarcinoma.

Conclusion: Our findings suggest that breastfeeding is associated with a decreased risk of oesophageal and gastric junction adenocarcinoma. The potential mechanism of this association warrants further investigation.

* *Corresponding author:* Address: Department of Clinical Epidemiology, Aarhus University Hospital, Olof Palmes Alle 43-45, 8200 Aarhus N, Denmark. Tel.: +45 89424816; fax: +45 89424800.
E-mail address: dc@dce.au.dk (D.P. Cronin-Fenton).
0959-8049/$ - see front matter
doi:10.1016/j.ejca.2010.03.032

1. Introduction

The incidence rate of oesophageal adenocarcinoma is, for reasons not fully understood, increasing rapidly in western countries, particularly among white men.[1–5] The strong (6:1) male predominance is not explained by gender-related differences in known risk factors (reflux, obesity or smoking) or protective factors (fruit and vegetable consumption or *Helicobacter pylori* infection).[6] The gender-associated difference in incidence rates may be attributable to an as yet unidentified protective factor in women, such as female sex hormones.

Few studies have investigated the association of exogenous hormones and risk of oesophageal adenocarcinoma. A cohort study in Sweden[7] found no association between the incidence of oesophageal adenocarcinoma among men who had previously received anti-androgenic treatment (i.e. oestrogen) for prostate cancer. However, research has suggested a decreased incidence of oesophageal adenocarcinoma among men with a history of prostate cancer.[8,9] A study conducted among women in the United Kingdom (UK) found no protective effect of hormone replacement therapy in the aetiology of oesophageal adenocarcinoma.[10] A population-based study which investigated the relation between body mass index (BMI) and reflux, two major risk factors for oesophageal adenocarcinoma, found stronger positive associations among pre-menopausal than post-menopausal women.[11] However, the use of hormone replacement therapy increased the strength of the association between BMI and reflux among post-menopausal women. Together, these data suggest that some of the key risk factors for oesophageal adenocarcinoma are modified by female hormones. A potential role of oral contraceptives has never been investigated.

Regarding endogenous reproductive factors, pregnancy may be associated with oesophageal adenocarcinoma risk. Gastrooesophageal reflux,[12] for example, is common during pregnancy.[13] Furthermore, an increased susceptibility to *H. pylori*, a potential protective factor in oesophageal adenocarcinoma development,[14] during pregnancy has been documented.[15] A Swedish case-control study reported no evidence of an association of parity with oesophageal adenocarcinoma.[16] However, a dose-dependent association between duration of breastfeeding and risk of oesophageal adenocarcinoma has been reported in a case-control study from the UK.[17] The impact of endogenous reproductive factors on oesophageal carcinogenesis has otherwise not been examined.

The relatively low incidence of oesophageal adenocarcinoma among women has prohibited much research of reproductive factors in the aetiology of oesophageal adenocarcinoma. The few available studies have been hampered by low statistical power. We therefore pooled data on female participants from four large and independent case-control studies which investigated risk factors for oesophageal and gastric junction adenocarcinomas and present the largest population-based study to date aiming to investigate whether endogenous and exogenous reproductive and hormonal factors play a role in the aetiology of oesophageal and gastric junction adenocarcinoma.

2. Patients and methods

2.1. Selection of studies for analysis

The Barrett's Esophagus and Adenocarcinoma Consortium (BEACON) was formed in 2005 by an international group of investigators with completed or ongoing case-control studies of oesophageal adenocarcinoma and/or Barrett's oesophagus. The consortium aims to provide an open scientific forum for epidemiologic research into the aetiology and prevention of these diseases by facilitating the sharing of data across population-based studies. Therefore rather than a meta-analytical approach relying on published data only, BEACON enables pooled analyses of individual-level data (both published and unpublished) from population-based studies. A total of 14 separate case-control studies are included in BEACON. We reviewed the questionnaires of the 14 case-control studies of oesophageal adenocarcinoma in BEACON. We identified four population-based studies that included details on reproductive and sex hormonal factors in their questionnaires: (1) the Factors INfluencing the Barrett's Adenocarcinoma Relationship (FINBAR) study,[18] (2) the UK women's study,[17] (3) the Australian Cancer Study[19] and (4) a US Kaiser Permanente case-control study.[20] We included only the female participants from each study. Cases included women with histologically confirmed adenocarcinoma of the oesophagus or the gastrooesophageal junction (ICD-0: C15.0–C15.9).

The Irish study (FINBAR)[21] was conducted in Ireland and Northern Ireland between 2002 and 2004. It included three groups of participants: patients with Barrett's oesophagus, patients with oesophageal adenocarcinoma and population-based controls matched on 5-year age bands and gender. Only oesophageal and gastric junction adenocarcinoma patients and controls were considered in the current study.

The UK women's study[17] included oesophageal adenocarcinoma cases incident between 1993 and 1996 in four areas of the UK. One female control was matched to each case by age (within 5 years) and general practice.

The Australian Cancer Study was conducted between 2001 and 2005.[19] Population-based controls were frequency matched by age (within 5 years) and gender to oesophageal and gastric junction adenocarcinoma cases.

The US Kaiser Permanente case-control study was nested within a cohort of Kaiser Permanente health plan members who underwent a health checkup and completed a questionnaire between 1964 and 1973. For each oesophageal and gastric junction adenocarcinoma case, eight controls, matched for age, gender and year of health checkup were selected from within the health plan.[20]

To ensure a uniform outcome, in the Australian study, we excluded patients with adenocarcinomas at sites denoted as 'cardia', 'gastrooesophageal/cardia', 'unknown' and 'biopsy' ($n = 10$) as these were not included in all studies. In the United States (US) study, we excluded patients with adenocarcinomas at the gastric cardia and gastric body ($n = 11$).

2.2. Study variables

Information available on reproductive factors included menstrual factors (age at menarche and age when periods

stopped), childbearing (number of pregnancies and number of children), breastfeeding (history and duration), use of hormone replacement therapy (ever or never) and use of oral contraceptives (ever or never). A pregnancy was defined as any pregnancy of at least 6 months duration, including still or live births, but not miscarriages. Not all of the variables were available for each study; studies have been included in the analysis for factors for which data were available.

Data on potential confounding factors included age at diagnosis or interview (categorised into three groups,<50, 50–65, ⩾65 years), tobacco smoking status (never or ever over lifetime), alcohol consumption (never or ever over lifetime), education (years of formal education), history of reflux (never or ever; assessed at 5 years before diagnosis for the Irish study, 10 years before diagnosis for the Australian, without latency period in the UK and US studies), BMI before diagnosis (1 year in Australian and US studies and 5 years in Irish) and at heaviest during their lifetime (UK study). Please see On-line Appendix A for details of questions from each study.

2.3. Statistical methods

A single file including comparable variables, coded in a uniform format, was compiled from the four datasets. In univariable analyses, χ^2 tests were used to examine differences in variables between case and control groups. The statistical analyses were carried out using two approaches, both of which generated similar results, therefore only the results of the aggregated analysis are presented.

2.3.1. Aggregated analysis approach

In the combined dataset, the odds ratios (ORs) and associated 95% confidence intervals (CIs) associating reproductive and hormone factors and risk of oesophageal and gastric junction adenocarcinoma were estimated using multiple logistic regression. All ORs were adjusted for age and study. In a multivariable model, ORs were also adjusted for BMI (in three groups: <24, 24–28, ⩾28), history of reflux (ever, never or unknown), years of education (<12 years or 12+years), alcohol drinking (ever or never) and tobacco smoking status (ever or never). These factors were included in models *a priori* due to their association with oesophageal and gastric junction adenocarcinoma risk. Forest plots were constructed to illustrate findings from logistic regression analyses in individual studies and the pooled analysis.

2.3.2. Meta-analysis approach (data not presented)

The analysis was carried out using two steps.[22] The ORs and associated 95% CIs associating reproductive and hormone factors and risk of oesophageal and gastric junction adenocarcinoma were estimated for each study using multiple logistic regression. Minimally adjusted ORs were adjusted for age. Multivariable ORs were further adjusted, as above, for BMI, history of reflux, years of education, alcohol and tobacco smoking status. The second step involved pooling the study-specific ORs using a random effects model.[22] Heterogeneity between the results of different studies was examined by inspecting the forest plot of a meta-analysis for variation in effects. Tests for heterogeneity were considered in conjunction with graphical approaches to determine between-study differences.

All statistical tests were 2-sided. Analyses were carried out using STATA 9.0 (StataCorp, Texas, USA).

2.4. Ethics

Ethical approval was obtained from the local ethical boards where each study was carried out.

3. Results

Characteristics of the 218 oesophageal and gastric junction adenocarcinoma female cases and 862 female control subjects included are outlined in Table 1. Compared to the control group, the case group had a higher prevalence of reflux and smoking and a higher BMI.

Data on reproductive factors are presented in Table 2. No associations were observed between menstruation variables, i.e. age at first period or age when periods ended and risk of oesophageal and gastric junction adenocarcinoma. Compared with women with three or more children, those with one or two children (OR = 1.20, 95% CI = 0.84–1.72) and no children (OR = 1.27, 95% CI = 0.77–2.10) had a possibly increased risk of oesophageal adenocarcinoma (p for trend = 0.048). The apparent protective effect for three or more children was not evident in the minimally adjusted model; a history of reflux was most responsible for this confounding. The suggested protective effect associated with parity remained after adjusting for breastfeeding in an analysis restricted to parous women (data not shown).

Compared with women who had children but did not breastfeed, a history of breastfeeding was associated with a statistically significantly reduced risk of oesophageal and gastric junction adenocarcinoma (OR = 0.58, 95% CI = 0.37–0.92). This association was dose-dependent (p for trend with increased duration of breastfeeding < 0.001), and women who breastfed for more than 12 months were at a 58% decreased risk of developing oesophageal and gastric junction adenocarcinoma (OR = 0.42, 95% CI = 0.23–0.77). Forest plots showing the association for occurrence and duration of breastfeeding with oesophageal and gastric junction adenocarcinoma are presented in Figs. 1a and 1b . As the UK study had previously reported an inverse association with breastfeeding[13] we also repeated our analysis excluding this study. The trend of a decreased risk of oesophageal and gastric junction adenocarcinoma associated with breastfeeding remained (ever breastfed compared with parous women who never breastfed: OR = 0.75, 95% CI = 0.43–1.33; breastfeeding duration: >0–6 months OR = 0.78, 95% CI = 0.40–1.52; 7–12 months: OR = 0.78, 95% CI = 0.38–1.60; >12 months: OR = 0.61, 95% CI = 0.30–1.23, p for trend = 0.017).

We repeated our analyses comparing oesophageal adenocarcinoma cases only with controls. We observed similar findings for women with a history of breastfeeding (compared with parous women who never breastfed), OR = 0.42, 95% CI = 0.24–0.75. Women who breastfed for over 12 months had a 78% decreased risk of oesophageal adenocarcinoma (OR = 0.22, 95% CI = 0.10–0.52).

Table 1 – Characteristics of controls and oesophageal and gastric junction adenocarcinoma cases: Irish, Australian, United Kingdom (UK) and United States (US) studies.

Variables	Controls (n = 862) Number (%)	Cases (n = 218) Number (%)	p-Value
Age (years)			<0.001
<50	289 (34)	32 (15)	
50–65	332 (39)	81 (37)	
⩾65	241 (28)	105 (48)	
Education (years)			<0.001
<12	412 (48)	136 (62)	
12+	424 (49)	78 (36)	
Missing/ invalid data[a]	26 (3)	4 (2)	
History of reflux			<0.001
No	387 (45)	72 (33)	
Yes	290 (34)	130 (60)	
Unknown	185 (21)	16 (7)	
Body mass index[b]			<0.001
<24	318 (37)	51 (23)	
24–28	266 (31)	62 (28)	
⩾28	278 (32)	105 (48)	
Smoking status			<0.001
Never	497 (58)	81 (37)	
Ever	362 (42)	137 (63)	
Missing[c]	3 (<1)	0	
Alcohol consumption			0.06
Never	222 (26)	70 (32)	
Ever	639 (74)	148 (67)	
Missing[c]	1 (<1)	0	
Study			
Australian	540 (63)	83 (38)	
Irish	40 (5)	35 (16)	
US	208 (24)	26 (12)	
UK	74 (9)	74 (34)	

[a] Missing/ invalid education data from 30 individuals included in the US study.
[b] Missing bodymass index data on 47 individuals.
[c] Missing smoking and alcohol data on three participants in the Australian study.

Ever users of hormone replacement therapy had a possibly decreased risk of oesophageal and gastric junction adenocarcinoma (OR = 0.75, 95% CI = 0.45–1.24), but this was not statistically significant. When we restricted this to oesophageal adenocarcinoma cases only, there was no evidence of a decreased risk (OR = 0.99, 95% CI = 0.49–2.01). Use of oral contraceptives was not associated with risk of oesophageal and gastric junction adenocarcinoma (Table 2).

4. Discussion

The current study indicated an inverse association between history of breastfeeding and risk of oesophageal and gastric junction adenocarcinoma. Other endogenous or exogenous reproductive factors did not appear to be strongly associated with risk of this tumour.

Data regarding the impact of breastfeeding on gastrointestinal disease are sparse. Research on lactation has suggested a protective effect regarding cancers of the stomach, pancreas and gallbladder.[23–25] Reasons for a reduced risk of oesophageal and gastric junction adenocarcinoma among women with a history of breastfeeding remain to be elucidated. Investigators in the UK study speculated that the protective effect was attributable to higher weight gain after pregnancy in women who did not breastfeed.[17] However, there is no evidence in published literature that lactation prevents obesity[26,27] Although we adjusted for BMI, we had no information on BMI during a woman's childbearing years, which may have been substantially different to their BMI shortly before oesophageal and gastric junction adenocarcinoma diagnosis. Such weight change may have been differential between cases and controls.

A reduced risk of oesophageal and gastric junction adenocarcinoma associated with breastfeeding is biologically plausible and may be similar to that observed in 'hormone-related' cancers (breast, endometrial and ovary[28–30]). For example, a high frequency of oestrogen receptor (ER) expression, particularly ER beta,[31] has been reported in oesophageal adenocarcinoma.[32–34] ER-expressing breast tumours seem to have a better prognosis if they also express the anti-apoptotic protein, bcl-2.[35,36] Likewise, a loss of bcl-2 expression in oesophageal adenocarcinoma may lead to tumour progres-

Table 2 – Reproductive factors and risk of oesophageal and gastric junction adenocarcinoma in Irish, United Kingdom (UK), United States (US) and Australian studies, expressed as odds ratios (ORs) with 95% confidence intervals (CIs).

Variables	Controls (n = 862) Number (%)[a]	Cases (n = 218) Number (%)[a]	Minimally adjusted ORs (95% CI) [b]	Adjusted ORs [c] (95% CI)
Age at first menstruation (years)[g]				
⩽13	473 (60)	86 (60)	1.00	1.00
>13	313 (40)	56 (39)	0.89 (0.39–2.04)	1.01 (0.35–2.91)
Missing	2 (<1)	2 (1.4)	–	–
Age when periods ended (years)[h]				
50–70	178 (31)	39 (33)	1.00	1.00
<50	217 (37)	58 (49)	1.15 (0.72–1.86)	1.06 (0.64–1.77)
Not stopped	39 (7)	5 (4)	0.64 (0.18–2.30)	0.65 (0.17–2.50)
Missing	146 (25)	16 (14)	–	–
Ever pregnant[f]				
No	74 (11)	22 (11)	1.00	1.00
Yes	578 (88)	166 (86)	0.91 (0.52–1.60)	1.02 (0.55–1.87)
Missing	2 (<1)	4 (2)	–	–
Number of children[e]				
3+ (ref)	368 (43)	90 (41)	1.00	1.00
1–2	334 (39)	90 (41)	1.18 (0.82–1.69)	1.20 (0.84–1.72)
0	158 (18)	34 (16)	1.03 (0.64–1.68)	1.27 (0.77–2.10)
Missing	2 (0.2)	4 (2)	–	–
Breastfeeding among women who had a live birth[f,d]				
Had children; never breastfed	101 (16)	52 (27)	1.00	1.00
Had children; ever breastfed	450 (69)	102 (53)	0.52 (0.33–0.80)	0.58 (0.37–0.92)
Unknown	14 (2)	11 (6)	–	–
Missing	89 (14)	27 (14)	–	–
Children and Breastfeeding Duration[f]				
Had children; never breastfed	101 (15)	52 (27)	1.00	1.00
Breastfed ⩽6 months	137 (21)	46 (24)	0.62 (0.37–1.04)	0.63 (0.37–1.08)
Breastfed 7–12 months	120 (18)	27 (14)	0.55 (0.31–0.98)	0.65 (0.35–1.18)
Breastfed > 12 months	189 (29)	26 (14)	0.34 (0.19–0.61)	0.42 (0.23–0.77)
Unknown	18 (3)	14 (7)	–	–
Missing	89 (14)	27 (14)	–	–
Use of hormone replacement therapy among women aged >50 years[h]				
Never	218 (52)	64 (61)	1.00	1.00
Ever	193 (46)	35 (33)	0.76 (0.47–1.23)	0.75 (0.45–1.24)
Missing	5 (1)	6 (6)	–	–
Use of oral contraceptives[g]				
No	373 (47)	78 (54)	1.00	1.00
Yes	411 (52)	60 (42)	1.00 (0.61–1.63)	0.92 (0.55–1.54)
Missing	4 (0.5)	6 (4)	–	–

[a] Persons with inapplicable or missing data in any covariate included in the models were excluded.
[b] Minimally adjusted odds ratios adjusted for age and study.
[c] Models adjusted for age, reflux symptoms (GOR and/or heartburn), years of education, smoking status, alcohol, BMI and study.
[d] Models for breastfeeding among parous women also adjusted for number of children.
[e] Models included data from Irish, UK, US and Australian studies.
[f] Models included data from Irish, UK and Australian studies (n = 846).
[g] Models included data from Irish, US and Australian studies (n = 932).
[h] Models included data from Irish and Australian studies (n = 698).

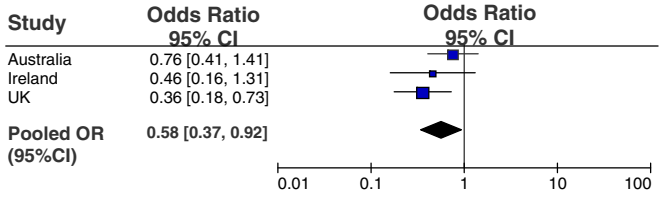

Fig. 1a – Forest plot showing odds ratios (ORs) and associated 95% confidence interval (95% CI) for the risk of oesophageal and gastric junction adenocarcinoma associated with ever/never breastfeeding among parous women. Estimates from logistic regression in individual studies and pooled analysis (total). Data from Australian, Irish and United Kingdom (UK) studies.

sion and poorer survival.[37] Oxytocin, a hormone associated with breastfeeding, can regulate tumour growth via activation of the oxytocin receptor. Both oxytocin and its receptor have shown expression throughout the gastrointestinal tract, although their functions in the tract are not known.[38] The relatively transient depletion of oestrogen and progesterone[39] and high levels of prolactin and oxytocin[26] during breastfeeding are unlikely to have a direct impact on oesophageal and gastric junction adenocarcinoma development later in life. However, lactation may cause long-term modification of endogenous hormones or their receptors; increasing prolactin and oxytocin and decreasing a woman's cumulative exposure to oestrogen, and in this way decreasing the risk of oesophageal and gastric junction adenocarcinoma. The androgen receptor has also been shown to be expressed on oesophageal adenocarcinoma cells, however, its impact on oesophageal adenocarcinoma aetiology and prognosis is not clear.[40]

The role of parity has been investigated in upper gastrointestinal cancers with inconsistent findings.[41–43] The only previous study on parity and oesophageal and gastric junction adenocarcinoma reported no association.[16] The suggestions of an inverse association between increasing parity and risk of oesophageal and gastric junction adenocarcinoma in the current study seem uncertain since the results were not statistically significant. Like the breastfeeding finding, our finding of a decreased risk of oesophageal and gastric junction adenocarcinoma associated with increased parity may be somewhat reflective of the decreased risk of breast, ovarian and endometrial cancers associated with multiparity.[44–46] Age at first birth, another important risk factor for breast cancer, was only available for one study, and so we were unable to assess the effect of this variable on oesophageal and gastric junction adenocarcinoma risk with any precision. It is difficult to draw conclusions from our parity findings, however, as we found no association between ever being pregnant and oesophageal and gastric junction adenocarcinoma.

In the only previous study of the role of hormone replacement therapy and oesophageal and gastric junction adenocarcinoma aetiology, based on prescription data, no protective effect was found[10] (OR = 1.17, 95% CI = 0.41–3.32). A lack of association with oesophageal and gastric junction adenocarcinoma was also reported in a cohort study of prostate cancer patients who used oestrogen therapy suggesting no role of exogenous female hormones on oesophageal and gastric junction adenocarcinoma aetiology among men.[7] Our findings may indicate a reduced risk of oesophageal and gastric junction adenocarcinoma associated with the use of hormone replacement therapy, but this was not evident when we restricted our analysis to oesophageal adenocarcinoma cases only.

Approximately 1–2% of the population have Barrett's metaplasia,[56] a precursor lesion to oesophageal and gastric junction adenocarcinoma. The incidence rate of oesophageal and gastric junction adenocarcinoma among individuals with Barrett's is approximately 6–7 per 1000-person years.[56] To the best of our knowledge, however, there are as yet no published studies investigating the association of reproductive and sex hormonal factors with the risk of Barrett's metaplasia or progression to adenocarcinoma in patients with Barrett's metaplasia. This warrants investigations, since any potential

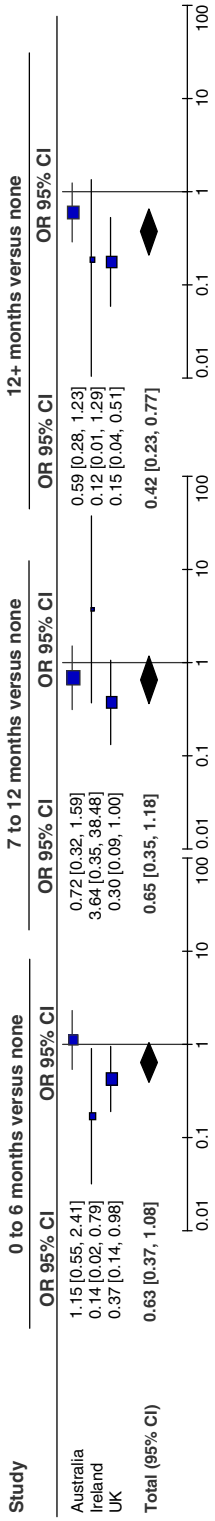

Fig. 1b – Forest plot showing odds ratios (ORs) and associated 95% confidence interval (95% CI) for the risk of oesophageal gastric junction adenocarcinoma with duration of breastfeeding among parous women. Estimates from logistic regression in individual studies and pooled analysis (total). Data from Australian, Irish and UK studies.

association could have major implications for our understanding of oesophageal carcinogenesis and prevention.

The present study has strengths and limitations. A major strength is the availability of individual-level data for the pooled analyses, which are not available in meta-analyses of published data. Through the pooling of four population-based datasets, this is the largest study to date to investigate the impact of reproductive factors on oesophageal and gastric junction adenocarcinoma risk in women. Yet, for at least some of the reproductive variables, our study had limited statistical power, partly because data were not collected on all exposures of interest in each study. Moreover, information on these variables was collected by slightly different questions (see Appendix), thus increasing the risk of misclassification.

Women included in the current study were mostly Caucasian, so our findings may not be generalisable to patients of other ethnicity. However, oesophageal and gastric junction adenocarcinoma has the highest incidence rate among Caucasians. We had no information on the type of hormone replacement therapy or on the use of injected contraceptives, which may have impacted on oesophageal and gastric junction adenocarcinoma risk, although the frequency of the latter is likely to be low among women of the age of those in the current studies. While we analysed age when menstrual periods stopped, we could not distinguish between natural menopause, hysterectomy or women who went straight onto hormone replacement therapy and whose periods continued. We were unable to adjust for dietary factors,[47,48] *H. pylori* infection or medications such as NSAIDs, since these data were not available from all of the studies. The timing of BMI measurement was not uniform for the four studies. However, a pattern of higher BMI among cases than controls was seen in each of the included studies. Moreover, we adjusted our analyses for the study to account for such differences in data coding and categorisation. The higher frequency of reflux and higher BMI among women with oesophageal and gastric junction adenocarcinoma compared with controls concur with the published research, thus lending validity to our data.[11,49–52] Case-control studies may be subject to recall bias. It seems likely, however, that recall of the number of children, pregnancies, use of hormone replacement therapy or oral contraceptives and history of breastfeeding is quite accurate.[53] It is unlikely that the recall of these factors differs substantially between cases and controls as they are not known to be associated with this cancer.

Our study may be prone to selection bias. Some of the included studies report low response rates among controls[21] – 65%, 48% and 42% in the UK, Australian and Irish studies, respectively. There was no evidence of a sex-related difference in response rates for the Australian study; this information was not available for the Irish study. Individuals who participated as controls may have been more health conscious than cases, which may be particularly relevant to the observed reduced risk of oesophageal and gastric junction adenocarcinoma among individuals who breastfed. Compared with women who did not breastfeed, those who breastfed had longer years of education, were more frequently alcohol drinkers, had lower BMI, lower prevalence of a history of reflux and were less frequently smokers. We observed a relatively high rate of breastfeeding among women included in the current study, particularly among controls (Australian study 82% controls versus 78% cases; Irish study 58% controls versus 38% cases, UK study 76% controls versus 53% cases). This compares to approximately 60% of women in the UK Million Women's Study[54] and 86% of women in Australia in 1995 (rates from earlier years were not available).[55]

In summary, through pooling of four population-based case-control studies, we were able to investigate the impact of reproductive variables on oesophageal and gastric junction adenocarcinoma incidence in women. The findings suggest an inverse association between breastfeeding and risk of oesophageal and gastric junction adenocarcinoma. The underlying biological mechanism(s) remains to be elucidated. Most studied reproductive and sex hormonal factors did not seem to be associated with oesophageal and gastric junction adenocarcinoma, but the uncertainty about some of these factors, particularly a possible decreased risk of oesophageal and gastric junction adenocarcinoma with increased parity and use of hormone replacement therapy, supports the need to further evaluate these factors in prospective studies.

Funding

At the outset of this study, Dr. Cronin-Fenton was an All-Ireland Cancer Consortium Cancer Epidemiology Research Fellow funded by the Health Research Board of Ireland. Drs. Whiteman, Webb and Jordan are supported by Research Fellowships from the National Health and Medical Research Council of Australia.

Irish study: All-Ireland Cancer Consortium; Health Research Board of Ireland and Research and Development Office, Northern Ireland.

US study: Kaiser Permanente, Community Benefits Grant, US NIH, R01 DK63616.

UK study: Funding provided by Chief Scientist Office (Scotland), the LORS (East Anglia), Special Trustees of the Nottingham University Hospitals and the Medical Research Council.

Australian study: Funding provided by the Queensland Cancer Fund and the National Health and Medical Research Council (NHMRC) of Australia (Programme No. 199600).

Conflict of interest statement

None declared.

Acknowledgements

The authors would like to thank Lesley A. Anderson (Irish study), Nirmala Pandeya (Australian study), Wei K Zhao (US study) for datasets and programming; Wong-Ho Chow, Tom Vaughan and Olof Nyren for establishing BEACON and for useful comments on the final manuscript; Christian Abnet for useful comments on the final manuscript; the nurses, interviewers and individuals who interviewed patients and collected data for these studies and all the women and their families included in the current study.

Appendix A

Questions used to derive variables for the pooled analysis of reproductive factors and oesophageal gastric junction adenocarcinoma: Irish FINBAR case-control study, Australian case-control study, US Kaiser Permanente case-control study, UK Women's case-control study.

		Irish	Australian	United States	United Kingdom
General factors					
Age (years)		Age at interview	Age at interview	Age at interview	Age at interview
Body mass index (BMI)	Height (cm) Weight (kg)	BMI 5 years before interview	Height (cm) Weight 1 year before interview	Height (inches) Weight (pounds)	Adult height Heaviest lifetime weight
Cigarette smoking status (current/ former/ never)		Derived Variable: 'In your entire lifetime did you smoke a total of 100 cigarettes or more?'	Current/ ex-smoker/ non-smoker	Derived Variable: 'Before one year ago did you ever smoke cigarettes? In the past year did you smoke cigarettes?'	Ever smoked as much as one cigarette/day; at approx 2 years prior to interview for cases, to accommodate those who gave up smoking as a result of disease; at interview for controls
Alcohol consumption (yes/no)		Derived variable: grams of alcohol consumed per week	Current, ex or non-drinkers (Where people stopped drinking <1.5 years previously they were classed as current drinkers)	Derived variable: At any time in the past were you a heavy alcohol drinker? In the past year did you drink alcohol?	Ever taken as much as one drink per month
Education (an ordinal variable specific to each study)		How many years in total did you spend in fulltime education – school, university or other training?	Derived variable: 'Completed any further study since leaving school?'	Derived variable: Years of education	Derived variable: Age in years on leaving school
Heartburn, reflux or indigestion (yes/no)	Reflux (yes/no)	Have you ever had frequent acid reflux i.e. a bitter taste of stomach acid which has come up to the back of your throat (not including the last 5 years)?	Have you ever had acid reflux?	Derived variable: Before one year ago had you often had heartburn, indigestion or stomach pain	Derived variable: Ever suffered from indigestion
	Heartburn (yes/no)	Have you ever had frequent heartburn (a burning or ache behind the breastbone that is not due to heart problems) not including the last 5 years?	Derived from duration of frequent heartburn/reflux		
Reproductive factors					
Age at menstruation (years)		At what age did you have your 1st menstrual period?	Age at first period	How old were you when monthly menstrual periods began?	–
Age when periods stopped (years)		At what age did you have your last menstrual period?	How old were you when your periods stopped completely?	If you no longer have menstrual periods, at what age did you stop having them?	–
Ever pregnant (yes/no)		Have you given birth?	Ever pregnant: No/ Yes	Derived variable: How many children have you had and how many miscarriages have you had?	Based on questions about number of children and whether had had stillbirths or miscarriages; information on terminations not sought

Appendix A (*continued*)

	Irish	Australian	United States	United Kingdom
Number of children	How many children have you had? Excluding miscarriages, including stillbirths	Derived from ever had a live or still birth?	How many children have you had?	Number of children
Ever breastfed (Yes/no)	Did u ever breastfeed any of your children?	Ever breast feed after any pregnancy?	–	Ever breastfed
Duration of breast-feeding (total duration in months for all pregnancies)	Thinking about all your children how long did you breastfeed in total?	Total duration of breastfeeding	–	Total months spent breastfeeding; summed over all children
Ever use of hormone replacement therapy (HRT) (yes/no)	Do you or have you ever used HRT (hormone replacement therapy)?	Derived variable: Yes if subject had taken either implant, patch, cream or tablet forms of HRT	–	–
Use of oral contraceptives (yes/no)	Did you ever take the pill (oral contraceptive)?	Ever use of pill, minipill or injected contraceptives	Derived variable: 'In the past year have you taken pills to control your periods? and In the past year have you taken pills to prevent pregnancy?'	–

[a] As the questions from all studies were slightly different, the most similar questions were used to derive variable in order to minimise misclassification.

REFERENCES

1. Devesa SS, Blot WJ, Fraumeni Jr JF. Changing patterns in the incidence of esophageal and gastric carcinoma in the United States. *Cancer* 1998;**83**(10):2049–53.
2. Lepage C, Rachet B, Jooste V, Faivre J, Coleman MP. Continuing rapid increase in esophageal adenocarcinoma in England and Wales. *Am J Gastroenterol* 2008;**103**(11):2694–9.
3. Voutilainen M. Epidemiological trends in oesophageal cancer in the Nordic countries. *Scand J Gastroenterol* 2008;**43**(3):323–7.
4. Botterweck AA, Schouten LJ, Volovics A, Dorant E, van Den Brandt PA. Trends in incidence of adenocarcinoma of the oesophagus and gastric cardia in ten European countries. *Int J Epidemiol* 2000;**29**(4):645–54.
5. Vizcaino AP, Moreno V, Lambert R, Parkin DM. Time trends incidence of both major histologic types of esophageal carcinomas in selected countries, 1973–1995. *Int J Cancer* 2002;**99**(6):860–8.
6. Lofdahl HE, Lu Y, Lagergren J. Sex-specific risk factor profile in oesophageal adenocarcinoma. *Br J Cancer* 2008;**99**(9):1506–10.
7. Lagergren J, Nyren O. Do sex hormones play a role in the etiology of esophageal adenocarcinoma? A new hypothesis tested in a population-based cohort of prostate cancer patients. *Cancer Epidemiol Biomarkers Prev* 1998;**7**(10):913–5.
8. Abazov VM, Abbott B, Abolins M, et al. Search for anomalous top-quark couplings with the D0 detector. *Phys Rev Lett* 2009;**102**(9):092002.
9. Hayat MJ, Howlader N, Reichman ME, Edwards BK. Cancer statistics, trends, and multiple primary cancer analyses from the Surveillance, Epidemiology, and End Results (SEER) Program. *Oncologist* 2007;**12**(1):20–37.
10. Lindblad M, Garcia Rodriguez LA, Chandanos E, Lagergren J. Hormone replacement therapy and risks of oesophageal and gastric adenocarcinomas. *Br J Cancer* 2006;**94**(1):136–41.
11. Nilsson M, Johnsen R, Ye W, Hveem K, Lagergren J. Obesity and estrogen as risk factors for gastroesophageal reflux symptoms. *JAMA* 2003;**290**(1):66–72.
12. Solaymani-Dodaran M, Logan RF, West J, Card T, Coupland C. Risk of oesophageal cancer in Barrett's oesophagus and gastro-oesophageal reflux. *Gut* 2004;**53**(8):1070–4.
13. Richter JE. Medical management of patients with esophageal or supraesophageal gastroesophageal reflux disease. *Am J Med* 2003;**115**(Suppl. 3A):179S–87S.
14. Rokkas T, Pistiolas D, Sechopoulos P, Robotis I, Margantinis G. Relationship between *Helicobacter pylori* infection and esophageal neoplasia: a meta-analysis. *Clin Gastroenterol Hepatol* 2007;**5**(12):1413–7. p. 1417 e1–2.
15. Lanciers S, Despinasse B, Mehta DI, Blecker U. Increased susceptibility to *Helicobacter pylori* infection in pregnancy. *Infect Dis Obstet Gynecol* 1999;**7**(4):195–8.
16. Lagergren J, Jansson C. Sex hormones and oesophageal adenocarcinoma: influence of childbearing? *Br J Cancer* 2005;**93**:859–61.
17. Cheng KK, Sharp L, McKinney PA, et al. A case-control study of oesophageal adenocarcinoma in women: a preventable disease. *Br J Cancer* 2000;**83**(1):127–32.
18. Anderson LA, Watson RG, Murphy SJ, et al. Risk factors for Barrett's oesophagus and oesophageal adenocarcinoma: results from the FINBAR study. *World J Gastroenterol* 2007;**13**(10):1585–94.

19. Whiteman DC, Sadeghi S, Pandeya N, et al. Combined effects of obesity, acid reflux and smoking on the risk of adenocarcinomas of the oesophagus. *Gut* 2008;**57**(2):173–80.
20. Corley DA, Kubo A, Zhao W. Abdominal obesity and the risk of esophageal and gastric cardia carcinomas. *Cancer Epidemiol Biomarkers Prev* 2008;**17**(2):352–8.
21. Anderson LA, Johnston BT, Watson RG, et al. Nonsteroidal anti-inflammatory drugs and the esophageal inflammation-metaplasia-adenocarcinoma sequence. *Cancer Res* 2006;**66**(9):4975–82.
22. Stukel TA, Demidenko E, Dykes J, Karagas MR. Two-stage methods for the analysis of pooled data. *Stat Med* 2001;**20**(14):2115–30.
23. Inoue M, Ito LS, Tajima K, et al. Height, weight, menstrual and reproductive factors and risk of gastric cancer among Japanese postmenopausal women: analysis by subsite and histologic subtype. *Int J Cancer* 2002;**97**(6):833–8.
24. Heuch I, Kvale G. Does breastfeeding affect the risk of gastric cancer? *Int J Cancer* 2003;**106**(6):982–3.
25. Heuch I, Jacobsen BK, Albrektsen G, Kvale G. Reproductive factors and pancreatic cancer risk: a Norwegian cohort study. *Br J Cancer* 2008;**98**(1):189–93.
26. Heinig MJ, Dewey KG. Health effects of breast feeding for mothers: a critical review. *Nutr Res Rev* 1997;**10**(1):35–56.
27. Ip S, Chung M, Raman G, et al. Breastfeeding and Maternal and Infant Health Outcomes in Developed Countries Rockville, MD: Agency for Healthcare Research and Quality, Tufts-New England Medical Center Evidence-based Practice Center, under Contract No. 290-02-0022; 2007.
28. Lukanova A, Lundin E, Akhmedkhanov A, et al. Circulating levels of sex steroid hormones and risk of ovarian cancer. *Int J Cancer* 2003;**104**(5):636–42.
29. Kim Y, Choi JY, Lee KM, et al. Dose-dependent protective effect of breast-feeding against breast cancer among ever-lactated women in Korea. *Eur J Cancer Prev* 2007;**16**(2):124–9.
30. Purdie DM, Green AC. Epidemiology of endometrial cancer. *Best Pract Res Clin Obstet Gynaecol* 2001;**15**(3):341–54.
31. Liu L, Chirala M, Younes M. Expression of estrogen receptor-beta isoforms in Barrett's metaplasia, dysplasia and esophageal adenocarcinoma. *Anticancer Res* 2004;**24**(5A):2919–24.
32. Tiffin N, Suvarna SK, Trudgill NJ, Riley SA. Sex hormone receptor immunohistochemistry staining in Barrett's oesophagus and adenocarcinoma. *Histopathology* 2003;**42**(1):95–6.
33. Akgun H, Lechago J, Younes M. Estrogen receptor-beta is expressed in Barrett's metaplasia and associated adenocarcinoma of the esophagus. *Anticancer Res* 2002;**22**(3):1459–61.
34. Utsumi Y, Nakamura T, Nagasue N, Kubota H, Morikawa S. Role of estrogen receptors in the growth of human esophageal carcinoma. *Cancer* 1989;**64**(1):88–93.
35. Ciocca DR, Elledge R. Molecular markers for predicting response to tamoxifen in breast cancer patients. *Endocrine* 2000;**13**(1):1–10.
36. O'Driscoll L, Linehan R, MK S, et al. Lack of prognostic significance of survivin, survivin-deltaEx3, survivin-2B, galectin-3, bag-1, bax-alpha and MRP-1 mRNAs in breast cancer. *Cancer Lett* 2003;**201**(2):225–36.
37. Raouf AA, Evoy DA, Carton E, et al. Loss of Bcl-2 expression in Barrett's dysplasia and adenocarcinoma is associated with tumor progression and worse survival but not with response to neoadjuvant chemoradiation. *Dis Esophagus* 2003;**16**(1):17–23.
38. Monstein HJ, Grahn N, Truedsson M, Ohlsson B. Oxytocin and oxytocin-receptor mRNA expression in the human gastrointestinal tract: a polymerase chain reaction study. *Regul Pept* 2004;**119**(1–2):39–44.
39. Battin DA, Marrs RP, Fleiss PM, Mishell Jr DR. Effect of suckling on serum prolactin, luteinizing hormone, follicle-stimulating hormone, and estradiol during prolonged lactation. *Obstet Gynecol* 1985;**65**(6):785–8.
40. Tihan T, Harmon JW, Wan X, et al. Evidence of androgen receptor expression in squamous and adenocarcinoma of the esophagus. *Anticancer Res* 2001;**21**(4B):3107–14.
41. Kaneko S, Tamakoshi A, Ohno Y, Mizoue T, Yoshimura T. Menstrual and reproductive factors and the mortality risk of gastric cancer in Japanese menopausal females. *Cancer Causes Control* 2003;**14**(1):53–9.
42. La Vecchia C, D'Avanzo B, Franceschi S, et al. Menstrual and reproductive factors and gastric-cancer risk in women. *Int J Cancer* 1994;**59**(6):761–4.
43. Furukawa H, Iwanaga T, Hiratsuka M, et al. Gastric cancer in young adults: growth accelerating effect of pregnancy and delivery. *J Surg Oncol* 1994;**55**(1):3–6.
44. Kelsey JL, Gammon MD, John EM. Reproductive factors and breast cancer. *Epidemiol Rev* 1993;**15**(1):36–47.
45. Sueblinvong T, Carney ME. Current Understanding of Risk Factors for Ovarian Cancer. *Curr Treat Options Oncol* 2009.
46. Pike MC, Pearce CL, Wu AH. Prevention of cancers of the breast, endometrium and ovary. *Oncogene* 2004;**23**(38): 6379–91.
47. Gonzalez CA, Pera G, Agudo A, et al. Fruit and vegetable intake and the risk of stomach and oesophagus adenocarcinoma in the European Prospective Investigation into Cancer and Nutrition (EPIC-EURGAST). *Int J Cancer* 2006;**118**(10):2559–66.
48. Terry P, Lagergren J, Hansen H, Wolk A, Nyren O. Fruit and vegetable consumption in the prevention of oesophageal and cardia cancers. *Eur J Cancer Prev* 2001;**10**(4):365–9.
49. Kocher HM, Linklater K, Patel S, Ellul JP. Epidemiological study of oesophageal and gastric cancer in south-east England. *Br J Surg* 2001;**88**(9):1249–57.
50. Lagergren J. Oesophageal cancer and gastro-oesophageal reflux: what is the relationship? *Gut* 2004;**53**(8):1064–5.
51. Lagergren J, Bergstrom R, Lindgren A, Nyren O. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. *N Engl J Med* 1999;**340**(11):825–31.
52. Nilsson M, Lagergren J. The relation between body mass and gastro-oesophageal reflux. *Best Pract Res Clin Gastroenterol* 2004;**18**(6):1117–23.
53. Karatela S, Purdie DM, Green AC, Webb PM, Whiteman DC. Repeatability of self-reported information for population-based studies of cancer. *Asian Pac J Cancer Prev* 2006;**7**(2):303–8.
54. Liu B, Beral V, Balkwill A. Childbearing, breastfeeding, other reproductive factors and the subsequent risk of hospitalization for gallbladder disease. *Int J Epidemiol* 2009;**38**(1):312–8.
55. Amir LH, Donath SM. Socioeconomic status and rates of breastfeeding in Australia: evidence from three recent national health surveys. *Med J Aust* 2008;**189**(5):254–6.
56. Reid BJ, Li X, Galipeau PC, Vaughan TL. Barrett's oesophagus and oesophageal adenocarcinoma: time for a new synthesis. *Nat Rev Cancer* 2010;**10**(2):87–101.