2017-02-21

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Clin Gastroenterol Hepatol. 2016;14(3):338-347.e1
http://doi.org/10.1016/j.cgh.2015.10.005
http://hdl.handle.net/10616/45542

The Male Predominance in Esophageal Adenocarcinoma

Short title: Male predominance in EAC

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Grant support: Supported by the Swedish Research Council (SIMSAM) and the Swedish Cancer Society.

Abbreviations: AR, androgen receptor; BMI, body mass index; CI, confidence interval; EAC, esophageal adenocarcinoma; ER, estrogen receptor; ESCC: esophageal squamous cell carcinoma; FGF, fibroblast growth factors; *H. pylori*, *Helicobacter pylori*; HRT, hormone replacement therapy; LH, luteinizing hormone; NSAIDs, nonsteroidal anti-inflammatory drugs; PGR, progesterone receptor; RR, relative risk; SNP, single nucleotide polymorphism

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Conflict of interests: No relevant conflicts of interest exist.

Author contributions: Both authors jointly conceived the review. Shao-Hua Xie performed literature searches and prepared the first draft of the paper. Jesper Lagergren contributed to the interpretation of existing evidence, and reviewed the manuscript. Both authors have approved the final manuscript for submission.

Abstract

The incidence of esophageal adenocarcinoma (EAC) has increased rapidly during the past four decades in many Western populations, including North America and Europe. The established etiological factors for EAC include gastro-esophageal reflux and obesity, *Helicobacter pylori* infection, tobacco smoking, and consumption of fruit and vegetables. There is a marked male predominance of EAC with a male-to-female ratio in incidence of up to 9-to-1. This review evaluates the available literature on the reasons for the male predominance, particularly an update on epidemiologic evidence from human studies during the past decade. The striking sex difference does not seem to be explained by established risk factors, given that the prevalence of the etiological factors and the strengths of associations between these factors and EAC risk are similar between the sexes. Sex hormonal factors may play a role in the development of EAC; estrogenic exposures may prevent such development, while androgens might increase the risk of EAC. However, continuing research efforts are still in need to fully understand the reasons for the male predominance of EAC.

Key words: Esophageal adenocarcinoma; male predominance; sex difference; estrogen; sex hormones; epidemiology.

The past four decades have witnessed a rapid increase in the incidence of esophageal adenocarcinoma (EAC) in the Western societies. EAC is presently the predominant histologic type of esophageal malignancy in several North American and European countries.[1, 2] Among 52,000 new cases of EAC (41,000 in men and 11,000 in women) worldwide in 2012, 12,000 (22.8%) occurred in Europe and 11,100 (21.2%) in North America.[3] The increasing prevalence of the main risk factors, gastro-esophageal reflux and obesity, as well as the decreasing prevalence of *Helicobacter pylori* (*H. pylori*) infection may have contributed to the unprecedented rise in EAC incidence.[1, 4] It is estimated that the incidence of EAC will continue to rise over the coming decades.[5]

EAC is characterized by a marked and enigmatic male predominance with a male-to-female ratio in incidence of up to 9-to-1.[1, 3, 6, 7] Such a striking sex difference may be explained by both extrinsic and intrinsic exposures which are differentially distributed between the sexes or more harmful in men than in women. In this review, we have evaluated the available literature on this issue, particularly focusing on the epidemiologic evidence from human studies from the past decade.

Search methods

A systematic search of the literature related to the sex difference of EAC was undertaken, starting with a PubMed search. The time period was from an unbounded start date to 30 June 2015, and only publications in English were reviewed. The full electronic search is listed in the supplementary material. Briefly, both key words for the diseases (esophageal cancer or Barrett's esophagus), the topic (sex difference), and the exposures (sex hormonal and reproductive factors) were used to identify relevant publications. Epidemiological studies included in this review met

the following criteria: (1) case-control or cohort studies published as original articles; (2) the studied outcome being esophageal cancer/Barrett's esophagus incidence rather than mortality; (3) the association between hypothesized risk factors and the risk of esophageal cancer or Barrett's esophagus being examined. In case of multiple reports on the same population, only the most recent or informative ones were included. We further reviewed the reference lists of relevant narrative reviews, systematic reviews and meta-analyses, and papers of interest to identify additional literatures.

Risk factors for esophageal adenocarcinoma

Gastro-esophageal reflux causing the premalignant condition Barrett's esophagus and obesity are two major established risk factors for EAC. The risk of EAC in individuals with reflux symptoms at least weekly is as high as 5 times that in those without reflux.[8] Obesity is associated with an increased risk of EAC in a seemingly linear pattern.[9-11] Moreover, tobacco smoking and low intake of fruit and vegetables also increase the risk of EAC,[12, 13] while *H. pylori* infection is associated with a decreased risk of this disease.[14, 15] All these established environmental risk factors seem to explain the majority of EAC cases. It has been estimated that combinations of reflux, overweight, tobacco smoking, and low intake of fruit and vegetables could account for nearly 80% of EAC cases. [16, 17] Studies also indicate a reduced risk of EAC associated with the use of nonsteroidal anti-inflammatory drugs (NSAIDs) or statins, but large randomized controlled trials with sufficient follow-up are needed.[1, 18, 19] A recent pooled analysis of population-based case-control studies revealed a reverse association between height and the risk of EAC.[20]

Male predominance

A male predominance in the incidence of EAC has been noted worldwide. A global assessment indicated an overall male-to-female ratio of 4.4, which ranged from 1.7 in sub-Saharan Africa to 8.5 in North America.[3] There are some variations across ethnic groups in the male predominance of EAC. In the United States, the highest male-to-female ratio has been observed in Hispanics followed by non-Hispanic Whites and then Blacks.[21, 22] The male predominance of EAC is also age-dependent. The sex ratio increases with age until the age of 50-59 years and decreases thereafter.[21, 23-26] The incidence ratios of EAC between sexes seem to have remained relatively stable during the past four decades.[2, 23]

Explanation of the male predominance by established risk factors

The striking male predominance in EAC is not readily explained by established risk factors. The prevalence of *reflux* is virtually the same between the sexes,[27, 28] and no stronger association between reflux and EAC risk has been observed in men.[28] Rather, a recent pooled analysis of five case-control studies revealed slightly higher risk estimates associated with reflux in women than in men.[29] However, reflux disease is seemingly more severe in men than in women.[30-32] Erosive reflux disease has been shown to be a stronger risk factor for EAC than nonerosive reflux disease. The magnitude of the association between erosive reflux disease and EAC risk is higher in men than in women.[30] Thus, more severe reflux among men may be a factor contributing to the male predominance of EAC.

The prevalence of *obesity* is similar between the sexes.[27] Existing evidence does not support a higher risk of EAC associated with obesity in men compared to women.[9, 28, 33] It has

been hypothesized that abdominal adiposity, the typical male fat distribution, may contribute to the male predominance of EAC, since abdominal obesity is associated with an elevated risk of EAC independent of BMI.[10, 34] However, a stratified analysis by BMI found no evidence of an increased male predominance among overweight individuals compared with lean, which argues against abdominal obesity as a factor contributing to the male predominance.[35]

Although *tobacco smoking* is more prevalent in men than in women,[27, 33] the male predominance of EAC is unlikely to be explained by this factor. A cohort study following 2 million person-years at risk indicated that the male predominance in EAC was similar among smokers and non-smokers, and the male-to-female incidence ratio was rather higher among non-smokers (14.2, 95% confidence interval [CI]: 5.1 - 39.5) than in smokers (7.3, 95% CI: 4.6 - 11.7).[36] The association between tobacco smoking and EAC risk was similar between the sexes or even slightly stronger in women than in men.[12, 28, 33, 36]

The male predominance in EAC seems unlikely to be explained by other etiological factors. *H. pylori* infection and intake of fruit and vegetables are equally distributed between the sexes, and their associations with EAC risk are no stronger in men than in women.[27, 28] The use of NSAIDs, which may protect against EAC, is slightly more prevalent in women than in men,[27, 37] but there is only a moderate and uncertain association between the use of NSAIDs and EAC risk, and the prevalence of long-term users is limited.[1]

Sex hormones and reproductive factors and the male predominance

The male predominance in EAC may be due to a delayed development of, on average, 16 years in women compared with men,[24] suggesting a protective role of sex hormones and reproductive factors in the development of EAC.

The hypothesis of sex hormonal influence in the etiology of EAC has been tested in patients diagnosed with sex hormone related cancers, namely breast and prostate cancers. If sex hormones play a role in the development of EAC, an altered risk of EAC might be evident among patients who receive long-term sex hormonal therapy. No significantly increased risk of EAC has been observed in breast cancer patients using adjuvant anti-estrogen tamoxifen therapy.[38-41] Interestingly however, two register-based studies have found a decreased risk of EAC in patients with prostate cancer who might have received anti-androgenic treatment,[42, 43] although an earlier study did not.[44]

Epidemiological studies on roles of sex hormonal exposures and reproductive factors on EAC risk in general populations are scarce and limited by the low incidence of this disease in women (Table 1). Several studies observed moderately reduced risk estimates associated with the use of hormone replacement therapy (HRT) in post-menopausal women, but none of them individually achieved statistical significance.[45-50] A recent meta-analysis based on five observational studies found a 25% decreased risk of EAC in post-menopausal women compared with non-users (relative risk [RR] = 0.75, 95% CI: 0.58-0.98).[51] None of the previous studies supported a reduced risk of EAC associated with use of oral contraceptives.[47-49] A series of epidemiological studies have investigated the associations between EAC risk and reproductive factors, including menarche, menopause, childbearing, and breastfeeding, and these have yielded conflicting results. A large UK prospective study which followed 1.3 million women for on average 9.1 years observed a decreased risk of EAC with increasing age at menarche (RR for per

year older = 0.89, 95% CI: 0.82-0.95) .[52] However, no altered risk of EAC has been associated with menarche or menopause in other studies.[47, 49] Most studies revealed no altered EAC risk in relation to childbearing history in terms of parity, number of pregnancies, or age at first birth.[46, 47, 49, 52-55] However, a decreased risk of EAC associated with breastfeeding has been consistently observed.[46, 47, 49, 52, 55] A pooled analysis of three population-based case-control studies found that ever breastfeeding was associated with a 40% reduced risk of EAC and the risk decreased with increasing duration of breastfeeding (RR for > 12 months = 0.42, 95% CI: 0.23 - 0.77).[49] The protective role of breastfeeding may be related to increased sex hormonal levels, not only estrogens, but also progestogens, and possibly also oxytocin, during pregnancy or breastfeeding. A protective effect of the single nucleotide polymorphism (SNP) rs572483 in the progesterone receptor (PGR) gene was observed among women carrying the variant G allele, which was not observed among men, suggesting that PGR in the sex hormone signaling pathway may be associated with the gender differences in EAC risk.[56]

Only one study has examined the association between circulating sex hormone levels and the risk of EAC. Higher levels of serum testosterone and luteinizing hormone (LH) were observed in 25 patients with EAC compared with 8 control subjects, and the testosterone levels in EAC patients decreased after curative resection.[57] Nevertheless, considering the small sample size and cross-sectional nature of the study, these findings require confirmation in further research.

Recent studies also suggest a decreased risk of EAC associated with higher intake of dietary phytoestrogens, including lignans, quercetin, resveratrol, and flavonoids.[58-61] These findings indicate a potential useful role of chemoprevention of EAC if the sex hormone hypothesis could be further confirmed.

Biological mechanisms of sex hormones

Sex hormones exert their biological effects through the ligation to nuclear receptors, i.e. the estrogen receptors (ERs) alpha (ERα) and beta (ERβ), and the androgen receptors (ARs). ERα is predominantly expressed in female sex organs, such as the breast, uterus, and ovaries, and is responsible for estrogen-reduced mitogenic signaling in epithelial cells in these organs.[62] ERβ exists not only in sex organs but in a wide range of organs in both sexes,[63] and has been found to be expressed in EAC tissues and adjacent normal esophageal mucosa.[64, 65] Previous studies have shown decreased ERβ expression in various cancer tissues as compared with benign tumors or normal tissues.[66] Possible mechanisms of the inhibition of estrogen on esophageal adenocarcinogenesis include induction of cell cycle and growth arrest, and initiating apoptosis in cancer cells through ER ligands.[67] The expression of ARs has also been confirmed in EAC tissue.[57, 68] However, the possible mechanisms for androgen/ARs' involvement in EAC development remain largely unknown. Androgen may induce over-expression of fibroblast growth factors (FGFs) or members of their receptors, which have an important role in hormone-dependent malignancies.[57]

Prognosis and the male predominance

The prognosis in patients with EAC is worse than that for most other types of tumors, with the overall 5-year survival lower than 15%.[1] A noteworthy sex difference in prognosis among patients with esophageal cancers has been consistently shown. Female patients have longer survival than male patents, which might be explained by the differences in extrinsic risk

factors for mortality, or possibly sex itself. [69-71] However, the sex difference in survival was apparent only in esophageal squamous cell carcinoma (ESCC) instead of EAC in a large register-based study in the United States.[69] The role of sex itself in the prognosis of EAC still needs to be verified in further independent studies, considering the lack of information on important possible confounders in previous studies.

Esophageal squamous cell carcinoma

ESCC is the other main histologic type of esophageal cancer. It accounts for nearly 90% of all cases of esophageal cancers worldwide. The global incidence rate of ESCC was 5.2 per 100 00 (7.2 in men and 2.8 in women) in 2012, and the majority (80%) of ESCC cases occur in Central and Southeastern Asia.[3] Alcohol and tobacco use are major risk factors for ESCC, while other factors such as dietary habits, esophageal injury (e.g., hot beverages, caustic injury and achalasia) and inherited susceptibilities may also contribute to the risk.[72-76]

ESCC is also overrepresented in men, but the male predominance is weaker than that of EAC. The global overall male-to-female incidence ratio of ESCC is 2.7, and the highest ratio was observed in Eastern Europe (7.8) and the lowest in Northern Africa and Western Asia (1.2).[3] The sex difference in ESCC is likely to be attributable to the two major established environmental factors, tobacco smoking and heavy alcohol consumption, given the substantially differential prevalence of the exposures between men and women.[77, 78] Yet, sex hormonal factors might also be involved in the development of ESCC. ERβ and ARs are expressed in ESCC tissues.[64, 79] *In vitro* studies have shown that the growth of ESCC cells could be inhibited by estrogen and enhanced by testosterone,[80] and overexpression of the AR could induce increases in ESCC cell invasion and proliferation.[79] The epidemiological evidence regarding the effects of sex hormonal

and reproductive factors on the risk of ESCC is inconclusive.[46-48, 52, 53, 81-84] Three studies found no significant association between HRT and the risk of ESCC,[46, 48, 81] while a large prospective cohort study in the United States observed a 60% decreased risk of ESCC associated with current use of HRT in postmenopausal women.[47] In contrast with EAC, no decreased risk of ESCC has been associated with breastfeeding. [46, 47, 52]

Barrett's esophagus

The metaplasia Barrett's esophagus precedes EAC, and Barrett's esophagus is characterized by considerable male predominance. A systematic review and meta-analysis comprising 32 studies suggested that the male-to-female ratio for Barrett's esophagus ranged from 1.08 to 4.43 with a pooled overall ratio of 1.95 (95% CI: 1.77- 2.17).[31] The sex difference in Barrett's esophagus seems not to be explained by differential distributions of the two major risk factors, reflux and obesity, between sexes, or stronger associations between these factors and the risk of BE in men.[31, 85] Sex hormones may play a role in the development of Barrett's esophagus. ERβ expression has been detected in Barrett's esophagus mucosa, but at lower levels compared to EAC tissues,[65, 86] while ARs have not been shown to be implicated in Barrett's oesophagus.[87, 88] A recent analysis has shown elevated levels of serum free testosterone and dihydrotestosterone and lower levels of estrone sulfate in individuals with Barrett's esophagus compared to healthy controls.[89]

Perspectives

There is an obvious need for further research to better understand the male predominance in EAC. Some areas of research might be of particular interest. First, the notable variation in the male predominance of EAC across different populations warrants further investigation. The variation could be explained by environmental exposures or intrinsic factors (e.g., genetic background). A thorough analysis on the racial and geographical variations with reference to possible contributing factors may provide clues for understanding the male predominance in EAC. Second, the strong male predominance in EAC is unlikely to be explained by any individual risk factor. However, quantitatively evaluating the contributions of combinations of established etiological factors is encouraged in future studies, where possible interactions between risk factors may provide new knowledge in this respect. Third, investigating the role of sex hormonal exposures and reproductive factors needs appropriate sample sizes to ensure sufficient statistical power. Most previous epidemiological studies have been under-powered, mainly due to the low incidence of EAC in women. Alternatively, the sample sizes can be enlarged when investigating the role of extrinsic sex hormonal exposures, for example dietary phytoestrogens and endocrine disrupting chemicals, in both sexes. Although meta-analyses combining results from different studies could achieve higher statistical power, results from meta-analyses on observational epidemiological studies should be interpreted with caution, considering different sources of bias and heterogeneities across studies. Instead, pooled analyses of different studies with primary data might be a more valid strategy. Fourth, and finally, direct evidence concerning the associations between sex hormone levels and EAC risk remains largely unexplored. Case-control studies nested in prospective cohorts may be a feasible measure of examining such associations. Furthermore, given the possible role of ERβ in the estrogenic protection against EAC, molecular epidemiological studies are needed to examine whether inherited predispositions influencing ERβ

expression are associated with EAC risk or can modify the effect of estrogenic exposures in the development of EAC.

Conclusions

The reasons for the male predominance of EAC have not been completely understood. It seems not to be explained by major established risk factors, although more severe reflux in men may be a contributing factor. A protective role of high estrogenic exposures is probably involved in the development of EAC. However, epidemiological studies have suffered from insufficient statistical power due to the low incidence of EAC in women and the existing evidence remains far from conclusive. Yet, synthesized results from meta- and pooled analyses during the past decade have generated evidence supporting the sex hormonal hypotheses, particularly the strongly protective effect of breastfeeding on the risk of EAC. Valid and large population-based studies are encouraged to clarify the role of sex hormonal exposures in the etiology of EAC and to identify the specific hormones contributing to the male predominance of EAC. The biological mechanisms of the protective role of estrogens in EAC development remain largely unknown, although ERβ ligand may play a key role in the protection against EAC development. It is worth further investigating whether and how ERβ expression is associated with the development and progression of EAC in basic scientific research. Overall, continuing research efforts are in need to fully understand the reasons for the male predominance of EAC, which could provide ground-breaking insights into the etiology of this cancer, and hopefully unravel novel targets for prevention and treatment of this aggressive disease with rapid increasing incidence in the population.

Table 1. Epidemiological studies examining associations between sex hormonal and reproductive factors and the risk of esophageal adenocarcinoma in general populations

First author and year of publication	Design	Setting	Number of cases / non-cases	Main findings
Hormonal replacement therapy				
Lindblad et al. 2006 [50]	Nested case-control study	UK 1994-2001	299/3191	No association with EAC (RR = 1.17, 95% CI: 0.4-3.32)
Freedman et al. 2010 [48]	Prospective cohort study	US 1995-2003	25/201 481	No association with EAC (RR = 0.90, 95% CI: 0.54-1.49)
Cronin-Fenton et al. 2010 [49]	Pooled analysis of case-control studies	Ireland 2002-2004, Australia 2001-2005	99/411	Inverse but not statistically significant association with EAC among women aged > 50 years (RR = 0.75, 95% CI: 0.45-1.24)
Bodelon et al. 2011 [47]	Prospective cohort study	US 1993-2009	23/161 057	Inverse but not statistically significant association with EAC (RR for current users = 0.87, 95% CI: 0.35-2.17; RR for past users = 0.74, 95% CI: 0.20-2.82)
Yu et al. 2011 [46]	Case-control study	China 2008-2010	44/132	No association with EAC risk (RR = 0.88, 95% CI: 0.42-1.79)
Menon et al. 2014 [45]	Matched cohort study	UK 1987-2008	13/103 689	No association with EAC risk (RR = 0.89, 95% CI: 0.28-2.82)
Use of oral contraceptives				
Freedman et al. 2010 [48]	Prospective cohort study	US 1995-2003	25/201 481	No association with EAC (RR for 1-10 years= 1.00, 95% CI: 0.55-1.83; RR for 10 years or longer = 1.50, 95% CI: 0.69-3.28; P for trend 0 0.422)
Cronin-Fenton et al. 2010 [49]	Pooled analysis of case-control studies	Ireland 2002-2004, US 1964-1973 Australia 2001-2005	138/784	No association with EAC (RR = 0.92, 95% CI: 0.55-1.54)
Bodelon et al. 2011 [47]	Prospective cohort study	US 1993-2009	23/161 057	No association with EAC (RR = 0.92, 95% CI: 0.37-2.28)
Menarche and menopause				
Cronin-Fenton et al. 2010 [49]	Pooled analysis of case-control studies	Ireland 2002-2004, US 1964-1973 Australia 2001-2005	142/786	No association between age at menarche and EAC (RR for over 13 years = 1.01 (95% CI: 0.35-2.91) compared with 13 years or younger); No significant association between age at menopause and EAC

				[RRs (95% CIs) for below 50 years and pre-menopause = 1.06 (0.64-1.77) and 0.65 (0.17-2.50), respectively, compared with 50-70 years]
Bodelon et al. 2011 [47]	Prospective cohort study	US 1993-2009	23/161 057	No association between age at menarche and EAC [RRs (95% CIs) for 12, 13, 14, and 15 years or above = 1.07 (0.30-3.79), 0.59 (0.15-2.36), 0.70 (0.15-3.15), and 0.72 (0.18-2.91), respectively]; No association between age at menopause and EAC [RRs (95% CIs) for 45-49, 50-54, and 55 years or above = 2.55 (0.70-9.30), 1.33 (0.31-5.78), and 2.63 (0.54-12.77), respectively, with less than 45 years as reference]
Yu et al. 2011 [46]	Case-Control study	China 2008-2010	44/132	No association between age of menarche and EAC (RR for over 13 years = 1.02, 95% CI: 0.51-2.23, compared with 13 years or younger); Increased risk of EAC associated with menopause at ages < 45 years (RR = 2.57, 95% CI: 1028-7.10) compared with at ages >50 years
Green et al. 2012 [52]	Prospective cohort study	UK 1996-2008	399/1 319 010	No association between age at menarche and EAC [RRs (95% CIs) for < 13 and ≥ 15 years = 1.29 (1.04-1.60) and 0.80 (0.59-1.10), respectively, compared with 13-14 years]; a decrease in EAC risk with increasing age at menarche treated as a continuous variable (RR per year older = 0.89, 95% CI: 0.82-0.95). No association between age at menopause and EAC [RRs (95% CIs) for 45-49 and < 45 years or above = 1.12 (0.80-1.57) and 0.89 (0.54-1.47), respectively, compared with 50 years or above].
Childbearing				
Cheng et al. 2000 [55]	Case-control study	UK 1993-1996	74/74	No association between number of children and EAC [RRs (95% CIs) for 1-2 and 3 or more = 0.46 (0.16-1.31) and 0.69 (0.23-2.01), respectively, compared with no children]
Lagergren et al. 2005 [54]	Case-control study	Sweden 1995-1997	63/141	No association between parity and EAC (RR for non-parous = 0.82, 95% CI: 0.25-2.73, compared with parous women); No association between number of children, age at first birth, or years between first and last birth, and EAC
Yu et al. 2011 [46]	Case-Control study	China 2008-2010	44/132	No significant association between being ever pregnant and EAC risk (RR = 0.79, 95% CI: 0.09-45.8);

				No association between age at first birth and EAC [RRs (95% CIs) for 23-26 and > 26 years = 1.12 (0.41-4.12) and 2.95 (0.97-11.1), respectively, compared with younger than 23 years]
Lu et al. 2012 [53]	Nested case-control study	Sweden 1932-2008	115/1150	No association between parity and EAC (RR for parous = 0.66, 95% CI: 0.38-1.14, compared with non-parous women); No significant association between number of children or age at first birth and EAC risk
Cronin-Fenton et al. 2010 [49]	Pooled analysis of case-control studies	Ireland 2002-2004, US 1964-1973, UK 1993-1996, Australia 2001-2005	218/862	Being ever pregnant not associated with an altered risk of adenocarcinoma of esophagus and gastric cardia (RR = 1.02, 95% CI: 0.55-1.87); No association between number of children and EAC
Bodelon et al. 2011 [47]	Prospective cohort study	US 1993-2009	23/161 057	No association between number of term pregnancies or age at first term pregnancy and EAC
Green et al. 2012 [52]	Prospective cohort study	UK 1996-2008	399/1 319 010	No significant association between number of term pregnancies or age at first birth and EAC
Breastfeeding				
Cheng et al. 2000 [55]	Case-control study	UK 1993-1996	74/74	Breastfeeding was associated with a reduced risk of EAC (RR = 0.41, 95% CI: 0.20-0.82; RR for over 6 months = 0.31, 95% CI: 0.09-1.02)
Cronin-Fenton et al. 2010 [49]	Pooled analysis of case-control studies	Ireland 2002-2004, UK 1993-1996, Australia 2001-2005	165/565	Breastfeeding was associated with a reduced risk of EAC (RR = 0.58, 95% CI: 0.37-0.92; RR for over 12 months = 0.42, 95% CI: 0.23-0.77)
Bodelon et al. 2011 [47]	Prospective cohort study	US 1993-2009	23/161 057	Inverse but not statistically significant association between breastfeeding and EAC (RR = 0.44, 95% CI: 0.18-1.07)
Yu et al. 2011 [46]	Case-Control study	China 2008-2010	44/132	Breastfeeding for over 12 months associated with a reduced risk of EAC (RR = 0.40, 95% CI: 0.13-0.92)
Green et al. 2012 [52]	Prospective cohort study	UK 1996-2008	399/1 319 010	Breastfeeding associated with a reduced risk of EAC (RR = 0.75, 95% CI: 0.58-0.97)

CI: confidence interval; EAC: esophageal adenocarcinoma; RR: relative risk;

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