available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Review

The mystery of male dominance in oesophageal cancer and the potential protective role of oestrogen

Evangelos Chandanos *, *Jesper Lagergren*

Upper Gastrointestinal Research, Department of Molecular Medicine and Surgery, Karolinska Institutet, SE-171 76 Stockholm, Sweden

ARTICLE INFO

Article history:
Received 30 May 2009
Received in revised form 24 August 2009
Accepted 2 September 2009
Available online 3 October 2009

Keywords:
Oestrogen
Adenocarcinoma
Squamous-cell carcinoma
Receptor
Neoplasm
Sex hormone

ABSTRACT

Oesophageal cancer is the sixth most common form of cancer death globally with almost 400,000 deaths annually. More than 90% of all cases are either adenocarcinomas (OAC) or squamous-cell carcinomas (OSCC). There is a strong male predominance with up to 8 and 3 men for every woman affected with OAC and OSCC, respectively. It has been hypothesised that sex hormonal factors may play a role in the development of oesophageal cancer or more specifically that oestrogen prevents such development. This article reviews the available literature on this topic. Basic science studies suggest an inhibitory effect of oestrogen in the growth of oesophageal cancer cells, and a possible mechanism of any oestrogen protection might be mediated through oestrogen receptors. But from the few epidemiological studies in which the hypothesis of oestrogen protection has been tested, no firm conclusions can yet be drawn of the role of oestrogen in human oesophageal cancer aetiology. More evidence from valid and large human studies is needed before any conclusions can be drawn.

1. Introduction

Oesophageal cancer is the eighth most common form of cancer worldwide with an incidence of almost half a million new cases each year.[1] It is a disease with a poor prognosis with a 5-year survival rate in the Western societies of only 10–16%.[2] In 2002 almost 400,000 deaths occurred due to oesophageal cancer worldwide, making it the sixth most common form of cancer death globally.[1] Oesophageal adenocarcinoma (OAC) and oesophageal squamous-cell carcinoma (OSCC) are the dominating histological types of malignant oesophageal tumours, as these two forms together constitute more than 90% of all cases.[3] Up to a few decades ago only a low percentage of oesophageal cancers was OAC.[4,5] During the last decades, however, a rapid increase in the incidence of OAC has been observed, particularly among males.[3,6–9] The increase has been most notable among Caucasians, and by the mid-1980s OAC constituted one third of all cases of oesophageal cancer in that group in the United States.[6] An increase in the incidence of OAC and a decrease in the incidence of ESSC have been reported in several European countries.[10–18]

2. Aetiology of oesophageal adenocarcinoma

Gastroesophageal reflux and Barrett's oesophagus (BO), an oesophageal metaplasia caused by reflux, are strongly linked with the risk of OAC.[19–22] Another established risk factor is high body mass index.[23–29] Tobacco smoking plays a moderate

* *Corresponding author:* Address: Norra Stationsgatan 67, II Karolinska Institutet, SE-171 76 Stockholm, Sweden. Tel.: +46 8 517 709 57; fax: +46 8 33 15 87.
E-mail address: evangelos.chandanos@ki.se (E. Chandanos).
0959-8049/$ - see front matter
doi:10.1016/j.ejca.2009.09.001

role as a risk factor for this cancer,[24,25,30,31] while alcohol drinking is not associated with OAC.[24,25,30,31] Among the few studies addressing *Helicobacter pylori* (*H. pylori*) infection in relation to risk of OAC, most investigations suggest that such infection protects against this tumour,[32–34] but not all agree[35] and has recently been challenged by a large Swedish cohort study.[36] A diet rich in fruit and vegetables offers protection, while the diet rich in fat and cholesterol increases the risk.[37] Some socioeconomic factors, including low socioeconomic status and living without a partner, seem to be linked with an increased risk of OAC.[31,38]

2.1. *Aetiology of oesophageal squamous-cell carcinoma*

Alcohol consumption and tobacco smoking are the main risk factors for developing OSCC, and in combination they further increase this risk substantially.[30] Other risk factors are low socioeconomic status,[31,38,39] and a diet low in fruit and vegetables.[40] Drinking hot beverages has been associated with an increased risk in some populations,[41] but this has not been confirmed in Western populations.[42] Achalasia,[43] previous caustic injury of the oesophagus[44] and Plummer-Vinson syndrome[45] are uncommon, but established risk factors for OSCC.

3. Male predominance

One of the most intriguing observations in the occurrence of OAC is the very strong male predominance, a worldwide observation. A male to female sex ratio of up to 8:1 has been reported in Western societies.[8–10,12,46] This ratio is not readily attributed to differences in the prevalence of known risk factors between the sexes, since the distribution of reflux, obesity and *H. pylori* is similar between genders. Interestingly, increasing abdominal diameter has been associated with an increased risk of OAC and BO, with a seemingly stronger link than high BMI alone.[47–50] This could partially explain the male dominance, since the fat distribution in men is predominantly abdominal. The reasons behind the sex difference in fat distribution are not completely understood[51] but some evidence implies that hormonal factors may play a role, including the fact that the fat distribution changes after menopause[52,53] and oestrogen receptors have been found in adipose tissue.[54,55] The incidence of BO is higher in males,[56,57] and most mysterious is the fact that there is a shift of about 20 years between males and females in its onset.[58,59] The relevance of these findings has been recently confirmed in a study from Scotland which showed a delay of 17 years in the incidence of OAC between males and females.

Moreover, leptin, an adipokine secreted by adipocytes which is closely associated with obesity,[60] has recently been linked with BO in men, but not in women.[61] This sex difference may be attributed to different leptin secretion patterns between men and women,[62] which theoretically may be due to hormonal differences between the sexes. It has been hypothesised that endogenous oestrogen may protect women against the development of OAC.[63]

The 3:1 male preponderance in the incidence of OSCC can be explained by the higher prevalence of tobacco smoking and alcohol drinking among males.[64] A study from Denmark though showed, similar to the findings of a delay in the onset of OAC in females mentioned above, a continuous rise in the incidence of OSSC in elderly females, in contrast to a decline in males of the same age group.[65] The hypothesis of sex hormonal influence in OSCC cannot be dismissed.[66]

4. Oestrogen exposure and oesophageal cancer – molecular mechanisms

Oestrogen exerts its biological actions through the activation of two nuclear receptors, oestrogen receptors (ERs) alpha (ERα) and beta (ERβ), with distinctive tissue distribution and a counteracting function.[67–69] Some research suggests that ERs might mediate a protective effect on oestrogen in the development of oesophageal cancer. The presence of ERs has repeatedly been shown in OAC[70–73] as well as in OSCC,[73–75] and both ERα and ERβ have been identified in oesophageal tissue.[70,71,73,76] In addition, a splicing variant of ERβ, namely ERβcx,[76,77] has been discovered in oesophageal cancer and its precursor lesion, i.e. Barrett's metaplasia.[72] An *in vitro* study indicated that the inhibition of oestrogen on oesophageal carcinogenesis is mediated by the interaction with ERs as only oesophageal cancer cells with ERs were inhibited by oestrogen exposure, and not the cells without ERs.[78] Moreover, oestrogen may initiate apoptosis in oesophageal cancer cells[79] and it can be induced by an increased ratio between the pro-apoptotic Bax protein and the anti-apoptotic Bcl-2 protein.[80] Studies of ERs on knockout mice have shown that ERβ has pro-apoptotic and pro-differentiating functions.[81] The specific role of each ER type in oesophageal cancer remains unknown. In cancer of the prostate,[82] breast,[83] stomach[84,85] and colon,[86] a decreased ERβ expression compared to normal tissue has been shown. In an immunohistochemical study on OSCC specimens from 73 patients, 47 (64%) were positive for ERα while only 21 (29%) expressed ERβ. Moreover, a positive expression of ERα in addition to negative expression of ERβ was an unfavourable independent prognostic factor in OSCC.[75] In addition, a reduction in the expression of E-cadherin, a cell adhesion molecule that correlates with the development and progression of OSCC, has been shown in patients with invasive OSCC.[87] Interestingly, E-cadherin is also reduced in tissues of mice lacking ERβ.[88] One could thus speculate that ERβ may mediate a protective effect against oesophageal cancer growth.

5. Oestrogen and other gastrointestinal malignancies

The idea of oestrogen protection with regard to gastrointestinal cancer is not new. The Women's Health Initiative study showed that women using hormone replacement therapy (HRT) with oestrogen and progestin had almost half the risk of colorectal cancer compared to a placebo group.[89] In addition, a meta-analysis of 18 observational studies showed a 20% reduction in the risk of colon cancer among women who had ever used HRT compared to never users.[90] It has also been hypothesised that oestrogen protects women against the development of gastric adenocarcinoma,[91] a hypothesis

that has gained support from several epidemiological[92–97] and animal studies.[98–101] It is therefore reasonable to hypothesise that oestrogen protects women also against oesophageal cancer, particularly since the male predominance in OAC is much stronger than that of colorectal and gastric cancer.

6. Oestrogen and oesophageal cancer in basic science studies

Evidence from some *in vivo* and *in vitro* studies suggests that oestrogen may have an inhibitory effect on oesophageal carcinogenesis. Although the male dominance is more striking in the incidence of OAC, basic science study has focused on the effect of oestrogen on OSCC. A suppressing effect of oestrogen on chemical induction of OSCC in mice was reported in 1985[66] [article in Japanese]. The first study conducted on cell lines from human OSCC in 1987 showed an inhibition of malignant cell growth through the oestrogen exposure, and the presence of oestrogen receptors (ERs) in these cell lines was identified.[102] *In vivo* studies of xenotransplanted OSCC cells to nude mice have shown an inhibition of tumour growth with systematic administration of oestradiol, without any difference between male and female mice.[103] The inhibition of cell growth by oestrogen administration has also been shown by some other studies,[78,74] but not all.[104] Finally, a study found that administration of aethinyl oestradiol on mice, pre-treated with various carcinogenic substances in their diet, had both an inhibitory and a stimulatory effect on oesophageal hyperplasia, depending on the carcinogenic substance given.[105] Taken together, most available animal studies seem to support the hypothesis that oestrogen is involved in inhibiting the carcinogenic process of oesophageal cancer.

7. Oestrogen and oesophageal cancer in human studies

The studies that have addressed the hypothesis that oestrogen protects against oesophageal cancer development in humans are summarised in Table 1. Unfortunately, not all of these studies did distinguish between OAC and OSCC. A Canadian population-based case-control study found no association between parity or age at first birth and risk of unspecified type of oesophageal cancer.[106] A pooled analysis of 58 cases of oesophageal cancer and 5619 controls, based on various case-control studies conducted in northern Italy during the period 1983 through 1992, found a positive trend towards an increased risk of unspecified oesophageal cancer with increasing parity, but no association with age at first birth or number of abortions.[107]

In a Swedish population-based case-control study of 63 cases and 141 controls, women with low parity (0–1 children) were not at an increased risk of OAC compared to women of higher parity (odds ratio [OR] 0.93, 95% confidence interval [CI] 0.35–2.49).[108] In a cohort study in Sweden, the risk of OAC was assessed in 100,215 prostate cancer patients, treated with oestrogen, compared to the corresponding background population, but no strong protection of oestrogen exposure was found (standardised incidence ratio [SIR] 0.9, 95% CI 0.5–1.5).[63] In the same cohort, however, the risk of OAC and OSCC combined was slightly decreased among those exposed to oestrogen (SIR 0.8, 95% CI 0.6–1.0). In a nested case-control study utilising data from the General Practice Research Database in the United Kingdom, the largest available computerised database of clinical records and prescriptions from primary care, no decreased risk of OAC was found among women using hormone replacement therapy (HRT) (OR 1.17, 95% CI 0.41–3.32).[109] Similarly, the risk of OSCC or OAC and OSSC combined was not statistically significantly decreased.[109] In a study in which three case-control studies from Italy and Switzerland were pooled, age at menarche was not associated with the risk of OSCC, but use of oral contraceptives (OR 0.24, 95% CI 0.06–0.96) and HRT (OR 0.32, 95% CI 0.09–1.13) was linked with a seemingly decreased risk, and late age at menopause (⩾50 years) was inversely associated with OSCC (OR 0.43, 95% CI 0.22–0.83).[110] The latter finding must however be interpreted with caution since smokers tend to have earlier menopause,[111] and smoking is a strong risk factor for OSCC. The influence of breastfeeding in the risk of OAC has been investigated in a case-control study of 74 cases and 74 controls in the United Kingdom, indicating a dose-dependently decreased risk of OAC among those who ever breastfed compared to those who never did (OR 0.41, 95% CI 0.20–0.82), while no such association was found for OSCC.[112]

Table 1 – Epidemiological studies assessing sex hormonal factors in relation to the risk of oesophageal cancer.

	Cancer studied	Age at menarche	Age at menopause	HRT	Parity	Breast-feeding
Miller et al. (Canada, 1980)[106]	OEC				X	
La Vecchia et al (Italy, 1993)[107]	OEC				↑ Increasing parity	
Lagergren (Sweden, 1998)[63]	OAC, OEC	Oestrogen in men did not affect risk of OAC but ↓ risk of OEC				
Cheng (UK)[112]	OAC					↓ Breast-feeding
Gallus (Italy & Switzerland, 2001)[110]	OSCC	X	↓ Higher age	↓ HRT, ↓ OC		
Lagergren (Sweden, 2005)[108]	OAC				X	
Lindblad (UK, 2006)[109]	OAC, OSCC			↓ HRT (OSCC)		

OEC: oesophageal cancer combined, OAC: oesophageal adenocarcinoma, OSCC: oesophageal squamous-cell carcinoma, HRT: hormone replacement therapy, OC: oral contraceptives, X: no association, ↑: increased risk with and ↓: decreased risk with. Not all associations were statistically significant.

High body mass index is a strong and dose dependent risk factor for OAC also in postmenopausal women,[113] This seems to contradict the hypothesis of oestrogen protection, since adipose tissue is a main source of oestrogen in women.[114] An explanation might be that oestrone, the oestrogen produced in extragonadal tissue, which is the main oestrogen during the postmenopausal period,[114] may not be as potent as 17β-estradiol during the fertile period.

8. Anti-oestrogen exposure and risk of oesophageal cancer

If the hypothesis of oestrogen protection is true, exposure to anti-oestrogen might instead increase the risk. Tamoxifen is an anti-oestrogen, acting as a selective oestrogen receptor modulator (SERM) with anti-proliferative action, which is often used in the treatment of breast cancer.[115] In a large population-based cohort study of 138,885 women with breast cancer, a statistically non-significantly 60% increased risk of OAC was found among women who were exposed to tamoxifen compared to unexposed (SIR 1.60, 95% CI 0.83–3.08), while no such association was indicated for OSCC (SIR 0.99, 95% CI 0.59–1.64).[116] In a Danish cohort study of more than 3500 postmenopausal women with a primary surgically treated breast cancer, women who had been exposed to tamoxifen did not have any increased risk of oesophageal cancer (no oesophageal cancer cases observed).[117] Similarly, no increased risk of any gastrointestinal cancer was found among women on tamoxifen therapy in an American study with more than 4000 breast cancer patients.[118] In contrast, a Swedish study of similar size and design found an increased risk of all gastrointestinal cancers combined, but this effect was not attributed to any increased risk of oesophageal cancer.[119] A non-significantly increased risk of oesophageal cancer was found in American investigation utilising data from the Surveillance, Epidemiology and End Results (SEER) Programme (SIR 1.49, 95% CI 0.54–3.24),[120] while no increased risk among women treated with tamoxifen was indicated in a retrospective cohort study from Japan (incidence rate ratio 0.73, 95% CI 0.05–11.7).[121] Most of these studies were, however, obviously hampered by poor statistical power.

Taken together, the available human research addressing oestrogen and anti-oestrogen exposure is contradictory and far from sufficient to establish any role of oestrogen in the aetiology of oesophageal cancer. Since few patients with BO develop OAC,[122] one may hypothesise that oestrogen or anti-oestrogen could affect the development of BA and that they may have little effect on the onset of OAC.

9. Conclusions and future research

Most basic science studies seem to suggest an inhibitory effect of oestrogen in the growth of OSCC cells, but from the few epidemiological studies in which the hypothesis of oestrogen protection has been tested, no firm conclusions can be drawn. Since the incidence of oesophageal cancer in women is low, epidemiological studies suffer from problems with low statistical power. Therefore, animal models in which the risk of OSCC and OAC is separately assessed after exposure to either oestrogen or anti-oestrogen would be valuable. Moreover, the utilisation of large, unselected and uniform epidemiological data sources, including pooling of studies, is needed to make conclusive results possible. Until then, it remains uncertain whether oestrogen is involved in the inhibition of oesophageal cancer, and the striking male predominance in the incidence of oesophageal cancer remains mysterious.

Conflict of interest statement

None declared.

Acknowledgements

The guarantor of the paper is Dr. Chandanos. This review was conceived by both authors, planned and written by Dr. Chandanos and critically reviewed by Prof. Lagergren. Financial support was received from the Swedish Cancer Society. There are no competing interests. The authors wish to thank Dr Chiara Gabbi, MD for reviewing the molecular Mechanisms part of the review.

REFERENCES

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin* 2005;**55**(2):74–108.
2. Ries LAG, Melbert D, Krapcho M, et al., editors. *SEER Cancer Statistics Review, 1975–2004*; 2006.
3. Daly JM, Fry WA, Little AG, et al. Esophageal cancer: results of an American College of Surgeons Patient Care Evaluation Study. *J Am Coll Surg* 2000;**190**(5):562–72 [discussion 572–3].
4. Turnbull AD, Goodner JT. Primary adenocarcinoma of the esophagus. *Cancer* 1968;**22**(5):915–8.
5. Bosch A, Frias Z, Caldwell WL. Adenocarcinoma of the esophagus. *Cancer* 1979;**43**(4):1557–61.
6. Blot WJ, Devesa SS, Kneller RW, Fraumeni Jr JF. Rising incidence of adenocarcinoma of the esophagus and gastric cardia. *JAMA* 1991;**265**(10):1287–9.
7. Pera M, Cameron AJ, Trastek VF, Carpenter HA, Zinsmeister AR. Increasing incidence of adenocarcinoma of the esophagus and esophagogastric junction. *Gastroenterology* 1993;**104**(2):510–3.
8. Dolan K, Sutton R, Walker SJ, et al. New classification of oesophageal and gastric carcinomas derived from changing patterns in epidemiology. *Br J Cancer* 1999;**80**(5–6):834–42.
9. Brown LM, Devesa SS, Chow WH. Incidence of adenocarcinoma of the esophagus among white Americans by sex, stage, and age. *J Natl Cancer Inst* 2008;**100**(16):1184–7.
10. Hansson LE, Sparen P, Nyren O. Increasing incidence of both major histological types of esophageal carcinomas among men in Sweden. *Int J Cancer* 1993;**54**(3):402–7.
11. Powell J, McConkey CC. The rising trend in oesophageal adenocarcinoma and gastric cardia. *Eur J Cancer Prev* 1992;**1**(3):265–9.
12. Powell J, McConkey CC, Gillison EW, Spychal RT. Continuing rising trend in oesophageal adenocarcinoma. *Int J Cancer* 2002;**102**(4):422–7.
13. Tuyns AJ. Oesophageal cancer in France and Switzerland: recent time trends. *Eur J Cancer Prev* 1992;**1**(3):275–8.

14. Liabeuf A, Faivre J. Time trends in oesophageal cancer incidence in Cote d'Or (France), 1976–93. *Eur J Cancer Prev* 1997;**6**(1):24–30.
15. Hansen S, Wiig JN, Giercksky KE, Tretli S. Esophageal and gastric carcinoma in Norway 1958–1992: incidence time trend variability according to morphological subtypes and organ subsites. *Int J Cancer* 1997;**71**(3):340–4.
16. Levi F, Randimbison R, La Vecchia C. Esophageal and gastric carcinoma in Vaud, Switzerland, 1976–1994. *Int J Cancer* 1998;**75**(1):160–1.
17. McKinney A, Sharp L, Macfarlane GJ, Muir CS. Oesophageal and gastric cancer in Scotland 1960–90. *Br J Cancer* 1995;**71**(2):411–5.
18. Moller H. Incidence of cancer of oesophagus, cardia and stomach in Denmark. *Eur J Cancer Prev* 1992;**1**(2):159–64.
19. Spechler SJ, Goyal RK. Barrett's esophagus. *New Engl J Med* 1986;**315**(6):362–71.
20. Lagergren J, Bergstrom R, Lindgren A, Nyren O. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. *New Engl J Med* 1999;**340**(11):825–31.
21. Wu AH, Tseng CC, Bernstein L. Hiatal hernia, reflux symptoms, body size, and risk of esophageal and gastric adenocarcinoma. *Cancer* 2003;**98**(5):940–8.
22. Ye W, Chow WH, Lagergren J, Yin L, Nyren O. Risk of adenocarcinomas of the esophagus and gastric cardia in patients with gastroesophageal reflux diseases and after antireflux surgery. *Gastroenterology* 2001;**121**(6):1286–93.
23. Abnet CC, Freedman ND, Hollenbeck AR, et al. A prospective study of BMI and risk of oesophageal and gastric adenocarcinoma. *Eur J Cancer* 2008;**44**(3):465–71.
24. Wu AH, Wan P, Bernstein L. A multiethnic population-based study of smoking, alcohol and body size and risk of adenocarcinomas of the stomach and esophagus (United States). *Cancer Causes Contr* 2001;**12**(8):721–32.
25. Lindblad M, Rodriguez LA, Lagergren J. Body mass, tobacco and alcohol and risk of esophageal, gastric cardia, and gastric non-cardia adenocarcinoma among men and women in a nested case-control study. *Cancer Causes Contr* 2005;**16**(3):285–94.
26. Lagergren J, Bergstrom R, Nyren O. Association between body mass and adenocarcinoma of the esophagus and gastric cardia. *Ann Intern Med* 1999;**130**(11):883–90.
27. Chow WH, Blot WJ, Vaughan TL, et al. Body mass index and risk of adenocarcinomas of the esophagus and gastric cardia. *J Natl Cancer Inst* 1998;**90**(2):150–5.
28. Engeland A, Tretli S, Bjorge T. Height and body mass index in relation to esophageal cancer; 23-year follow-up of two million Norwegian men and women. *Cancer Causes Contr* 2004;**15**(8):837–43.
29. Vaughan TL, Davis S, Kristal A, Thomas DB. Obesity, alcohol, and tobacco as risk factors for cancers of the esophagus and gastric cardia: adenocarcinoma versus squamous cell carcinoma. *Cancer Epidemiol Biomark Prev* 1995;**4**(2):85–92.
30. Lagergren J, Bergstrom R, Lindgren A, Nyren O. The role of tobacco, snuff and alcohol use in the aetiology of cancer of the oesophagus and gastric cardia. *Int J Cancer* 2000;**85**(3):340–6.
31. Gammon MD, Schoenberg JB, Ahsan H, et al. Tobacco, alcohol, and socioeconomic status and adenocarcinomas of the esophagus and gastric cardia. *J Natl Cancer Inst* 1997;**89**(17):1277–84.
32. Weston AP, Badr AS, Topalovski M, et al. Prospective evaluation of the prevalence of gastric *Helicobacter pylori* infection in patients with GERD, Barrett's esophagus, Barrett's dysplasia, and Barrett's adenocarcinoma. *Am J Gastroenterol* 2000;**95**(2):387–94.
33. Chow WH, Blaser MJ, Blot WJ, et al. An inverse relation between cagA+ strains of *Helicobacter pylori* infection and risk of esophageal and gastric cardia adenocarcinoma. *Cancer Res* 1998;**58**(4):588–90.
34. Ye W, Held M, Lagergren J, et al. *Helicobacter pylori* infection and gastric atrophy: risk of adenocarcinoma and squamous-cell carcinoma of the esophagus and adenocarcinoma of the gastric cardia. *J Natl Cancer Inst* 2004;**96**(5):388–96.
35. Wu AH, Crabtree JE, Bernstein L, et al. Role of *Helicobacter pylori* CagA+ strains and risk of adenocarcinoma of the stomach and esophagus. *Int J Cancer* 2003;**103**(6):815–21.
36. Bahmanyar S, Zendehdel K, Nyren O, Ye W. Risk of oesophageal cancer by histology among patients hospitalised for gastroduodenal ulcers. *Gut* 2007;**56**(4):464–8.
37. Mayne ST, Navarro SA. Diet, obesity and reflux in the etiology of adenocarcinomas of the esophagus and gastric cardia in humans. *J Nutr* 2002;**132**(11 Suppl):3467S–70S.
38. Jansson C, Johansson AL, Nyren O, Lagergren J. Socioeconomic factors and risk of esophageal adenocarcinoma: a nationwide Swedish case-control study. *Cancer Epidemiol Biomark Prev* 2005;**14**(7):1754–61.
39. Brown LM, Hoover R, Silverman D, et al. Excess incidence of squamous cell esophageal cancer among US Black men: role of social class and other risk factors. *Am J Epidemiol* 2001;**153**(2):114–22.
40. 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.
41. Garidou A, Tzonou A, Lipworth L, et al. Life-style factors and medical conditions in relation to esophageal cancer by histologic type in a low-risk population. *Int J Cancer* 1996;**68**(3):295–9.
42. Terry P, Lagergren J, Wolk A, Nyren O. Drinking hot beverages is not associated with risk of oesophageal cancers in a Western population. *Br J Cancer* 2001;**84**(1):120–1.
43. Sandler RS, Nyren O, Ekbom A, et al. The risk of esophageal cancer in patients with achalasia. A population-based study. *JAMA* 1995;**274**(17):1359–62.
44. Csikos M, Horvath O, Petri A, Petri I, Imre J. Late malignant transformation of chronic corrosive oesophageal strictures. *Langenbecks Arch Chir* 1985;**365**(4):231–8.
45. Larsson LG, Sandstrom A, Westling P. Relationship of Plummer-Vinson disease to cancer of the upper alimentary tract in Sweden. *Cancer Res* 1975;**35**(11 Pt 2):3308–16.
46. Corley DA, Buffler PA. Oesophageal and gastric cardia adenocarcinomas: analysis of regional variation using the Cancer Incidence in Five Continents database. *Int J Epidemiol* 2001;**30**(6):1415–25.
47. MacInnis RJ, English DR, Hopper JL, Giles GG. Body size and composition and the risk of gastric and oesophageal adenocarcinoma. *Int J Cancer* 2006;**118**(10):2628–31.
48. Corley DA, Kubo A, Levin TR, et al. Abdominal obesity and body mass index as risk factors for Barrett's esophagus. *Gastroenterology* 2007;**133**(1):34–41 [quiz 311].
49. Corley DA, Kubo A, Zhao W. Abdominal obesity and the risk of esophageal and gastric cardia carcinomas. *Cancer Epidemiol Biomark Prev* 2008;**17**(2):352–8.
50. Edelstein ZR, Farrow DC, Bronner MP, Rosen SN, Vaughan TL. Central adiposity and risk of Barrett's esophagus. *Gastroenterology* 2007;**133**(2):403–11.
51. Santosa S, Jensen MD. Why are we shaped differently, and why does it matter? *Am J Physiol Endocrinol Metab* 2008;**295**(3):E531–5.
52. Haarbo J, Marslew U, Gotfredsen A, Christiansen C. Postmenopausal hormone replacement therapy prevents central distribution of body fat after menopause. *Metabolism* 1991;**40**(12):1323–6.
53. Gambacciani M, Ciaponi M, Cappagli B, et al. Body weight, body fat distribution, and hormonal replacement therapy in

early postmenopausal women. *J Clin Endocrinol Metab* 1997;**82**(2):414–7.
54. Pedersen SB, Bruun JM, Hube F, et al. Demonstration of estrogen receptor subtypes alpha and beta in human adipose tissue: influences of adipose cell differentiation and fat depot localization. *Mol Cell Endocrinol* 2001;**182**(1):27–37.
55. Dieudonne MN, Leneveu MC, Giudicelli Y, Pecquery R. Evidence for functional estrogen receptors alpha and beta in human adipose cells: regional specificities and regulation by estrogens. *Am J Physiol Cell Physiol* 2004;**286**(3):C655–61.
56. Corley DA, Kubo A, Levin TR, et al. Race, ethnicity, sex and temporal differences in Barrett's oesophagus diagnosis: a large community-based study, 1994–2006. *Gut* 2009;**58**(2):182–8.
57. Cook MB, Wild CP, Forman D. A systematic review and meta-analysis of the sex ratio for Barrett's esophagus, erosive reflux disease, and nonerosive reflux disease. *Am J Epidemiol* 2005;**162**(11):1050–61.
58. van Soest EM, Siersema PD, Dieleman JP, Sturkenboom MC, Kuipers EJ. Age and sex distribution of the incidence of Barrett's esophagus found in a Dutch primary care population. *Am J Gastroenterol* 2005;**100**(11):2599–600.
59. van Blankenstein M, Looman CW, Johnston BJ, Caygill CP. Age and sex distribution of the prevalence of Barrett's esophagus found in a primary referral endoscopy center. *Am J Gastroenterol* 2005;**100**(3):568–76.
60. Garofalo C, Surmacz E. Leptin and cancer. *J Cell Physiol* 2006;**207**(1):12–22.
61. Kendall BJ, Macdonald GA, Hayward NK, et al. Leptin and the risk of Barrett's oesophagus. *Gut* 2008;**57**(4):448–54.
62. Williams LB, Fawcett RL, Waechter AS, et al. Leptin production in adipocytes from morbidly obese subjects: stimulation by dexamethasone, inhibition with troglitazone, and influence of gender. *J Clin Endocrinol Metab* 2000;**85**(8):2678–84.
63. 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 Biomark Prev* 1998;**7**(10):913–5.
64. Khushalani N. Cancer of the esophagus and stomach. *Mayo Clin Proc* 2008;**83**(6):712–22.
65. van Blankenstein M, Looman CW, Hop WC, Bytzer P. The incidence of adenocarcinoma and squamous cell carcinoma of the esophagus: Barrett's esophagus makes a difference. *Am J Gastroenterol* 2005;**100**(4):766–74.
66. Kobayashi K. Effect of sex hormone on the experimental induction of esophageal cancer. *Nippon Geka Gakkai Zasshi* 1985;**86**(3):280–9.
67. Kuiper GG, Enmark E, Pelto-Huikko M, Nilsson S, Gustafsson JA. Cloning of a novel receptor expressed in rat prostate and ovary. *Proc Natl Acad Sci USA* 1996;**93**(12):5925–30.
68. Greene GL, Gilna P, Waterfield M, et al. Sequence and expression of human estrogen receptor complementary DNA. *Science* 1986;**231**(4742):1150–4.
69. Green S, Walter P, Kumar V, et al. Human oestrogen receptor cDNA: sequence, expression and homology to v-erb-A. *Nature* 1986;**320**(6058):134–9.
70. 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.
71. 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.
72. 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.
73. Kalayarasan R, Ananthakrishnan N, Kate V, Basu D. Estrogen and progesterone receptors in esophageal carcinoma. *Dis Esophagus* 2008;**21**(4):298–303.
74. 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.
75. Nozoe T, Oyama T, Takenoyama M, et al. Significance of immunohistochemical expression of estrogen receptors alpha and beta in squamous cell carcinoma of the esophagus. *Clin Cancer Res* 2007;**13**(14):4046–50.
76. Moore JT, McKee DD, Slentz-Kesler K, et al. Cloning and characterization of human estrogen receptor beta isoforms. *Biochem Biophys Res Commun* 1998;**247**(1):75–8.
77. Ogawa S, Inoue S, Watanabe T, et al. Molecular cloning and characterization of human estrogen receptor betacx: a potential inhibitor of estrogen action in human. *Nucl Acids Res* 1998;**26**(15):3505–12.
78. Utsumi Y, Nakamura T, Nagasue N, et al. Effect of 17 beta-estradiol on the growth of an estrogen receptor-positive human esophageal carcinoma cell line. *Cancer* 1991;**67**(9):2284–9.
79. Joubert A, Marais S. In vitro effects of 2-methoxyestradiol on cell morphology and Cdc2 kinase activity in SNO oesophageal carcinoma cells. *Cell Biochem Funct* 2007;**25**(3):357–62.
80. Joubert A, Maritz C, Joubert F. Bax/Bcl-2 expression levels of 2-methoxyestradiol-exposed esophageal cancer cells. *Biomed Res* 2005;**26**(3):131–4.
81. Morani A, Warner M, Gustafsson JA. Biological functions and clinical implications of oestrogen receptors alfa and beta in epithelial tissues. *J Intern Med* 2008.
82. Horvath LG, Henshall SM, Lee CS, et al. Frequent loss of estrogen receptor-beta expression in prostate cancer. *Cancer Res* 2001;**61**(14):5331–5.
83. Roger P, Sahla ME, Makela S, et al. Decreased expression of estrogen receptor beta protein in proliferative preinvasive mammary tumors. *Cancer Res* 2001;**61**(6):2537–41.
84. Chandanos E, Rubio C, Lindblad M, Jia C, Tsolakis A, Warner M, et al. Endogenous estrogen exposure in relation to distribution of histological type and estrogen receptors in gastric adenocarcinoma. *Gastric Cancer* 2008;**11**(3):168–74.
85. Wang M, Pan JY, Song GR, et al. Altered expression of estrogen receptor alpha and beta in advanced gastric adenocarcinoma: correlation with prothymosin alpha and clinicopathological parameters. *Eur J Surg Oncol* 2007;**33**(2):195–201.
86. Konstantinopoulos PA, Kominea A, Vandoros G, et al. Oestrogen receptor beta (ERbeta) is abundantly expressed in normal colonic mucosa, but declines in colon adenocarcinoma paralleling the tumour's dedifferentiation. *Eur J Cancer* 2003;**39**(9):1251–8.
87. Uchikado Y, Natsugoe S, Okumura H, et al. Slug expression in the E-cadherin preserved tumors is related to prognosis in patients with esophageal squamous cell carcinoma. *Clin Cancer Res* 2005;**11**(3):1174–80.
88. Wada-Hiraike O, Hiraike H, Okinaga H, et al. Role of estrogen receptor beta in uterine stroma and epithelium: insights from estrogen receptor beta–/– mice. *Proc Natl Acad Sci USA* 2006;**103**(48):18350–5.
89. Chlebowski RT, Wactawski-Wende J, Ritenbaugh C, et al. Estrogen plus progestin and colorectal cancer in postmenopausal women. *New Engl J Med* 2004;**350**(10):991–1004.
90. Nelson HD, Humphrey LL, Nygren P, Teutsch SM, Allan JD. Postmenopausal hormone replacement therapy: scientific review. *JAMA* 2002;**288**(7):872–81.

91. Chandanos E, Lagergren J. Oestrogen and the enigmatic male predominance of gastric cancer. *Eur J Cancer* 2008;**44**(16):2397–403.
92. Palli D, Cipriani F, Decarli A, et al. Reproductive history and gastric cancer among post-menopausal women. *Int J Cancer* 1994;**56**(6):812–5.
93. La Vecchia C, D'Avanzo B, Franceschi S. Menstrual and reproductive factors and gastric-cancer risk in women. *Int J Cancer* 1994;**59**(6):761–4.
94. 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 Contr* 2003;**14**(1):53–9.
95. Lindblad M, Ye W, Rubio C, Lagergren J. Estrogen and risk of gastric cancer: a protective effect in a nationwide cohort study of patients with prostate cancer in Sweden. *Cancer Epidemiol Biomark Prev* 2004;**13**(12):2203–7.
96. Frise S, Kreiger N, Gallinger S, Tomlinson G, Cotterchio M. Menstrual and reproductive risk factors and risk for gastric adenocarcinoma in women: findings from the Canadian national enhanced cancer surveillance system. *Ann Epidemiol* 2006;**16**(12):908–16.
97. Freedman ND, Chow WH, Gao YT, et al. Menstrual and reproductive factors and gastric cancer risk in a large prospective study of women. *Gut* 2007.
98. Furukawa H, Iwanaga T, Koyama H, Taniguchi H. Effect of sex hormones on the experimental induction of cancer in rat stomach – a preliminary study. *Digestion* 1982;**23**(3):151–5.
99. Furukawa H, Iwanaga T, Koyama H, Taniguchi H. Effect of sex hormones on carcinogenesis in the stomachs of rats. *Cancer Res* 1982;**42**(12):5181–2.
100. Campbell-Thompson M, Lauwers GY, Reyher KK, Cromwell J, Shiverick KT. 17Beta-estradiol modulates gastroduodenal preneoplastic alterations in rats exposed to the carcinogen N-methyl-N′-nitro-nitrosoguanidine. *Endocrinology* 1999;**140**(10):4886–94.
101. Furukawa H, Iwanaga T, Hiratsuka M, et al. Suppressive effect of sex hormones on spreading of stomach cancer. *Gan To Kagaku Ryoho* 1989;**16**(12):3691–5.
102. Matsuoka H, Sugimachi K, Ueo H. Sex hormone response of a newly established squamous cell line derived from clinical esophageal carcinoma. *Cancer Res* 1987;**47**(15):4134–40.
103. Ueo H, Matsuoka H, Sugimachi K. Inhibitory effects of estrogen on the growth of a human esophageal carcinoma cell line. *Cancer Res* 1990;**50**(22):7212–5.
104. Yamashita Y, Hirai T, Mukaida H, et al. Detection of androgen receptors in human esophageal cancer. *Jpn J Surg* 1989;**19**(2):195–202.
105. Shirai T, Tsuda H, Ogiso T, Hirose M, Ito N. Organ specific modifying potential of ethinyl estradiol on carcinogenesis initiated with different carcinogens. *Carcinogenesis* 1987;**8**(1):115–9.
106. Miller AB, Barclay TH, Choi NW, et al. A study of cancer, parity and age at first pregnancy. *J Chronic Dis* 1980;**33**(10):595–605.
107. La Vecchia C, Negri E, Franceschi S, Parazzini F. Long-term impact of reproductive factors on cancer risk. *Int J Cancer* 1993;**53**(2):215–9.
108. Lagergren J, Jansson C. Sex hormones and oesophageal adenocarcinoma: influence of childbearing? *Br J Cancer* 2005;**93**(8):859–61.
109. 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.
110. Gallus S, Bosetti C, Franceschi S, et al. Oesophageal cancer in women: tobacco, alcohol, nutritional and hormonal factors. *Br J Cancer* 2001;**85**(3):341–5.
111. Midgette AS, Baron JA. Cigarette smoking and the risk of natural menopause. *Epidemiology* 1990;**1**(6):474–80.
112. 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.
113. Reeves GK, Pirie K, Beral V. Cancer incidence and mortality in relation to body mass index in the Million Women Study: cohort study. *BMJ* 2007;**335**(7630):1134.
114. Gruber CJ, Tschugguel W, Schneeberger C, Huber JC. Production and actions of estrogens. *New Engl J Med* 2002;**346**(5):340–52.
115. Osborne CK. Tamoxifen in the treatment of breast cancer. *New Engl J Med* 1998;**339**(22):1609–18.
116. Chandanos E, Lindblad M, Jia C, et al. Tamoxifen exposure and risk of oesophageal and gastric adenocarcinoma: a population-based cohort study of breast cancer patients in Sweden. *Br J Cancer* 2006;**95**(1):118–22.
117. Andersson M, Storm HH, Mouridsen HT. Incidence of new primary cancers after adjuvant tamoxifen therapy and radiotherapy for early breast cancer. *J Natl Cancer Inst* 1991;**83**(14):1013–7.
118. Fisher B, Costantino JP, Redmond CK, et al. Endometrial cancer in tamoxifen-treated breast cancer patients: findings from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14. *J Natl Cancer Inst* 1994;**86**(7):527–37.
119. Rutqvist LE, Johansson H, Signomklao T, et al. Adjuvant tamoxifen therapy for early stage breast cancer and second primary malignancies. Stockholm Breast Cancer Study Group. *J Natl Cancer Inst* 1995;**87**(9):645–51.
120. Curtis RE, Boice Jr JD, Shriner DA, Hankey BF, Fraumeni Jr JF. Second cancers after adjuvant tamoxifen therapy for breast cancer. *J Natl Cancer Inst* 1996;**88**(12):832–4.
121. Matsuyama Y, Tominaga T, Nomura Y, et al. Second cancers after adjuvant tamoxifen therapy for breast cancer in Japan. *Ann Oncol* 2000;**11**(12):1537–43.
122. Hage M, Siersema PD, van Dekken H, et al. Oesophageal cancer incidence and mortality in patients with long-segment Barrett's oesophagus after a mean follow-up of 12.7 years. *Scand J Gastroenterol* 2004;**39**(12):1175–9.