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Review

Oestrogen and the enigmatic male predominance of gastric cancer

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ABSTRACT

Gastric cancer is the second most common cause of cancer death worldwide, and annually it causes over 150,000 deaths in Europe and 700,000 deaths globally. The incidence of gastric cancer shows an enigmatic male dominance with a male-to-female ratio of about 2:1. This sex ratio cannot be entirely attributed to the differences in the prevalence of known risk factors between the sexes. This review focuses on the potential role of oestrogen in explaining the male predominance in gastric cancer. Some data argue in favour of sex hormonal influence. Women with a longer fertility life and those on hormone replacement therapy seem to have a decreased risk of gastric cancer, and men who have been treated with oestrogen for prostate cancer have a decreased risk. Use of tamoxifen in women seems to increase their risk of gastric cancer. Animal studies indicate that oestrogen may offer protection against the development of this cancer as for example ovariectomised mice are at an increased risk, whilst administration of female sex hormones decreases the incidence of gastric cancer. Oestrogen may exert its effect by acting on oestrogen receptors (ERs). Both ER α , ER β and the latest discovered ER β cx have been identified in gastric tissue. The biological means behind this is not yet clear but various mechanisms have been suggested. There are indications that oestrogen may lead to an increased expression of trefoil factor proteins, which protect mucous epithelia or inhibit the expression of c-erb-b2 oncogene.

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1. Occurrence

Gastric cancer has a high death rate (700,000 per year) making it the second most common cause of cancer death, after lung cancer.¹ In the year 2000, almost 200,000 cases were diagnosed in Europe and more than 150,000 deaths occurred² with a steady and persistent fall in mortality rates.³ The survival rate is better in Japan (52%)¹ where endoscopic mass screen-

ing has been implemented since the 1960s, whilst the survival chance is about 25% in the Western World.^{1,4} The incidence of gastric cancer has been declining in most countries during the last decades,⁵ probably due to better preservation of foods, a change in dietary pattern and a decrease in the prevalence of *Helicobacter pylori* (*H. pylori*). Nevertheless, it is the fourth most common cancer worldwide with 930,000 cases diagnosed in 2002.

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2. Histology

As more than 90% of all gastric cancers are adenocarcinomas, the remainder being mainly non-Hodgkin's lymphomas, or leiomyosarcomas,⁶ for the purpose of this review 'gastric cancer' refers to gastric adenocarcinoma. According to Laurén's classification, there are two histological types of gastric adenocarcinoma: intestinal and diffuse.⁷

The intestinal type is characterised by the glandlike appearance of neoplastic cells, whilst in the diffuse type, as the name implies, the cells lack cohesion and infiltrate the stomach wall without forming a distinct mass.⁷ The intestinal type occurs more often in older patients^{8–11} and in men^{8,10,11} mainly affecting the distal part of the stomach.¹² In contrast, the diffuse type is more often encountered in young patients,^{10–12} whilst men and women are equally affected,^{11,12} and it is found more often in the corpus and fundus of the stomach.¹² The diffuse type has been more closely associated with heredity, whilst the intestinal type is more often preceded by precancerous conditions such as atrophic gastritis and intestinal metaplasia.¹²

3. Aetiology

The aetiology of gastric cancer is multifactorial (Fig. 1). *H. Pylori* infection is a well-established risk factor^{13,14} and tobacco smoking is a moderate one.¹⁵ A diet rich in fruit and vegetables seems to offer protection¹⁶ in contrast to intake of salt, which seems to possibly increase the risk¹⁷ as obesity does in the risk of cardia gastric cancer.^{18,19} A higher socioeconomic status has also been found to be associated with a reduced risk of gastric cancer, and that risk was stronger for the cardia site or for the intestinal histological type.²⁰

Previous gastric surgery for benign conditions is linked to an increased risk as well.²¹ One of the most intriguing risk factors for developing gastric cancer is the male sex.

4. Hypothesis of oestrogen protection

There is a strong and enigmatic male dominance in the incidence of this cancer with a male-to-female ratio of about 2:1. This male predominance has been observed in different populations of the world, and cannot entirely be explained on the basis of sex differences in the prevalence of known risk factors.²² Therefore, endogenous factors that either provide protection in women alone or imply an increased risk only in men should play a role. A potentially protective effect of oestrogen against gastrointestinal cancer development has been studied, e.g. with respect to colorectal cancer. In the Women's Health Initiative cohort, in which 16,608 women were randomised to either receive hormone replacement therapy (HRT) with oestrogen and progestin or placebo, the risk of colorectal cancer was almost half in the HRT group compared to that of the non-HRT group (hazard ratio 0.56, 95% confidence interval (CI) 0.38–0.81).²³ Moreover, a meta-analysis of 18 observational studies showed a 20% reduction in the risk of colon cancer amongst ever users of HRT compared to never users (relative risk 0.80, 95% CI 0.74–0.86).²⁴ Thus, the notion

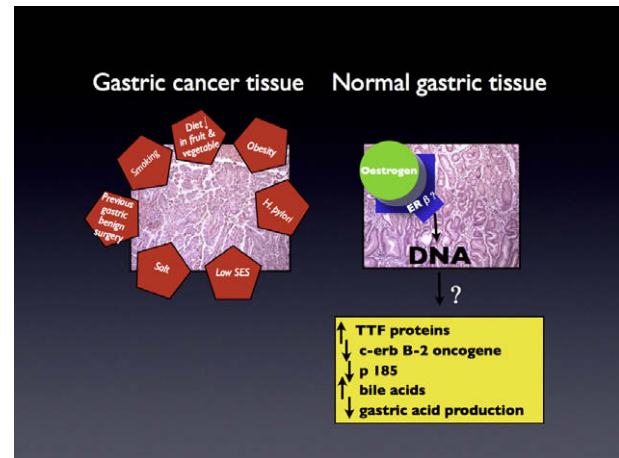


Fig. 1 – Risk factors for gastric cancer and the suggested mechanisms through which oestrogen may offer protection. (SES: socioeconomic status, TTF:trefoil factor, ↓: low/decreased, ↑: increased).

that oestrogen might protect against the development of gastrointestinal cancer is not new.

5. Animal studies

Some animal studies suggest that hormonal factors may play a suppressive role in the development of gastric cancer. The carcinogenic *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (MNNG) added to drinking water induced gastric cancer in male rats but not in female. In the same experiment, castrated or oestrogen-treated male rats had a lower incidence of gastric cancer compared to untreated male rats.²⁵ Another study reported that the incidence of gastric cancer increased in castrated female rats.²⁶ Moreover, administration of oestrogen in previously MNNG-treated rats reversed MNNG-induced gastroduodenal preneoplastic alterations.²⁷ Furthermore, administration of female sex hormones to male rats decreased their incidence of gastric cancer.²⁸ On the other hand, oestrogen effects on the growth of human gastric cancer xenografts in nude mice have been contradictory; some gastric cancers have been stimulated, whilst others have been inhibited or not affected at all.²⁹

6. Human studies

A global pattern in the sex distribution, unique of gastric cancer, has given further support to the hypothesis of oestrogen protection. Sipponen and colleagues showed that women develop the intestinal type of gastric cancer 10–15 years later than men and that the incidence increases after menopause.³⁰ This pattern was consistent in all the 18 cancer registries used in the study and in populations with high and low gastric cancer incidence. The hypothesis that oestrogen might prevent gastric cancer has been evaluated in several epidemiological studies (Table 1). These studies investigated factors related to oestrogen exposure, including effects of age at menarche, age at menopause, length of fertility life, use of HRT and parity. Some more details of these studies are presented here.

Table 1 – Epidemiological studies assessing the risk of gastric cancer in relation to hormonal factors

	Age at menarche	Age at menopause	Length of fertility life	HRT	Parity
Miller et al. (Canada, 1980) ⁴²					X
Plesko et al. (Slovakia, 1985) ⁴¹					↑ Increasing parity
La Vecchia et al. (Italy, 1993) ⁹⁵					X
Palli et al. (Italy, 1994) ³⁸	X	↑ Lower age	↓ Longer fertility life		X
La Vecchia et al. (Italy, 1994) ³²	X	↓ Higher age	↓ Longer fertility life	↓ HRT, ↑ OC	↑ Increasing parity
I. Heuch et al (Norway, 2000) ⁴⁰	↓ Higher age	X	X		X
Inoue et al. (Japan, 2002) ³⁹	X	X	X		X
Fernandez et al. (Italy, 2003) ³⁶				Tendency for lower risk	
Kaneko et al. (Japan, 2003) ³³	X	X	↓ Longer fertility life	↓ HRT	↓ Increasing parity
Lindblad et al. (Sweden 2004) ³¹	Reduced risk in men treated with oestrogen				
Lindblad et al. (UK 2006) ³⁴				↓ HRT	
Frise et al. (Canada, 2006) ³⁵	↑ Higher age	↑ In post-menopause	↓ Longer fertility life	↓ HRT or OC	↓ 4 or more births
Freedman (China, 2007) ³⁷	X	↓ Higher age	↑ Shorter fertility life	X	X

Not all associations were significant.
HRT: hormone replacement therapy, OC: oral contraceptives, X: no association, ↑: increased risk with, ↓: decreased risk with.

6.1. Exogenous oestrogen

In a male cohort of prostate cancer patients, the risk of developing gastric cancer was lower amongst those who had been treated with oestrogen than in those without such treatment (standardised incidence ratio (SIR) 0.87, 95% CI 0.78–0.98).³¹ Fifteen years after the prostate cancer diagnosis the risk was further decreased, and amongst patients with a latency of more than 15 years after a prostate cancer diagnosis the SIR was 0.57 (95% CI 0.30–0.97), suggesting a dose-response relation. A seemingly protective effect of HRT on gastric cancer risk has been reported in five studies from four different populations.^{32–36} In one of them, there was a statistically significant decreased risk of gastric cancer by more than 50% for those on HRT, and this inverse association was even stronger for when cardia adenocarcinomas were excluded (odds ratio (OR) 0.34, 95% CI 0.14–0.78).³⁴ In a recent study from China, however, no association between HRT and gastric cancer was found (HR 1.05, 95% CI 0.33–3.36).³⁷

6.2. Reproductive factors

Results from the studies of menstrual factors and parity and risk of gastric cancer are partly conflicting. A longer period of fertility amongst females, i.e. the time from menarche to menopause, increases the lifetime exposure to endogenous oestrogens and has been reported to possibly reduce the risk of gastric cancer in several studies,^{32,33,35,37,38} although a lack of such association,³⁹ and an inverse association with age at menarche has also been reported.⁴⁰ Multiparity has been associated with an increased^{32,41} as well as a decreased risk^{33,35} of gastric cancer, whilst other investigations have found no association.^{37–39,42,98} In a study conducted in a Norwegian population, women with many pregnancies over a short period of time had an increased risk of cancer of the proximal part of the stomach, whilst pregnancies over a long period seemed to increase the risk of the distal part.⁴⁰

6.3. Anti-oestrogen exposure

If the hypothesis of oestrogen protection is true, then anti-oestrogen exposure might increase the risk of gastric cancer. Tamoxifen, an anti-proliferative agent clinically used in the treatment of breast cancer, is the most commonly known selective oestrogen receptor modulator. It reduces the risk of recurrence and death of breast cancer, and has an antagonistic effect in the breast tissue.⁴³ Tamoxifen exposure as a risk for gastric cancer has been tested in a cohort of post-menopausal women with breast cancer.⁴⁴ Those who were defined tamoxifen treated had an increased risk of developing gastric cancer compared to breast cancer patients who were not treated with tamoxifen, and the risk was stronger for non-cardia adenocarcinoma. Moreover, the risk increased with increasing latency interval between the breast and gastric cancer diagnosis, representing longer duration of tamoxifen. Others have found similar results. In a pooled analysis of three studies in Scandinavia a non-significant, but nearly 3-fold increase in the risk of gastric cancer was found.⁴⁵ In another report, stomach cancer was the second most frequent secondary cancer after endometrial cancer with a statistically significant increased risk in the tamoxifen-treated group (SIR = 1.49, $p = 0.01$).⁴⁶ Correspondingly elevated risks have been reported in other studies, but without statistically significant results.^{47,48} On the other hand, from two small and uncontrolled Japanese studies it was reported that patients with a diffuse or scirrhous gastric cancer who were given tamoxifen had a survival advantage, thus not confirming the hypothesis of oestrogen protection.^{49,50} Nevertheless in a recently conducted study, tamoxifen seemed to decrease the latency interval between breast and gastric cancer, indicating that tamoxifen use might accelerate the tumour progression or increase the overall risk of gastric adenocarcinoma.⁵¹ Finally, in a randomised, controlled trial, 100 patients with gastric cancer who received conventional surgical management were assigned either to additional tamoxifen treatment or to join an untreated control group. The conclusions drawn were that tamoxifen had no overall effect on survival,

and that there was a significant decrease in the survival time of patients with tumours positive for oestrogen receptors (ERs).⁵²

7. Biological mechanisms

The discovery of oestrogen receptors in gastric tissue in 1983 ignited an enormous interest in the possible implication of this finding for the treatment of gastric cancer.⁵³ The potential role of involvement of hormonal factors was discussed and some suggested evaluation of hormonal therapy with oestrogen⁵⁴ or anti-oestrogen.^{49,50} It is proposed that the possible protective effect of oestrogen against gastric cancer is exerted through ERs. Two types of ERs are known: ER alpha (ER α)^{55,56} and ER beta (ER β),⁵⁷ both of which have been identified in non-cancerous^{51,58,59,71} and cancerous gastric tissue.^{51,53,58–66,71} Two years after the first report on ER β , a splice variant of ER β , termed ER β cx, was characterised.^{67,68} ER β cx is expressed in the breast,⁶⁹ the prostate, the testis⁶⁸ and the esophagus,⁷⁰ and it was recently identified in gastric tissue as well.^{51,71} Several researchers, using various methods, have identified ERs in gastric tissue, either in the cytoplasm or in the nucleus^{51,58,62,72,73,71} and some have reported on the ER status in association with clinopathological data.^{51,59–61,63,65,71,73–79} These studies were, however, too small for the findings to make strong conclusions about the mechanisms or effects.

ERs belong to the nuclear receptor family of transcription factors and are attached to their receptor-associated proteins in the cytoplasm or the nucleus of the cell.⁸⁰ Any effects of oestrogen are mediated to the cells through the binding to these receptors. Oestrogen may bind directly to its receptors which in turn bind either to DNA (the classical pathway) or to other proteins (transcription factors) and these finally bind to DNA (tethered pathway). A third mechanism involves activation of ERs which leads to a rapid physiological response without DNA binding (non-nuclear action) as for example when ion channels are activated. Finally, a fourth mechanism exists, in which ERs are activated independently of oestrogen, for example by growth factors (ligand-independent pathway). It is unclear how oestrogen may act in the gastric tissue and what the physiological responses may be. It has been proposed that oestrogen affects the expression of trefoil factor (TTF) genes (Fig. 1). TTF proteins protect mucous epithelia from a range of insults and contribute to mucosal repair.⁸¹ The expression of these genes is reduced in precancerous conditions and in gastric cancer,⁸² and oestrogen has been found to stimulate their expression.⁸³ Others have proposed that oestrogen may bind to ERs and inhibit the expression of c-erbB-2 oncogene or the expression of p185.⁵⁴ The latter is associated with the progression of gastric cancer.⁵⁴

In ovariectomised rats the cell mass as well as basal acid secretion increases,⁸⁴ suggesting that oestrogen might regulate gastric acid production. Moreover, it has been hypothesised that bile acids may be carcinogenic,⁸⁵ although this is debated.⁸⁶ Oestrogen may prevent colon cancer development by decreasing the bile acid concentration or by direct effects on the colonic mucosa, as suggested by *in vitro* studies.⁸⁷ This could explain why HRT with oestrogen might reduce the risk of non-cardia gastric adenocarcinoma,³⁴ as this region of

the stomach is exposed to bile acids to a greater extent than the cardia. In addition, in breast cancer cells it has been found that bile acids down-regulate the expression of ERs.⁸⁸

Another interesting finding with regard to the presence of oestrogen receptors in gastric cancer is the fact that the expression of ER β in gastric cancer tissue is decreased.^{71,89} This receptor has been linked to promoting epithelial differentiation and plays a role in the organisation and architectural maintenance of the colon.⁹⁰ It may have a similar function on the gastric mucosa. ER β cx does not bind oestrogen.⁶⁸ Instead it inhibits ER α from binding DNA, whilst it does not influence ER β . The role of the presence of ER β cx in the gastric tissue needs to be further investigated.

The potential action of tamoxifen on the gastric tissue remains to be clarified. It might have a direct anti-estrogenic effect in gastric mucosa. Another suggested mechanism is through the inhibition of the binding of histamine to cytochrome P450 enzymes. A histamine–P450 interaction could disturb normal homeostatic maintenance of intracellular levels of lipid mediators. These mediators modulate gene function, including expression of the cytochrome P450, and thus affect cell growth and proliferation.⁹¹ Moreover, tamoxifen has been found to regulate the expression of transforming growth factor- α and β and to bind to calcium channels and protein kinase C.⁹²

8. Summary and future research

The male dominance in the incidence of gastric cancer can at least be partly explained by a protective effect of oestrogen in women. This is probably true for the intestinal type of gastric adenocarcinoma. A summary of the available studies seems to support this hypothesis, but more research is warranted before this can be established. Especially large series in which the two histological subtypes are distinguished need to be done. Another area of research would be to investigate whether changes in trends of HRT use affect the incidence of gastric cancer as studies suggest that the decline of breast cancer incidence in some populations may be due to the reduction of HRT use.^{93,94}

If an important role of oestrogen and ERs in relation to gastric cancer is established, it might open the way for clinical studies in the future, e.g. in adjuvant or preventive strategies in the treatment of gastric cancer.

Conflict of interest statement

None declared.

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