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Sex differences in the incidence of gastrointestinal adenocarcinoma in Sweden 1970–2006

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ABSTRACT

Background: Oesophageal and gastric adenocarcinoma share a male predominance not seen for other adenocarcinomas of the gastrointestinal tract. These sex differences are not explained by known risk factors. An endogenous factor, such as premenopausal oestrogen exposure, may act protectively in favour of women and might be detected by scrutinising sex ratios and incidence rates stratified by age.

Methods: The Swedish Cancer Register was used to collect primary oesophageal, gastric cardia, non-cardia gastric, colonic and pancreatic adenocarcinoma cases aged 25–84, during the study period of 1970–2006. Cases were divided into five-year age groups and crude incidence rates and male: female ratios were calculated. Evaluating potential time period effect, the corresponding results from 1970–1986 and 1987–2006 were also derived.

Results: The sex ratio for oesophageal adenocarcinoma ranged from approximately 10:1 to 4:1, presenting a seemingly consistent decline with age. The sex ratio for non-cardia gastric adenocarcinoma, however, increased with age to reach 2:1 at a point one to two decades after menopause, where the ratio levelled off and eventually declined. There was no discernible time period effect concerning any type of adenocarcinoma. The ratios for gastric cardia, colonic and pancreatic adenocarcinoma were stable with age.

Conclusion: This study indicates separate patterns of age-dependency of the sex difference in oesophageal and non-cardia gastric adenocarcinoma incidence. The non-cardia gastric adenocarcinoma pattern might be due to a protective effect during premenopausal years for the female population, while the seemingly steady decline in sex ratio in oesophageal adenocarcinoma indicates a mechanism independent of menopause.

1. Introduction

The last decade's remarkable change in the incidences of oesophageal and gastric adenocarcinoma has attracted a lot of attention in the Western world.[1] Adenocarcinoma in the oesophagus and gastric cardia has become increasingly common in the West while adenocarcinoma of non-cardia gastric location is steadily decreasing.[1–3]

Oesophageal and gastric adenocarcinoma share an unexplained male predominance. For gastric adenocarcinoma the sex ratio of 2–3:1 has been shown to be constant throughout different populations and in different time periods, and seems to be due to a 10- to 15-year delay in the appearance and onset of gastric adenocarcinoma of the intestinal subtype in females.[4] A similar delay among females was recently suggested also for oesophageal adenocarcinoma,[5] a disease even

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more common in men, with a sex ratio of 7–10:1 in worldwide cancer registries.[6] The male predominance of these tumours has not been explained by differences between the sexes in the prevalence of the known risk factors.[7,8] It has been postulated that sex hormones, oestrogen in particular, could account for the difference in the observed sex ratio by a protective effect of endogenous oestrogen production during premenopausal years both in oesophageal adenocarcinoma[9] and in gastric adenocarcinoma development[4] but this has yet to be fully demonstrated.

Our aim was therefore to further evaluate the potential impact of oestrogen, using age as a proxy, on the incidence of oesophageal and gastric adenocarcinoma in comparison with other gastrointestinal tract adenocarcinomas with a less pronounced sex ratio such as colonic or pancreatic adenocarcinoma. We hypothesised that a supposed protective effect of oestrogen on developing adenocarcinoma of the oesophagus or stomach would be reflected in an age-dependent sex ratio of the annual incidence where a stable male predominance before menopause would decline as a consequence of decreased hormonal protection in females. The effect should also persist through different time periods, but should not be seen for other adenocarcinomas of the gastrointestinal tract, where the male predominance is not as consistent. We also hypothesised, as previously shown,[4,5] that such an equalisation of the sex ratio would be due to a delay in the onset of disease among females compared to males.

2. Methods

2.1. Data source

The Swedish Cancer Register was established in 1958 to build a complete cancer database for clinical and research purposes. All clinicians and pathologists in Sweden are obliged to report all cancer cases to the Register. Validation studies have shown that the register has a completeness rate of 98%[10,11] and virtually all cancer cases (99%) are morphologically verified.[12] The tumour localisation is coded according to the International Classification of Diseases for Oncology (ICD-O) version 2 and then converted to a modified version of the ICD-7. From 1970 and onwards, the Register has differentiated gastric cardia cancer from non-cardia gastric cancer. In addition to information on site, the Register contains specific codes for cancer histology, data on sex, date of birth and date of diagnosis.

2.2. Identification of patients

Study participants were identified in the Cancer Register from 1970 through 2006 by the following, predefined, criteria: (a) a first diagnosed cancer was oesophageal (ICD-7 150.0, 150.8 or 150.9), gastric cardia (ICD-7 151.1), non-cardia gastric (ICD-7 151.0, 151.8 or 151.9), pancreatic (ICD-7 157) or colonic (ICD-7 153.0, 153.1, 153.2, 153.3, 153.4, or 153.9) in origin, (b) the cancer was an adenocarcinoma (histology code 096) and (c) the cancer was the only cancer registered on the same date (thus ensuring primary cancer identification). Information on cancer type, age at diagnosis and sex was retrieved for each patient from the Cancer Register and demographical population data, including distribution of age and sex for each year, was retrieved from Statistics Sweden. The Regional ethical board of Stockholm approved the study.

2.3. Statistical analysis

Cases were divided into five-year age groups, beginning from 25 to 29 and ending with 80–84. For the different age groups, annual incidence rates were calculated by dividing the number of incident cancer cases each year by the annual male or female population, as appropriate. The male-to-female ratio of the incidence rates was subsequently derived for the corresponding age groups. Assuming a Poisson distribution, 95% confidence intervals for the incidence rate and the male-to-female incidence rate ratio were calculated, respectively. To evaluate any period effects, the results were stratified into two time periods: 1970–1986 and 1987–2006. The specific periods were chosen to reflect the potential effect on tumour registration of introducing ICD-9 in 1987. Due to the small number of young cases, the age groups below 40 years were merged when evaluating oesophageal adenocarcinoma and gastric cardia adenocarcinoma; for comparison purposes, analyses were conducted and graphs constructed when merging age groups below 50 years as well. The age-specific incidences of oesophageal, cardia gastric and non-cardia gastric adenocarcinoma were modelled, using non-linear regression analysis. The equation $I(t) = a \times (t - d)^b$ was fitted to the age-specific incidence, where $I(t)$ is the age-specific incidence (per 100,000 person-years) at age t, which represents the mean age of the age group. The three parameters a, d and b are estimated regression constants. All analyses were conducted in STATA 10.1, StataCorp, Texas, United States of America.

3. Results

3.1. Overview

In all, 147,919 patients aged 25–84 years with a primary gastrointestinal adenocarcinoma were identified during the study period. The site of origin was in 2544 patients the oesophagus, 4692 the gastric cardia, 36,124 non-cardia stomach, 78,690 the colon, and 25,869 the pancreas. Mean age at onset of oesophageal adenocarcinoma was for men 67.1 years and women 71.6 years, gastric cardia adenocarcinoma 66.9 and 69.4 years, non-cardia gastric adenocarcinoma 69.4 and 69.6 years, colonic adenocarcinoma 68.9 and 69.6 years, pancreatic adenocarcinoma 67.5 and 69.2 years, respectively. In the study population, the crude male and female incidence rates were for adenocarcinoma of the oesophagus 2.0 and 0.4, gastric cardia 3.7 and 1.0, non-cardia stomach 21.4 and 13.0, colon 37.4 and 37.2, and pancreas 13.0 and 11.5 per 100,000 person-years, respectively.

3.2. Sex ratio

The overall male: female ratio for adenocarcinoma incidence was for oesophagus 5.1:1, gastric cardia 3.7:1, non-cardia stomach 1.6:1, colon 1.0:1, and pancreas 1.1:1. Age group-specific sex ratios of the annual incidence rates for oesophageal

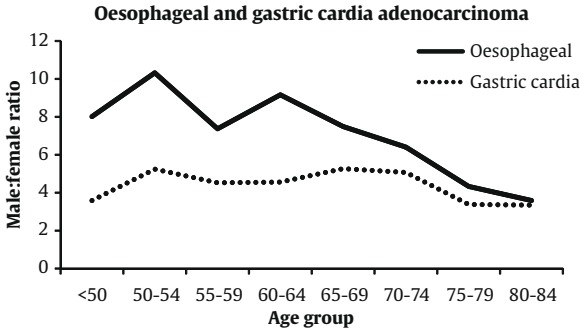


Fig. 1 – Sex ratio stratified by age groups for oesophageal and gastric cardia adenocarcinoma in Sweden from 1970 to 2006, inclusive.

and gastric cardia adenocarcinoma are shown in Fig. 1 and Table 1. Considering oesophageal adenocarcinoma, there is a marked sex difference in the younger age groups; the male-to-female ratio is in its extreme approaching 10:1, but declines gradually in older age groups to below 4:1 in the last age group. For gastric cardia adenocarcinoma, the sex ratio differences display a more constant ratio of about 4:1, with a slight decline in the oldest age groups (Fig. 1). The corresponding sex ratios for non-cardia gastric, colonic and pancreatic adenocarcinoma are displayed in Fig. 2. While the male-to-female ratios for colonic and pancreatic adenocarcinoma are approximately 1:1 throughout the different age groups, the corresponding ratios for non-cardia gastric adenocarcinoma display a pattern of male predominance, growing steadily larger in older age groups, reaching a plateau in age groups 65–74, with a sex ratio of just more than 2:1. Thereafter, the ratio declines slightly in the subsequent age groups (Fig. 2, Table 2).

3.3. *Sex-specific incidence*

In Fig. 3, Tables 1 and 2, the age-group stratified incidence rates for oesophageal, gastric cardia and non-cardia gastric adenocarcinoma are displayed. The male incidence rises steadily with age for both oesophageal and gastric cardia adenocarcinoma, up to age-group 70–74, after which the incidence rate seems to level out. In comparison, the corresponding female incidence slopes indicate a delayed rise of incidence until the age group of 70–74; this rise stabilises in the subsequent age groups, never reaching the same steep slope as the male counterpart (Fig. 3, Table 1). In Fig. 3, modelling of the incidence curves using non-linear regression analysis indicated

Table 1 – Distribution of oesophageal and gastric cardia adenocarcinoma in different age groups, stratified by sex, in Sweden from 1970 to 2006, inclusive.

Age group	Male		Female		Male-to-female
	Cases	Rate[a] (95% CI)	Cases	Rate[a] (95% CI)	Rate ratio[b] (95% CI)
Oesophageal adenocarcinoma					
<40	20	0.06 (0.04–0.09)	1	0.00 (0.00–0.02)	19.05 (2.56–141.94)
40–44	29	0.27 (0.18–0.39)	2	0.02 (0.00–0.07)	13.98 (3.33–58.58)
45–49	68	0.67 (0.52–0.85)	11	0.11 (0.06–0.20)	6.03 (3.19–11.41)
50–54	146	1.49 (1.26–1.76)	14	0.14 (0.08–0.24)	10.32 (5.97–17.86)
55–59	219	2.37 (2.06–2.70)	30	0.32 (0.22–0.46)	7.37 (5.03–10.80)
60–64	316	3.75 (3.35–4.19)	36	0.41 (0.29–0.57)	9.16 (6.49–12.94)
65–69	358	4.84 (4.35–5.37)	53	0.65 (0.48–0.85)	7.49 (5.61–10.00)
70–74	403	6.50 (5.88–7.16)	76	1.01 (0.80–1.27)	6.41 (5.01–8.19)
75–79	328	7.06 (6.32–7.87)	103	1.63 (1.33–1.98)	4.33 (3.47–5.40)
80–84	228	7.10 (6.21–8.08)	103	1.98 (1.61–2.40)	3.59 (2.84–4.53)
<50	117	0.21 (0.18–0.26)	14	0.03 (0.01–0.04)	8.01 (4.60–13.95)
All ages	2115	2.04 (1.96–2.13)	429	0.40 (0.36–0.44)	5.11 (4.61–5.67)
Gastric cardia adenocarcinoma					
Age group	Cases	Rate[a] (95% CI)	Cases	Rate[a] (95% CI)	Rate ratio[b] (95% CI)
<40	46	0.14 (0.10–0.18)	13	0.04 (0.02–0.07)	3.38 (1.82–6.24)
40–44	86	0.82 (0.65–1.01)	27	0.27 (0.17–0.39)	3.07 (1.99–4.73)
45–49	130	1.29 (1.07–1.53)	30	0.3 (0.21–0.43)	4.23 (2.84–6.29)
50–54	249	2.55 (2.24–2.88)	47	0.49 (0.36–0.65)	5.24 (3.84–7.16)
55–59	372	4.02 (3.62–4.45)	83	0.89 (0.71–1.10)	4.53 (3.57–5.74)
60–64	520	6.17 (5.66–6.73)	119	1.35 (1.12–1.62)	4.56 (3.74–5.57)
65–69	670	9.06 (8.39–9.77)	141	1.72 (1.45–2.03)	5.27 (4.39–6.32)
70–74	743	11.98 (11.13–12.87)	177	2.36 (2.03–2.74)	5.07 (4.30–5.97)
75–79	592	12.75 (11.74–13.82)	238	3.77 (3.31–4.28)	3.38 (2.91–3.93)
80–84	415	12.92 (11.70–14.22)	201	3.86 (3.34–4.43)	3.35 (2.83–3.96)
<50	262	0.48 (0.42–0.54)	70	0.13 (0.10–0.17)	3.59 (2.76–4.67)
All ages	3823	3.69 (3.57–3.81)	1076	1.00 (0.94–1.06)	3.69 (3.45–3.94)

CI = confidence interval.

a Age-specific incidence rate per 100,000 person-years.

b Age-specific incidence rate ratio.

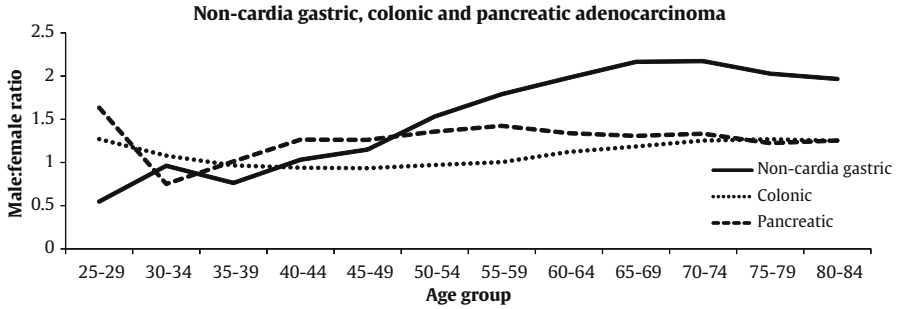


Fig. 2 – Sex ratio stratified by age groups for non-cardia gastric, colonic and pancreatic adenocarcinoma in Sweden from 1970 to 2006, inclusive.

Table 2 – Distribution of non-cardia gastric adenocarcinoma in different age groups, stratified by sex, in Sweden from 1970 to 2006, inclusive.

Age group	Male		Female		Male-to-female
	Cases	Rate[a] (95% CI)	Cases	Rate[a] (95% CI)	Rate ratio[b] (95% CI)
Non-cardia gastric adenocarcinoma					
25–29	23	0.20 (0.13–0.30)	40	0.37 (0.26–0.50)	0.55 (0.33–0.92)
30–34	78	0.68 (0.54–0.85)	77	0.70 (0.56–0.88)	0.96 (0.70–1.32)
35–39	124	1.12 (0.93–1.33)	155	1.46 (1.24–1.71)	0.76 (0.60–0.97)
40–44	302	2.86 (2.55–3.20)	282	2.77 (2.46–3.12)	1.03 (0.88–1.21)
45–49	509	5.03 (4.61–5.49)	432	4.38 (3.97–4.81)	1.15 (1.01–1.31)
50–54	901	9.21 (8.62–9.83)	582	6.01 (5.53–6.52)	1.53 (1.38–1.70)
55–59	1568	16.95 (16.12–17.81)	884	9.46 (8.85–10.11)	1.79 (1.65–1.94)
60–64	2511	29.82 (28.66–31.01)	1323	15.05 (14.25–15.88)	1.98 (1.85–2.12)
65–69	3631	49.09 (47.51–50.71)	1860	22.68 (21.66–23.73)	2.16 (2.05–2.29)
70–74	4606	74.26 (72.13–76.44)	2560	34.16 (32.85–35.51)	2.17 (2.07–2.28)
75–79	4589	98.83 (95.99–101.73)	3077	48.73 (47.02–50.48)	2.03 (1.94–2.12)
80–84	3295	102.56 (99.09–106.12)	2715	52.14 (50.20–54.14)	1.97 (1.87–2.07)
All ages	22,137	21.37 (21.09–21.65)	13,987	13.02 (12.8–13.23)	1.64 (1.61–1.68)

CI = confidence interval.
a Age-specific incidence rate per 100,000 person-years.
b Age-specific incidence rate ratio.

different slopes for men and women and an increasing female incidence delay for oesophageal and gastric cardia adenocarcinoma (Fig. 3). The non-cardia gastric adenocarcinoma incidence rate shows a delayed and less steep rise for the female population as compared to males (Fig. 3, Table 2). Modelling of the curves showed divergent slopes for men and women, pointing towards a female incidence delay of 10–15 years in incidence for non-cardia gastric adenocarcinoma (Fig. 3).

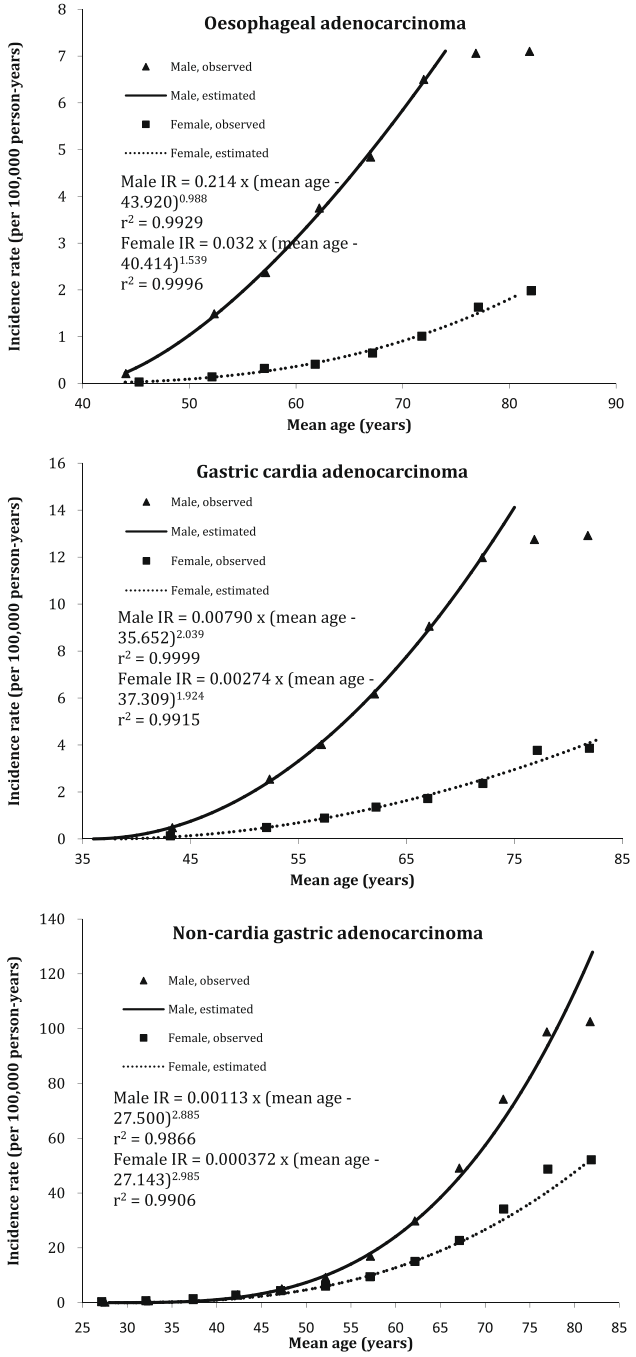
3.4. *Two time periods*

The evaluation of the period effect is shown in Fig. 4. Sex ratios for oesophageal, gastric cardia and non-cardia gastric adenocarcinoma in 1970–1986 and 1987–2006 display approximately the same pattern in both periods, (Fig. 4) which also holds true for colonic and pancreatic adenocarcinoma (data not shown).

4. Discussion

The present study indicates different patterns of association between age and sex ratio for different gastrointestinal adenocarcinomas. For oesophageal adenocarcinoma the strong male predominance at a young age steadily decreases with age. The pattern for gastric cardia adenocarcinoma is more consistent between age groups, with a stable male predominance. For non-cardia gastric adenocarcinoma, the male predominance increases with age up to 65–74 years, after which it declines slightly, seemingly due to a delayed rise in incidence among females. There were no clear associations between sex ratio and age for adenocarcinomas of the colon and pancreas.

Advantages of the current study include the use of a highly valid and complete national register, ensuring identification of virtually all adenocarcinomas in Sweden during the past five decades.[10,11] Moreover, the large number of patients and years of follow-up allowed us to perform subgroup analyses of anatomical sub-site and period effects. The use of register data, however, relies on data that might be prone to misclassification. Site misclassification is however impossible to entirely avoid in any study of tumours of the oesophagogastric junction since firm anatomical borders for classifying large tumours are lacking.[10] Any tumour misclassification should nevertheless be non-differential and similar between the



IR = Incidence rate

Fig. 3 – Modelling of age-specific incidence rates (per 100,000 person-years) by sex for oesophageal, gastric cardia and non-cardia gastric adenocarcinoma from 1970 to 2006, inclusive.

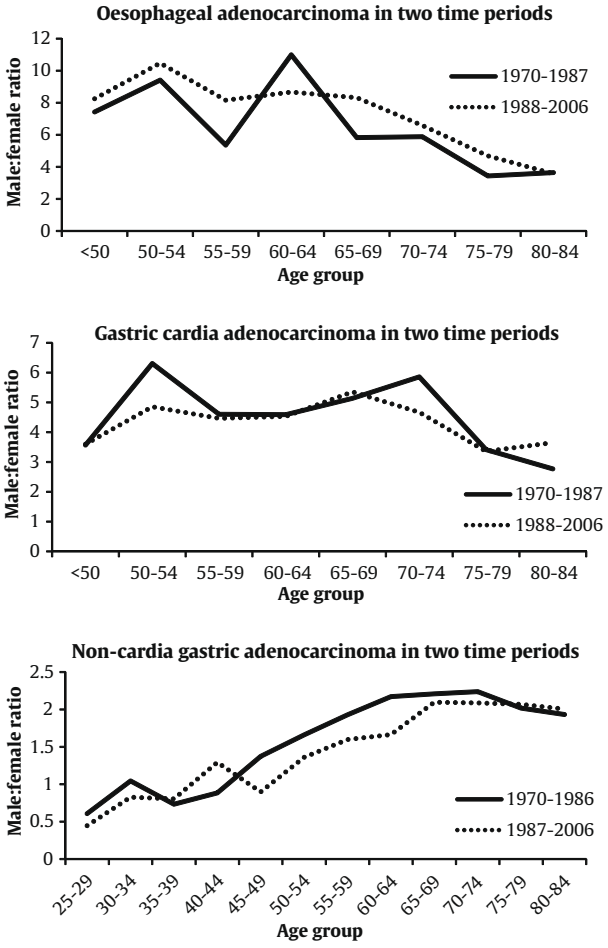


Fig. 4 – Age-group stratified sex ratios for oesophageal, gastric cardia and non-cardia gastric adenocarcinoma in two periods of time: 1970–1987 and 1988–2006.

sexes. Furthermore, the Register does not include information on histological subtype of gastric adenocarcinoma and discrimination between the diffuse and intestinal type of adenocarcinoma was therefore not available. Such a mix of histological subtype might explain our absence of a sex difference in the younger age groups for non-cardia gastric adenocarcinoma since it has been shown that the diffuse type is more abundant in younger age and is equally distributed between the sexes, while the more common intestinal type typically develops among the elderly and among men.[5,13] In the elderly, bias might be introduced by decreasing diagnostic effort or competing causes of death; the first should be non-differential as regards to sex and would thus only dilute the results towards the null, while the second possibility of bias could have a differential impact on the male as compared to the female population. However, this type of bias should not only affect oesophageal adenocarcinoma incidence where the sex ratio decline is most pronounced, but also the other cancer types, in which the sex ratio does not fall with age.

We found an age-dependent sex ratio for the incidence of oesophageal and non-cardia gastric adenocarcinoma, but not for gastric cardia, colonic or pancreatic adenocarcinoma. Our à priori hypothesis was that the pattern of age-dependency would reflect a protective effect of oestrogen and, thus, there would be a delay in the onset of disease among women and the male predominance would be constant up to menopause and decrease thereafter.

Regarding oesophageal adenocarcinoma, our data rather indicated a steadily decreasing male predominance throughout all age groups and the non-linear regression modelling suggested an increasing delay by age among women; these

findings plausibly speak against a strong effect of menopause. This is not in total agreement with a recent study from Scotland concluding that the male predominance of upper gastrointestinal adenocarcinoma is due to a delayed development in females prior to 50–60 years of age.[5] However, the Scottish study's data regarding oesophageal adenocarcinoma exclusively are in coherence with our findings.[5] Interpretations from both studies should, nevertheless, be made cautiously, as they are hampered by few young female cases. On the other hand, the present study reproduces results from a large American study evaluating the sex ratios of several cancer types, including oesophageal adenocarcinoma for which a similar steadily decreasing sex ratio with age was described.[14] The male predominance could, speculatively, be due to an earlier onset among men of important risk factors for oesophageal adenocarcinoma, as gastro-oesophageal reflux[15] or obesity.[16] Indeed, the prevalence in young age of these risk factors is higher among men as compared to women in population-based studies.[17–19] Further, android-type obesity[20] has been shown to be an independent risk factor for oesophageal and gastric cardia adenocarcinoma, and hiatal hernia and a defective lower oesophageal sphincter have been found to be more prevalent in men.[21] An alternate explanation could be that the carcinogenesis of oesophageal adenocarcinoma is androgen driven. Experimental studies have identified not only oestrogen[22] but also androgen receptors[23] in the oesophagus, with a change from epithelial to stromal receptor expression in adenocarcinoma cells as compared to normal tissue.[23,24] Taking into account the gradually falling testosterone levels with age,[25] this could speculatively provide a molecular link to the declining male-to-female ratio of oesophageal adenocarcinoma shown in the current study. Epidemiological studies of the association between oestrogen and oesophageal adenocarcinoma are few. Our group evaluated the effect of childbearing as well as hormone replacement therapy with negative results,[26,27] while there are conflicting reports on the presumed lower incidence of oesophageal adenocarcinoma due to oestrogen and antiandrogen therapy in prostate cancer cohorts.[9,28]

For non-cardia gastric adenocarcinoma the age-dependency pattern identified in this study is in line with the hypothesis of a protective effect of oestrogen, lending support to two previous studies.[4,5] There is still much uncertainty to what the age-specific sex difference can be attributed and several other explanations for this incidence pattern are possible. Nevertheless, the hypothesis finds some support in experimental studies, where the intake of the carcinogenic nitroso-amine compounds was found to induce gastric cancer development in male, but not in female rats, while castration reduced the risk in males but induced gastric cancer in females.[29] Furthermore, nitroso-amine induced gastric neoplasia in Sprague–Drawley rats can be reversed by giving them 17ß-estradiol.[30] In a recent rodent study, 42% of males and 10% of oophorectomised females developed *Helicobacter pylori*-induced gastric cancer in transgenic hypergastrinemic INS-GAS mice, while no neoplasia developed in intact females or in oophorectomised females treated with 17ß-estradiol.[31] Lastly, an association between genetic polymorphisms involved in oestrogen inactivation and modulation of hormone bioavailability and gastric cancer has recently been found.[32] Several observational studies have addressed the impact of different reproductive factors on gastric cancer, with partly conflicting results. Studies in support[33–39] of a longer period of fertility or parity reducing the risk of gastric cancer stand against studies that oppose such an effect.[40–43] Our group has previously found that treated men with prostate cancer have a statistically significant 13% reduced risk of a second primary gastric cancer,[44] and that women on hormone replacement therapy are at a more than 50% reduced risk of gastric cancer,[26] of which the latter finding has been contradicted elsewhere.[33] Thus, there are some experimental and observational reports in favour of a protective effect of oestrogen on gastric cancer development, while the potential biological mechanism remains to be clarified.

Our finding of a lack of association between age and sex ratio for gastric cardia adenocarcinoma incidence was unexpected, but most likely it does not represent another pattern of male predominance. Instead, considering the disagreement of classification between adenocarcinomas in the oesophagogastric junction, the results could be interpreted as a mix of misclassified adenocarcinomas from the oesophagus and more distally in the stomach.[10,11] Interestingly, the intestinal histological subtype of gastrointestinal adenocarcinoma might be associated with male predominance rather than the anatomical location.[5] It nevertheless seems to be of importance to continue to distinguish between the anatomically separate upper gastrointestinal adenocarcinomas in aetiological and epidemiological research due to their diverging incidence trends, different risk factor profiles as well as different associations between male predominance and age identified in the present study. Further, a recent study has indicated that, when considering comorbidity patterns, oesophageal and gastric cardia adenocarcinomas have more in common than either anatomical site has with non-cardia gastric cancer.[45]

In conclusion, this study supports the existence of a period-independent, age-dependent sex ratio in oesophageal and non-cardia gastric adenocarcinoma, but not of adenocarcinoma of the gastric cardia, colon or pancreas. The male predominance for non-cardia gastric adenocarcinoma could be due to a protective effect of female hormones, while this does not seem to be the case for the other gastrointestinal adenocarcinomas studied. The steady and substantial decline in sex ratio with increasing age in oesophageal adenocarcinoma, seemingly unrelated to menopause, might present a clue to the striking male predominance of this tumour.

Conflict of interest statement

None declared.

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