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ABSTRACT

Background and aims: Upper gastrointestinal adenocarcinomas show an unexplained male predominance that is more apparent in oesophagus than stomach and in intestinal than diffuse histological subtype. We have conducted a population-based study to determine whether the gender phenomenon is primarily related to the anatomical site or the histological subtype.

Method and materials: Of 3270 gastric and oesophageal cancers recorded in the West of Scotland Cancer Registry, 1998–2002, 812 were randomly selected for detailed analysis. The Lauren histological subtype of adenocarcinoma was determined by reviewing 1204 original reports and 3241 biopsies.

Results: Analysis included 405 non-cardia cancers, 173 cardia cancers and 209 oesophageal adenocarcinomas. Crude incidence rate of intestinal subtype was higher in males (23.86/100 000 person-years) versus females (9.00/100 000 person-years), giving a male/female (M/F) ratio of 2.65 whereas diffuse subtype was similar for both genders (5.58 vs 5.20/100 000 person-years) yielding M/F of 1.07. The M/F ratios for oesophageal, cardia and non-cardia gastric cancer were 3.5, 2.0 and 1.6, respectively. Multiple logistic regression indicated that the odds of male gender was related to the histological subtype rather than anatomical location (odds ratio 2.6, 95% confidence interval 1.78 to 3.9). Curve fitting of the age-specific incidence of intestinal subtype indicated that similar functions describe the rise in incidence with age in males and in females. However, the age-specific incidence of female intestinal subtype was delayed by 17.3 years. The M/F ratio of intestinal subtype was 3.41 at age <50 years, peaked at 7.86 at age 50–59 years and then showed a progressive decrease after 50–60 years of age.

Conclusion: Male predominance of upper gastrointestinal adenocarcinoma is related to the intestinal histological subtype rather than tumour location and is due to marked delayed development of this subtype in females prior to 50–60 years of age.

A remarkable and unexplained characteristic of upper gastrointestinal adenocarcinoma is its male predominance. This male predominance of gastric cancer is related to the histological subtype of the tumour. Gastric adenocarcinoma may be of the intestinal or diffuse histological subtype as described by Lauren.[1] The intestinal subtype is strongly linked to chronic *Helicobacter pylori* superficial gastritis. According to Correa *et al*,[2] the latter may induce intestinal metaplasia of the gastric mucosa from which the intestinal subtype cancer is thought to develop. The diffuse histological subtype of gastric cancer is less strongly associated with *H pylori* infection and genetic predisposition is thought to be more important.[3–5] The gender phenomenon is more marked in gastric cancer of the intestinal versus diffuse histological subtype and this has been described well by Sipponen and colleagues.[6] However, few, if any, cancer registries have reliable records of the histological subtype of gastric and oesophageal cancer and therefore true population-based incidence studies of the influence of gender on intestinal versus diffuse gastric cancer are lacking.

Interest in the role of gender in upper gastrointestinal cancer has been rekindled by the rapidly rising incidence of adenocarcinoma of the oesophagus in the Western world.[7] These cancers also demonstrate a marked male predominance and tend to present at a younger age in males.[8] Adenocarcinoma of the oesophagus is considered to be a consequence of chronic damage to the squamous mucosa of the distal oesophagus by acid, pepsin and probably bile refluxing from the stomach and small intestine.[9 10] In response to this chronic damage, the oesophageal squamous epithelium undergoes metaplasia to become columnar in type and eventually resembling that of the small or large intestine.[11 12] Oesophageal adenocarcinoma is thought to arise from this intestinal metaplasia and histologically resembles the intestinal subtype of gastric adenocarcinoma.

Global data from cancer registries suggest that the male predominance of upper gastrointestinal cancer is related to the anatomical location, being higher for adenocarcinoma of the oesophagus and lower for adenocarcinoma of the distal stomach.[13] The male-to-female ratio of age-standardised incidence rates for oesophageal adenocarcinoma in Scotland is of the order of 4.5:1, for adenocarcinoma of the proximal cardia region of the stomach or gastro-oesophageal junction it is 3.5:1 and for more distal gastric cancer it is 2.0:1.[14] However, the proportion of the intestinal histological subtype differs according to anatomical site and it is unclear whether it is the anatomical site or the histological subtype which is associated with the gender phenomenon.

Understanding the point at which the gender phenomenon is acting will facilitate unravelling its mechanism. We have therefore conducted a population-based study to determine whether the gender phenomenon is primarily related to the

anatomical site or to the histological subtype of adenocarcinoma of the upper gastrointestinal tract. This has been conducted in the west of Scotland, a region with a moderately high incidence of gastric cancer and with the highest recorded incidence of oesophageal adenocarcinoma in the world.[14] Our findings indicate that the intestinal subtype has the greatest impact on the gender ratio and this is unrelated to whether the carcinoma has developed in the oesophagus or distal stomach. Our study also indicates that the gender phenomenon is due to the development of the intestinal subtype of cancer being delayed by 17.3 years in females.

METHODS AND MATERIALS

The study was based on patients with a diagnosis of gastric or oesophageal cancer recorded in the West of Scotland Cancer Registry between 1998 and 2002. The Cancer Registry covered more than half the Scottish population at this time. The registry constantly monitors data quality to evaluate reliability of recorded diagnosis. According to a recent reliability report in 1997, there was a 97% agreement in coding the major tumour site category based on ICD-10 and only 2% discrepancy in microscopic verifications of tumours.[15] Registration of cancers based on "death certificate only" criteria for all malignant neoplasma, excluding non-melanoma skin cancer was only 0.4% in 1997.[15] For the time period included in our study, the estimated completeness of cancer registration was >96%.[16]

Selection process

We collected the tumour identification number of all cases of gastric and oesophageal adenocarcinoma recorded in the west of Scotland during the 5 year period 1998–2002. The study was conducted on histology slides and records of 812 randomly selected patients from a total of 3270 cases of gastric and oesophageal cancers recorded in the database. The number of samples was stratified by tumour site to ensure that the sites are present in the sample in the same proportion as in the population. A random sample of pre-defined size was selected from each group of cancers (approximately 25% for each site). Randomisation was performed with a computerised random number generator (SPSS, Chicago, Illinois, USA). To be included in the study, all cases were required to have histological samples available for microscopic verification.

Histological study

All pathology records of sampled subjects were reviewed for microscopic diagnosis and anatomical site of tumour using ICD-10 and ICD O-2. The histological subtype of adenocarcinoma was determined by the Lauren classification.[1] When the information on the pathology reports was inadequate, the original microscopy slides were re-evaluated by the study pathologists using the Lauren classification. In order to ensure compatibility of reported classifications with our study definitions, at least 10% of all specimens with complete histology records were selected randomly for re-examination using the same protocol.

Statistical analysis

Binary logistic regression models were used to estimate the relationship between the odds of male gender (dependent variable) and histological subtype, tumour location and age (independent variables). The histological subtype included intestinal and diffuse subtypes but not mixed subgroup due to a very small percentage of this type in the population sample. All gastric and oesophageal tumours of histology other than adenocarcinoma were excluded from analysis. Tumour location was defined as oesophageal, gastric cardia and gastric non-cardia as defined in the cancer registry database. Patients were categorised into five age groups: <50, 50–59, 60–69, 70–79 and ≥80. The 10 year groupings were arbitrarily chosen on common-sense grounds; the top and bottom groups extend beyond a decade to ensure all groups have an adequate number of patients. Grouping age in this way for the logistic regression means that no assumptions have to be made about the form of the relationship (eg, linear) between age and the odds of male gender. The logistic regression models were used to estimate the odds of male gender for the categories of the independent variables, the associated 95% confidence intervals and the associated p values. Logistic regression models were fitted initially for each independent variable separately. A multiple logistic regression model was finally fitted including all the independent variables. All two-way interactions between the independent variables were initially considered in this multivariable model, but as none were statistically significant at 10% they were omitted from the final analysis.

Supplementary studies

As the above analysis indicated that male predominance was associated with the intestinal histological subtype and not tumour location, we proceeded to investigate characteristics of the male predominance affecting the intestinal versus diffuse subtype of tumours. This included modelling the age specific incidence in males versus females in the intestinal and diffuse tumours and also of other tumours in our cancer registry.

Curve fitting age-specific cancer incidence data

A curve fitting approach was taken to quantitatively describe the age-specific incidence of cancer using non-linear regression analysis. The equation $I_{(t)} = a \times (t-d)^b$ was fitted to the age-specific incidence data using the SOLVER function of Excel.[17] In this equation, I_t is the age-specific incidence of cancer (per 100 000 person-year) at age t (the mean age of the group); and a, b and d are regression constants, where a is a scaling factor, b is a power term that reflects the rate of incidence with age and d is a delay term for the time between birth and age of increased incidence above zero. A logic IF function was used in Excel such that when $t<d$ $(t-d<0)$, $I_{(t)} = 0$. Thus only when $d>t$ was $I_{(t)}>0$.

The difference between the data and the model (sum of the square differences (SS)) was computed and the target function which was minimismed by non-linear regression analysis using generalised reduced gradient (GRG2) non-linear optimisation was the root mean square of SS. Curve fits were obtained using similar starting estimates for all age-specific incidence data.

Comparison of gender related, age-specific incidence with other cancers

The 1998–2002 average age-group-specific incidence (per 100 000 person-years) were extracted from the ISD Scottish Cancer Registry for cancer of the oesophagus, adenocarcinoma (ICD-10: C15, ICD-O-2 various); cancer of the oesophagus, squamous cell (ICD-10: C15, ICD-O-2 8050-8076); cancer of the lung, squamous cell carcinoma (ICD-10: C33-34; ICD-O-2: 8050–8076), cancer of the lung, adenocarcinoma (ICD-10: C33-34; ICD-O-2: various); cancer of the lung, small cell carcinoma (ICD-10: C33-34; ICD-O-2: 8040–8045); cancer of the bladder, squamous cell carcinoma (ICD-10: C67; ICD-O-2: 8051–8076);

Table 1 Crude incidence rates of upper gastrointestinal cancer of the random sample from the West of Scotland by histology and tumour location

	Tumour location											
	Gastric non-cardia				Gastric cardia				Oesophageal adenocarcinoma			
	Number		Incidence rate*		Number		Incidence rate*		Number		Incidence rate*	
Histology	M	F	M	F	M	F	M	F	M	F	M	F
Intestinal	151	76	10.14	4.66	76	36	5.10	2.20	128	35	8.60	2.14
Diffuse	57	62	3.82	3.79	17	15	1.14	0.91	9	8	0.60	0.49
Mixed	9	6	0.60	0.37	4	3	0.27	0.18	6	2	0.40	0.12
Undifferentiated	7	8	0.47	0.49	6	4	0.40	0.24	9	2	0.60	0.12
Other	10	19	0.67	1.16	5	7	0.34	0.43	8	2	0.54	0.12
All types	234	171	15.73	10.48	108	65	7.26	3.98	160	49	10.75	3.00

*Crude annual incidence rate, per 100 000 person-years.
F, female; M, male.

cancer of the bladder, transitional cell carcinoma (ICD-10: C67; ICD–O-2: 8050, 8120–8122, 8130); cancer of the colon (ICD-10: C18; ICD-O-2: various); and cancer of the pancreas (ICD-10: C25; ICD-O-2: various). These cancers were recorded for the West of Scotland Cancer Registry matching the population for gastric and oesophageal cancer. The age-specific incidence of these cancers were also analysed by curve fitting, as described previously, to examine gender differences in the incidence rate and the age at which incidence increased above zero.

RESULTS

In total 812 incident cancers with histological diagnosis of oesophageal adenocarcinoma (C15), gastric cardia cancer (C16.0) and gastric non-cardia cancer (C16.1–16.9) were reviewed. Of these, 25 records (3.1%) were excluded because both original reports and materials were missing (n = 9) or they were recorded in duplicate (n = 16). After the first round of document review, 3241 slides from 463 cancer cases were reviewed because their original records had inadequate information regarding the Lauren histological subtypes. Among 349 reports with adequate information, 42 reports were selected randomly and related slides were re-evaluated. Classification of only two cases (<5%) required to be changed (from diffuse subtype to mixed subtype). The distribution of cancers by sex and anatomical site in the sample studied showed no statistical difference from the correspondent entire cancer registry data.

Regardless of anatomical subsite, the upper gastrointestinal (GI) cancers were more common in males (502, 63.8%) than females (285, 36.2%). Four hundred and five (51.5%) of the cancers originated from the non-cardia region of the stomach, 173 (22.0%) from the gastric cardia and 209 (26.6%) from the oesophagus.

Histologically, 63.8% of all tumours were of intestinal and 21.3% of diffuse subtype (table 1). Of the remaining 117, 25.6% were mixed type of Lauren classification, 30.8% undifferentiated carcinoma, and 43.6% of other histological diagnosis. The last group included adenosquamous carcinoma (n = 1), large cell carcinoma (n = 1), leiomyosarcoma (n = 1), lymphoma (n = 1), carcinoid tumour (n = 7), carcinoma in situ (n = 7), squamous cell carcinoma (n = 10) and metastatic tumours of unknown origin (n = 23). For the purpose of this study, we only analysed the data of patients with either intestinal or diffuse type carcinoma which included more than 85% of incident cancers.

The proportion of histological subtypes varied with tumour location. Intestinal/diffuse subtype ratio was 163/17 (9.6: 1) for oesophageal adenocarcinomas, 102/32 (3.2: 1) for cardia and 227/119 (1.9: 1) for non-cardia adenocarcinomas.

Association of male predominance with tumour location vs histological subtype

Gender and histological subtypes

Regardless of anatomical site, the crude incidence rate of intestinal subtype upper GI adenocarcinoma was higher in males, at 23.86 per 100 000 person-years, versus females, at 9.00 per 100 000 person-years, resulting in an M/F ratio of 2.65. In contrast, the crude incidence rate of diffuse subtype adenocarcinoma was similar in males and females (5.58 vs 5.20 per 100 000 person-years) yielding an M/F ratio of 1.07 (table 2 and fig 1). The gender effect expressed as M/F incidence ratio varied with age and histological subtype. As shown in fig 2, the M/F ratio of intestinal subtype cancer was 3.41 at age less than 50, reached a peak of 7.86 at age 50–59 years, and then showed a progressive decrease with a minimum of 2.29 at age group 80 years and over. In contrast, M/F ratio of diffuse subtype cancer was 0.89 at age less than 50 and did not show any significant changes with increasing age.

Gender and tumour location

Regardless of histological subtype, the male predominance of adenocarcinoma incidence varied with anatomical location (table 3). Male predominance was greatest in the oesophagus with crude incidence rates of 9.21 and 2.63 in males versus females, respectively (M/F = 3.50). For cardia cancer the crude incidence rates were 6.25 and 3.12 for males and females, respectively (M/F = 2.00), and for non-cardia cancer 13.98 and 8.46 (M/F = 1.65).

Multivariable analysis of male predominance risk factors

Multivariable logistic regression including histological subtype, tumour location and age indicated that the odds of male gender was mainly related to the histological subtype and age rather than anatomical location. Although the odds of male gender was higher for oesophageal versus non-cardia adenocarcinoma when anatomical location was considered alone in a logistic regression model (odds ratio (OR) 2.11, 95% confidence interval (CI) 1.41 to 3.17), this relationship with anatomical location lost statistical significance in the multivariable analysis when histological subtype and age were added (OR = 1.37, 95% CI 0.88 to 2.12). In addition, the overall significance level in the logistic regression model for anatomical location diminished from $p<0.001$ when it was considered alone to $p = 0.333$ when considered together with age and histological subtype. This suggests that male predominance in upper GI adenocarcinomas was not primarily a function of tumour location but rather related to histological subtype and age (table 4). Intestinal subtype

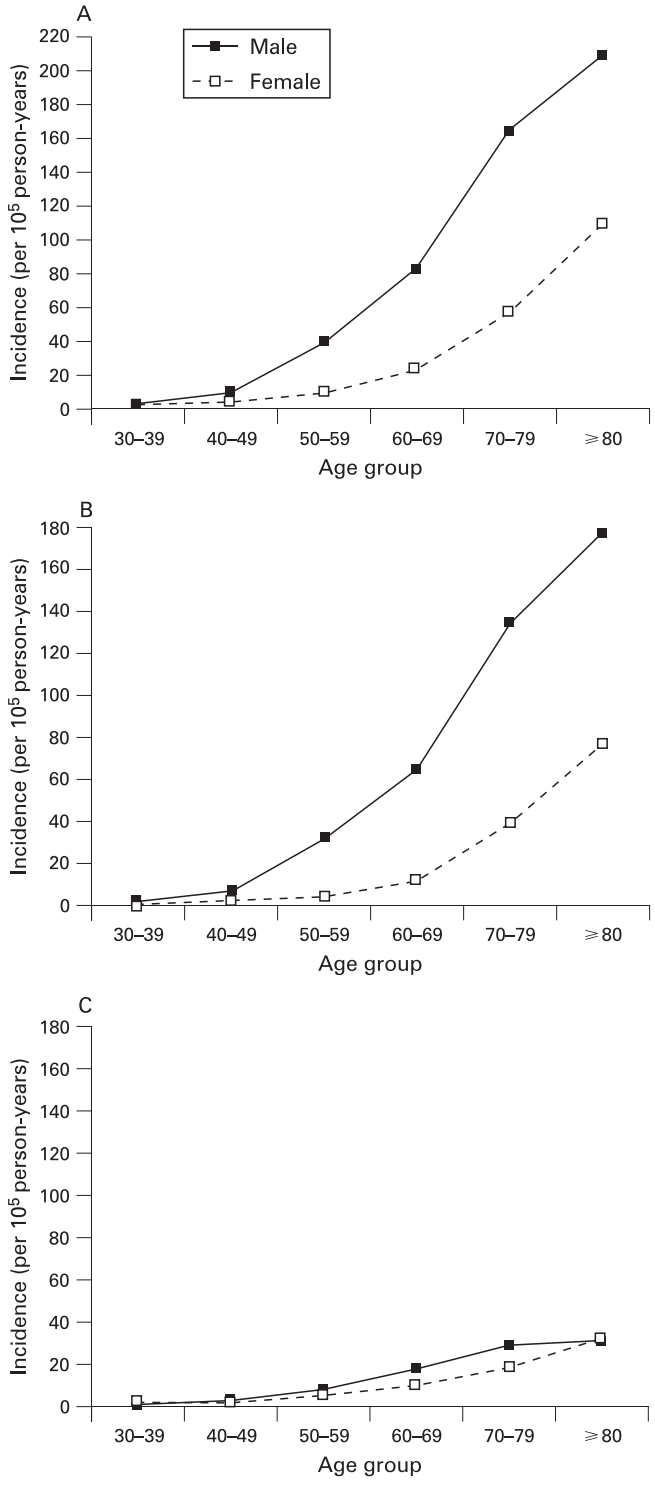

Figure 1 Age specific incidence rates of upper gastrointestinal adenocarcinoma by gender. (A) combined intestinal and diffuse subtypes; (B) intestinal subtype; and (C) diffuse subtype.

adenocarcinoma was associated with increased odds of male gender irrespective of anatomical location or age (OR 2.6, 95% CI 1.78 to 3.90). Increasing age showed an overall inverse relationship with the odds of male gender excluding those aged <50 years; again this relationship persisted when anatomical location and histological subtype were considered in the same logistic regression model.

Characteristics of male predominance of upper gastrointestinal adenocarcinoma

The rise in incidence with increasing age was much more marked in the intestinal versus diffuse subtype (fig 3A,B). For the diffuse histological subtype the crude and age-specific incidence rates were similar for males and females. Curve fitting of the age-specific incidence data for diffuse subtypes resulted in similar equations: $y = 0.016 \times \text{mean age}^{2.007}$, $R^2 = 0.999$ and $y = 0.016 \times \text{mean age}^{1.954}$, $R^2 = 0.989$, for male and females, respectively. The age at which the age-specific incidence curve rose above zero was similar in males (33.0 years) and females (35.8 years). For the intestinal histological subtype, the age-specific incidence data were different for males and females. Curve fitting indicated a similar incidence rate in males ($y = 0.016 \times \text{mean age}^{2.315}$, $R^2 = 0.990$) and in females ($y = 0.016 \times \text{mean age}^{2.316}$, $R^2 = 0.998$). However, the age-specific incidence curve for females did not appear to deviate from zero until an older age compared with male intestinal subtype. The age at which the age-specific incidence curve rose above zero was 28.8 years in males versus 46.1 years in females indicates a delay of 17.3 years in the appearance of intestinal subtype cancer in females.

Characteristics of male predominance in other cancers

Analysis of all recorded cases of oesophageal adenocarcinoma in the Scottish Cancer Registry between 1998 and 2002 produced similar age-specific incidence curves to that observed in our random sample of oesophageal adenorcarcinoma with an age delay in the appearance of intestinal subtype cancer in females of 15.6 years (table 5). Analysis of age-specific incidence curves of squamous cell carcinoma of oesophagus, lung cancer (three common histological types), bladder cancer (two common histological types), colon cancer (all histologies) and pancreatic cancer (all histologies) showed no evidence of a gender-related delay in the incidence of these cancers. This analysis included squamous cell carcinoma of lung and transitional cell carcinoma of bladder, which have an M/F ratio of 2.1 and 2.6, respectively. In the latter cancers, the higher male incidence was due to a higher rate of increase rate rather than any gender specific delay in the rise of incidence (table 5).

DISCUSSION

This study confirms the long-recognised male predominance of adenocarcinoma of the upper gastrointestinal tract, the crude incidence rates being 29.44 in males and 14.21 in females. It also confirms that the degree of male predominance varies by anatomical site of the adenocarcinoma, being greatest in the oesophagus (M/F ratio = 3.50), less at the cardia (M/F ratio = 2.00), and least in the more distal non-cardia region of the stomach (M/F ratio = 1.65). This relationship between anatomical site and male predominance has been observed in several previous studies from different regions of the world.[8 18]

The proportion of the intestinal to diffuse histological subtypes varied with anatomical locations, being 9.6:1 in the oesophagus, 3.2:1 at the cardia and 1.9:1 in the distal stomach (table 1). A high ratio of the intestinal/diffuse histological subtypes has been reported in the cardia and non-cardia region of the stomach in previous studies.[4 19–22]

A strong association was observed between male predominance and histological subtype. Regardless of anatomical subtype, the crude incidence rate of intestinal type upper gastrointestinal tract adenocarcinoma was higher in males, with an M/F ratio of 2.65:1. In contrast, the crude incidence rates of

Table 2 Distribution of upper gastrointestinal adenocarcinoma in different age groups by sex and histological subtypes

		Age group											
		<50		50–59		60–69		70–79		⩾80		All ages	
Histology		n	Rate*	n	Rate*	n	Rate*	n	Rate*	n	Rate*	n	Rate†
Intestinal subtype	Male	20	2.51	60	32.56	94	65.38	124	134.74	57	177.11	355	23.86
	Female	6	0.57	8	4.14	21	12.50	52	38.94	60	77.44	147	9.00
	Total	26		68		115		176		117		502	
	M/F		3.41		7.86		5.23		3.46		2.29		2.65
Diffuse subtype	Male	7	0.68	14	7.56	25	17.38	27	29.34	10	31.07	83	5.58
	Female	8	0.75	11	5.69	17	10.11	24	17.98	25	32.26	85	5.20
	Total	15		25		42		51		35		168	
	M/F		0.89		1.33		1.72		1.63		0.96		1.07
Both subtypes	Male	27	2.60	74	40.16	119	82.77	151	164.07	67	208.18	438	29.44
	Female	14	1.32	19	9.83	38	22.62	76	56.93	85	109.71	232	14.21
	Total	41		93		157		227		152		670	
	M/F		1.97		4.09		3.66		2.90		1.90		2.07

*Age-specific incidence rate per 100 000 person-years.
†Crude incidence rate per 100 000 person-years.

the diffuse subtype were similar in male and female, with an M/F ratio of 1.07:1.

Applying multivariable analysis to our population-based data allowed us to investigate for the first time whether the gender phenomenon was related to the anatomical site of upper gastrointestinal cancer or to the histological subtype. This indicated that it was the intestinal subtype that was associated with male predominance rather than anatomical location. The higher male predominance in oesophageal versus gastric adenocarcinoma is explained by the higher incidence of intestinal subtype in the former.

The Lauren histological classification was originally devised to classify gastric adenocarcinoma and has proved to be of aetiopathogenic value.[1] The intestinal histological subtype of gastric cancer develops against a background of chronic *H pylori*-induced gastritis.[2 23] The chronic inflammation causes atrophy of specialised gastric glands that are replaced by intestinal metaplasia from which the intestinal type of gastric adenocarcinoma is believed to originate. Oesophageal adenocarcinoma is nearly always intestinal in subtype and histologically indistinguishable from the intestinal subtype of adenocarcinoma of the stomach. Oesophageal adenocarcinoma also resembles intestinal subtype gastric cancer in its pathogenesis in that it develops against a background of chronic mucosal damage. Exposure of the squamous epithelium of the distal oesophagus to refluxing gastric juice causes it to undergo metaplasia to columnar type epithelium resembling the stomach and then to the intestinal type of epithelium,[24 25] from which the oesophageal adenocarcinoma of intestinal phenotype develops. The finding in our current study, that the intestinal type of adenocarcinoma of the oesophagus and stomach show the same male predominance, provides further evidence of similarity of pathogenesis and supports applying the Lauren classification to oesophageal cancers.

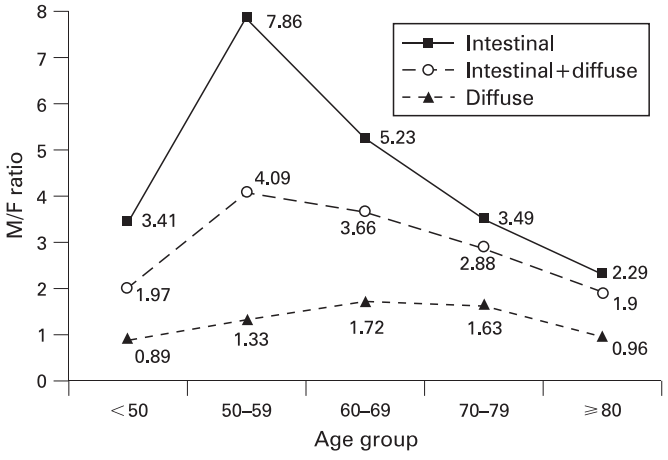

Figure 2 Male-to-female ratios of age-specific incidence rate of upper gastrointestinal adenocarcinoma by histological subtype. Note that the ratio of the intestinal subtype increases to a maximum at age group 50–59 years followed by a progressive decrease. F, female; M, male.

We further investigated the male predominance of intestinal type upper gastrointestinal adenocarcinoma by comparing the age-specific incidence rates of the two sexes. Curve fitting indicated that the male and female were described by similar power terms in the functions describing the curves. The only difference between the curves was that the rise in the incidence of female cancer lagged behind that of the male by 17.3 years. The male predominance of this cancer is due to the rise of cancer incidence with age in males commencing at 28.8 years of age compared to 46.1 years of age for females. Sipponen and Correa have previously reported a delay in the development of the intestinal subtype of gastric cancer in females in the Finnish population.[26] A delay in development of oesophageal carcinoma in females has not been reported previously but there are reports of a delay in development of Barrett's oesophagus in females versus males.[27 28]

The fact that the rise in age-specific incidence is occurring 17.3 years later in females than males, but has the same slope, indicates that there is temporary delay in development of the cancer in females which then disappears around age 46. If the protection against the development of cancer persisted throughout life the power term in the function describing the incidence rate would be expected to be different in females compared with males. The maximum difference in the gender incidence ratio will occur at whatever age the process differentially influencing the carcinogenic process in males versus females disappears. The difference in M/F ratio increased to a maximum at 50–59 years of age (7.9:1) and then showed a marked progressive decrease (fig 2). This indicates the difference in the age-specific incidence of cancer between males and females is limited to <55 years of age.

Table 3 Distribution of upper gastrointestinal adenocarcinoma in different age groups by gender and tumour location

		Age group											
		<50		50–59		60–69		70–79		⩾80		All ages	
Tumour location		n	Rate*	n	Rate*	n	Rate*	n	Rate*	n	Rate*	n	Rate†
Gastric non-cardia	Male	9	0.86	28	15.20	54	37.56	69	74.97	48	149.15	208	13.98
	Female	11	1.04	10	5.17	25	14.88	41	30.71	51	65.73	138	8.46
	Total	20		38		79		110		99		346	
	M/F		0.83		2.94		2.52		2.44		2.27		1.65
Gastric cardia	Male	9	0.86	15	8.14	24	16.69	36	39.12	9	27.97	93	6.25
	Female	2	0.18	5	2.59	5	2.98	18	13.48	21	27.11	51	3.12
	Total	11		20		29		54		30		144	
	M/F		4.78		3.14		5.69		2.90		1.03		2.00
Distal oesophagus	Male	9	0.86	31	16.82	41	28.52	46	49.98	10	31.07	137	9.21
	Female	1	0.09	4	2.07	8	4.76	17	12.73	13	16.78	43	2.63
	Total	10		35		49		63		23		180	
	M/F		9.56		8.13		5.99		3.93		1.85		3.50
All sites	Male	27	2.60	74	40.16	119	82.77	151	164.07	67	208.18	438	29.44
	Female	14	1.32	19	9.83	38	22.62	76	56.93	85	109.71	232	14.21
	Total	41		93		157		227		152		670	
	M/F		1.97		4.09		3.66		2.90		1.90		2.07

*Age-specific incidence rate per 100 000 person-years.
†Crude incidence rate per 100 000 person-years.
F, female; M, male.

In contrast to intestinal type adenocarcinoma, the diffuse subtype showed no difference in age-specific incidence between males and females. In addition, the power term in the function describing the incidence rate for diffuse subtype was lower than that for the intestinal subtype. This is consistent with a stronger genetic predisposition being involved in the development of the diffuse subtype of cancer and thus fewer mutations are required to complete the carcinogenic process.[29]

Applying similar curve-fitting analysis to a range of other types of cancers in the same population over the same time period revealed no evidence of a gender-based delay phenomenon. In particular, cancers such as squamous carcinoma of lung and transitional cell carcinoma of bladder which have a strong male predominance related to smoking[30 31] showed differences in power term in the function describing the incidence rate between the genders but no evidence of a delay in onset.

In summary, our study indicates (1) that the male predominance of gastrointestinal adenocarcinoma is related to the intestinal subtype and is independent of whether the cancer arises in the oesophagus or proximal or distal stomach; (2) that the male predominance of the intestinal subtype is due to a delay of 17.3 years in its rise in incidence in females; and (3) that this delay is due to differences between males and females of less than 55 years of age.

The reason for the difference in the development of the intestinal subtype of upper gastrointestinal cancer in females versus males is unclear and deserves further consideration and investigation. The fact that the delay is occurring at age less than 55 years makes it likely to be related to an endogenous protective effect associated with the reproductive years in the female. Fox *et al* reported gender specific *H pylori*-related carcinogenesis in insulin gastrin transgenic (INS-GAS) mice

Table 4 Logistic regression analysis of association between gender (in favour of male) and histological subtype, tumour location and age

	Independent variable considered individually		Multivariable model	
	p Value	OR (95% CI for OR)	p Value	OR (95% CI for OR)
Histological subtype				
Diffuse (referent)		1.000		1.000
Intestinal	0.00	2.473 (1.728 to 3.539)	0.00	2.637 (1.784 to 3.896)
Tumour site				
Gastric non-cardia (referent)		1.000		1.000
Gastric cardia	0.36	1.210 (0.808 to 1.811)	0.98	0.995 (0.648 to 1.529)
Distal oesophagus	0.00	2.114 (1.410 to 3.168)	0.16	1.368 (0.883 to 2.121)
p Value for overall effect	0.00		0.33	
Age band (years)				
<50 (referent)		1.000		1.000
50–59	0.09	2.019 (0.890 to 4.581)	0.17	1.821 (0.782 to 4.240)
60–69	0.20	1.624 (0.773 to 3.409)	0.33	1.466 (0.681 to 3.155)
70–79	0.93	1.030 (0.511 to 2.079)	0.72	0.876 (0.423 to 1.813)
⩾80	0.02	0.409 (0.199 to 0.840)	0.01	0.347 (0.164 to 0.736)
p Value for overall effect		0.000		0.000

CI, confidence interval; OR, odds ratio.

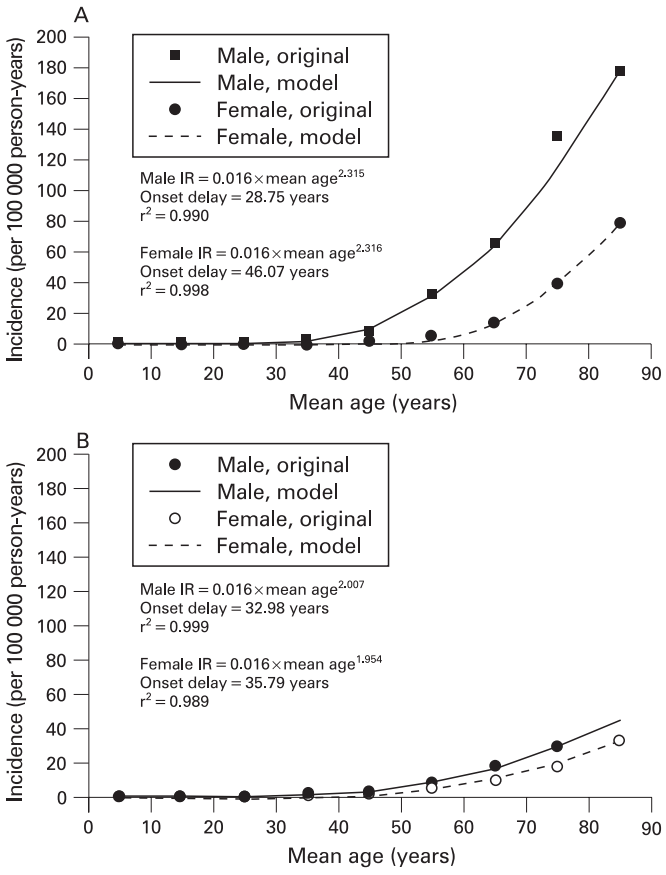

Figure 3 (A) Modelling of age-specific incidence rate curve of intestinal subtype upper gastrointestinal (GI) adenocarcinoma by gender. This shows similar slope of curves but delayed rise in curve in female. (B) Modelling of age-specific incidence rate curve of diffuse subtype upper GI adenocarcinoma by gender. This shows similar slope of curves and also similar age of rise in age-specific incidence rate in males and females.

which was explained by a protective effect of 17β-oestradiol.[32–34] In humans, delayed menopause and hormone replacement therapy may protect against gastric cancer.[35–37] The intestinal subtype of cancer arises against a background of chronic inflammation and tissue damage. The female sex hormone, oestrogen, is known to suppress the inflammatory response and cytokine production in certain tissues and might be exerting similar effects in the upper GI tract.[38 39] In addition, females have lower body iron stores during their reproductive years and this might modify the degree of DNA damage arising from chronic inflammation.[40–43]

Several observations indicate that the delayed development in females is unlikely to be explained by different lifestyle factors, such as smoking. First, in cancers with male predominance due to exogenous lifestyle factors (ie, lung, bladder), the age specific incidence data demonstrate differences in the power terms for the function describing the data rather than a delay in appearance of the cancer. Second, recent studies have reported male predominance of gastric cancer in never-smokers.[44 45] Third, male predominance is observed in animal models of gastric cancer raised in an identical environment.[46] Fourth, smoking rates in the United Kingdom available from 1978 to 1998 are similar for males and females under 50 years of age.[47]

The intestinal subtype of gastric adenocarcinoma arises due to progression of chronic superficial gastritis to atrophic gastritis to intestinal metaplasia to dysplasia and finally cancer.[2] The incidence of atrophic gastritis is the same in males and females and some studies have suggested a higher incidence of intestinal metaplasia and dysplasia in males.[48–50] This suggests that the gender phenomenon is acting at or after the metaplastic stage. With respect to the oesophagus, columnar epithelial metaplasia is more common in males than females (M/F 1.7:1) and specialised intestinal epithelial more markedly so (M/F = 2.1:1). This again indicates the gender phenomenon is evident at and after the metaplastic stage.[51]

In conclusion, this study indicates that the marked male predominance of upper gastrointestinal adenocarcinoma is due to a more than 17 years delay in the development of the intestinal subtype of the cancer. The basis of this phenomenon requires investigation as it accounts for a substantial proportion of upper GI cancers and of such cancers occurring at a younger age when the personal, social and economical implications are greatest. It is likely also to give valuable new insights into the control of the carcinogenic process.

Table 5 Parameters from the fit of the equation $I_{(t)} = a \times (t-d)^b$ to age-specific incidence rates of upper gastrointestinal adenocarcinomas compared with other cancers from the West of Scotland 1998–2002

	M/F ratio (of crude incidence)	Male			Female			Gender bias		
		a	*b*	*d*	*a*	*b*	*d*	Δ*a*	Δ*b*	Δ*d*
Upper GI adenocarcinoma, intestinal subtype	2.65	0.02	2.32	28.8	0.02	2.32	46.1	0.0	0.0	17.3
Upper GI adenocarcinoma, diffuse subtype	1.07	0.02	2.01	33.0	0.01	1.95	35.8	0.0	−0.1	2.8
Oesophageal adenocarcinoma	2.96	0.02	2.21	33.1	0.01	2.09	48.7	0.0	−0.1	15.6
Oesophageal squamous cell carcinoma	1.07	0.02	2.16	34.7	0.01	2.15	37.0	−0.1	−0.1	2.3
Squamous cell carcinoma of lung	2.10	0.02	2.64	38.2	0.02	2.47	38.7	0.0	−0.2	0.5
Adenocarcinoma of lung	1.32	0.03	2.24	34.5	0.02	2.18	32.5	0.0	−0.1	−2.0
Small cell carcinoma of lung	1.14	0.02	2.38	34.4	0.04	2.16	37.3	0.0	−0.2	2.9
Squamous cell carcinoma of bladder	0.88	0.001	2.22	38.2	0.001	2.31	38.8	0.0	0.1	0.6
Transitional cell carcinoma of bladder	2.57	0.01	2.63	40.0	0.01	2.20	36.0	0.0	−0.4	−4.0
Cancer of the colon	1.06	0.02	2.49	34.8	0.06	2.21	36.7	0.0	−0.1	1.9
Cancer of the pancreas	1.07	0.09	1.84	39.4	0.04	1.90	36.2	−0.1	0.1	−3.2

In the equation, *I* is the incidence rate of cancer at age *t*, which is the mean age of the age group; *a* is a scaling factor, *b* is a power term that reflect the rate of increasing incidence with age, and *d* is a delay term for the time between birth and age of rise of age-specific incidence curve above zero.
F, female; GI, gastrointestinal; M, male.

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