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Oesophageal and gastric cardia adenocarcinomas: analysis of regional variation using the Cancer Incidence in Five Continents database

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Background	Adenocarcinomas of the oesophagus and proximal stomach are the most rapidly increasing malignancies in some countries; however, there are no comparative studies on global disease incidence, and the relationships between these two malignancies are undefined.
Methods	We evaluated the cumulative rates and age-specific incidence rates per 100 000 population for adenocarcinomas of the oesophagus and proximal stomach for all countries in the Cancer Incidence in Five Continents database, and compared them with rates for oesophageal squamous cell carcinoma.
Results	Substantial variations in cumulative cancer rates were found between genders, between countries, between different ethnicities within the same country, and within the same ethnicity residing in different countries. Cumulative rates (ages 0–74 years) for oesophageal adenocarcinoma varied from 0 (e.g. Thailand) to 0.6 (Scotland, males, 95% CI : 0.56, 0.64); for proximal stomach cancer from 0 (Singapore, Malay females, 95% CI : –0.01, 0.11) to 0.52 (The Netherlands, males, 95% CI : 0.49, 0.55); and for oesophageal squamous cell carcinomas from 0 (non-Jews in Israel, females) to 1.84 (Brazil, Porto Alegre, males, 95% CI : 1.42, 2.26). There was a continuous increase in age-specific incidence rates with advancing age for oesophageal/proximal stomach adenocarcinomas, but a decrease in age-specific incidence rates for oesophageal squamous cell carcinoma after age 75 years. The cumulative rate trends for adenocarcinomas of the oesophagus and proximal stomach were often dissimilar, and varied by country, gender, and ethnicity.
Conclusions	These results suggest that different risk factors may be associated with adenocarcinomas of the oesophagus versus the proximal stomach; the marked rate variation implies a substantial environmental component to the recent incidence changes.

Keywords	Oesophageal cancer, oesophageal adenocarcinoma, gastric cardia adenocarcinoma, cancer incidence, epidemiology
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Historically, oesophageal cancer has received considerable attention, however most of this attention has been focused on squamous cell carcinoma of the oesophagus rather than adenocarcinomas of the oesophagus and the proximal stomach/gastro-oesophageal junction (i.e. the gastric cardia).[1] Although all of these malignancies are characterized by a high mortality rate, the overall one-year survival for oesophageal adenocarcinoma is less than 50%.[2]

In countries where incidence rates of oesophageal and gastric cardia adenocarcinomas have been examined, there has been a sharp increase in cancer incidence over the last few decades, compared with stable or declining rates for oesophageal squamous cell carcinoma.[3–9] Indeed, the incidences of oesophageal and

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proximal stomach adenocarcinomas have recently risen more rapidly than any other malignancy in some countries; with average annual incidence increases of up to 17% for oesophageal adenocarcinoma.[3–15] The rising incidence of proximal gastric cancer (i.e. in the gastric cardia, just below the stomach's junction with the oesophagus) occurred despite decreases in the overall incidence of distal gastric adenocarcinoma.[16]

When epidemiological data for adenocarcinomas of the oesophagus and gastric cardia have been examined, they have frequently been considered together rather than as separate entities, precluding an examination of potentially distinct epidemiological patterns between the two anatomical sites. Oesophageal and gastric cardia adenocarcinomas may have different risk factors, and global differences in the distributions of these two cancers are unknown.

The changes in oesophageal and gastric adenocarcinoma incidence rates are largely unexplained, and do not appear related solely to changes in diagnostic criteria.[6] The increased incidence of gastric cardia and oesophageal adenocarcinomas in the US occurred despite a decreasing prevalence of some strong risk factors (e.g. smoking).[17]

The underlying reasons for regional differences in cancer incidence may provide clues to modifying these diseases, for which the most effective approaches are prevention and early detection. National, regional, and ethnic trends may suggest environmental and behavioural risk factors. Well-studied malignancies, such as oesophageal squamous cell carcinomas, can provide comparison data for age-specific incidence and regional trends. Incidence studies to date, however, have been limited primarily to a relatively few developed countries.[14–16,18] No studies have evaluated detailed global incidence patterns, published works from the international databases do not provide analyses by histological subtypes of oesophageal cancer, and existing studies have not accounted for cancers of unknown histological type.[14–16,18,19]

We thus used the Cancer Incidence in Five Continents database to evaluate geographical variability between oesophageal adenocarcinoma and adenocarcinoma of the gastric cardia, and compare these patterns with rates for oesophageal squamous cell carcinoma; such comparisons may provide insights into potential aetiological factors for these malignancies.

Materials and Methods

The Cancer Incidence in Five Continents, Volume 7 (Ci5vii) database uses national cancer registries for tracking global cancer incidence.[20] It contains age-specific, country-specific incidence data for major cancers from 183 populations in 50 countries, raw count data for each cancer, and person-years in the cancer registry population base for the years 1988–1992. Efforts are made to standardize the reporting techniques, and registries are excluded if they do not meet standards for quality and comparability. Adenocarcinoma was defined using the International Classification of Diseases for Oncology, Second Edition (ICD-O-2) codes 8140–8560, as outlined in the Cancer Incidence in Five Continents, Volume 7.[20] Anatomical sites were defined using ICD-O-2 codes C15.0–C15.9 for oesophageal carcinoma, and C16.0 for the gastric cardia (defined as cardio-oesophageal junction, oesophagogastric junction, and gastro-oesophageal junction).[20]

The Ci5vii database divides gastric cancers into the following sites: cardia, pylorus and antrum, and other/unspecified. The last category includes cancers of the stomach's body and fundus, as well as cancers without a specified site. Gastric cancers in Ci5vii are not separated by histological type; we assumed all cancers were adenocarcinomas.

The Ci5vii database divides cancers into those with a morphological diagnosis (by histology or cytology) and those without morphology. Cancers with no microscopic verification lack microscopic analysis of biopsy tissue; cancers with no morphological verification lack both microscopic and cytological analysis (e.g. cytological brushings).[20] The Ci5vii database treats these categories as mutually exclusive (i.e. each patient is only counted once).

Statistical analysis

Analyses were performed using the Ci5vii statistical package (International Agency for Research on Cancer, Lyon, France) and STATA (release 6, STATA corporation, College Station, Texas).[20]

Age-standardized rates were calculated using the 1970 World Standard Population, for ages 0–74. The assumption of proportionality was tested using the test for heterogeneity and the test for trend.[20,21] There were frequent failures of these tests, thus only cumulative rates and age-specific incidence rates are reported.

Cumulative rates (i.e. lifetime cancer rates) were calculated for ages 0–74.[20] The cumulative rate is the sum of the age-specific incidence rates, is dimensionless, and is frequently expressed as a percentage. It closely approximates the probability that an individual will develop the disease of interest within a certain age range, in the absence of any competing cause of death (i.e. the cumulative risk) when the cumulative risk is $<10\%$.[20]

Cumulative rates for oesophageal adenocarcinomas and oesophageal squamous cell carcinomas were adjusted for oesophageal cancers without verification of histological type. The reported cumulative rates for microscopically/cytologically verified cancers were added to the estimated cumulative rate of each cancer type among oesophageal cancers of unknown type. The rate for oesophageal cancers of unknown type was calculated as the sum of two cumulative rates from the registry data: oesophageal cancers with no microscopic verification; and oesophageal cancers of unknown morphology. This sum provides the total cumulative rate of oesophageal cancers of unknown histological type. The proportion of adenocarcinomas and squamous cell carcinomas among oesophageal cancers of unknown type were assumed to be the same as among oesophageal cancers of known type. Countries with a proportion of oesophageal cancers of unknown type >0.5 were excluded from all calculations. If the average proportion of cancers of unknown type for an entire country exceeded 0.5, but individual registries within the country had proportions of <0.5, the largest eligible registry for that country was chosen. The variance for the adjusted cumulative rate was calculated using the delta method.[22] The cumulative rates of gastric cancers with no microscopic or morphological verification are not reported separately in the database; thus, we report an unadjusted cumulative rate for cardia adenocarcinomas.

Cumulative rate comparisons use two-tailed *P*-values calculated from the z-statistic for the normal distribution.[21]

The countries with the lowest, median, and highest cumulative rates of oesophageal adenocarcinoma were used for the

unadjusted age-specific incidence graphs. To maximize stability of the incidence estimates, only countries with >80% microscopic/morphological verification of the oesophageal cancer histological types and at least 5 million person-years in their registry population bases were eligible for inclusion.

Results

Exclusion of countries with >50% oesophageal cancers of unknown type provided 39 countries for the primary analysis. Exclusion of countries with >20% oesophageal cancers of unknown type provided 18 countries for calculation of the age-specific rates.

Oesophageal adenocarcinoma

The cumulative rates of oesophageal adenocarcinoma (0–74 years of age) vary 60-fold between the countries studied, from approximately 0% (e.g. for both genders in Korea, Thailand, and Estonia) to 0.6% [males, Scotland, $P < 0.001$]) (Tables 1–4). A Scottish male thus has an approximately 0.6% risk of developing oesophageal adenocarcinoma by age 74, in the absence of competing causes of death. There are also significant differences within small geographical areas, with a twofold difference between The Irish Republic and Scotland (males, 0.29% versus 0.60%, $P < 0.001$) (Tables 3 and 4). Rates vary substantially by ethnicity, even within the same country (Tables 3 and 4). There is a fourfold difference, for example, in cumulative rates between African American males and Caucasian males within the US (0.06% versus 0.27%, $P < 0.001$), and a threefold difference between the Chinese and Malay male populations within Singapore (0.06% versus 0.02%, $P = 0.11$).

Significant differences in cumulative cancer rates within the same ethnic group between different countries of residence are evident between mainland India and the Indian population in

Table 1 Oesophageal and gastric cardia carcinomas, males, cumulative rates, ages 0–74 years (95% CI), by country and region

Country	Stomach cardia	(95% CI)	Squamous oesophagus[a]	(95% CI)	Adenocarcinoma oesophagus[a]	(95% CI)
Korea, Kangwha	[b]	([b], [b])	1.18	(0.56, 1.81)	0.00	([b], [b])
Thailand	0.04	(0.02, 0.06)	0.22	(0.15, 0.30)	0.00	([b], [b])
Estonia	0.34	(0.27, 0.41)	0.63	(0.51, 0.74)	0.03	(–0.00, 0.05)
Ecuador, Quito	0.12	(0.05, 0.19)	0.24	(0.11, 0.37)	0.04	(–0.01, 0.09)
Japan	0.49	(0.4, 0.52)	1.19	(1.14, 1.24)	0.04	(0.03, 0.06)
Peru	0.02	(0.00, 0.04)	0.15	(0.09, 0.22)	0.05	(0.01, 0.08)
Philippines, Manila	0.04	(0.01, 0.07)	0.27	(0.18, 0.37)	0.06	(0.02, 0.11)
Austria, Tyrol	0.34	(0.21, 0.47)	0.39	(0.24, 0.53)	0.06	(–0.00, 0.13)
Germany	0.23	(0.20, 0.26)	0.45	(0.41, 0.49)	0.06	(0.04, 0.08)
Slovenia	0.32	(0.25, 0.39)	0.64	(0.54, 0.73)	0.07	(0.04, 0.10)
French Polynesia	0.05	(–0.04, 0.14)	0.94	(0.35, 1.53)	0.07	(–0.04, 0.18)
Poland, Warsaw City	0.22	(0.16, 0.28)	0.43	(0.33, 0.53)	0.07	(0.04, 0.11)
Costa Rica	0.42	(0.34, 0.50)	0.27	(0.18, 0.36)	0.08	(0.03, 0.12)
Finland	[b]	([b], [b])	0.29	(0.26, 0.33)	0.08	(0.06, 0.09)
India	0.08	(0.06, 0.10)	1.07	(1.00, 1.14)	0.08	(0.06, 0.10)
Slovakia	0.33	(0.29, 0.37)	0.74	(0.67, 0.81)	0.08	(0.06, 0.10)
Spain	0.20	(0.18, 0.22)	0.65	(0.60, 0.69)	0.08	(0.06, 0.09)
Italy	0.22	(0.20, 0.24)	0.47	(0.43, 0.50)	0.08	(0.06, 0.10)
Sweden	0.24	(0.22, 0.26)	0.28	(0.26, 0.30)	0.08	(0.07, 0.09)
Uruguay, Montevideo	0.06	(0.02, 0.10)	1.22	(0.98, 1.47)	0.08	(0.02, 0.15)
Norway	[b]	([b], [b])	0.29	(0.26, 0.33)	0.09	(0.07, 0.12)
Czech Republic	0.35	(0.32, 0.38)	0.32	(0.29, 0.35)	0.12	(0.10, 0.14)
Switzerland	0.39	(0.34, 0.44)	0.54	(0.48, 0.59)	0.12	(0.10, 0.15)
France	0.28	(0.24, 0.32)	1.40	(1.32, 1.47)	0.14	(0.12, 0.17)
Hong Kong	[b]	([b], [b])	1.53	(1.44, 1.62)	0.15	(0.12, 0.18)
Colombia, Cali	0.15	(0.08, 0.22)	0.22	(0.12, 0.32)	0.16	(0.06, 0.25)
Argentina, Concordia	0.05	(–0.04, 0.14)	1.46	(0.77, 2.16)	0.19	(–0.04, 0.43)
Canada	0.32	(0.30, 0.34)	0.27	(0.26, 0.29)	0.19	(0.18, 0.21)
Australia	0.32	(0.30, 0.34)	0.32	(0.29, 0.34)	0.23	(0.21, 0.25)
Denmark	0.34	(0.30, 0.38)	0.32	(0.28, 0.35)	0.24	(0.21, 0.27)
Iceland	0.33	(0.15, 0.51)	0.51	(0.28, 0.74)	0.28	(0.10, 0.45)
The Netherlands	0.52	(0.49, 0.55)	0.33	(0.30, 0.35)	0.28	(0.26, 0.31)
Brazil, Porto Alegre	0.06	(0.02, 0.10)	1.84	(1.42, 2.26)	0.30	(0.13, 0.46)

[a] Adjusted for oesophageal cancers of unknown type.

[b] Not available or could not be calculated.

Table 2 Oesophageal and gastric cardia carcinomas, females, cumulative rates, ages 0–74 years (95% CI), by country and region

Country	Stomach cardia	(95% CI)	Squamous oesophagus[a]	(95% CI)	Adenocarcinoma oesophagus[a]	(95% CI)
Korea, Kangwha	[b]	([b], [b])	0.04	(–0.04, 0.12)	0.00	([b], [b])
Thailand	0.02	(0.00, 0.04)	0.13	(0.07, 0.20)	0.00	([b], [b])
Estonia	0.11	(0.08, 0.14)	0.06	(0.03, 0.09)	0.01	(0.00, 0.03)
Ecuador, Quito	0.04	(0.00, 0.08)	0.08	(0.02, 0.14)	0.01	(–0.01, 0.03)
Japan	0.15	(0.14, 0.16)	0.15	(0.14, 0.17)	0.00	([b], [b])
Peru	0.00	(–0.01, 0.01)	0.06	(0.03, 0.10)	0.01	(0.00, 0.03)
Philippines, Manila	0.02	(0.00, 0.04)	0.19	(0.12, 0.27)	0.00	([b], [b])
Austria, Tyrol	0.05	(0.01, 0.09)	0.04	(0.00, 0.08)	0.00	([b], [b])
Germany	0.06	(0.05, 0.07)	0.05	(0.04, 0.07)	0.02	(0.01, 0.02)
Slovenia	0.06	(0.04, 0.08)	0.08	(0.05, 0.11)	0.00	([b], [b])
French Polynesia	0.11	(–0.11, 0.33)	0.25	(–0.02, 0.52)	0.00	([b], [b])
Poland, Warsaw City	0.06	(0.03, 0.09)	0.07	(0.04, 0.11)	0.02	(0.00, 0.04)
Costa Rica	0.11	(0.07, 0.15)	0.14	(0.09, 0.20)	0.03	(0.00, 0.05)
Finland	[b]	([b], [b])	0.14	(0.12, 0.16)	0.01	(0.00, 0.02)
India	0.02	(0.01, 0.03)	0.84	(0.78, 0.90)	0.03	(0.02, 0.04)
Slovakia	0.08	(0.06, 0.10)	0.03	(0.02, 0.05)	0.02	(0.01, 0.03)
Spain	0.03	(0.02, 0.04)	0.03	(0.02, 0.04)	0.01	(0.01, 0.01)
Italy	0.05	(0.04, 0.06)	0.08	(0.06, 0.09)	0.01	(0.01, 0.02)
Sweden	0.05	(0.04, 0.06)	0.09	(0.08, 0.10)	0.01	(0.01, 0.01)
Uruguay, Montevideo	0.03	(0.01, 0.05)	0.27	(0.17, 0.36)	0.06	(0.02, 0.11)
Norway	[b]	([b], [b])	0.07	(0.05, 0.09)	0.01	(0.00, 0.02)
Czech Republic	0.10	(0.09, 0.11)	0.03	(0.02, 0.04)	0.02	(0.01, 0.02)
Switzerland	0.08	(0.06, 0.10)	0.12	(0.10, 0.14)	0.02	(0.01, 0.03)
France	0.04	(0.03, 0.05)	0.11	(0.09, 0.13)	0.02	(0.01, 0.03)
Hong Kong	[b]	([b], [b])	0.32	(0.27, 0.36)	0.05	(0.03, 0.07)
Colombia, Cali	0.06	(0.02, 0.10)	0.22	(0.13, 0.32)	0.00	([b], [b])
Argentina, Concordia	0.00	(0.00, 0.00)	0.36	(0.04, 0.68)	0.05	(–0.05, 0.15)
Canada	0.05	(0.04, 0.06)	0.12	(0.11, 0.13)	0.02	(0.02, 0.03)
Australia	0.06	(0.05, 0.07)	0.21	(0.19, 0.22)	0.03	(0.03, 0.04)
Denmark	0.07	(0.05, 0.09)	0.11	(0.09, 0.13)	0.04	(0.03, 0.05)
Iceland	0.10	(0.01, 0.19)	0.14	(0.02, 0.26)	0.11	(0.01, 0.21)
The Netherlands	0.10	(0.09, 0.11)	0.13	(0.12, 0.14)	0.06	(0.05, 0.07)
Brazil, Porto Alegre	0.01	(–0.01, 0.03)	0.31	(0.16, 0.45)	0.04	(–0.01, 0.08)

[a] Adjusted for oesophageal cancers of unknown type.

[b] Not available or could not be calculated.

Singapore (0.08% versus 0.02%, $P = 0.005$) (Tables 1–4). High proportions of oesophageal cancer without microscopic verification in the African and mainland Chinese cancer registries preclude meaningful comparisons of similar ethnicities between some other countries of interest (e.g. between African countries and African Americans, or between mainland Chinese and the Chinese population of Singapore).

Substantial differences in cancer incidence exist between genders, with all countries having an equivalent or higher incidence of oesophageal adenocarcinoma in the male versus female populations (Tables 1–4). These differences are most marked in the high incidence countries (e.g. US Caucasian males versus females 0.27% versus 0.02%, $P < 0.001$) (Tables 3 and 4).

Age-specific incidence rates demonstrate an increased incidence starting at 45–55 years of age in high incidence populations, and at approximately 65 years of age in low incidence populations (Figure 1). There is a steady increase in incidence with age in both high and low incidence populations, with no substantial country-specific crossover of age-specific incidence rates with increasing age.

Gastric cardia adenocarcinoma

The cumulative rates of gastric cardia adenocarcinoma (0–74 years of age) vary 50-fold between the countries studied, from approximately 0% (females; Concordia, Argentina) to 0.52% (males, The Netherlands, $P < 0.001$) (Tables 1 and 2). Similar to oesophageal adenocarcinoma, there is substantial variation by ethnicity within countries, however these trends are sometimes different than for oesophageal adenocarcinoma (Table 3 and 4). Cardia cancers are more common than oesophageal adenocarcinomas among all ethnicities in Singapore, but with a sixfold

Table 3 Oesophageal and gastric cardia carcinomas, males, cumulative rate ages 0–74 years (95% CI), by ethnic group/region within countries

Country	Gastric cardia	(95% CI)	Oesophageal squamous cell[a]	(95% CI)	Oesophageal adenocarcinoma[a]	(95% CI)
Kuwait						
Non-Kuwaitis	0.14	([b], [b])	0.07	([b], [b])	0.00	([b], [b])
Kuwaitis	0.05	(–0.06, 0.18)	0.12	(–0.06, 0.18)	0.06	(–0.06, 0.18)
Israel						
Non-Jews	0.09	(0.00, 0.18)	0.06	(–0.05, 0.18)	0.00	([b], [b])
Jews born in Africa or Asia	0.16	(0.10, 0.22)	0.13	(0.07, 0.19)	0.04	(0.00, 0.07)
Jews born in America or Europe	0.31	(0.25, 0.37)	0.11	(0.07, 0.15)	0.05	(0.02, 0.07)
Jews born in Israel	0.09	(0.04, 0.14)	0.08	(–0.02, 0.17)	0.08	(–0.05, 0.21)
Singapore						
Malay	0.05	(–0.01, 0.11)	0.03	(–0.02, 0.08)	0.02	(–0.02, 0.06)
Indian	0.15	(0.01, 0.29)	0.60	(0.34, 0.85)	0.02	(–0.02, 0.06)
Chinese	0.29	(0.22, 0.36)	0.92	(0.79, 1.06)	0.06	(0.03, 0.10)
Unites States						
Black	0.25	(0.19, 0.31)	1.61	(1.46, 1.75)	0.06	(0.03, 0.09)
White	0.37	(0.35, 0.39)	0.28	(0.26, 0.30)	0.27	(0.26, 0.29)
United Kingdom/Irish Republic						
Irish Republic	0.34	(0.22, 0.46)	0.46	(0.32, 0.59)	0.29	(0.18, 0.40)
England and Wales	0.37	(0.35, 0.39)	0.27	(0.26, 0.29)	0.45	(0.43, 0.47)
Scotland	0.38	(0.35, 0.41)	0.53	(0.49, 0.57)	0.60	(0.56, 0.64)

[a] Adjusted for oesophageal cancers of unknown type (see Methods).

[b] Not available or could not be calculated.

Table 4 Oesophageal and gastric cardia carcinomas, females, cumulative rate ages 0–74 years (95% CI), by ethnic group/region within countries

Country	Gastric cardia	(95% CI)	Oesophageal squamous cell[a]	(95% CI)	Oesophageal adenocarcinoma[a]	(95% CI)
Kuwait						
Non-Kuwaitis	0.02	([b], [b])	0.05	([b], [b])	0.02	([b], [b])
Kuwaitis	0.03	(–0.06, 0.18)	0.32	(0.03, 0.61)	0.00	([b], [b])
Israel						
Non-Jews	0.05	(–0.02, 0.12)	0.00	([b], [b])	0.00	([b], [b])
Jews born in Africa or Asia	0.05	(0.02, 0.08)	0.12	(0.07, 0.17)	0.01	(0.00, 0.02)
Jews born in America or Europe	0.10	(0.07, 0.13)	0.11	(0.07, 0.15)	0.01	(0.00, 0.02)
Jews born in Israel	0.02	(–0.01, 0.05)	0.04	(0.00, 0.08)	0.00	([b], [b])
Singapore						
Malay	0.00	([b], [b])	0.06	(–0.05, 0.17)	0.00	([b], [b])
Indian	0.03	(–0.03, 0.09)	0.57	(0.19, 0.95)	0.00	([b], [b])
Chinese	0.07	(0.04, 0.10)	0.21	(0.15, 0.27)	0.00	(–0.01, 0.01)
Unites States						
Black	0.05	(0.03, 0.07)	0.46	(0.39, 0.53)	0.02	(0.01, 0.03)
White	0.06	(0.05, 0.07)	0.12	(0.11, 0.13)	0.02	(0.02, 0.02)
United Kingdom/Irish Republic						
Irish Republic	0.04	(0.00, 0.08)	0.31	(0.20, 0.43)	0.09	(0.02, 0.15)
England and Wales	0.08	(0.07, 0.09)	0.23	(0.21, 0.24)	0.09	(0.08, 0.10)
Scotland	0.10	(0.09, 0.11)	0.42	(0.38, 0.45)	0.15	(0.13, 0.17)

[a] Adjusted for oesophageal cancers of unknown type (see Methods).

[b] Not available or could not be calculated.

higher cumulative rate in the Chinese versus the Malay male populations (0.29% versus 0.05%, $P < 0.001$). In the US, in contrast, the ethnic differences narrow markedly. Caucasians have only a 1.5-fold higher cumulative rate for cardia adenocarcinomas versus African American males (0.37% versus 0.25%, $P < 0.001$), compared with a fourfold higher rate of oesophageal adenocarcinoma.

Differences within ethnic groups based on the country of origin are also sometimes different for gastric cardia adenocarcinoma compared with oesophageal adenocarcinoma. Jews born in

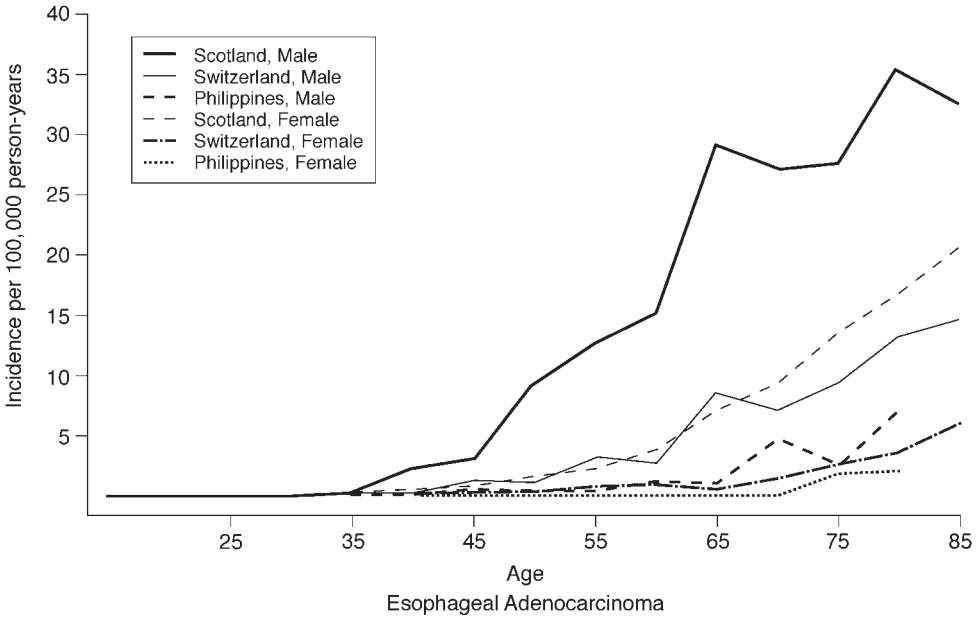

Figure 1 Esophageal adenocarcinoma, age specific incidence (per 100 000 person-years) by country and gender

America or Europe have a significantly higher cumulative rate of cardia adenocarcinoma compared with Jews born in Israel (0.31% versus 0.09%, $P < 0.001$), despite similar rates of oesophageal adenocarcinoma (0.05% versus 0.08%, $P = 0.7$). We were not able to evaluate potential ethnic heterogeneity of these Jewish populations.

Gender differences for cardia adenocarcinoma are similar to oesophageal adenocarcinoma, with equivalent or higher rates for males versus females in all countries studied.

The age-specific incidence trends demonstrate an increased incidence starting at 45 years of age in high incidence populations, and approximately 55 years of age in low incidence populations (Figure 2). Similar to oesophageal adenocarcinoma, there is a steady increase in incidence with age in both high and low incidence populations, with no substantial country-specific crossover of age-specific incidence rates with advancing age.

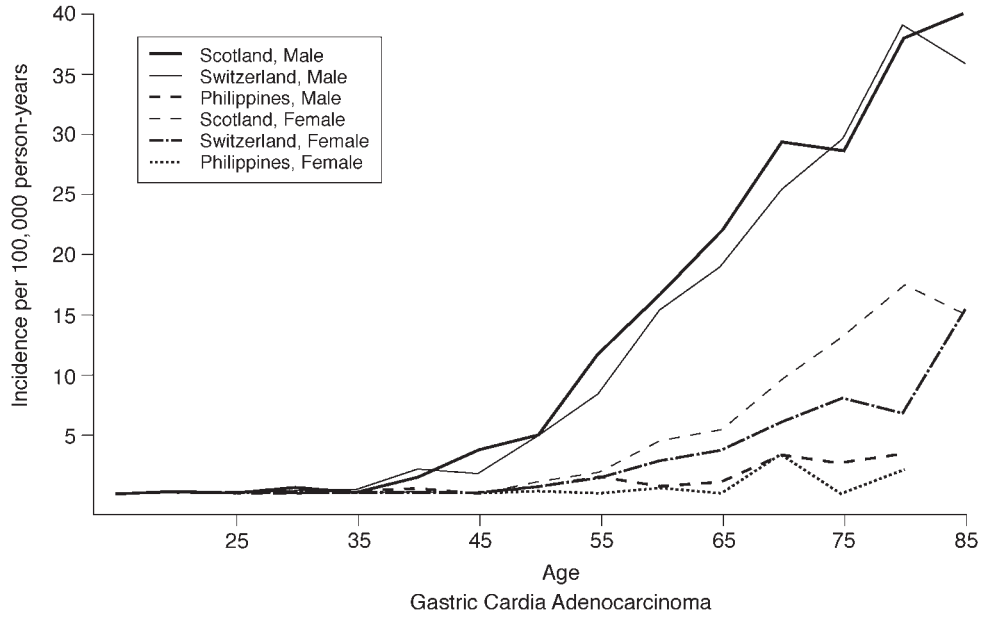

Figure 2 Gastric cardia adenocarcinoma, age specific incidence (per 100 000 person-years) by country and gender

Oesophageal squamous cell carcinoma

The cumulative rates of oesophageal squamous cell carcinoma (0–74 years) vary 180-fold between the countries studied, from 0.01% (e.g. females; Kielce, Poland) to 1.84% (males, Brazil, $P < 0.001$) (Tables 1–4). There are also significant differences within small geographical areas, with a twofold difference between Scotland and England/Wales (males, 0.53% versus 0.27%, $P < 0.001$). These trends differ from adenocarcinomas of the cardia and oesophagus. Rates of cardia adenocarcinoma are statistically identical throughout England/Wales, Scotland, and the Irish Republic, whereas rates of oesophageal adenocarcinoma are over 50% higher in England/Wales than in the Irish Republic, the opposite of squamous cell carcinoma. Rates of oesophageal squamous cell carcinoma also vary substantially by ethnicity within the same country (Tables 3 and 4). There is a fivefold difference in cumulative rates between African American males and Caucasian males (1.61% versus 0.28%, $P < 0.001$) within the US, and a 30-fold difference between the Malay and Chinese (0.03% versus 0.92%, $P < 0.001$) male populations within Singapore.

Differences in squamous cancer cumulative rates within ethnic groups based on the country of residence are evident between mainland India and the Indian population in Singapore (1.07% versus 0.6%, respectively, $P < 0.001$).

There are differences in squamous cell cancer incidence between genders, though these are generally less marked than with the adenocarcinoma malignancies (Tables 1–4). These differences are most pronounced in the high incidence countries, with up to a sixfold higher cumulative rate in males versus females (e.g. Brazil cumulative rates 1.84% versus 0.31%, $P < 0.001$).

The age-specific incidence trends demonstrate an increased incidence starting at approximately 45 years of age in all populations. Unlike adenocarcinoma, however, squamous cell carcinoma incidence decreases for patients greater than 75 years old (Figure 3). In addition, we observe a substantial country-specific crossover of age-specific incidence rates with increasing age. Scottish women, for example, experience some of the lowest squamous cancer rates prior to age 55, but some of the highest rates after age 65.

Total oesophageal and gastric cardia cancer incidence

The total cancer incidence for all three cancers varies markedly, even within countries (Figure 4). Combining the cumulative rates of oesophageal adenocarcinoma, oesophageal squamous cell carcinoma and gastric cardia adenocarcinoma demonstrates a 13-fold difference in total cancer cumulative rates between the Malay and Chinese male populations in Singapore, but less than a 1.5-fold difference between England/Wales, Scotland, and the Irish Republic. The rates of gastric cardia adenocarcinoma vary sixfold between ethnic groups within Singapore, but contribute proportionally little to overall cancer cumulative rates compared with oesophageal squamous cell cancer. In contrast, the gastric cardia cancer rates are comparable between England/Wales, Scotland, and the Irish Republic and provide a substantial contribution to the total cancer cumulative rates, with the majority of total cancer cumulative rate variability provided by differences in oesophageal squamous cell carcinoma and oesophageal adenocarcinoma.

Discussion

This report confirms individual studies suggesting substantial regional incidence variations for adenocarcinomas of the oesophagus and gastric cardia, and for oesophageal squamous cell carcinoma. Although we could not analyse temporal trends, our results demonstrate that the cumulative rates of oesophageal adenocarcinoma, oesophageal squamous cell carcinoma, and gastric cardia adenocarcinoma vary widely between countries, between ethnic groups within countries, between the same

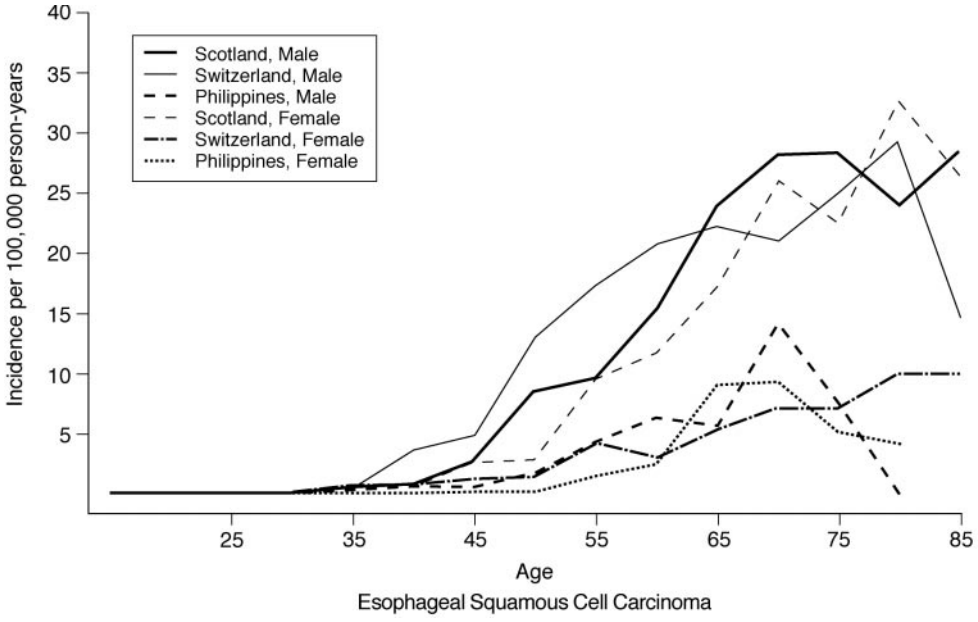

Figure 3 Esophageal squamous cell carcinoma, age specific incidence (per 100 000 person-years) by country and gender

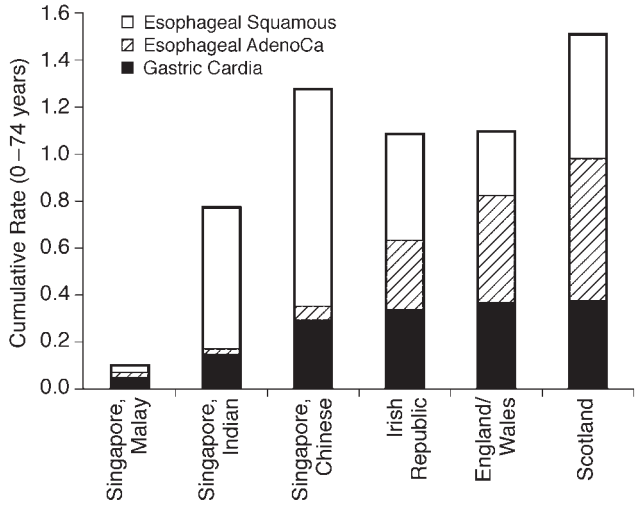

Figure 4 Cumulative risk (age 0–74 years) of esophageal/gastric carcinomas by ethnic group/region (males)

ethnic group in different countries, and between genders. A striking finding is the high rate of oesophageal adenocarcinoma in Scotland, by far the highest cumulative rate in the world. Scotland's high rates are found in both genders, and are significantly different from its neighbouring countries (i.e. England/Wales, and the Irish Republic). Scotland's high rates are unexplained and, in contrast to oesophageal squamous cell cancer and other gastric cancers, they do not appear related to differences in socioeconomic status.[23]

One possibility for the international rate differences is different diagnostic site criteria between countries. The Ci5vii uses the oesophageal/cardia classification outlined in the methods section; newer classification nomenclature identifying the gastro-oesophageal junction as a unique site separate from the cardia and oesophagus have been proposed, but not universally adopted.[24] The lower oesophagus is immediately adjacent to the proximal stomach/gastric cardia; small differences in site specification could thus lead to substantial differences in the proportions of gastro-oesophageal junction cancers listed as either gastric cardia or oesophageal malignancies.[6,25] If this occurred, gastric cardia rates would be relatively lower in countries with higher rates of oesophageal adenocarcinoma, and vice versa; however, this pattern was not seen. Gastric cardia cancer rates were almost identical throughout England/Wales, Scotland, and the Irish Republic, for example, despite substantial differences in oesophageal adenocarcinoma rates; similar rate patterns were also found between blacks and whites in the US. This suggests that the rate variability of cardia/oesophageal junction cancers is not solely related to preferential classification of cardia/oesophageal junction tumours as either cardia or oesophageal malignancies.

Alternatively, if an increased proportion of gastric cancers were specified as gastric cardia cancers, we might observe an increase in the relative rate of gastric cardia cancers. Since a proportion of unspecified location gastric cancers are likely gastric cardia cancers, the reported cumulative rates for cardia cancers would underestimate the true rates, particularly for countries with a high proportion of unspecified cancers. This would be unlikely to completely explain the rate differences seen in this study, however, as there is still marked cardia/oesophageal adenocarcinoma rate variability between countries with similar proportions of gastric body/fundus/unspecified cancers (data not shown). In addition, there are similar gastric cardia cancer rates between ethnicities within single countries with low rates of unspecified cancers, despite substantial differences in non-cardia gastric cancer rates (e.g. the US, data not shown). This finding of similar cardia cancer rates despite differing non-cardia gastric cancer rates suggests that the cardia cancer rate variability is not solely related to unspecified gastric cancer rate variability. Differences in diagnostic criteria may thus contribute a proportion of the rate variability between countries, however, other studies also suggest that the oesophageal/cardia cancer rate variability is not wholly due to changes in site classification, earlier diagnosis, or improved specificity of histological subtype.[6]

Other possibilities for the variable incidence rates include differences in underlying risk factors. One possibility is a change in the prevalence of *Helicobacter pylori (H. pylori)*, a bacterium that colonizes the gastric mucosa; colonization is inversely associated with oesophageal and gastric cardia adenocarcinomas.[26] The prevalence of virulent *H. pylori* strains varies widely between countries, from less than 10% in parts of North America to over 80% in Peru.[27,28] Gastro-oesophageal reflux is also associated with oesophageal/cardia adenocarcinomas; medications that may decrease lower oesophageal sphincter pressure, thereby potentially increasing reflux, have also been associated with oesophageal adenocarcinoma.[29–31]

Additional hypotheses for the incidence variability are differences in fat intake/composition, micronutrients intake and the prevalence of obesity.[32] Obesity is an independent risk factor for oesophageal adenocarcinoma, possibly by increasing gastro-oesophageal reflux.[33] An increasing prevalence of obesity is described in some high incidence countries; the proportion of overweight American adults, for example, increased by one-third between 1976–1980 and 1986–1991, despite a decreasing average fat intake.[34] No regional/ethnic comparisons of micronutrient distribution relative to oesophageal/cardia adenocarcinoma incidence are available, however, oesophageal adenocarcinoma is inversely associated with intakes of vitamins A & C, fibre, and raw fruits.[32,35]

Smoking is associated with oesophageal adenocarcinoma, and possibly with gastric cardia adenocarcinoma.[36] Some high incidence countries experienced a high prevalence of smoking in the decades prior to the increase in cancer incidence.[6] The persistence of risk after discontinuation of smoking may thus cause changes in cancer incidence to lag behind changes in the prevalence of smoking.[36] Despite a strong association between alcohol consumption and oesophageal squamous cell carcinoma, a consistent relationship has not been found between alcohol consumption and oesophageal/cardia adenocarcinomas.[35–38]

The gender and ethnic differences within countries are largely unexplained. No substantial studies document sufficient variability in the known risk factors between genders and ethnicities to account for the differences in adenocarcinoma incidence. Indeed, some risk factors are distributed inversely to the observed cancer trends (e.g. higher smoking rates among African Americans in the US, yet a lower adenocarcinoma risk in this ethnic group).[17] Differences in gastro-oesophageal reflux

between groups may partially explain some variability in incidence, but these differences have not been extensively studied.[31]

Our finding of different rate distributions for gastric cardia and oesophageal adenocarcinomas supports the hypothesis that these cancers may represent biologically different malignancies. Although oesophageal and gastric cardia carcinomas have a similar male:female ratio, median age at diagnosis and survival, studies suggest several epidemiological and molecular differences between the cancers.[24,39] Oesophageal adenocarcinomas are strongly associated with gastro-oesophageal reflux and obesity and are inversely associated with *H. pylori* and antioxidant intake.[29–31,40–42] Gastric cardia cancers, in contrast, are minimally associated with gastro-oesophageal reflux, only modestly associated with obesity, have no association with antioxidant intake, and have an unclear association with *H. pylori*.[29,41–44]

Inflammation has been proposed as a potential risk factor for carcinogenesis, and it is associated with premalignant changes of the oesophagus; however, studies linking gastric cardia inflammation with *H. pylori*, gastro-oesophageal reflux, or gastric cancer have been contradictory.[43,45,46] Both cancers are thought to have a similar precursor lesion, a change in the cell type lining the distal oesophagus and gastric cardia (a.k.a. 'intestinal metaplasia').[47] Oesophageal intestinal metaplasia, however, stains for cytokeratin 13 (a squamous cell marker) and for an antibody to colonic-type cells (antibody MAbDAS-1). In contrast, gastric cardia intestinal metaplasia does not stain for cytokeratin 13, and gastric cardia cells do not stain for the antibody MAbDAS-1; these patterns suggest that cardia cells are derived from a different cell line than oesophageal metaplastic cells.[48–51] Finally, data indicate possible genetic mutational differences between gastric cardia and oesophageal adenocarcinomas, although other genetic defects (e.g. p53 gene defects) are similar between the two cancers.[52–54]

Strengths of this study include the use of standardized cancer registry data, cumulative rate data, and adjustment for carcinomas of unknown type. Cumulative rate data provide an intuitive means of comparing lifetime cancer risk. The adjustment for cancers without microscopic/morphological verification permits less biased comparisons of countries with lower rates of histological verification, by decreasing under-reporting of histological subtypes.

Weaknesses of this study include the probable persistence of some variability in reporting techniques between registries, and the inability to test whether cancers without microscopic/morphological verification have a similar distribution to cancers with verification. A higher proportion of cancers without microscopic/morphological verification occurs at more advanced ages; since there may be a relatively higher incidence of oesophageal adenocarcinoma versus oesophageal squamous cell carcinoma at advanced ages, this adjustment method may still underestimate the incidence of oesophageal adenocarcinoma.[20] It still, however, provides a substantially less biased estimate than an unadjusted cumulative rate.

In summary, these results document substantial regional and ethnic differences in the distributions of oesophageal/cardia adenocarcinomas. The regional incidences of oesophageal and cardia adenocarcinomas differ from each other, as well as from oesophageal squamous cell carcinoma despite many similar risk factors for each of these cancers. Further ecologic studies that evaluate variability of the known risk factors between populations may provide additional information on this paradox. A component of the international rate differences may be related to differences in site specification of these cancers, although our results do not support this as the sole or even primary cause of the variability seen. Research on international variability in site specification is needed to evaluate the influence of different diagnostic criteria on these international differences in cancer incidence. More definitive studies of individual patients examining the roles of potential risk factors such as *H. pylori*, medications that relax the lower oesophageal sphincter, nutrition, etc, will provide firmer data for potential interventions; such large case-control and cohort studies are currently underway. Plausible explanations for the increasing incidence of oesophageal and cardia adenocarcinomas must be able to account for these regional, gender, and ethnic incidence differences, and for the incidence differences between the two cancers.

Acknowledgements

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KEY MESSAGES

- There is marked international variability in the incidence rates of oesophageal adenocarcinoma and gastric cardia adenocarcinoma.
- Regions with high incidence rates of oesophageal adenocarcinoma do not necessarily have high incidence rates of gastric cardia adenocarcinoma, suggesting that these cancers may have different risk factors.

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Commentary: Regional variations in oesophageal and gastric cardia cancers—implications and practice

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The incidence of oesophageal adenocarcinoma (OA) has seen a rapid increase throughout the last 20 years in the western world and has now surpassed that of oesophageal squamous carcinomas in developed countries. The diagnosis is often at an advanced stage and is almost uniformly associated with a poor prognosis and mean survival of less than one year.[1] Oesophageal adenocarcinoma is strongly associated with gastro-oesophageal reflux disease (GORD) and Barrett's Metaplasia (BM). It is now widely accepted that OA does not develop *de novo* but rather along a sequence of phenotypic and genetic alterations that have been termed the metaplasia-dysplasia-neoplasia sequence.[2]

Much attention has been devoted in this context to BM and subsequently the potential to curtail the increase in OA by surveillance programmes for patients with BM. Surveillance programmes were initially widely advocated but unfortunately so far have failed to impact on the rising incidence of OA and some studies have questioned their cost-effectiveness.[3] At least some of these failures have been attributed to problems related to sampling errors and inaccuracies in the diagnosis of BM due to the lack of accurate landmarks at the gastro-oesophageal junction. Another reason has been a lack of accurate figures regarding the incidence of OA, the incidence of BM and the annual conversion rates from BM to OA.

Gastro-oesophageal reflux is very common in the western world with up to 30% of the population expected to suffer symptoms per month.[4] Barrett's metaplasia is often asymptomatic and only develops in the minority of patients with an estimated incidence of 0.5% in the US and possibly twice that in the UK. Conversion rates for BM to dysplasia and OA are generally low and are thought to be around 0.2–2% annually (Table 1). Regional variations in the western world have also become apparent with an annual incidence of OA of 3–5/100 000 in the US compared with 12–16/100 000 in the UK.[5,6] Some of these figures have, however, recently been questioned as higher than expected due to a possible reporting bias, but they tend uniformly to suggest regional differences.[7] The success of surveillance programmes and the provision of cancer resources depend heavily on these facts and highlight's the importance of the paper by Corley and Buffler[8] in this issue of the *International Journal of Epidemiology*.

The paper confirms the suspicions of many clinicians that Scotland is not only renowned for it's high rates of ischaemic heart disease, but also reins supreme as far as OA is concerned. The Scottish population has long been renowned for their high intake of saturated fats and high rates of obesity and cigarette smoking, all of which are known risk factors for OA and confirms to an extent the importance of lifestyle factors in the development of OA.

Similarities between adenocarcinoma of the oesophagus and the nearby, but distinct gastric cardia have led epidemiologists to present adenocarcinoma at these sites as the same disease. Corley and Buffler highlight the need to precisely discriminate between the sites. Differences in their pathogenesis have emerged in recent years with strong associations between GORD with OA and *Helicobacter pylori* infection with gastric cardia adenocarcinomas (GCA). These differences are to an extent confirmed by the discordance of incidences in the populations studied. Gastric cardia adenocarcinomas, as well as *H. pylori* infection are particularly common in populations of Chinese and Malaysian ethnicity and suggest a possible genetic predisposition. Host responses to *H. pylori* infection and in particular polymorphisms

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Table 1 Pooled results of published data on the incidence of Barrett's associated adenocarcinomas in the UK and US

Papers (date of publication)	Study population (patients)	Cancers detected	Study period (patient years)	Incidence (%)
UK based studies				
Cooper *et al.* (1987)[12]	52	0	45	0
Robertson *et al.* (1988)[13]	56	3	168	1.79
Watson *et al.* (1991)[14]	45	1	158	0.63
Iftikhar *et al.* (1992)[15]	102	4	462	0.87
Moghissi *et al.* (1993)[16]	26	4	229	1.75
Wright *et al.* (1996)[17]	166	6	461	1.3
Rana *et al.* (2000)[18]	44	2	418	0.48
Bani-Hani *et al.* (2000)[19]	357	12	1293	0.93
McDonald *et al.* (2000)[20]	143	5	629	0.79
Pooled UK data	991	37	3863	0.96
US based studies				
Spechler *et al.* (1984)[21]	105	2	350	0.57
Cameron *et al.* (1985)[22]	104	2	882	0.24
Achtar *et al.* (1988)[23]	62	1	166	0.6
Williamson *et al.* (1991)[24]	176	5	497	1.0
Reid *et al.* (1992)[25]	62	5	176	2.8
McDonald *et al.* (1996)[26]	112	3	728	0.41
Drewitz *et al.* (1997)[27]	170	4	834	0.48
Weston *et al.* (1997)[28]	55	2	94	2.1
Streitz *et al.* (1998)[29]	149	7	510	1.4
Katz *et al.* (1998)[30]	102	3	563	0.53
Pooled US data	1097	34	4800	0.71

of cytokines such as Interleukin 1β are increasingly recognized as being important in gastric carcinogenesis.[9] Obesity also varies in its association with adenocarcinomas at the gastro-oesophageal junction. It is strongly associated with OA and less so with GCA and in one study this finding was independent of GORD.[4] The mechanism for the link with body fat and the role other putative risk factors needs to be clarified.

Possibly the greatest importance of the paper by Corley and Buffler lies in identifying groups most at risk of OA or GCA and hence most likely to benefit from interventional strategies such as surveillance endoscopies or *H. pylori* eradication. Acid suppression for BM by long-term treatment with proton pump inhibitors (PPI) have been the mainstay of treatment with encouraging reports of partial regression of areas of BM.[10] There are, however, no long-term outcome data and hence closer follow-up of populations at high risk such as Scotland might yield answers in a cost effective manner.

The benefits are not only restricted to favourable clinical outcomes and cost effectiveness, but have huge implications for basic research and drug development. Our knowledge about the molecular mechanisms involved in the BM-dysplasia-neoplasia sequence of OA has identified several targets, ranging from cytokines such as tumour necrosis factor α (TNFα) to enzymes involved with oncogene activation such as tyrosine kinases and cyclo-oxygenase 2 (COX-2), for pharmaceutical intervention and potential chemoprevention.[11] Targeting of at-risk populations will be crucial in the design of future experimental pharmaceutical trials and establishes the UK as likely candidate.

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