CANCER EPIDEMIOLOGY

Global and national trends in the age-specific sex ratio of esophageal cancer and gastric cancer by subtype

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Abstract

A male predominance was observed in esophageal and gastric cancers, though present limited data has revealed variations by age. We aim to investigate the global age-specific sex differences in esophageal squamous cell carcinoma (ESCC), esophageal adenocarcinoma (EAC), gastric cardia cancer (GCC) and gastric noncardia cancer (GNCC). Data on esophageal and gastric cancers incidence by diagnosis year, sex, histology, subsite and age group were extracted from 171 registries in 54 countries included in the last two volumes (X and XI, 2003-2012) of *Cancer Incidence in Five Continents*, which contributing to over 80% of the global burdens of these cancers. Age-standardized incidence rates (ASIRs) and male-to-female ASIRs ratios were estimated for esophageal and gastric cancers, by histological subtype and subsite, globally and by country. We consistently observed a male predominance in esophageal and gastric cancers across the world from 2003 to 2012, with male-to-female ASIRs ratios of 6.7:1 for EAC, 3.3:1 for ESCC, 4.0:1 for GCC and 2.1:1 for GNCC. The sex differences were consistent across time periods but varied significantly by age across the life span. Across the four cancer types, the male-to-female incidence rate ratios increased from young ages, approaching a peak at ages 60-64, but sharply declined thereafter. Similar "low-high-low" trends of age-specific sex ratio were observed in other digestive cancers including liver, pancreas, colon and rectum with peak ages ranging from 50 to 65. Age-dependent risk factors warrant further investigation to aid our understanding of the underlying etiologies of esophageal and gastric cancers by histological subtype and subsite.

KEYWORDS
esophageal adenocarcinoma, esophageal squamous cell carcinoma, gastric cardia cancer, gastric noncardia cancer, male-to-female age-standardized incidence rates ratio

What's new?

Marked differences exist between men and women in the incidence of esophageal and gastric cancers. These disparities, however, are not explained solely by variances between the sexes in the distribution of major risk factors, suggesting that other factors are involved. Here, investigation of esophageal and gastric cancer incidence in 54 countries worldwide reveals consistent male predominance in the incidence of these malignancies. The ratio of male-to-female incidence increased through life, peaking at ages 60-64 and declining thereafter. The findings warrant further investigation to identify mechanisms underlying age-related changes in risk and possible shared etiologies of esophageal and gastric cancers.

1 | INTRODUCTION

Gastric cancer (GC) and esophageal cancer (EC) rank as the fifth and seventh most common cancer sites worldwide in 2020.[1] Striking sex differences in esophageal cancer and gastric cancer are well-described and have been attributed to differences in the distributions of major risk factors between the sexes.[2-5] These include smoking, alcohol drinking and family history, as well as subtype-specific factors, including gastroesophageal reflux diseases and *Helicobacter pylori* (*H. pylori*).[2-4] More recent research has however shown that these determinants cannot fully explain the sex-specific differences.[5-7]

Moreover, accruing evidence has shown that the gender differences in gastrointestinal cancers varied by age and major histological subtypes and subsites,[6,8,9] including esophageal adenocarcinoma (EAC), esophageal squamous cell carcinoma (ESCC), gastric cardia cancer (GCC) and gastric noncardia cancer (GNCC).[1,8,10,11] Previous results reported the highest male-to-female incidence ratio of up to 10:1 in EAC,[8] and the lowest ratio of 1.6:1 in GNCC,[11] though these studies were limited to specific regions or countries.[8,11,12] In addition, studies showed different changing patterns of sex differences with age by subtype, with a declining trend of the male-to-female incidence ratio of EAC with age, but a "low-high-low" pattern of sex ratio curve for GCC with age.[8,13]

Over the past decades, the global cancer burden and profiles of various risk factors have evolved with rapid economic development.[1] For gastrointestinal cancers, it is important to better understand the sex-specific variations in esophageal and gastric cancers and how they change over time. It is also informative to illustrate the changing patterns of the sex differences by age to generate hypotheses for future etiological studies, given age is a vital indicator highly relevant to economy, life span and various known or putative risk factors (eg, reproductive and hormonal factors).

This global study aims to assess the long-term changing patterns of age- and sex-specific differences in esophageal cancer and gastric cancer, by pathological subtype and anatomic subsite. Using the detailed information available in the Cancer Incidence in Five Continents (CI5) from 2003 to 2012, we investigate the population-based male-to-female incidence rates ratios of esophageal and gastric cancers by subtype, sex and 5-year age group, in selected countries. The identified patterns in our study seek to aid our understanding of the underlying etiological mechanisms of sex differences in these two common cancers, and inform future cancer prevention and control studies.

2 | MATERIALS AND METHODS

2.1 | Data source

We extracted EC and GC incidence and population data from the CI5 website, which contains incidence data from cancer registries worldwide of high quality.[14,15] The last two volumes from X to XI were used, containing detailed data for new cases diagnosed from 2003 to 2012 by morphology, subsite, sex and 5-year age group. EC and GC were evaluated overall and by subtype and subsite, including EAC, ESCC, GCC and GNCC. We also extracted data from CI5 X to XI for other digestive cancers including liver, colon, rectum and pancreas, to compare the age-specific sex differences among different gastrointestinal cancer sites.[14,15]

There were 171 population-based cancer registries from 54 countries reporting 10 consecutive years of data from 2003 to 2012. We used data from the National Program of Cancer Registries to estimate the burdens in the United States to reach a higher coverage of the population-based cancer registry. Multiple subnational cancer registries in the same countries were aggregated to obtain a national proxy of cancer risk. For the EC analysis, we further excluded nine registries which recorded less than five EAC or ESCC cases in each volume, and four registries with more than 75% of EC cases assigned unspecified histology. Finally, a total of 158 out of 171 registries were included covering 53 countries (Table S1), which contributed to 83.49% of the global EC burden.[16] We further imputed EC cases which were reported as unspecified type into EAC, ESCC or other histological types according to the proportion of each type by sex and 5-year age group in the available reported morphological category. The subsites of GC were defined according to the International Classification of Diseases, 10th Revision as follows: GCC (C16.0) and GNCC (C16.1-9), whereby cancers with overlapping (C16.8) or undefined (C16.9) topography were considered GNCC according to evidence from the clinical observations along with previous results.[17] We additionally excluded one registry which reported

TABLE 1 Global and national estimations of male-to-female age-standardized incidence rate ratios and 95% CIs for esophageal cancer and gastric cancer, overall and by subtype and subsite (2003-2012)[a]

World region	Population	Time period	Esophageal cancer	ESCC	EAC	Gastric cancer	GCC	GNCC
Global	Total	2003-2012	4.28 (4.25, 4.31)	3.27 (3.24, 3.30)	6.68 (6.61, 6.76)	2.23 (2.22, 2.24)	3.99 (3.94, 4.03)	2.05 (2.04, 2.05)
		2003-2007	4.24 (4.20, 4.28)	3.30 (3.26, 3.34)	6.62 (6.51, 6.73)	2.22 (2.21, 2.23)	3.94 (3.88, 4.00)	2.04 (2.03, 2.05)
		2008-2012	4.31 (4.27, 4.35)	3.25 (3.21, 3.29)	6.74 (6.63, 6.84)	2.24 (2.23, 2.25)	4.03 (3.97, 4.09)	2.05 (2.04, 2.06)
Northern America	Canada	2003-2012	3.84 (3.69, 4.00)	1.90 (1.79, 2.02)	6.82 (6.41, 7.26)	2.17 (2.11, 2.24)	4.23 (3.99, 4.48)	1.67 (1.62, 1.73)
		2003-2007	3.67 (3.46, 3.89)	1.89 (1.74, 2.06)	6.73 (6.13, 7.39)	2.29 (2.20, 2.38)	4.68 (4.28, 5.11)	1.77 (1.69, 1.85)
		2008-2012	3.99 (3.77, 4.21)	1.91 (1.75, 2.07)	6.87 (6.33, 7.46)	2.07 (1.99, 2.16)	3.89 (3.60, 4.21)	1.59 (1.52, 1.66)
	United States	2003-2012	4.70 (4.64, 4.76)	2.34 (2.30, 2.39)	7.87 (7.73, 8.02)	2.01 (2.00, 2.03)	4.48 (4.39, 4.57)	1.50 (1.48, 1.51)
		2003-2007	4.61 (4.52, 4.69)	2.35 (2.29, 2.42)	7.82 (7.61, 8.03)	2.04 (2.01, 2.06)	4.48 (4.36, 4.62)	1.54 (1.51, 1.56)
		2008-2012	4.79 (4.71, 4.87)	2.33 (2.27, 2.39)	7.92 (7.72, 8.12)	2.00 (1.97, 2.02)	4.47 (4.36, 4.59)	1.46 (1.44, 1.48)
South America	Argentina	2003-2012	2.68 (2.40, 3.01)	2.10 (1.83, 2.40)	5.14 (4.11, 6.43)	2.57 (2.33, 2.84)	4.96 (3.27, 7.52)	2.45 (2.22, 2.71)
		2003-2007	2.79 (2.38, 3.27)	2.44 (2.03, 2.94)	4.11 (2.98, 5.68)	2.59 (2.25, 2.98)	6.33 (2.95, 13.56)	2.47 (2.14, 2.86)
		2008-2012	2.58 (2.19, 3.03)	1.76 (1.45, 2.15)	6.31 (4.62, 8.61)	2.56 (2.23, 2.94)	4.44 (2.70, 7.31)	2.43 (2.10, 2.80)
	Brazil	2003-2012	4.28 (3.54, 5.18)	4.16 (3.42, 5.05)	9.90 (3.23, 30.33)	2.19 (1.99, 2.41)	3.21 (2.27, 4.52)	2.11 (1.91, 2.33)
		2003-2007	4.00 (3.09, 5.18)	3.84 (2.97, 4.98)	–	2.10 (1.84, 2.40)	3.09 (1.92, 4.97)	2.03 (1.76, 2.33)
		2008-2012	4.85 (3.67, 6.43)	4.66 (3.47, 6.25)	10.38 (3.25, 33.19)	2.26 (1.96, 2.59)	2.95 (1.79, 4.86)	2.20 (1.90, 2.55)
	Chile	2003-2012	2.17 (1.86, 2.54)	2.26 (1.91, 2.68)	4.58 (2.81, 7.47)	2.41 (2.21, 2.63)	3.56 (2.61, 4.85)	2.32 (2.12, 2.54)
		2003-2007	2.06 (1.67, 2.56)	2.32 (1.83, 2.94)	2.75 (1.52, 4.96)	2.46 (2.17, 2.80)	4.01 (2.54, 6.35)	2.35 (2.06, 2.69)
		2008-2012	2.18 (1.73, 2.74)	2.04 (1.59, 2.60)	4.87 (1.97, 12.06)	2.68 (2.38, 3.02)	3.68 (2.42, 5.60)	2.59 (2.29, 2.93)
	Colombia	2003-2012	2.05 (1.76, 2.38)	1.55 (1.30, 1.87)	4.09 (3.04, 5.50)	1.88 (1.78, 1.99)	3.79 (3.07, 4.69)	1.78 (1.68, 1.88)
		2003-2007	2.15 (1.76, 2.63)	1.67 (1.31, 2.12)	4.53 (2.95, 6.95)	1.92 (1.78, 2.08)	3.42 (2.55, 4.60)	1.84 (1.69, 1.99)
		2008-2012	1.91 (1.53, 2.39)	1.39 (1.05, 1.84)	3.74 (2.47, 5.65)	1.84 (1.70, 1.99)	4.18 (3.09, 5.66)	1.71 (1.58, 1.86)
	Ecuador	2003-2012	2.87 (2.11, 3.91)	3.20 (2.19, 4.67)	3.38 (1.75, 6.53)	1.44 (1.35, 1.54)	2.42 (1.74, 3.38)	1.41 (1.32, 1.51)
		2003-2007	3.54 (2.26, 5.53)	4.64 (2.59, 8.32)	1.71 (0.77, 3.84)	1.49 (1.36, 1.63)	3.49 (2.03, 5.98)	1.44 (1.32, 1.58)
		2008-2012	2.16 (1.43, 3.26)	2.03 (1.22, 3.37)	6.21 (2.20, 17.51)	1.43 (1.31, 1.57)	2.08 (1.37, 3.15)	1.40 (1.28, 1.54)
Eastern Asia	Republic of Korea	2003-2012	14.72 (14.03, 15.45)	16.12 (15.31, 16.97)	5.87 (4.97, 6.94)	2.53 (2.51, 2.55)	3.62 (3.47, 3.78)	2.50 (2.48, 2.52)
		2003-2007	15.00 (14.00, 16.08)	16.57 (15.38, 17.86)	5.42 (4.33, 6.77)	2.54 (2.51, 2.57)	3.43 (3.22, 3.66)	2.51 (2.48, 2.54)
		2008-2012	14.49 (13.56, 15.48)	15.73 (14.66, 16.88)	6.59 (5.13, 8.47)	2.52 (2.50, 2.55)	3.77 (3.56, 4.00)	2.48 (2.46, 2.51)
	China	2003-2012	2.57 (2.51, 2.63)	2.54 (2.48, 2.61)	3.10 (2.80, 3.42)	2.03 (2.00, 2.06)	3.11 (2.99, 3.24)	1.89 (1.86, 1.92)
		2003-2007	2.53 (2.44, 2.61)	2.49 (2.41, 2.58)	3.53 (3.01, 4.15)	2.03 (1.99, 2.07)	3.06 (2.89, 3.24)	1.89 (1.85, 1.94)
		2008-2012	2.60 (2.52, 2.69)	2.59 (2.50, 2.69)	2.79 (2.46, 3.17)	2.02 (1.98, 2.06)	3.15 (2.97, 3.33)	1.88 (1.84, 1.92)

(Continues)

TABLE 1 (Continued)

World region	Population	Time period	Male-to-female age-standardized incidence rate ratios (95% CIs)					
			Esophageal cancer	ESCC	EAC	Gastric cancer	GCC	GNCC
	Japan	2003-2012	6.37 (6.18, 6.57)	6.38 (6.18, 6.58)	7.72 (6.74, 8.84)	2.71 (2.69, 2.74)	3.85 (3.69, 4.02)	2.66 (2.63, 2.68)
		2003-2007	6.74 (6.42, 7.07)	6.89 (6.55, 7.25)	6.56 (5.32, 8.09)	2.65 (2.61, 2.69)	3.59 (3.35, 3.85)	2.60 (2.56, 2.64)
		2008-2012	6.11 (5.87, 6.36)	6.03 (5.79, 6.29)	8.67 (7.26, 10.35)	2.76 (2.73, 2.80)	4.06 (3.84, 4.29)	2.69 (2.66, 2.73)
South-Eastern Asia	Thailand	2003-2012	6.72 (6.05, 7.46)	7.32 (6.53, 8.19)	4.50 (3.08, 6.57)	1.59 (1.42, 1.78)	1.89 (1.31, 2.73)	1.56 (1.39, 1.76)
		2003-2007	6.13 (5.32, 7.07)	6.74 (5.77, 7.88)	4.55 (2.73, 7.59)	1.58 (1.35, 1.86)	1.49 (0.85, 2.62)	1.59 (1.34, 1.89)
		2008-2012	7.45 (6.38, 8.69)	7.98 (6.76, 9.41)	4.48 (2.54, 7.89)	1.57 (1.35, 1.83)	2.24 (1.38, 3.63)	1.50 (1.28, 1.77)
South-Central Asia	India	2003-2012	1.55 (1.49, 1.61)	1.50 (1.44, 1.56)	2.87 (2.40, 3.43)	1.96 (1.86, 2.06)	2.52 (2.14, 2.97)	1.90 (1.81, 2.01)
		2003-2007	1.52 (1.43, 1.61)	1.49 (1.41, 1.58)	2.04 (1.53, 2.71)	1.96 (1.82, 2.11)	2.30 (1.76, 3.00)	1.94 (1.79, 2.09)
		2008-2012	1.58 (1.50, 1.66)	1.50 (1.43, 1.58)	3.50 (2.77, 4.42)	1.95 (1.82, 2.08)	2.67 (2.17, 3.29)	1.87 (1.74, 2.01)
Western Asia	Saudi Arabia	2003-2012	1.26 (1.00, 1.59)	0.99 (0.76, 1.30)	2.44 (1.52, 3.94)	1.83 (1.58, 2.13)	3.24 (2.23, 4.71)	1.60 (1.35, 1.88)
		2003-2007	1.34 (0.95, 1.90)	1.10 (0.75, 1.62)	3.15 (1.30, 7.62)	1.98 (1.57, 2.49)	2.74 (1.59, 4.72)	1.84 (1.42, 2.37)
		2008-2012	1.23 (0.90, 1.68)	0.93 (0.63, 1.36)	2.23 (1.26, 3.95)	1.73 (1.42, 2.11)	3.94 (2.35, 6.60)	1.42 (1.14, 1.76)
	Turkey	2003-2012	1.67 (1.49, 1.89)	1.36 (1.19, 1.56)	4.21 (3.07, 5.77)	2.06 (1.97, 2.16)	2.56 (2.26, 2.90)	1.98 (1.89, 2.09)
		2003-2007	1.64 (1.38, 1.94)	1.29 (1.07, 1.56)	5.89 (3.33, 10.41)	1.94 (1.81, 2.08)	2.21 (1.81, 2.69)	1.91 (1.77, 2.05)
		2008-2012	1.65 (1.40, 1.94)	1.36 (1.13, 1.64)	3.57 (2.43, 5.25)	2.12 (1.99, 2.26)	2.74 (2.34, 3.21)	2.02 (1.88, 2.16)
	Israel	2003-2012	2.01 (1.79, 2.25)	1.17 (1.00, 1.35)	4.67 (3.81, 5.71)	1.82 (1.74, 1.91)	3.10 (2.75, 3.51)	1.65 (1.56, 1.73)
		2003-2007	1.97 (1.69, 2.29)	1.20 (0.98, 1.46)	4.10 (3.17, 5.30)	1.82 (1.70, 1.94)	2.89 (2.44, 3.42)	1.66 (1.55, 1.79)
		2008-2012	2.10 (1.80, 2.45)	1.15 (0.93, 1.41)	5.51 (4.13, 7.35)	1.81 (1.69, 1.93)	3.38 (2.86, 4.00)	1.60 (1.49, 1.72)
	Cyprus	2003-2012	3.12 (1.98, 4.90)	1.86 (1.06, 3.27)	6.23 (2.63, 14.74)	1.82 (1.57, 2.11)	5.83 (3.34, 10.16)	1.60 (1.37, 1.86)
		2003-2007	3.87 (1.91, 7.83)	2.41 (0.92, 6.32)	4.93 (1.63, 14.93)	2.15 (1.70, 2.72)	10.08 (3.09, 32.89)	1.85 (1.45, 2.37)
		2008-2012	2.64 (1.46, 4.78)	1.56 (0.77, 3.17)	8.67 (2.14, 35.12)	1.60 (1.32, 1.94)	4.26 (2.23, 8.13)	1.42 (1.16, 1.74)
Eastern Europe	Belarus	2003-2012	18.00 (16.27, 19.92)	20.77 (18.46, 23.36)	9.38 (7.61, 11.56)	2.41 (2.36, 2.47)	3.60 (3.28, 3.96)	2.35 (2.30, 2.41)
		2003-2007	17.11 (14.84, 19.74)	20.85 (17.58, 24.73)	7.67 (5.80, 10.14)	2.42 (2.34, 2.49)	3.67 (3.23, 4.18)	2.35 (2.28, 2.43)
		2008-2012	19.24 (16.67, 22.20)	21.00 (17.85, 24.71)	12.31 (8.96, 16.92)	2.42 (2.34, 2.49)	3.60 (3.13, 4.13)	2.36 (2.28, 2.44)
	Czech Republic	2003-2012	6.42 (5.98, 6.89)	5.50 (5.03, 6.01)	8.69 (7.70, 9.80)	1.98 (1.92, 2.04)	3.86 (3.51, 4.24)	1.80 (1.74, 1.86)
		2003-2007	6.89 (6.20, 7.66)	6.09 (5.33, 6.96)	8.67 (7.23, 10.39)	2.05 (1.96, 2.14)	4.26 (3.73, 4.87)	1.85 (1.76, 1.94)
		2008-2012	6.05 (5.51, 6.65)	5.06 (4.49, 5.70)	8.60 (7.32, 10.10)	1.90 (1.82, 1.99)	3.48 (3.05, 3.98)	1.75 (1.66, 1.83)
	Poland	2003-2012	6.38 (5.72, 7.12)	6.38 (5.66, 7.19)	6.29 (4.71, 8.40)	2.54 (2.43, 2.66)	4.96 (4.25, 5.80)	2.36 (2.25, 2.48)
		2003-2007	6.57 (5.61, 7.69)	6.98 (5.87, 8.29)	5.11 (3.42, 7.62)	2.49 (2.34, 2.66)	4.27 (3.41, 5.34)	2.36 (2.21, 2.53)
		2008-2012	6.13 (5.26, 7.15)	5.84 (4.95, 6.89)	7.59 (4.99, 11.55)	2.56 (2.40, 2.73)	5.66 (4.56, 7.03)	2.33 (2.17, 2.49)

TABLE 1 (Continued)

World region	Population	Time period	Male-to-female age-standardized incidence rate ratios (95% CIs)					
			Esophageal cancer	ESCC	EAC	Gastric cancer	GCC	GNCC
	Slovakia	2003-2012	11.39 (9.98, 12.99)	12.06 (10.41, 13.96)	8.25 (6.04, 11.26)	2.23 (2.13, 2.33)	3.92 (3.38, 4.53)	2.07 (1.98, 2.18)
		2003-2007	11.62 (9.81, 13.77)	12.16 (10.07, 14.68)	8.36 (5.59, 12.51)	2.28 (2.15, 2.42)	4.18 (3.48, 5.02)	2.11 (1.98, 2.24)
		2008-2012	11.04 (8.96, 13.60)	11.83 (9.36, 14.96)	8.28 (5.08, 13.50)	2.15 (2.00, 2.32)	3.50 (2.74, 4.48)	2.03 (1.88, 2.20)
	Bulgaria	2003-2012	5.75 (5.16, 6.41)	5.50 (4.84, 6.25)	6.81 (5.52, 8.40)	2.19 (2.12, 2.26)	3.14 (2.84, 3.48)	2.10 (2.03, 2.17)
		2003-2007	5.82 (4.98, 6.79)	5.81 (4.81, 7.02)	5.58 (4.24, 7.34)	2.20 (2.11, 2.30)	3.41 (2.93, 3.97)	2.11 (2.02, 2.20)
		2008-2012	5.70 (4.89, 6.63)	5.28 (4.43, 6.29)	8.46 (6.09, 11.76)	2.17 (2.07, 2.27)	2.94 (2.57, 3.36)	2.08 (1.98, 2.18)
	Ukraine	2003-2012	12.80 (12.26, 13.37)	15.70 (14.90, 16.54)	6.51 (6.01, 7.06)	2.40 (2.37, 2.43)	3.50 (3.38, 3.63)	2.30 (2.27, 2.32)
		2003-2007	12.53 (11.80, 13.30)	16.11 (14.95, 17.35)	6.15 (5.52, 6.84)	2.38 (2.34, 2.42)	3.39 (3.22, 3.56)	2.29 (2.25, 2.32)
		2008-2012	13.13 (12.34, 13.97)	15.42 (14.33, 16.60)	6.95 (6.16, 7.85)	2.42 (2.38, 2.46)	3.66 (3.47, 3.87)	2.31 (2.27, 2.35)
Northern Europe	Iceland	2003-2012	4.29 (3.07, 5.99)	1.95 (1.17, 3.23)	7.64 (4.60, 12.70)	1.59 (1.27, 1.99)	3.79 (1.96, 7.33)	1.39 (1.09, 1.77)
		2003-2007	3.00 (1.86, 4.85)	2.54 (1.32, 4.89)	3.88 (1.81, 8.31)	1.83 (1.35, 2.50)	3.31 (1.38, 7.95)	1.66 (1.20, 2.32)
		2008-2012	5.92 (3.70, 9.47)	1.37 (0.60, 3.08)	12.54 (6.26, 25.10)	1.38 (0.99, 1.92)	4.55 (1.66, 12.45)	1.16 (0.81, 1.66)
	Ireland	2003-2012	2.33 (2.18, 2.49)	1.19 (1.08, 1.31)	4.83 (4.33, 5.38)	2.11 (1.99, 2.24)	3.00 (2.70, 3.34)	1.81 (1.69, 1.94)
		2003-2007	2.34 (2.12, 2.58)	1.22 (1.06, 1.40)	4.78 (4.08, 5.59)	2.10 (1.93, 2.29)	2.82 (2.39, 3.33)	1.89 (1.72, 2.09)
		2008-2012	2.33 (2.12, 2.56)	1.17 (1.02, 1.35)	4.86 (4.18, 5.64)	2.12 (1.95, 2.29)	3.13 (2.72, 3.61)	1.73 (1.57, 1.90)
	Lithuania	2003-2012	9.80 (8.62, 11.15)	10.77 (9.27, 12.52)	6.20 (4.71, 8.16)	2.37 (2.27, 2.47)	4.70 (3.80, 5.83)	2.30 (2.21, 2.40)
		2003-2007	10.73 (8.90, 12.95)	11.32 (9.11, 14.07)	8.60 (5.70, 12.96)	2.48 (2.34, 2.62)	4.48 (3.30, 6.10)	2.42 (2.28, 2.56)
		2008-2012	9.04 (7.57, 10.79)	10.30 (8.36, 12.68)	4.52 (3.10, 6.60)	2.25 (2.12, 2.39)	5.01 (3.72, 6.75)	2.17 (2.04, 2.31)
	Norway	2003-2012	3.50 (3.18, 3.85)	2.25 (1.95, 2.59)	5.42 (4.71, 6.23)	1.89 (1.78, 2.00)	3.75 (3.28, 4.27)	1.54 (1.45, 1.64)
		2003-2007	3.58 (3.11, 4.12)	2.29 (1.87, 2.81)	5.99 (4.84, 7.40)	1.85 (1.71, 2.00)	3.63 (3.02, 4.36)	1.52 (1.40, 1.66)
		2008-2012	3.45 (3.02, 3.93)	2.24 (1.84, 2.73)	5.05 (4.19, 6.08)	1.93 (1.78, 2.10)	3.84 (3.18, 4.64)	1.57 (1.44, 1.73)
	Denmark	2003-2012	3.12 (2.92, 3.34)	2.14 (1.95, 2.34)	5.15 (4.63, 5.72)	2.23 (2.11, 2.36)	4.44 (4.03, 4.90)	1.39 (1.30, 1.50)
		2003-2007	2.89 (2.62, 3.18)	1.94 (1.70, 2.21)	4.99 (4.28, 5.82)	2.16 (2.00, 2.34)	4.32 (3.75, 4.98)	1.39 (1.26, 1.54)
		2008-2012	3.33 (3.04, 3.64)	2.32 (2.05, 2.63)	5.26 (4.55, 6.07)	2.30 (2.13, 2.49)	4.56 (3.98, 5.21)	1.39 (1.25, 1.54)
	Estonia	2003-2012	8.29 (6.78, 10.14)	8.52 (6.84, 10.61)	7.78 (4.42, 13.71)	2.07 (1.94, 2.21)	3.74 (2.95, 4.72)	1.97 (1.84, 2.10)
		2003-2007	7.97 (5.90, 10.75)	8.06 (5.85, 11.12)	6.71 (2.87, 15.72)	1.96 (1.80, 2.15)	3.19 (2.29, 4.44)	1.88 (1.72, 2.07)
		2008-2012	8.68 (6.62, 11.39)	9.01 (6.67, 12.18)	9.03 (4.23, 19.26)	2.20 (2.01, 2.41)	4.36 (3.12, 6.09)	2.07 (1.88, 2.28)
	Latvia	2003-2012	10.60 (8.81, 12.75)	11.04 (9.00, 13.55)	9.49 (5.92, 15.23)	2.25 (2.12, 2.39)	4.25 (3.08, 5.87)	2.19 (2.06, 2.33)
		2003-2007	8.55 (6.76, 10.81)	8.94 (6.92, 11.56)	6.86 (3.75, 12.53)	2.31 (2.13, 2.49)	5.35 (3.45, 8.30)	2.24 (2.07, 2.42)
		2008-2012	14.37 (10.60, 19.47)	14.96 (10.63, 21.06)	15.68 (7.24, 33.94)	2.15 (1.95, 2.37)	3.20 (1.97, 5.19)	2.11 (1.91, 2.34)

(Continues)

TABLE 1 (Continued)

World region	Population	Time period	Male-to-female age-standardized incidence rate ratios (95% CIs)					
			Esophageal cancer	ESCC	EAC	Gastric cancer	GCC	GNCC
	United Kingdom	2003-2012	2.71 (2.67, 2.75)	1.14 (1.12, 1.17)	5.06 (4.95, 5.17)	2.39 (2.35, 2.42)	4.00 (3.88, 4.13)	1.96 (1.92, 1.99)
		2003-2007	2.62 (2.56, 2.68)	1.15 (1.11, 1.19)	5.00 (4.84, 5.15)	2.42 (2.37, 2.47)	3.88 (3.72, 4.05)	2.03 (1.98, 2.07)
		2008-2012	2.79 (2.73, 2.85)	1.14 (1.10, 1.18)	5.11 (4.96, 5.26)	2.36 (2.31, 2.41)	4.14 (3.96, 4.33)	1.89 (1.85, 1.94)
Southern Europe	Malta	2003-2012	4.14 (2.90, 5.93)	2.83 (1.74, 4.60)	6.66 (3.69, 12.03)	2.21 (1.84, 2.65)	6.22 (3.57, 10.83)	1.82 (1.50, 2.22)
		2003-2007	3.80 (2.24, 6.46)	1.72 (0.87, 3.39)	10.99 (3.54, 34.08)	2.06 (1.58, 2.69)	6.99 (3.27, 14.92)	1.58 (1.18, 2.12)
		2008-2012	4.50 (2.77, 7.31)	5.47 (2.63, 11.34)	4.70 (2.33, 9.48)	2.33 (1.81, 3.00)	5.73 (2.54, 12.93)	2.03 (1.55, 2.65)
	Portugal	2003-2012	–	–	–	2.44 (2.02, 2.95)	6.72 (3.13, 14.46)	2.24 (1.84, 2.74)
		2003-2007	–	–	–	2.31 (1.79, 2.98)	4.24 (1.70, 10.56)	2.17 (1.66, 2.84)
		2008-2012	–	–	–	2.62 (1.97, 3.48)	21.61 (4.97, 93.96)	2.34 (1.75, 3.14)
	Italy	2003-2012	4.09 (3.87, 4.32)	3.59 (3.37, 3.83)	6.80 (6.08, 7.61)	1.95 (1.91, 1.98)	4.28 (4.00, 4.60)	1.79 (1.76, 1.83)
		2003-2007	4.32 (3.99, 4.67)	4.01 (3.65, 4.39)	7.29 (6.15, 8.64)	1.98 (1.92, 2.03)	4.24 (3.83, 4.70)	1.84 (1.78, 1.89)
		2008-2012	3.88 (3.60, 4.18)	3.22 (2.94, 3.52)	6.47 (5.57, 7.52)	1.92 (1.87, 1.97)	4.32 (3.92, 4.76)	1.75 (1.70, 1.81)
	Slovenia	2003-2012	6.42 (5.41, 7.62)	6.06 (5.01, 7.34)	10.23 (6.61, 15.82)	2.32 (2.19, 2.46)	4.13 (3.45, 4.94)	2.12 (1.99, 2.26)
		2003-2007	6.96 (5.45, 8.87)	6.68 (5.11, 8.73)	8.47 (4.63, 15.48)	2.40 (2.20, 2.61)	4.91 (3.77, 6.39)	2.16 (1.97, 2.36)
		2008-2012	5.91 (4.64, 7.53)	5.49 (4.18, 7.20)	12.91 (6.86, 24.31)	2.25 (2.07, 2.45)	3.52 (2.76, 4.50)	2.09 (1.92, 2.29)
	Spain	2003-2012	7.35 (6.80, 7.94)	7.04 (6.41, 7.72)	8.89 (7.68, 10.29)	2.26 (2.19, 2.33)	5.25 (4.74, 5.82)	2.03 (1.96, 2.09)
		2003-2007	8.44 (7.56, 9.42)	8.41 (7.36, 9.61)	9.26 (7.53, 11.40)	2.31 (2.22, 2.41)	5.05 (4.37, 5.83)	2.10 (2.01, 2.20)
		2008-2012	6.37 (5.72, 7.10)	5.85 (5.14, 6.66)	8.49 (6.91, 10.44)	2.20 (2.10, 2.30)	5.47 (4.73, 6.33)	1.94 (1.85, 2.04)
Western Europe	Belgium	2003-2012	3.76 (3.58, 3.95)	2.70 (2.53, 2.87)	7.04 (6.47, 7.66)	2.22 (2.14, 2.30)	5.04 (4.62, 5.50)	1.74 (1.67, 1.81)
		2003-2007	3.82 (3.55, 4.12)	2.89 (2.62, 3.18)	6.60 (5.82, 7.48)	2.33 (2.20, 2.46)	4.97 (4.33, 5.71)	1.91 (1.80, 2.03)
		2008-2012	3.71 (3.48, 3.96)	2.56 (2.35, 2.78)	7.39 (6.60, 8.27)	2.15 (2.05, 2.26)	5.08 (4.54, 5.68)	1.61 (1.52, 1.70)
	Switzerland	2003-2012	3.78 (3.47, 4.11)	2.74 (2.47, 3.05)	7.29 (6.27, 8.47)	2.00 (1.88, 2.12)	3.96 (3.45, 4.54)	1.61 (1.51, 1.73)
		2003-2007	3.82 (3.38, 4.33)	2.90 (2.49, 3.38)	6.63 (5.30, 8.30)	2.00 (1.84, 2.18)	3.80 (3.13, 4.61)	1.65 (1.50, 1.82)
		2008-2012	3.73 (3.33, 4.18)	2.60 (2.25, 3.00)	7.85 (6.41, 9.62)	1.99 (1.83, 2.17)	4.08 (3.37, 4.95)	1.58 (1.44, 1.75)
	Austria	2003-2012	5.29 (4.89, 5.72)	4.54 (4.11, 5.01)	6.99 (6.13, 7.98)	1.84 (1.78, 1.91)	4.08 (3.67, 4.52)	1.64 (1.58, 1.70)
		2003-2007	5.74 (5.12, 6.44)	4.85 (4.21, 5.59)	8.03 (6.58, 9.81)	1.81 (1.73, 1.90)	4.08 (3.51, 4.76)	1.63 (1.55, 1.72)
		2008-2012	4.92 (4.42, 5.49)	4.24 (3.70, 4.88)	6.30 (5.27, 7.52)	1.90 (1.81, 1.99)	4.07 (3.53, 4.69)	1.67 (1.58, 1.76)
	France	2003-2012	5.98 (5.63, 6.35)	5.32 (4.95, 5.71)	9.01 (7.97, 10.18)	2.48 (2.39, 2.59)	6.17 (5.57, 6.85)	1.94 (1.85, 2.03)
		2003-2007	6.37 (5.83, 6.97)	5.77 (5.20, 6.40)	9.39 (7.80, 11.30)	2.63 (2.48, 2.78)	7.69 (6.52, 9.06)	2.07 (1.94, 2.21)
		2008-2012	5.62 (5.17, 6.11)	4.88 (4.43, 5.39)	8.72 (7.40, 10.26)	2.36 (2.23, 2.49)	5.27 (4.62, 6.02)	1.82 (1.70, 1.94)

TABLE 1 (Continued)

World region	Population	Time period	Male-to-female age-standardized incidence rate ratios (95% CIs)					
			Esophageal cancer	ESCC	EAC	Gastric cancer	GCC	GNCC
	Germany	2003-2012	4.17 (3.96, 4.39)	3.27 (3.06, 3.48)	6.94 (6.34, 7.60)	1.83 (1.78, 1.88)	3.97 (3.72, 4.25)	1.49 (1.45, 1.54)
		2003-2007	4.18 (3.87, 4.50)	3.27 (2.99, 3.58)	7.91 (6.85, 9.15)	1.79 (1.72, 1.86)	3.93 (3.56, 4.34)	1.49 (1.42, 1.56)
		2008-2012	4.15 (3.87, 4.45)	3.24 (2.96, 3.55)	6.41 (5.71, 7.20)	1.88 (1.81, 1.96)	3.99 (3.65, 4.37)	1.50 (1.43, 1.57)
	The Netherlands	2003-2012	3.34 (3.23, 3.45)	1.66 (1.57, 1.75)	5.59 (5.34, 5.86)	2.15 (2.08, 2.21)	4.00 (3.76, 4.26)	1.74 (1.68, 1.80)
		2003-2007	3.33 (3.17, 3.50)	1.67 (1.55, 1.80)	5.88 (5.47, 6.31)	2.25 (2.16, 2.35)	4.22 (3.86, 4.62)	1.82 (1.74, 1.91)
		2008-2012	3.34 (3.19, 3.49)	1.64 (1.53, 1.77)	5.39 (5.07, 5.73)	2.05 (1.97, 2.14)	3.80 (3.48, 4.15)	1.67 (1.59, 1.75)
Australia/New Zealand	Australia	20032012	3.08 (2.97, 3.20)	1.51 (1.43, 1.59)	6.70 (6.29, 7.14)	2.22 (2.16, 2.29)	4.10 (3.86, 4.36)	1.74 (1.69, 1.81)
		20032007	2.95 (2.79, 3.11)	1.54 (1.42, 1.66)	6.34 (5.78, 6.95)	2.23 (2.14, 2.33)	4.41 (4.02, 4.83)	1.75 (1.66, 1.83)
		2008-2012	3.21 (3.04, 3.38)	1.49 (1.38, 1.60)	7.03 (6.45, 7.67)	2.21 (2.12, 2.30)	3.85 (3.55, 4.18)	1.74 (1.66, 1.83)
	New Zealand	2003-2012	2.72 (2.50, 2.94)	1.09 (0.96, 1.23)	6.44 (5.63, 7.36)	1.94 (1.82, 2.08)	4.24 (3.67, 4.89)	1.48 (1.37, 1.59)
		20032007	2.72 (2.42, 3.05)	1.17 (0.98, 1.40)	6.44 (5.31, 7.80)	1.90 (1.73, 2.09)	4.72 (3.80, 5.87)	1.43 (1.29, 1.59)
		2008-2012	2.72 (2.43, 3.04)	1.02 (0.85, 1.21)	6.44 (5.34, 7.75)	2.00 (1.82, 2.20)	3.91 (3.23, 4.73)	1.53 (1.37, 1.71)

Abbreviations: EAC, esophageal adenocarcinoma; ESCC, esophageal squamous cell carcinoma; GCC, gastric cardia cancer; GNCC, gastric noncardia cancer.
aUsing Segi's World Standard Population as reference.

less than five GCC or GNCC cases in each volume and 27 registries with more than 85% of GC cases assigned unspecified histology (C16.5-9), hence, a total of 143 out of 171 registries were included in the GC analysis, corresponding to 43 countries covering 81.56% of the global GC burden[16] (Table S1). We further extracted 10 consecutive years of GC data from 2003 to 2012 from 18 registries from Surveillance, Epidemiology, and End Results (SEER) in the United States and 22 registries from Chinese National Central Cancer Registry which covered 3.34% (44.4 million) of the Chinese population.[18,19] GCC and GNCC was classified into one of four types: intestinal, diffuse, mixed carcinomas, or indeterminate, according to the Laurén classification, which has proven useful in evaluating the natural history of GC, especially with regard to its association with environmental factors. The age-specific trends in incidence rates of intestinal type and diffuse type of GCC and GNCC in the United States and China were analyzed by sex.

2.2 | Statistical analyses

According to the CI5 volumes, we assessed cancer incidence data overall and by two time periods: 2003-2007, 2008-2012. Cancer cases were grouped into 5-year age groups to calculate age-specific rates, beginning from 20 to 24 and ending with 85 years onward. Due to the small number of young cases, the age groups below 20 years were not included. For the different age groups, incidence rates by time period were calculated by dividing the number of incident cancer cases in each period by the male or female population in each period, as appropriate. The global and national age-standardized incidence rates (ASIRs) and the 95% confidence intervals (CIs) of EC and GC were calculated using the direct method with the Segi's World Standard Population as the reference, by sex, cancer subtype or subsite and time period. Moreover, the global and national male-to-female incidence rates ratios of EC and GC were calculated, overall and by histological subtype and subsite, and subsequently derived for the corresponding age groups. The 95% CIs were estimated assuming the count data had a Poisson distribution. Analyses were performed with SAS, version 9.4, software (SAS Institute, Cary, NC).

3 | RESULTS

Table 1 presents the global and national estimations of the male-to-female ASIRs ratios for esophageal cancer and gastric cancer, overall and by cancer subtype and subsite. We observed a significant international male predominance of EC and GC with a male-to-female ASIRs ratio of 6.7:1 for EAC and 3.3:1 for ESCC from 2003 to 2012. The male-to-female ASIRs ratio was lower in GC compared to that of EC, with a stable ratio of 4.0:1 for GCC and 2.1:1 for GNCC. Similar patterns of sex differences were found for different subtypes and
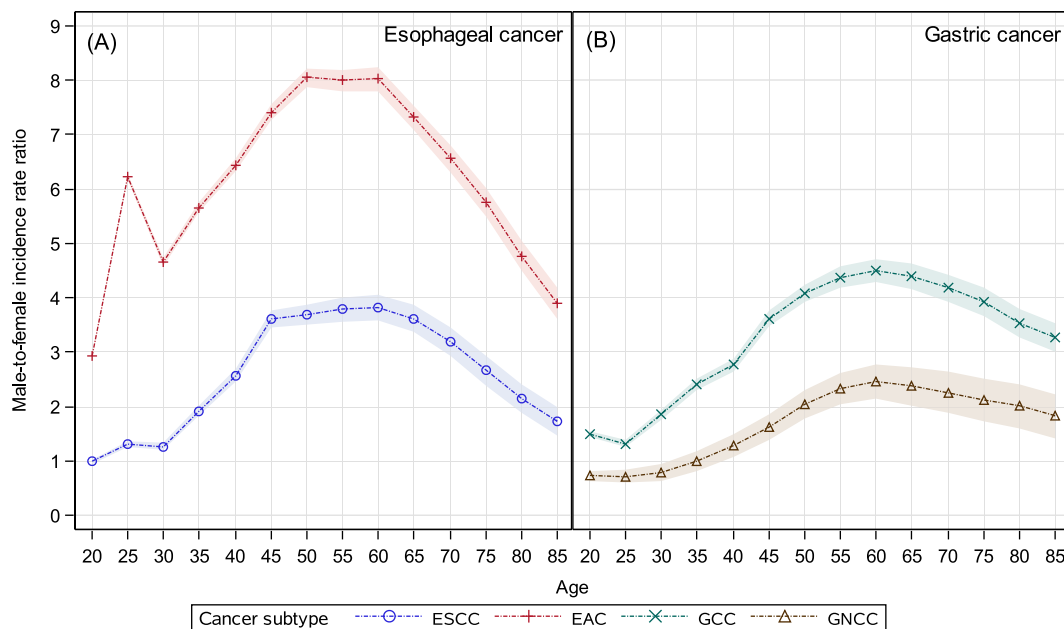
FIGURE 1 Global patterns of age-specific male-to-female incidence rate ratios of esophageal squamous cell carcinoma, esophageal adenocarcinoma, gastric cardia cancer and gastric noncardia cancer (2003-2012). EAC, esophageal adenocarcinoma; ESCC, esophageal squamous cell carcinoma; GCC, gastric cardia cancer; GNCC, gastric noncardia cancer [Color figure can be viewed at wileyonlinelibrary.com]

subsites of EC and GC across the world, yet some variations existed by country. In Republic of Korea and a belt of Baltic/European countries, including Belarus, Ukraine, Slovakia, Lithuania, Latvia, Estonia, we observed extremely high sex ratio exceeding 10:1 for ESCC, but not for EAC or GC. In contrast, comparable rates of ESCC and EAC were found in the United Kingdom, Ireland, New Zealand and some Western Asian countries, including Saudi Arabia, Turkey and Israel. The estimations of the international ASIRs for EAC, ESCC, GCC and GNCC from 2003 to 2012 by sex, age group and country are shown in Tables S2 and S3.

The identified sex differences significantly varied by age and cancer subtype and subsite (Figure 1). The most notable male predominance was found in EAC across all age groups with double peaks. The male-to-female incidence rate ratios of EAC began to increase from young ages at 3:1 in age group of 20-24 years, and reached the first peak at age of 25-29 years with a sex ratio of 6:1 (male vs female rate: 0.06 vs 0.01) (Table 2). After a slightly decline, the ratio approached the second peak in age group of 50-64 years for a ratio of 8:1, thereafter declined to 4:1 at age of 85 onward. For ESCC, males presented higher incidence rates than females from a young age, with a peak ratio of 3.8:1 (male vs female: 16.17 vs 4.24) at age of 60-64 years with declines thereafter. A similarly changing pattern was found for GCC with a peak ratio of 4.5:1 (male vs female: 10.96 vs 2.43) at age of 60-64 years. In contrast, we observed lower incidence rates of GNCC in males than in females in age groups younger than 40, nevertheless the incidence rates of males surpassed those of females approaching a peak male-to-female

ratio of just 2.5:1 (male vs female: 49.14 vs 19.93) at age of 60-64 years.

We additionally analyzed the age-specific sex difference of other digestive cancer types, and found that the male-to-female incidence rates ratios of cancers of the liver, colon, rectum and pancreas consistently presented a "low-high-low" pattern, with a declining age from 50 to 65 years (Figure 2). Males presented a higher incidence rate than that of females across different ages in gastrointestinal cancers, except for cancers of stomach before age of 40 and colon and pancreas before age of 30.

Further analysis on the trends of age-specific incidence rate of the intestinal type and diffuse type of GCC and GNCC with available data from China and the United States is shown in Figure S1. In general, the intestinal and diffuse types were more equally distributed between sexes before age of 40 in GCC, but became to be more prevalent in males than females after 40 years. In GNCC, however, females presented a higher incidence rate than males for the diffuse type before age of 40.

Globally, we found significant higher sex ratios of EAC than those of ESCC across all age groups, and identified similar patterns of age-specific sex differences in many European countries (Austria, Belgium, Denmark, France, Germany, Ireland, Italy, Norway, Switzerland, the Netherlands and the United Kingdom), some North American countries (Canada and the United States), Oceanian countries (Australia and New Zealand) and a few Asian countries (Israel and Japan). However, higher sex ratios of ESCC than EAC were observed in Belarus, Republic of Korea and Ukraine, while comparable sex ratios between EAC and ESCC were observed in China, Philippines and Uruguay (Figure 3). For gastric

TABLE 2   Global patterns of age-specific incidence rate, male-to-female incidence rate ratios and 95% CIs for esophageal squamous cell carcinoma, esophageal adenocarcinoma, gastric cardia cancer and gastric noncardia cancer (2003-2012)

Cancer type	Age group	Incidence rate per 100 000 in males (95% CIs)	Incidence rate per 100 000 in females (95% CIs)	Male-to-female incidence rate ratios (95% CIs)
Esophageal squamous cell carcinoma (ESCC)	20-24	0.01 (0.01, 0.01)	0.01 (0.01, 0.01)	0.98 (0.57, 1.69)
	25-29	0.03 (0.02, 0.03)	0.02 (0.02, 0.03)	1.31 (0.93, 1.83)
	30-34	0.08 (0.07, 0.09)	0.06 (0.06, 0.07)	1.26 (1.04, 1.54)
	35-39	0.28 (0.26, 0.30)	0.14 (0.13, 0.16)	1.92 (1.70, 2.16)
	40-44	0.96 (0.92, 0.99)	0.37 (0.35, 0.39)	2.57 (2.40, 2.76)
	45-49	2.89 (2.82, 2.95)	0.80 (0.77, 0.83)	3.61 (3.44, 3.78)
	50-54	6.42 (6.32, 6.52)	1.74 (1.69, 1.79)	3.69 (3.57, 3.81)
	55-59	11.14 (11.00, 11.28)	2.94 (2.87, 3.01)	3.78 (3.68, 3.89)
	60-64	16.17 (15.99, 16.36)	4.24 (4.15, 4.34)	3.81 (3.72, 3.90)
	65-69	21.22 (20.98, 21.46)	5.86 (5.75, 5.98)	3.62 (3.54, 3.70)
	70-74	24.21 (23.93, 24.50)	7.60 (7.46, 7.75)	3.19 (3.12, 3.26)
	75-79	24.09 (23.77, 24.43)	9.06 (8.90, 9.24)	2.66 (2.60, 2.72)
	80-84	23.34 (22.93, 23.76)	10.90 (10.68, 11.12)	2.14 (2.09, 2.20)
	85+	21.53 (21.04, 22.03)	12.48 (12.24, 12.73)	1.72 (1.67, 1.78)
Esophageal adenocarcinoma (EAC)	20-24	0.02 (0.01, 0.02)	0.01 (0.00, 0.01)	2.92 (1.61, 5.31)
	25-29	0.06 (0.05, 0.07)	0.01 (0.01, 0.01)	6.23 (4.08, 9.51)
	30-34	0.14 (0.12, 0.15)	0.03 (0.02, 0.04)	4.66 (3.67, 5.92)
	35-39	0.38 (0.36, 0.40)	0.07 (0.06, 0.08)	5.66 (4.84, 6.60)
	40-44	1.04 (1.00, 1.07)	0.16 (0.15, 0.18)	6.44 (5.84, 7.10)
	45-49	2.40 (2.34, 2.45)	0.32 (0.30, 0.34)	7.41 (6.92, 7.94)
	50-54	5.00 (4.91, 5.09)	0.62 (0.59, 0.65)	8.05 (7.64, 8.47)
	55-59	8.89 (8.76, 9.01)	1.11 (1.07, 1.15)	8.00 (7.68, 8.34)
	60-64	13.77 (13.60, 13.95)	1.72 (1.66, 1.78)	8.03 (7.74, 8.32)
	65-69	17.68 (17.46, 17.90)	2.42 (2.34, 2.49)	7.31 (7.07, 7.56)
	70-74	21.79 (21.52, 22.06)	3.32 (3.23, 3.42)	6.56 (6.35, 6.76)
	75-79	26.73 (26.39, 27.08)	4.63 (4.51, 4.76)	5.77 (5.60, 5.94)
	80-84	32.86 (32.37, 33.35)	6.89 (6.71, 7.06)	4.77 (4.63, 4.91)
	85+	34.47 (33.85, 35.10)	8.84 (8.63, 9.05)	3.90 (3.79, 4.02)
Gastric cardia cancer (GCC)	20-24	0.04 (0.03, 0.05)	0.03 (0.02, 0.03)	1.49 (1.09, 2.02)
	25-29	0.08 (0.07, 0.09)	0.06 (0.05, 0.07)	1.32 (1.07, 1.62)
	30-34	0.23 (0.22, 0.25)	0.13 (0.11, 0.14)	1.85 (1.62, 2.12)
	35-39	0.52 (0.50, 0.55)	0.22 (0.20, 0.24)	2.41 (2.18, 2.66)
	40-44	1.11 (1.07, 1.15)	0.40 (0.38, 0.43)	2.76 (2.58, 2.96)
	45-49	2.28 (2.23, 2.34)	0.63 (0.60, 0.66)	3.62 (3.43, 3.82)
	50-54	4.16 (4.08, 4.24)	1.02 (0.98, 1.06)	4.08 (3.91, 4.26)
	55-59	7.25 (7.14, 7.37)	1.66 (1.60, 1.71)	4.38 (4.22, 4.53)
	60-64	10.96 (10.81, 11.12)	2.43 (2.36, 2.50)	4.51 (4.37, 4.65)
	65-69	15.70 (15.49, 15.91)	3.57 (3.48, 3.66)	4.40 (4.27, 4.53)
	70-74	20.28 (20.02, 20.55)	4.85 (4.74, 4.97)	4.18 (4.07, 4.30)
	75-79	23.79 (23.46, 24.12)	6.05 (5.91, 6.19)	3.93 (3.83, 4.04)
	80-84	25.21 (24.78, 25.65)	7.16 (6.98, 7.34)	3.52 (3.42, 3.63)
	85+	22.88 (22.38, 23.40)	6.98 (6.79, 7.17)	3.28 (3.17, 3.40)

(Continues)

TABLE 2 (Continued)

Cancer type	Age group	Incidence rate per 100 000 in males (95% CIs)	Incidence rate per 100 000 in females (95% CIs)	Male-to-female incidence rate ratios (95% CIs)
Gastric noncardia cancer (GNCC)	20-24	0.22 (0.20, 0.23)	0.30 (0.28, 0.32)	0.73 (0.65, 0.81)
	25-29	0.61 (0.58, 0.64)	0.86 (0.82, 0.90)	0.71 (0.67, 0.76)
	30-34	1.59 (1.54, 1.64)	2.03 (1.98, 2.09)	0.78 (0.75, 0.81)
	35-39	3.34 (3.27, 3.41)	3.38 (3.32, 3.46)	0.99 (0.96, 1.02)
	40-44	6.73 (6.63, 6.82)	5.28 (5.19, 5.37)	1.27 (1.25, 1.30)
	45-49	12.16 (12.03, 12.29)	7.49 (7.39, 7.60)	1.62 (1.59, 1.65)
	50-54	20.99 (20.81, 21.17)	10.28 (10.15, 10.40)	2.04 (2.01, 2.07)
	55-59	32.17 (31.93, 32.41)	13.80 (13.65, 13.96)	2.33 (2.30, 2.36)
	60-64	49.14 (48.81, 49.47)	19.93 (19.73, 20.13)	2.47 (2.44, 2.50)
	65-69	73.73 (73.28, 74.18)	31.04 (30.77, 31.32)	2.38 (2.35, 2.40)
	70-74	98.87 (98.28, 99.46)	43.87 (43.52, 44.22)	2.25 (2.23, 2.28)
	75-79	113.4 (112.7, 114.1)	53.56 (53.15, 53.99)	2.12 (2.10, 2.14)
	80-84	122.1 (121.1, 123.1)	60.86 (60.34, 61.38)	2.01 (1.98, 2.03)
	85+	119.7 (118.5, 120.9)	65.46 (64.89, 66.03)	1.83 (1.80, 1.85)
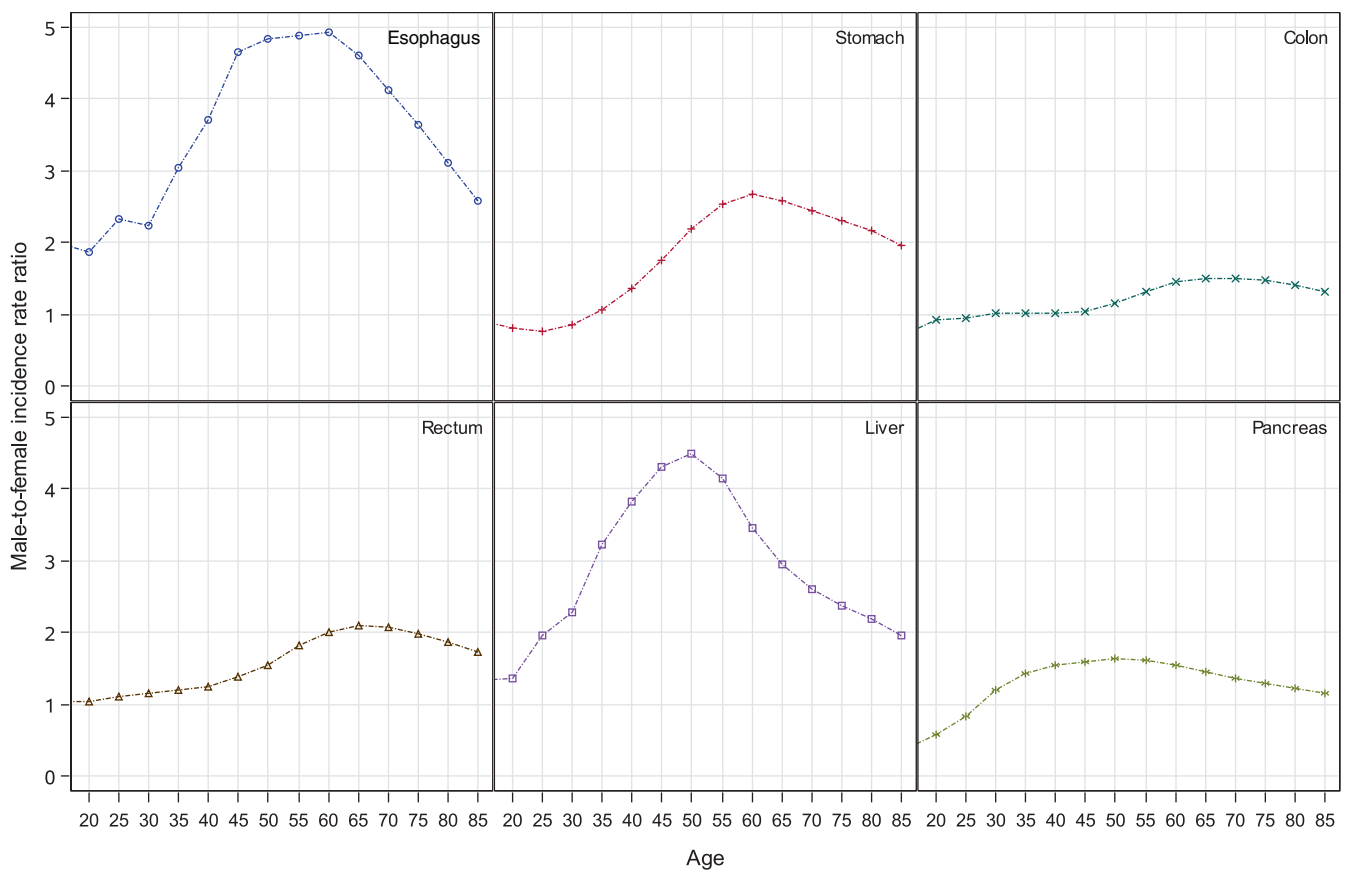
FIGURE 2 Global patterns of age-specific male-to-female incidence rate ratios of gastrointestinal cancers (2003-2012) [Color figure can be viewed at wileyonlinelibrary.com]

cancer, the sex ratios were significantly higher in GCC than that in GNCC across the world, and similar "low-high-low" trends of GCC were observed in many countries, including Australia, Austria, Belgium, Canada, Czech Republic, France, Germany, Italy, Japan, Latvia, Lithuania, Slovakia, the United Kingdom and the United States (Figure 4).
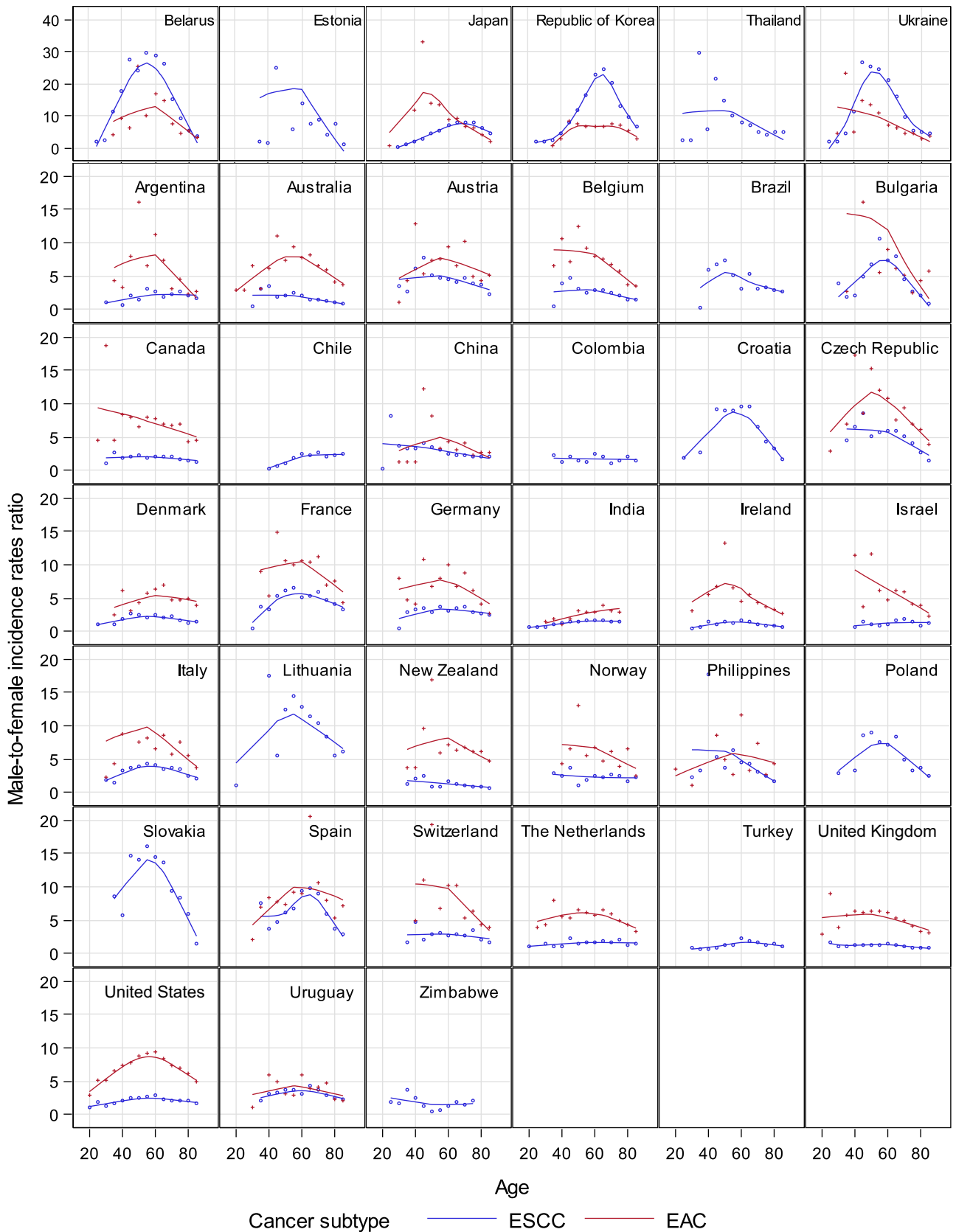
FIGURE 3 Trends of age-specific male-to-female incidence rates ratios of esophageal squamous cell carcinoma and esophageal adenocarcinoma in 39 selected countries (2003-2012). Countries that reported sex-specific incidence data of ESCC or EAC with more than ten 5-year age groups and with data of age groups younger than 45 were included in this analysis. EAC, esophageal adenocarcinoma; ESCC, esophageal squamous cell carcinoma
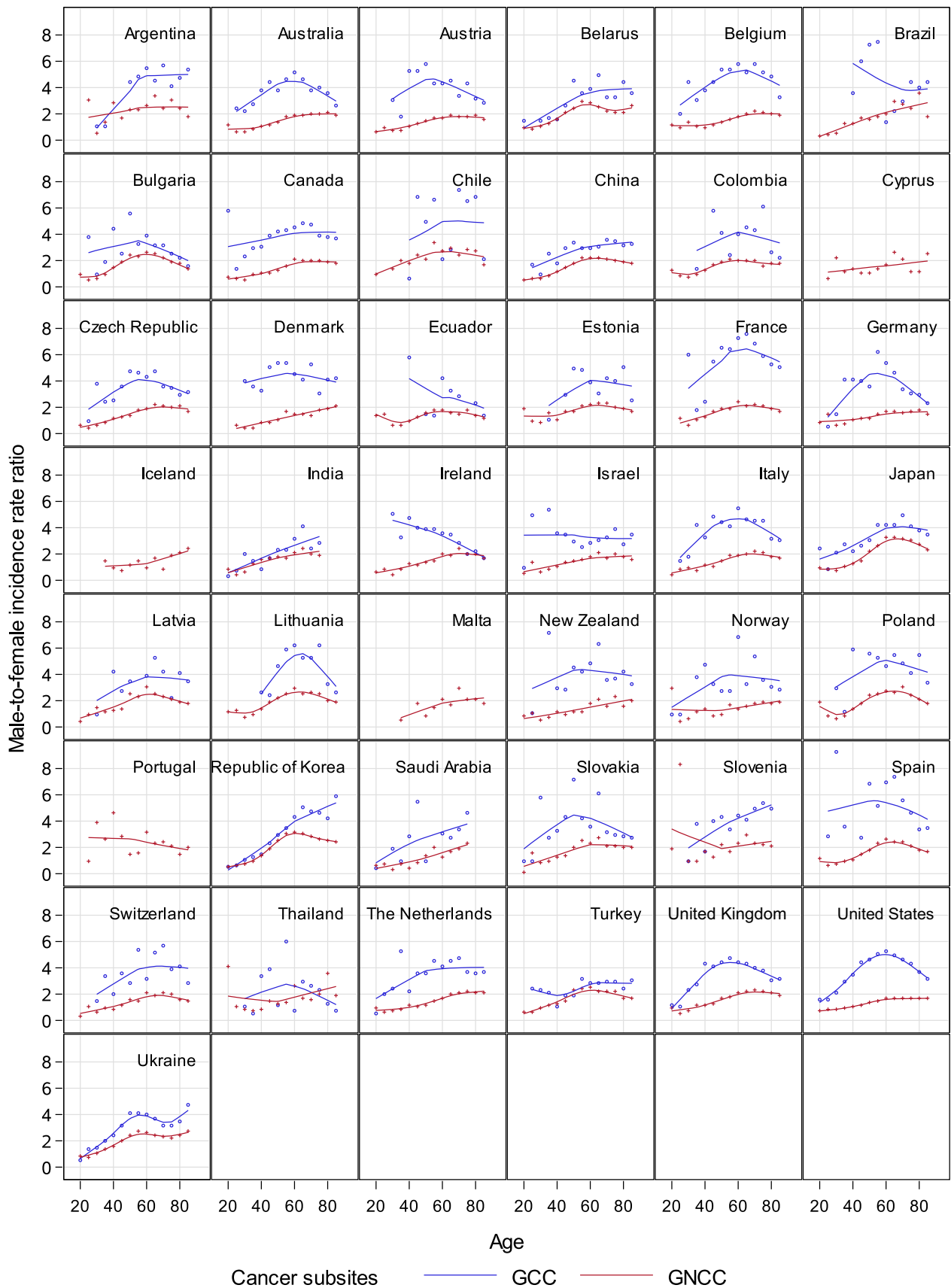
FIGURE 4 Trends of age-specific male-to-female incidence rates ratios of gastric cardia cancer and gastric noncardia cancer in 43 selected countries (2003-2012). Countries that reported sex-specific incidence data of GCC or GNCC with more than ten 5-year age groups and with data of age groups younger than 45 were included in this analysis. GCC, gastric cardia cancer; GNCC, gastric noncardia cancer

4 | DISCUSSION

A male predominance was observed worldwide in esophageal cancer and gastric cancer, with male-to-female ASIRs ratios of 6.7:1 for EAC, 3.3:1 for ESCC, 4:1 for GCC and 2.1:1 for GNCC. Notably, the sex differences varied by age. The male-to-female incidence rate ratios of four target cancer types consistently increased from young ages approaching peak ages around 60-64 years, though the EAC presented an additional peak age at 25-29 years. The consistent sharp decline of sex differences from the age of 65 across four cancer types suggest important underlying etiological mechanisms linked to age that warrant future investigation.

The observed male predominance appears age-dependent, and varies by country. Globally, we identified a "double-peak" pattern of age-specific male-to-female incidence rates ratios for EAC, with two peaks at age of 25-29 and 50-64 years. Other studies conducted in older people showed a single peak at 50-59 years in the United States,[10] but double peaks at age of 50-54 and 60-64 years in Sweden.[8] For ESCC, GCC and GNCC, we found a consistent "low-high-low" pattern of sex ratios with peak age at 60-64 years, which was consistent with previous findings from Sweden and the United States.[8] Notably, the male predominance was inversed in GNCC before age of 40 years. Available data from China and the United States indicated an attribution from a higher incidence of the diffuse type of GNCC in females than males at younger ages, which was in line with the results from the United Kingdom and Finland.[13,20]

Over past decades, we observed marked declines in the incidence of GNCC and ESCC,[21,22] slight decline trend of GCC,[23-25] but an upward trend of EAC[26] in both sexes. Similar patterns between the sexes indicated substantial transitions in major environmental risk factor profiles, including significant declines in smoking and heavy alcohol consumption for ESCC,[1,21,26] a decreased prevalence of *H. pylori* infection and improvements in the preservation and storage of foods for GNCC,[1,27] and an increased prevalence of obesity and gastroesophageal reflux disease paralleled with reduction of *H. pylori* infection for EAC and GCC.[1,17,21,26,28]

The changing prevalence of these aforementioned risk factors contributed to different changing patterns of EC and GC burden with a mix of birth cohort and period effects,[21] however, they cannot fully explain the observed male predominance which consistent across four cancer types and over time.[5,9,29] Some risk factors, including smoking and alcohol consumption, may partly contribute to the extremely high sex ratios of ESCC in some Baltic/European countries.[5,9,29] Other factors highly relevant to age, that is, endogenous hormones,[5,6,9,30] have been suspected considering the consistent "low-high-low" trends of age-specific sex ratio in different digestive cancers with peak ages at 50-64 years. A hypothesis was postulated that sex hormones, for example, estrogen, may act as a protective factor and delay the cancer onset in females at younger age but lead to a catch-up of cancer onset after menopause. This hypothesis is supported by the accruing evidences that later menopause, reproductive factors and estrogen hormone replacement therapies were associated with lower risks of EC and GC.[31-34] Furthermore, recent results from prospective studies

showed an inverse association between circulating estradiol levels and risks of EAC and GCC.[35] An alternative explanation could be that the carcinogenesis of EC and GC are partly driven by androgen, with sex differences diminishing at older ages because of the gradually decreasing levels of androgen. This is supported by studies reporting prostate cancer patients receiving antiandrogen therapies had lower rates of EC and GC,[36] and higher levels of circulating testosterone decreased the risk of EAC.[37] Given complex interactions between environmental exposures and endogenous hormones, sex differences in immune function and response may also play a role.[38,39] Future basic and experimental studies are required to help elucidate the underlying etiological mechanisms of the marked age-dependent sex differences.

There are a number of strengths associated with our study. We used 10 consecutive years of high-quality data from population-based cancer registries to ensure comparability and validity of cancer incidence of EC and GC from an international perspective. Secondly, we evaluated the age-specific sex differences with the male-to-female incidence rates ratios in concert with the absolute risk differences in incidence between sexes. The sex ratios are less likely to be affected by changes in diagnostic techniques, tumor definitions, misclassifications and coding practices. There were also several limitations. First, we used the best available data from CI5 which included cancer incidence data from high-quality population-based cancer registries, but nevertheless the data was limited by the extent to which histological and subsite information were available from each cancer registry and the results need to be interpreted with caution. Secondly, CI5 does not include information on histological subtypes of GC, thus we cannot discriminate the major subtypes such as diffuse and intestinal cancer across the world. Yet, we explored the country-specific histological analysis using available data from China and the United States. Thirdly, we assigned C16.8-16.9 as GNCC which may led to a slight underestimation of ASIRs of GCC.[17] However, the impact of possible misclassifications of overlapping or unspecified GC on the sex ratios are likely to be minor using the most recent 10-year data, equally affecting males and females, and this would not materially affect the overall patterns reported here.

In conclusion, we observed an age-dependent male predominance of esophageal cancer and gastric cancer internationally. The consistent changing patterns with age and a sharp decline after the age of 65 across all four cancer types implies important underlying pathological or etiological mechanisms, or common changes of environmental or endogenous risk factors with age. Hence, age-dependent risk factors warrant further investigations to aid our understanding of the mechanism behind the sex-specific differences of EC and GC observed today.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.