


BMJ Open Sex difference in incidence of gastric cancer: an international comparative study based on the Global Burden of Disease Study 2017

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ABSTRACT

Objectives To investigate sex difference in global gastric cancer incidence by year, age and socioeconomic status.

Design An international comparative study.

Setting We obtained the global and national sex-specific incidence of gastric cancer by year and age from the Global Burden of Disease Study 2017. The human development index (HDI) in 2017 as an indicator of national socioeconomic status was extracted from the Human Development Report.

Main outcome measures Sex-specific incidence of gastric cancer was compared by year and age at the global level. Linear regression analyses were performed to explore socioeconomic-associated sex difference in gastric cancer incidence.

Results Despite declining incidence of global gastric cancer in both sexes between 1990 and 2017, relative sex difference showed an increasing trend, with male to female ratios of age-standardised incidence rates (ASRs) rising from 1.86 to 2.20. Sex difference was almost negligible under 45 years of age and relative difference maximised in the age range of 65–69 years with male to female ratios of ASRs being 2.74. Both absolute sex difference (standardised $\beta=0.256$, $p<0.001$) and relative difference (standardised $\beta=0.387$, $p<0.001$) in ASRs were positively associated with HDI.

Conclusions This study revealed that decreasing incidence of global gastric cancer was accompanied by widening sex difference in the past few decades. Men always had higher incidence than women. Greater sex difference was found in older age and in more developed countries. These findings highlight the importance of making sex-sensitive health policy to cope with the global gastric cancer burden.

INTRODUCTION

Gastric cancer is a major contributor to the global cancer burden. According to the GLOBOCAN 2018 estimates, gastric cancer is the fifth most commonly diagnosed cancer (5.7% of the total cases) and the third leading cause of cancer death (8.2% of the total cancer deaths) after lung cancer, breast cancer, prostate cancer and colorectal cancer for incidence, and lung

Strengths and limitations of this study

- This study has investigated sex difference in incidence of gastric cancer at the global level, using the most reliable data from the Global Burden of Disease Study.
- Although this study provided a global view of sex difference in gastric cancer, the conclusions may not be applicable to a specific district.
- Because the Global Burden of Disease Study will update annually, sex difference in gastric cancer in the long term could be further explored.

cancer and colorectal cancer for mortality.¹ The GLOBOCAN 2018 had reported 1 033 701 new cases of gastric cancer (683 754 men and 349 947 women) and 782 685 gastric cancer related deaths (513 555 men and 269 130 women) worldwide in 2018, which suggested great sex difference in the global burden of gastric cancer.¹ About 60% of world total cases occurs in Eastern Asia, and the highest incidence rates are also in Eastern Asia (32.1 per 100 000 in men and 13.2 per 100 000 in women).¹ Most cases of gastric cancer are diagnosed in an advanced stage and the overall 5-year survival rate was below 30% in most countries, according to the latest CONCORD programme.² A recent study from USA revealed that men always had higher incidence of gastric cancer than women, regardless of race and ethnicity.³ Many other epidemiological studies also confirmed the male predominance in gastric cancer, such as those performed in Europe,⁴ Asia^{5 6} and Africa.^{7 8}

Most epidemiological studies were conducted in one region over a certain period and few studies had focused on the overview of sex difference in gastric cancer at the global level. Since the epidemiological patterns of cancer incidence would be important for health policy making to reduce the burden of cancer diseases, more efforts

should be made to explore the global patterns of sex difference in gastric cancer. Therefore, the purpose of this study was to compare multiple aspects of sex difference in incidence of gastric cancer by year, age and socio-economical status, using the reliable data from the most recent Global Burden of Disease Study 2017 (GBD 2017).

MATERIALS AND METHODS

Study design

This is an international, sex-comparative study.

Patient and public involvement

This study was based on an open-access database with no identifiable information on the patients. Patients or the public were not involved in the design, or conduct, or reporting, or dissemination of our research.

Incidence estimates of gastric cancer

Standardised analytical approaches for estimating incidence have been provided by the GBD 2017.^{9,10} The GBD used the GBD world population age standard to calculate age-standardised incidence rates (ASRs). For GBD 2017, the non-weighted mean of 2017 age-specific proportional distributions from the GBD 2017 population estimates for all national locations with a population greater than 5 million people in 2017 was used to generate an updated standard population age structure.¹¹ The following data regarding gastric cancer were extracted from the GBD Results Tool¹²: (1) global sex-specific ASRs (per 100 000 population) from 1990 to 2017; (2) global sex-specific and age-specific (above 15 years of age) incidence rates (per 100 000 population) in 2017; (3) national sex-specific ASRs for 195 countries and territories in 2017.

Human development index

The human development index (HDI), which was created by the United Nations Development Program, is an indicator of national socioeconomical status.¹³ It was determined by three components, namely health, educational attainment and income. The value of HDI ranges from 0 to 1, with higher values indicating higher levels of socioeconomical development. The HDIs for 185 countries and territories (which were also included in the GBD 2017) in 2017 were extracted from the 2018 Statistical Update of Human Development Reports.¹³

Statistical analyses

Absolute (man minus woman) and relative (male to female ratio) sex difference in ASRs, as well as risk ratios, were calculated by year and age. Sex-specific ASRs across 195 countries and territories were compared by Mann-Whitney U test.¹⁴ Linear regression analyses were conducted to explore the association of absolute and relative sex difference with HDI across 185 countries and territories. All statistical analyses were performed using SPSS V.23 (IBM). P values of <0.05 were considered statistically significant.

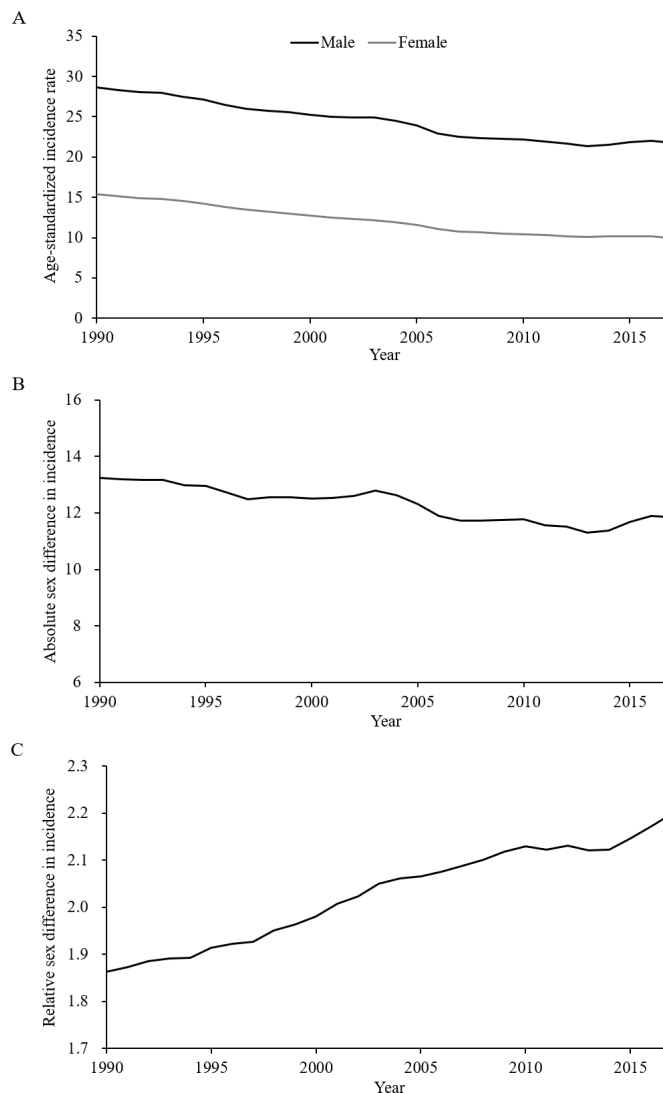


Figure 1 Sex comparisons of global age-standardised incidence rates (ASRs) of gastric cancer between 1990 and 2017. (A) Sex-specific ASRs; (B) absolute sex difference (man minus woman) in ASRs; (C) relative sex difference (male to female ratio) in ASRs.

RESULTS

Trends in sex difference in gastric cancer

As seen in figure 1, ASRs of global gastric cancer in both sexes showed a declining trend between 1990 and 2017, as well as absolute sex difference in ASRs. However, relative sex difference in ASRs kept increasing during the same period, with men having higher ASRs of gastric cancer than women. The global ASRs in men versus in women were 28.60 (95% CI: 27.83 to 29.34) versus 15.36 (14.90 to 16.10) in 1990, and 21.75 (21.01 to 22.59) versus 9.89 (9.58 to 10.20) in 2017. Despite absolute sex difference in ASRs decreased from 13.24 to 11.86, relative sex difference rose from 1.86 to 2.20 between 1990 and 2017. Men had significantly higher risk of gastric cancer than women between 1990 (risk ratio: 1.550 (1.543 to 1.557)) and 2017 (risk ratio: 1.883 (1.876 to 1.890)). The global and WHO regional incident cases and ASRs of gastric cancer for both sexes in 1990 and 2017 are shown in

Table 1 The global and WHO regional incident cases and age-standardised incidence rates of gastric cancer for both sexes in 1990 and 2017

| Year and region | 1990 | | | | 2017 | | | | |
|-------------------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|------|--------|-------------|
| | Male | Female | RR (95% CI) | Male | Female | RR (95% CI) | Male | Female | RR (95% CI) |
| Incident cases (95% CI) (thousands) | | | | | | | | | |
| Worldwide | 528.5 (513.5 to 543.0) | 335.9 (325.7 to 352.1) | 1.550 (1.543 to 1.557) | 799.3 (771.0 to 830.4) | 421.4 (408.1 to 434.4) | 1.883 (1.876 to 1.890) | | | |
| African Region | 12.6 (11.3 to 13.7) | 9.4 (8.5 to 10.5) | 1.367 (1.331 to 1.404) | 17.8 (16.4 to 19.2) | 12.5 (11.6 to 13.4) | 1.463 (1.430 to 1.497) | | | |
| Eastern Mediterranean Region | 11.1 (9.6 to 12.4) | 7.5 (6.5 to 8.8) | 1.388 (1.348 to 1.429) | 19.1 (17.7 to 20.6) | 12.9 (11.9 to 14.1) | 1.365 (1.334 to 1.395) | | | |
| European Region | 132.6 (130.0 to 135.1) | 95.4 (93.6 to 97.3) | 1.483 (1.471 to 1.495) | 117.4 (113.3 to 121.9) | 75.8 (72.5 to 79.3) | 1.642 (1.627 to 1.657) | | | |
| Region of the Americas | 45.0 (44.4 to 45.8) | 28.4 (28.0 to 28.8) | 1.638 (1.614 to 1.663) | 69.6 (67.6 to 71.7) | 43.6 (42.3 to 44.9) | 1.653 (1.633 to 1.672) | | | |
| South-east Asia Region | 46.0 (42.0 to 50.0) | 38.6 (34.6 to 44.1) | 1.127 (1.112 to 1.142) | 64.4 (60.5 to 68.3) | 57.7 (54.0 to 61.2) | 1.083 (1.071 to 1.095) | | | |
| Western Pacific Region | 275.3 (266.0 to 285.2) | 153.6 (147.2 to 163.0) | 1.715 (1.705 to 1.726) | 499.8 (473.9 to 527.8) | 213.9 (202.2 to 225.0) | 2.269 (2.258 to 2.281) | | | |
| ASRs per 100 000 (95% CI) | | | | | | | | | |
| Worldwide | 28.6 (27.8 to 29.3) | 15.4 (14.9 to 16.1) | | 21.7 (21.0 to 22.6) | 9.9 (9.6 to 10.2) | | | | |
| African Region | 11.6 (10.5 to 12.7) | 7.9 (7.2 to 8.8) | | 8.4 (7.8 to 9.1) | 5.1 (4.7 to 5.5) | | | | |
| Eastern Mediterranean Region | 11.6 (10.1 to 12.9) | 8.2 (7.3 to 9.5) | | 9.6 (8.9 to 10.3) | 6.3 (5.9 to 6.9) | | | | |
| European Region | 30.1 (29.5 to 30.6) | 14.5 (14.2 to 14.8) | | 17.5 (16.9 to 18.2) | 8.4 (8.0 to 8.7) | | | | |
| Region of the Americas | 16.4 (16.2 to 16.7) | 8.1 (7.9 to 8.2) | | 12.4 (12.0 to 12.8) | 6.4 (6.2 to 6.6) | | | | |
| South-east Asia Region | 12.5 (11.3 to 13.6) | 10.2 (9.1 to 11.7) | | 8.2 (7.7 to 8.7) | 6.7 (6.3 to 7.1) | | | | |
| Western Pacific Region | 50.1 (48.5 to 51.8) | 25.0 (24.0 to 26.6) | | 40.6 (38.6 to 42.8) | 15.8 (14.9 to 16.6) | | | | |

ASR, age-standardised incidence rate; RR, risk ratio.

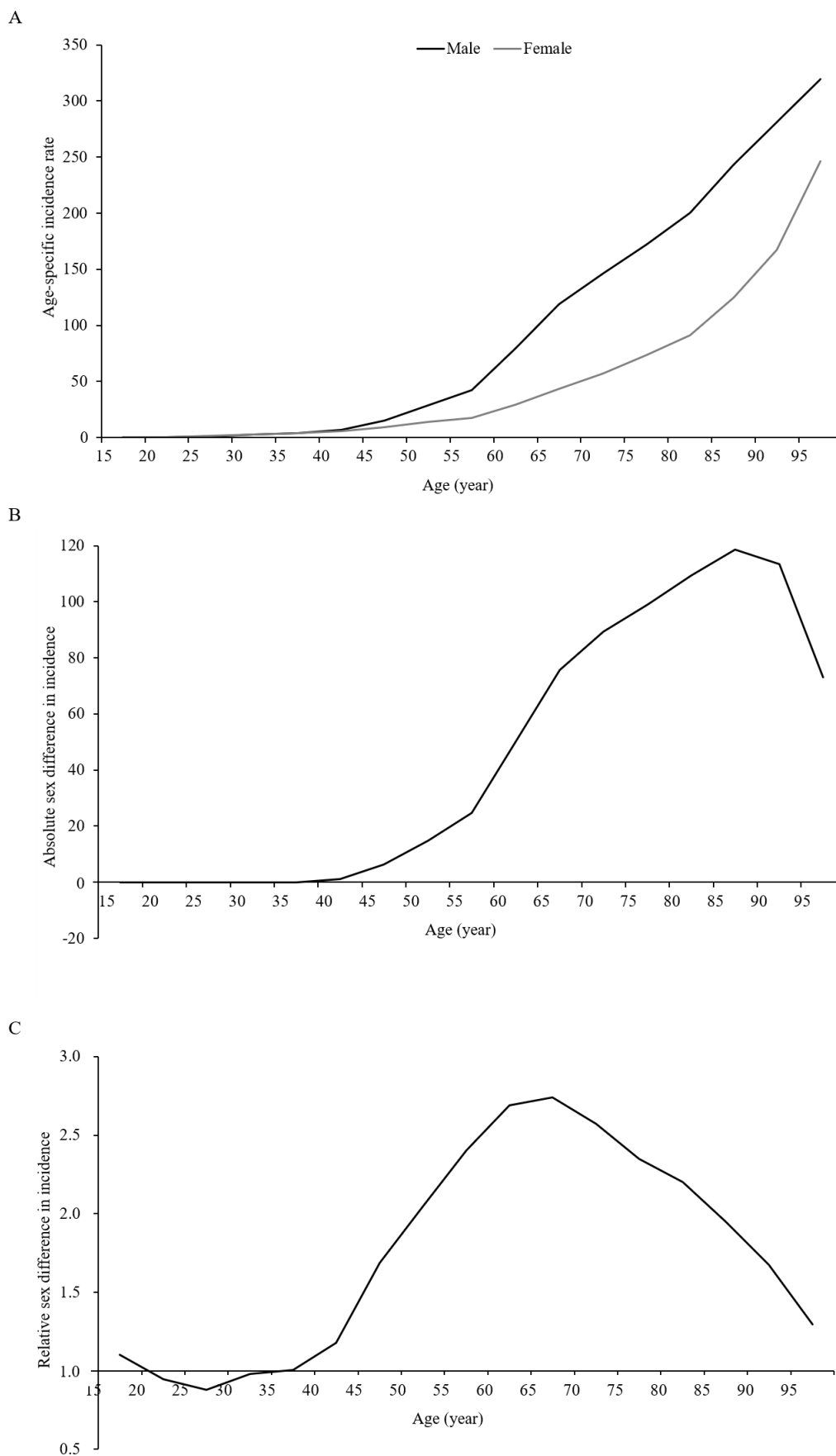


Figure 2 Sex comparisons of global age-specific incidence rates of gastric cancer in 2017. (A) Sex-specific and age-specific incidence rates; (B) absolute sex difference (man minus woman) in age-specific incidence rates; (C) relative sex difference (male to female ratio) in age-specific incidence rates.

Table 2 The global age-specific incident cases and incidence rates of gastric cancer for both sexes in 2017

| Age (years) | Incident cases No.×10 ³ (95% CI) | | Incidence rate per 100 000 No. (95% CI) | | Risk ratio (95% CI) |
|-------------|------------------------------------------------|------------------------|--------------------------------------------|------------------------|------------------------|
| | Male | Female | Male | Female | |
| All age | 799.3 (771.0 to 830.4) | 421.4 (408.1 to 434.4) | 20.8 (20.1 to 21.7) | 11.1 (10.7 to 11.4) | 1.883 (1.876 to 1.890) |
| 15–19 | 0.55 (0.50 to 0.60) | 0.47 (0.44 to 0.51) | 0.17 (0.16 to 0.19) | 0.16 (0.15 to 0.17) | 1.103 (0.975 to 1.248) |
| 20–24 | 1.4 (1.3 to 1.5) | 1.4 (1.3 to 1.6) | 0.46 (0.43 to 0.49) | 0.48 (0.45 to 0.52) | 0.945 (0.878 to 1.017) |
| 25–29 | 3.8 (3.6 to 4.0) | 4.2 (4.0 to 4.5) | 1.22 (1.16 to 1.29) | 1.38 (1.31 to 1.46) | 0.880 (0.843 to 0.920) |
| 30–34 | 7.6 (7.2 to 8.0) | 7.7 (7.3 to 8.0) | 2.6 (2.5 to 2.7) | 2.6 (2.5 to 2.8) | 0.979 (0.948 to 1.011) |
| 35–39 | 10.2 (9.8 to 10.7) | 10.0 (9.6 to 10.6) | 3.9 (3.7 to 4.1) | 3.9 (3.7 to 4.1) | 1.006 (0.978 to 1.034) |
| 40–44 | 17.5 (16.7 to 18.5) | 14.6 (13.9 to 15.4) | 7.0 (6.7 to 7.4) | 6.0 (5.7 to 6.3) | 1.180 (1.154 to 1.206) |
| 45–49 | 36.1 (33.9 to 38.3) | 21.1 (20.1 to 22.1) | 15.2 (14.3 to 16.2) | 9.0 (8.6 to 9.5) | 1.689 (1.661 to 1.718) |
| 50–54 | 61.0 (57.4 to 65.3) | 30.1 (28.5 to 31.6) | 28.9 (27.2 to 30.9) | 14.1 (13.4 to 14.9) | 2.047 (2.019 to 2.076) |
| 55–59 | 72.2 (68.6 to 75.6) | 30.9 (29.7 to 32.2) | 42.2 (40.1 to 44.2) | 17.6 (16.9 to 18.3) | 2.404 (2.373 to 2.437) |
| 60–64 | 118.4 (111.7 to 125.8) | 46.4 (44.0 to 48.7) | 79.5 (74.9 to 84.4) | 29.5 (28.0 to 31.0) | 2.691 (2.662 to 2.720) |
| 65–69 | 137.2 (129.4 to 146.4) | 54.5 (51.7 to 57.3) | 119.0 (112.3 to 127.0) | 43.4 (41.2 to 45.7) | 2.745 (2.717 to 2.772) |
| 70–74 | 115.5 (109.2 to 122.4) | 50.6 (48.0 to 53.3) | 146.2 (138.2 to 155.0) | 56.8 (54.0 to 59.8) | 2.576 (2.549 to 2.603) |
| 75–79 | 95.2 (90.7 to 99.8) | 50.2 (47.9 to 52.7) | 172.3 (164.2 to 180.6) | 73.3 (70.0 to 77.0) | 2.351 (2.326 to 2.377) |
| 80–84 | 67.0 (64.3 to 70.1) | 42.6 (41.0 to 44.5) | 200.3 (192.1 to 209.5) | 91.0 (87.5 to 95.0) | 2.204 (2.177 to 2.230) |
| 85–89 | 38.3 (36.8 to 40.0) | 32.4 (31.1 to 33.7) | 243.5 (233.9 to 253.6) | 124.9 (120.0 to 129.8) | 1.952 (1.923 to 1.981) |
| 90–94 | 14.0 (13.4 to 14.6) | 17.5 (16.7 to 18.2) | 281.0 (269.6 to 293.0) | 167.6 (159.9 to 174.5) | 1.679 (1.642 to 1.716) |
| 95+ | 3.3 (3.1 to 3.4) | 6.8 (6.4 to 7.1) | 319.2 (305.8 to 332.5) | 246.2 (232.2 to 257.3) | 1.297 (1.244 to 1.353) |

table 1, which indicated the greatest sex difference in the Western Pacific Region.

Sex difference in gastric cancer by age

In 2017, global incidence rates of gastric cancer increased with age in both sexes (figure 2). In the age range of 15–39 years, men had similar rates with women, except the age range of 25–29 years in which men had significantly lower risk than women with risk ratio being 0.880 (0.843 to 0.920). Though both sexes had the highest incidence rates above 95 years of age, the greatest absolute difference was observed in the age range of 85–89 years being 118.61, and the greatest relative difference in the age range of 65–69 years with male to female ratio being 2.74 and risk ratio being 2.745 (2.717 to 2.772). The global age-specific incident cases and incidence rates of gastric cancer for both sexes in 2017 are shown in table 2.

Sex difference in gastric cancer by national socioeconomic status

For 195 countries and territories included in the GBD 2017, Mann-Whitney U test revealed that men had significant higher ASRs ($Z=-10.576$, $p<0.001$) of gastric cancer than women in 2017, with median (IQR) of ASRs in men versus in women being 12.62 (8.43 to 17.42) versus 6.24 (4.76 to 8.97). Linear regression analyses across 185 countries and territories indicated that (figure 3), both absolute sex difference (standardised $\beta=0.256$, $p<0.001$) and relative sex difference (standardised $\beta=0.387$, $p<0.001$) in ASRs, were positively associated with HDI, implying

greater sex difference in countries with higher levels of socioeconomic status.

DISCUSSION

This study focused on the sex difference in gastric cancer from a global perspective. The findings indicated that men always had higher gastric cancer incidence than women between 1990 and 2017. Despite declining incidence in both sexes, relative sex difference showed an increasing trend over the past few decades. Worldwide, sex difference was almost negligible under the age of 44 years and then increased gradually, reaching a peak at the age range of 65–69 years with a male to female ratio of 2.74. Last but not least, countries with higher levels of socioeconomic status were found to have greater sex difference in gastric cancer incidence.

Both environmental and genetic risk factors would contribute to the patterns of sex difference in gastric cancer. *Helicobacter pylori* infection has been proven as the most detrimental risk factor of gastric cancer.¹⁵ The male predominance of *H. pylori* infection would lead to an increased risk of gastric cancer.¹⁶ Smoking is also an important but relatively weaker risk factor for gastric cancer, comparing with *H. pylori* infection.^{17 18} The role of alcohol in gastric cancer depends on the level of alcohol intake. More recently a consensus has been reached that moderate alcohol intake may be not associated with gastric cancer, but heavy alcohol intake does increase the risk of gastric cancer.¹⁹ Therefore, more consumption

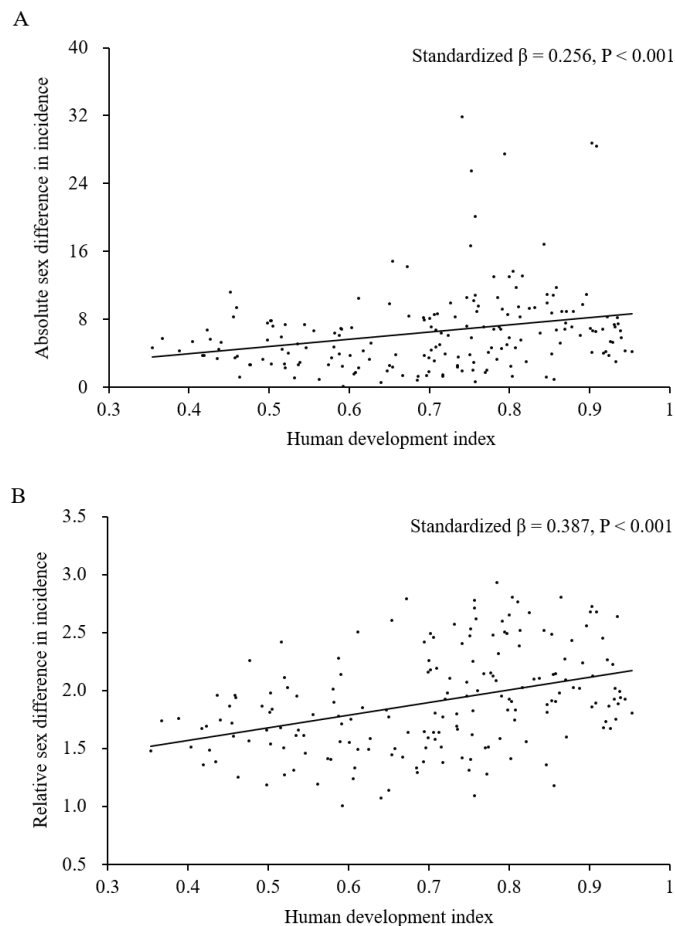


Figure 3 (A) Absolute sex difference (man minus woman) in age-standardised incidence rates (ASRs) and (B) relative sex difference (male to female ratio) in ASRs were positively related to the level of national socioeconomic status. Note: the lines represent the linear fits.

of tobacco and alcohol in men could result in a higher risk of gastric cancer. A meta-analysis had supported the hypothesis that longer exposure to oestrogen effects of either ovarian or exogenous origin may decrease risk of gastric cancer.²⁰ The underlying reasons is not yet clear but various mechanisms have been suggested. There is evidence that oestrogen may lead to increased expression of trefoil factor proteins, which protect mucous epithelia or inhibit oncogene expression.²¹

Gastric cancer incidence in both sexes had shown a continuing decline over the past decades. The decreasing incidence is strongly related to decreasing prevalence of *H. pylori* and increasing use of refrigeration resulting in less exposure to dietary carcinogens like salted and stale food.²² Previous study revealed that men had greater perceived risk for developing cancers.²³ Since risk perceptions for cancer were associated with worry about cancer,²⁴ men may seek healthcare more frequently and benefit more from the progress in gastric cancer screening. Screening of high-risk populations rather than mass population screening might be more cost effective in many countries, which makes screening more relevant for men.²⁵ In addition, prolonged exposure to perceived

stress at work was associated with greater risk of gastric cancer.²⁶ In modern society, which is characterised by a rapid pace of life, high demands and competitiveness, men are more likely to use alcohol and women more likely to use direct action when coping with work stress.²⁷ The interaction of a stressful work environment and the individual's responses to it may be related to an increased risk of gastric cancer among men.

Studies have shown that gastric cancer is a consequence of the accumulation of multiple epigenetic and genetic alterations.²⁸ Thus, it is natural that the incidence rates of gastric cancer increased with age in both sexes. The increasing sex difference under the age of 70 years could be attributed to differences in exposures to environmental carcinogens such as tobacco and alcohol consumption,^{18 19} as well as biological differences such as sex hormones and the metabolic system.^{28 29} Interestingly, sex difference in incidence rates decreased above the age of 70 years. Spouses tend to share lifestyle factors like dietary intake and living environment over many years especially in old ages in which there is a high risk of cancer. A study of the importance of family factors in cancer had shown a significant familial risk for almost all types of cancer including gastric cancer.³⁰ Besides, decreased levels of sex hormones in old women may weaken protection against gastric cancer, which could also reduce sex difference in the elderly. It is noteworthy that women had higher incidence than men in younger population. Evidence had shown rising incidence of gastric cancer in younger adults in recent decades, while more common autoimmune gastritis of which gastric cancers are important long-term complications and more antibiotics use which disrupts indigenous constituents of digestive tract microbiota in women would help explain the findings.^{31 32}

Countries with higher levels of socioeconomic status were found to have greater sex difference in gastric cancer incidence. There are several likely explanations for this phenomenon. The longer life expectancy was observed among the rich, the more educated and those in the labour force.³³ Since sex difference in gastric cancer increases with age, socioeconomic advantage on longevity in developed countries would lead to greater sex difference. There is evidence that overweight and obesity are related to an increased risk of gastric cancer.³⁴ Socioeconomic status has more impact on males' body mass index (BMI) changes than females', with faster BMI growth rates in men of high-socioeconomic status.³⁵ The lower quality and less affordability of medical care in developing countries might contribute to less difference in gastric cancer screening among men and women.

This study was subject to the limitations of the GBD 2017, such as statistical assumption and data sources, as detailed in the GBD 2017 reports.^{9 10} Due to geographical variations in incidence estimates, bias might come from the use of aggregate data at the country level instead of district data. Though this study provided a global view of sex difference in gastric cancer incidence, the conclusions may not be applicable to a specific district. As annual updates of GBD

data are available, sex differences in gastric cancer during the long term could be further explored.

In summary, this study demonstrated that although global incidence of gastric cancer is decreasing, sex difference showed an increasing trend in the past few decades. Men, especially those who are older and live in more developed countries, have higher incidence of gastric cancer than women. Equal provision of cancer care is not enough to correct sex difference, but more attention should be paid to male disadvantage in gastric cancer. These findings call for sex-sensitive health policy to cope with the global gastric cancer burden.

Contributors LLo, LW and JC were responsible for study design and LLo, LW, YZ and GC for data collection. LLo, LW, LLI, XJ and YH analysed the data. LLo, LW and JC drafted the paper. All authors read, commented on and approved the final manuscript.

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Competing interests None declared.

Patient consent for publication Not required.

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Data availability statement Data are publicly available from the Global Burden of Disease Study (<http://ghdx.healthdata.org/gbd-results-tool>) and Human Development Reports (<http://hdr.undp.org/en/2018-update>).

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