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EDITORIAL

- 5625** Serrated lesions: A challenging enemy
Trovato A, Turshudzhyan A, Tadros M

REVIEW

- 5630** Liver disorders in COVID-19, nutritional approaches and the use of phytochemicals
Vargas-Mendoza N, García-Machorro J, Angeles-Valencia M, Martínez-Archundia M, Madrigal-Santillán EO, Morales-González Á, Anguiano-Robledo L, Morales-González JA
- 5666** Recent advances in blood-based and artificial intelligence-enhanced approaches for gastrointestinal cancer diagnosis
Li LS, Guo XY, Sun K
- 5682** Liver disease and COVID-19: The link with oxidative stress, antioxidants and nutrition
Ristic-Medic D, Petrovic S, Arsic A, Vucic V

MINIREVIEWS

- 5700** Updates in diagnosis and management of pancreatic cysts
Lee LS
- 5715** Artificial intelligence for hepatitis evaluation
Liu W, Liu X, Peng M, Chen GQ, Liu PH, Cui XW, Jiang F, Dietrich CF
- 5727** Machine perfusion of the liver: Putting the puzzle pieces together
Boteon YL, Martins PN, Muiesan P, Schlegel A

ORIGINAL ARTICLE

Retrospective Cohort Study

- 5737** MTNR1B polymorphisms with CDKN2A and MGMT methylation status are associated with poor prognosis of colorectal cancer in Taiwan
Lee CC, Kuo YC, Hu JM, Chang PK, Sun CA, Yang T, Li CW, Chen CY, Lin FH, Hsu CH, Chou YC

Retrospective Study

- 5753** Validation of conventional non-invasive fibrosis scoring systems in patients with metabolic associated fatty liver disease
Wu YL, Kumar R, Wang MF, Singh M, Huang JF, Zhu YY, Lin S

Observational Study

- 5764** Secular decreasing trends in gastric cancer incidence in Taiwan: A population-based cancer registry study
Lin YT, Chiang CJ, Yang YW, Huang SP, You SL

META-ANALYSIS

- 5775** Dietary intake in patients with chronic pancreatitis: A systematic review and meta-analysis
Ul Ain Q, Bashir Y, Kelleher L, Bourne DM, Egan SM, McMahon J, Keaskin L, Griffin OM, Conlon KC, Duggan SN

LETTER TO THE EDITOR

- 5793** Relationship between nonalcoholic fatty liver disease and chronic kidney disease could start in childhood
Di Sessa A, Guarino S, Melone R, De Simone RF, Marzuillo P, Miraglia del Giudice E

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Observational Study

Secular decreasing trends in gastric cancer incidence in Taiwan: A population-based cancer registry study

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Abstract

BACKGROUND

Gastric cancer remains a leading cause of cancer death worldwide. In Taiwan, gastric cancer is the sixth leading cause of cancer mortality in both males and females.

AIM

To evaluate secular trends in gastric cancer incidence according to age, sex, and *Helicobacter pylori* (*H. pylori*) treatment in Taiwan.

METHODS

In this population-based study, we used the national Taiwan Cancer Registry database. Annual percent changes in incidence rates were used to describe secular trends in incidence rates and sex ratios of gastric cancer in Taiwan. Pearson's product-moment correlation coefficients were used to analyze the correlation between annual age-adjusted incidence rates and the annual number of patients treated with antibiotic therapy for *H. pylori* infection.

RESULTS

The annual percent changes showed continuously decreasing rates of gastric

additional data are available.

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cancer among both males and females. However, the decreasing trends differed by sex, with an annual percent change of -2.58% in males and -2.14% in females. The age-specific incidence rates increased with age. Within the same age group, more recent time periods showed lower incidence rates than greater time periods. Similarly, the sex ratio was lower in later birth cohorts than in earlier birth cohorts. Age-adjusted incidence rates substantially decreased with increasing numbers of patients being treated with antibiotic therapy for *H. pylori* infection during 2005 to 2016 ($r = 0.72$).

CONCLUSION

We observed steadily decreasing trends with differential sex ratios in the incidence of gastric cancer in Taiwan. These results support *H. pylori* eradication programs in Taiwan.

Key Words: Gastric cancer; Population-based study; Taiwan Cancer Registry; Sex difference; *Helicobacter pylori*; *Helicobacter pylori* eradication

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Core Tip: Gastric cancer remains a leading cause of cancer death worldwide. In this population-based study, we used the national Taiwan Cancer Registry database to evaluate secular trends in gastric cancer incidence in Taiwan. Annual percent changes showed continuously decreasing rates of gastric cancer among both males and females, with an annual percent change of -2.58% in males and -2.14% in females. Age-specific incidence rates increased with age. Within the same age group, the sex ratio was lower in later birth cohorts than in earlier birth cohorts. Age-adjusted incidence rates substantially decreased with the increase in patients newly treated with anti-*Helicobacter pylori* treatment.

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INTRODUCTION

Gastric cancer is one of the leading causes of cancer death worldwide. Data from GLOBOCAN 2020 shows an age-standardized incidence rate of gastric cancer of 15.8 per 100000 persons for males and 7.0 per 100000 persons for females, with a mortality rate of 11.0 per 100000 persons in males and 4.9 per 100000 persons in females[1]. In Taiwan, gastric cancer was the sixth leading cause of cancer death for both males and females in 2018[2].

Gastric cancer is a multifactorial disease; its risk factors include alcohol drinking, tobacco smoking, gastric ulcer, and atrophic gastritis, whereas the intake of fresh fruits and vegetables is probably protective[3]. A previous study demonstrated that anti-*Helicobacter pylori* (*H. pylori*) treatment has the potential to decrease the risk of gastric cancer[4]. Moreover, a study by Chiang *et al*[5] showed that the effectiveness of *H. pylori* eradication in reducing gastric cancer incidence and mortality was 53% [95% confidence interval (CI): 30% to 69%, $P < 0.001$] and 25% (95%CI: -14% to 51%, $P = 0.18$), respectively. This study aimed to investigate secular trends in the incidence of gastric cancer and its association with *H. pylori* eradication programs in Taiwan.

MATERIALS AND METHODS

Data sources

We obtained data on gastric cancer incidence from 1979 to 2016 from the national

population-based Taiwan Cancer Registry (TCR) database. The TCR database has been collecting data on newly diagnosed cancer cases since 1979. The TCR's accuracy was such that the percentage of death certificate only cases was 0.91%, and the proportion of morphologically verified cases reached 92.23%[6]. In addition, the completeness of the TCR database was reported to be 98.44% in 2016[6]. All cases of primary gastric cancer in this analysis were classified based on the International Classification of Diseases for Oncology, third edition (codes C16.0–C16.9)[7]. We identified subjects who received anti-*H. pylori* treatment from 2005 to 2016, based on Anatomical Therapeutic Chemical Classification codes from Taiwan's National Health Insurance Research Database, which included treatment with clarithromycin, amoxicillin, metronidazole, and tetracycline[8].

Statistical analysis

Age-specific and age-adjusted incidence rates per 100000 person-years were calculated according to the 2000 World Health Organization standard population[9]. The incidence data were divided into ten 5-year age groups (25–29, 30–34, 35–39, 40–44, 45–49, 50–54, 55–59, 60–64, 65–69, and 70–74) and seven 5-year time periods. Birth cohorts were divided into five 10-year age groups (25–34, 35–44, 45–54, 55–64, and 65–74). We calculated age-adjusted incidence rates for the period from 1979 to 2016 and age-specific incidence rates for the period from 1981 to 2015, for birth cohorts representing the years 1906 to 2005.

To describe linear trends by time period, we computed the annual percent change (APC) in incidence rate and tested whether the corresponding changes in rates were significant. We also used the Pearson's product-moment correlation coefficient to analyze the correlation between the annual age-adjusted incidence rate and the annual number of patients treated with antibiotic therapy for *H. pylori* infection. The research protocol was approved by the Institutional Review Board of Fu-Jen Catholic University (C107034).

RESULTS

Age-adjusted incidence rates

The age-adjusted incidence rates of gastric cancer show that rates for males were volatile between the years of 1981 to 2002 but steadily decreased from 2002 to 2016, with an average APC (AAPC) of -2.58% (Figure 1). However, the incidence rates for females slightly increased between the years of 1979 to 1997 and then gradually decreased from 1997 to 2016, with an AAPC of -2.14% (Figure 1).

Age-specific incidence rates

Looking at age-specific incidence rates by sex for the years of 1981 to 2015, we found that age-specific incidence rates of gastric cancer increased with age, with the highest incidence rate occurring among the oldest age group across all time periods (Figure 2). Among the same age group, more recent time periods showed lower incidence rates than earlier time periods. For example, among males aged 60–64 years, the incidence rate per 100000 persons during 2011–2015 was 44.42, which was lower than the incidence rate for 1996–2000, which had an incidence rate of 62.41. Moreover, among the same age group, the decreasing trend in age-specific incidence was more evident in males than in females (Figure 2).

The age-specific incidence rates by birth cohort for both males and females are shown in Figure 3. In both males and females, older birth cohorts had higher incidence rates than younger birth cohorts within the same age group. Moreover, among the same birth cohort, incidence rates increased more significantly by age in males than in females (Figure 3).

Sex ratios of age-adjusted incidence rates

We also found that the sex ratios of age-adjusted incidence rates decreased from 1981 to 2016 (Figure 4A). Males had higher age-adjusted incidence rates than females, with sex ratios ranging from 2.5 in 1979 to 1.9 in 2016, with an AAPC of -0.67% during the study period. During time periods prior to 1990, age-specific sex ratios were higher in older age groups, whereas the sex ratios were more consistent during time periods after 1996 (Figure 4B). Sex ratios of age-specific incidence rates by birth cohort showed that among the same age group, sex ratios were higher in earlier birth cohorts than in later birth cohorts. Whereas the sex ratios were close to 1 in the 35–44 age group, the

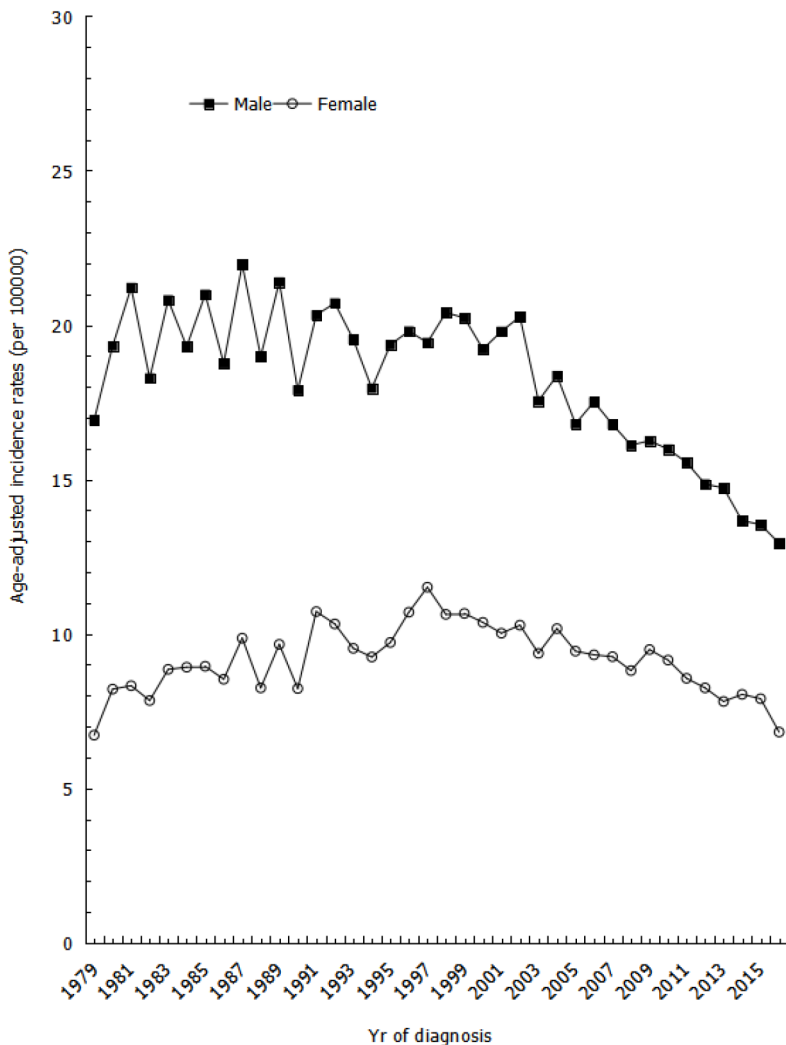


Figure 1 Secular trends in age-adjusted incidence rates of gastric cancer in Taiwan. 1979–2016, showing steadily decreasing rates in males from 2002 to 2016, with an Average Annual Percent Change (AAPC) of -2.58%, and gradually decreasing rates in females from 1997 to 2016, with an AAPC of -2.14%.

sex ratios were all less than 1 in the 25–34 age group (Figure 4C).

Association with *H. pylori* treatment

Furthermore, we also investigated the association between gastric cancer incidence and *H. pylori* treatment (Figure 5). During 2005 to 2016, the age-adjusted incidence rates decreased substantially along with increasing numbers of patients newly treated with antibiotic therapy for *H. pylori* infection ($r = 0.72$).

DISCUSSION

This population-based study found an overall secular trend of declining gastric cancer incidence in Taiwan from 1979 to 2016. Age-adjusted incidence rates decreased after 2002, with a statistically significant trend in both males and females; although, our results were slightly lower than estimates from other East Asian countries in terms of proportion changes. For example, one study from Japan found a decreasing trend with an AAPC of -1.4%, while another study from China found an AAPC of -3.7% [10]. Meanwhile, Taiwan showed an AAPC in incidence rate of -1.62% from 1996 to 2013 [11]. The downward trend in incidence was greater in males during earlier years, but this difference has since diminished in recent years. Furthermore, the downward trend observed from 2002 to 2016 was higher in males than in females, with an AAPC of -2.59% in males and -2.40% in females. Our proportion changes were slightly lower than estimates from other Asian countries, as shown in a study by Bertuccio *et al* [12]. One possible reason for the discrepancy may be that our study period began in the 1980s, after the incidence of gastric cancer had already been steadily declining for

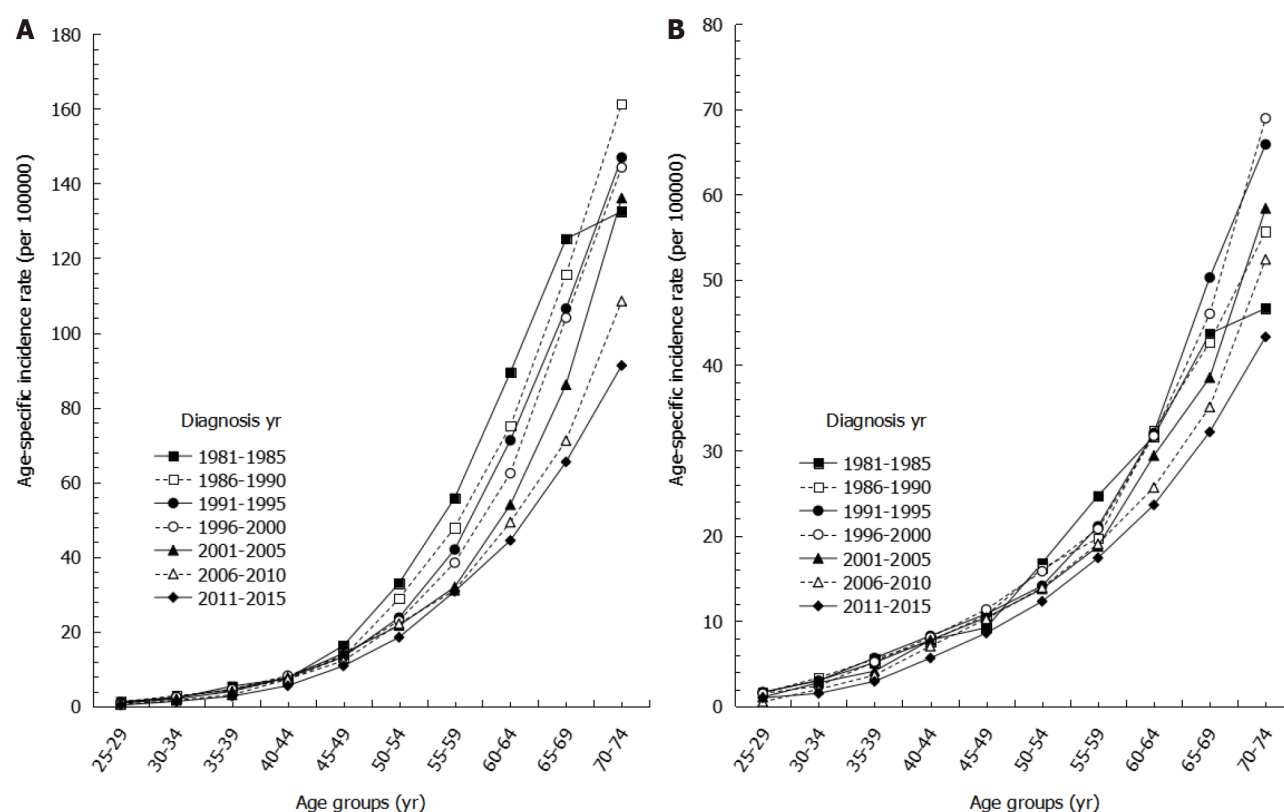


Figure 2 Age-specific incidence rates of gastric cancer in Taiwan by time period during 1981-2015. A: Among males; B: Females, showing lower incidence rates in more recent time periods than in earlier time periods. The decreasing trend was more evident in males than in females.

several decades.

As the development of gastric cancer is a multistage process arising from different risk factors, the decline in incidence rates in Taiwan may be attributable to the following reasons. First, the Taiwanese government launched an *H. pylori* eradication program in 1997[13]. Although anti-*H. pylori* treatments started in 1997, the number of patients treated with antibiotic therapy was unstable during the first decade. Therefore, we show results ranging from 2005 to 2016, which show a strong association between the number of patients treated with *H. pylori* treatment and age-adjusted incidence rates ($r = 0.72$) (Figure 5).

Several clinical studies have demonstrated the prophylactic role of *H. pylori* eradication in the prevention of gastric cancer. For instance, in a Swedish study[14] of 39154 patients undergoing hip replacement, prophylactic antibiotic treatment conferred a reduction in gastric cancer risk after 5 years (odds ratio: 0.6; 95%CI: 0.3 to 1.2). In addition, another Japanese study reported that *H. pylori* eradication inhibited the development of gastric cancer after endoscopic resection during a follow-up period of 3 years[15]. Ever since the government approved *H. pylori* eradication, there has been a decreasing trend in peptic ulcers in Taiwan[13,16]. The mass eradication of *H. pylori* infection was launched in 2004 among a high-risk Taiwanese population with prevalent *H. pylori* infection that were living on the Matsu Islands, and continued until 2018. As a result of this effort, the prevalence rates of *H. pylori* decreased from 64.2% to 15.0%, with reinfection rates of less than 1% per person-year[5]. In one Taiwanese study of 80255 peptic ulcer patients, early *H. pylori* eradication conferred a reduction in early gastric cancer risk (hazard ratio: 0.77)[17]. In addition, this study also showed that early *H. pylori* eradication reduced the standardized incidence ratio of gastric cancer from 1.60 to 1.05 (95%CI: 0.96 to 1.14). Together with results from these studies, our findings provide supportive evidence that the eradication of *H. pylori* infection may be associated with a substantial reduction in gastric cancer incidence.

Second, dietary and lifestyle habits in Taiwan have improved in the past few decades. Earlier studies showed that the consumption of foods containing nitrosamine [18] and cigarette smoking[19] were risk factors for gastric cancer. However, the increased use of refrigerators as a method of food preservation led to a decreased consumption of preserved foods containing nitrosamine and provided the constant availability of fresh food[20]. In Taiwan, a national public survey claimed that the

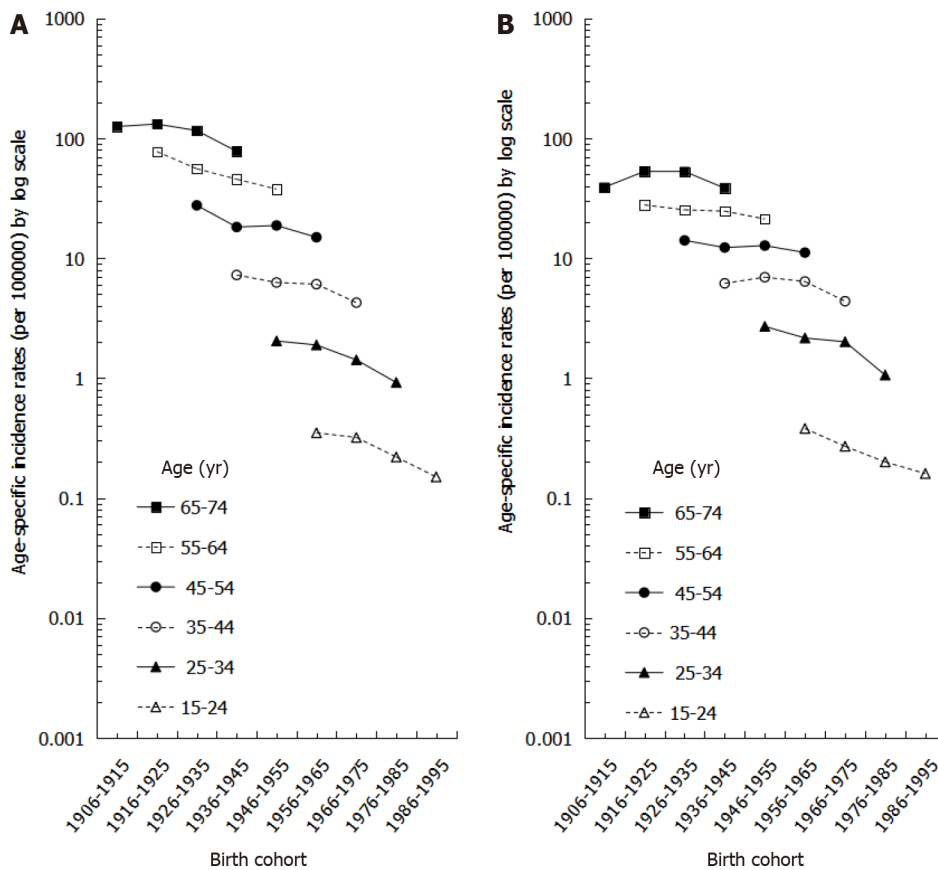


Figure 3 Age-specific incidence rates of gastric cancer in Taiwan by birth cohort during 1906-2005. A: Among males; B: Females, showing higher incidence rates in older birth cohorts than in younger birth cohorts within the same age group. Within the same birth cohort, incidence rates increased by age more evidently in males than in females.

popularization rate of refrigerators was approximately 99.14% in 1991 compared to a popularization rate of only 74.19% in 1976, with 3.6% of families even owning two refrigerators[21]. In regard to cigarette smoking, the Tobacco Hazards Prevention Act was implemented in January 2009, and the prevalence of smoking in adults over 40 years of age dropped from 12.25% in 2001 to 8.18% in 2013[22].

Our age-adjusted incidence rates were slightly lower than estimates from other East Asian countries in terms of proportion change. The reason may be that there has been no evident decline in alcohol consumption, another known risk factor for gastric cancer[23]. Surveys in Taiwan showed that the prevalence of alcohol drinking among males was 38.2% in 2001 and 24.2% in 2013, while the prevalence among females was 9.2% in 2001 and 9.3% in 2013[24]. Furthermore, obesity is also associated with an increased risk of gastric cancer[25-27]. The body mass index of the Taiwanese population has increased over time. The prevalence of having a body mass index ≥ 24 kg/m² among males rose from 33.4% during 1993-1996 to 52.1% during 2013-2016 and among females, rose from 33.0% during 1993-1996 to 37.4% during 2013-2016[28].

We also showed a steady decrease in sex ratios. In our results examining sex ratios by birth cohort, younger age groups had lower sex ratios, especially in the 25-34 age group, which had a ratio lower than 1, indicating that males accounted for a lower incidence of gastric cancer. The trends in sex ratios by birth cohort are similar to the intestinal type of gastric cancer based on histopathology and non-cardia site based on anatomic site[29]. We speculate that the decreasing trend in gastric cancer may be mainly attributed to declines in the intestinal type histology because the intestinal type of gastric cancer affects males and older age groups more frequently[30], leading to a greater decrease in incidence among males than among females. Furthermore, the dominant risk factors for gastric cancer, especially for non-cardia cancer, are diet, cigarette smoking, and *H. pylori* infection, whereas the risk factors for cardia cancer are obesity, gastroesophageal reflux, and Barrett's esophagus[31]. This may explain why the corresponding decrease in Taiwan is mainly in non-cardia gastric cancer, as the prevalence of risk factors such as poor diet, smoking, and *H. Pylori* infection are decreasing in Taiwan.

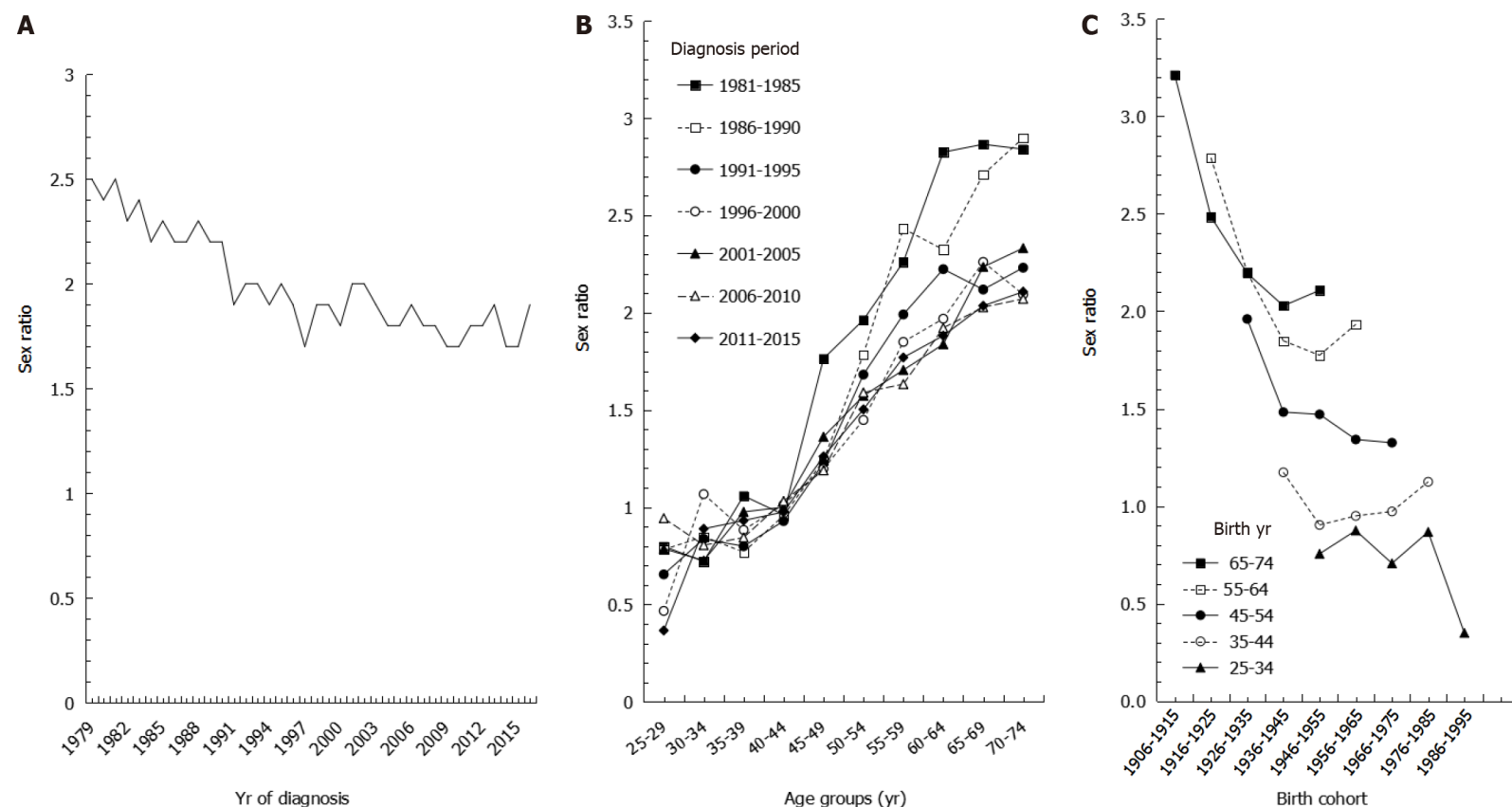


Figure 4 Sex ratios of gastric cancer in Taiwan during 1979-2016. A: Decreasing trends in age-adjusted incidence rates; B: Sex ratios by time period, showing a more consistent trend after 1996; C: Sex ratios in earlier birth cohorts were higher than later birth cohorts.

Regarding the sex ratios in age-specific incidence, we found a large curve in sex ratios around 45-59 years of age. Lindblad *et al*[32] indicated that estrogen may prevent gastric cancer, and our results are in accordance with females in this age group being exposed to some protective factors against gastric cancer, such as estrogen and reproductive factors. The growth of gastric cancer cells may be stimulated during low concentrations of estrogen, such as in young females and postmenopausal women, while the growth of cancer cells may be inhibited in females with high concentrations of estrogen[33,34].

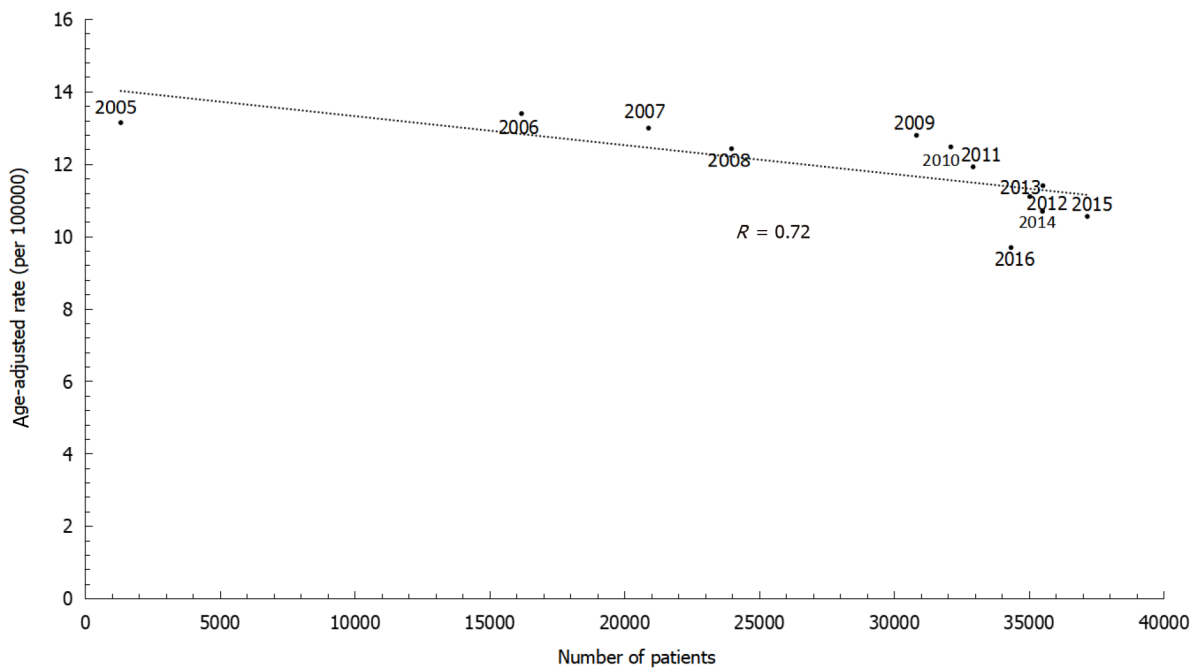


Figure 5 Correlation between numbers of patients with *Helicobacter pylori* infection newly treated with antibiotic therapy and age-adjusted incidence rates showed a substantial decrease with an r coefficient of 0.72 in Taiwan, 2005-2016.

In this study, we summarize the descriptive epidemiology of gastric cancer incidence in Taiwan during a period of almost 40 years and show that gastric cancer incidence has steadily declined during this period. However, there are several limitations to our study. First, due to limitations of the database, we were unable to confirm whether the declines in gastric cancer incidence are attributable to differential histologic types and anatomic sites. An earlier study showed a decreased standardized incidence ratio of non-cardia gastric cancer after *H. pylori* eradication, but this eradication did not influence the overall risk for cardia gastric cancer[35]. Also, as for pathological patterns, another study in Taiwan showed significantly decreasing trends in the incidence of adenocarcinoma. However, there was no evident decrease in the incidences of mucosa-associated lymphoid tissue lymphoma and diffuse large B-cell lymphoma[11]. Therefore, further studies are needed to investigate the relationship between *H. pylori* and the histologic type and anatomic site of gastric cancer. Second, this study did not investigate ecological correlations since there was no adjustment for other confounders, such as dietary and lifestyle habits, due to the limitations of the databases.

CONCLUSION

In conclusion, we show continuously decreasing rates of gastric cancer in both sexes, increasing age-specific incidence rates with age, lower sex ratios in later birth cohorts, and decreasing age-adjusted incidence rates with increasing anti-*H. pylori* treatment. The results support the need to further address the issue of mass anti-*H. pylori* treatment in areas with a high prevalence rate of *H. pylori* infection in order to eliminate the threat of *H. pylori*-associated gastric cancer.

ARTICLE HIGHLIGHTS

Research background

Gastric cancer is a multifactorial cancer and is a leading cause of cancer death worldwide. In Taiwan, gastric cancer is the sixth leading cause of cancer mortality.

Research motivation

We desired to discover the association between gastric cancer incidence and potential

factors, including anti-*Helicobacter pylori* (*H. pylori*) treatment.

Research objectives

The objective of this study was to observe secular trends in gastric cancer incidence according to age, sex, and the implementation of a nationwide *H. pylori* treatment program in Taiwan.

Research methods

We used the national Taiwan Cancer Registry database in this population-based study. Annual percent changes in incidence rates were used to describe secular trends in incidence rates and sex ratios of gastric cancer in Taiwan and to study the relationship between its incidence and potential risk factors, including anti-*H. pylori* treatment. Pearson's product-moment correlation coefficients were used to analyze the correlation between annual age adjusted incidence rates and the annual number of patients treated with antibiotic therapy for *H. pylori* infection.

Research results

The annual percent changes showed steadily decreasing rates of gastric cancer in both sexes. However, the decreasing trends differed by sex, with an annual percent change of -2.58% in males and -2.14% in females. The age-specific incidence rates increased with age. Among the same age group, more recent time periods showed lower incidence rates than earlier time periods. Within the same age group, the sex ratio was lower in later birth cohorts than in earlier birth cohorts. In addition, age-adjusted incidence rates decreased substantially with increasing numbers of patients newly treated with antibiotic therapy during 2005 to 2016 for *H. pylori* infection ($r = 0.72$).

Research conclusions

We observed steadily decreasing trends with differential sex ratios in the incidence of gastric cancer in Taiwan. The results also support the association between trends in gastric cancer incidence and the implementation of *H. pylori* eradication programs in Taiwan.

Research perspectives

Further long-term cohort studies are needed to investigate the relationship between *H. pylori* treatment and gastric cancer histologic type and anatomic site and should include adjusting for other confounders, such as dietary and lifestyle habits and genetic susceptibility.

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