The epidemiology of gastric cancers in the era of Helicobacter pylori eradication: a nation-wide cancer registry-based study in Taiwan

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Abstract

Background

Helicobacter pylori (H.P.) eradication has been shown to decrease gastric adenocarcinoma risk. The epidemiology of gastric lymphoma, which is also associated with H.P., and other rare subtypes of gastric cancer is less clear. This study comprehensively evaluated the incidence trend and the survival of gastric cancer in Taiwan by histologic subtype.

Methods

The incidence trends of gastric cancer in Taiwan from 1996 and 2013 were evaluated using data from the Taiwan Cancer Registry. The life-table method and the Cox proportional hazards analysis were used to evaluate the survival of gastric cancer.

Results

The incidence of all gastric cancers in Taiwan decreased from 15.97 per 100,000 in 1996 to 11.57 per 100,000 in 2013. The most frequent histologic subtype of gastric cancer in Taiwan was adenocarcinoma, followed by lymphoma, and sarcoma (mainly gastrointestinal stromal tumor). The best survival was in patients with sarcoma, followed by lymphoma, neuroendocrine tumor and adenocarcinoma. Generally women had a better survival than men. The incidence of adenocarcinoma significantly decreased from 13.56 per 100,000 in 1996 to 9.82 per 100,000 in 2013 ($P<0.0001$). In contrast, the incidences of mucosa-associated lymphoid tissue lymphoma and diffuse large B cell lymphoma did not decrease.

Conclusions

The incidence of adenocarcinoma and lymphoma, both of which are associated with H.P., showed diverging trends. The survival of gastric cancer differed by histologic subtype and sex.
Impact

The disparity in the incidence trends between gastric lymphoma and adenocarcinoma, both associated with H.P., warranted the need to search for additional risk factors of gastric lymphoma.
Introduction

Gastric cancer is the fifth most common cancer worldwide. Its incidence is even higher in Asia, being the fourth most common cancer in Asia and the third most common cancer in Japan and China (http://gco.iarc.fr/). In Taiwan, gastric cancer was the sixth most common cancer in 1996 and the ranking dropped to ninth in 2016 (https://www.hpa.gov.tw/Pages/Detail.aspx?nodeid=269&pid=10227). Helicobacter pylori (H.P.) infection is a major risk factor of gastric cancer.[1,2] The treatment guideline for H.P. eradication has been established by medical authorities around the world, including those in Asia.[3,4] The Health Insurance Bureau of Taiwan began to reimburse the agents used for gastric ulcer, including bismuth, H2 blocker, and proton pump inhibitor, for H.P. eradication in the case of non-ulcer lesion since 2003. The antibiotics used for H.P. eradication such as amoxicillin and metronidazole had not been restricted by the Health Insurance Bureau of Taiwan whereas clarithromycin had been reimbursed by the Health Insurance Bureau in Taiwan since 2009. The prevalence of H.P. infection in Taiwan decreased from 54.4% in 1993 to 25.4% in the period between 2012 to 2014.[5,6] Many studies have shown that eradication of H.P. could decrease the risk of gastric cancer.[7-16] Besides adenocarcinoma, a lower proportion of gastric cancers belongs to other histologic subtypes, including lymphoma and gastrointestinal stromal tumor (GIST). The development of gastric lymphoma, particularly mucosa-associated lymphoid tissue (MALT) lymphoma, has also been associated with H.P. infection.[17-21] However, it is unclear whether the risk of gastric MALT lymphoma has also declined in a trend similar to that of gastric adenocarcinoma after successful H.P. eradication. Furthermore, the distributions and incidences of other histologic subtypes of gastric cancer are not well understood. This study analyzed the incidence and survival of gastric cancers using the 1996-2013 data.
from the Taiwan Cancer Registry (TCR), a nation-wide population-based cancer registry. We also analyzed the incidence trend and survival of the gastric cancer by histologic subtype and the time period of diagnosis.

**Materials and Methods**

The Research Ethics Committee of the National Health Research Institutes, Taiwan approved the execution of this study. This study did not require individual consent because de-identified secondary data were used for analysis.

Data were extracted from the TCR and the Death Registry Database housed at the Center for Medical Informatics and Statistics established by the Ministry of Health and Welfare. The TCR, which covers approximately 97% of the cancer cases diagnosed in Taiwan, was established in 1979 to track the incidence and mortality rates of cancers in Taiwan.

The incident cases of gastric cancer diagnosed in Taiwan between January 1, 1996 and December 31, 2013 were identified from the TCR using the topography codes of the International Classification of Diseases for Oncology, Third Edition (ICD-O-3). The morphology (M) codes were used to determine the histologic subtypes of gastric cancer, including adenocarcinoma, lymphoma, sarcoma, neuroendocrine tumors (NET), squamous cell carcinoma, small cell carcinoma, and carcinoma (cases coded only as carcinoma and not specified as adenocarcinoma, squamous cell carcinoma or small cell carcinoma) as shown in Supplementary Table S1.

The denominators used to calculate the crude annual incidence rates of gastric cancer in Taiwan from 1996 to 2013 were based on the annual populations reported by the Directorate-General of Budget, Accounting, and Statistics of Taiwan.
Direct standardization using the 2000 WHO standard population was performed to generate the age-standardized incidence rates. The changes in the incidence trends overall and by histologic subtype were evaluated by calculating the annual percentage change (APC) using linear regression: \( \log(\text{rate}_y) = b_0 + b_1 y \), with \( \log(\text{rate}_y) = \) natural log of incidence rate in year \( y \). \( APC = (e^{b_1}-1) \times 100 \).

Data extraction of Death Registry Database was performed to ascertain information on vital status and the date of death. Life-table method was used to calculate the one-, three-, five-, and ten-year survival of gastric cancer overall, by sex, by histologic subtype, and by the time period of diagnosis (T1: from 1996 to 2001, T2: from 2002 to 2007, and T3: from 2008 to 2013). Cox proportional hazards survival analysis was performed to estimate the hazard ratio (HR) and 95% confidence interval (CI) of gastric cancer death associated with histologic subtype, age, sex, and the time period of diagnosis. Each of the variables was first analyzed separately in the univariate survival analysis and then included together in the multivariate analysis. Because stage and treatment were incompletely recorded by the TCR, we were unable to include these two variables in the multivariable analysis.

**Results**

*The incidence and survival of gastric cancers in Taiwan*

A total of 67,861 cases of gastric cancers were recorded by the TCR from 1996 to 2013. The male to female ratio was 1.79. The mean age was 66.90 years old for all cases, 67.97 years old for men, and 64.98 years old for women. Gastric cancers occurred more frequently in the older age groups and most commonly among the 70-80-year-olds (Supplementary Figure S1). The age-standardized incidence of gastric cancer was 15.97 per 100,000 in 1996 and decreased to 11.57 per 100,000 in
2013 (APC= -1.97, \( P<0.0001 \)) (Figure 1 and Supplementary Table S2). A decrease in incidence was observed in both men and women with similar trends.

The most common subtype of gastric cancer was adenocarcinoma (85.01%), followed by lymphoma (4.9%), sarcoma (4.69%), carcinoma (2.78%), NET (0.53%), squamous cell carcinoma (0.52%), and small cell carcinoma (0.1%). The remaining subtypes accounted for 0.16%. In addition, 1.31% were diagnosed without pathologic proof. The overall 1-, 3-, 5-, and 10-year survival rates of gastric cancer patients were 58.74%, 39.07%, 32.4%, and 24.38%, respectively (Table 1). Women had a better survival than men. The 1-, 3-, 5- and 10-year survival rates for men, women and both for all gastric cancers and for each subtype are shown in Table 1. The survival curves of gastric cancers, by sexes and by histologic subtypes are shown in Figure 2.

**Gastric adenocarcinoma in Taiwan**

Gastric adenocarcinoma accounted for 85.01% of all gastric cancers from 1996 to 2013. The mean age of patients diagnosed with gastric adenocarcinoma was 67.2 years old. The incidence of adenocarcinoma was 13.56 per 100,000 in 1996 and decreased to 9.82 per 100,000 in 2013 (Figure 3A and Supplementary Table S2). The overall decrease of gastric cancer was attributed mainly to the decrease in the number of adenocarcinoma cases. We analyzed the incidence of gastric adenocarcinoma by anatomic site. The incidence of adenocarcinoma in cardia decreased from 1.36 per 100,000 in 1996 to 1.0 per 100,000 in 2013 (APC=-2.0, \( P<0.0001 \)) whereas the incidence of adenocarcinoma in non-cardia decreased from 12.2 per 100,000 in 1996 to 8.82 per 100,000 in 2013 (APC=-2.15, \( P<0.0001 \)) (Supplementary Table S2). The decreasing incidence trends of adenocarcinoma in cardia and non-cardia was not significantly different (\( P\)-heterogeneity=0.68). Men had a higher incidence of gastric
adenocarcinoma than women (Supplementary Table S2). The male to female ratio did not change significantly, with a ratio of 1.93 in 1996 and 1.97 in 2013 (Supplementary Table S2). The overall 1-, 3-, 5-, and 10-year survival rates of adenocarcinoma patients from 1996 to 2013 were 57.3%, 36.13%, 29.24%, and 21.65%, respectively (Table 1).

**Gastric lymphoma in Taiwan**

Gastric lymphoma accounted for 4.9% of all gastric cancers in Taiwan from 1996 to 2013. The mean age of patients diagnosed with gastric lymphoma was 63.1 years old. The annual incidence of gastric lymphoma did not change significantly (Figure 3B). The case number of lymphoma was similar for men (1,650 cases) and women (1,678 cases). Because diffuse large B cell lymphoma (DLBCL) and MALT lymphoma are the two common subtypes of lymphoma in the stomach, we divided the subtypes of gastric lymphoma into DLBCL, MALT lymphoma and “other lymphoma”, which was lymphoma not coded as DLBCL or MALT lymphoma. The most common types of “other lymphoma” recorded by the TCR were malignant lymphoma, not otherwise specified (NOS) and malignant lymphoma, non-Hodgkin’s, which accounted for 68.17% of “other lymphoma”. The third edition of the International Classification of Disease for Oncology (ICD-O3) was published in 2000[22] and newly introduced the morphology code for marginal zone lymphoma (ICD-O3 morphology code M-9699), which indicates MALT lymphoma in stomach. Moreover, the incidence of MALT lymphoma in the TCR increased significantly in 2002. Therefore, we analyzed the annual incidence and distribution of gastric lymphoma by subtype from 2002 to 2013. Figure 4A shows the annual incidence of DLBCL, MALT lymphoma and “other lymphoma” in Taiwan from 2002 to 2013. DLBCL accounted for 54.62% and MALT lymphoma accounted for 34.16% of all gastric lymphomas,
respectively. The incidence of all gastric lymphomas was 0.64 per 100,000 in 1996, increased to 0.82 per 100,000 in 2002, and then decreased to 0.68 per 100,000 in 2013. For DLBCL, the incidence was 0.24 per 100,000 in 1996, increased to 0.41 per 100,000 in 2002, and then became 0.37 per 100,000 in 2013. For MALT lymphoma, the incidence was 0.25 per 100,000 in 2002 and became 0.26 per 100,000 in 2013. The incidence of “other lymphoma” decreased from 0.40 per 100,000 in 1996 to 0.04 per 100,000 in 2013 (Supplementary Table S2). Overall, the incidence of total gastric lymphoma did not change significantly from 1996 to 2013 with an APC of -0.09 ($P=0.78$). The incidence of DLBCL increased significantly with an APC of 2.13 ($P=0.002$) from 1996 to 2013. The incidence of MALT lymphoma increased non-significantly with an APC of 1.5 ($P=0.11$) from 2002 to 2013. The incidences of total lymphoma, DLBCL, and “other lymphoma” decreased with an APC of, -1.29 ($P=0.03$), -1.12 ($P=0.009$), and -10.92 ($P=0.003$), respectively from 2002 to 2013 (Supplementary Table S2). The 5- and 10-years overall survival of all gastric lymphomas was 59.19% and 49.1%, respectively, from 1996 to 2013 (Table 1). The overall survival was the best for MALT lymphoma, followed by DLBCL, and the worst for “other lymphoma”. The 5- and 10-year overall survival rates for MALT lymphoma were 80.4% and 67.12%, respectively, while those for DLBCL were 50.92% and 41.78%, respectively, from 2002 to 2013. The 5- and 10-year overall survival rates for “other lymphoma” were 39.62% and 31.65%, respectively, from 2002 to 2013. The survival curves of DLBCL, MALT lymphoma, and other lymphoma are shown in Figure 4B.

**Gastric sarcoma in Taiwan**

Gastric sarcoma accounted for 4.69% of all gastric cancers in Taiwan from 1996 to
The mean age of patients diagnosed with gastric sarcoma was 62.84 years old. Like lymphoma, the case number of sarcoma for men (1,638) and women (1,544) was not obviously different. The incidence of gastric sarcoma increased from 0.35 per 100,000 in 1996 to 1.02 per 100,000 in 2011 and then decreased to 0.53 per 100,000 in 2013 (Figure 3B, Supplementary Table S2). The diagnosis of GIST by CD117 or KIT staining became available in 2002 and we found that the percentage of GIST significantly increased since 2002. GIST accounted for 95.1% of all sarcomas from 2002 to 2013. The annual incidences of sarcoma and GIST are shown in Figure 4C and Supplementary Table S2. The incidence of GIST was 0.49 per 100,000 in 2002. It increased rapidly to the peak of 1.01 per 100,000 in 2011 and then decreased to 0.52 per 100,000 in 2013. The incidence of sarcoma increased significantly from 1996 to 2013 with an APC of 4.91 \( (P<0.0001) \) (Supplementary Table S2). The 5- and 10-year overall survival rates of sarcoma from 1996 to 2013 were 71.06% and 55.97%, respectively. (Table 1)

**Carcinoma and other subtypes of gastric cancer in Taiwan**

The annual incidences of carcinoma and other rare histologic subtypes of gastric cancer are shown in Figure 3B. Gastric carcinoma accounted for 2.78% of all gastric cancers from 1996 to 2013. The mean age of patients diagnosed with gastric carcinoma was 71.6 years old. The annual incidence of carcinoma fluctuated with time. It was 0.30 per 100,000 in 1996, increased to 0.56 per 100,000 in 2002, and then decreased to 0.27 per 100,000 in 2013 (Supplementary Table S2). The 1-, 3-, 5-, and 10-year survival rates of carcinoma were 38.07%, 25.28%, 21.42%, and 15.72%, respectively (Table 1).

NET accounted for 0.53% of all gastric cancers from 1996 to 2013. The mean age
of gastric NET patients was 65.0 years old. The incidence of gastric NET increased gradually from 0.02 per 100,000 in 1996 to 0.18 per 100,000 in 2013 with an APC of 14.13 ($P<0.0001$) (Supplementary Table S2). The survival of gastric NET was similar to that of lymphoma. The 5- and 10-year overall survival rates of gastric NET were 50.92% and 41.18%, respectively (Table 1).

Squamous cell carcinoma accounted for 0.52% of all gastric cancers from 1996 to 2013. The mean age of patients diagnosed with gastric squamous cell carcinoma was 62.2 years old. The incidence of gastric squamous cell carcinoma did not change significantly from 1996 to 2013 with the incidence of 0.09 per 100,000 in 1996 and 0.07 per 100,000 in 2013 (Supplementary Table S2). The 1-, 3-, 5-, and 10-year survival rates of squamous cell carcinoma were 37.5%, 23.5%, 19.62%, and 15.62%, respectively (Table 1).

Small cell carcinoma accounted for only 0.1% of gastric cancers from 1996 to 2013. The mean age of patients diagnosed with gastric small cell carcinoma was 72.0 years old. The incidence from 1996 to 2013 fluctuated with 0.004 per 100,000 in 1996 and 0.008 per 100,000 in 2013 (Supplementary Table S2). The survival of gastric small cell carcinoma was the worst of all gastric cancers. The 1-, 3-, 5-, and 10-year survival rates of small cell carcinoma were 27.14%, 15.71%, 14.29%, and 6.45%, respectively (Table 1).

**Prognostic analysis for gastric cancer in Taiwan**

To analyze the prognostic factors of gastric cancer, we performed Cox proportional hazards survival analysis by histologic subtypes, sex, age, and diagnosis periods from 1996 to 2013 and the results are presented in Table 2. In addition, we also performed the analysis separately for men and women. Because adenocarcinoma was the most
common type of gastric cancer, we used it as the reference group for comparison. Patients with lymphoma, sarcoma, and NET had a better survival than those with adenocarcinoma by univariate analysis for both men and women. The results remained statistically significant in the multivariate analysis, where the HR was 0.55 (95% CI, 0.52-0.57) for lymphoma, 0.37 (95% CI, 0.35-0.39) for sarcoma, and 0.66 (95% CI, 0.57-0.76) for NET (Table 2). When men and women were analyzed separately, the survival of men with NET (HR, 0.88; 95% CI, 0.74-1.04) was not significantly better than that of men with adenocarcinoma in the multivariate analysis. The survival for the other subtypes of gastric cancer, including carcinoma, squamous cell carcinoma, and small cell carcinoma, was significantly worse than that of adenocarcinoma both in men and women. Women had a better survival than men with the HR of 0.91 (95% CI, 0.9-0.93). Generally, the prognosis was worse when the patient was diagnosed at an older age.

To evaluate the prognosis of gastric cancer patients diagnosed at different time periods, we analyzed the survival of the gastric cancer patients diagnosed in three time periods (T1: from 1996 to 2001, T2: from 2002 to 2007, and T3: from 2008 to 2013) by histologic subtypes and sex (Supplementary Table S3). The 5-year survival rate of all gastric cancers was 32.01%, 31.43%, and 33.65% in T1, T2, and T3, respectively. The Cox proportional hazards survival analysis for each histologic subtype was also performed by sex, age and diagnosis periods (Supplementary Table S4). For patients with gastric adenocarcinoma, the 1- and 3-year survival rates were 56.37% and 36.94% in T1, 56.58% and 35.18% in T2, and 58.82% and 36.29% in T3, respectively (Supplementary Table S3). The survival improved in T3 (HR=0.93, 95% CI, 0.91-0.96 by multivariate analysis) when compared to T1 (Supplementary Table S4). For patients with lymphoma, the 5-year survival rates of lymphoma patients were
57.72%, 57.88%, and 61.61% in T1, T2, and T3, respectively (Supplementary Table S3). The survival rate improved in T3 (HR=0.80, 95% CI, 0.70-0.90 by multivariate analysis) compared to T1 (Supplementary Table S4). For patients with sarcoma, the 5-year survival rate was 60.18% in T1, 69.92% in T2, and 76.06% in T3 (Supplementary Table S3). The overall survival improved from T1 to T2 (HR=0.84, 95% CI, 0.73-0.97 by multivariate analysis) and the improvement continued in T3 (HR=0.62, 95% CI, 0.53-0.72 by multivariate analysis) (Supplementary Table S4). Most of the sarcoma was diagnosed as GIST particularly after 2002. The 5-year survival rate of GIST was 71.38% in T2 and improved to 77.1% in T3 (Supplementary Table S3). The 5-year survival rates of gastric NET patients were 40.63% in T1, 46.24% in T2, and 54.65% in T3, respectively (Supplementary Table S3). The survival improved but not statistically significant from T1 to T2 (HR=0.84, 95% CI, 0.52-1.36 by multivariate analysis) and T3 (HR=0.69, 95% CI, 0.44-1.08 by multivariate analysis) (Supplementary Table S4). Women had a better survival than men in patients with adenocarcinoma, lymphoma, sarcoma, carcinoma, and NET (Supplementary Table S4). For all gastric cancer patients, the survival in T3 was better than that in T1 with a HR of 0.93 (95% CI, 0.91-0.95) and the improvement was also observed both in men (HR=0.93, 95% CI, 0.91-0.96) and women (HR=0.93, 95% CI, 0.89-0.96) (Table 2).

Discussion

The incidence of all gastric cancers in Taiwan decreased from 15.97 per 100,000 in 1996 to 11.57 per 100,000 in 2013 according to the TCR. The most frequent histologic subtype of gastric cancer in Taiwan was adenocarcinoma, followed by lymphoma, sarcoma, carcinoma, NET, squamous cell carcinoma, and small cell
carcinoma. The best survival was observed in patients with sarcoma, followed by lymphoma, NET and then adenocarcinoma. Generally women had a better survival than men. The survival improved for patients diagnosed in the later time period from 2008 to 2013 compared to patients diagnosed in the earlier time period from 1996 to 2001.

Gastric cancer is a multi-factorial cancer. The risk factors include diet, lifestyle, genetic predisposition, family history, treatment and medical conditions, infections, demographic characteristics, occupational exposure, and ionizing radiation.[23,24] H.P. infection is an important risk factor for gastric adenocarcinoma.[1,2] The risk of gastric adenocarcinoma has been decreased by H.P. eradication in pre-gastric, early gastric cancer and asymptomatic patients.[7-16] In our study, the incidence of gastric adenocarcinoma decreased significantly from 13.56 per 100,000 in 1996 to 9.82 per 100,000 in 2013 (APC=-2.13, P<0.0001) (Supplementary Table S2). The decrease in the annual incidence of adenocarcinoma was significant both in cardia and non-cardia. Although the prevalence of H.P. infection was lower in gastric cancer in cardia (50%) than that in non-cardia (64.8%), a large percentage of (50%) of the cardia gastric cancer patients were infected with H.P., according to the analysis of a large series of patients in Taiwan.[25] This might explain why the decreasing incidence trends of gastric adenocarcinoma in cardia and non-cardia were not significantly different (P=0.68). This result supported a decreased risk of gastric cancer in the era of H.P. eradication. However, this result raised the question whether H.P. eradication could reduce the incidence of all H.P.-associated cancers. Gastric MALT lymphoma is a low grade B cell lymphoma associated with H.P. infection.[17,21,26] In addition, H.P. infection was significantly associated with an increased risk of gastric DLBCL.[20] Given the association between H.P. and gastric MALT lymphoma and DLBCL, the
incidences of gastric MALT lymphoma and DLBCL are expected to decrease after H.P. eradication. Capelle et al reported that the incidence of gastric MALT lymphoma in the Netherlands increased from 0.28 per 100,000 in 1991 to a maximum of 0.72 in 1997 and then decreased to 0.27 per 100,000 in 2006.[27] Kuper-Hommel et al reported that the incidence of gastric MALT lymphoma decreased from 0.16 per 100,000 in 1994 to 0.13 per 100,000 in 2010.[28] Luminari et al reported that the incidence of gastric MALT lymphoma in North Italy dropped from 1.4 per 100,000 in 1997 to 0.2 per 100,000 in 2002 and remained stable until the end of study period in 2007 (0.1 per 100,000).[29] They suggested that the decline of gastric MALT lymphoma incidence was due to the decreased prevalence of H.P. infection from 67% during 1997-2001 to 19% during 2002-2007. Using data from the 18 U.S. Surveillance, Epidemiology and End Results, Khalil et al reported that the incidence of gastric marginal zone lymphoma decreased significantly with an incidence rate ratio of 0.85 comparing the incidence rate between 2006 and 2009 to the incidence rate between 2001 and 2005.[30] In contrast to the above-mentioned studies, Howell et al reported an increasing trend in the incidence of primary gastrointestinal lymphoma in a population-based study from the Calgary Health Region, Canada.[31] In our study, the incidence of all gastric lymphomas did not change significantly from 1996 to 2013 (APC= -0.09, P=0.78). The incidence of gastric MALT lymphoma increased slightly but non-significantly from 2002 to 2013 (APC=1.5, P=0.11). Moreover, the incidence of gastric DLBCL increased significantly from 1996 to 2013 (APC=2.13, P=0.002) (Supplementary Table S2). Therefore, this hypothesis of H.P. eradication reducing the incidence of H.P.-associated gastric MALT lymphoma and DLBCL, was not verified by our study and the study by Howell et al. MALT lymphoma is thought to be induced by chronic inflammation in extra-nodal site. H.P is thought to be the major pathogen.
to induce chronic inflammation, leading to the development of MALT lymphoma.[32] However, there are other risk factors associated with the development of gastric lymphoma, including occupational exposure to pesticides or solvents.[33] Genetic factors have also been associated with an increased risk of development of gastric lymphoma, such as HLA-DQA*0103, HLA-DQB1*0601 and R702W mutation in the NOD2/CARD15 gene. Polymorphisms in Toll-like receptor 4 (TLR4 Asp299Gly) and MALT1 gene (rs12969413) were also reported to be the risk factors of gastric lymphoma.[34] In Taiwan, H.P. treatment is routinely given to H.P.-infected patients and is thought to contribute to the decreasing incidence of gastric adenocarcinoma. However, the decrease in the incidence did not occur for gastric MALT lymphoma and DLBCL in Taiwan. This suggested that although H.P. infection is a risk factor of gastric lymphoma its level of contribution to the development of gastric lymphoma is unclear.

The relationship between H.P. and gastric adenocarcinoma or lymphoma is interesting. H.P. is risk factor for both gastric adenocarcinoma and lymphoma (MALT lymphoma and DLBCL). However, H.P. eradication can cure gastric MALT lymphoma and even DLBCL but not adenocarcinoma, which is mainly treated with surgery, chemotherapy and targeted therapy.[35] First-line H.P. eradication therapy could induce approximately 75% complete remission in H.P.-positive gastric MALT lymphoma patients.[36] First-line H.P. eradication therapy also achieved a complete remission of 68.8% and 56.3% among H.P.-positive gastric de novo DLBCL and high-grade transformed MALT lymphoma patients, respectively.[37] H.P. eradication also induced a complete remission of 16-46% for H.P.-negative gastric MALT lymphoma patients.[38-40] It has been speculated that bacteria other than H.P. may be involved in the occurrence of H.P.-negative MALT lymphoma, it is possible that the
antibiotics used to treat H.P. may also be effective to eradicate these bacteria.[41] In contrast, H.P. eradication did not have anti-tumor effect on gastric adenocarcinoma. These results suggested that the roles of H.P. in the pathogenesis and progression of H.P.-associated adenocarcinoma and lymphoma may be different.

The incidence of sarcoma (mainly GIST) has increased in Taiwan in a trend similar to that in the US.[42] The reason for these trends is not clear.[42] Although increased diagnostic rate by the identification of GIST marker, KIT, is a possible reason[43], risk factors should be identified for the prevention of this disease. Although our results showed an overall increasing trend in the incidence of gastric sarcoma, a decrease in incidence was noted since 2011 (Figure 4C and Supplementary Table S2), which was likely attributed to the modification of the GIST recorded by the TCR according to the prognostic classification of GIST by Miettinen et al.[44] Beginning in 2011, the TCR stopped recording the cases diagnosed as gastric GIST with prognostic group of 1, 2, 3a, and 4, and as non-gastric GIST with prognostic group of 1. This may explain the decrease of sarcoma (GIST) cases since 2011 in our study.

NET was the most rapidly increased cancer type in stomach in Taiwan during our study period. The trend is also similar to that in US.[45] There is a limited number of studies investigating the risk factors of developing gastric NET. Only family history of cancer and history of diabetes have been reported to be associated with gastric NET,[46] but these results still need to be confirmed. Further investigations are warranted to identify the risk factors to prevent the development of gastric NET.

We found that the survival of gastric cancer varied significantly by histologic subtypes. The survival of sarcoma improved from T1 to T2 and T3 (Supplementary Table S4), which was likely attributed to the use of KIT mutation to improve the diagnosis of GIST starting in 1998 and the approval of imatinib to treat GIST starting...
in 2002.[43,47] For NET patients, the 5-year survival increased from 40.63% in T1 to 46.24% and 54.65% in T2 and T3, respectively (Supplementary Table S3). Although the survival improved in T2 (HR=0.84, 95% CI, 0.52-1.36) and T3 (HR=0.69, 95% CI, 0.44-1.08) compared with T1, the results were not statistically significant, likely due to the small sample size of gastric NET (n=360) (Supplementary Table S4). Our data showed a similar trend with those reported by Dasari et al, which showed a significantly better survival of distant gastrointestinal NETs diagnosed in the period of 2005-2008 (HR=0.76) and 2009-2012 (HR=0.71) compared to those diagnosed in the period of 2000-2004.[45] The prolonged survival of NET could be attributed to treatment improvement for gastric NET, particularly after the introduction of somatostatin analogues.[48,49] Recently, everolimus was approved to improve the progression-free survival of gastrointestinal tract NET,[50] thus, the survival of gastric NET is expected to be improved further in the future. For gastric adenocarcinoma, the 1-year survival increased slightly from T1 (56.37%) to T3 (58.82%) (Supplementary Table S3). The survival improvement in adenocarcinoma has been limited. The stage III and IV gastric adenocarcinomas accounted for more than 50% of all gastric cancers according to the TCR. Many chemotherapeutic or targeted agents were used for advanced gastric adenocarcinoma to prolong the survival, such as oxaliplatin, fluoropyrimidine, docetaxel, irinotecan, and trastuzumab.[35] However, only oxaliplatin and fluoropyrimidine-based chemotherapies have been reimbursed for advanced gastric adenocarcinoma in Taiwan, which may partially explain the poor survival of gastric adenocarcinoma in Taiwan. Recently, novel chemotherapeutic agents, targeted therapies with anti-angiogenesis effect, and check point inhibitors have been evaluated for the treatment of gastric adenocarcinoma.[51-53] The introduction of new therapeutic
agents are expected to improve the survival of gastric adenocarcinoma further in the future. However, improving the early diagnosis of gastric adenocarcinoma is also important.

This study has several limitations, first, we did not have information on the H.P. status of each individual and we could only rely on the decreasing prevalence of HP infection in the Taiwanese population and the strong association between gastric adenocarcinoma and H.P. infection to speculate that the decline in the incidence of gastric cancer in Taiwan was likely attributed to the successful H.P. eradication practice. Second, the TCR lacks complete information on the stage of diagnosis and treatment for gastric cancer; therefore, we could not examine the survival of gastric cancer by stage or treatment nor could we adjust for the confounding effect of stage or treatment in the multivariate survival analysis. Finally, our results may not be extrapolated to the Chinese population outside of Taiwan or other Asian populations with similar burden of gastric cancer because the occurrence and the survival of gastric cancer is multifactorial, influenced by the combination of genetic and lifestyle factors and the medical practice of each region.

In conclusion, the incidence of gastric adenocarcinoma in Taiwan decreased significantly from 1996 to 2013 while no decrease in the incidences of gastric MALT lymphoma and DLBCL, which are related to H.P. infection, was observed. These results suggested that although H.P. infection is an important risk factor for gastric MALT lymphoma and DLBCL, there may be other contributing factors. During the same time period, the incidence of NET increased significantly. It is important to identify the risk factors for the different subtypes of gastric cancer to prevent their development. The best survivals were observed in gastric sarcoma (GIST), lymphoma and NET, largely due to the improvement in diagnosis and treatment, while the
survivals of adenocarcinoma and other subtypes were still unsatisfactory. Identification of new methods for early diagnosis and development of new therapeutic agents are warranted to improve the survival of gastric cancer.

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Table 1. The 1, 3, 5, and 10-year survival rate of gastric cancer by histologic subtypes and sex in Taiwan from 1996 to 2013.

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<th>_subtype</th>
<th>1-year survival rate</th>
<th>3-year survival rate</th>
<th>5-year survival rate</th>
<th>10-year survival rate</th>
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<td></td>
<td>All</td>
<td>Men</td>
<td>Women</td>
<td>All</td>
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<tr>
<td>All</td>
<td>0.5874</td>
<td>0.574</td>
<td>0.6115</td>
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<td>Adenocarcinoma</td>
<td>0.573</td>
<td>0.568</td>
<td>0.5826</td>
<td>0.3613</td>
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<tr>
<td>Sarcoma</td>
<td>0.9</td>
<td>0.8704</td>
<td>0.9313</td>
<td>0.787</td>
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<td>GIST</td>
<td>0.9242</td>
<td>0.9059</td>
<td>0.9426</td>
<td>0.8268</td>
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<td>Lymphoma (all)</td>
<td>0.7232</td>
<td>0.6848</td>
<td>0.7609</td>
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<tr>
<td>DLBCL</td>
<td>0.6471</td>
<td>0.6048</td>
<td>0.6899</td>
<td>0.5501</td>
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<td>MALT lymphoma</td>
<td>0.9122</td>
<td>0.8852</td>
<td>0.9333</td>
<td>0.8542</td>
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<tr>
<td>Other lymphoma</td>
<td>0.5311</td>
<td>0.5217</td>
<td>0.5446</td>
<td>0.4166</td>
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<tr>
<td>Carcinoma</td>
<td>0.3807</td>
<td>0.3615</td>
<td>0.4177</td>
<td>0.2528</td>
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<tr>
<td>NET</td>
<td>0.6861</td>
<td>0.5646</td>
<td>0.8543</td>
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<tr>
<td>Squamous cell carcinoma</td>
<td>0.375</td>
<td>0.3986</td>
<td>0.25</td>
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<tr>
<td>Small cell carcinoma</td>
<td>0.2714</td>
<td>0.2833</td>
<td>0.2</td>
<td>0.1571</td>
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*, The survival rate was calculated from 2002 to 2013
Table 2. Cox proportional hazards survival analysis for the patients with gastric cancers by subtypes, sex, age, and diagnosis periods from 1996 to 2013

<table>
<thead>
<tr>
<th>Histologic subtype</th>
<th>ALL Univariate HR</th>
<th>95% CI</th>
<th>ALL Multivariate* HR</th>
<th>95% CI</th>
<th>Men Univariate HR</th>
<th>95% CI</th>
<th>Men Multivariate** HR</th>
<th>95% CI</th>
<th>Women Univariate HR</th>
<th>95% CI</th>
<th>Women Multivariate** HR</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>Lymphoma (total)</td>
<td>0.49</td>
<td>0.46-0.51</td>
<td>0.55</td>
<td>0.52-0.57</td>
<td>0.56</td>
<td>0.52-0.59</td>
<td>0.61</td>
<td>0.57-0.65</td>
<td>0.44</td>
<td>0.41-0.48</td>
<td>0.48</td>
<td>0.45-0.52</td>
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<tr>
<td>Sarcoma</td>
<td>0.33</td>
<td>0.31-0.35</td>
<td>0.37</td>
<td>0.35-0.39</td>
<td>0.4</td>
<td>0.37-0.43</td>
<td>0.43</td>
<td>0.41-0.48</td>
<td>0.28</td>
<td>0.25-0.3</td>
<td>0.29</td>
<td>0.27-0.32</td>
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<tr>
<td>Carcinoma</td>
<td>1.47</td>
<td>1.40-1.51</td>
<td>1.39</td>
<td>1.32-1.46</td>
<td>1.53</td>
<td>1.44-1.63</td>
<td>1.45</td>
<td>1.37-1.54</td>
<td>1.37</td>
<td>1.25-1.5</td>
<td>1.27</td>
<td>1.16-1.39</td>
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<td>NET</td>
<td>0.59</td>
<td>0.51-0.68</td>
<td>0.66</td>
<td>0.57-0.76</td>
<td>0.83</td>
<td>0.70-0.98</td>
<td>0.88</td>
<td>0.74-1.04</td>
<td>0.35</td>
<td>0.26-0.46</td>
<td>0.4</td>
<td>0.30-0.52</td>
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<tr>
<td>Squamous cell carcinoma</td>
<td>1.41</td>
<td>1.26-1.58</td>
<td>1.6</td>
<td>1.42-1.79</td>
<td>1.32</td>
<td>1.17-1.50</td>
<td>1.55</td>
<td>1.37-1.75</td>
<td>1.75</td>
<td>1.31-2.33</td>
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<td>1.5-2.66</td>
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<tr>
<td>Small cell carcinoma</td>
<td>1.84</td>
<td>1.44-2.34</td>
<td>1.66</td>
<td>1.3-2.12</td>
<td>1.65</td>
<td>1.26-2.15</td>
<td>1.59</td>
<td>1.22-2.07</td>
<td>3.25</td>
<td>1.75-6.03</td>
<td>2.32</td>
<td>1.25-4.31</td>
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<tr>
<td>Women</td>
<td>0.83</td>
<td>0.81-0.84</td>
<td>0.91</td>
<td>0.9-0.93</td>
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<td>Referent: Age &lt;30</td>
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<tr>
<td>30=&lt;age&lt;40</td>
<td>1.03</td>
<td>0.9-1.16</td>
<td>0.97</td>
<td>0.86-1.10</td>
<td>1.11</td>
<td>0.92-1.33</td>
<td>1.04</td>
<td>0.87-1.26</td>
<td>0.96</td>
<td>0.81-1.14</td>
<td>0.93</td>
<td>0.78-1.10</td>
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<tr>
<td>40=&lt;age&lt;50</td>
<td>1.07</td>
<td>0.95-1.20</td>
<td>1</td>
<td>0.89-1.13</td>
<td>1.18</td>
<td>0.99-1.41</td>
<td>1.1</td>
<td>0.93-1.32</td>
<td>0.97</td>
<td>0.82-1.14</td>
<td>0.93</td>
<td>0.79-1.10</td>
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<tr>
<td>50=&lt;age&lt;60</td>
<td>1.09</td>
<td>0.97-1.23</td>
<td>1.03</td>
<td>0.93-1.16</td>
<td>1.28</td>
<td>1.07-1.52</td>
<td>1.2</td>
<td>1.01-1.42</td>
<td>0.89</td>
<td>0.76-1.05</td>
<td>0.89</td>
<td>0.76-1.05</td>
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<tr>
<td>60 =&lt; age &lt; 70</td>
<td>1.3</td>
<td>1.16-1.46</td>
<td>1.19</td>
<td>1.06-1.34</td>
<td>1.5</td>
<td>1.27-1.79</td>
<td>1.37</td>
<td>1.15-1.63</td>
<td>1.06</td>
<td>0.9-1.24</td>
<td>1.04</td>
<td>0.89-1.22</td>
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<tr>
<td>70 =&lt; age &lt; 80</td>
<td>1.86</td>
<td>1.66-2.09</td>
<td>1.67</td>
<td>1.48-1.87</td>
<td>2.09</td>
<td>1.76-2.48</td>
<td>1.88</td>
<td>1.58-2.23</td>
<td>1.58</td>
<td>1.35-1.85</td>
<td>1.52</td>
<td>1.29-1.78</td>
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<td>80 =&lt; age</td>
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<td>2.57</td>
<td>2.29-2.89</td>
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<td>2.64-3.72</td>
<td>2.84</td>
<td>2.39-3.37</td>
<td>2.62</td>
<td>2.23-3.07</td>
<td>2.44</td>
<td>2.08-2.86</td>
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Diagnosed period
Referent: 1996-2001 (T1)

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<th>0.97-1.04</th>
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<tr>
<td>2002-2007 (T2)</td>
<td>1.02</td>
<td>0.99-1.04</td>
<td>1.01</td>
<td>0.99-1.03</td>
<td>1.03</td>
<td>1.01-1.06</td>
<td>1.01</td>
<td>0.99-1.04</td>
<td>0.99</td>
<td>0.96-1.03</td>
<td>1</td>
<td>0.97-1.04</td>
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<tr>
<td>2008-2013 (T3)</td>
<td>0.94</td>
<td>0.92-0.96</td>
<td>0.93</td>
<td>0.91-0.95</td>
<td>0.96</td>
<td>0.94-0.99</td>
<td>0.93</td>
<td>0.91-0.96</td>
<td>0.91</td>
<td>0.88-0.95</td>
<td>0.93</td>
<td>0.89-0.96</td>
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</tbody>
</table>

* The multivariate analysis for hazard ratio was adjusted for histologic subtype, sex, age, and diagnosed period.
** The multivariate analysis for hazard ratio was adjusted for histologic subtype, age, and diagnosed period.
Figure legends

Figure 1. The annual age-standardized incidence of gastric cancers in Taiwan, overall and by sex, from 1996 to 2013.

Figure 2. The survival of gastric cancers by histologic subtype in men, women and both in Taiwan from 1996 to 2013.

Figure 3. The annual age-standardized incidence of gastric cancers in Taiwan from 1996 to 2013. (A) The annual age-standardized incidence of gastric cancer by histologic subtype (adenocarcinoma, lymphoma, sarcoma, carcinoma, NET, squamous cell carcinoma, and small cell carcinoma). (B) The annual age-standardized incidence of the rare histologic subtypes of gastric cancer (lymphoma, sarcoma, carcinoma, NET, squamous cell carcinoma, and small cell carcinoma).

Figure 4. The age-standardized incidence of gastric lymphoma and sarcoma by histologic subtypes and survival of gastric lymphoma by histologic subtype in Taiwan. (A) The annual age-standardized incidence of gastric lymphoma by histologic subtype (DLBCL, MALT lymphoma, and other lymphoma) in Taiwan from 2002 to 2013. (B) The survival of gastric lymphomas by histologic subtype (MALT lymphoma, DLBCL, and “other lymphoma”) from 2002 to 2013. (C) The annual age-standardized incidence of all sarcoma and GIST in Taiwan from 1996 to 2013.
Figure 1

Incidence (per 100,000)

(Year)


ALL

Men

Women
Figure 2

Survival rate (%)

(years)

NET
Squamous cell carcinoma
Sarcoma
Carcinoma
Adenocarcinoma
Small cell carcinoma
Lymphoma (total)
Figure 4

A

Per 100,000

lymphoma (Total)
DLBCL
MALT lymphoma
other lymphoma

(year)

B

All

Men

Women

Survival rate (%)

MALT lymphoma
DLBCL
Other lymphoma

(years) 0 2.5 5 7.5 10 12.5 15

0 25 50 75 100

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The epidemiology of gastric cancers in the era of Helicobacter pylori eradication: a nation-wide cancer registry-based study in Taiwan


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