EFFECTS OF *HELICOBACTER PYLORI* TREATMENT ON INCIDENCE OF GASTRIC CANCER IN OLDER INDIVIDUALS

Short Title: HP treatment and gastric cancer in elderly

Wai K Leung[1], Irene OL Wong[2], Ka Shing Cheung[1], Kar Fu Yeung[2], Esther W Chan[3], Angel YS Wong[3,4], Lijia Chen[1], Ian CK Wong[3,5], David Y Graham[6]

[1]Department of Medicine, University of Hong Kong, Hong Kong

[2]School of Public Health, University of Hong Kong, Hong Kong

[3]Centre of Safe Medication Practice and Research, Department of Pharmacology & Pharmacy, University of Hong Kong, Hong Kong

[4]Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, United Kingdom

[5]UCL School of Pharmacy, University College London, London, United Kingdom

[6]Department of Medicine, Michael DeBakey VAMC and Baylor College of Medicine, Houston, Texas, USA

Grant Support: Nil

Abbreviations: CI, confidence interval; HP, *Helicobacter pylori*; SIR, standardized incidence ratio

Correspondence to:

Wai K. Leung, MD, Department of Medicine, University of Hong Kong, Queen Mary Hospital, 102 Pokfulam Road, Hong Kong

Email: waikleung@hku.hk; Phone: +852 2255 3348; Fax: +852 2816 2863

Disclosure: WKL has received honorarium for attending advisory board meetings of Takeda and Abbot Laboratories. None to declare for other authors.

Authors' Contribution: WKL is responsible for the conception and design of this study; as well as data interpretation and drafting of the manuscript. EWC, AYW and LJC are involved in data collection. IOLW, KSC and KFY are involved in data analysis, data interpretation and drafting of the manuscript. ICKW and DYG are responsible for data interpretation and critical review of the manuscript.

ABSTRACT

Background & Aims: Although eradication of *Helicobacter pylori* infection reduces the risk of gastric cancer, few data are available on its effects in older subjects. We compared the age-specific risk of gastric cancer in a large cohort of subjects who received *H pylori* eradication therapy vs a matched general population.

Methods: We searched the Hospital Authority database of Hong Kong to identify individuals with *H pylori* infection who had received a course of clarithromycin-containing eradication therapy from January 2003 through December 2012. We compared the gastric cancer incidence in this cohort with the expected incidence for the local general population by retrieving the gastric cancer incidence of the age- and sex-matched population from 2003 through 2014 (the latest available year) from the Hong Kong Cancer Registry. The primary outcome was the incidence of gastric cancer development in the cohort treated for *H pylori* infection vs the expected number of gastric cancer cases in the general population. Analyses were conducted by a priori age groups of less than 40 years, 40–59 years, and 60 years or older.

Results: Among 73,237 subjects infected with *H pylori* who received eradication therapy, 200 (0.27%) developed gastric cancer during a median follow-up time of 7.6 years. Compared with the matched general population, the gastric cancer risk was significantly lower in subjects 60 years or older who had received *H pylori* treatment (standardized incidence ratio [SIR], 0.82; 95% CI, 0.69–0.97; *P*=.02) but not in younger groups. When data were stratified based on time from *H pylori* treatment (less than 5 years, 5–9 years, and 10 or more years), the risk of gastric cancer was significantly lower than the general population 10 or more years after eradication in the group 40–59 years old (SI, 0.32; 95% CI 0.08–0.88; *P*=.04) and the group 60 years or older (SIR, 0.42; 95% CI 0.42–0.84; p = 0.02) than the other age groups.

Conclusions: In an analysis of data from a public hospital database on Hong Kong, we associated treatment of *H pylori* infection with a lower risk of gastric cancer, particularly in older subjects, 10 or more years after treatment.

Keywords: chemoprevention; antibiotics; stomach cancer; bacteria

INTRODUCTION

Gastric cancer is the fifth most common cancer in the world with approximately one million new cases diagnosed each year; and the majority are from less developed regions including Asia.[1] Although the incidences of gastric cancer are generally declining, it is estimated that the total number of cases, or the actual disease burden, will maintain at a constant level for next few decades due to the ageing population.[2]

Helicobacter pylori, which infects more than 50% of individuals in less developed regions,[3] has been identified as the major etiological factor for gastric cancer. *H pylori* associated gastric carcinogenesis involves a long process which progresses through multiple histological stages including chronic gastritis, atrophic gastritis, metaplastic mucosa, intramucosal neoplasia and finally invasive cancer. [4, 5] As the incidence of pre-neoplastic gastric lesions parallels with the increase in age,[6, 7] the age at gastric cancer diagnosis is usually quite high In Hong Kong, the median age of gastric cancer diagnosis in men and women is 71 and 68 years, respectively, with the corresponding age-standardized rate of 9.5 and 6.1 per 100,000 population.[8]

Recent meta-analyses have shown that eradication of *H pylori* reduces the incidence of gastric cancer by approximately 33-47%.[9, 10] However, a randomized controlled trial from China suggested that patients with pre-existing pre-neoplastic lesions may not benefit from *H pylori* eradication in terms of gastric cancer prevention,[11] implying a point of no return in the *H pylori*-associated gastric carcinogenesis cascade. In the Maastricht V Consensus Report, it is also recommended that the risk of developing gastric cancer can be reduced more effectively by employing eradication treatment before the development of atrophy and intestinal metaplasia [12]. Although it is intuitive to give *H pylori* eradication therapy before the

development of pre-neoplastic gastric lesions for gastric cancer prevention, majority of older infected population already have some atrophic changes and the actual benefits of treating *H pylori* in these subjects remains uncertain. Because the increase in cancer risk increases exponentially with age, if eradication aborted the exponential increase, *H pylori* eradication should benefit the older age population and reduce their risk of developing gastric cancer.

Based on a large cohort of *H pylori* infected subjects who had received clarithromycin-containing eradication therapy in Hong Kong, we determined the age-stratified risk of gastric cancer development and compared with the expected gastric cancer risk in the matched local general population.

METHODS

Study Design and Data Source

We identified subjects who had received a course of clarithromycin-containing triple therapy for *H pylori* infection between January 2003 and December 2012 in all public hospitals managed by the Hospital Authority in Hong Kong.[13] The Hospital Authority is the sole public health service provider serving a local population of 7.3 million under a heavily subsidized public health care system.[14] It manages 87% of all hospital beds in Hong Kong and has more than 7.5 million outpatient specialist consultations per year. These subjects were identified from the Clinical Data Analysis and Reporting System (CDARS) of the Hospital Authority which is a territory-wide health care database. The CDARS contained all essential clinical information including patients' demographics, hospitalization, visits to outpatient clinics and emergency departments, diagnoses, laboratory results, procedures, prescriptions, dispensing of medications and death. Individual patient's information is anonymized and each patient is

given a unique patient's identifier in the CDARS. The International Classification of Diseases, Ninth Revision (ICD-9), was used for disease coding and our previous studies had verified the accuracy of the coding in CDARS with high positive and negative predictive values.[15] The study protocol was approved by the Institutional Review Board of the University of Hong Kong and the Hong Kong West Cluster of Hospital Authority, Hong Kong (reference no: UW 16-545).

Subjects

We identified all adults, aged 18 or above, who had been prescribed their first course of clarithromycin-containing triple therapy for *H pylori* infection. Treatment with clarithromycin triple therapy was identified by the co-prescription of one of the proton pump inhibitors (PPIs) with clarithromycin and either amoxicillin or metronidazole, with doses as described previously.[17] The start date of the prescriptions should be the same, with an overlapping duration of 7 to 14 days. Since clarithromycin-containing triple therapy is the most commonly prescribed first-line therapy for *H pylori* in Hong Kong with a high success rate[16], it is still the current first line treatment for *H pylori*. Treatment for *H pylori* with non-clarithromycin-containing therapy as first-line treatment, mainly bismuth-based therapy, were only noted in 2,285 patients during the study period and hence were not included in this analysis. We excluded subjects who had prior history of gastrectomy, with gastric cancer prior to or within 12-month after receiving *H pylori* eradication therapy, or diagnosis of gastric ulcer after *H pylori* therapy as these may represent missed cancers. (Supplementary Figure 1).

***H pylori* Treatment Outcomes**

We performed subgroup analysis by dividing the *H pylori* treated subjects into two groups according to the treatment outcomes. As post-treatment *H pylori* status was not available in the CDRAS, we identified subjects who failed the first line clarithromycin-containing treatment and needed retreatment for *H pylori*. These subjects were identified by the subsequent prescription of another course of eradication therapies including a second line (bismuth-containing quadruple therapy or PPI-levofloxacin-amoxycillin) or a third line therapy (rifabutin-containing therapy) or a repeated prescription of clarithromycin-containing triple therapy with an overlapping duration of 7 to 14 days. This group of subjects who needed repeat treatment for *H pylori* was labelled the "Retreatment" group whereas the patients with a single course of clarithromycin-containing triple therapy were designated as the "Treatment Success" group in subsequent analysis.

General population as the comparison group

H pylori testing is not routinely performed in the local public health care system except in symptomatic patients such as dyspepsia or performed during upper endoscopic examinations for other reasons such as anemia work up. The currently available pre-treatment testing for *H pylori* included urea breath test and biopsy-based tests such as rapid urease test, histology and bacterial culture. Serological tests and *H pylori* stool antigen tests are not available in local hospitals. Our current practices would treat all patients with confirmed *H pylori* infection. Hence, it would not be possible to identify a group of *H pylori* infected patients who had not received treatment for comparison. Instead, we compared the gastric cancer incidence in this *H pylori* treated cohort with the expected gastric cancer incidence in the local general population by retrieving the gastric cancer incidence of the age- and sex-matched population from year 2003 to 2014 (the latest available year) in the Hong Kong Cancer Registry[8]. This cancer registry is a population-based registry covering the entire local population and is one

of the accredited members of the International Association of Cancer Registries. The data available in the registry enabled the calculation of the expected number of gastric cancer cases in the study cohort after adjusting for the age and sex effect.

Outcome

The primary outcome was the incidence of gastric cancer development in the cohort treated for *H pylori* infection vs the expected number of gastric cancer cases in the general population. The date of diagnosis of gastric cancer (ICD-9 coding 151) for the study cohort was defined as the first date of hospitalization for gastric cancer workup or treatment. Other gastric malignancy including gastric lymphoma were not included.

Statistical analyses

Person-years at risk of gastric cancer were derived for each patient from the first date of clarithromycin-containing triple therapy until the date of gastric cancer diagnosis in the respective years or the date of censoring in this cohort. Patients were censored at death, diagnosis of gastric cancer or the end of 2015. All analyses were conducted by a priori age groups of <40 years, 40-59.9 years and ≥60 years.

We estimated the standardized incidence ratio (SIR) and the expected cumulative incidence curve based on the methods outlined in Finkelstein et al.[18] The mean incidence rates by five-year age group in the years of 2003-2014 were used in this estimation. The observed number of gastric cancer cases was assumed to follow a Poisson distribution. The SIR was estimated in terms of the ratio of observed to expected gastric cancer cases with the exact 95% confidence interval (CI). One-sample log-rank test for incidence rates[18] was used to contrast any statistical difference between the observed and the expected values. The observed

cumulative incidence curves for each age group were derived as the complement of the Kaplan-Meier survival curves. Stratified analyses were performed according to the treatment outcome ("Treatment Success" and "Retreatment") and subject's sex. A *p* value of 0.05 or less was used to indicate statistical significance. All analyses were performed by using R 3.4.1.

RESULTS

Gastric cancer risk in the *H pylori* treated cohorts

A total of 73,237 patients had received a course of clarithromycin-containing triple therapy for *H pylori* during the study period. The baseline characteristics of these patients are shown in Table 1. Among them, 9,840 (13.4%) patients needed re-treatment for *H pylori*, including 130 patients who needed third-line therapy. The median duration from the time of prescription of clarithromycin-containing triple therapy to the second-line and third-line therapy was 1.5 years (IQR: 0.2 – 4.8) and 2.3 years (IQR: 1.1 – 4.9). The remaining 63,397 patients who had no re-treatment for *H pylori* were included in the "Treatment Success" group (Supplementary Figure 1).

Overall, 200 (0.27%) patients developed gastric cancer with a median follow-up of 7.6 (IQR 5.1 to 10.3 years) and the overall incidence rate was 3.6 per 10,000 person-years). The number of gastric cancer cases in the "Treatment Success" and "Re-treatment" group was 153 (0.24%; 3.2 per 10,000 person-years) and 47 (0.48%; 6.2 per 10,000 person-years), respectively. The relative risk (RR) of gastric cancer in the Retreatment group as compared to the Treatment Success group was 2.0 (95% confidence interval (CI) 1.4 to 2.7; p <0.001).

The risks of gastric cancer after stratification by age of *H pylori* treatment, sex and treatment outcomes were shown in Table 2. The risk of gastric cancer was significantly higher in male subjects who received *H pylori* treatment at older age (≥60 years) than the corresponding female subjects (RR 1.8; 95% CI 1.3 to 2.6; $p = 0.001$). The risk of gastric cancer was also higher among middle-aged (40-59 years) subjects who required re-treatment for *H pylori* (RR 2.5; 95% CI 1.4 to 4.4; p = 0.003).

Comparison to the matched general population

Figure 1A showed the cumulative incidence of gastric cancer in the whole *H pylori* treated cohort when compared to the expected gastric cancer incidence in the age- and sex-matched local population ($p = 0.28$), and Figure 1B showed the results after stratification by treatment outcomes. The "Treatment Success" group tended to have lower incidence of gastric cancer ($p = 0.06$) whereas the "Re-treatment" group tended to have a higher incidence than expected in the general population ($p = 0.13$).

Table 3 compared the gastric cancer incidences in our cohort, after stratification by age of *H pylori* treatment, with the expected incidences from the matched general population. The incidence of gastric cancer was significantly lower than the general population in the older (≥60 years) age group (SIR, 0.82; 95% CI, 0.69 to 0.97; p=0.02) but not in the other two younger age groups (Figure 2). Similar results were observed in the Treatment Success group but not in the Re-treatment group (Table 3; Supplementary Figure 2). Notably, the SIR of gastric cancer among those receiving treatment between 40 and 59 years of the Re-treatment group was significantly higher than the corresponding general population (SIR, 2.43; 95% CI, 1.44 to 3.86). As the difference in gastric cancer risk was observed in older subjects, stratified

analysis was conducted according to patient's sex in this group (Male, SIR: 0.81 [0.65 -1.00], *p*=0.05; Female, SIR: 0.84 [0.62 – 1.12], *p*=0.25).

Follow-up durations after *H pylori* treatment and risk of gastric cancer

We also determined the risk of gastric cancer during different time points after *H pylori* treatment (<5, 5-9 and ≥10 years). The incidences of gastric cancer in the *H pylori*-treated cohort were comparable to the age-matched general population in the first 10 years' after eradication (Figures 3A and 3B). However, after ≥10 years of *H pylori* treatment, the risk of gastric cancer among the older (≥60years) and middle (40-59 years) age groups became significantly lower than the matched general population (≥60 years: SIR 0.42, 95% CI 0.18 to 0.84; and 40-59 years: SIR 0.32, 95% CI 0.08 to 0.88; Figure 3C). Similar results were observed among the Treatment Success group (Table 4; Supplementary Figure 3).

DISCUSSION

The results from this territory-wide study from Hong Kong provides strong support that *H pylori* treatment, even when given to those aged 60 or above who are the highest risk group, could still lower the risk of gastric cancer development. When compared to matched general population, which comprises of both *H pylori*-infected and non-infected individuals, the risk of gastric cancer was reduced by 18% in the older (≥60) age group who had received *H pylori* treatment. When further stratified by the time from *H pylori* treatment, the risk reduction was more significant ≥10 years after receiving eradication therapy. Since both *H pylori* infection and gastric cancer are more prevalent among the older populations, these findings carry

major clinical and public health impact that even older subjects would still benefit from eradication therapy.

H pylori infection, which is usually acquired early in life, leads to chronic gastric inflammation in all, and gastric cancer in a small proportion of subjects. If left untreated, most subjects would remain infected unless they reach a stage of severe atrophy that is unfavourable for *H pylori* to thrive. Treatment of *H pylori* have been shown, in recent meta-analyses,[9, 10] to reduce the risk of gastric cancer by at least 33%. While treatment before atrophy develops should prevent most of the subsequent cancers, the role, if any, of *H pylori* eradication therapy after development of pre-neoplastic changes is unclear. For example, the study by Wong et al. suggested that individuals with pre-existing pre-neoplastic gastric lesion still progressed to gastric cancer despite eradication of *H pylori*.[11] In contrast, *H pylori* eradication even after endoscopic resection of early gastric cancer, which should be associated with concurrent pre-neoplastic lesions in the remaining stomach, has been shown to reduce development of metachronous cancers.[19] Our findings therefore provide further support that eradication therapy given in later part of life could still significantly reduce the risk of gastric cancer development. The findings of significant difference in gastric cancer incidence in the older age group are not unexpected as the gastric cancer incidence is generally very low among the younger age group and increases exponentially with age. Early treatment at the time of exponential increase would be expected to have the greatest numerical effect on gastric cancer in that the risk would likely be stabilized at the time of eradication whereas the untreated would continue to increase in risk[20]. Although subsequent gastric cancer risk is not totally prevented by *H pylori* eradication therapy, the gastric cancer incidence is still significantly lower among older subjects. These results are consistent with results of the long-term follow-up of a randomized trial from China which showed that *H*

pylori treatment could still benefit subjects older than 55 years in terms of gastric cancer prevention with an odds ratio of 0.36 against those receiving placebo.[21] Importantly, our study showed that the risk of gastric cancer in the older eradicated group was actually lower than that of the matched general population which included both *H pylori* infected and non-infected subjects. While it is estimated that the local prevalence of *H pylori* infection to be about 56%,[3] the expected population gastric cancer risk in the matched general population should be substantially lower than the risk of gastric cancer of our *H pylori* infected cohort.

Our results showed that the risk of gastric cancer decreased with longer time lapsed from *H pylori* eradication therapy, consistent with eradication aborting or markedly decreasing the exponential increase in cancer experienced by the untreated subjects. Ten years after eradication, the risk of gastric cancer was 58% lower in the ≥60 years group and 68% lower in the 40-59 year groups when compared to the age- and sex-matched general population. The risks were even lower in these two age groups with treatment success (Table 3). Although there was no significant difference in the gastric cancer risk of the younger age group (<40 years), the risk of gastric cancer was actually very low in this age group which reflects the relative slow annual increase in gastric cancer in young subjects. It is therefore particularly important to determine the long-term risk of gastric cancer in this younger age group to confirm whether early *H pylori* eradication could possibly eliminate gastric cancer in future studies.

We showed that those who received re-treatment for *H pylori* after failure of clarithromycin-containing triple therapy had a two-fold increase in risk of gastric cancer development as compared to those with treatment success. This group largely consisted of individuals who have delayed rather than actual failure of eradication. These results are consistent with a

study from Taiwan showing a marked difference in gastric cancer risks on early *versus* delayed *H pylori* eradication.[22] In particular, the risk of gastric cancer among the middle (40-59) age group who required retreatment in this study was significantly higher than general population (SIR = 2.43). Due to the long lag time of *H pylori* eradication to prevent gastric cancer development as shown in Figure 3, *H pylori* should be given earlier to maximize the potential benefits of *H pylori* eradication.

This study has several strengths. First, this is a territory-wide study that included more than 73,000 unselected *H pylori* infected subjects who had received a course of clarithromycin-containing triple therapy for *H pylori* in Hong Kong with follow-up of up to 13 years. It is in marked contrast to previous randomized trials that included a relatively small number of high-risk patients only. Second, with the use of a very comprehensive electronic health database of the Hong Kong Hospital Authority that has been used to publish high quality studies previously,[8, 15, 23], we were able to determine the risk of gastric cancer in subjects according to age of *H pylori* treatment. We further utilized the gastric cancer incidence data from the Hong Kong Cancer Registry, a population registry, to estimate the expected gastric cancer incidences in the age- and sex-matched local population, which comprises of both *H pylori*-positive and negative subjects. Although the Cancer Registry includes all cancer patients in Hong Kong and the Hospital Authority is responsible for about 90% of the local health care services only, most cancer patients would be managed under the Hospital Authority due to resource and cost issues.

At the same time, this study has limitations. First, we did not have a similar cohort of untreated *H pylori*-infected subjects as the comparison group. As the local practices are to treat all *H pylori*-infected subjects, these untreated subjects would not be available as control.

Instead, we compared the risk of gastric cancer in our cohort with the general population in Hong Kong based on data from the Hong Kong Cancer Registry. Even with the inclusion of both *H pylori* infected and non-infected subjects in the general population, we could still demonstrate a significantly lower risk of gastric cancer among the older subjects who had received treatment for *H pylori*. Second, the baseline histology of these subjects was not available in the electronic database and hence we could not further stratify the gastric cancer risk according to baseline gastric pathology. However, it is anticipated that the percentage of patients with pre-neoplastic gastric lesions would increase with ages [6,7] and a large proportion of our *H pylori* infected subjects would harbour pre-neoplastic lesions in the stomach. Third, while *H pylori* infection is more associated with non-cardia gastric cancer, the analysis should include subgroup analysis according to tumor location. However, information on tumor location is not available in the Hong Kong Cancer Registry, hence further analysis regarding non-cardia cancer was not possible. Fourth, although it is a routine local practice to check for *H pylori* status after treatment, this piece of information is not available in the electronic database. Hence, we could only broadly classify the treatment outcome based on need of re-treatment. The overall re-treatment rate in this cohort was 13.4%, which is comparable to the reported treatment success rate of clarithromycin-containing triple therapy during the study period in Hong Kong.[16] Moreover, the primary analysis included all patients who had received *H pylori* treatment rather than restricted to those with successful eradication only. Lastly, we only included patients who had received clarithromycin-containing triple therapy in this analysis as this regimen is still, up to this moment, the most commonly prescribed first-line treatment for *H pylori* in Hong Kong. During this study period, only 2,285 (or 3% of all first-line therapy for *H pylori*) of subjects were given non-clarithromycin containing therapy as first line therapy for *H pylori*.

In conclusion, our findings from this territory-wide cohort study support the notion that although prevention of most gastric cancers may require treatment before the onset of atrophic changes, *H pylori* eradication could still reduce gastric cancer development in the older populations. There was a 18% reduction in gastric cancer incidences among older (≥60 years of age) subjects who had received *H pylori* treatment, when compared to matched general population who may not even have *H pylori* infection and hence a low risk of gastric cancer. Our findings would be in strong support for *H pylori* eradication in all age groups to prevent gastric cancer development.

REFERENCES

1. Ferlay J, Soerjomataram I, Ervik M, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available at: http://globocan.iarc.fr. Accessed: July 12, 2017.
2. IARC *Helicobacter pylori* Working Group (2014). *Helicobacter pylori* Eradication as a Strategy for Preventing Gastric Cancer. Lyon, France: International Agency for Research on Cancer (IARC Working Group Reports, No. 8). Available at: http://www.iarc.fr/en/publications/pdfs-online/wrk/wrk8/index.php. Accessed: July 12, 2017.
3. **Hooi JKY, Lai WY, Ng WK**, **Suen MM**, et al. Global Prevalence of Helicobacter pylori Infection: Systematic Review and Meta-analysis. Gastroenterology 2017;153:420-9
4. Correa P. Human gastric carcinogenesis: a multistep and multifactorial process--First American Cancer Society Award Lecture on Cancer Epidemiology and Prevention. Cancer Res 1992;52:6735-40.
5. Graham DY. Helicobacter pylori update: gastric cancer, reliable therapy, and possible benefits. Gastroenterology 2015;148:719-31.e3.
6. de Vries AC, Meijer GA, Looman CW, et al. Epidemiological trends of pre-malignant gastric lesions: a long-term nationwide study in the Netherlands. Gut 2007;56:1665-70.
7. Sonnenberg A, Lash RH, Genta RM. A national study of *Helicobactor pylori* infection in gastric biopsy specimens. Gastroenterology 2010;139:1894-1901.e2; quiz e12.
8. Hong Kong Hospital Authority. Hong Kong Cancer Registry. Available at: http://www3.ha.org.hk/cancereg/. Accessed: July 12, 2017.
9. Ford AC, Forman D, Hunt RH, Yuan Y, Moayyedi P. Helicobacter pylori eradication therapy to prevent gastric cancer in healthy asymptomatic infected individuals: systematic review and meta-analysis of randomised controlled trials. BMJ 2014;348:g3174.
10. **Lee YC, Chiang TH**, Chou CK, et al. Association Between *Helicobacter pylori* Eradication and Gastric Cancer Incidence: A Systematic Review and Meta-analysis. Gastroenterology 2016;150:1113-1124.e5.
11. Wong BC, Lam SK, Wong WM, et al. *Helicobacter pylori* eradication to prevent gastric cancer in a high-risk region of China: a randomized controlled trial. JAMA 2004;291:187-94.
12. Malfertheiner P, Megraud F, O'Morain CA, et al. Management of Helicobacter pylori infection - the Maastricht V/Florence Consensus Report. Gut 2017;66:6-30.
13. Cheung KS**,** Chan EW, Wong AY, et al. Long-term proton pump inhibitors and risk of gastric cancer development after treatment for *H. pylori*: A population-based study. Gut 2018;67:28-35.
14. The Hospital Authority. Hospital Authority statistical report 2012–2013. Available at: http://www.ha.org.hk/haho/ho/stat/HASR1415_2.pdf. Accessed: July 12, 2017.
15. **Chan EW, Lau WC**, Leung WK, et al. Prevention of Dabigatran-Related Gastrointestinal Bleeding With Gastroprotective Agents: A Population-Based Study. Gastroenterology 2015;149:586-95.e3.
16. Hung IF, Chan P, Leung S, et al. Clarithromycin-amoxycillin-containing triple therapy: a valid empirical first-line treatment for *Helicobacter pylori* eradication in Hong Kong? Helicobacter 2009;14:505-11.
17. Wong AY, Wong IC, Chui CS, et al. Association Between Acute Neuropsychiatric Events and *Helicobacter pylori* Therapy Containing Clarithromycin. JAMA Intern Med 2016;176:828-34.

18. Finkelstein DM, Muzikansky A, Schoenfeld DA. Comparing survival of a sample to that of a standard population. J Natl Cancer Inst 2003;95:1434-9.
19. Yoon SB, Park JM, Lim CH, et al. Effect of Helicobacter pylori eradication on metachronous gastric cancer after endoscopic resection of gastric tumors: a meta-analysis. Helicobacter 2014;19:243-8.
20. Shiotani A, Cen P, Graham DY. Eradication of gastric cancer is now both possible and practical. Semin Cancer Biol 2013;23:492-501
21. Li WQ, Ma JL, Zhang L, et al. Effects of Helicobacter pylori treatment on gastric cancer incidence and mortality in subgroups. J Natl Cancer Inst 2014;106.
22. Wu CY, Kuo KN, Wu MS, et al. Early Helicobacter pylori eradication decreases risk of gastric cancer in patients with peptic ulcer disease. Gastroenterology 2009;137:1641-8.e1-2.
23. Wong AY, Root A, Douglas IJ, et al. Cardiovascular outcomes associated with use of clarithromycin: population based study. BMJ 2016;352:h6926.

Footnote: Author names in bold designate shared co-first authorship.

FIGURE LEGEND

Figure 1: Cumulative gastric cancer incidences in the *H pylori* treated subjects as compared with the expected gastric cancer incidence in the general population for the (A) whole cohort (n = 73,237) and (B) according to treatment outcomes (treatment success vs re-treatment).

"Expected" refers to the expected number of cases for individuals in the general population with similar age and sex of the entire cohort based on data from the Hong Kong Cancer Registry.

Figure 2: Cumulative incidences of gastric cancer in all *H pylori* treated subjects (n = 73,237), after stratification by age of treatment, as compared with the expected cumulative incidence in the matched general population.

The curves were censored at 13 years. The expected number of gastric cancer cases was calculated using data from the Hong Kong Cancer Registry on individuals in the general population with similar age and sex.

Figure 3: Observed (red line) and expected (black line) incidence rates of gastric cancer in all *H pylori* treated subjects (n = 73,237) and matched general population, according to age and follow-up durations.

Table 1: The baseline characteristics of all *H pylori* treated subjects

	Whole cohort (n=73,237)
Age at triple therapy	55.2 (46.3 – 66.5)*
Male sex	34345 (46.9%)
Duration of follow-up in years	7.6 (5.1 – 10.3)*
History of gastric ulcer	1620 (2.2%)
History of duodenal ulcer	2277 (3.1%)
Upper endoscopy at diagnosis of *H pylori* infection	60,948 (83.2%)
Upper endoscopy during follow-up	25,738 (35.1%)
Need retreatment for *H pylori*	9840 (13.4%)
Diabetes mellitus	9243 (12.6%)
Hypertension	16293 (22.2%)
Dyslipidemia	6243 (8.5%)
Ischemic heart disease	7312 (10.0%)
Atrial fibrillation	3200 (4.4%)
Congestive heart failure	3542 (4.8%)
Cirrhosis	1305 (1.8%)

* interquartile range (IQR)

Numbers in brackets are percentage unless specified

Table 2. Comparison of the risks of gastric cancer in the *H pylori* eradication cohort according to subject's sex and treatment outcomes.

	Age group	Number of subjects	Person-years at risk	Observed number of cases	Relative risk (95% CI)	*p* value*
Sex						
Male	<40 yr	4,376	37,003	2	1.2 (0.2-8.7)	>0.99
Female		5,377	44,710	2		
Male	40-59 yr	15,855	126,740	34	1.3 (0.8-2.0)	0.33
Female		20,206	160,577	34		
Male	≥60 yr	14,114	94,813	84	1.8 (1.3-2.6)	0.001
Female		13,309	95,458	44		
Treatment Outcome						
Re-treatment	<40 yr	1,111	9,701	1	2.6 (0.3-24.9)	0.38
Treatment Success		8,642	72,012	3		
Re-treatment	40-59 yr	3,936	32,370	16	2.5 (1.4-4.4)	0.003
Treatment Success		32,125	254,947	52		
Re-treatment	≥60 yr	4,793	33,970	30	1.4 (0.9-2.2)	0.08
Treatment Success		22,630	156,301	98		

* Fisher's exact test was used to compare the observed incidence in the two treatment groups (success/re-treatment), for each age group.

yr, year

Table 3. Observed number of gastric cancer cases in the *H pylori* treated subjects and the expected number of gastric cancer cases in the general population as stratified by age of *H pylori* eradication and treatment outcomes.*

		HP treatment cohort			General population		
Treatment outcome	**Age group**	**Number of subjects**	**Person-years at risk**	**Observed number of cases**	**Expected number of cases**	**SIR (95% CI)**	***p* value**
All treated patients (n = 73237)	<40 yr	9,753	81,713	4	3.0	1.34 (0.43-3.24)	0.55
	40-59 yr	36,061	287,317	68	56.8	1.20 (0.94-1.51)	0.14
	⩾60 yr	27,423	190,271	128	156.1	0.82 (0.69-0.97)	0.02
Treatment Success (n = 63397)	<40 yr	8,642	72,012	3	2.6	1.15 (0.29-3.13)	0.81
	40-59 yr	32,125	254,947	52	50.2	1.04 (0.78-1.35)	0.80
	≥60 yr	22,630	156,301	98	125.2	0.78 (0.64-0.95)	0.01
Retreatment (n = 9840)	<40 yr	1,111	9,701	1	0.4	2.70 (0.13-13.29)	0.30
	40-59 yr	3,936	32,370	16	6.6	2.43 (1.44-3.86)	<0.001
	≥60 yr	4,793	33,970	30	30.9	0.97 (0.67-1.37)	0.88

*Data on gastric cancer incidence in the general population are from the Hong Kong Cancer Registry. The incidence tables gave annual incidence rates for each sex in 5-year age categories. For each 5-year category, the mean incidence rate between 2003 and 2014 (the latest available year) was used. The Standardized Incidence Ratio (SIR) is for the cohort as compared with the general population.

HP, *Helicobacter pylori;* yr, year

Table 4. Gastric cancer incidence in the *H pylori* treated patients as compared with gastric cancer incidence in the general population, stratified by age of *H pylori* eradication and year of follow-up.*

	HP treatment cohort				General population		
Age group	**Year of follow-up**	**Number of subjects**	**Person-years at risk**	**Observed number of cases**	**Expected number of cases**	**SIR (95% CI)**	***p* value**
All treated patients (n = 73,237)							
<40 yr	<5	9,753	38,948	3	1.0	3.14 (0.80-8.55)	0.04
	5-9	8,076	33,646	1	1.4	0.73 (0.04-3.60)	0.75
	≥10	3,517	9,124	0	0.6	0.00 (0.00-4.61)	0.42
40-59 yr	<5	36,061	143,157	32	21.7	1.48 (1.03-2.06)	0.03
	5-9	28,757	116,811	33	25.9	1.28 (0.89-1.77)	0.16
	≥10	10,851	27,439	3	9.2	0.32 (0.08-0.88)	0.04
≥60 yr	<5	27,423	103,602	66	74.4	0.89 (0.69-1.12)	0.33
	5-9	18,943	72,987	55	65.2	0.84 (0.64-1.09)	0.21
	≥10	5,747	14,198	7	16.6	0.42 (0.18-0.84)	0.02
Treatment success group (n = 63,397)							
<40 yr	<5	8,642	34,500	2	0.8	2.37 (0.40-7.84)	0.21
	5-9	7,114	29,538	1	1.2	0.84 (0.04-4.12)	0.86
	≥10	3,076	7,979	0	0.6	0.00 (0.00-5.30)	0.45
40-59 yr	<5	32,125	127,592	25	19.3	1.30 (0.86-1.89)	0.19
	5-9	25,488	103,252	26	22.8	1.14 (0.76-1.65)	0.50
	≥10	9,551	24,181	1	8.1	0.12 (0.01-0.61)	0.01
≥60 yr	< 5	22,630	85,519	51	59.8	0.85 (0.64-1.11)	0.25
	5-9	15,510	59,648	42	52.1	0.81 (0.59-1.08)	0.16
	≥ 10	4,685	11,586	5	13.3	0.37 (0.14-0.83)	0.02

* Data on gastric cancer incidence in the general population are from the Hong Kong Cancer Registry. The incidence tables gave annual incidence rates for each sex in 5-year age categories. For each 5-year category, the mean incidence rate between 2003 and 2014 (the latest available year) was used. The Standardized Incidence Ratio (SIR) is for the cohort as compared with the general population.

HP, *Helicobacter pylori*