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LETTER

National prevention programs and their effects on gastric cancer Incidence and mortality in East Asian countries

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Gastric cancer (GC) remains one of the most common cancers and leading causes of cancer deaths globally[1] with 60.0% of cases and 56.6% of deaths occurring in East Asia. South Korea and Japan have conducted nationwide GC screening programs for decades but with essential differences in strategies, organization, and coverage[2]. However, China has not implemented any nationwide programs to reduce the heavy burden of gastric malignancies. Although decreasing trends in the incidence and mortality of GC have been observed in all three countries[3,4], the effectiveness of distinct prevention strategies remains unclear.

Incidence and mortality GC data (ICD-10: C16) from the Cancer Information Service for Japan, the Korean Statistical Information Service for South Korea, and the Cancer Registration Annual Reports for China were extracted in this retrospective second data analysis. Surveillance data from the International Agency for Research on Cancer, the World Health Organization mortality database, and the data from the 2021 Global Burden of Disease (GBD) study were used as supplemental data. Summary exposure values of major lifestyle risk factors for GC in Asian populations[5] were sourced from the 2021 GBD study (**Table S1**). Coverage of GC screening and infection rates for *Helicobacter pylori* (*Hp*) were estimated based on nationwide surveys and/or meta-analyses (**Table S2**). The GC screening and infection rates were standardized for age according to Segi's world standard population. The details are described in the Supplementary Material.

Temporal trends in GC incidence and mortality and related policies

Joinpoint regression was used to compute the annual percent change (APC) and 95% confidence interval (95% CI) of the GC age-standardized incidence (ASIR) and mortality (ASMR) during specific time periods[6]. The most significant decrease in the ASIR and ASMR in South Korea occurred since 2010 [$APC_{2010–2021}$: −4.6% (−5.3 to −4.0)] and between 2005 and 2021 [$APC_{2005–2021}$: −6.9% (−7.3 to −6.6)], respectively, 2 years subsequent to the screening expansion in 2003 (**Figure 1A**). The most remarkable decline in the ASIR and ASMR in Japan occurred between 2013 and 2019 [$APC_{2013–2019}$: −6.0% (−7.4 to −4.9)] and throughout the nationwide GC screening since 1983 and along with the increased adoption of endoscopy since 2016, respectively. There was a decline in the ASIR [APC: −5.3% (−5.9 to −4.7)] and ASMR [APC: −4.9% (−5.8 to −4.2)] for GC in China between 2010 and 2018. The timing suggests that the decline in the ASIR and ASMR for GC is likely due to the protective effect of local screening programs in part, as summarized in **Table S3.**

Table S4 shows the changes in ASIR and ASMR between 2004 and 2018, a period for which data were available for the three countries. The ASIR average APC (AAPC) was −2.5% (−2.8 to −2.1) in Japan (from 42.2 to 29.8/100,000) and −2.2% (−2.7 to −1.7) in South Korea (from 41.2 to 30.7/100,000), which is comparable to the ASIR AAPC in China [−2.6% (−2.9 to −2.3)]. However, the ASMR AAPC decreased most rapidly in South Korea [−6.8% (−6.9 to −6.7)], followed by Japan [−3.8% (−3.9 to −3.7)] and China [−2.7% (−3.1 to −2.3)].

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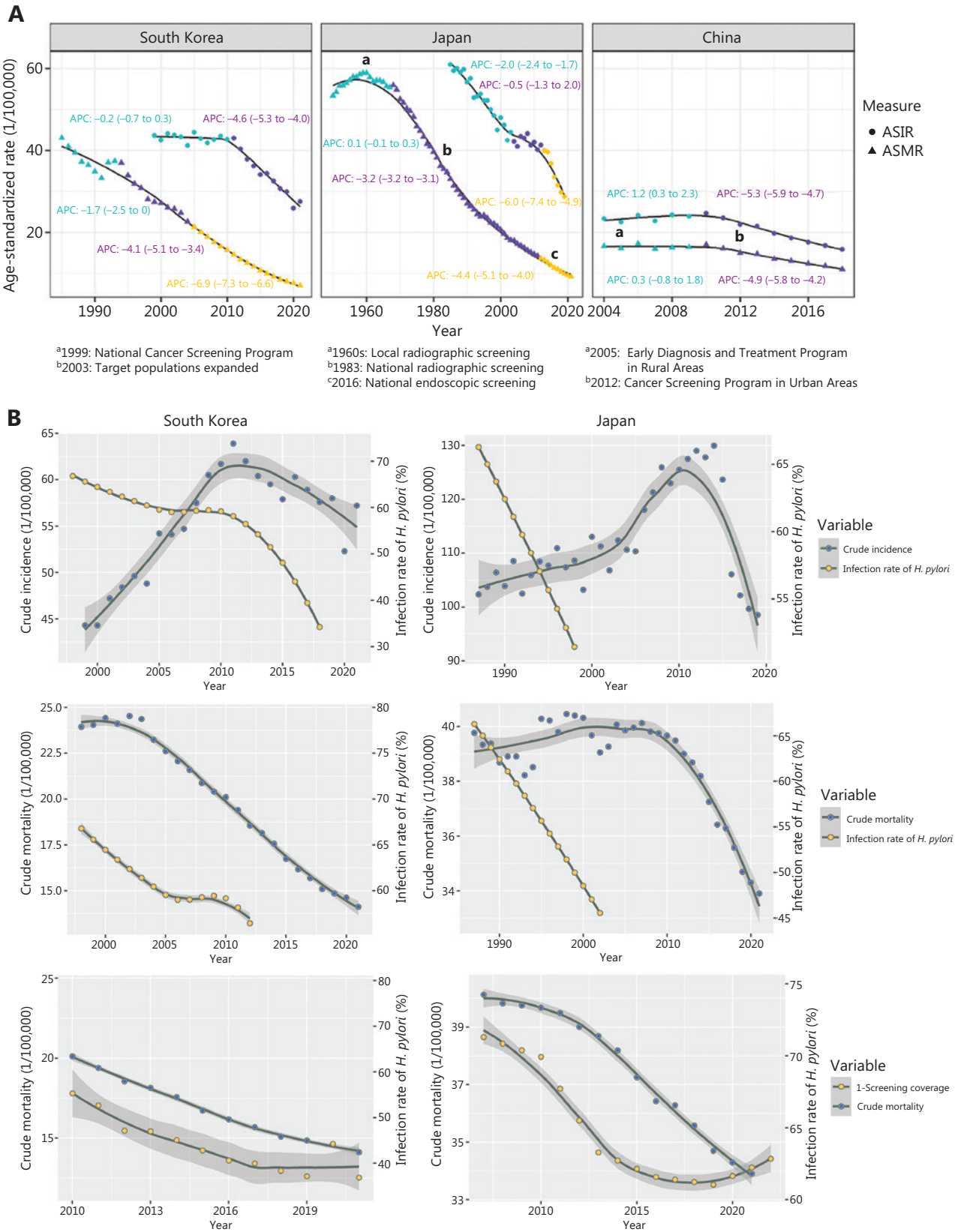
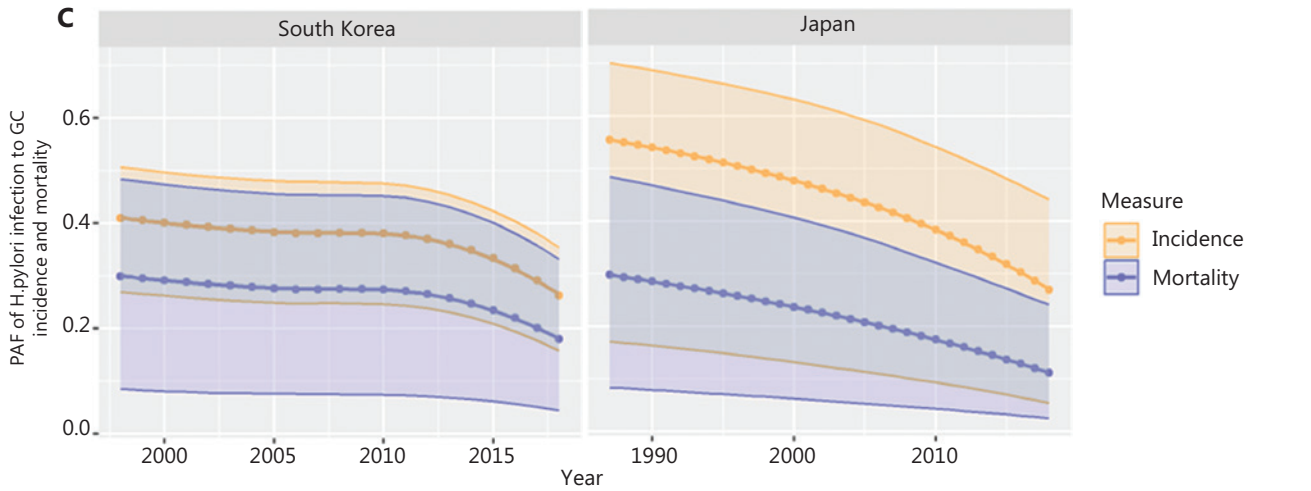
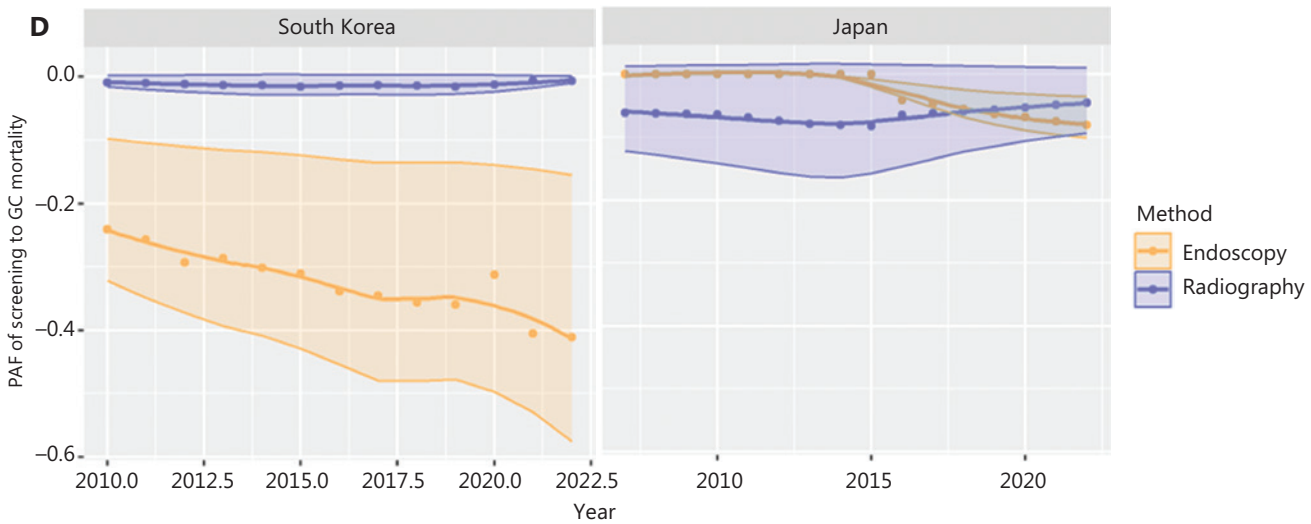


Figure 1 Continued



PAF (95%CI) of *H. pylori* to	1987	1998	2018
Incidence in South Korea	–	0.41 (0.27 to 0.51)	0.26 (0.15 to 0.35)
Incidence in Japan	0.55 (0.17 to 0.70)	0.49 (0.14 to 0.64)	0.27 (0.05 to 0.44)
Mortality in South Korea	–	0.30 (0.09 to 0.48)	0.18 (0.04 to 0.33)
Mortality in Japan	0.30 (0.08 to 0.48)	0.25 (0.07 to 0.42)	0.11 (0.02 to 0.24)



PAF (95%CI) of GC death of	2007	2010	2022
Endoscopy in South Korea	–	−0.24 (−0.32 to −0.10)	−0.41 (−0.57 to −0.16)
Endoscopy in Japan	0.00 (0.00 to 0.00)	0.00 (0.00 to 0.00)	−0.08 (−0.10 to −0.04)
Radiography in South Korea	–	−0.01 (−0.02 to 0.00)	−0.01 (−0.01 to 0.00)
Radiography in Japan	−0.06 (−0.13 to 0.01)	−0.06 (−0.13 to 0.01)	−0.05 (−0.09 to 0.01)

Figure 1 Continued

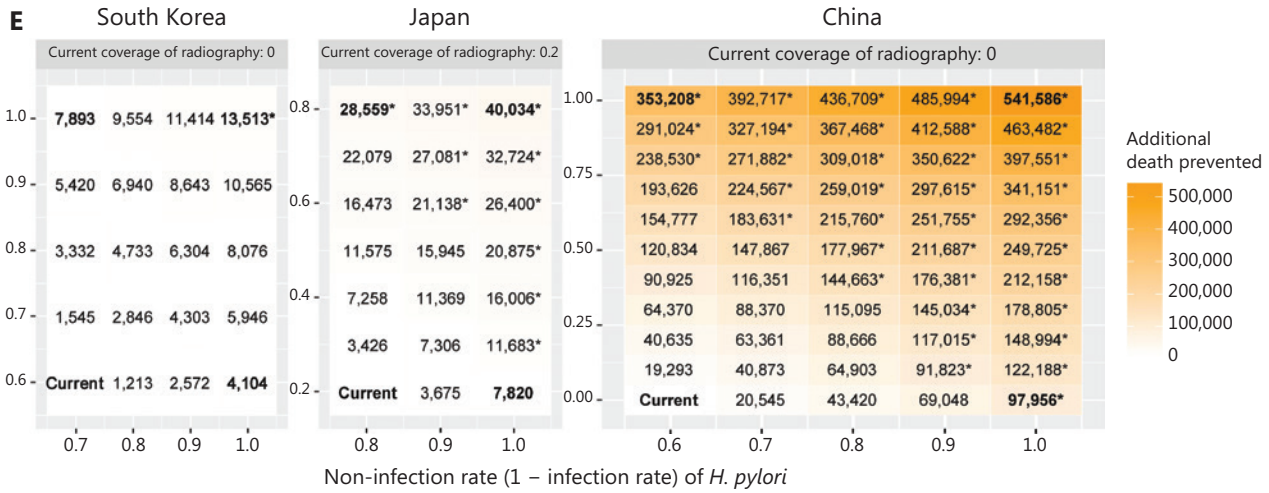


Figure 1 Secular trends of age-standardized gastric cancer incidence and mortality and issuance of related preventive policies (A); Covariates of *Hp* infection rate and coverage of screening with gastric cancer (B); PAFs of *Hp* infection (C), endoscopy and radiography (D) to gastric cancer incidence and/or mortality; Gastric cancer deaths prevented in different scenarios in 2030 (E) in South Korea, Japan, and China. The estimated number of GC cases and deaths prevented by different strategies in 2030 based on the latest exposure rates with a gradient of 0.1 as follows: *Hp* infection rate of 0.2 in Japan and 0.3 in South Korea in 2018, and 0.4 in China between 2015 and 2019; endoscopy coverage of 0.2 in Japan in 2022 and 0.6 in South Korea in 2021; and radiography coverage of 0.2 in Japan and 0 in South Korea in 2022. The screening coverage was far below 0.05 and assumed to be zero in China because there was no nationwide screening for GC. Bold values represented current status and three ideal conditions, including 100% coverage of endoscopy, 0% infection rate of H.plori, and both. *Results with statistical significance.

Covariation of *Hp* infection and screening coverage with GC

Increased GC screening was recorded in South Korea between 2010 and 2021 [AAPC: 2.7% (1.6–3.7)], covering 63.8% of the eligible population in 2022 with endoscopy as the major modality (60.7% in 2022; **Table S5**). The overall coverage of screening in Japan increased from 28.7% in 2007 to 37.2% in 2022 [AAPC: 2.0% (−0.5 to 4.7)]. Radiography was more common but decreased over time, whereas endoscopy was initially applied less often but was on the rise since the nationwide implementation in 2016.

Figure 1B demonstrates the reduced *Hp* infection rates in parallel to the decreasing incidence and mortality of GC 10–20 years later in South Korea and Japan. The increasing coverage of screening was followed by a declining mortality rate within 3–10 years. Ridge regression or generalized linear mixed models demonstrated a positive association between the *Hp* infection rate and the incidence in South Korea [β: 1.13 (0.14–2.12)] and with mortality in both South Korea [β: 0.65 (0.04–1.25)] and Japan [β: 0.87 (0.74–1.01)]. An inverse association was also noted between endoscopy coverage and crude mortality in South Korea [β: −1.14 (−1.82 to −0.47)] and Japan [β: −0.77 (−1.02 to −0.53)], but not for radiography coverage (**Table S6**). The associations did not change substantially in Japan with respect to the sensitivity analysis based on the imputed data (**Table S7**).

GC attributable to *Hp* infection and nationwide screening

The population attributable fractions (PAFs) of *Hp* infection were estimated for endoscopic or radiographic screening based on the level of exposure in the general populations (P) and relative risks (RRs) of factors with GC incidence and death (**Table 1**). Considering the lag effect of the exposures and the average clinical course of GC over 5 years[7], the number of cases in 2022 attributable to the factors in 2012 and the number in 2030 to the latest exposures with an approximate 10-year lag time were estimated.

The *Hp* infection PAF for the GC incidence in Japan decreased from 55% in 1987 to 27% in 2018, while GC-associated deaths decreased from 30% to 11%, leading to 45,538 cases and 6,522 deaths in 2022, and 28,169 cases and 6,667 deaths in 2030 (**Figure 1C**). The *Hp* infection PAF was slightly declined in South Korea between 1998 and 2018, resulting in 10,826 cases and 1,895 deaths in 2022, and 10,218 cases and 3,258 deaths in 2030. The number of cases and deaths attributable to *Hp*

Table 1 Gastric cancer cases and deaths attributable to *Hp* infection and nationwide cancer screening in 2022 and 2030 under current strategies

Cancers attributable to *Hp* infection or screening	RR (95% CI)	Exposure in 2012 (%)	Most recent exposure (%)	Number (95% UI)	
				In 2022	In 2030
South Korea					
Cases attributable to *Hp* infection	2.04 (1.53–2.54)	56.45	34.24[a]	10,826 (7,186–13,434)	10,218 (6,304 to 13,512)
Deaths attributable to *Hp* infection	0.61 (0.40–0.92)	56.45	34.24[a]	1,895 (560–3,092)	3,258 (985–5,873)
Deaths prevented by endoscopy	0.52 (0.39–0.79)	47.19	60.74[b]	2,093 (880–2,773)	7,467 (3,021–10,196)
Deaths prevented by radiography	0.80 (0.60–1.06)	5.67	3.08[b]	82 (−14–157)	44 (−21–214)
Japan					
Cases attributable to *Hp* infection	2.88 (1.23–4.53)	29.84	19.64[a]	45,538 (12,284–63,944)	28,169 (6,605–45,658)
Deaths attributable to *Hp* infection	0.61 (0.40– 0.92)	29.84	19.64[a]	6,522 (1,875–11,903)	6,667 (1,795–14,420)
Deaths prevented by endoscopy	0.52 (0.39–0.79)	0.00	15.50[b]	0	4,804 (2,222–6,019)
Deaths prevented by radiography	0.80 (0.60–1.06)	34.50	21.66[b]	3,017 (457–6,170)	2,705 (491–5,349)
China					
Cases attributable to *Hp* infection	1.86 (1.23–2.48)	41.80[c]	40.00[d]	94,928 (37,846–132,885)	215,382 (84,892–302,339)
Deaths attributable to *Hp* infection	0.61 (0.40—0.92)	41.80[c]	40.00[d]	54,831 (16,356–93,672)	97,877 (28,379–168,588)

[a]Exposure in 2018; [b]exposure in 2022; [c]exposure between 2010 and 2014; [d]exposure between 2015 and 2019.

infection reached 94,928 and 54,831 in 2022, and is estimated to be 215,382 and 97,877 in 2030 (**Table 1**).

The absolute values endoscopy PAFs for GC screening increased in Japan and South Korea between 2010 and 2022, while the radiography PAFs decreased slightly in Japan (**Figure 1D**), resulting in 2,039 deaths prevented by endoscopy in South Korea and, 3,017 by radiography in Japan. Under current strategies, the number of deaths prevented by endoscopy would be 7,467 in South Korea and 4,804 in Japan in 2030 (**Table 1**). The number of GC deaths prevented by screening in China was assumed to be 0 due to a lack of nationwide screening program.

Sensitivity analyses were performed using the exposure data in 2017 (5 years before) and 2007 (15 years before) to test the robustness of the 2022 estimates. More deaths attributable to *Hp* infection occurred than deaths prevented by endoscopy and radiography in Japan, but fewer *Hp*-related deaths occurred than deaths prevented by screening in South Korea (**Table S8**).

Reduced GC burden due to *Hp* eradication and screening

The number of additional GC cases and deaths prevented by multiple enhanced strategies, including several ideal scenarios, was predicted. The projected number of GC deaths prevented through full coverage of endoscopy alone in 2030 reached 7,893 in South Korea, 28,559 in Japan, and 353,208 in China, which far exceeded the reduced numbers (4,104, 7,820, and 97,957 in corresponding countries) by cutting down the *Hp* infection rate to zero alone, both of which are impractical and unattainable in real-world conditions (**Figure 1E**). Full coverage of endoscopy combined with a zero *Hp* infection rate is expected to decrease GC deaths to the greatest extent, with 13,513 deaths prevented in South Korea, 40,034 in Japan, and 541,586 in China.

By linking the changes in GC incidence and mortality with the national preventive strategies in Asian countries, that the most rapid decline in mortality was shown to occur within several years of the issuance of related preventive policies in South Korea and Japan. In contrast, GC mortality decreased more slowly in China, a country without nationwide screening programs. The results are suggestive of an early diagnosis of GC due to the interventions and the improvements in GC treatment on secular trends of incidence and mortality.

A major finding in the current study was the superior efficacy of endoscopy in reducing GC deaths compared to radiography. The endoscopy-dominant strategy in South Korea was shown to outperform the radiography-focused approach

in Japan, which was also observed in a synthetic control study[8]. The South Korea strategy holds essential reference value for China, a country with a heavy GC burden but without a nationwide cancer screening program. GC deaths attributable to *Hp* infection were also shown to exceed the deaths prevented by endoscopy in most circumstances. A significant number of GC deaths could be prevented in China by endoscopic screening alone and the number would be significantly increased by jointly implementing *Hp* eradication, according to the 2030 predictions. *Hp* eradication reduces GC mortality by decreasing the incidence, which is highly significant in public health as a primary prevention approach. These conventional effective approaches may not be cost-effective in Western countries with a low incidence of GC. The potential harms of endoscopy or radiography also limit extensive applications of the examinations. Novel non-invasive techniques, such as liquid biopsy, may be highly valuable in countries with a low incidence[9].

This is the first epidemiologic study to quantify and compare the potential impact of nationwide *Hp* eradication on radiographic and endoscopic screeningon the GC burden. Despite the potential ecologic fallacy, unmeasured confounders, such as changes in healthcare access, dietary patterns, diagnostic improvements, and overestimated PAF by assuming an independent effect of *Hp* infection and non-screening of endoscopy, the results herein indicated the benefits of nationwide endoscopic screening in reducing GC mortality and the long-term effect of *Hp* eradication. The findings provide evidence for policy making in GC prevention and control in East Asian countries heavily burdened by GC.

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Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

Conceived and designed the analysis: Wanghong Xu, Ruoxin Zhang.
Collected the data: Min Cai, Ruiqi Xia, Ziyang Wang.
Contributed data or analysis tools: Min Cai, Ruiqi Xia, Ziyang Wang.
Wrote the paper: Min Cai.

Data availability statement

The datasets supporting this article are publicly available. The details were listed in the Supplementary Material.

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