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ARTICLE

The Changing Face of Noncardia Gastric Cancer Incidence Among US Non-Hispanic Whites

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Abstract

Background: The initial step for noncardia gastric carcinogenesis is atrophic gastritis, driven by either *Helicobacter pylori* infection or autoimmunity. In recent decades, the prevalence rates of these two major causes declined and increased, respectively, with changes in Western lifestyles. We therefore assessed gastric cancer incidence trends for US race/ethnic groups, 1995–2013.

Methods: Age-standardized rates (ASRs) from 45 North American Association of Central Cancer Tumor Registries were summarized by estimated annual percentage change (EAPC) and 95% confidence intervals (CIs). Age period cohort models supplemented standard descriptive techniques and projected future trends.

Results: There were 137 447 noncardia cancers in 4.4 billion person-years of observation. Among non-Hispanic whites, the ASR was 2.2 per 100 000 person-years, with an EAPC of –2.3% (95% CI = –2.0% to –2.6%). Notwithstanding this overall decline, EAPCs rose 1.3% (95% CI = 0.6% to 2.1%) for persons younger than age 50 years and fell –2.6% (95% CI = –2.4% to –2.9%) for older individuals. These converging trends manifested a birth cohort effect more pronounced among women than men, with incidence among women born in 1983 twofold (95% CI = 1.1-fold to 3.6-fold) greater than those born in 1951. Age interaction was also statistically significant among Hispanic whites, with slightly increasing vs decreasing EAPCs for younger and older individuals, respectively. Incidence declined regardless of age for other races. Current trends foreshadow expected reversals in both falling incidence and male predominance among non-Hispanic whites.

Conclusions: Dysbiosis of the gastric microbiome associated with modern living conditions may be increasing risk of autoimmune gastritis and consequent noncardia cancer. The changing face by age and sex of gastric cancer warrants analytical studies to identify potential causal mechanisms.

Gastric cancer represents a complex and heterogeneous disease. In general, cardia (upper stomach) tumors may start with damage from acid reflux and/or metabolic syndrome, similar to esophageal adenocarcinoma (1), while noncardia (lower stomach) tumors are preceded by nonatrophic gastritis and a sequence of increasingly severe mucosal lesions (2). Chronic *Helicobacter pylori* infection is a well-known cause of this pathologic cascade, variably progressing to atrophic gastritis, intestinal metaplasia, and dysplasia. However, autoimmune gastritis is increasingly recognized as a contributing etiology, with or without the presence of *H. pylori* (3,4).

H. pylori is an indigenous member of the gastric microbiome, but infection prevalence has been slowly disappearing across recent birth cohorts in the United States and other countries (5). Improvements in standard of living and widespread use of antibiotics over the last 50 years have decreased childhood exposure to diverse infectious and noninfectious antigens. These associations are also relevant to the hygiene hypothesis (6),

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which posits that exposure to microbes early in life prevents later development of allergic and autoimmune diseases. Indeed, epidemiological data indicate rising incidence of many of these conditions, including asthma, type I diabetes mellitus, autoimmune thyroiditis, and Crohn's disease (7), and autoimmune gastritis may be similarly increasing (8).

To explore associations of shifting risk factors with US noncardia gastric cancer incidence, we have analyzed data from the large-scale and population-based North American Association of Central Cancer Registries (NAACCR).

Methods

Data Source

We obtained gastric cancer incidence data representing approximately 80% of the US population for 1995 to 2013 from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Database and 45 NAACCR Deluxe Tumor Registries (Supplementary Table 1, available online) (9), for which more than 95% of cancer cases are histologically confirmed. Our project was approved by the NAACCR Institutional Review Board (study No. 16-07).

Analytic Cohort

We evaluated incident gastric cancers, excluding cases of leukemia, lymphoma, mesothelioma, and Kaposi sarcoma (*International Classification for Diseases for Oncology*, 3rd ed., ICD-O-3, histology codes 9050-9055, 9140, and 9590-9989). Cases were stratified by sex and NAACCR's codes for race/ethnicity (non-Hispanic whites, non-Hispanic blacks, Hispanics all races, and non-Hispanic others—excluding persons with unknown race/ethnicity). Anatomic subsite code (SEER*Stat Primary Site) C16.0 denoted gastric cardia. Codes for noncardia cancers were C16.1-Fundus, C16.2-Body, C16.3-Antrum, C16.4-Pylorus, C16.5-Lesser curvature, and C16.6-Greater curvature. Codes for overlapping and unspecified (NOS) cancers were C16.8 and C16.9, respectively. For comparison, we also analyzed esophageal adenocarcinomas, defined by combining SEER*Stat Site Recode (ICD-O-3/WHO 2008) "Esophagus" and histologic type ICD-O-3 codes 8050, 8140-8147, 8160-8162, 8180-8221, 8250-8507, 8514, 8520-8551, 8560, 8570-8574, 8576, and 8940-8941.

Statistical Analysis

Data were analyzed with MatLab R2017a and the National Cancer Institute's SEER*Stat 8.3.4 software (10). We calculated age-specific and age-standardized rates (ASRs; age-adjusted to the 2000 US standard population) for each race/ethnic group. Secular trends in the ASR were summarized as estimated annual percentage change (EAPC) with 95% confidence intervals (CIs), using weighted log-linear regression and assuming Poisson distribution (11). To increase statistical precision, age at diagnosis was dichotomized into younger than 50 years vs 50 years or older. To assess heterogeneity among gastroesophageal tumors, we calculated EAPCs by age group and sex for each anatomic subsite.

We used the age period cohort framework to account for the interrelated patterns of age at diagnosis (age), year of diagnosis (period), and year of birth (cohort), and to forecast future incidence rates (12). We combined single-year data into equally spaced two- and/or four-year time intervals to facilitate modeling. We had 30 two-year age groups (25–26 through 83–84) and 9 two-year calendar-periods (1996–1997 through 2012–2013), spanning 38 partially overlapping birth cohorts referred to by mid-year of birth (1913 through 1987). There were 15 corresponding four-year age groups, 4 four-year time periods, and 18 birth cohorts. Age period cohort models were assessed based on overdispersion (σ^2), with values near 1.0 indicating successful fit (13).

The age period cohort parameter estimates included net drifts, local drifts, and cohort rate ratios (14). Net drift measured the overall log-linear trend of the sum of calendar time plus birth cohort as the age period cohort conceptual equivalent of EAPC in the ASR. Local drifts furnished efficient estimates of analogous EAPCs for age-specific rates, and corresponding Wald tests for heterogeneity assessed age interactions. Cohort rate ratios compared a given birth cohort with the mid-1951 reference cohort. We also evaluated age period cohort forecasting models, as described elsewhere (12). All statistical tests were two-sided, with *P* values of less than .05 considered statistically significant.

To further inform interpretation of the observed trends among non-Hispanic whites, we performed several sensitivity analyses. We separately examined histologic subtypes with more than 200 cases and Lauren intestinal- and diffuse-type cancers (15). As a proxy for risk of *H. pylori* infection, socioeconomic status was inferred from 2000 Census county-level percentage of residents with income below the poverty line, categorized as low (<10%), intermediate (10%–19.9%), or high (20+%). To assess effects of possible underreporting of Hispanic ethnicity, states were stratified based on 2010 population percentage of Hispanics (<5%, n = 13, vs ≥5%, n = 32) (16). We evaluated possible systematic differences between states with SEER (n = 13) and non-SEER tumor registries (n = 32) (9,10). To minimize variation in base population, we ran analyses restricting to registries with complete data for the entire study period (n = 24).

Results

There were 137 447 noncardia gastric cancers in 4.4 billion person-years of observation in the NAACCR database from 1995 through 2013. Most of the adenocarcinomas occurred among non-Hispanic whites, persons age 50 years or older at diagnosis, and in counties with less than 20% poverty (Table 1). The overall ASRs per 100 000 person-years were 2.2 for non-Hispanic whites, 6.4 for non-Hispanic blacks, 6.2 for Hispanics all races, and 7.7 for non-Hispanic others. Incidence trends for non-Hispanic whites were particularly noteworthy, as presented in detail below.

Among non-Hispanic whites, 12.8% of noncardia cancers were localized to the gastric fundus, 19.8% to the corpus, 35.0% to the antrum, and 5.5% to the pylorus (Table 2). EAPCs for noncardia cancers overall were –3.0% (95% CI = –3.3% to –2.7%), –1.7% (95% CI = –2.0% to –1.4%), and –2.3% (95% CI = –2.6% to –2.0%) per year for men, women, and both sexes combined, respectively. Notwithstanding these overall negative trends for all ages combined, incidence rates increased 1.3% (95% CI = 0.6% to 2.1%) among persons younger than age 50 years and decreased –2.6% (95% CI = –2.4% to –2.9%) among persons age 50 years or older ($P_{interaction} < .001$ for age). The difference was especially pronounced for women, with EAPCs of 2.6% (95% CI = 1.7% to 3.4%) per year for those younger than age 50 years vs –2.2% (95% CI = –2.5% to –1.9%) per year for women age 50 years or older.

Table 1. Incident noncardia gastric cancers in the North American Association of Central Cancer Registries database covering 80% of the US population, 1995–2013

	No. (%)	ASR*
Age at diagnosis, y		
<50	14 163 (10.3)	0.46
50+	123 284 (89.7)	9.90
Year of diagnosis		
1995–1999	37 788 (23.1)	3.52
2000–2004	36 079 (26.2)	3.15
2005–5009	37 481 (27.3)	2.90
2010–2013	32 099 (23.4)	2.83
Race/ethnicity		
Non-Hispanic whites	77 660 (56.5)	2.16
Non-Hispanic blacks	24 992 (18.2)	6.43
Hispanics all races	19 441 (14.1)	6.15
Non-Hispanic others	14 718 (10.7)	7.70
Unknown	636 (0.5)	–‡
County-level % poverty†		
Low, <10%	42 310 (30.8)	2.67
Intermediate, 10%–19.9%	77 530 (56.4)	3.11
High, 20+%	17 564 (12.8)	4.38
Unknown	43 (0)	–‡

*Age-standardized incidence rate (2000 US standard population) per 100 000 person-years. ASR = age-standardized incidence rate.
†2000 Census county-level prevalence of residents with income below the poverty line.
‡Indicates ASR not calculable for strata with unspecified population.

All age period cohort models were successfully fitted, with observed age-specific incidence rates consistently bounded by the 95% confidence intervals of fitted rates. Figure 1 manifests the age interaction as a converging "wedge" pattern of age-specific rates in both men (Figure 1A) and women (Figure 1B), with rising trends for younger non-Hispanic whites and stable or falling rates for older individuals. Consequently, the local drifts decreased with advancing age (Supplementary Figure 1, available online), declining on average by –0.11% (95% CI = –0.14% to –0.08%) per year of age among women and by –0.09% (95% CI = –0.12% to –0.05) per year of age among men. Supplementary Figure 2 (available online) shows the age interaction as a generational or birth cohort effect, with falling cohort rate ratios prior to the 1951 referent birth cohort, after which rate ratios were stable for men and rose for women. These converging trends were more pronounced among women than men, with incidence among women born in 1983 twofold (95% CI = 1.1- to 3.6-fold) greater than those born circa 1951.

Figure 2 shows current (1995–2013) and expected (2014–2030) noncardia cancer incidence trends for non-Hispanic whites by sex and age. For individuals younger than age 50 years, sex-specific ASRs crossed circa 2005, reversing the prior male predominance (Figure 2A). By 2020, the long-term falling ASRs for all ages combined are expected to stabilize for men and increase for women. Based on our age period cohort model, noncardia cancer incidence among women is expected to surpass incidence in men circa 2025 (Figure 2B).

Analyses by anatomic subsite are presented in Table 2 for non-Hispanic whites, stratified by sex and age. The largest EAPCs were observed for tumors localized to the gastric corpus among persons younger than age 50 years, with EAPCs of 6.0% per year for women and 3.0% per year for men. For both age groups, cardia cancers increased statistically significantly in women and were stable in men while esophageal adenocarcinoma incidence rates rose among men as well as women.

Noncardia gastric cancer incidence trends in Hispanics also showed a statistically significant age interaction, with slightly rising vs falling rates for individuals younger than age 50 years and age 50 years or older, respectively (Supplementary Table 2, available online). Like non-Hispanic whites, the largest increases were observed for tumors localized to the corpus among persons younger than age 50 years, with EAPCs of 4.2% per year for women and 1.6% per year for men. In contrast, noncardia incidence trends declined for non-Hispanic blacks and for non-Hispanic others, irrespective of age.

Sensitivity analyses for noncardia cancers among non-Hispanic whites are presented in Supplementary Tables 3 through 8 (available online). Within the common histologic subtypes (Supplementary Table 3), adenocarcinoma NOS (ICD-O-3 code 8140) represented about half of the noncardia cancers and had a strong negative EAPC, irrespective of age. The largest positive EAPCs were observed for gastrointestinal stromal sarcoma (8936), intestinal (8144) and diffuse (8145) adenocarcinomas, and carcinoid (8240) and neuroendocrine cancers (8246). EAPCs were negative for multiple histologies, including signet ring (8490). In persons younger than age 50 years, Lauren intestinal-type cancers increased more than diffuse-type, although neither EAPC was statistically significant (Supplementary Table 4, available online).

Convergent age-specific noncardia incidence rates were observed in counties with fewer than 10% and 10% to 19.9% prevalence of poverty but not for 20% or more (Supplementary Table 5, available online). EAPCs among persons younger than age 50 years were greater for states with less than 5% Hispanics than for states with 5% or more (Supplementary Table 6, available online). Findings were qualitatively similar in separate analyses for states with SEER and non-SEER registries (Supplementary Table 7, available online) and for states with complete data during the entire study period (Supplementary Table 8, available online).

Discussion

Our analysis based on cancer registration data covering approximately 80% of the US population indicates that the epidemiology of gastric cancer is changing among non-Hispanic whites, extending prior observations for different population groups (17–19). Our key finding is an age interaction over time, with rising noncardia incidence among younger persons and falling rates among older persons. These trends are consistent with a birth cohort effect, with rising incidence rates from older to younger generations. Increases were more pronounced among women than men and preferentially involved the corpus of the stomach. If current patterns continue, forecasting models predict two notable reversals by 2030: overall incidence will no longer be decreasing, and female incidence will exceed male incidence rates.

The paradox of rising noncardia gastric cancer incidence in younger birth cohorts despite declining incidence overall was largely limited to non-Hispanic whites, with a more modest increase among young Hispanics. Rising rates were also restricted to counties with less than 20% prevalence of poverty, suggesting that factors other than *H. pylori*, which is relatively less prevalent among affluent individuals, may be driving the trends. Inmigration from high-incidence areas such as Latin America and Eastern Europe would tend to increase rates, but numbers are too small to have substantial impact. We did not observe an increase of noncardia cancer in blacks or in other races, who

Table 2. Gastric and esophageal cancer cases and incidence trends among non-Hispanic whites by anatomic subsite, 1995–2013

	Overall (all ages)			Age < 50 y			Age 50+ y		
Anatomic subsite (code)	Cases	ASR*	EAPC† (95% CI)	Cases	ASR*	EAPC† (95% CI)	Cases	ASR*	EAPC† (95% CI)
Noncardia (C16.1–16.6)									
Male and female	77 660	2.16	–2.3 (–2.6 to –2.0)	5317	0.25	1.3 (0.6 to 2.1)	72 343	7.15	–2.6 (–2.9 to –2.4)
Male	41 986	2.76	–3.0 (–3.3 to –2.7)	2727	0.26	0.2 (–0.9 to 1.3)	39 259	9.31	–3.2 (–3.5 to –2.9)
Female	35 674	1.74	–1.7 (–2.0 to –1.4)	2590	0.25	2.6 (1.7 to 3.4)	33 084	5.63	–2.2 (–2.5 to –1.9)
Fundus (C16.1)									
Male and female	9964	0.28	–0.9 (–1.5 to –0.3)	738	0.03	1.6 (–0.2 to 3.5)	9226	0.91	–1.2 (–1.7 to –0.6)
Male	5698	0.37	–1.7 (–2.4 to –1.1)	422	0.04	0.7 (–1.5 to 3.0)	5276	1.23	–2.0 (–2.6 to –1.3)
Female	4266	0.21	0.1 (–0.7 to 1.0)	316	0.03	2.8 (0.6 to 5.1)	3950	0.68	–0.2 (–1.1 to 0.7)
Corpus (C16.2)									
Male and female	15 347	0.43	0 (–0.3 to 0.3)	1168	0.06	4.6 (3.5 to 5.6)	14 179	1.40	–0.5 (–0.7 to –0.2)
Male	7922	0.52	–0.9 (–1.4 to –0.5)	542	0.05	3.0 (0.8 to 5.3)	7380	1.75	–1.2 (–1.6 to –0.8)
Female	7425	0.37	0.8 (0.3 to 1.2)	626	0.06	6.0 (4.7 to 7.4)	6799	1.17	0.1 (–0.3 to 0.5)
Antrum (C16.3)									
Male and female	27 217	0.75	–2.9 (–3.1 to –2.7)	1629	0.08	0.4 (–0.9 to 1.8)	25 588	2.53	–3.2 (–3.4 to –3.0)
Male	14 191	0.94	–3.4 (–3.7 to –3.0)	851	0.08	–0.6 (–2.7 to 1.4)	13 340	3.20	–3.6 (–3.9 to –3.2)
Female	13 026	0.62	–2.6 (–3.1 to –2.1)	778	0.07	1.3 (–0.7 to 3.3)	12 248	2.05	–2.9 (–3.4 to –2.5)
Pylorus (C16.4)									
Male and female	4267	0.12	–4.2 (–4.7 to –3.7)	281	0.01	–0.4 (–2.5 to 1.7)	3986	0.39	–4.6 (–5.0 to –4.1)
Male	2302	0.15	–4.8 (–5.6 to –4.0)	136	0.01	0.6 (–3.1 to 4.4)	2166	0.52	–5.1 (–6.0 to –4.3)
Female	1965	0.09	–3.7 (–4.5 to –2.9)	145	0.01	–0.1 (–3.7 to 3.6)	1820	0.30	–4.1 (–4.7 to –3.4)
Lesser curvature (C16.5)									
Male and female	12 660	0.35	–3.8 (–4.4 to –3.2)	841	0.04	–0.5 (–1.6 to 0.5)	11 819	1.17	–4.0 (–4.6 to –3.5)
Male	7485	0.49	–4.4 (–5.1 to –3.7)	459	0.04	–1.6 (–3.4 to 0.2)	7026	1.65	–4.6 (–5.2 to –4.0)
Female	5175	0.25	–3.2 (–3.8 to –2.5)	382	0.04	0.3 (–1.5 to 2.2)	4793	0.82	–3.6 (–4.3 to –2.9)
Greater curvature (C16.6)									
Male and female	8205	0.23	–2.9 (–3.6 to –2.2)	660	0.03	0.6 (–0.9 to 2.0)	7545	0.75	–3.3 (–4.0 to –2.5)
Male	4388	0.28	–3.4 (–4.3 to –2.6)	317	0.03	–1.0 (–2.7 to 0.8)	4071	0.95	–3.6 (–4.5 to –2.7)
Female	3817	0.19	–2.5 (–3.4 to –1.7)	343	0.03	2.0 (–0.3 to 4.3)	3474	0.60	–3.1 (–3.9 to –2.3)
Overlapping (C16.8)									
Male and female	12 505	0.35	–3.7 (–4.4 to –2.9)	1031	0.05	–1.0 (–1.9 to –0.1)	11 474	1.14	–3.9 (–4.7 to –3.2)
Male	6996	0.45	–4.2 (–5.0 to –3.5)	547	0.05	–1.8 (–3.5 to 0.0)	6449	1.50	–4.4 (–5.2 to –3.6)
Female	5509	0.27	–3.2 (–4.1 to –2.3)	484	0.05	–0.2 (–1.6 to 1.2)	5025	0.87	–3.6 (–4.6 to –2.6)
Unspecified (C16.9)									
Male and female	44 709	1.24	–2.7 (–3.0 to –2.5)	3478	0.16	0.4 (–0.3 to 1.2)	41 231	4.07	–3.1 (–3.3 to –2.8)
Male	23 833	1.56	–3.3 (–3.6 to –3.1)	1774	0.17	–0.7 (–1.5 to 0.2)	22 059	5.22	–3.5 (–3.8 to –3.3)
Female	20 876	1.01	–2.2 (–2.5 to –1.9)	1704	0.16	1.6 (0.2 to 3.1)	19 172	3.24	–2.6 (–2.9 to –2.4)
Cardia (C16.0)									
Male and female	78 509	2.18	0.3 (0.0 to 0.7)	6489	0.30	0.3 (–0.2 to 0.8)	72 020	7.11	0.3 (–0.1 to 0.7)
Male	62 222	3.86	0.0 (–0.4 to 0.4)	5276	0.49	0.0 (–0.6 to 0.5)	56 946	12.68	0.0 (–0.4 to 0.5)
Female	16 87	0.81	0.6 (0.3 to 0.9)	1213	0.11	1.7 (0.8 to 2.7)	15 074	2.62	0.5 (0.1 to 0.9)
Esophagus									
Adenocarcinoma (C15)									
Male and female	115 395	3.19	1.8 (1.2 to 2.4)	8709	0.40	1.3 (0.6 to 2.1)	106 686	10.5	1.9 (1.3 to 2.5)
Male	99 029	6.09	1.6 (1.0 to 2.2)	7709	0.71	1.1 (0.4 to 1.8)	91 320	20.18	1.7 (1.0 to 2.3)
Female	16 366	0.81	1.8 (1.0 to 2.5)	1000	0.09	2.9 (1.4 to 4.5)	15 366	2.67	1.6 (1.0 to 2.3)

*Age-standardized incidence rate (2000 US standard population), expressed per 100 000 person-years. ASR = age-standardized incidence rate.
†EAPC = estimated annual percentage change in the ASR; CI = confidence interval.

mainly represent Asian descent. These groups continue to have higher age-specific prevalence of *H. pylori* infection (20), presumably reflecting higher mother-to-child transmission and/or persistence of lifestyle factors that have historically favored bacterial acquisition during childhood.

Among Swedish adults age 35 to 44 years, the prevalence of atrophic corpus gastritis defined as low-serum pepsinogen I nearly tripled between 1990 and 2009 (21). Although chronic *H. pylori* infection is considered the major cause of antral- or pan-gastritis, autoimmunity is thought to play a more important causal role in corpus-predominant gastritis. Autoimmune gastritis, as diagnosed by the presence of autoantibodies directed against parietal cells and/or intrinsic factor, is roughly threefold more common in women than men and seems to be increasing over time (8,22). Progression to severe atrophy may manifest clinically as either pernicious (vitamin B12-deficient) or iron deficiency anemia (23). The pathophysiology of autoimmune gastritis is poorly understood, although a subgroup of cases has been hypothesized to be triggered through molecular mimicry by *H. pylori* antigens (24). This entity is a frequent finding in other autoimmune disorders, including up to one-third of patients with autoimmune thyroid disease and approximately 10% of patients with type I diabetes mellitus (22). Gastric cancers are particularly important long-term complications,

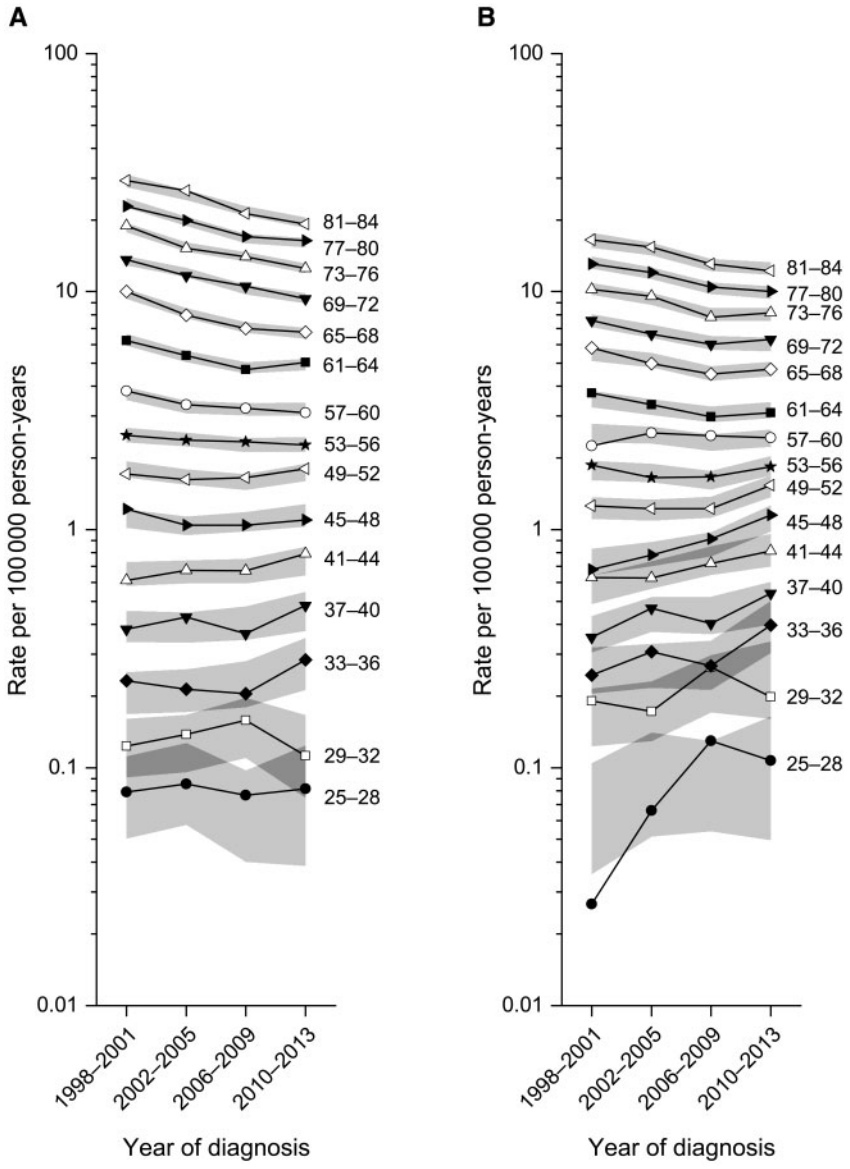

Figure 1. Age-specific incidence trends of noncardia gastric cancer among non-Hispanic white men **(A)** and women **(B)**. **Symbols** represent the observed incidence rates in 15 four-year age groups over 4 four-year time periods, with the **shaded areas** denoting 95% confidence intervals from the age period cohort models. The modeled 95% confidence intervals provide a good fit to the observed data for every age group except women age 25 to 28 years.

including not only adenocarcinomas but also carcinoid and other neuroendocrine histologies (23,25–27). Given the large and declining fraction of gastric cancers classified as adenocarcinomas, NOS, and other nonspecific histologies, any changes in gastric neuroendocrine tumors must be interpreted with caution. Nevertheless, these complementary clues implicate trends in autoimmune gastritis as a potential explanation for many of our findings.

Furthermore, there is much interest in the hypothesis that epidemiologic shifts in disease may be related to the disappearance of indigenous constituents of the microbiota (5,28). Specifically, human exposure to antibiotics has been steadily increasing since their introduction in the 1950s, and women use 50% to 70% more antibiotics than men (29,30). There are limited but tantalizing data about adverse health effects, including neoplasia. In particular, long-term antibiotic use in early-to-middle adulthood was associated with increased risk of colorectal adenoma in the US Nurses' Health Study (31). Similarly, changes in digestive tract microbiomes may be affecting prevalence of autoimmune gastritis linked to noncardia gastric cancer and/or have direct carcinogenic effects.

The strong cohort effect that we observed implies a relatively recent change in one or more exposures that influence risk among persons born after 1950. In addition to *H. pylori* infection and autoimmunity, other established risk factors for noncardia gastric cancer include family history, tobacco use, high salt intake, and alcohol consumption. Prevalence of each of these exposures has been stable or declining across recent birth cohorts (32–34), and thus would not explain the increasing incidence of noncardia cancer.

The possible carcinogenicity of acid inhibition therapy, widely used since the late 1990s, should also be considered. Acid suppression alters the gastric microbiome (35) and, in particular, the distribution of *H. pylori* infection within the stomach,

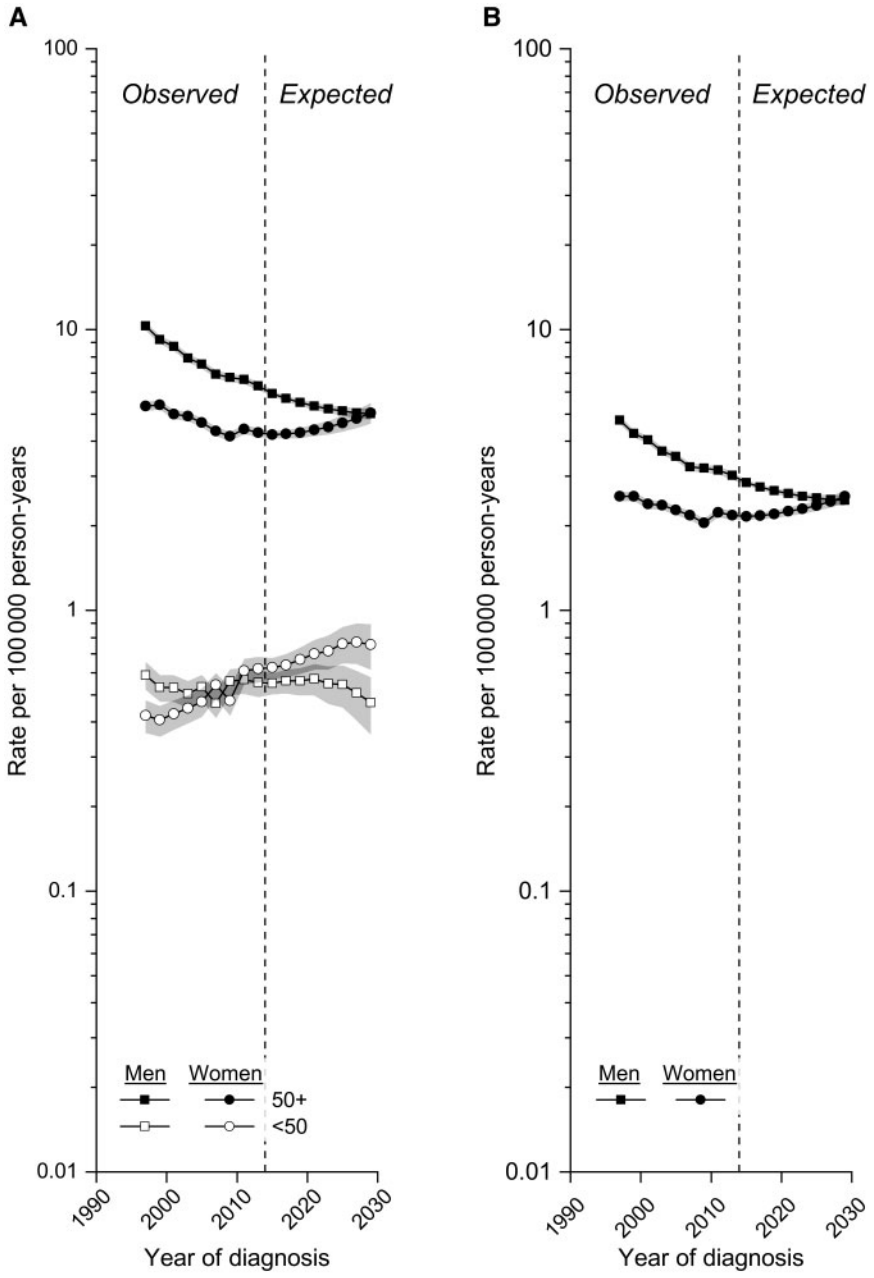

Figure 2. Age-standardized incidence trends of noncardia gastric cancer among non-Hispanic whites by age group **(A)** and overall **(B). Symbols** represent current (1995–2013) and expected (2014–2030) incidence rates by age group (<50 vs 50+ years) and overall for men (shown as **squares**) and women (shown as **circles**).

secondarily leading to development of a corpus-predominant atrophic gastritis, a precursor lesion for cancer (36). Although tumors of the proximal stomach did not disproportionately increase relative to distal tumors among individuals prescribed acid-suppressing drugs in a Danish registry-based study (37), a proximal shift may emerge in the future with longer durations of therapy. Considering that Epstein-Barr virus–positive tumors are preferentially located to proximal subsites of the stomach (38), it seems possible that this carcinogenic agent or other members of the gastric microbiota may also be involved in the increase of corpus tumors.

The second enigma suggested by our analyses is the waning male predominance in noncardia cancer. Worldwide, men have 1.5- to 2.0-fold higher incidence than women across different ages, time periods, geographic regions, and national gross domestic products (39). In general, the male-to-female incidence rate ratio increases from approximately 1.0 for age 25 to 29 years and peaks near 2.5 for age 60 to 74 years (39–41). Because these sex differences cannot be totally explained by variations in sociodemographic characteristics, environmental factors, and/or *H. pylori* infection (42), estrogens have been proposed to be protective. A meta-analysis found reduced risk among women with longer intervals between menarche and menopause or exposure to exogenous estrogens and increased risk with the administration of the antiestrogen tamoxifen (43). Interestingly, the previously declining trend in age at menarche reversed among US birth cohorts since 1950 (44), which may portend decreasing lifetime estrogen exposure with potentially adverse impact on

gastric cancer. In contrast, although obesity is considered a hyperestrogenic state and has increased markedly in recent decades, excess weight is not associated with subsite-specific or noncardia tumors overall (45), despite its suspected role in cardia cancer.

Population-based *H. pylori* eradication has been proposed for gastric cancer prevention, but this approach is controversial. Unanswered questions about safety and efficacy include exacerbation of antibiotic resistance among *H. pylori* and other pathogens as well as potential increases in gastroesophageal junction adenocarcinoma and autoimmune disorders. Intentional (or unintentional) eradication of *H. pylori* may also have unanticipated consequences that increase noncardia cancer risk. Our findings thus highlight an additional caution that mass eradication may fail to reduce the burden of gastric cancer.

This descriptive study has the usual limitations affecting population-based registries, such as missing individual-level data, lack of risk factor information, changing diagnostic patterns, and incomplete reporting of anatomical subsite, histology, and other tumor characteristics. However, these deficiencies would not be associated with age at diagnosis and, therefore, would not produce a generational or birth cohort effect. Gastric cancer with unspecified subsite declined from 22.8% in 1995 to 17.6% in 2013, so some of the increase in corpus cancers might reflect redistribution from the unspecified category.

Our findings for population subgroups defined by race/ethnicity, age, sex, and socioeconomic status signify major changes in the epidemiology of noncardia gastric cancer. These ominous trends for the US population warrant examination in other Western populations. Taken together, our data and other studies reveal an evolving pattern of factors with suggestive links to the hygiene hypothesis. Analytic studies are needed to determine the causal mechanisms that are adversely changing the face of gastric cancer incidence in the United States.

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