

Age-Specific Trends in Incidence of Noncardia Gastric Cancer in US Adults

William F. Anderson, MD

M. Constanza Camargo, MSc

Joseph F. Fraumeni Jr, MD

Pelayo Correa, MD

Philip S. Rosenberg, PhD

Charles S. Rabkin, MD

GASTRIC CANCER IS THE FOURTH most common type of cancer and the second most common among cancer deaths worldwide.¹ While tumors of the cardia, the upper part of the stomach adjoining the esophagus, may be related to gastroesophageal reflux, the majority of noncardia gastric cancers are attributable to chronic mucosal infection by the bacterium *Helicobacter pylori*.² The presumed mechanism of carcinogenesis is the induction of inflammation and consequent gastritis, the initial lesions in a multistage process.³ In both high- and low-prevalence populations, *H pylori* infection is commonly acquired in childhood and generally not later. In the United States, prevalence of infection increases with age, reflecting improvements in hygienic conditions and decreased crowding during childhood for younger generations.⁴ Prevalence also varies by race, socioeconomic status, and geographic region,⁵ contributing to population differences in gastric cancer risk.⁶

Apart from *H pylori* infection, nutritional exposures are implicated as risk factors for noncardia gastric cancer. Consumption of salt and salt-preserved foods is associated with increased incidence, whereas consumption of fresh fruits and vegetables is protective.⁷ Thus, mod-

See also pp 1729 and 1753 and Patient Page.

Context For the last 50 years, overall age-standardized incidence rates for noncardia gastric cancer have steadily declined in most populations. However, overall rates are summary measures that may obscure important age-specific trends.

Objective To examine effects of age at diagnosis on noncardia gastric cancer incidence trends in the United States.

Design, Setting, and Participants Descriptive study with age-period-cohort analysis of cancer registration data from the National Cancer Institute's Surveillance, Epidemiology, and End Results Program, which covers approximately 26% of the US population. From 1977 through 2006, there were 83 225 adults with incident primary gastric cancer, including 39 003 noncardia cases.

Main Outcome Measures Overall and age-specific incidence rates, adjusted for period and cohort effects using age-period-cohort models. Results were stratified by race, sex, and socioeconomic status.

Results Overall age-standardized annual incidence per 100 000 population declined during the study period from 5.9 (95% confidence interval [CI], 5.7-6.1) to 4.0 (95% CI, 3.9-4.1) in whites, from 13.7 (95% CI, 12.5-14.9) to 9.5 (95% CI, 9.1-10.0) in blacks, and from 17.8 (95% CI, 16.1-19.4) to 11.7 (95% CI, 11.2-12.1) in other races. Age-specific trends among whites varied significantly between older and younger age groups ($P < .001$ for interaction by age): incidence per 100 000 declined significantly from 19.8 (95% CI, 19.0-20.6) to 12.8 (95% CI, 12.5-13.1) for ages 60 to 84 years and from 2.6 (95% CI, 2.4-2.8) to 2.0 (95% CI, 1.9-2.1) for ages 40 to 59 years but increased significantly from 0.27 (95% CI, 0.19-0.35) to 0.45 (95% CI, 0.39-0.50) for ages 25 to 39 years. Conversely, rates for all age groups declined or were stable among blacks and other races. Age-period-cohort analysis confirmed a significant increase in whites among younger cohorts born since 1952 ($P < .001$).

Conclusions From 1977 through 2006, the incidence rate for noncardia gastric cancer declined among all race and age groups except for whites aged 25 to 39 years, for whom it increased. Additional surveillance and analytical studies are warranted to identify risk factors that may explain this unfavorable trend.

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ern practices of food preservation and refrigeration have favorably influenced components of diet associated with gastric cancer risk.

Overall, gastric cancer incidence has steadily declined in many countries over the past 50 years or longer. However, overall trends may mask important age-

specific differences.⁸ Furthermore, the overall decline runs counter to the subsite-specific rise in cardia cancers that may be related to obesity and gastroesophageal reflux.⁹ We therefore analyzed US population-based age-specific data for noncardia gastric cancer.

Author Affiliations: Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, Maryland (Drs Anderson, Fraumeni, Rosenberg, and Rabkin and Ms Camargo); Division of Epidemiology and Biostatistics, University of Illinois at Chicago (Ms Camargo); and Division of Gastroenterology, Hepatology, and Nutrition, Department of Medicine, School

of Medicine, Vanderbilt University, Nashville, Tennessee (Dr Correa).

Corresponding Author: Charles S. Rabkin, MD, Infections and Immunoepidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, 6120 Executive Blvd, Ste 7082, Rockville, MD 20852 (rabkinc@mail.nih.gov).

METHODS

We obtained cancer incidence data from the US National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program for the period 1977-2006. We combined case and census data from SEER 9 (covering Atlanta, Georgia; Connecticut; Detroit, Michigan; Hawaii; Iowa; New Mexico; San Francisco-Oakland, California; Seattle-Puget Sound, Washington; and Utah), SEER 13 (also including Los Angeles and San Jose-Monterey, California; rural Georgia; and Alaskan native lands), and SEER 17 (adding Califor-

nia, Kentucky, Louisiana, and New Jersey) catchment areas for the registration years 1973-1991, 1992-1999, and 2000-2006, respectively.¹⁰ The SEER registries databases cover up to 26% of the US population. Diagnoses are validated by microscopic confirmation and case ascertainment is greater than 96% for cancers diagnosed or treated in hospitals in the geographic areas SEER covers.¹¹ Our research did not involve interaction with human subjects or use of personal identifying information from these publicly available SEER data, so institutional review board approval

and informed consent were not applicable.

We analyzed incident primary cancers of the stomach (*International Statistical Classification of Diseases, 10th Revision [ICD-10]* site codes 16.0-16.9), excluding cases of leukemia, lymphoma, mesothelioma, or Kaposi sarcoma (*ICD for Oncology 3* histology codes 9050-9055, 9140, and 9590-9989). To focus on noncardia gastric cancer (*ICD-10* codes 16.1-16.6), we excluded cases in cardia (*ICD-10* code 16.0), overlapping (*ICD-10* code 16.8), and unspecified (*ICD-10* code 16.9) subsites. Analysis was restricted to cases diagnosed at ages 25 to 84 years and was grouped by 5-year intervals. Race was categorized as white, black, or other (including unspecified). Socioeconomic status was inferred from prevalence of poverty in county of residence, with less than 10% of the population below the poverty level in the 2000 US Census categorized as low, 10% to 19.9% as intermediate, and 20% or more as high.¹²

Annual incidence rates were age-standardized to the 2000 US population by the direct method. Temporal trends in the age-standardized rates were quantified by the estimated annual percentage change (EAPC) using least squares linear regression.¹³ We used the age-period-cohort framework to account for effects that might vary over the interrelated time scales of chronologic age, calendar period of diagnosis, and year of birth. Age patterns reflect in part the biological determinants of disease between younger and older persons; calendar period effects reflect secular trends that may affect all ages simultaneously (eg, changing diagnostic or screening practices); and birth cohort effects reflect risk factor exposures that may vary from one generation to the next.

To facilitate age-period-cohort analysis, we used equally spaced 5-year calendar periods and age groups.¹⁴ There were six 5-year calendar periods (1977-1981, 1982-1986, . . . , 2002-2006) and twelve 5-year age groups (25-29, 30-34, . . . , 80-84), spanning 17 partially overlapping 10-year birth cohorts

Table 1. Selected Demographic and Clinical Characteristics for Gastric Cancer Cases by Age, US Surveillance, Epidemiology, and End Results Program, 1977-2006^a

Characteristics	Age Group, y		
	25-39 (n = 2704)	40-59 (n = 19 257)	60-84 (n = 61 264)
Race			
White	64.5	69.7	74.2
Black	15.3	14.5	11.4
Other or unspecified	20.2	15.8	14.4
Ethnicity			
Non-Hispanic	72.0	84.3	89.8
Hispanic	28.0	15.7	10.2
Sex			
Male	54.5	65.5	62.8
Female	45.5	34.5	37.2
Year of diagnosis			
1977-1981	7.0	10.6	10.8
1982-1986	8.1	9.6	11.2
1987-1991	9.2	9.2	11.5
1992-1996	17.7	14.6	16.2
1997-2001	24.5	21.5	21.5
2002-2006	33.5	34.5	28.8
County of residence, poverty, %			
<10	35.1	39.9	41.6
10-19.9	60.3	55.1	53.9
≥20	4.6	5.0	4.5
Subsite			
Noncardia	46.7	42.8	48.2
Cardia	18.9	28.7	23.9
Overlapping	12.1	9.4	9.1
Unspecified	22.3	19.1	18.8
Histology			
Intestinal subtypes ^b	8.0	9.2	12.6
Diffuse subtypes ^c	38.9	26.0	16.3
Other or unspecified	53.1	64.8	71.1
Diagnostic confirmation			
Microscopic	98.8	98.5	96.8
Other or unspecified	1.2	1.5	3.2

^aData are presented as percentages.

^b*International Classification of Diseases for Oncology 3* codes: 8012, 8021, 8022, 8031, 8032, 8046, 8050, 8082, 8143, 8144, 8201, 8210, 8211, 8220, 8221, 8255, 8260, 8261, 8262, 8263, 8310, 8323, 8480, 8481, 8510, 8512, 8570, and 8576.

^c*International Classification of Diseases for Oncology 3* codes: 8020, 8041, 8044, 8141, 8142, 8145, 8490, and 8806.

(1897, 1902, . . . , 1977, referred to by mid year of birth). To increase statistical precision for tabular presentation, the twelve 5-year age groups were further collapsed into 25 to 39 years, 40 to 59 years, and 60 to 84 years.

Age-period-cohort models were used to obtain smoothed (“denoised”), fitted age-specific incidence rates,¹⁵ to calculate long-term log-linear trends due to period and cohort effects (“net drift”),^{16,17} and to quantify deviations from log-linear trends associated with calendar period and birth cohort,¹⁸ as previously described.¹⁹ We assessed significant period and cohort deviations using a “moving window” that contrasted the 3 intervals preceding a given targeted year (calendar period or birth cohort) with the 3 intervals subsequent to that year.²⁰

Generalized linear regression models were used to test whether time trends (1977-2006) varied for the 9 subgroups defined by race (white, black, and other) and age (25-39, 40-59, and 60-84 years). The complete model included main effects for combinations of race and age, the linear trend for calendar time, and terms for their interaction. We compared the fit of this model with the fit of a model without interaction terms to obtain a likelihood ratio test.

Statistical analyses were performed in Matlab, version R2009b (MathWorks Inc, Natick, Massachusetts). Based on the expected declines for noncardia gastric carcinoma among whites aged 60 to 84 years, there was a sufficient number of observed cases in whites aged 25 to 39 years to detect as alternatives a stable incidence trend with 91% power and a 1%-per-year increasing trend with greater than 99% power. All statistical tests were 2-sided and assessed for statistical significance at $P < .05$.

RESULTS

In 718 677 778 person-years of observation, the SEER 9, 13, and 17 registries identified 83 225 total cases of gastric cancer diagnosed at ages 25 to 84 years during 1977-2006 (TABLE 1). Excluding 20 661 cases of cardia, 7743

Table 2. Numbers of Men and Women, Age-Standardized Incidence Rates, and EAPCs of Noncardia Gastric Cancer for Selected Age Groups by Race, US Surveillance, Epidemiology, and End Results Program, 1977-2006

Race by Age, y	No. of Cases		Rate per 100 000 Person-Years (95% CI)	EAPC, % (95% CI)
	Men	Women		
White				
25-39	370	364	0.34 (0.31-0.36)	2.7 (1.5 to 3.9)
40-59	2810	2032	2.13 (2.07-2.19)	-0.8 (-1.2 to -0.3)
60-84	11 295	8495	14.8 (14.5-15.0)	-1.8 (-2.0 to -1.6)
Overall	14 475	10 891	4.4 (4.3-4.5)	-1.5 (-1.7 to -1.3)
Black				
25-39	114	108	0.72 (0.62-0.81)	-1.7 (-3.6 to +0.3)
40-59	1002	555	5.6 (5.3-5.9)	-2.1 (-2.8 to -1.5)
60-84	2455	1625	33.0 (31.9-34.0)	-1.4 (-1.9 to -0.9)
Overall	3571	2288	8.2 (8.0-8.4)	-1.6 (-2.0 to -1.2)
Other races				
25-39	138	169	1.02 (0.90-1.14)	-1.5 (-2.9 to -0.1)
40-59	1030	808	6.8 (6.5-7.1)	-2.7 (-3.2 to -2.1)
60-84	3358	2275	43.1 (42.0-44.3)	-1.8 (-2.4 to -1.3)
Overall	4526	3252	11.3 (11.1-11.6)	-2.0 (-2.4 to -1.5)

Abbreviations: CI, confidence interval; EAPC, estimated annual percentage change.

overlapping, and 15 818 unspecified subsites, there were 39 003 cases of noncardia gastric cancer during this period. A total of 25 366 of these cases were among whites, 5859 among blacks, and 7778 among other races.

In all 3 race groups, the overall age-standardized incidence rates of noncardia gastric cancer per 100 000 person-years for ages 25 to 84 years declined significantly over time: among whites, from 5.9 (95% confidence interval [CI], 5.7-6.1) in 1977-1981 to 4.0 (95% CI, 3.9-4.1) in 2002-2006, among blacks, from 13.7 (95% CI, 12.5-14.9) to 9.5 (95% CI, 9.1-10.0), and among other races, from 17.8 (95% CI, 16.1-19.4) to 11.7 (95% CI, 11.2-12.1), respectively. The corresponding EAPCs for the entire 1977-2006 study period were -1.5% per year in whites overall, -1.6% per year in blacks overall, and -2.0% per year in other races overall (TABLE 2).

Notwithstanding these overall trends, there was striking variation among age and race groups ($P < .001$ for age \times race interaction). Among white men, age-specific rates increased for each age group younger than 40 years but decreased for older age groups (FIGURE 1A). Among white women, the pattern was similar, with age-specific

rates increasing for each age group younger than 50 years (Figure 1B). For both sexes combined, incidence per 100 000 person-years increased significantly for whites aged 25 to 39 years, from 0.27 (95% CI, 0.19-0.35) in 1977-1981 to 0.45 (95% CI, 0.39-0.50) in 2002-2006. In contrast, incidence per 100 000 person-years decreased significantly from 2.6 (95% CI, 2.4-2.8) to 2.0 (95% CI, 1.9-2.1) for ages 40 to 59 years and from 19.8 (95% CI, 19.0-20.6) to 12.8 (95% CI, 12.5-13.1) for ages 60 to 84 years. However, age-specific rates decreased for all 5-year age groups among blacks (FIGURE 2A) and all except the youngest age group among other races (Figure 2B). The corresponding EAPCs for persons aged 25 to 39 years were +2.7% per year among whites, -1.7% per year among blacks, and -1.5% per year among other races (Table 2).

For successive birth cohorts of whites, age-specific incidence of noncardia gastric cancer decreased through the 1947 cohort, then progressively increased for the 1952 and subsequent cohorts. Specifically, incidence declined by 1.6% per year over the 1932 to 1942 cohorts then increased by 2.2% per year over the 1952 to 1962 cohorts. The difference between these slopes before and after the 1947 mid year of birth was

3.9% per year (95% CI, 2.1%-5.6%; $P < .001$ for the slope contrast). Stratified by sex, cohort-specific slope contrasts centered around the 1947 year of birth were similar among white men (3.9% per year; 95% CI, 2.1%-5.6%; $P < .001$) and white women (3.9% per year; 95% CI, 1.5%-6.2%; $P = .001$). In contrast, corresponding birth cohort changes were not significant among blacks (1.4% per year; 95% CI, -2.1% to 5.0%; $P = .42$) or among other races (2.6% per year; 95% CI, -0.2% to 5.5%; $P = .07$). There were no appreciable calendar period deviations from linear trends among any of the 3 race groups.

When stratified by county-level socioeconomic status, the patterns of increasing rates in younger whites and decreasing rates in older whites were similar for counties with less than 10% and 10%

to 19.9% population below the poverty level; there were too few cases among whites in counties with 20% poverty or more to assess age-specific temporal trends. For all 3 strata, rates for younger individuals decreased or were stable among blacks and other races.

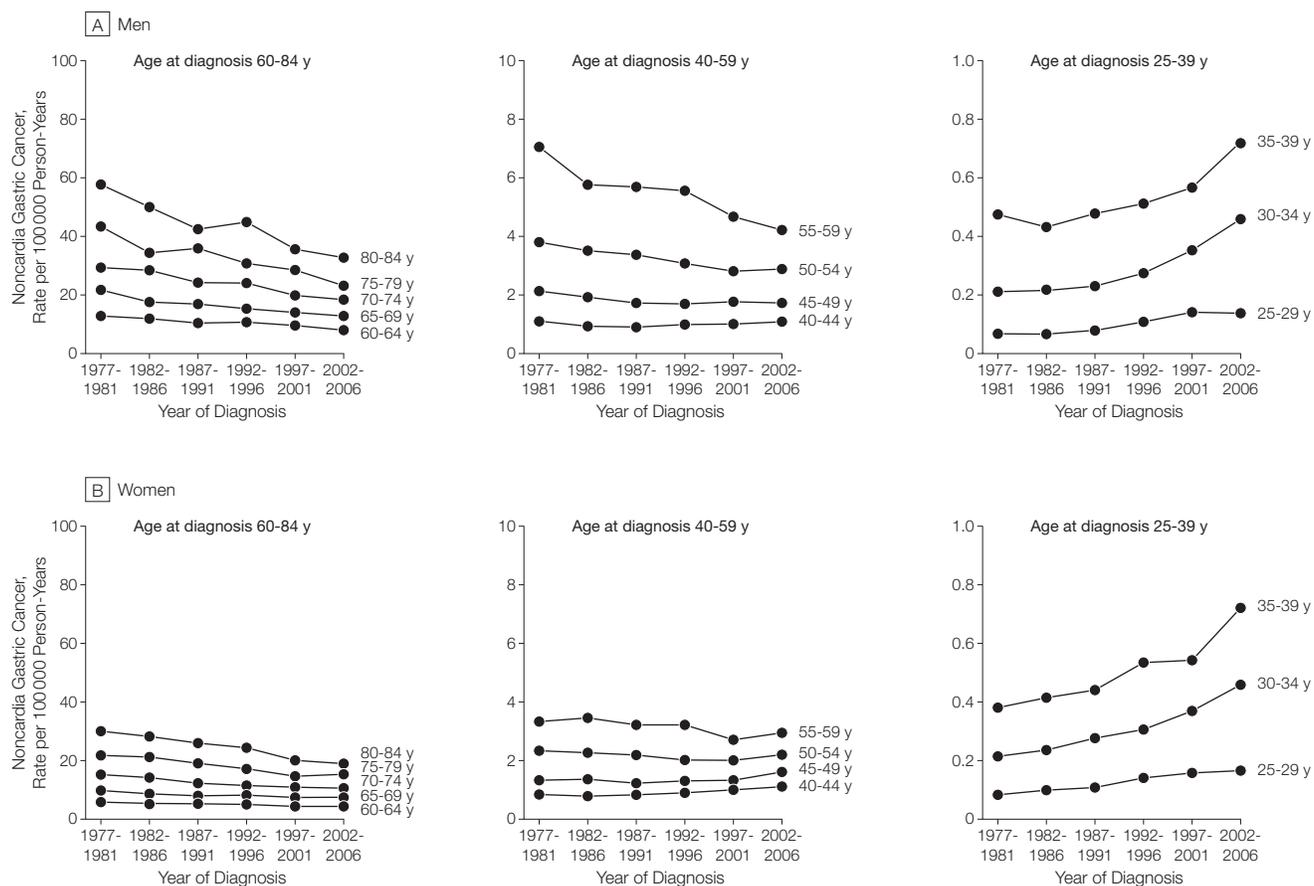
In contrast with noncardia gastric cancer, incidence of cardia cancer was relatively stable during the study period for all race and age groups. Overall age-standardized incidence per 100 000 changed from 2.4 (95% CI, 2.3-2.5) in 1977-1981 to 2.9 (95% CI, 2.9-3.0) in 2001-2006 among whites, from 1.6 (95% CI, 1.2-2.0) to 1.9 (95% CI, 1.7-2.1) among blacks, and from 2.1 (95% CI, 1.6-2.7) to 2.0 (95% CI, 1.8-2.2) among other races. Corresponding EAPCs were 0.4% per year (95% CI, 0.02%-0.7%) for whites, 0% per year

(95% CI, -0.8% to 0.8%) for blacks, and -0.7% per year (95% CI, -1.5% to 0.11%) for other races. Among the 9 subgroups of race (white, black, and other) and age (25-39, 40-59, and 60-84 years), rates per 100 000 changed significantly only for whites aged 60 to 84 years, from 7.4 (95% CI, 6.9-7.9) to 9.9 (95% CI, 9.6-10.2), with a corresponding EAPC of 0.4% per year (95% CI, 0.02%-0.7%). Furthermore, there were no significant cohort changes for any target year of birth among whites, blacks, or other races.

COMMENT

Our analysis revealed divergent trends in US noncardia gastric cancer incidence rates by age. Among whites, rates are declining in older adults but unexpectedly increasing in persons born

Figure 1. Fitted Age-Specific Incidence Rates of Noncardia Gastric Cancer Among White Men and Women, US Surveillance, Epidemiology, and End Results Program, 1977-2006



since 1952. This variation contrasts with temporal trends for cardia cancer, which varied little in our race and age groups during the study period.

Diagnostic and/or nosologic practice patterns for gastric cancer could potentially affect trends for anatomical subsites. In particular, reclassification of unspecified cases could lead to an apparent increase in noncardia gastric cancer; however, such reclassification would need to be differential by age to account for an increase restricted to younger individuals. Indeed, while the percentage of gastric cancer cases with unspecified subsites decreased during the study period, decreases were similar in whites aged 60 to 84 years (decreasing from 27% in 1977-1981 to 17% in 2002-2006) and whites aged 25 to 39

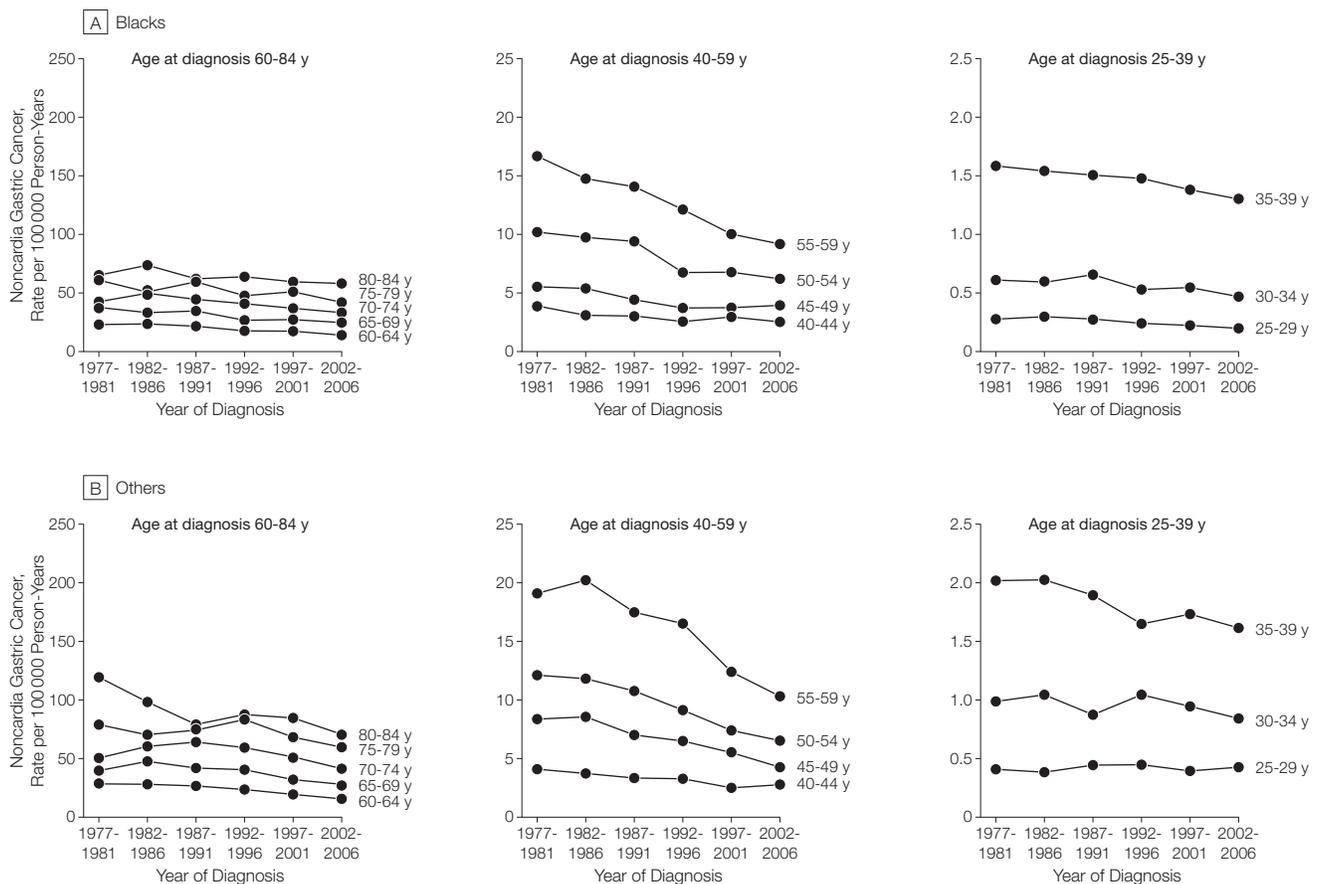
years (decreasing from 29% to 23%, respectively).

Declining noncardia gastric cancer rates in older adults may reflect cohort-specific decreases in *H pylori* acquisition during childhood as well as favorable changes in diet; however, the reasons for discrepant trends in younger adults are unclear. Given the established role of *H pylori* exposure in the development of noncardia gastric adenocarcinoma, changes in *H pylori* infection patterns following the 1952 birth cohort may have contributed to the increasing incidence rates among younger persons. Hypothetically, the long-term decline in the prevalence of *H pylori* could have reversed or the age at infection could have changed, since early-life infection has been linked to cancer risk.²¹ It is also possible that can-

cers in younger adults may point to the emergence of a new carcinogenic process, perhaps unmasked by the eradication of *H pylori* in gastric mucosa.²² Because Epstein-Barr virus has been linked to a subset of gastric cancer,²³ it seems possible that this or other agents may play a greater role as the gastric microbial flora has changed.

Another potential explanation is the role of diet, notably salt intake, which has been increasing among all age groups in the United States.²⁴ Obesity has been linked to the increasing incidence of cardia cancer, but it has not been found to be a risk factor for noncardia tumors as a group.²⁵ Tobacco smoking is a risk factor for both cardia and noncardia gastric cancer,²⁶ but tobacco use is slowly but steadily declining among adults, including young adults.

Figure 2. Fitted Age-Specific Incidence Rates of Noncardia Gastric Cancer Among Blacks and Other Races, US Surveillance, Epidemiology, and End Results Program, 1977-2006



The possible role of long-term gastric acid inhibitory therapy as a potential cancer initiator should also be considered.²⁷ Histamine 2 receptor blockers were in widespread use at the beginning of our study period, supplanted by the more potent proton-pump inhibitors starting in September 1989.²⁸ However, this hypothesis seems unlikely to explain an increase in rates restricted to younger cohorts.

Gastric cancer risk is substantially greater for Hispanic than non-Hispanic whites.²⁹ However, SEER did not provide population estimates for these subgroups until 1992, so we were unable to distinguish ethnicity-specific rates for the entire study period. Nevertheless, in a sensitivity analysis for the period 1992-2006 among non-Hispanic whites, we observed similar age-specific trends as seen for the entire study period 1977-2006 among whites overall. Specifically, the slope differences before and after the 1947 mid year of birth did not substantially change and remained statistically significant despite the smaller number of cases and shorter time frame (3.4% per year; 95% CI, 0.6%-6.1%; $P=.02$). Thus, the age-specific differences among whites overall for the entire study period 1977-2006 cannot be fully explained by immigration of Hispanics into the SEER catchment areas.

Finally, this study has the usual caveats of descriptive epidemiology, such as missing data, lack of individual-level information, and nonstandardized histopathological review. We were also unable to examine trends by individual subsite of noncardia tumors or for the Lauren classifications of intestinal and diffuse histologic subtypes because of incomplete reporting and small numbers. However, the SEER database covered 17 regional population-based tumor registries with meticulous data collection and standards. Targeting all cancer cases in residents of defined geographic areas, the large-scale SEER database is broadly representative of cancer incidence in the United States as a whole. Further age-specific analyses of noncardia gastric

cancer incidence trends for low-risk populations will be informative.

Author Contributions: Dr Rabkin had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Anderson, Camargo, Rosenberg, Rabkin.

Acquisition of data: Anderson, Camargo, Rosenberg, Analysis and interpretation of data: Anderson, Camargo, Fraumeni, Correa, Rosenberg, Rabkin.

Drafting of the manuscript: Anderson, Camargo, Fraumeni, Rosenberg, Rabkin.

Critical revision of the manuscript for important intellectual content: Anderson, Fraumeni, Correa, Rosenberg, Rabkin.

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