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Early-onset gastric cancer is a distinct disease with worrisome trends and oncogenic features

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ABSTRACT

Background: Overall the incidence of gastric cancer is declining in the United States; however, the incidence of early-onset gastric cancer is increasing. We sought to elucidate clinical and genomic characteristics and risk factors for early-onset gastric cancer compared with late-onset gastric cancer.

Methods: We utilized the Surveillance, Epidemiology, and End Results database (1973–2015), the Behavioral Risk Factor Surveillance Survey, and The Cancer Genome Atlas to characterize early-onset gastric cancer.

Results: The incidence of early-onset gastric cancer increased during the study period and now comprises >30% of all gastric cancer in the United States. Early-onset gastric cancer was associated with higher grade (55.2 vs 46.9%), signet-ring cells (19.0 vs 10.4%), diffuse histology (25.7 vs 15.0%), and metastatic disease (49.5 vs 40.9%, all $P < .01$) compared with late-onset gastric cancer. Early-onset gastric cancer was more likely to be Epstein-Barr virus (7.7 vs 5.1%) or genomically stable (22.5 vs 8.1%) subtype, whereas late-onset gastric cancer was more likely to be microsatellite instability subtype (18.6 vs 5.6%; all $P < .01$). Risk factors for gastric cancer were less correlated with early-onset gastric cancer compared with late-onset gastric cancer.

Conclusion: The incidence of early-onset gastric cancer has been steadily increasing in the United States, comprising >30% of new gastric cancer cases today. Early-onset gastric cancer is genetically and clinically distinct from traditional gastric cancer. Additional investigations are warranted to better understand this alarming phenomenon.

Introduction

Gastric cancer is the third leading cause of cancer-related deaths worldwide despite the decreased incidence of gastric cancer within the United States during the past several decades.[1,2] This decrease is likely a result of changes in meat curing practices, reduction in smoking, and the treatment of *Helicobacter pylori*.[3,4] Paradoxically, the incidence of early-onset gastric cancer (EOGC) is increasing.[5] Although EOGC suggests a hereditary component, hereditary diffuse gastric cancer explains only a minority of EOGC cases.[6,7] Mechanisms for the increased incidence in the younger population have not been clearly defined but may be related to genetic susceptibility expressed in a single-nucleotide polymorphism, various acquired mutations such as chromosomal instability (CIN), microsatellite instability (MSI), somatic gene mutations, and epigenetic alterations.[8] Thus, EOGC is likely genetically and clinically distinct from traditional gastric cancer.

Reports to date on the clinical and molecular phenotype of EOGC have been conflicting. Some authors report a female predominance, whereas others report male predominance.[9,10] Similarly, some studies have found a lack of MSI and infrequent loss of heterozygosity in EOGC, although others report MSI in ≤30% of patients.[9,11] No prior study has reported on the relationship between established risk factors and the development of gastric cancer in younger

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patients. Despite EOGC being associated with poor prognostic factors, such as diffuse histologic subtype, poorly differentiated histology, the presence of signet ring cells, and increased frequency of lymph node metastasis, the stage-specific survival has been reported to be similar when compared with patients with traditional gastric cancer.[12,13] The mechanism for this is unclear but may be related to overall better performance status and ability to tolerate perioperative multimodality therapy in younger patients.[14]

Given the lack of clear data on EOGC epidemiology, histopathology, risk factors, and genomic characteristics, we sought to better define these attributes. Through this effort, we aim to prompt improved clinical understanding of EOGC and identification of targeted treatment opportunities for this subset of gastric cancer patients, with the ultimate goal of improved outcomes.

Methods

SEER data analysis

The Surveillance Epidemiology and End Results (SEER) registry contains population-based data on patients with cancer from 9 geographically defined registries, going back to 1973.[15] We compared incident cases of gastric cancer aged 20 to 59 years and ≥60 years from 1973 to 2015. In the study, 60 was chosen as a cutoff because it is the upper bound of the first quartile of patients in the population. A sensitivity analysis of incidence during the study period was performed utilizing age cutoffs of 40 and 50 years as well. ICD-O-3 topographical codes (C16.0-16.9) and histologic (8010, 8140-47, 8210-14, 8220-21, 8260-63, 8480-81, 8490, 8510, 8560, 8562, 8570-76) codes were utilized to identify cases of gastric adenocarcinoma. Incidence rates were computed per 100,000 population and age-adjusted to the 2000 US standard population. Annual percent changes were determined with the method of linear least-squares and were tested for statistical deviation from zero using the t-distribution in the regression model, and trends were tested with the Cochran-Armitage trend test for significance. For clinical-pathologic comparisons, age, sex, race and ethnicity, tumor stage, histologic subtype (Lauren classification), tumor location, and the presence of signet ring features were evaluated.

Risk factors and GC incidence mapping

For geographic mapping analysis, county-level age-adjusted GC incidence rates in 2011 were computed from the SEER data; 2011 was chosen as it is the last year when Behavioral and Risk Factor Surveillance Survey (BRFSS) county-level data are available. County-level GC incidence rates were stratified by age group at diagnosis (≤60, >60), race (white, black, other), histologic type (intestinal versus diffuse), and presence of signet ring histology. For risk factor assessment, the BRFSS, a large, cross-sectional health survey[16] is conducted by the Centers for Disease Control and Prevention on an annual basis. BRFSS is a cross-sectional survey of 500,000 people that has been previously described and extensively validated.[17] Rates of self-reported risk factors for GC (diabetes, obesity, tobacco usage, and binge drinking) were determined at the county level for 2011. Geographically oriented data from the SEER and BRFSS analyses were then joined utilizing the Federal Information Processing Standard codes for each county. Evaluation of EOGC in particular ethnic groups was performed by calculating the rate of EOGC in each ethnic group, relative to the at-risk population in that ethnic group. These methods are consistent with those of prior publications that have utilized Federal Information Processing Standard codes to link data from SEER and BRFSS.[18]

Analysis of The Cancer Genome Atlas data

Investigation of underlying genetic differences as a potentially explanatory factor in the difference between EOGC and LOGC was performed using The Cancer Genome Atlas (TCGA),[19] which is a publicly available dataset that catalogs genome alterations in many types of human tumors. Prior studies have identified specific genomic subtypes of gastric cancer using these data and a validated, integrated, multidimensional analysis. TCGA includes 438 samples from patients with gastric cancer, and these are characterized by gene expression, somatic alterations, copy number changes, and methylation levels.[20] For this study, GC adenocarcinoma TCGA genetic profiling data was downloaded from FireBrowse (Broad Institute of MIT and Harvard Cambridge, MA) (January 28, 2016 data release).[21] FireBrowse provides analysis results from all pipelines that profile TCGA results for genetic alterations using a suite of open-source software tools to ensure that all studies are analyzed uniformly. Correlation between mutation rates and age group was determined using Spearman rank correlation. Interactions between genetic mutations and age were assessed by selecting genes with significant mutation burden in the GC adenocarcinoma cohort based on the MutSig2.0CV analysis (available through FireBrowse) with q values <0.1.[22] A similar approach was used to correlate important focal amplification or deletion events with age distribution. This was done through assessment of copy number variants (CNV) identified through GISTIC2 (also available through FireBrowse).[23] CNV event determination is influenced by tumor purity and aneuploidy. Therefore, amplification event threshold was set at exceedance of the 80% quantile of CNV score, and the deletion event threshold was set at below 20% quantile. Wilcox rank-sum tests for age distributions were performed between the groups. Methods applied were similar to previously published analysis of SEER, BRFSS, and TCGA stratified by age in colorectal cancer.[18]

Statistical analysis

Normally distributed continuous data are expressed as mean (standard deviation) with equivalence interrogation performed using the 2-tailed Student *t* test. Non-normally distributed continuous data are expressed as median (inter-quartile range), and interrogated for equivalence with the Mann-Whitney *U* test. Pearson χ^2 tests interrogated uniformly distributed categorical variables while Fisher exact test interrogated categorical variables with nonuniform distribution. Statistical analysis was conducted with R version 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria) (Eggshell Igloo', www.r-project.org). The SEERaBomb package was used to manipulate SEER data, FirebrowseR package used for TCGA, and lodown package utilized for BRFSS data. This study was deemed exempt by the Institutional Review Board at Mayo Clinic and conforms to the terms of the SEER data use agreement.

Results

A total of 75,225 GC cases were identified (EOGC: 18,608, LOGC: 56,617). EOGC incidence declined by 1.9% annually from 1973 to 1995, then has increased 1.5% annually until 2013 ($P < .05$). By contrast, LOGC incidence steadily declined by 1.8% annually during the study period ($P < .05$; Fig 1, *A*). As a percentage of all gastric cancer cases, the proportion of EOGC cases has increased rapidly from a nadir of 18.4% in 1990 to >30.0% in every year since 2012 ($P < .05$, Fig 2). Trends of gastric cancer incidence in all ethnic groups mirrored the overall trend with LOGC incidence declining monotonically during the study period, whereas EOGC cases among

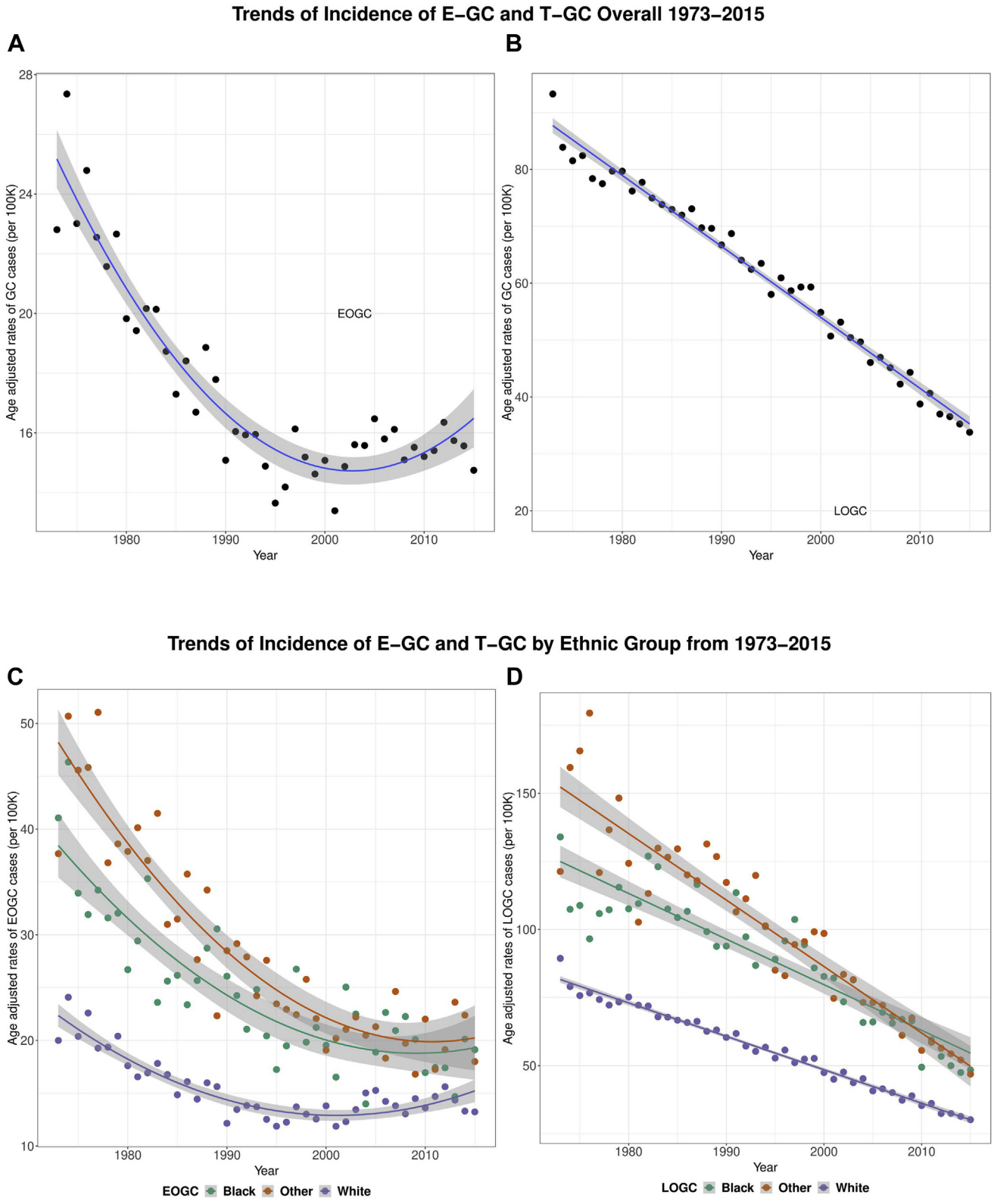

Fig 1. Age-adjusted incidence of (*A*) EOGC and (*B*) LOGC in the overall population and (*C*) EOGC and (*D*) LOGC in specific ethnic groups.

white, black, and other ethnic groups reached a nadir and then increased. Although the proportion of LOGC cases in nonwhite populations decreased during the course of the study period (trendline convergence), this proportion in the EOGC population remained relatively stable (trendlines parallel, Fig 1*C* and *D*). Sensitivity analysis demonstrated that if the age cutoff of 40 years was used, incidence increased monotonically from a low of 1.7% in 1973 to 3.5% in 2015, effectively doubling (Supplementary Digital Content Fig 1, *A*). With 50 as the age cutoff, incidence marginally decreased from an age-adjusted level of 7.6% in 1973 to 6% in 1982,

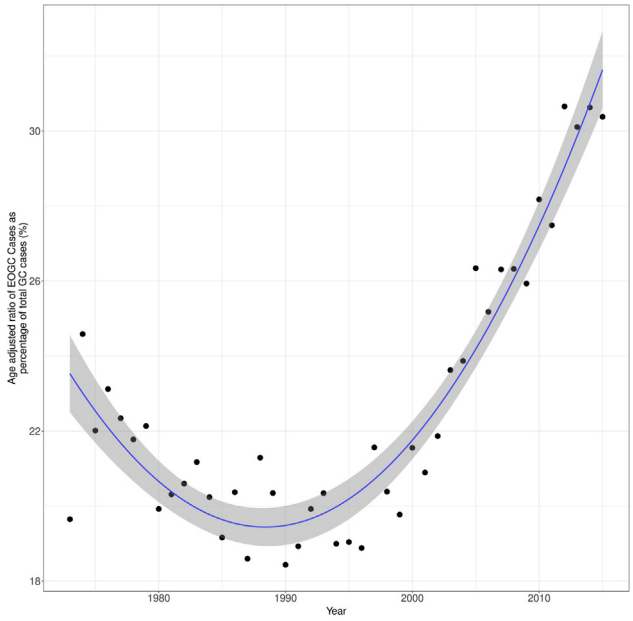

Fig 2. Ratio of EOGC cases to all GC cases per annum.

then increased to 12.5% in 2015, again effectively doubling from its nadir (Supplementary Digital Content Fig 1, *B*). Demographic and histopathologic comparisons of EOGC and LOGC were similar for age cutoffs of 40, 50, and 60 years.

EOGC patients were more often male (66.9% vs 61.1%), nonwhite (31.6% vs 23.2%), with proximally located tumors (40.0% vs 34.7%). Patients with EOGC were also more likely to have poorly differentiated histologic grade (55.2% vs 46.9%), signet-ring cells (19.0% vs 10.4%), Lauren-diffuse histologic type (25.7% vs 15.0%), and regional or distant metastasis at presentation (49.5% vs 40.9% of those with available data). EOGC patients were also more likely to have regional or distant metastatic disease at presentation (all $P < .01$; Table I).

Among 443 cases with clinical and genomic data identified in TGCA, EOGC was more likely to be an Epstein-Barr virus (EBV) (7.7% vs 5.1%) or genomically stable (GS; 22.5% vs 8.1%) subtype, whereas LOGC was more likely to be an MSI (18.6% vs 5.6%) subtype (all $P < .01$). Additionally, the clinical TCGA data pointed to the same clinicopathologic trends seen in the SEER data regarding clinical stage, Lauren diffuse histologic subtype, the presence of signet ring cells, and escalating T-stage (Table II).

In the 2011 BRFSS, 95,490 patients had responses with 60% of respondents being female and a median age of 56 years. This analysis assessed self-reported risk factors from BRFSS at the county level coupled to county-level rates of EOGC and LOGC. Rates of elevated GC were correlated with some previously described GC risk factors. In particular, smoking and binge drinking were correlated in the LOGC cohort, but not in the EOGC cohort (Table III). Unfortunately, strong risk factors for GC such as *H. pylori* status and the consumption of nitrites or smoked foods are not part of the BRFSS risk assessment survey and therefore could not be assessed.

Analysis of genomic mutation burden showed a general trend toward increased mutation rate as a continuous function of age (Fig 3). Patients with hypermutated DNA were grouped separately to prevent the influence of syndromic cases on the analysis of mutation burden as a function of age. We found a significant correlation between GC sample mutation rates and age (Spearman rank = 0.26, $P < .001$) with mutation rates increasing as a function of age. When silent and nonhomogenous mutations were considered separately the same result held (both $P < .001$), supporting the notion that GC mutation burden increases with age.[24]

Our analysis identified 10 genes whose mutation status density was correlated with age (Fig 4, *B*). CDH1 mutations, for example, were significantly more common in younger patients (blue line shifted left of the black line), whereas BRAF mutations were more common in older patients (blue line to the right of the black line). In addition, we identified 10 focal amplification or deletion events with significant differences in distribution as a function of age (Fig 4, *A*).

Table I
SEER cohort demographics, pathologic characteristics, and outcomes

	LOGC N = 56,617	EOGC n = 18,608	*P* value
Age, median (interquartile range)	75 (68–81)	53 (47–57)	
Female	22,030 (38.9%)	6,165 (33.1%)	<.001
Race			<.001
White	4,508 (76.8%)	12,195 (69.4%)	
Black	6,086 (10.7%)	2,836 (15.2%)	
Other	7, 023 (12.5%)	2,857 (15.4%)	
Stage			<.001
Localized	5,672 (10.0%)	1,344 (7.2%)	
Regional	6,378 (11.3%)	2,691 (14.5%)	
Distant	7,265 (12.8%)	3,675 (19.7%)	
Missing	37,302 (65.9%)	10,898 (58.6%)	
Histologic grade			<.001
I	2,736 (4.8%)	707 (3.8%)	
II	11,272 (19.9%)	2,877 (15.5%)	
III	24,957 (44.1%)	9,633 (51.8%)	
IV	1,559 (2.8%)	636 (3.4%)	
Missing	16,093 (28.4%)	4,755 (25.6%)	
Lauren intestinal type	48,147 (85.0%)	13,382 (74.3%)	<.001
Signet ring histology	5,892 (10.4%)	3,530 (19.0%)	<.001
Location			.004
Proximal	19,622 (34.7%)	7,447 (40.0%)	
Distal	12,369 (21.8%)	3,239 (17.4%)	
Missing	24,626 (43.5%)	7,922 (42.6%)	
State			<.001
California	10,639 (18.8%)	3,401 18.3%)	
Connecticut	10,019 (17.7%)	2,843 (15.3%)	
Georgia	3,051 (5.4%)	1,640 (8.8%)	
Hawaii	3,768 (6.7%)	1,187 (6.4%)	
Iowa	6,250 (11.0%)	1,613 (8.7%)	
Michigan	10,722 (18.9%)	3,399 (18.3%)	
New Mexico	3,231 (5.7%)	1,256 (6.7%)	
Utah	2,155 (3.8%)	859 (4.6%)	
Washington	6,782 (12.0%)	2,410 (13.0%)	

Discussion

In this comprehensive study of EOGC, we found that although the incidence in early years declined similar to LOGC, the incidence of EOGC has been steadily increasing since the late 1980s, and this is true regardless of the age cutoff used. We further identified specific genomic characteristics of EOGC and demonstrated a lack of association with risk factors important for LOGC. Our study is the most comprehensive 4-decade trend analysis of a large population-based cancer registry with cross-sectional survey data on risk factors and detailed genomic analysis for gastric cancer. We know from prior studies that traditional gastric cancer has declined dramatically in incidence in the United States during the past several decades, owing in large part to risk-factor reduction including smoking cessation, improvements in medical management of acid reflux, and increased treatment of *H. pylori*.[25–27] However, our data demonstrate that EOGC is not associated with traditional risk factors and has been steadily increasing as a proportion of all GC cases for nearly 3 decades, now comprising >30%

Table II
Clinical data on patients in the TCGA dataset

	LOGC n = 296 (67.6%)	EOGC n = 142 (32.4%)	*P* value
Median age	71 [67–76]	55 [51–58]	<.001
Female	185 (37.5%)	33.1%	<.001
Race			.201
White	189 (74.4%)	89 (70.1%)	
Black	11 (4.3%)	2 (1.6%)	
Asian	53 (20.9%	36 (28.3%)	
Other	1 (0.4%)	0 (0%)	
Molecular subtype			<.001
CIN	100 (33.8%)	45 (31.7%)	
EBV	15 (5.1%)	11 (7.7%)	
GS	26 (8.8%)	32 (22.5%)	
MSI	55 (18.6%)	8 (5.6%)	
Missing or not calculable	100 (33.8%)	46 (32.4%)	
Clinical stage (%)			.138
Stage I	45 (15.2%)	12 (8.5%)	
Stage II	84 (28.4%)	44 (31.0%)	
Stage III	130 (43.9%)	62 (43.7%)	
Stage IV	25 (8.4%)	20 (14.1%)	
Missing	12 (4.1%)	4 (2.8%)	
Lauren intestinal type	177 (59.8%)	66 (46.5%)	<.001
Signet ring histology	6 (2.0%)	6 (4.2%)	.031
N1 status	80 (27.0%)	38 (26.8%)	.728
T status			.035
T1	19 (6.4%)	3 (2.1%)	
T2	67 (22.6%)	23 (16.2%)	
T3	132 (44.6%)	65 (45.8%)	
T4	70 (23.6%)	49 (34.5%)	
Missing	8 (2.7%)	2 (1.4%)	

Table III
Age-adjusted risk of GC development based on geographic incidence of GC risk factors

	LOGC		EOGC	
	R^2	*P* value	R^2	*P* value
Smoking	0.02989	.08964	−0.01444	.7664
Obesity	−0.01433	.7581	−0.01449	.7707
Diabetes	−0.01493	.8098	−0.01416	.7453
Binge drinking	0.05726	.0307	−0.01584	.9633

of all new gastric cancer cases as of 2015, with an increased incidence in nonwhite populations during the 4 decades of the study period. Among GC risk-factors assessable in the BRFSS, we have shown that the risk factors of smoking and binge drinking are only associated with LOGC and not EOGC. Additional investigation is necessary to identify risk factors for EOGC to inform public health policy on risk reduction strategies. In addition, the histopathologic characteristics are similar for EOGC using lower age cutoffs suggesting that EOGC may not be bounded by an arbitrary number.

EOGC is associated with unique molecular characteristics as we demonstrated a predominance of the GS genomic subtypes, which unfortunately is associated with the worst prognosis and the least amount of benefit from traditional systemic chemotherapy.[28] Therefore, novel therapeutic strategies are necessary for this increasing group of treatment refractory gastric cancer. The GS molecular subtype is characterized by increased frequency of CDH1 and RHOA mutations and CLDNA18-ARHGAP fusions that are not currently targetable mutations. However, Aurora kinase and polo-like kinase are potential candidate targeted therapies for GS gastric cancer. Aurora kinase and polo-like kinase inhibitors have shown promising safety and efficacy profiles in preclinical and early clinical studies.[29–31] Additional investigation is necessary to determine if these kinase inhibitors will have clinically efficacy in EOGC.

Another common molecular subtype in EOGC is CIN, which had a similar incidence between EOGC and LOGC. The CIN molecular subtype is associated with extensive somatic copy-number aberrations and amplifications in genes involved in the RTK-RAS pathway including FGFR2, KRAS, EGFR, Her2, MET, and VEGF. Treatment with HER2 monoclonal antibody have demonstrated clinical efficacy in the metastatic setting in the TOGA trial but have not been investigated prospectively in the perioperative setting for locally advanced but resectable gastric cancer.[32] Receptor tyrosine kinase inhibitors are another promising molecular target in EOGC and LOGC alike. The multikinase inhibitor dovitinib has demonstrated substantial treatment induced apoptosis and growth inhibition of gastric cancer in preclinical studies.[33] This potentially represents a subtype-specific targeted therapy for nearly one-third of EOGC patients.

The EBV-positive genomic subtype was significantly enriched in the EOGC cohort and is associated with a high level (80%) of mutations in the PIK3-AKT-mTOR pathway. Activation of this pathway can increase cell proliferation by promoting transcriptional activity and decreasing apoptosis. This pathway can be inhibited at the PIK3CA level or further downstream at AKT or mTOR. Clinical trials are currently underway with a number of PIK3CA and AKT inhibitors in gastric cancer. A phase II trial of the mTOR inhibitor everolimus demonstrated a disease control rate of 54.7%, median PFS of 2.7 months, and median OS in heavily pretreated metastatic gastric cancer patients.[34] Unfortunately, the GRANITE-1 study failed to demonstrate efficacy with nonsignificant improvements in PFS (1.7 vs 1.4 months) and OS (5.4 vs 4.3 months).[35] PIK3-AKT-mTOR pathway inhibitors remain a promising targeted therapy for EBV positive genomic subtype, which may have important genetic testing and treatment implications in EOGC. The EBV positive genomic subtype is also associated with a high level of amplification of the genes encoding the immune checkpoint ligands PD-L1 and PD-L2 suggesting that these tumors may be particularly susceptible to immune checkpoint blockade. The phase 1b Keynote 012 trial demonstrated a 22% overall response rate with a median duration of response of 24 weeks, a 24% 6-month PFS, and a 69% 6-month OS in patients with heavily pretreated metastatic PD-L1 positive gastric cancer.[36] Pembrolizumab is now being investigated in the neoadjuvant setting for locally advanced resectable gastric cancer in the randomized phase III KEYNOTE-585 trial (NCT03221426).[37] Lastly, the MSI molecular subtype was the least commonly found in the EOGC cohort, suggesting that MSI testing should be done selectively in this population.

The finding of particular genomic characteristics for a population of gastric cancer patients is important because knowledge of the probability of specific mutations based on demographic information can drive trial enrollment in targeted therapy trials. Therapeutic targets shown to differ based on age in this study, which have literature supporting their targeting include ARID1A[38–40] and PTEN.[41–43] Our analysis does not demonstrate a differing rate of ERBB2 mutation as a function of age, suggesting that patients with EOGC will have trastuzumab-sensitive tumors at similar rates as those with LOGC. The decreased rate of BRAF mutation in EOGC in our study, coupled with increased rates of ARID1A, ARHGAP, and PTEN, suggests that novel treatment strategies are needed for patients with EOGC and represents an unmet clinical need. Prior studies have demonstrated that comprehensive genomic profiling can help facilitate identification of targeted therapies for gastric cancer patients.[44] Our data provide further evidence that this practice should be applied in particular to young patients with gastric cancer.

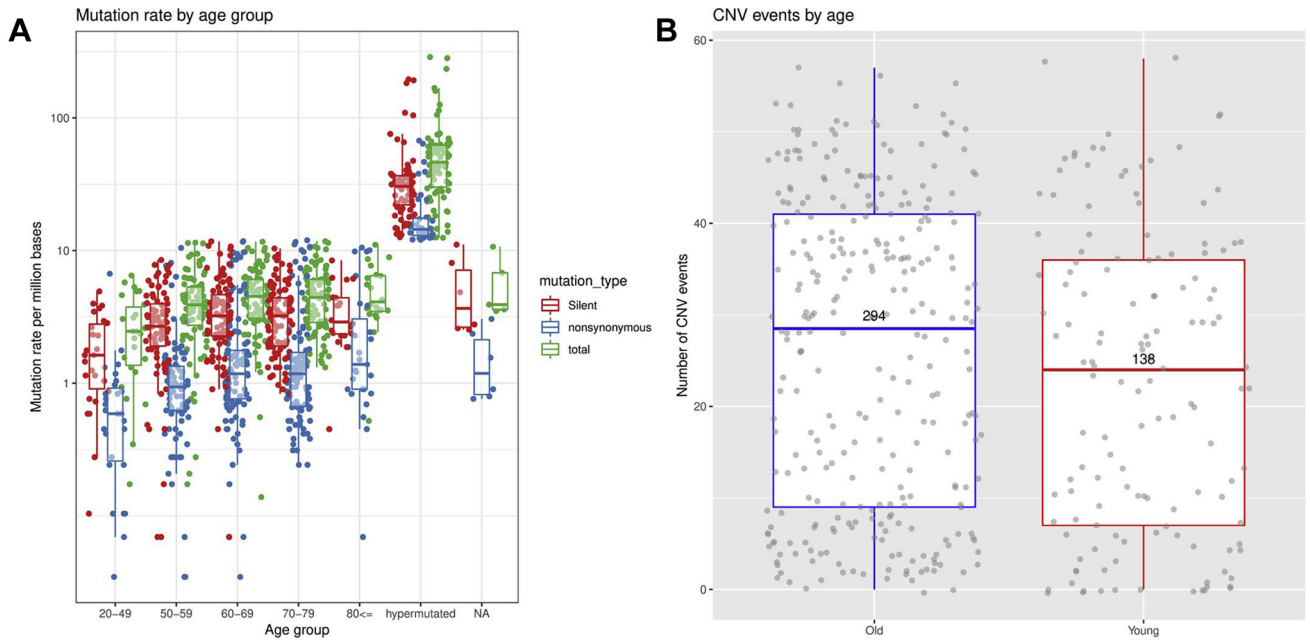

Fig 3. (*A*) Mutation rate as a function of age. (*B*) Copy number events by age group.

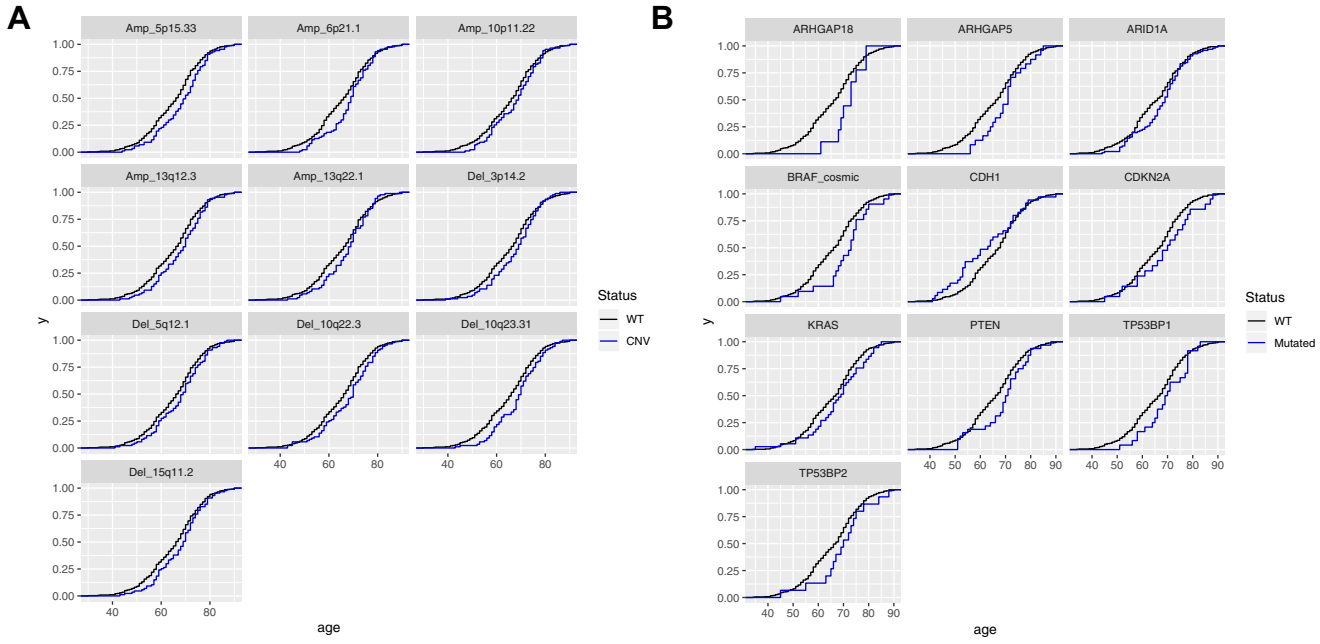

Fig 4. Cumulative density function plots of (*A*) amplification or deletion events and (*B*) selected genes with distributions varying significantly by age.

Limitations

Our study is limited by its retrospective and nonrandomized nature introducing the possibility of selection bias. However, our analysis does not include survival or assessment based on therapeutic strategy. During the course of 4 decades of data collection, the SEER data dictionary has undergone several changes, resulting in noncollection of data in many categories, particularly therapy (including surgical therapy) and pathology from cases predating 1992. In addition, there is a risk of sampling bias with any population-based registry data source and SEER is no exception. However, SEER is extensively described and utilized in the medical literature as a top-level population-based registry. There may be criticism of our use of an age cutoff of 60 years as the criterion for early onset. Prior studies have utilized much lower age cutoffs such as 40 or 45 years and these studies have almost exclusively focused on patients with familial disease and CDH-1 mutations, which can be predicted so reliably that prophylactic gastrectomy is indicated for those patients.[45,46] However, the clinical, pathologic, and genetic characteristics of EOGC are consistent regardless of the arbitrary age cutoff chosen. Our objective was to not only understand epidemiology of these patients, but also detect incidence trends unrelated to CDH1 and familial gastric cancer. Therefore, we set our age cutoff somewhat higher to better capture these trends and

genomic signals. We sought to characterize the epidemiology using BRFSS, a cross-sectional database that relies on voluntary survey responses and does not have guaranteed correlation with background population density. BRFSS, therefore, can be subject to detection and response bias. Furthermore, BRFSS lacks data on known risk factors for gastric cancer including family history, *H. pylori* infection, and the presence or treatment of gastroesophageal reflux disease. Therefore, our ability to assess risk associations was limited to relatively weak risk factors, although the increased risk associated with smoking and drinking remain substantial. The TCGA cohort is limited in size and scope and can be expected to be subject to sampling and selection bias. TCGA samples were obtained from multiple countries and, therefore, are not from the same population as the epidemiologic analysis we have conducted with SEER, which is a US-based registry. Still, our study possesses several strengths, namely a long study period of 42 years, allowing for comprehensive trend analysis of the disease incidence. The large temporal and spatial sample size from SEER facilitates both high statistical power and the potential to gain understanding of long-term incidence trends.

Although LOGC incidence has dramatically declined over the years, EOGC incidence has been steadily increasing since 1995, now comprising >30% of new gastric cancer cases. EOGC is a clinically and histopathologically distinct disease associated with a more aggressive phenotype. EOGC is more likely to be associated with defined genomic subtypes, which are more aggressive than those associated with LOGC. Additional evaluation of genetic and molecular differences is needed to better understand the pathophysiology of EOGC and to facilitate optimal treatment and surveillance strategies.

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Conflict of interest/Disclosure

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.surg.2019.04.036.

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Discussion

Dr Robert C.G. Martin (Louisville, KY): Thank you for sending me the manuscript. Well presented.

Obviously, you are, I think, stating some of the obvious, and that we know that an early-onset gastric cancer is probably going to behave a little bit differently or worse than a late onset. We see that pretty much in almost all solid tumors.

You have taken on an aggressive and almost ambitious sort of methodology of trying to merge 3 different national databases to try to hopefully create more of a unique process.

My first question is, obviously I think is the biggest crux of it, is your definition of early. Almost every other early gastric cancer would start really at 50 years of age or younger, and there is even a greater incidence now of 45 or younger. Thus, we need to see a more quartile-based evaluation, because I am concerned that the 30% increase that you are seeing in gastric cancer may actually be from the 50 to 59 years, where we are seeing obesity, reflux, diet related. We have seen that completely sort of flip on its edge just in the 17 years that I have been practicing.

The second is your reliance on the SEER database for true incidence. We have always had significant problems with the SEER database from a quality assurance standpoint, and I wonder if a lot of your incidences are actually GE junction. To that end, why did not just use the 443 cases from the genome as your initial subset and then validate it with a larger subset?

I am just curious as to how confident you are that trying to link all of these, given the limitations that you showed us, really is what is really happening, or do we need to keep a greater eye on it?

The last question is around the cancer genome atlas. I am going to push you a little bit because the paper and your presentation did not really say much from that. What I mean by that is, are you stating now that physicians taking care of gastric cancer, whether it be early or late, should be doing this molecular subtyping that you have eloquently accessed and presented? Because if we are not, then maybe that is the main message from this manuscript, that we need to do a better job of pushing our pathologists to identifying that molecular subtype so that we really can risk stratify patients both old and young in regards to how aggressive they need to be. Do we need to maybe look at more palliative options in the 85-year-old who has a more aggressive subtype?

So, I want to push you a little bit more to make this message a little bit stronger so hopefully help people who are managing gastric cancer can make that type of quality and change in the management of these patients. Great job.

Dr John Bergquist: I would like to thank Dr Martin for those thoughtful and insightful questions.

First on the question of age, as you accurately pointed out, there is a lack of consensus in terms of where the age cut-off between early and late onset should be in the literature. We initially chose the cut-off of 60 because if you look at the overall SEER data, 60 is the upper limit of the lower quartile of age.

We actually did additional analysis running the cut-off at age 40 as well as at age 50 and while these numbers are different, the trends are pretty close to the same in terms of increased poorly differentiated, increased defuse, increased signet ring cells, regardless of whether you draw the cut line at 40 or 50.

Additionally, if we looked at incidence, cutting it off at 40 years of age, you can see there is pretty well monotonically increased incidence. So again, I apologize, these numbers are really hard to read, but this is 2%. This is 4%. So obviously the absolute percentage goes way down if you move the cut-off. But you can see that the trend and incidence remains concerning.

This is if you draw the line at 50. This is 7.5%. This is 15%. So, doubling of incidence if the line is drawn at 50 over the 4 decades of the study period.

So, I do not think that the trend in incidence would be any less be concerning if you draw the cut-off at 50 or 40.

In terms of the question about quality control and the comparison between SEER and TCGA, I want to clarify a couple of things. First, the only linkage that we did was between SEER and BRFSS, and that linkage was done using the county level ZIP code, so basically we looked at counties that had a high or low incidence of risk factors in the BRFSS, and we compared those with the incidence rates that we computed from SEER in the year 2011. The limitation of BRFSS is because it is cross sectional, it cannot give you an incidence trend, so you can really only analyze 1 year at a time.

SEER is a population-based data source that is funded and supervised by the National Cancer Institute. There are a lot of problems with the analysis of SEER. Those have been extremely well

described in the literature. But in terms of computing population-based incidence of a disease, SEER is about the best we have and is made up of data that is submitted by multiple different state or local administrative level cancer registries, including the state of Iowa, the state of California, and so on.

So, while your recognition of quality control in SEER is noted, we felt that this was the best way to look at how the trend and incidence was going to be progressing as a function of time.

In terms of the TCGA and trying to answer the question of should we be doing genomic subtyping, I think that as genomic subtyping becomes more available, less expensive, and is increasingly utilized clinically, certainly in some scenarios for patients that have metastatic disease and want to go on trial, genomic subtyping is required. We have to know, did they have a PD-L1 mutation, for example, and so on.

So, I would say yes, that is one of the messages of our paper that you astutely point out that we do need to do a better job of genomically subtyping these patients and stratifying them to the most appropriate potential targeted therapy.

Dr Jeff Hardacre (Cleveland, OH): John, as with all of your previous presentations as a resident, this was a great job.

Your last slide talked about trying to figure out who could get targeted therapy. Have you thought about your work in terms of, can we identify a subgroup of people that are young that we should be doing screening upper endoscopies on to try to prevent them from getting cancer in the first place?

Dr John Bergquist: That is a great question. Obviously, there are guidelines out there for patients with CDH1 mutations or family history of hereditary diffuse cancer syndromes and recommendations that they have screening at an early age and potentially have prophylactic gastrectomy.

I think expanding that beyond that population, it would be great if we could come up with a way to do that, and perhaps some of these subtypes could facilitate that in patients that had Epstein-Barr positivity if that were to be something that had come up earlier in their clinical course, it might be something that could be looked at. That, I think, is the best potential, other than the CDH1 mutation.

Dr Alfonso Torquati (Chicago, IL): I have one question. Have you seen any cluster of the early-onset of gastric cancer in some region of the United States?

Dr John Bergquist: That is a great question. I do have, obviously, because we did linkage of the county level data, there were hot spots, and that data was really for one specific year. It was not something that I looked at longitudinally over the course of time, because it was only doing that one particular analysis. But I do think that that would be a great option for future studies—to look at the time variance of areas of early-onset gastric cancer incidence. Thank you for that.