Nature versus nurture: the impact of nativity and site of treatment on survival for gastric cancer

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Abstract

Background The prognosis of gastric cancer patients is better in Asia than in the West. Genetic, environmental, and treatment factors have all been implicated. We sought to explore the extent to which the place of birth and the place of treatment influences survival outcomes in Korean and US patients with localized gastric cancer.

Methods Patients with localized gastric adenocarcinoma undergoing potentially curative gastrectomy from 1989 to 2010 were identified from the SEER registry and two single institution databases from the US and Korea. Patients were categorized into three groups: Koreans born/treated in Korea (KK), Koreans born in Korea/treated in the US (KUS), and White Americans born/treated in the US (W), and disease-specific survival rates compared.

Results We identified 16,622 patients: 3,984 (24.0%) KK, 1,046 (6.3%) KUS, and 11,592 (69.7%) W patients. KK patients had longer unadjusted median (not reached) and 5-year disease-specific survival (81.6%) rates than KUS (87 months, 55.9%) and W (35 months, 39.2%; $p < 0.001$ for all comparisons) patients. This finding persisted on subset analyses of patients with stage IA tumors, without cardia/GEJ tumors, with > 15 examined lymph nodes, and treated at a US center of excellence. On multivariable analysis, KUS (HR 2.80, $p < 0.001$) and W (HR 5.79, $p < 0.001$) patients had an increased risk of mortality compared to KK patients.

Conclusions Both the place of birth and the place of treatment significantly contribute to the improved prognosis of patients with gastric cancer in Korea relative to those in the US, implicating both nature and nurture in this phenomenon.

Keywords Gastric cancer · Nativity · Ethnicity · Treatment · Survival · Outcomes

Introduction

Gastric cancer is the fourth leading cause of cancer-related death worldwide [1]. Though the incidence rate of gastric cancer in the West has been declining in recent decades, gastric cancer remains highly prevalent in Russia, Eastern

Europe, East Asia and South America [2]. In fact, cancer rates vary up to tenfold between countries, with Japan and Korea having the highest rates of gastric cancer in the world [3, 4]. However, countries in East Asia report significantly better survival rates compared to those reported in the West [5–8]. Several potential hypotheses have been proposed to explain this superior survival, including differences in tumor histology, tumor location, pathologic staging, extent of surgery, and patient comorbidities [6–12]. Conversely, other authors have proposed that the improved gastric cancer survival seen in Asian patients is not due to any particular anatomic, pathologic, or surgical factors but is rather due to Asian ethnicity itself [13–15].

Though these prior studies are intriguing, many are limited in their design by utilizing only the SEER database for their analyses, [11, 14, 15] thus lacking outcomes data from high-volume centers of excellence (COE) in Asia and the US. Furthermore, many of these studies consider “Asian”

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patients as a single ethnic group, lumping patients from Korea, Japan, China, Southeast Asia, the Philippines, Pacific Islands, and other regions into a single group [11, 14, 15], in spite of the fact that these groups are known to have highly variable gastric cancer survival rates when treated in the US [16]. Finally, other authors compared only Korean patients treated at a Korean COE to US patients treated at a US COE, thereby limiting their ability to examine the influence of Korean ethnicity on outcomes after treatment in the US [5, 17].

In this study, utilizing a unique combination of US cancer registry data as well as data from high-volume COEs in Korea and the US, we sought to explore the extent to which birthplace and ethnicity (nature) and the place of treatment (nurture) influence survival outcomes in Korean and US patients with localized gastric cancer.

Methods

The Surveillance, Epidemiology, and End Results (SEER) database was queried from 1989 to 2010 to identify patients undergoing potentially curative surgical treatment for gastric adenocarcinoma in the US. Patients > 18 years of age with a diagnosis of invasive adenocarcinoma of the stomach [identified by International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3) codes] who underwent a primary operation for gastric cancer were included in the study. Patients with metastatic disease, > 1 primary lifetime malignancy, and undergoing local destruction or excision of the tumor as their primary operation were excluded. Patients were categorized by race, nativity, and country of residence and divided into three groups: Koreans born in Korea who received their healthcare in Korea (KK), Koreans born in Korea who emigrated to the US and received their healthcare in the US (KUS), and White Americans born in the US who received healthcare in the US (W).

The gastric cancer registry from Seoul St. Mary's Hospital in South Korea was queried over the same time period (1989–2010), and the gastric cancer database from the Massachusetts General Hospital was queried from 1995 to 2010, utilizing the same search and exclusion criteria. Disease status at last follow-up was determined by retrospective review of medical records, telephone interviews, and registration data at the Korean National Cancer Center or the Social Security Death Index.

The primary outcome was disease-specific survival. Unadjusted analyses were performed with Pearson chi-squared tests for categorical dependent variables, and *t* tests or ANOVA for numerical dependent variables. For the patients treated in Korea, survival was collected and calculated starting at the date of surgery, whereas for patients in the SEER database, survival was collected and calculated

starting at the date of gastric cancer diagnosis. Unadjusted Kaplan–Meier survival curves were generated and compared using the log-rank tests. Multivariable analysis was performed using the Cox proportional hazards model to calculate adjusted hazards ratios (HR) and 95% confidence intervals (CI), controlling for age of diagnosis, gender, year of diagnosis, extent of primary operation, tumor location, lymph node involvement, AJCC tumor histology, Lauren classification, tumor histologic differentiation, and lymph node examination. All analyses were performed using STATA 13.1/IC software (Stata Corp), and statistical significance was assessed at the $P < 0.05$ level.

Results

The final cohort consisted of 16,622 patients with gastric adenocarcinoma who underwent potentially curative surgery as identified in either the SEER database ($n = 12,638$) or the Seoul St. Mary's Hospital database ($n = 3984$). As outlined in Table 1, a majority of the patients were male (66.3%), with a mean age of diagnosis of 64.9 (SD 13.3) years. There were 3984 (24.0%) KK patients, 1046 (6.3%) KUS patients, and 11,592 (69.7%) W patients. Nearly half (46.3%) of the patients had > 15 lymph nodes examined. The median number of lymph nodes examined was 18.5 (IQR 5–27), and the median number of positive lymph nodes was 3.3 (IQR 0–4).

On unadjusted analysis (Table 2), KK patients were more likely to be diagnosed at a younger age versus KUS patients (57.6 vs 63.8 years) and W patients (67.5 years, all $p < 0.001$; Fig. 1a, b). Not surprisingly, the number of lymph nodes examined was significantly higher in the KK group (median 39) compared to the KUS (median 12) and W groups (median 9; all $p < 0.001$), but KK patients were less likely to have metastatic disease to the lymph nodes than KUS or W patients (40.0 vs. 51.9 vs. 56.9%, respectively, $p < 0.001$). Additionally, KK patients were much more likely to have stage IA tumors than KUS and W patients (45.3 vs. 34.2 vs. 14.4%, respectively, $p < 0.001$).

On unadjusted disease-specific survival analysis, KK patients had a significantly longer median survival, with 75% survival at 92.5 months, than both KUS (87 months) and W (35 months) patients (all $p < 0.001$). Similarly, the 5-year disease-specific survival rate for KK patients was significantly longer than that for KUS or W patients (81.6 vs. 55.9 vs. 39.2%, $p < 0.001$ for all comparisons, Fig. 2a). This survival benefit for Korean patients treated in Korea persisted even after excluding patients with < 15 lymph nodes examined (Fig. 2b). Moreover, in subset analyses of patients with node-positive disease, node-negative disease, and Stage 1A patients (Fig. 2c, e, g), as well as in these same analyses limited to patients with > 15 lymph nodes examined (Fig. 2d, f, h), and subset analyses excluding cardia/GEJ

Table 1 Clinicopathologic features of the entire patient cohort

	Number (%), mean (SD), or median (IQR) Total <i>n</i> = 16,662
Ethnicity/nativity/residence (<i>n</i> , %)	
Korean/Korean born/Korean resident	3984 (24.0)
Korean/Korean born/US resident	1046 (6.3)
White/US born/US resident	11,592 (69.7)
Gender (<i>n</i> , %)	
Male	11,019 (66.3)
Female	5603 (33.7)
Age at diagnosis (mean, SD)	64.9 (13.3)
Age (<i>n</i> , %)	
< 55	3677 (22.1)
55–59	1749 (10.5)
60–64	2133 (12.8)
65–69	2323 (14.0)
70–74	2382 (14.3)
75–79	2124 (12.8)
> 79	2234 (13.4)
Number nodes examined (median, IQR)	18.5 (5–27)
> 15 nodes examined (<i>n</i> , %)	7702 (46.3)
Number positive nodes (median, IQR)	3.3 (0–4)
Any positive nodes (<i>n</i> , %)	8.736 (52.6)
Lauren classification (<i>n</i> , %)	
Intestinal	2376 (15.2)
Diffuse	3416 (21.8)
Indeterminate	9859 (63.0)
Tumor histology (<i>n</i> , %)	
Well differentiated	636 (5.0)
Moderately differentiated	3079 (24.4)
Poorly differentiated	7146 (56.5)
Undifferentiated	378 (3.0)
Not determined/unknown	1399 (11.1)
AJCC stage (<i>n</i> , %)	
Stage 0	36 (0.5)
Stage IA	2422 (31.5)
Stage IB	950 (12.3)
Stage IIA	1468 (19.1)
Stage IIB	443 (5.8)
Stage IIIA	800 (10.4)
Stage IIIB	752 (9.8)
Stage IIIC	384 (5.0)
Not applicable	330 (4.3)
Unknown	113 (1.5)
Site (<i>n</i> , %)	
Cardia/GEJ	4493 (27.0)
Fundus	868 (5.2)
Body	4146 (24.9)
Antrum/pylorus	4913 (29.6)
Other	2202 (13.3)

tumors (Fig. 2i, j), KK patients continued to demonstrate significantly increased 5-year disease-specific survival rates compared to W patients. For all comparisons except Stage 1A and node positive patients, there is a clear incremental survival benefit for KK patients versus KUS patients versus W patients. For node positive patients, KUS and W patients behave more similarly, and for stage 1A patients, all three groups behave more similarly.

On adjusted multivariable analysis (Table 3), KUS patients had a nearly threefold increased risk of mortality when compared to KK patients (HR 2.80, 95%CI 2.07–3.78, $p < 0.001$), whereas W patients had a nearly six-fold increased mortality risk than KK patients (HR 5.79, 95%CI 4.56–7.34, $p < 0.001$). Other independent predictors of mortality included increasing age, each additional positive lymph node, tumor differentiation, tumor location, and increasing AJCC stage, with Stages IIA and above conveying a statistically significant increased risk of death. Protective factors include the examination of > 15 lymph nodes.

To address the potential limitation that the dramatic differences in survival might be due to KK patients being treated by expert surgeons at a Korean COE whereas KUS and W patients were largely treated at low-volume centers in the US, we examined overall survival data from our own high-volume center (MGH). As seen in Fig. 3, though survival rates of patients treated at MGH are better than those treated at SEER hospitals, there persists a large survival gap between the KK patients and those treated at MGH, reflecting the fact that non-treatment-related factors, such as nativity and/or environmental factors, contribute significantly to survival differences.

Discussion

Survival after potentially curative surgery for gastric cancer is dictated by an uncertain combination of biological, environmental, and treatment-related factors. Our study is unique, in that its design allows us to examine the relative contributions of all of these factors on gastric cancer outcomes. In this study, we demonstrate the importance of birthplace and ethnicity (“nature”) on gastric cancer mortality, as we show that Korean patients born in Korea but treated in the US have superior outcomes than White patients born and treated within the same healthcare system in the US. We also demonstrate the importance of the environment and of treatment-related factors (“nurture”) on gastric cancer mortality, as we show that patients born and treated in Korea have much lower mortality than those patients born in Korea who emigrate and receive their gastric cancer treatment in the US. Similarly, US patients treated at a center of excellence in the US enjoy better outcomes than those patients treated at a SEER registry

Table 2 Unadjusted comparisons between patients born in Korea and treated in Korea (KK), patients born in Korea and treated in the US (KUS), and White Americans born in the US and treated in the US (W)

	Korean/Korean, KK, <i>n</i> = 3984	Korean/US, KUS, <i>n</i> = 1046	White/US, W, <i>n</i> = 11,592	<i>P</i> value*	<i>P</i> value [§]	<i>P</i> value [#]
Median survival (months)	Not reached	87	35	<0.001	<0.001	<0.001
5 year DSS (%; IQR)	81.6 (80.2–83.0)	55.9 (52.2–59.4)	39.2 (38.0–40.5)	<0.001	<0.001	<0.001
Male (<i>n</i> , %)	2671 (67.0)	616 (58.9)	7732 (66.7)	<0.001	0.693	<0.001
Age at diagnosis (mean, SD)	57.6 (12.0)	63.8 (12.9)	67.5 (12.8)	<0.001	<0.001	<0.001
Age categories (<i>n</i> , %)				<0.001	<0.001	<0.001
< 55	1527 (38.3)	249 (23.8)	1901 (16.4)			
55–59	570 (14.3)	114 (10.9)	1065 (9.2)			
60–64	681 (17.1)	122 (11.7)	1330 (11.5)			
65–69	526 (13.2)	176 (16.8)	1621 (14.0)			
70–74	403 (10.1)	164 (15.7)	1815 (15.7)			
75–79	214 (5.4)	114 (10.9)	1796 (15.5)			
> 79	63 (1.6)	107 (10.2)	2064 (17.8)			
Number examined lymph nodes (median, IQR)	39 (29–50)	12 (6–21)	9 (3–15)	<0.001	<0.001	<0.001
> 15 nodes examined (<i>n</i> , %)	3837 (96.3)	440 (42.1)	3525 (29.6)	<0.001	<0.001	<0.001
Positive lymph nodes (median, IQR)	0 (0–3)	1 (0–5)	1 (0–5)	<0.001	<0.001	0.023
Any positive nodes (<i>n</i> , %)	1594 (40.0)	543 (51.9)	6599 (56.9)	<0.001	<0.001	0.002
Lauren classification (<i>n</i> , %)				<0.001	<0.001	0.001
Intestinal	1686 (43.7)	39 (3.8)	651 (6.0)			
Diffuse	1427 (37.0)	205 (20.0)	1786 (16.6)			
Indeterminate	749 (19.4)	779 (76.2)	8331 (77.4)			
Histology (<i>n</i> , %)				<0.001	<0.001	<0.001
Well differentiated	447 (12.7)	43 (4.1)	593 (5.1)			
Moderately differentiated	1251 (35.6)	237 (22.7)	2842 (24.5)			
Poorly differentiated	1789 (50.9)	677 (64.7)	6469 (55.8)			
Undifferentiated	0 (0.0)	16 (1.5)	362 (3.1)			
Not specified/unknown	30 (0.9)	73 (7.0)	1326 (11.4)			
AJCC stage (<i>n</i> , %)				<0.001	<0.001	<0.001
Stage 0	0 (0.0)	11 (2.5)	25 (0.8)			
Stage IA	1,800 (45.3)	148 (34.2)	474 (14.4)			
Stage IB	229 (5.8)	82 (18.9)	639 (19.4)			
Stage IIA	505 (12.7)	74 (17.1)	889 (27.0)			
Stage IIB	443 (11.2)	0 (0.0)	0 (0.0)			
Stage IIIA	60 (1.5)	66 (15.2)	674 (20.5)			
Stage IIIB	551 (13.9)	25 (5.8)	176 (5.3)			
Stage IIIC	384 (9.7)	0 (0.0)	0 (0.0)			
Not applicable	0 (0.0)	6 (1.4)	324 (9.8)			
Unknown	0 (0.0)	21 (4.9)	92 (2.8)			
Site (<i>n</i> , %)				<0.001	<0.001	<0.001
Cardia/GEJ	20 (0.5)	40 (3.8)	4433 (38.2)			
Fundus	411 (10.3)	24 (2.3)	433 (3.7)			
Body	1444 (36.2)	350 (33.5)	2352 (20.3)			
Antrum/pylorus	2059 (51.9)	459 (43.9)	2385 (20.6)			
Other	40 (1.0)	173 (16.5)	1989 (17.2)			
Operation (<i>n</i> , %)				<0.001	<0.001	<0.001
Distal/subtotal gastrectomy	2890 (72.5)	658 (62.9)	6,097 (52.6)			
Near total/total gastrectomy	760 (19.1)	168 (16.1)	1301 (11.2)			
Esophagogastrectomy	10 (0.3)	89 (8.5)	2355 (20.3)			

Table 2 (continued)

	Korean/Korean, KK, <i>n</i> = 3984	Korean/US, KUS, <i>n</i> = 1046	White/US, W, <i>n</i> = 11,592	<i>P</i> value*	<i>P</i> value [§]	<i>P</i> value [#]
Radical gastrectomy with en bloc resection of other organs	324 (8.1)	117 (11.2)	1662 (14.3)			
Gastrectomy, NOS	0 (0.0)	14 (1.3)	177 (1.5)			

DSS disease-specific survival

**P* value between Korean/Korean born/Korean resident and Korean/Korean born/US resident

[§]*P* value between Korean/Korean born/Korean resident and White/US born/US resident

[#]*P* value between Korean/Korean born/US resident and White/US born/US resident

hospital, perhaps the result of higher quality surgical treatment and multidisciplinary care at a high-volume center.

Our findings are consistent with prior studies—namely, that Asian gastric cancer patients have superior survival outcomes to Western patients [5–8, 13, 18]. A recent study utilizing the SEER database to examine the gastric cancer survival gap between Asians and non-Hispanic whites (NHWs) in the US found that all Asian groups enjoyed higher 5-year survival rates than NHWs, with Korean patients having the highest survival at 45.4%. This finding was predominantly attributed to higher proportions of localized disease and lower proportions of cardia tumors [19]. Other studies have also suggested that an increased proportion of localized disease,[6, 7] favorable tumor location,[7] improved surgical technique leading to more accurate staging,[7–9, 20] and fewer patient comorbidities [10] are possible explanations for the improved survival of Asian gastric cancer patients. Our study analogously compares Korean immigrants in the US to White patients in the US and demonstrates a survival benefit for Korean immigrants. This is an important finding, as immigrant populations are generally considered to be a vulnerable population, with worse access to health care, lower socioeconomic status, and social marginalization [21]. Our study similarly found higher rates of early-stage disease and lower rates of cardia tumors in both groups of Koreans when compared to White US patients. Recognizing that cardia/GEJ tumors have been excluded from some studies since they are classified as esophageal cancers in the 7th edition of the AJCC Cancer Staging Manual, we performed a subset analysis excluding cardia/GEJ tumors and found that the survival benefit for Koreans versus White Americans persists, suggesting that there are other factors beyond tumor location that contribute to the survival difference. Furthermore, in our multivariable analysis controlling for most important clinical and pathologic factors, including tumor site, histology, lymph node status, and stage, Korean birthplace/ethnicity remained an independent predictor of decreased mortality for both Koreans treated in Korea and Koreans treated in the US.

Our study builds upon what has been previously published by uniquely comparing patients born, raised, and treated in Korea to patients born in Korea but raised (for some period of time) and treated in the US. Our study design allows us to control for race and nativity, in essence controlling for “nature,” to isolate the effects of environmental factors and quality of care on influencing mortality. By demonstrating a mortality benefit for KK patients when compared to KUS patients, we propose that differences in the quality of care between the US and Korea as well as differences in environmental factors, such as a high-salt diet [22] and *H. pylori* infection rates, may influence gastric cancer-related mortality rates.

Of course, differences in the quality of care delivered influence cancer outcomes. Hospital-level factors that may affect the quality of care include the existence of a gastric cancer screening program, the volume of gastric cancer patients treated, and the presence of a skilled multidisciplinary team experienced in the treatment of gastric cancer. Korean hospitals see many more gastric cancer patients, and thus Korean surgeons perform far more gastrectomies per year, than do US surgeons [23]. Interestingly, the majority of gastrectomies for gastric cancer in the US are not performed at “high-volume” centers (centers performing > 20 gastrectomies per year) [24, 25]. Surgeon-level factors that may affect the quality of gastric cancer care include the performance of an adequate lymphadenectomy to accurately stage the disease and to lower regional recurrence rates. While a D2 lymphadenectomy is the standard of care in both Japan and Korea, the majority of patients in the US rarely undergo even a D1 lymphadenectomy [26]. Though randomized trials comparing D1–D2 lymphadenectomy in the West have failed to demonstrate a survival benefit for patients undergoing the more extensive D2 dissection,[27–29] upon further examination and exclusion of patients requiring distal pancreatectomies and splenectomies, a survival benefit for patients undergoing extended lymphadenectomy was observed [30]. The National Comprehensive Cancer Network (NCCN) guidelines, therefore, recommend dissecting a minimum of 15 lymph nodes to appropriately stage the disease. In our

Fig. 1 Diagnosis (a) and cumulative diagnosis (b) of gastric cancer by patient age

study, 96.3% of KK patients had > 15 lymph nodes examined, yet only 42.1% of Korean patients treated in the US and 29.6% of White patients achieved this goal. Our data suggest that the majority of gastric cancer patients in the US receive an inadequate lymph node dissection, which may lead to inaccurate staging and higher rates of locoregional recurrence [31–33]. In our cohort, the examination of > 15 lymph nodes was an independent predictor of reduced mortality,

almost certainly the result of improved staging and, perhaps, an enhanced therapeutic effect. To limit the impact of inadequate nodal dissection on survival outcomes, we performed subset analyses excluding patients with < 15 nodes examined and found persistent, substantial survival differences between Koreans and White Americans, suggesting the importance of birthplace and ethnicity on gastric cancer outcomes. Similarly, in an analysis of Stage 1A patients, in

Fig. 2 Unadjusted Kaplan–Meier disease-specific survival curves for **a** all patients, **b** all patients with > 15 nodes examined, **c** all patients with positive lymph nodes, **d** all patients with > 15 nodes examined with positive lymph nodes, **e** all patients with negative lymph nodes, **f** all patients with > 15 nodes examined with negative lymph nodes, **g** Stage IA patients, **h** Stage IA patients with > 15 lymph nodes examined, **i** all patients, excluding cardia/GEJ tumors, and **j** all patients with > 15 nodes examined, excluding cardia/GEJ tumors

whom a nodal dissection is of less importance given the low incidence of nodal metastasis in T1a tumors, KK and KUS patients had similar survival curves that were superior to W

patients, again suggesting that there are true biologic/ethnic differences unrelated to surgical technique.

Furthermore, our study demonstrates that Koreans and White Americans have significantly different mean ages

Table 3 Multivariable analysis of clinicopathologic factors on the risk of mortality

	Hazard ratio (95% CI)	<i>p</i> value
Race/nativity/residence		
Korean/Korean born/Korean resident	Reference	
Korean/Korean born/US resident	2.80 (2.07–3.78)	<0.001
White/US born/US resident	5.79 (4.56–7.34)	<0.001
Gender		
Male	Reference	
Female	1.02 (0.92–1.14)	0.67
Age categories		
< 55	Reference	
55–59	1.03 (0.85–1.24)	0.27
60–64	1.29 (1.09–1.53)	0.003
65–69	1.27 (1.06–1.51)	0.008
70–74	1.74 (1.46–2.08)	<0.001
75–79	1.75 (1.45–2.11)	<0.001
> 79	2.17 (1.80–2.61)	<0.001
Additional positive lymph node	1.03 (1.02–1.04)	<0.001
> 15 lymph nodes examined	0.70 (0.61–0.80)	<0.001
Lauren classification (<i>n</i> , %)		
Intestinal	Reference	
Diffuse	0.95 (0.80–1.14)	0.62
Indeterminate	0.97 (0.82–1.15)	0.71
Histology (<i>n</i> , %)		
Well differentiated	Reference	
Moderately differentiated	1.48 (1.09–2.01)	0.01
Poorly differentiated	1.79 (1.32–2.43)	0.001
Undifferentiated	2.19 (1.35–3.55)	0.001
Not specified/unknown	1.49 (0.98–2.30)	0.07
AJCC stage		
Stage 0	Reference	
Stage IA	2.63 (0.36–19.1)	0.34
Stage IB	6.67 (0.92–48.1)	0.06
Stage IIA	11.02 (1.53–79.46)	0.02
Stage IIB	16.91 (2.32–123.57)	0.005
Stage IIIA	17.34 (2.40–125.05)	0.005
Stage IIIB	22.52 (3.11–162.82)	0.002
Stage IIIC	44.48 (6.10–324.64)	<0.001
Unknown	14.51 (1.97–107.06)	0.009
Site		
Cardia/GEJ	Reference	
Fundus	1.71 (1.30–2.23)	<0.001
Body	1.95 (1.59–2.38)	<0.001
Antrum/pylorus	2.12 (1.72–2.59)	<0.001
Other	2.64 (2.13–3.28)	<0.001

of diagnosis. KK patients were diagnosed at a younger age than KUS patients, a fact that may be partially explained by the existence of an endoscopic screening program in Korea, which does not exist in the US. Furthermore, pathologists

in Eastern countries are more likely to utilize cellular and glandular abnormalities as diagnostic criteria for carcinoma, whereas pathologists in Western countries require tumor invasion [9, 34]. These factors lead to an earlier age of, and stage of, diagnosis amongst patients in Korea. However, there still exists a significant difference in age at diagnosis between KUS and W patients, suggesting that ethnic factors, as opposed to health care system factors, also contribute to this difference.

Our study has numerous strengths. First, our study is one of the first to use a specific Asian ethnicity—in this case Korean ethnicity—as a covariate and to examine Korean immigration status as a risk factor for gastric cancer mortality. This is extremely important in the current era, when in 2015 approximately 244 million people reside in a country other than where they were born [35]. We believe that clinical research needs to adapt to reflect the true population within a country rather than just the historically major population. Our study is also strengthened by our inclusion of data from a Korean COE, allowing us to make comparisons between two nations' health care systems. Moreover, we utilized large sample sizes, leading to an adequately powered study. The SEER database also allowed us to examine all age groups, rather than just a subset of ages if we had used the SEER-Medicare database, leading to improved generalizability. Lastly, we were able to adjust in our multivariable model for the most important prognostic factors in gastric cancer—specifically node status and AJCC stage—and therefore, controlled for the possibility that the decreased mortality amongst Koreans is solely due to an earlier stage of diagnosis [36–38].

Despite these strengths, our study is not without limitations. First, as mentioned in the methods, the calculation of survival differed between patients. Since patients treated in the US had their survival calculated based on the date of diagnosis rather than the date of surgery, they have more months of follow-up than the patients treated in Korea, which should bias our survival analysis towards the null, and therefore, make our survival rates for the US groups appear better than they may be. Additionally, due to the limitation of the SEER database, we were unable to study the impact of chemotherapy or patient comorbidities on survival. Third, we do not know the actual dates of immigration of the Korean patients who ultimately received their care in the US and thus do not know the lengths of exposure to the environment of the native versus the adopted country. Lastly, we were unable to include a fourth group of Koreans born in the US who received their health care in the US because of a limited sample size.

In conclusion, our study demonstrates that biologic factors, such as nativity and ethnicity, as well as environmental factors, such as the quality of care, significantly contribute to the improved prognosis of patients with gastric cancer in

Fig. 3 Unadjusted Kaplan–Meier survival curves for **a** all patients, including patients treated at MGH, and **b** all patients with > 15 nodes examined, including patients treated at MGH

Korea relative to those in the US, implicating both nature and nurture in this phenomenon. Additionally, our study confirms the importance of examining at least 15 lymph nodes in the pathologic specimen as an independent predictor of decreased mortality. Furthermore, our study highlights the importance of considering nativity as a covariate in future studies, as we have shown that the place of birth does significantly affect outcomes. We propose that as the world becomes increasingly globalized and immigration more ubiquitous, scientific inquiries should reflect this evolving international diversity and include nativity as a potential risk factor in predicting patient outcomes.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical standards All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions.

Informed consent Informed consent or substitute for it was obtained from all patients for being included in the study.

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