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TOPIC HIGHLIGHT

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Racial and ethnic disparities in gastric cancer outcomes: More important than surgical technique?

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Abstract

Racial and ethnic disparities in cancer care are major public health concerns and their identification is necessary to develop interventions to eliminate these disparities. We and others have previously observed marked disparities in gastric cancer outcomes between Eastern and Western patients. These disparities have long been attributed to surgical technique and extent of lymphadenectomy. However, more recent evidence suggests that other factors such as tumor biology, environmental factors such as *Helicobacter pylori* infection and stage migration may also significantly contribute to these observed disparities. We review the literature surrounding disparities in gastric cancer and provide data pertaining to potential contributing factors.

Key words: Race; Ethnicity; Disparities; Gastric cancer; Gastric adenocarcinoma

Core tip: Our prior investigations and review of the literature suggest that racial and ethnic disparities in gastric cancer outcomes in Eastern and Western patients may not be solely attributed to surgical technique and extent of lymphadenectomy. More recent evidence from the Asian population of Los Angeles County and a broad spectrum of the United States suggests that racial disparities exist independent of the number of lymph nodes harvested. Our data suggests that gastric cancer outcomes are not comparable among different racial and ethnic groups. Therefore, a one size fits all approach to gastric cancer management appears to be inappropriate.

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INTRODUCTION

Cancer health disparities are "differences in the incidence, prevalence, mortality and burden of cancer and related adverse health conditions that exist among specific population groups"[1]. Such disparities related to race and ethnicity are well described and are major public health concerns. Indeed, cancer incidence and death rates vary considerably among select racial and ethnic groups[2,3]. For example, when considering all cancer sites combined, black men have higher incidence and death rates compared to white men; black women also have higher death rates compared to white women[2-4]. These disparities apply to much of the United States, where whites and blacks are the predominant racial groups. However, in states such as California that have a large population of immigrants, racial disparity investigations have included the Asian population.

Our research group and others have previously investigated gastrointestinal cancer outcomes in Asians

Table 1 Investigations performed by our group demonstrating racial and ethnic disparities in gastrointestinal cancer outcomes

Ref.	Histology	Cancer registry	Groups	Findings
Artinyan *et al*[5], 2010	Hepatocellular carcinoma	SEER	white, black, Hispanic, and Asian	Blacks have shortest OS Race/ethnicity independently predicts OS Asian race independently predicts improved OS
Kim *et al*[7], 2011	Rectal cancer	LAC CSP	white, black, Hispanic, and Asian	Asians have longest OS Race/ethnicity independently predicts OS
Lee *et al*[8], 2012	Rectal cancer	LAC CSP	white, black, Hispanic, and Asian	Of patients who received neoadjuvant radiation, blacks have the poorest survival Race/ethnicity independently predicts survival
Lee *et al*[9], 2012	Colon cancer	LAC CSP	white, black, Hispanic, and Asian	Asians have longest OS
Kim *et al*[16], 2010	Gastric cancer	LAC CSP	white, black, Hispanic, and Asian	Asians have longest OS Asian race independently predicts improved OS for surgical patients
Kim *et al*[59], 2009	Gastric cancer	LAC CSP	Korean, Chinese, Japanese, Filipino, and Vietnamese	Koreans have longest MS Filipinos have shortest MS Japanese and Filipino ethnicities independently predict worse OS
Nelson *et al*[18], 2013	Gastric cancer	SEER	Korean-Americans and whites	Korean-Americans have prolonged OS independent of LNs

SEER: Surveillance, Epidemiology, and End Results; LAC CSP: Los Angeles County Cancer Surveillance Program; MS: Median survival; OS: Overall survival.

revealing better survival outcomes in a variety of cancers including hepatocellular carcinoma and rectal and colon cancer[5-9] (Table 1). In addition to differences in incidence and survival, there are differences in the type of treatment received. This is more prominent in the management and subsequent outcomes of gastric cancer, one of the most common cancers in Asia[10]. Disparities in gastric cancer outcomes has been an area of active investigation, with many striving to explain the dramatic differences in survival between Eastern and Western patients. Here, we explore the literature on racial and ethnic disparities in gastric cancer and the factors that may contribute to this phenomenon.

Racial and ethnic disparities in gastric cancer

Despite a decreasing incidence in the United States, gastric cancer remains a leading cause of cancer-related death worldwide[11]. In the United States, the estimated new number of gastric cancer cases was 21600 with a corresponding estimated number of deaths of 10990[2]. Although the number of deaths from gastric cancer has been steadily declining since 1930, the disease continues to be common in Asian countries where nearly 60% of new cases occur[12]. Notwithstanding the higher prevalence of gastric cancer in Asia, significantly better outcomes have been reported in Asian compared to Western countries[13]. For example, 5-year gastric cancer survival in Japan is 60% compared to the much lower 20% in the United States and Europe[10]. However, the outcomes disparities are not limited to survival alone. In fact, important differences have also been observed in gastric cancer presentation and anatomic location and patient receipt of multi-modality therapy and surgery.

When considering disease presentation and location (proximal - cardia, fundus; distal - body, antrum, pylorus), Asian patients are more likely to be younger at initial diagnosis and to have a higher proportion of distal gastric cancers[14,15]. Our group's investigation of gastric cancer in southern California revealed that Asians, Hispanics and blacks had the lowest percentage of proximal tumors, whereas whites had the highest percentage of proximal tumors. Furthermore, Asians were more likely to have localized disease[16]. When examining receipt of therapy, our group also observed that Asians were more likely to undergo curative intent surgery[16]. Gill *et al*[15] observed that Asians also received chemotherapy more often than non-Asians. Regarding the quality of surgical resection, Al-Refaie *et al*[17] demonstrated that Asians were less likely to have inadequate lymphadenectomy compared to whites. It is no surprise then that studies have repeatedly demonstrated that Asian patients have better gastric cancer survival compared to other racial and ethnic groups[10,15,16,18]. This disparity in survival when viewed in a larger context between Eastern and Western countries has been attributed largely to surgical technique and extent of lymphadenectomy[19-21]. However, our investigations suggest that other factors such as differences in tumor biology[14,22,23] and infectious etiologies such as *Helicobacter pylori* (*H. pylori*)[24] may influence these disparities to variable extents. We discuss these factors below.

Surgical technique and extent of lymphadenectomy

One of the historical areas of controversy in the surgical management of gastric cancer is the extent of lymphadenectomy. Lymph node disease is an independent prognostic factor in gastric cancer[19,20,25,26] and prospective randomized trials have shown mixed results pertaining to the value of extended lymphadenectomy. One such study performed by the Medical Research Council in the United Kingdom[27] examined gastrectomy with D1 *vs* D2 lymph node dissection (LND) and the results showed higher morbidity and mortality in the D2 LND group.

Furthermore, 5-year overall and recurrence-free survival were not significantly different between the 2 groups[28]. The Dutch Gastric Cancer Group also conducted a major investigation, randomizing patients to undergo gastrectomy with D1 *vs* D2 LND[29]. The analysis demonstrated that D2 LND was associated with significantly greater peri-operative morbidity and mortality compared to D1 LND. Although there was no survival benefit initially observed with D2 LND[30,31], a 15-year analysis of the data showed that D2 LND was associated with lower locoregional recurrence and gastric cancer-related death rates[32]. Nevertheless, Western data is generally different from studies performed in Eastern countries. In Japan, numerous retrospective, observational, and prospective studies have shown improved survival in patients undergoing extended lymphadenectomy[19-21]. As such, D2 LND is regarded as standard of care and nearly all centers in Asia have embraced the routine performance of extended LND, whereas its performance in the United States and Western centers is likely to occur only at specialty centers.

The degree of LND is based on the Japanese staging system in which nodal stations are categorized as N1, N2, N3 or N4[19,20]. For example, D1 dissection entails removal of the N1 lymph node basin (*i.e.*, perigastric, lesser and greater curvature, suprapyloric and infrapyloric), whereas D2 dissection involves D1 dissection plus removal of nodes along the major named arteries (left gastric artery, splenic artery, common hepatic artery and celiac trunk). More extended lymph node dissections involve the removal of lymph nodes in the hepatoduodenal ligament and retropancreatic and para-aortic regions. In a randomized controlled trial comparing D1 and D3 LND, the more extensive LND was associated with higher 5-year overall and recurrence-free survival[21].

The adoption of D2 LND in Western countries has been slow and may contribute to the reported differences in survival outcomes between Eastern and Western patients undergoing surgery for gastric cancer. Interestingly, our own data suggests that the superior survival outcomes noted in Eastern populations may not be directly related to extent of lymphadenectomy. Using the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) registry, we observed that the outcomes of Korean-American gastric cancer patients were independent of lymph node number[18]. Remarkably, despite a consistently low number of examined lymph nodes for Korean-American patients, survival rates were comparable to previously reported outcomes from East Asian centers with higher lymph node yields. These findings suggest that the higher gastric cancer survival in the East may not be attributed solely to surgical technique. However, our own group firmly adheres to the routine performance of D2 LND dissection in our patients with gastric adenocarcinoma.

Stage migration

Variability in the extent of lymphadenectomy and the number of lymph nodes examined may affect nodal staging[33-35]. Thus, the comparison of outcomes between Eastern centers with extended LND and Western centers with inadequate LND may produce disparities because of potential under-staging in Western patients. Originally described by Feinstein *et al*[36] as the Will Rogers phenomenon, there is a migration of disease into more advanced stages by the identification of lymph node disease with more extensive dissection (in Eastern patients) that would otherwise remain unidentified (in Western patients) with inadequate surgical dissection. Therefore, stage migration associated with more radical lymphadenectomy in the East may contribute to the disparate survival differences between Eastern and Western patients.

Tumor biology

The different patterns of gastric cancer in the East and West are so apparent that many have suggested inherent differences in biologic behaviour. This theory may be supported by the distinct anatomic patterns of gastric cancer location between Eastern and Western patients. Distal cancers constitute the majority of stomach cancer cases worldwide[10] whereas the incidence rates of proximal cancers have increased in Western countries[10,37,38]. While the distinct anatomic patterns and histologic subtypes of cancer may suggest differing tumor biology, studies have been unable to consistently support this notion.

From a molecular perspective, McCulloch *et al*[39,40] showed that the oncogenes *c-erbB2* and *TP53* were expressed in a similar fashion in gastric cancers from Japanese and British patients, but Theuer *et al*[23] demonstrated higher frequency of microsatellite stability in gastric cancers from Japanese compared to American patients. Theuer *et al*[22] demonstrated that normal E-cadherin expression was more common in Japanese intestinal-type gastric cancer whereas *c-erbB2* expression was higher in American gastric cancers. These findings are relevant because abnormal E-cadherin expression is associated with adverse features in gastric cancer such as loss of cell-cell adhesion (a more common feature of diffuse-type gastric cancer)[41,42] and increased *c-erbB2* expression may correlate with depth of invasion and metastasis[43]. Furthermore, tumors in British patients have a significantly greater mean cell nuclear antigen proliferation index than Japanese tumors and increased levels of an "anti-metastasis" factor have been reported in specimens from Japanese compared to British patients[44].

Different genetic backgrounds in various ethnic populations may alter susceptibility to developing gastric cancer. More recently, there has been a plethora of information pertaining to genetic polymorphisms in gastric cancer. Various genes, including but not limited to, CD14[45], glutathione S-transferase T1[46] and XRCC3[47] have been shown to alter gastric cancer susceptibility in ethnic groups, particularly Asians and Caucasians. These molecular studies suggest that differences in tumor biology among various ethnic groups exist and may contribute to racial disparities in gastric cancer outcomes.

H. pylori

Globally, *H. pylori* infection affects 50% of the worldwide population[48]. In addition to its indisputable role in chronic gastritis and peptic ulcer disease[49,50], the association between *H. pylori* and gastric cancer is also well accepted[25,50-52] and epidemiologic studies estimate that the risk of gastric cancer in *H. pylori*-infected individuals is increased by 20-fold[53]. In general, the seroprevalence rates in less developed or developing countries are higher than in developed countries[24]. Compared to the United States, Asian countries have higher seroprevalence rates and Asian immigrants have much higher rates of *H. pylori* seropositivity than whites[24,54]. Thus, the high rates of gastric cancer in Asia may occur from a complex interaction between host factors, environmental factors and *H. pylori* infection[24].

Different *H. pylori* strains occur across diverse geographic regions and differences in these strains have correlated with variations in gastric cancer epidemiology[24]. For example, cytotoxin-associated gene A (CagA) and vacuolating cytotoxin A are major pathogenic factors that may dysregulate host intracellular signalling pathways and lower the threshold for neoplastic transformation[50]. Strains that produce CagA are more likely to cause cancer[55,56]. Finally, differences in *H. pylori* genomes have been demonstrated between East Asian and non-Asian populations[57] and may also conceivably contribute to disparities in gastric cancer outcomes.

Our research observations

Our group has taken great interest in racial and ethnic disparities in gastric cancer. Within the state of California, Los Angeles County is an ethnically diverse population in which the percentage of Asians is approximately 3-fold higher than in the general United States population and where Hispanics comprise the largest ethnic group[58]. This milieu provides a unique opportunity to study the potential association between race and ethnicity and gastric cancer outcomes. Using the Los Angeles County Cancer Surveillance Program database, we demonstrated that Asian patients with gastric cancer demonstrated longer survival than whites, Hispanics and blacks[16]. Furthermore, in patients that underwent surgical resection, superior survival was again demonstrated in Asian patients compared to whites, Hispanics and blacks[16] and remained significant even when cancer location and extent of lymphadenectomy were taken into account. Even more intriguing is the observation that there was no improvement in 5-year survival for patients with increased lymph node retrieval. Our results support the presence of persistent racial and ethnic differences despite controlling for technical factors

We subsequently compared outcomes among the different Asian ethnic groups and discovered differences in gastric cancer survival among Asian ethnicities[59]. Again using the Los Angeles County Cancer Surveillance Program database, we showed stark survival differences between Korean, Chinese, Japanese, Filipino and Vietnamese populations, with the greatest difference between Koreans and Filipinos, who had the best and worst overall survival, respectively. Korean patients were least likely to have nodal or distant disease and had a lower rate of proximal tumors; conversely, Filipino patients had amongst the highest rates of nodal and distant disease as well as proximal gastric cancers. These results suggest that there are differences in gastric cancer presentation and survival among Asian ethnicities and that combining diverse Asian ethnic populations as one single race may be grossly inappropriate.

In a more recent study utilizing the SEER registry, we compared characteristics of Korean-American patients who had high or low lymph node counts and attempted to determine whether extent of lymphadenectomy during curative-intent gastric surgery would impact survival[18]. Remarkably, overall survival was not different in Korean-American patients undergoing excision of 1-15 lymph nodes compared to 16+ lymph nodes for all stages of disease. A similar analysis was conducted for whites, which showed that overall survival diverged according to examined lymph node groups. Specifically, white patients with 16+ examined lymph nodes had significantly longer overall survival than for 1-15 examined lymph nodes for all stages of disease. These findings suggest that extent of lymphadenectomy may not contribute to survival outcomes in Eastern patients as much as previously believed and that it may be more important in Western patients.

DISCUSSION

Much literature shows that the issue of racial and ethnic disparities and cancer outcomes remains important and thus it continues to be under active investigation. These disparities are likely influenced by a number of different factors (*e.g.*, access to screening, quality of surgical care, access and response to multimodality therapy, *etc.*) and a better understanding of these disparities can lead to interventions that may help to abolish these disparities.

Stark differences in gastric cancer outcomes between Eastern and Western patients have been investigated and debated. Although many Eastern surgeons are convinced that these disparities are largely secondary to surgical technique, the importance of race and ethnicity in impacting these disparities has gained traction. As a surgical unit, we strongly advocate the routine performance of D2 lymphadenectomy for curative resection of gastric adenocarcinoma, but we also strongly suspect that factors beyond surgical control influence outcomes.

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