**Name of Journal:** **World Journal of Gastroenterology**

**ESPS Manuscript No: 6610**

**Columns: TOPIC HIGHLIGHTS**

WJG 20th Anniversary Special Issues (8): Gastric cancer

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

Merchant SJ *et al*. Disparities in gastric cancer

Shaila J Merchant, Lily Li, Joseph Kim

**Shaila J Merchant, Lily Li, Joseph Kim,** Division of Surgical Oncology, Department of Surgery, City of Hope National Medical Center, Duarte, CA 91010, United States

**Joseph Kim,** City of Hope Comprehensive Cancer Center, Duarte, CA 91010, United States

**Author contributions:** Merchant SJ performed the literature review; Merchant SJ, Li L and Kim J wrote the manuscript

**Correspondence to: Joseph Kim, MD, Associate Professor** of Surgery, City of Hope Comprehensive Cancer Center, 1500 East Duarte Road, Duarte, CA 91010, United States. jokim@coh.org

**Telephone:** +1- 626-4717100 **Fax:** +1- 626-3018865

**Received:** October 25, 2013 **Revised:** February 8, 2014

**Accepted:** May 28, 2014

**Published online:**

**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.

© 2014 Baishideng Publishing Group Inc. All rights reserved.

**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.

Merchant SJ, Li L, Kim J. Racial and ethnic disparities in gastric cancer outcomes: More important than surgical technique? *World J Gastroenterol* 2014; In press

**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 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 differences in racial 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.

**REFERENCES**

1 **Trans-HHS Cancer Health Disparities Progress Review Group.** Making cancer health disparities history. United States Department of Health and Human Services, March 2004. Available from: URL: http: //planning.cancer.gov/library/2004chdprg.pdf

2 **Siegel R**, Naishadham D, Jemal A. Cancer statistics, 2013. *CA Cancer J Clin* 2013; **63**: 11-30 [PMID: 23335087 DOI: 10.3322/caac.21166]

3 **Morris AM**, Rhoads KF, Stain SC, Birkmeyer JD. Understanding racial disparities in cancer treatment and outcomes. *J Am Coll Surg* 2010; **211**: 105-113 [PMID: 20610256 DOI: 10.1016/j.jamcollsurg.2010.02.051]

4 **Rhoads KF**, Cullen J, Ngo JV, Wren SM. Racial and ethnic differences in lymph node examination after colon cancer resection do not completely explain disparities in mortality. *Cancer* 2012; **118**: 469-477 [PMID: 21751191 DOI: 10.1002/cncr.26316]

5 **Artinyan A**, Mailey B, Sanchez-Luege N, Khalili J, Sun CL, Bhatia S, Wagman LD, Nissen N, Colquhoun SD, Kim J. Race, ethnicity, and socioeconomic status influence the survival of patients with hepatocellular carcinoma in the United States. *Cancer* 2010; **116**: 1367-1377 [PMID: 20101732 DOI: 10.1002/cncr.24817]

6 **Mathur AK**, Osborne NH, Lynch RJ, Ghaferi AA, Dimick JB, Sonnenday CJ. Racial/ethnic disparities in access to care and survival for patients with early-stage hepatocellular carcinoma. *Arch Surg* 2010; **145**: 1158-1163 [PMID: 21173289 DOI: 10.1001/archsurg.2010.272]

7 **Kim J**, Artinyan A, Mailey B, Christopher S, Lee W, McKenzie S, Chen SL, Bhatia S, Pigazzi A, Garcia-Aguilar J. An interaction of race and ethnicity with socioeconomic status in rectal cancer outcomes. *Ann Surg* 2011; **253**: 647-654 [PMID: 21475002 DOI: 10.1097/SLA.0b013e3182111102]

8 **Lee W**, Nelson R, Akmal Y, Mailey B, McKenzie S, Artinyan A, Ashing-Giwa KT, Chen YJ, Garcia-Aguilar J, Kim J. Racial and ethnic disparities in outcomes with radiation therapy for rectal adenocarcinoma. *Int J Colorectal Dis* 2012; **27**: 737-749 [PMID: 22159751 DOI: 10.1007/s00384-011-1378-2]

9 **Lee W**, Nelson R, Mailey B, Duldulao MP, Garcia-Aguilar J, Kim J. Socioeconomic factors impact colon cancer outcomes in diverse patient populations. *J Gastrointest Surg* 2012; **16**: 692-704 [PMID: 22258868 DOI: 10.1007/s11605-011-1809-y]

10 **Kamangar F**, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. *J Clin Oncol* 2006; **24**: 2137-2150 [PMID: 16682732]

11 **American Cancer Society.** Cancer Facts and Figures 2014. Available from: URL: http: //www.cancer.org/acs/groups/content/@research/documents/document/acspc-041770.pdf

12 **Crew KD**, Neugut AI. Epidemiology of gastric cancer. *World J Gastroenterol* 2006; **12**: 354-362 [PMID: 16489633]

13 **Patel SH**, Kooby DA. Gastric adenocarcinoma surgery and adjuvant therapy. *Surg Clin North Am* 2011; **91**: 1039-1077 [PMID: 21889029 DOI: 10.1016/j.suc.2011.06.009]

14 **Theuer CP**, Kurosaki T, Ziogas A, Butler J, Anton-Culver H. Asian patients with gastric carcinoma in the United States exhibit unique clinical features and superior overall and cancer specific survival rates. *Cancer* 2000; **89**: 1883-1892 [PMID: 11064344]

15 **Gill S**, Shah A, Le N, Cook EF, Yoshida EM. Asian ethnicity-related differences in gastric cancer presentation and outcome among patients treated at a canadian cancer center. *J Clin Oncol* 2003; **21**: 2070-2076 [PMID: 12775731]

16 **Kim J**, Sun CL, Mailey B, Prendergast C, Artinyan A, Bhatia S, Pigazzi A, Ellenhorn JD. Race and ethnicity correlate with survival in patients with gastric adenocarcinoma. *Ann Oncol* 2010; **21**: 152-160 [PMID: 19622590 DOI: 10.1093/annonc/mdp290]

17 **Al-Refaie WB**, Gay G, Virnig BA, Tseng JF, Stewart A, Vickers SM, Tuttle TM, Feig BW. Variations in gastric cancer care: a trend beyond racial disparities. *Cancer* 2010; **116**: 465-475 [PMID: 19950130 DOI: 10.1002/cncr.24772]

18 **Nelson R**, Ko EB, Arrington A, Lee W, Kim J, Garcia-Aguilar J, Kim J. Race and correlations between lymph node number and survival for patients with gastric cancer. *J Gastrointest Surg* 2013; **17**: 471-481 [PMID: 23288716 DOI: 10.1007/s11605-012-2125-x]

19 **Kodama Y**, Sugimachi K, Soejima K, Matsusaka T, Inokuchi K. Evaluation of extensive lymph node dissection for carcinoma of the stomach. *World J Surg* 1981; **5**: 241-248 [PMID: 7245793]

20 **Maruyama K**, Sasako M, Kinoshita T, Sano T, Katai H, Hada M, Schmidt-Matthiesen A, Dahl O. Should systematic lymph node dissection be recommended for gastric cancer? *Eur J Cancer* 1998; **34**: 1480-1489 [PMID: 9893618]

21 **Wu CW**, Hsiung CA, Lo SS, Hsieh MC, Chen JH, Li AF, Lui WY, Whang-Peng J. Nodal dissection for patients with gastric cancer: a randomised controlled trial. *Lancet Oncol* 2006; **7**: 309-315 [PMID: 16574546]

22 **Theuer CP**, Al-Kuran R, Akiyama Y, Okumura M, Ziogas A, Carpenter PM. Increased epithelial cadherin expression among Japanese intestinal-type gastric cancers compared with specimens from American patients of European descent. *Am Surg* 2006; **72**: 332-338 [PMID: 16676859]

23 **Theuer CP**, Campbell BS, Peel DJ, Lin F, Carpenter P, Ziogas A, Butler JA. Microsatellite instability in Japanese vs European American patients with gastric cancer. *Arch Surg* 2002; **137**: 960-95; discussion 960-95; [PMID: 12146999]

24 **Fock KM**, Ang TL. Epidemiology of Helicobacter pylori infection and gastric cancer in Asia. *J Gastroenterol Hepatol* 2010; **25**: 479-486 [PMID: 20370726]

25 **National Comprehensive Cancer Network Guidelines**. Gastric Adenocarcinoma V2.2013. Accessed October 18, 2013. Available from: URL: http: //www.nccn.org/professionals/physician\_gls/pdf/gastric.pdf

26 **Snyder RA**, Castaldo ET, Bailey CE, Phillips SE, Chakravarthy AB, Merchant NB. Survival Benefit of Adjuvant Radiation Therapy for Gastric Cancer following Gastrectomy and Extended Lymphadenectomy. *Int J Surg Oncol* 2012; **2012**: 307670 [PMID: 22778937 DOI: 10.1155/2012/307670]

27 **Cuschieri A**, Fayers P, Fielding J, Craven J, Bancewicz J, Joypaul V, Cook P. Postoperative morbidity and mortality after D1 and D2 resections for gastric cancer: preliminary results of the MRC randomised controlled surgical trial. The Surgical Cooperative Group. *Lancet* 1996; **347**: 995-999 [PMID: 8606613]

28 **Cuschieri A**, Weeden S, Fielding J, Bancewicz J, Craven J, Joypaul V, Sydes M, Fayers P. Patient survival after D1 and D2 resections for gastric cancer: long-term results of the MRC randomized surgical trial. Surgical Co-operative Group. *Br J Cancer* 1999; **79**: 1522-1530 [PMID: 10188901]

29 **Bonenkamp JJ**, Songun I, Hermans J, Sasako M, Welvaart K, Plukker JT, van Elk P, Obertop H, Gouma DJ, Taat CW. Randomised comparison of morbidity after D1 and D2 dissection for gastric cancer in 996 Dutch patients. *Lancet* 1995; **345**: 745-748 [PMID: 7891484]

30 **Bonenkamp JJ**, Hermans J, Sasako M, van de Velde CJ, Welvaart K, Songun I, Meyer S, Plukker JT, Van Elk P, Obertop H, Gouma DJ, van Lanschot JJ, Taat CW, de Graaf PW, von Meyenfeldt MF, Tilanus H. Extended lymph-node dissection for gastric cancer. *N Engl J Med* 1999; **340**: 908-914 [PMID: 10089184]

31 **Hartgrink HH**, van de Velde CJ, Putter H, Bonenkamp JJ, Klein Kranenbarg E, Songun I, Welvaart K, van Krieken JH, Meijer S, Plukker JT, van Elk PJ, Obertop H, Gouma DJ, van Lanschot JJ, Taat CW, de Graaf PW, von Meyenfeldt MF, Tilanus H, Sasako M. Extended lymph node dissection for gastric cancer: who may benefit? Final results of the randomized Dutch gastric cancer group trial. *J Clin Oncol* 2004; **22**: 2069-2077 [PMID: 15082726]

32 **Songun I**, Putter H, Kranenbarg EM, Sasako M, van de Velde CJ. Surgical treatment of gastric cancer: 15-year follow-up results of the randomised nationwide Dutch D1D2 trial. *Lancet Oncol* 2010; **11**: 439-449 [PMID: 20409751 DOI: 10.1016/S1470-2045(10)70070-X]

33 **Bunt AM**, Hermans J, Smit VT, van de Velde CJ, Fleuren GJ, Bruijn JA. Surgical/pathologic-stage migration confounds comparisons of gastric cancer survival rates between Japan and Western countries. *J Clin Oncol* 1995; **13**: 19-25 [PMID: 7799019]

34 **Smith DD**, Schwarz RR, Schwarz RE. Impact of total lymph node count on staging and survival after gastrectomy for gastric cancer: data from a large US-population database. *J Clin Oncol* 2005; **23**: 7114-7124 [PMID: 16192595]

35 **Yoshikawa T**, Sasako M, Sano T, Nashimoto A, Kurita A, Tsujinaka T, Tanigawa N, Yamamoto S. Stage migration caused by D2 dissection with para-aortic lymphadenectomy for gastric cancer from the results of a prospective randomized controlled trial. *Br J Surg* 2006; **93**: 1526-1529 [PMID: 17051601]

36 **Feinstein AR**, Sosin DM, Wells CK. The Will Rogers phenomenon. Stage migration and new diagnostic techniques as a source of misleading statistics for survival in cancer. *N Engl J Med* 1985; **312**: 1604-1608 [PMID: 4000199]

37 **Meyers WC**, Damiano RJ, Rotolo FS, Postlethwait RW. Adenocarcinoma of the stomach. Changing patterns over the last 4 decades. *Ann Surg* 1987; **205**: 1-8 [PMID: 3800453]

38 **Hundahl SA**, Phillips JL, Menck HR. The National Cancer Data Base Report on poor survival of U.S. gastric carcinoma patients treated with gastrectomy: Fifth Edition American Joint Committee on Cancer staging, proximal disease, and the "different disease" hypothesis. *Cancer* 2000; **88**: 921-932 [PMID: 10679663]

39 **McCulloch PG**, Ochiai A, O'Dowd GM, Nash JR, Sasako M, Hirohashi S. Comparison of the molecular genetics of c-erb-B2 and p53 expression in stomach cancer in Britain and Japan. *Cancer* 1995; **75**: 920-925 [PMID: 7842412]

40 **McCulloch P**, Taggart T, Ochiai A, O'Dowd G, Nash J, Sasako M. c-erbB2 and p53 expression are not associated with stage progression of gastric cancer in Britain or Japan. *Eur J Surg Oncol* 1997; **23**: 304-309 [PMID: 9315057]

41 **Becker KF**, Atkinson MJ, Reich U, Becker I, Nekarda H, Siewert JR, Höfler H. E-cadherin gene mutations provide clues to diffuse type gastric carcinomas. *Cancer Res* 1994; **54**: 3845-3852 [PMID: 8033105]

42 **Wang ZS**, Shen Y, Li X, Zhou CZ, Wen YG, Jin YB, Li JK. Significance and prognostic value of Gli-1 and Snail/E-cadherin expression in progressive gastric cancer. *Tumour Biol* 2014; **35**: 1357-1363 [PMID: 24081672 DOI: 10.1007/s13277-013-1185-1]

43 **Mizutani T**, Onda M, Tokunaga A, Yamanaka N, Sugisaki Y. Relationship of C-erbB-2 protein expression and gene amplification to invasion and metastasis in human gastric cancer. *Cancer* 1993; **72**: 2083-2088 [PMID: 8397058]

44 **Livingstone JI**, Yasui W, Tahara E, Wastell C. Are Japanese and European gastric cancer the same biological entity? An immunohistochemical study. *Br J Cancer* 1995; **72**: 976-980 [PMID: 7547252]

45 **Zhou W**, Jia L, Guo S, Hu Q, Shen Y, Li N. The -159C/T polymorphism in the CD14 gene and cancer risk: a meta-analysis. *Onco Targets Ther* 2013; **7**: 5-12 [PMID: 24376358 DOI: 10.2147/OTT.S54547]

46 **Chen B**, Cao L, Zhou Y, Yang P, Wan HW, Jia GQ, Liu L, Wu XT. Glutathione S-transferase T1 (GSTT1) gene polymorphism and gastric cancer susceptibility: a meta-analysis of epidemiologic studies. *Dig Dis Sci* 2010; **55**: 1831-1838 [PMID: 19960261 DOI: 10.1007/s10620-009-1000-4]

47 **Qin XP**, Zhou Y, Chen Y, Li NN, Wu XT. XRCC3 Thr241Met polymorphism and gastric cancer susceptibility: A meta-analysis. *Clin Res Hepatol Gastroenterol* 2014; **38**: 226-234 [PMID: 24315014 DOI: 10.1016/j.clinre.2013.10.011]

48 **Marshall BJ**, Warren JR. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. *Lancet* 1984; **1**: 1311-1315 [PMID: 6145023]

49 **Plummer M**, Franceschi S, Muñoz N. Epidemiology of gastric cancer. *IARC Sci Publ* 2004;**(157)**: 311-326 [PMID: 15055304]

50 **Wang F**, Meng W, Wang B, Qiao L. Helicobacter pylori-induced gastric inflammation and gastric cancer. *Cancer Lett* 2014; **345**: 196-202 [PMID: 23981572 DOI: 10.1016/j.canlet.2013.08.016]

51 **Huang JQ**, Sridhar S, Chen Y, Hunt RH. Meta-analysis of the relationship between Helicobacter pylori seropositivity and gastric cancer. *Gastroenterology* 1998; **114**: 1169-1179 [PMID: 9609753]

52 **American Cancer Society**. Cancer Facts and Figures 2005. Available from: URL: http: //www.cancer.org/acs/groups/content/@nho/documents/document/caff2005f4pwsecuredpdf.pdf

53 **Brenner H**, Arndt V, Stegmaier C, Ziegler H, Rothenbacher D. Is Helicobacter pylori infection a necessary condition for noncardia gastric cancer? *Am J Epidemiol* 2004; **159**: 252-258 [PMID: 14742285]

54 **Siao D**, Somsouk M. Helicobacter pylori: evidence-based review with a focus on immigrant populations. *J Gen Intern Med* 2014; **29**: 520-528 [PMID: 24065381]

55 **Matos JI**, de Sousa HA, Marcos-Pinto R, Dinis-Ribeiro M. Helicobacter pylori CagA and VacA genotypes and gastric phenotype: a meta-analysis. *Eur J Gastroenterol Hepatol* 2013; **25**: 1431-1441 [PMID: 23929249]

56 **González CA**, Figueiredo C, Lic CB, Ferreira RM, Pardo ML, Ruiz Liso JM, Alonso P, Sala N, Capella G, Sanz-Anquela JM. Helicobacter pylori cagA and vacA genotypes as predictors of progression of gastric preneoplastic lesions: a long-term follow-up in a high-risk area in Spain. *Am J Gastroenterol* 2011; **106**: 867-874 [PMID: 21285949 DOI: 10.1038/ajg.2011.1]

57 **Duncan SS**, Valk PL, McClain MS, Shaffer CL, Metcalf JA, Bordenstein SR, Cover TL. Comparative genomic analysis of East Asian and non-Asian Helicobacter pylori strains identifies rapidly evolving genes. *PLoS One* 2013; **8**: e55120 [PMID: 23383074 DOI: 10.1371/journal.pone.0055120]

58 **State and County Quick facts.** US Census Bureau. Available from: URL: http: //quickfacts.census.gov/qfd/states/06000.html

59 **Kim J**, Mailey B, Senthil M, Artinyan A, Sun CL, Bhatia S. Disparities in gastric cancer outcomes among Asian ethnicities in the USA. *Ann Surg Oncol* 2009; **16**: 2433-2441 [PMID: 19582508 DOI: 10.1245/s10434-009-0584-4]

**P-Reviewers:** Crea F, Lesquereux-Martinez L **S-Editor:** Ma YJ **L-Editor:** **E-Editor:**

**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 OSRace/ethnicity independently predicts OSAsian 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 survivalRace/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 MSFilipinos have shortest MSJapanese 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.