Chapter 8
Molecular Subtypes and Driver Mutations in Latinos with Gastric Cancer: Implications for Etiological and Translational Research

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Gastric Cancer Is a Common Malignancy with Poor Outcomes

Worldwide, gastric cancer (GC) is the third leading cause of cancer mortality [1]. Each year ~1 million new gastric cancer (GC) cases are diagnosed and >720,000 patients die of GC [2, 3]. GC prognosis is dismal because early-stage tumors, where survival is high, are clinically silent and difficult to detect. Most GCs are detected in late stages and have 5-year survival rates <10% [2, 4, 5]. To improve GC outcomes, major limitations need to be addressed. First, new prevention and early detection tools must be developed, including the identification of susceptibility genes that allow the identification of high-risk individuals. Until recently, E-cadherin (also known as *CDH1*) was the only known GC gene; it accounts for ~40% of cases with hereditary diffuse GC (HDGC) syndrome and a very small fraction of non-HDGC cases [2, 6, 7]. We recently identified a second familial GC form, involving germline mutations in recombination DNA repair genes, which account for ~2–6% of all cases [1, 8, 9]. Even though this recent gene discovery represents an important advance, few individuals currently benefit from genetic-guided prevention. Another major limitation is the need to develop effective therapies to improve GC outcomes. The Cancer Genome Atlas (TCGA) study found that >70% of all GCs have mutations that can be targeted with existing drugs [10]. Despite this large fraction of "druggable" mutations, only two GC-targeted therapies have been approved by the

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Table 8.1 Disparities in gastric cancer incidence and mortality in Latinos and in non-Latino whites (NLW) (data from the American Cancer Society report [15])

	Incidence per 100,000 individuals			Mortality per 100,000 individuals		
	Latinos	NLW	Disparity ratio	Latinos	NLW	Disparity ratio
Men	13.5	7.8	1.7	7.2	3.6	2.0
Women	7.8	3.5	2.2	4.2	1.8	2.3

Food and Drug Administration (FDA) [11, 12]. Hence, major advances in etiological and translational research are needed to improve GC outcomes through prevention, early detection, and better treatments.

Gastric Cancer in Latinos

GC exemplifies a malignancy with strong disparities in incidence, mortality, and survival that disproportionately affects Latinos, the largest and youngest US minority population [13–16]. Table 8.1 shows incidence and mortality rates (per 100,000 people) in NLW, Latinos, and their associated disparities [15]. Latinos are between 1.7- and 2.2-fold more likely than NHWs to be diagnosed with GC and between 2.0- and 2.3-fold more likely to die when diagnosed. These disparities are among the highest in the country and are not fully accounted for by differences in the prevalence of known risk factors or access to healthcare. Addressing these disparities should be a priority in etiological and outcome research in the country.

Genomic and Genetic Research Disparities

Relative to NLW, very limited GC genetic or genomic research has been carried out in Latino populations. All published GC genome-wide association studies (GWAS) have been carried out in Asians [17–20] or NLW [21], and no data are available on the risk that GWAS variants confer in Latino populations. Furthermore, all gastric tumor whole exome or whole genome sequencing studies carried out to date have only involved either Asian [22–28] or, as in the TCGA, predominantly NLW [10]. Table 8.2 shows the ethnic/racial composition of the TCGA patients, where Latinos represent only 1% of the participants. It is unfortunate that the minority population with the highest GC burden in the country was not fully represented in such an important study. To my knowledge, there is no published Latino data on the prevalence of the four TCGA molecular subtypes (Epstein–Barr virus associated, EBV; microsatellite instable, MSI; genomically stable, GS; and chromosomally instable, CIN) or of the mutation prevalence of the TCGA driver genes. Investigating Latino GC genomics is needed, because many somatic alterations are druggable and the TCGA new molecular subtypes show important differences in prognosis and response to therapy [29]. Having such information on population-specific molecular

Table 8.2 The racial/ethnic composition of the GC patients included in TCGA [10]

Race/ethnicity	Fraction of patients (n = 295) (%)
Non- Latino whites	63
Asians	20
Latinos	1
Other	14

Table 8.3 Epidemiological profiles of gastric cancers in Latinos and NLWs from California (2010–2014) (data from [31])

	Latinos (n = 3879)	NLW (n = 4612)
Sex		
Men	2166 (56%)	3048 (66%)
Women	1713 (44%)	1564 (34%)
Age		
Early onset (≤50 years)	880 (23%)	363 (8%)
Late onset (>50 years)	2999 (77%)	4249 (92%)
Socioeconomic status		
Lowest	1285 (37%)	435 (14%)
Medium/high	2145 (63%)	2736 (86%)
Histology		
Intestinal	1929 (62%)	2739 (77%)
Diffuse	1187 (38%)	828 (23%)
Stage		
Localized	887 (23%)	1282 (38%)
Regional/remote	2580 (77%)	2895 (62%)

profiles will empower studies aimed at improving GC outcomes in this minority population. Furthermore, Latino-focused genomic research efforts will help avoid widening the pervasive gap in cancer disparities [30].

The Unique Epidemiology of Gastric Cancer in Latinos

Table 8.3 presents GC incidence and mortality data for Latinos and NLWs from California. These data are interesting because GC profiles show important population differences. Latinos have a higher fraction of women with GC (44% vs. 34% in NLWs) and more GC patients with lower socioeconomic status (37% vs. 14% in NLWs). Furthermore, Latinos are more often diagnosed with GC by age 50 years (23% vs. 8% in NLWs), diffuse tumors (38% vs. 23% in NLWs), and regional and distant metastasis (77% vs. 62% in NLWs). These data therefore suggest that the epidemiology of GC in Latinos is unique and highlights the need for research that uncovers etiological differences between Latinos and other populations.

Table 8.4 Mutation frequency data of known gastric cancer driver genes in Latinos and TCGA (Luis Carvajal-Carmona laboratory, unpublished)

Gene	Mutation frequency	
	TCGA (n = 295)	Latinos (n = 30)
ARID1A	0.14	0.00
PIK3CA	0.12	0.04
CDH1	0.11	0.04

Molecular GC Profiles in Latinos Are Unique

The new TCGA GC molecular classification is important, because some of these subtypes have been associated with the prognosis or with response to therapy. Specifically, GC patients with EBV subtype tumors have excellent prognoses, while those with the GS subtype have poorer outcomes [29]. A recent study by Sohn et al. [29] also showed that patients with GS tumors do not benefit from chemotherapy, highlighting the need for research aiming at developing effective therapies for this subtype. To establish the prevalence of GC molecular subtypes in Latinos, our group recently carried out a pilot study of targeted sequencing in 30 tumors from Latino patients. Relative to TCGA, our unpublished study found that Latinos have a lower prevalence of CIN (33% vs. 49%) tumors and a higher prevalence of the GS (39% vs. 19%) subtype. We also found that the prevalence of mutations in driver genes is very different in Latinos (see Table 8.4 for some examples). These unpublished data suggest that the molecular profiles of GCs in Latinos are unique and highlight the need for larger and more comprehensive tumor genomic studies in the population.

Conclusions

Latinos have the highest GC burden in the United States. Published data and ongoing research suggest that the epidemiology of GC in Latinos is unique. It is now critically important to carry out studies that help us understand the etiology of GC in this minority population and that further characterize genetic and genomic patterns in GC patients of Latino ancestry. Furthermore, the unique molecular patterns in Latino GCs warrants future preclinical and translation studies in driver genes and molecular subtypes that are more prevalent in this minority population.

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