Cancer Causes Control (2013) 24:1985–1994
DOI 10.1007/s10552-013-0274-1

ORIGINAL PAPER

Nativity disparities in late-stage diagnosis and cause-specific survival among Hispanic women with invasive cervical cancer: an analysis of Surveillance, Epidemiology, and End Results data

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Received: 31 August 2012 / Accepted: 31 July 2013 / Published online: 11 August 2013

Abstract
Purpose While cervical cancer screening and risk behaviors have been found to vary among US- and foreign-born Hispanic women, many cancer epidemiology studies have conceptualized Hispanics as a homogenous group. Here, we examine differences in cervical cancer stage at diagnosis and survival among Hispanic women by nativity.
Methods We use data from the Surveillance, Epidemiology, and End Results program, 1998–2008. Nativity was based on place of birth and was categorized as US versus foreign born. Distant and regional tumors were classified as late stage, while local tumors were classified as early stage.
Results Forty-seven percent of cases of invasive cervical cancer among Hispanics were diagnosed at a late stage, and over half of invasive cervical cancer cases were among foreign-born women. Foreign-born Hispanic women were significantly more likely than US-born Hispanics to have late-stage diagnosis, after adjusting for age at diagnosis and tumor histology (adjusted odds ration = 1.09, p value = 0.003). There was heterogeneity in the association between nativity and survival by stage at diagnosis. Among cases with early-stage diagnosis, survival was poorer among foreign-born versus US-born Hispanics after adjusting for age at diagnosis, histology, and cancer-directed therapy [adjusted hazard ratios (HR) = 1.31, p value = 0.030]. However, among cases with late-stage diagnosis, survival was better among foreign-born Hispanics (adjusted HR = 0.81, p value < 0.001).
Conclusions We hypothesize that nativity differences in survival may be indicative of diverse risk, screening, and treatment profiles. Given such differences, it may be inappropriate to aggregate Hispanics as a single group for cervical cancer research.

Keywords Cervical cancer · Hispanic · SEER program · Survival · Stage at diagnosis · Nativity

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Introduction

Although the incidence of cervical cancer in the United States has declined dramatically since the introduction of widespread screening in the 1940s–1960s, significant racial and ethnic disparities in cervical cancer incidence and survival still exist [1]. In particular, Hispanic women represent a population disproportionately affected by cervical cancer. Among women ages 30 years and older, the incidence of cervical cancer among Hispanic women is twice that of non-Hispanic white women [2]. Additionally, Hispanics are more likely than non-Hispanic whites to be

diagnosed with cervical cancer at a later stage and to have poorer survival (due primarily to late-stage diagnoses [3, 4]). Stage at diagnosis and survival are considered as indicators of the efficacy of screening, as screening should allow earlier stage diagnosis and consequently a more favorable prognosis [5].

Although there are several studies that have examined racial/ethnic differences in cervical cancer stage at diagnosis and survival between Hispanic and non-Hispanic women [2, 6–9], most studies have conceptualized Hispanics as a homogenous group. However, the Hispanic population is comprised of culturally distinct subgroups with significant heterogeneity in terms of nativity [10], particularly between US- and foreign-born Hispanics. Likewise, cervical cancer screening and risk behaviors have been found to vary by nativity. For example, foreign-born Hispanics have less frequent cervical cancer screening than US-born Hispanics [11–13]. However, they are also less likely to engage in cervical cancer-associated risk behaviors, including early initiation of sexual activity [14–16], smoking [12], and use of oral contraceptives [14, 15]. Furthermore, pre-immigration factors, including utilization of cervical cancer screening in the country of origin, may affect recent immigrants' risk and survival from cervical cancer [17, 18]. The importance of these differences is augmented by the large number of foreign-born Hispanics residing in the United States. The foreign-born population currently represents almost 40 % of the US Hispanic population [19].

In this paper, we examine differences in cervical cancer stage at diagnosis and survival among Hispanic women by nativity, using data from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute. We describe differences in overall, as well as stage-specific, cervical cancer survival to elucidate potential nativity disparities in cancer screening and treatment. Disaggregating cervical cancer data for Hispanics by nativity may help identify subpopulations that differ in cervical cancer screening and treatment, which may, in turn, be used to target more effective prevention efforts.

Materials and methods

Data source

Data were obtained from the SEER Program (November 2011 release), which provides population-based data on cancer incidence and survival in the United States [20]. SEER registries cover the following geographic areas: Alaska, Arizona, Connecticut, Hawaii, Iowa, Louisiana, Kentucky, New Jersey, New Mexico, Utah, San Jose-Monterey, Los Angeles, San Francisco-Oakland, Greater California, Rural Georgia, Atlanta, Detroit, and Seattle-Puget Sound. Together these areas represent approximately 28 % of the US population and 41 % of the US Hispanic population [21]. Regional SEER registries obtain case information through abstraction of medical records, and determination of vital status is based on data from medical records, death certificates, and registers of driver's licenses and voter registration [22].

Study cases

Cases were Hispanic women living in a SEER catchment area who were diagnosed with microscopically confirmed, primary invasive cervical cancer (International Classification of Diseases for Oncology, 3rd edition [ICD-O-3] codes C53.0-53.9 [23]) between 1 January 1988 and 31 December 2008. The year 1988 was chosen as the lower time limit because it was the first year in which Hispanic ethnicity was collected for SEER cases [20]. In SEER, Hispanic ethnicity is most often abstracted from medical records. Additionally, surnames of cases with unknown Hispanic ethnicity are linked to the 1980 U.S. Census Spanish Surname list, and cases that match are classified as "Spanish surname only" if no other evidence of ethnicity is available [7]. In this study, we included cases with known Hispanic ethnicity and those with evidence of Hispanic ethnicity based on surname. We excluded cases with unknown stage at diagnosis and those born outside of the United States, Latin America, or the Caribbean.

Measures

Nativity

Nativity was based on place of birth and was classified as US-born versus foreign-born. US-born cases were those born in one of the 50 states or the District of Columbia. Foreign-born cases included those born in Mexico, Central America (Belize, Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua, and Panama), South America (Argentina, Bolivia, Brazil, Chile, Colombia, Ecuador, Guyana, Paraguay, Peru, Suriname, Uruguay, and Venezuela), or the Caribbean (Cuba, Puerto Rico, and Dominican Republic). Nativity status was classified as missing if the state or country of birth was unknown.

Late-stage diagnosis

Tumor stage at diagnosis was defined using the SEER historic staging scheme, which classifies tumors as local, regional, or distant [24]. Regional and distant tumors were defined as late-stage tumors.

Survival

Survival was defined as the number of months from the date of diagnosis to the date of death or last follow-up (31 December 2008). Deaths were defined as cervical cancer-specific mortality. Individuals who died of causes other than cervical cancer and those who were alive at the date of last follow-up were censored.

Other patient and tumor characteristics

Age of diagnosis was classified as ≤29, 30–39, 40–49, 50–59, and ≥60 years. Histology was categorized as squamous cell carcinoma (ICD-O-3 codes 8050-8082), adenocarcinoma (8140-8555), adenosquamous carcinoma (8560, 8570), or other (8000-8004, 8010-8034, 8041, 8800-8932, 8990-8991, 9040-9044, 9120-9134, 9540-9581, 9990). Other histologic types included neuroendocrine, non-keratinizing small cell carcinoma, lymphoepithelial carcinoma, transitional cell carcinoma, and sarcoma. Cancer-directed therapy was defined as having received radiation therapy and/or site-specific surgery. Those with unknown radiation and surgery ($n = 590$, 6.44 %) were considered to not have received cancer-directed therapy.

Statistical analyses

Statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC, USA).

Imputation of nativity

We used the SAS multiple imputation (MI) procedure to generate nativity values by the logistic regression imputation method [25]. Specifically, among those not missing nativity data, a logistic regression model was fitted for nativity using the parameters age at diagnosis, stage at diagnosis, histology, cancer-directed therapy, Hispanic ethnicity (Mexican; Puerto Rican; Cuban; Dominican Republic; South or Central American excluding Brazil; other specified Spanish/Hispanic Origin including Europe; Spanish/Hispanic/Latino, not otherwise specified; or surname match only), and reporting source (hospital inpatient or managed health plan; radiation treatment or medical oncology center; laboratory only; physician's office or private medical practitioner; nursing home, convalescent home, or hospice; death certificate only; or other hospital outpatient or surgery center). To impute the missing values for nativity, a new regression model was simulated using the posterior predictive distribution of parameters based on the fitted regression coefficients. The process was repeated in 20 imputation datasets (i.e., 20 iterations). In subsequent analyses (described below), logistic and Cox regression models were built in each of the 20 datasets and the results were combined using the SAS MIANALYZE procedure [26]. The imputation strategy was validated in a random sample of 20 % of the observed data with known nativity status.

Patient and tumor characteristics

The distribution of patient and tumor characteristics by nativity was assessed using χ^2 tests, and associations with p value < 0.05 were considered statistically significant.

Late diagnosis

Univariable logistic regression was used to assess the crude associations between late-stage diagnosis and nativity, as well as other patient and tumor characteristics. Multivariable logistic regression was used to assess the association between late-stage diagnosis and nativity after adjusting for age at diagnosis, histology, and SEER registry site. Registry site was removed from the final model as it was not significant and did not meaningfully impact the other adjusted odds ratios.

Survival analysis

Unadjusted survival, overall and stratified by stage at diagnosis, was visualized using the Kaplan–Meier method. The logrank test was used to assess the statistical significance of the observed differences between the cause-specific survival curves by nativity. Univariable Cox regression was used to estimate the unadjusted cause-specific mortality hazard by nativity and other patient and tumor characteristics. Multivariable Cox regression was used to assess the association between cause-specific survival and nativity after adjusting for age at diagnosis, histology, cancer-directed therapy, and SEER registry site. Analyses were stratified by stage at diagnosis in order to elucidate potential nativity disparities in cancer screening and treatment. Registry site was removed from the final model as it was not significant and did not meaningfully impact the other adjusted hazard ratios (HR). The proportional hazards assumption for all patient and tumor characteristics were assessed graphically by comparing log–log plots.

Results

Imputation

Between 1988 and 2008, there were 10,155 cases of invasive cervical cancer among Hispanic women reported in the SEER registry (Table 1). We excluded 469 cases with non-primary malignancies, 94 without microscopic

confirmation, 427 with unknown stage at diagnosis, and 1 with unknown age at diagnosis. After these exclusions, there were a total of 9,164 cases in our analyses. Of these, birthplace data were missing for 2,876 (31.4 %) cases. There were significant differences between those with and without birthplace data. Notably, cases with unknown place of birth were significantly more like to have an early-stage diagnosis (data not shown, 63.0 vs. 48.6 %, $p < 0.001$) and to have non-specified Hispanic origin (68.5 vs. 16.8 %, $p < 0.001$) or to be classified as Hispanic based on surname match only (19.3 vs. 4.8 %, $p < 0.001$). After imputation, 2,564 (89.2 %) of cases with unknown place of birth were classified as US-born and 312 (10.9 %) were classified as foreign-born. In the validation test on a random sample of 20 % of the observed data, the imputation strategy correctly classified 95.5 % of cases. The concordance between the observed and imputed nativity values was high, with a kappa score of 0.88.

Patient and tumor characteristics

Overall, foreign-born women accounted for 5,011 of the 9,164 cases (54.7 %) of invasive cervical cancer (Table 1). Almost 47 % of cases overall were late-stage diagnoses (i.e., regional or distant), with a significantly greater prevalence of late-stage diagnosis among foreign-born versus US-born cases (50.3 and 42.8 %, respectively, p value < 0.001). Age at diagnosis was significantly associated with nativity, with an almost twofold higher prevalence of diagnosis at age ≤29 years among US-born Hispanics compared to those born outside the United States. There were also small but statistically significant differences in histology and cancer-directed therapy among US- and foreign-born Hispanics.

Late-stage diagnosis

There were statistically significant differences in the stage at cervical cancer diagnosis by nativity (Table 2). In univariable analyses, foreign-born Hispanic women were significantly more likely than US-born Hispanics to have late-stage diagnosis (OR = 1.15, p value < 0.001). The effect estimate remained largely unchanged after adjusting for age at diagnosis and tumor histology (adjusted OR = 1.10, p value < 0.001).

Survival

The mean length of follow-up for the survival analysis was 60.1 months (standard deviation: 55.6 months), with

Table 1 Patient and tumor characteristics of Hispanic women diagnosed with invasive cervical cancer by nativity, Surveillance, Epidemiology, and End Results (SEER) program, United States, 1988–2008

	Total (n = 9,164)	Nativity		US- versus Foreign-born
		US-born (n = 4,153)	Foreign-born (n = 5,011)	
	%	%	%	χ^2 p value
SEER historic stage				<0.001
Localized	53.11	57.21	49.71	
Regional	38.23	34.82	41.05	
Distant	8.66	7.97	9.24	
Stage at diagnosis				<0.001
Early	53.11	57.21	49.71	
Late	46.89	42.79	50.29	
Age at diagnosis, years				<0.001
≤29	7.17	9.57	5.21	
30–39	26.57	29.11	24.47	
40–49	29.21	28.24	30.01	
50–59	17.32	15.46	18.86	
≥60	19.73	17.65	21.45	
Histology				<0.001
Squamous cell carcinoma	74	73.01	74.82	
Adenocarcinoma	16.9	17.82	16.14	
Adenosquamous cell carcinoma	4.91	4.12	5.57	
Other*	4.19	5.06	3.47	
Cancer-directed therapy				<0.001
No or unknown	6.44	5.47	7.24	
Yes	93.56	94.53	92.76	

* Other tumor histologies include neuroendocrine, non-karatinizing small cell carcinoma, lymphoepithelial carcinoma, transitional cell carcinoma, and sarcoma

statistically significant differences in follow-up time by nativity (62.0 months among US-born versus 58.5 months among foreign-born cases, $p = 0.003$). The Kaplan–Meier curve and logrank test for overall cervical cancer survival indicated no statistically significant differences in survival among US- and foreign-born Hispanic women (logrank p value $= 0.097$, Fig. 1a). However, the stratified curves indicated variation in the association between nativity and survival by stage at diagnosis (Fig. 1b, c). Specifically, among cases with early-stage diagnosis, survival was better among US- versus foreign-born Hispanics (logrank p value < 0.001); however, among cases with late-stage diagnosis, survival was better among foreign-born Hispanics (logrank p value $= 0.001$). While the Kaplan–Meier curves for late-stage diagnosis overlapped in the latter time periods, the proportional hazards assumption was not violated according to the log–log plots.

For overall cervical cancer-specific survival, the unadjusted Cox proportional hazards model indicated no statistically significant differences in survival among US- and foreign-born Hispanic women (Table 3). However, after adjusting for age at diagnosis, tumor histology, and cancer-directed therapy, the cause-specific mortality hazard was significantly lower among foreign- versus US-born women (adjusted HR $= 0.88$, $p = 0.007$). The stratified models again indicated variation in the association between nativity and survival by stage at diagnosis (Table 4). In the unadjusted model, the cause-specific mortality hazard among cases with early-stage diagnosis was significantly greater among foreign-born versus US-born Hispanics (HR $= 1.42$, p value $= 0.004$). The increased mortality hazard among foreign-born women remained after adjusting for age at diagnosis, tumor histology, and cancer-directed therapy (adjusted HR $= 1.31$, p value $= 0.026$). Among cases with late-stage diagnosis, the cause-specific mortality hazard was significantly lower among foreign-born women (HR $= 0.83$, p value < 0.001), even after adjusting for age at diagnosis, histology, and cancer-directed therapy (adjusted HR $= 0.81$, p value < 0.001). For both early and late-stage cancers, the effect of cancer-directed therapy was negligible, accounting for less than 4 % of the increased mortality hazard among foreign-born women (results not shown). Adjusted all-cause mortality was similar among US- and foreign-born women (adjusted HR $= 0.94$, p value $= 0.137$, results not shown).

Discussion

Overall, late-stage cervical cancer diagnosis was more common among foreign-born Hispanic women compared to those born in the United States. This was an expected finding given that screening rates are known to be lower among foreign-born versus US-born Hispanics [11–13], due primarily to their reduced access to health care [11]. Our results suggest that the increased early detection of pre-cancerous lesions through Papanicolaou test screening among US-born Hispanics leads to a decreased prevalence of late-stage cervical cancer diagnoses among US-born Hispanics compared to their foreign-born counterparts. We

Table 2 Unadjusted and adjusted odds ratios (OR) for late-stage diagnoses among Hispanic women diagnosed with invasive cervical cancer by nativity, Surveillance, Epidemiology, and End Results (SEER) program, United States, 1988–2008

	OR	p value	Adjusted OR*	p value
Nativity				
US-born	1.00		1.00	
Foreign-born	1.15 (1.10–1.20)	<0.001	1.10 (1.05–1.15)	<0.001
Age at diagnosis, years				
≤29	1.00		1.00	
30–39	1.34 (1.11–1.62)	0.002	0.63 (0.58–0.69)	0.003
40–49	2.09 (1.73–2.51)	<0.001	0.99 (0.92—1.07)	0.886
50–59	3.62 (2.97–4.41)	<0.001	1.70 (1.55–1.86)	<0.001
≥60	4.33 (3.57–5.27)	<0.001	1.98 (1.81–2.16)	<0.001
Histology				
Squamous	1.00		1.00	
Adenocarcinoma	0.54 (0.48–0.61)	<0.001	0.64 (0.57–0.71)	<0.001
Adenosquamous	1.13 (0.93–1.37)	0.218	1.35 (1.16–1.58)	<0.001
Other**	0.84 (0.68–1.03)	0.094	1.00 (0.85–1.19)	0.966

* Adjusted for other variables in the table. SEER site was removed from model because it was not statistically significant in the z-score test and its removal from the model did not change any adjusted hazard ratio by ten percent or more

** Other tumor histologies include neuroendocrine, non-karatinizing small cell carcinoma, lymphoepithelial carcinoma, transitional cell carcinoma, and sarcoma

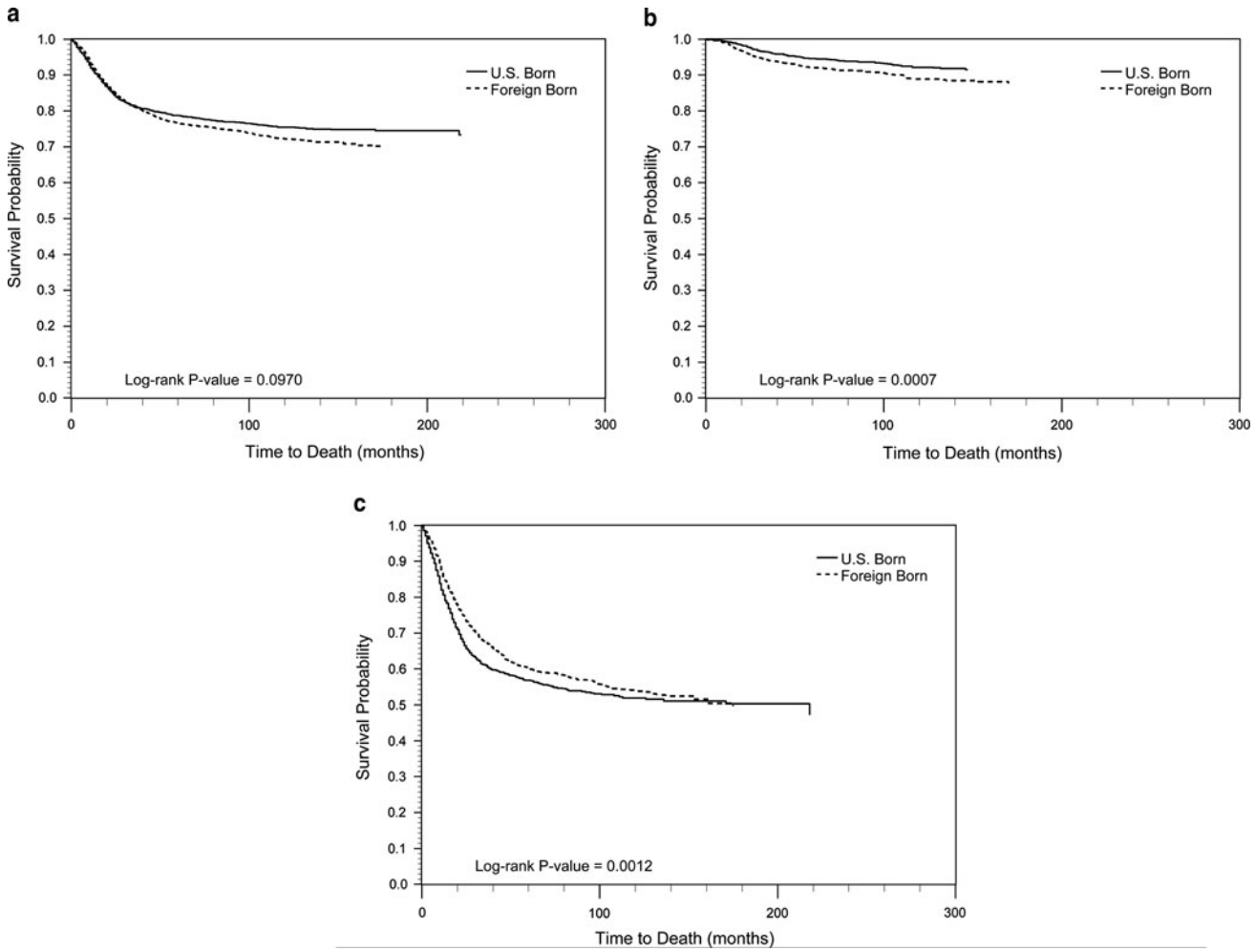

Fig. 1 Kaplan–Meier survival curves by nativity among Hispanic women diagnosed with **a** overall, **b** early-stage, and **c** late-stage invasive cervical cancer. Surveillance, Epidemiology, and End Results (SEER) program, United States, 1988–2008

expected the increased prevalence of late-stage diagnosis among foreign-born Hispanics to result in an overall decreased survival among foreign-born cases. However, we found that foreign-born women had better overall survival after adjusting for age at diagnosis, histology, and cancer-directed therapy. Interestingly, there was significant heterogeneity in the association between nativity and survival by stage at diagnosis. Specifically, when cervical cancer is diagnosed at a late stage, foreign-born Hispanic women appear to have improved survival over their US-born counterparts. However, when cervical cancer is diagnosed at an early stage, our results suggest decreased survival among foreign-born Hispanics compared to those born in the United States.

We hypothesize that the heterogeneity in survival among US- and foreign-born Hispanic cervical cancer cases by stage at diagnosis is due to disparities in health status and healthcare access that exist between these populations. Our findings of nativity disparities for late-stage cervical cancer mirror similar disparities that have been documented for overall cancer survival [12, 27]. For all cancers combined, US-born Hispanics have increased cancer mortality rates compared to Hispanic immigrants. The poorer cancer survival of US-born Hispanics has been attributed to changes in risk profiles associated with acculturation, including increased smoking, obesity, and alcohol consumption, as well as decreased nutrition quality [12, 27]. A growing body of literature also suggests that US-born Hispanics have an increased prevalence of chronic diseases (e.g., obesity, diabetes, and heart disease) relative to their foreign-born counterparts [28–33]. Comorbid illness is known to contribute to poorer cancer treatment outcomes and to negatively affect cancer survival [34–40]. We hypothesize that the increased prevalence of cervical cancer risk factors and comorbidities among US-born Hispanic women may explain their decreased survival from late-stage cervical cancer compared to Hispanic women born outside the United States.

Table 3 Unadjusted and adjusted hazard ratios (HR) for Hispanic women diagnosed with invasive cervical cancer by nativity, Surveillance, Epidemiology, and End Results (SEER) program, United States, 1988–2008

	All cervical cancer-specific death			
	HR	*p* value	Adjusted HR	*p* value
Nativity				
US-born	1.00		1.00	
Foreign-born	1.05 (0.95–1.15)	0.335	0.88 (0.79–0.96)	0.007
Stage at diagnosis				
Early	1.00		1.00	
Late	7.63 (6.74–8.63)	<0.001	7.39 (6.51–8.39)	<0.001
Age at diagnosis, years				
≤29	1.00		1.00	
30–39	1.32 (1.03–1.68)	0.028	1.19 (0.93–1.52)	0.168
40–49	1.76 (1.39–2.24)	<0.001	1.28 (1.01–1.63)	0.044
50–59	2.22 (1.73–2.84)	<0.001	1.31 (1.02–1.68)	0.033
≥60	2.75 (2.16–3.50)	<0.001	1.53 (1.20–1.95)	<0.001
Histology				
Squamous	1.00		1.00	
Adenocarcinoma	0.84 (0.74–0.96)	0.013	1.14 (0.99–1.30)	0.065
Adenosquamous	1.30 (1.06–1.58)	0.010	1.29 (1.06–1.57)	0.010
Other*	1.66 (1.36–2.03)	<0.001	1.99 (1.62–2.43)	<0.001
Cancer-directed therapy				
No or unknown	1.00		1.00	
Yes	0.30 (0.26–0.35)	<0.001	0.35 (0.30–0.40)	<0.001

* Other tumor histologies include neuroendocrine, non-karatinizing small cell carcinoma, lymphoepithelial carcinoma, transitional cell carcinoma, and sarcoma

Table 4 Unadjusted and adjusted hazard ratios (HR) for Hispanic women diagnosed with early- and late-stage invasive cervical cancer by nativity, Surveillance, Epidemiology, and End Results (SEER) program, United States, 1988–2008

	Stage at diagnosis							
	Early stage				Late stage			
	HR	*p* value	Adjusted HR	*p* value	HR	*p* value	Adjusted HR	*p* value
Nativity								
US-born	1.00		1.00		1.00		1.00	
Foreign-born	1.42 (1.12–1.79)	0.004	1.31 (1.03–1.67)	0.026	0.83 (0.75–0.92)	<0.001	0.81 (0.73–0.90)	<0.001
Age at diagnosis, years								
≤29	1.00		1.00		1.00		1.00	
30–39	1.30 (0.79–2.15)	0.298	1.29 (0.78–2.14)	0.317	1.02 (0.77–1.36)	0.870	1.11 (0.84–1.48)	0.458
40–49	1.73 (1.06–2.83)	0.029	1.74 (1.06–2.86)	0.028	1.06 (0.81–1.40)	0.673	1.12 (0.85–1.47)	0.426
50–59	1.54 (0.88–2.67)	0.129	1.52 (0.87–2.65)	0.143	1.11 (0.84–1.46)	0.480	1.17 (0.88–1.55)	0.274
≥60	3.08 (1.86–5.11)	<0.001	2.98 (1.79–4.95)	<0.001	1.22 (0.93–1.61)	0.157	1.27 (0.96–1.68)	0.090
Histology								
Squamous	1.00		1.00		1.00		1.00	
Adenocarcinoma	0.87 (0.64–1.18)	0.363	0.91 (0.67–1.24)	0.561	1.19 (1.02–1.38)	0.023	1.20 (1.03–1.40)	0.016
Adenosquamous	1.95 (1.28–2.98)	0.002	2.01 (1.31–3.07)	0.001	1.12 (0.89–1.39)	0.331	1.17 (0.94–1.46)	0.164
Other*	1.28 (0.76–2.16)	0.361	1.35 (0.80–2.28)	0.268	2.36 (1.90–2.94)	<0.001	2.13 (1.71–2.66)	<0.001
Cancer-directed therapy								
No or unknown	1.00		1.00		1.00		1.00	
Yes	0.53 (0.33–0.85)	0.008	0.56 (0.35–0.90)	0.017	0.33 (0.28–0.38)	<0.001	0.33 (0.29–0.39)	<0.001

* Other tumor histologies include neuroendocrine, non-karatinizing small cell carcinoma, lymphoepithelial carcinoma, transitional cell carcinoma, and sarcoma

Among those with early-stage disease, nativity disparities in health status may play a less important role compared to disparities in health care access that exist between immigrants and those born in the United States. Cervical cancer is different from most cancers in that it can be detected at an early stage at which it can be successfully treated with surgical and therapeutic intervention. Thus, the observed nativity disparities in survival from early-stage cervical cancer may be related to nativity disparities in cervical cancer treatment. Numerous studies have documented reduced use of healthcare services and reduced healthcare coverage among immigrant populations [41–43]. Additionally, foreign-born women (and especially those who have recently immigrated) disproportionately face barriers such as non-English proficiency, unfamiliarity with the healthcare system, and discrimination [42, 44], which may negatively affect their ability to access healthcare services. Reduced access to health care among foreign-born Hispanic women may result in greater time delay between the date of cancer diagnosis and the date of treatment, as well as the quality of treatment and post-treatment follow-up [45]. While a detailed exploration of potential treatment differences between US- and foreign-born Hispanics is beyond the scope of this manuscript, nativity disparities in cancer treatment have been documented for breast, lung, and colorectal cancer [46, 47] and may exist for cervical cancer. We also cannot rule out other explanations (e.g., characteristics related to human papillomavirus infection) as we rely on variables available in SEER.

Overall, our results suggest important differences between US- and foreign-born women in regard to late-stage diagnosis and survival. Differences that exist within the Hispanic population have been largely overlooked in cancer research, in which Hispanics are commonly treated as a homogenous group. This may be partly due to the limited ability to conduct analyses by birthplace due to the high prevalence and non-random distribution of missing birthplace data [43, 48–52]. Specifically, registry studies suggest that the distribution of missing birthplace is related to variables including nativity, hospital ownership status, hospital teaching status, hospital size, and year of diagnosis [43, 48–50]. We present an imputation strategy that allowed us to impute nativity status with a high degree of accuracy and thus analyze important subgroups that exist within the Hispanic population. While other groups have imputed nativity based on social security number [53, 54], our strategy is the first, to our knowledge, to impute nativity based on variables that exist within the main SEER dataset. Use of similar imputation strategies may allow researchers to disaggregate analyses by nativity and uncover important nativity disparities in regard to cancer diagnosis, treatment, and survival.

Our findings are subject to at least six limitations related to our use of registry data. First, while our imputation strategy correctly assigned nativity in over 95 % of cases in the test group, the small proportion of misclassified data may have caused minor errors in our effect estimates. Second, Hispanic ethnicity determined on the basis of medical record review and surname is subject to misclassification, and such misclassification is known to vary by subgroup [9]. Third, SEER registries may not be representative of the diverse Hispanic population, as the populations covered by SEER registries are generally more urban [21]. More urban populations could potentially have better access to cervical cancer screening and treatment, limiting the generalizability of our findings. Nevertheless, SEER is the largest US cancer registry and encompasses a substantial proportion of the US Hispanic population (41 %). Fourth, stage at diagnosis was more commonly unknown for foreign-born versus US-born cases (3.7 vs. 2.3 %). Although this may have resulted in slight under- or over-estimation of late-stage diagnoses in specific groups, it is unlikely to have an impact on our results given the relatively small proportion of tumors with unknown stage at diagnosis. Fifth, we lack data regarding patients' health seeking and risk behaviors, as well as their comorbidities and the details of their cancer-directed treatment, which may help explain the heterogeneity in nativity-based survival patterns across different stages of diagnoses. It is possible that access to health care may have been more limited for foreign-born individuals, potentially attenuating the protective survival effect that may be attributable to generally better health status among foreign-born cases—a phenomenon that has been observed and reported in other studies as the Hispanic paradox [55]. However, we cannot definitively assess how these factors would have impacted our analyses due to the lack of data. While information regarding cancer-directed treatment is available in SEER, it is difficult to interpret whether the treatment received was appropriate given the stage and behavior of the cancer, and whether this would have been differential by nativity. Finally, we recognize that the foreign-born population is heterogeneous, with important differences in regard to region of origin, degree of acculturation, and length of residence in the United States. While there is evidence of disparities cancer incidence and survival by region of origin [56, 57], we were unable to conduct such disaggregated analyses given the large number of cases with missing birthplace data. Analyses regarding the role of acculturation on stage at diagnosis and survival were not possible given that length of residence and other indicators of acculturation are not available in the SEER database.

While there are limitations to using registry data for these types of studies, the SEER database includes a diverse Hispanic patient population representing both US-

and foreign-born cases. Additionally, our results suggest that it is possible to use specific variables available in the SEER database to accurately impute nativity status for the large proportion of cases missing these data. This imputation strategy allowed us to examine differences in the prevalence of late-stage diagnosis and cervical cancer survival by nativity. Our results suggest that foreign-born Hispanic women may be at greater risk for late-stage diagnosis, but are also less likely to die from late-stage cancer relative to their US-born counterparts. Most importantly, however, our results suggest that it may be inappropriate to aggregate Hispanics as a single group for cervical cancer research. The US Hispanic population is a diverse population with different cultural, social, and risk profiles that vary by nativity status. Given differences in cervical cancer diagnosis and survival that may be indicative of diverse risk, screening, and treatment profiles, cervical cancer prevention programs may benefit from tailoring interventions to specific Hispanic nativity subgroups. Potential strategies include targeted efforts within immigrant neighborhoods using lay health workers and health linkage programs that aid immigrants' entry into the healthcare system [58].

Acknowledgments This research is partly supported by a grant from the National Institutes of Health (Grant P01CA082710, PI: M. Follen). JRM and RZ are supported by a UTHealth Innovation for Cancer Prevention Research Postdoctoral (JRM)/Predoctoral (RZ) Fellowship (The University of Texas School of Public Health—Cancer Prevention and Research Institute of Texas Grant # RP101503). The content of this manuscript is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or the Cancer Prevention and Research Institute of Texas.

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