Original Investigation

Differences in Breast Cancer Stage at Diagnosis and Cancer-Specific Survival by Race and Ethnicity in the United States

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IMPORTANCE Women with early-stage breast cancers are expected to have excellent survival rates. It is important to identify factors that predict diagnosis of early-stage breast cancers.

OBJECTIVE To determine the proportion of breast cancers that were identified at an early stage (stage I) in different racial/ethnic groups and whether ethnic differences may be better explained by early detection or by intrinsic biological differences in tumor aggressiveness.

DESIGN, SETTING, AND PARTICIPANTS Observational study of women diagnosed with invasive breast cancer from 2004 to 2011 who were identified in the Surveillance, Epidemiology, and End Results (SEER) 18 registries database (N = 452 215). For each of 8 racial/ethnic groups, biological aggressiveness (triple-negative cancers, lymph node metastases, and distant metastases) of small-sized tumors of 2.0 cm or less was estimated. The odds ratio (OR) for being diagnosed at stage I compared with a later stage and the hazard ratio (HR) for death from stage I breast cancer by racial/ethnic group were determined. The date of final follow-up was December 31, 2011.

MAIN OUTCOMES AND MEASURES Breast cancer stage at diagnosis and 7-year breast cancer–specific survival, adjusted for age at diagnosis, income, and estrogen receptor status.

RESULTS Of 373 563 women with invasive breast cancer, 268 675 (71.9%) were non-Hispanic white; 34 928 (9.4%), Hispanic white; 38 751 (10.4%), black; 25 211 (6.7%), Asian; and 5998 (1.6%), other ethnicities. Mean follow-up time was 40.6 months (median, 38 months). Compared with non-Hispanic white women diagnosed with stage I breast cancer (50.8%), Japanese women (56.1%) were more likely to be diagnosed (OR, 1.23 [95% CI, 1.15-1.31], $P < .001$) and black women (37.0%) were less likely to be diagnosed (OR, 0.65 [95% CI, 0.64-0.67], $P < .001$). Actuarial risk of death from stage I breast cancer at 7 years was higher among black women (6.2%) than non-Hispanic white women (3.0%) (HR, 1.57 [95% CI, 1.40-1.75]; $P < .001$), and lower among South Asian women (1.7%) (HR, 0.48 [95% CI, 0.20-1.15]; $P = .10$). Black women were more likely to die of breast cancer with small-sized tumors (9.0%) than non-Hispanic white women (4.6%) (HR, 1.96 [95% CI, 1.82-2.12]; $P < .001$); the difference remained after adjustment for income and estrogen receptor status (HR, 1.56 [95% CI, 1.45-1.69]; $P < .001$).

CONCLUSIONS AND RELEVANCE Among US women diagnosed with invasive breast cancer, the likelihood of diagnosis at an early stage, and survival after stage I diagnosis, varied by race and ethnicity. Much of the difference could be statistically accounted for by intrinsic biological differences such as lymph node metastasis, distant metastasis, and triple-negative behavior of tumors.

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In the United States, incidence rates of breast cancer among women vary substantially by racial/ethnic group.[1-3] The age-adjusted rates for breast cancer are 129 per 100 000 for non-Hispanic white women, 93 per 100 000 for Hispanic women, 123 per 100 000 for black women, and 94 per 100 000 for Asian women.[1] There are differences in survival as well; crude 10-year survival rates are 80% for white women, 78% for Hispanic American women, 66% for black women, and 82% for Asian women.[4]

Over the last few decades, breast cancer mortality has decreased in the United States and the proportion of breast cancers that are localized at diagnosis has increased. Ten-year survival rates improved from 61% for cases who were diagnosed in 1973 to 83% for cases who were diagnosed in 1992.[4] It is not clear to what extent trends in the reduction of breast cancer mortality are due to increased awareness and better access and use of screening, leading to earlier presentation and improved survival.

Race/ethnicity and sociodemographic factors may influence a woman's adherence to recommendations for clinical breast examination, breast self-examination, or screening mammogram and the likelihood of her seeking appropriate care in the event that a breast mass is noticed.[5-8]

A growing body of evidence suggests that biological factors may also be important in determining stage at diagnosis (ie, the growth rate and metastatic potential of small-sized breast cancer tumors may vary between women due to inherent differences in grade, receptor status, and other or unknown pathological features).[9-12] The ultimate aim of public awareness and breast screening is to detect the majority of breast cancers when they are small and confined to the breast.

We sought to determine the proportion of breast cancers that were identified at an early stage (stage I) in different racial/ethnic groups in the United States and to determine if observed ethnic differences were better statistically accounted for by early detection or by intrinsic biological differences in tumor aggressiveness.

Methods

Data Source

We abstracted data from the Surveillance, Epidemiology, and End Results (SEER) 18 registries research database. The SEER 18 database contains data from the SEER 9 registries (Atlanta, Georgia; Connecticut; Detroit, Michigan; Hawaii; Iowa; New Mexico; San Francisco-Oakland, California; Seattle-Puget Sound, Washington; and Utah), the SEER 13 registries (SEER 9 plus Los Angeles, California; San Jose-Monterey, California; rural Georgia; and the Alaska Native Tumor Registry), and registries of greater California, Kentucky, Louisiana, New Jersey, and greater Georgia. In total, SEER 18 covers approximately 28% of the total US population (based on the 2010 Census). The data reported in this study represent the most recent follow-up (December 31, 2011) available in the SEER database.

The research protocol was approved by the research ethics board of the Women's College Hospital, University of Toronto, Toronto, Ontario, Canada. Because patients cannot be identified, the research ethics board of the Women's College Hospital exempted this study from review. However, a data use agreement submission was required to access the SEER Research Data File.[13] We submitted the data agreement form to the SEER administration. Upon acceptance of the agreement, the SEER*Stat software and data files were downloaded directly from the SEER website.

Cohort Selection

We used SEER*Stat version 8.1.5 to generate a case listing. We extracted cases of female breast cancer diagnosed from 2004 to 2011. We selected women who had a diagnosis of histologically confirmed first invasive breast cancer. We generated a case listing with information on the following variables: year of diagnosis, age at diagnosis, race/ethnicity, median household income per year (US $), American Joint Committee on Cancer pathological stage, estrogen receptor (ER) and progesterone receptor (PR) status, ERBB2 status (formerly HER2 or HER2/neu), cause of death, and survival (months). The median household income was estimated from the Census 2007-2011 American Community Survey based on the Census tract (residence).[14] We classified median yearly household income into the categories of less than $50 000, $50 000 to $75 000, and greater than $75 000.

Vital Status

We used the cause of death to site recode variable in the SEER 18 to extract status of patients at the time of last follow-up. Based on this information, we grouped all patients into categories of alive, dead due to breast cancer, and dead due to other causes. We used the survival time months variable to extract information on time from date of diagnosis to last follow-up. The SEER*Stat estimates survival time in months by subtracting the date of diagnosis from the date of last contact (the study cutoff).

The study cutoff date was December 31, 2011, which is the date of the last update on the follow-up time. We used the survival months flag (a 1-digit number) variable to identify missing or incomplete data on survival time. Of all women who qualified for the study, only 1968 (0.5%) were missing information on survival follow-up time due to 1 of the following reasons: (1) reporting source was either autopsy or death certificate only, (2) unknown survival time, and (3) survival time was not coded. We excluded these women from the survival analyses.

Race/Ethnicity

The SEER program assigns race/ethnicity based on state cancer registries, which collect data on race and ethnicity from various data sources, including hospital records, medical records, pathology reports, hospital discharge data, and death certificates.[15,16] SEER instructs state registries to categorize patient's race/ethnicity by 1 of the designated categories, and uses specific algorithms to assign Hispanic, Asian, and Native Hawaiian/other Pacific Islander status.[17] The age and race (case data only) variable in the SEER*Stat software was used to extract extended information on

ethnicity. The SEER 18 database classified all patients into 30 groups based on their racial or ethnic origins. These groups included (in alphabetical order) American Indian/Alaska Native, Asian Indian, Asian Indian or Pakistani, black, Chamorran, Chinese, Fiji Islander, Filipino, Guamanian, Hawaiian, Hmong, Japanese, Kampuchean, Korean, Laotian, Melanesian, Micronesian, New Guinean, other, other Asian, Pacific Islander, Pakistani, Polynesian, Samoan, Tahitian, Thai, Tongan, unknown, Vietnamese, and white.

We used the origin recode [Hispanic, non-Hispanic] NHIA variable to further classify white into non-Hispanic white and Hispanic white (NHIA stands for North American Association of Central Cancer Registries Hispanic/Latino identification algorithm). We prespecified race/ethnicity into the major groups of white, black, Asian, and other. Given the small relative frequencies for most Asian racial/ethnic groups, we further classified Asian race/ethnicity into the groups of Chinese, Japanese, South Asian, and other Asian. For this study, we then grouped all breast cancer cases into the racial/ethnic groups of (1) non-Hispanic white, (2) Hispanic white, (3) black, (4) Chinese, (5) Japanese, (6) South Asian (Asian Indian, Asian Indian or Pakistani, Pakistani), (7) other Asian (Filipino, Thai, Vietnamese, Korean, Kampuchean, Laotian, Hmong), and (8) other ethnicities (American Indian/Alaska Native, Chamorran, Fiji Islander, Guamanian not otherwise specified (NOS), Hawaiian, Melanesian NOS, Micronesian NOS, New Guinean, other, Pacific Islander NOS, Polynesian NOS, Samoan, Tahitian, Tongan, and unknown).

Statistical Analyses

Descriptive statistics were used to examine the following baseline characteristics of breast cancer cases: age of diagnosis, race/ethnicity, income, stage at diagnosis, ER status, PR status, ERBB2 status. For each racial/ethnic group, we calculated the distribution of breast cancer stage at diagnosis. For some subgroup analyses, we selected women whose breast cancer tumors were 2.0 cm or less at the time of diagnosis.

For the analyses based on hormone receptors, we selected women for whom the summary results of ER and PR were coded as positive/elevated or negative/normal/within normal limits in the database. To create a subcohort of women for whom the positivity or negativity of all 3 receptors (ER, PR, and ERBB2) was known, we excluded women whose ER and PR status were coded as borderline, undetermined whether positive or negative, or unknown. We further excluded women whose ERBB2 status was coded as borderline, equivocal, indeterminate, undetermined whether positive or negative, or unknown. We classified breast cancers into 2 groups: (1) positive for ER, PR, or ERBB2 and (2) triple negative (ie, those negative for ER, PR, and ERBB2). We calculated the distribution of receptor-positive (ER, PR, or ERBB2) vs triple-negative breast cancers for each racial/ethnic group.

The χ^2 test was used to compare frequency distributions between subgroups for categorical variables. We used unconditional logistic regression to estimate the odds ratios (ORs) for factors that were potentially predictive for receiving a breast cancer diagnosis at stage I, including age at diagnosis, income, ER status, and race/ethnicity. For each variable, we estimated the crude (unadjusted) OR for being diagnosed at stage I. We then performed multivariable logistic regression to estimate the ORs, adjusted for all variables in the analysis. We conducted the analysis on all cases combined and then on subgroups defined by age at diagnosis (≤40 years, 41-50 years, and >50 years).

To assess the relative aggressiveness of small-sized breast cancer tumors (diagnosed at ≤2.0 cm) according to racial/ethnic group, we determined the proportions that were triple negative, presented with lymph node metastases, and presented with distant metastatic disease within each racial/ethnic group.

We defined breast cancer-specific survival as the time from diagnosis of breast cancer to death due to breast cancer. We performed a Cox proportional hazards regression analysis to examine the association of age at diagnosis, income, ER status, and race/ethnicity with the hazard ratio (HR) of death in patients with stage I breast cancer. We performed bivariable (unadjusted) and multivariable (adjusted) analyses. We used the actuarial method to calculate breast cancer-specific survival for women with stage I breast cancers, according to race/ethnicity. We created separate survival curves for women with ER-positive and ER-negative breast cancer.

The difference in survival across strata was compared with the log-rank test. We computed 95% confidence intervals for all point estimates (ORs and HRs). A *P* value of .05 or less was considered statistically significant. All *P* values were 2-tailed. All statistical analyses were performed using SAS version 9.3 (SAS Institute Inc).

Results

Descriptive Statistics

We identified 452 215 women with invasive breast cancer, who had been diagnosed between 2004 and 2011. We excluded women with stage 0 and stage unknown breast cancer (n = 28 184, 6.2%), those with borderline, undetermined, or unknown ER status (n = 22 859, 5.0%), and those with prior history of any cancer (n = 27 609, 6.1%), leaving 373 563 for the study.

The demographic and clinical characteristics of the study population according to racial/ethnic group appear in **Table 1**. The mean follow-up time was 40.6 months (or 3.4 years) (median, 38 months; range, 0-95 months). The mean age at time of breast cancer diagnosis was 60.5 years (median, 60.0 years). The majority of cases were diagnosed among non-Hispanic white women (71.9% of cohort; 95% CI, 71.8%-72.1%), followed by black women (10.4% of cohort; 95% CI, 10.3%-10.5%) and Hispanic white women (9.4% of cohort; 95% CI, 9.3%-9.4%). Japanese women were significantly more likely to be diagnosed at stage I (56.1%; 95% CI, 54.5%-57.7%) than non-Hispanic white women (50.8%; 95% CI, 50.6%-51.0%) (*P* < .001). In contrast, black women were significantly less likely to be diagnosed at stage I (37.0%; 95% CI, 36.4%-37.4%) than non-Hispanic white women (50.8%) (*P* < .001). Women of South Asian ethnicity (Asian Indian, Pakistani) were also less

Table 1. Characteristics of the Study Population From the Surveillance, Epidemiology, and End Results 18 Registries Research Database, 2004-2011

		Race/Ethnicity							
		White							
	Total	Non-Hispanic	Hispanic	Black	Chinese	Japanese	South Asian	Other Asian	Other Ethnicity
Patients									
No.	373 563	268 675	34 928	38 751	4937	3751	2191	14 332	5998
% (95% CI)		71.9 (71.8-72.1)	9.4 (9.3-9.4)	10.4 (10.3-10.5)	1.32 (1.29-1.36)	1.00 (0.97-1.04)	0.59 (0.56-0.61)	3.84 (3.78-3.90)	1.61 (1.57-1.65)
Age at diagnosis, y									
Mean (95% CI)	60.5 (60.4-60.5)	61.9 (61.8-61.9)	56.1 (55.9-56.2)	57.8 (57.6-57.9)	56.5 (56.1-56.8)	62.6 (62.1-63.0)	54.4 (53.8-54.9)	55.8 (55.3-60.0)	57.5 (57.2-57.8)
Median (range)	60 (10-114)	61 (10-114)	55 (19-102)	57 (18-103)	55 (20-97)	62 (24-101)	54 (23-92)	55 (18-102)	57 (21-103)
Household income/y, US $									
Mean (95% CI)	60 314.0 (60 267.8-60 360.2)	60 402.1 (60 346.5-60 457.6)	60 831.0 (60 701.8-60 960.2)	54 042.4 (53 909.8-54 175.0)	69 293.8 (68 956.5-69 631.0)	67 233.2 (66 923.6-67 542.7)	69 113.2 (68 498.2-69 728.2)	66 930.9 (66 735.5-67 126.4)	63 135.3 (62 830.6-63 441.1)
Median (range)	58 080 (19 340-104 910)	58 370 (19 340-104 910)	56 270 (25 770-104 910)	55 880 (22 360-103 880)	70 820 (34 150-103 880)	71 260 (34 190-98 840)	70 570 (29 560-103 880)	64 580 (26 970-104 910)	64 500 (22 300-104 910)
Cancer stage at diagnosis, % (95% CI)									
I	48.0 (47.9-48.2)	50.8 (50.6-51.0)	40.1 (39.5-40.6)	37.0 (36.4-37.4)	50.1 (48.7-51.5)	56.1 (54.5-57.7)	40.4 (38.3-42.5)	45.2 (44.4-46.1)	43.6 (42.3-44.8)
II	34.6 (34.4-34.7)	33.2 (32.9-33.3)	38.7 (38.1-39.2)	38.6 (38.2-39.1)	35.7 (34.4-37.1)	32.4 (30.9-34.0)	38.7 (36.7-40.8)	38.1 (37.3-38.9)	37.2 (35.9-38.4)
III	12.4 (12.3-12.5)	11.4 (11.2-11.5)	15.9 (15.9-16.4)	16.6 (16.2-17.0)	10.7 (9.8-11.6)	8.5 (7.6-9.4)	15.3 (13.8-16.9)	12.4 (11.8-12.9)	13.5 (12.7-14.4)
IV	5.0 (4.9-5.1)	4.6 (4.6-4.7)	5.3 (5.1-5.5)	7.8 (7.6-8.1)	3.5 (3.0-4.1)	3.0 (2.5-3.6)	5.6 (4.6-6.6)	4.3 (4.0-4.6)	5.7 (5.2-6.4)
Receptor positive, % (95% CI)									
Estrogen	79.8 (79.6-79.9)	82.1 (82.0-82.3)	76.0 (75.3-76.5)	66.3 (65.9-66.8)	79.7 (78.6-80.8)	83.8 (82.4-84.8)	76.4 (74.5-78.1)	79.2 (78.5-79.9)	81.1 (80.1-82.1)
Progesterone[a]	68.2 (68.1-68.4)	70.6 (70.4-70.8)	64.9 (64.4-65.4)	54.4 (53.9-54.9)	68.4 (67.0-69.7)	72.7 (71.2-74.1)	66.4 (64.4-68.4)	67.6 (66.8-68.3)	70.9 (69.7-72.0)
ERBB2[a]	14.8 (14.6-15.0)	13.5 (13.3-13.8)	17.4 (16.6-18.2)	17.2 (16.4-17.9)	18.9 (16.8-21.1)	10.9 (9.0-13.1)	17.4 (14.6-20.4)	20.9 (19.7-22.3)	17.1 (15.4-18.9)
Follow-up time, mo									
Mean (95% CI)	40.6 (40.5-40.7)	41.4 (41.3-41.5)	38.3 (38.0-38.6)	37.6 (37.3-37.8)	40.8 (40.0-41.5)	42.4 (41.5-43.2)	36.3 (35.2-37.4)	39.7 (39.3-40.2)	36.4 (35.7-37.1)
Median (range)	38 (0-95)	39 (0-95)	34 (0-95)	33 (0-95)	39 (0-95)	41 (0-95)	32 (0-95)	37 (0-95)	32 (0-95)
Mortality status, % (95% CI)[b]									
Alive	87.3 (87.1-87.4)	87.3 (87.2-87.5)	89.1 (88.7-89.4)	81.2 (80.8-81.6)	92.8 (92.0-93.5)	91.7 (90.7-92.5)	92.5 (91.3-93.5)	92.4 (92.0-92.9)	89.6 (88.7-90.3)
Dead									
Due to breast cancer	7.3 (7.2-7.4)	6.8 (6.7-6.9)	7.4 (7.1-7.6)	12.5 (12.2-12.8)	4.6 (4.1-5.3)	3.5 (3.3-4.5)	5.3 (4.4-6.3)	5.0 (4.6-5.3)	6.1 (5.5-6.8)
Due to other causes	5.5 (5.4-5.5)	5.9 (5.8-6.0)	3.5 (3.3-3.7)	6.3 (6.0-6.5)	2.6 (2.2-3.1)	4.5 (3.8-5.2)	2.2 (1.6-2.9)	3.6 (2.3-2.8)	4.3 (3.8-4.9)

Abbreviation: ERBB2, formerly HER2 or HER2/neu.

[a] Analyses restricted to women with a known positive or negative progesterone receptor and ERBB2 status.

[b] As of December 31, 2011.

likely to be diagnosed with stage I breast cancer (40.4%, 95% CI, 38.3%-42.5%) than non-Hispanic white women (50.8%) ($P < .001$).

The ORs for being diagnosed at stage I for women of different racial/ethnic groups adjusted for age, income, ER status, and race/ethnicity appear in **Table 2**. Compared with non-Hispanic white women diagnosed with stage I cancer (50.8%), black women (37.0%) were significantly less likely to be diagnosed (OR, 0.65 [95% CI, 0.64-0.67], $P < .001$) and Japanese women (56.1%) were more likely to be diagnosed (OR 1.23 [95% CI, 1.15-1.31], $P < .001$). The ORs for being diagnosed with stage I breast cancer according to income, ER status, and race/ethnicity among different age groups are shown in the eTable in the Supplement.

Compared with older women (>50 years; 51.2%), the ORs for stage I breast cancer were significantly lower for women aged 41 to 50 years (42.2%) (OR, 0.73 [95% CI, 0.71-0.74], $P < .001$) and women 40 years or younger (29.4%) (OR, 0.45

Table 2. Stage I Breast Cancer at Diagnosis

	Total No. of Patients (N = 373 563)	Stage I Breast Cancer at Diagnosis		Bivariable Analysis		Multivariable Analysis[a]	
		No. of Patients	% (95% CI)	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Age, y							
≤40	24 326	7151	29.4 (28.8-30.0)	0.40 (0.39-0.41)	<.001	0.45 (0.44-0.46)	<.001
41-50	73 530	31 004	42.2 (41.8-42.5)	0.69 (0.68-0.70)	<.001	0.73 (0.71-0.74)	<.001
>50	275 707	141 259	51.2 (51.0-51.4)	1 [Reference]		1 [Reference]	
Income/y, US $							
<50 000	89 752	41 499	46.2 (45.9-46.5)	1 [Reference]		1 [Reference]	
50 000-75 000	218 014	104 862	48.1 (47.9-48.3)	1.08 (1.06-1.09)	<.001	1.07 (1.05-1.09)	<.001
>75 000	65 756	33 030	50.2 (49.8-50.6)	1.17 (1.15-1.20)	<.001	1.13 (1.11-1.16)	<.001
Estrogen receptor status							
Negative	75 658	26 554	35.1 (34.8-35.4)	1 [Reference]	<.001	1 [Reference]	<.001
Positive	297 905	152 860	51.3 (51.1-51.5)	1.95 (1.92-1.98)		1.80 (1.77-1.83)	
Race/ethnicity							
White							
Non-Hispanic	268 675	136 558	50.8 (50.6-51.0)	1 [Reference]		1 [Reference]	
Hispanic	34 928	13 992	40.1 (39.5-40.6)	0.64 (0.63-0.66)	<.001	0.71 (0.70-0.73)	<.001
Black	38 751	14 302	37.0 (36.4-37.4)	0.56 (0.55-0.57)	<.001	0.65 (0.64-0.67)	<.001
Chinese	4937	2473	50.1 (48.7-51.5)	0.97 (0.92-1.02)	.31	1.04 (0.98-1.10)	.24
Japanese	3751	2105	56.1 (54.5-57.7)	1.24 (1.16-1.32)	<.001	1.23 (1.15-1.31)	<.001
South Asian	2191	885	40.4 (38.3-42.5)	0.66 (0.60-0.71)	<.001	0.73 (0.67-0.79)	<.001
Other Asian	14 332	6485	45.2 (44.4-46.1)	0.80 (0.77-0.83)	<.001	0.85 (0.82-0.88)	<.001
Other ethnicity	5998	2614	43.6 (42.3-44.8)	0.75 (0.71-0.79)	<.001	0.78 (0.74-0.82)	<.001

Abbreviation: OR, odds ratio.

[a] Included age, income per year, estrogen receptor status, and race/ethnicity.

Table 3. Distribution of Stage IV, Node-Positive, Estrogen-Receptor Positive, and Triple-Negative Breast Cancers

	% (95% CI) of Women With Breast Cancer Tumor Size ≤ 2.0 cm, by Race/Ethnicity								
		White							
	All (n = 223 895)	Non-Hispanic (n = 168 507)	Hispanic (n = 18 376)	Black (n = 19 031)	Chinese (n = 3042)	Japanese (n = 2481)	South Asian (n = 1156)	Other Asian (n = 8007)	Other Ethnicity (n = 3295)
Stage IV	1.0 (0.9-1.0)	1.0 (0.9-1.0)	1.2 (1.1-1.4)	1.5 (1.4-1.7)	0.8 (0.5-1.2)	0.8 (0.4-1.1)	1.2 (0.6-1.8)	0.8 (0.6-1.0)	0.8 (0.5-1.1)
Node positive	19.3 (19.2-19.5)	18.4 (18.3-18.5)	23.3 (22.7-23.9)	24.1 (23.5-24.7)	18.1 (16.8-19.6)	14.6 (13.2-16.0)	23.2 (20.8-25.7)	18.6 (17.7-19.4)	20.2 (18.8-21.6)
ER positive	84.7 (84.5-84.8)	86.1 (86.0-86.3)	82.6 (82.0-83.1)	73.6 (73.0-74.3)	83.8 (82.5-85.1)	88.5 (87.1-89.7)	82.4 (80.1-84.6)	84.1 (83.3-84.9)	86.8 (85.6-87.9)
Triple negative[a]	9.0 (8.7-9.2)	8.0 (7.8-8.3)	10.0 (9.2-10.9)	17.2 (16.2-18.3)	8.8 (6.8-10.8)	8.2 (6.1-10.6)	10.4 (7.2-13.6)	6.2 (5.2-7.3)	6.0 (4.5-7.5)

Abbreviation: ER, estrogen receptor.

[a] Analyses restricted to 53 577 women with a known ER, progesterone receptor, and ERBB2 status (39 145 non-Hispanic white, 4834 Hispanic white, 4799 black, 785 Chinese, 613 Japanese, 356 South Asian, 2093 other Asian, and 952 who were other ethnicities).

[95% CI, 0.44-0.46], *P* < .001). Compared with women with an estimated income below $50 000 (46.2%), the ORs for having stage I breast cancer were modestly increased for those with an income between $50 000 and $75 000 (48.1%) (OR, 1.07 [95% CI, 1.05-1.09], *P* < .001) and those with an income of more than $75 000 (50.2%) (OR, 1.13 [95% CI, 1.11-1.16], *P* < .001). The OR for stage I breast cancers for women with ER-positive status was significantly higher (51.3%) compared with women with ER-negative status (35.1%) (OR, 1.80 [95% CI, 1.77-1.83], *P* < .001).

Aggressiveness of Small-Sized Breast Cancer Tumors

In the cohort of 223 895 women, 43 281 (19.3%; 95% CI, 19.2%-19.5%) with small-sized breast cancer tumors (≤ 2.0 cm) presented with nodal metastases and 2300 (1.0%; 95% CI, 0.9%-1.0%) presented with distant disease. The distribution of stage IV, node-positive, ER-positive, and triple-negative breast cancers according to race/ethnicity for women with tumor sizes of 2.0 cm or less appears in **Table 3**. The probability of a black woman with small-sized breast cancer tumors presenting with nodal metastases was higher

than for a non-Hispanic white woman (24.1% vs 18.4%, respectively; $P < .001$).

The probability of a black woman with small-sized breast cancer tumors presenting with distant metastases also was higher than for a non-Hispanic white woman (1.5% vs 1.0%, respectively; $P < .001$). Japanese women were significantly less likely than non-Hispanic white women to present with nodal metastases (14.6% vs 18.4%, respectively; $P < .001$). The proportion of small-sized breast cancer tumors that were ER positive was lower for black women (73.6%; 95% CI, 73.0%-74.3%) than for Japanese women (88.5%; 95% CI, 87.1%-89.7%) and non-Hispanic white women (86.1%; 95% CI, 86.0%-86.3%). Black women also had the highest proportion of triple-negative breast cancers (17.2%; 95% CI, 16.2%-18.3%).

Risk of Death From Stage I Cancer

In the entire cohort, the 7-year actuarial breast cancer survival rate for women with stage I breast cancer was 96.8% (95% CI, 96.6%-96.9%). Seven-year survival was 98.6% (95% CI, 97.2%-99.0%) for Japanese women, 98.2% (95% CI, 97.9%-99.4%) for Chinese women, 97.0% (95% CI, 96.8%-97.1%) for white women (non-Hispanic and Hispanic combined), and 93.9% (95% CI, 93.2%-94.6%) for black women (eFigure 1 in the Supplement). Among white women, 7-year survival was similar for non-Hispanic women (97.0%; 95% CI, 96.8%-97.2%) and Hispanic women (96.5%; 95% CI, 96.0%-97.1%) (eFigure 2 in the Supplement).

The HR for death due to stage I breast cancer according to race/ethnicity, age, income, and ER status appears in **Table 4**. In a multivariable analysis, the 7-year actuarial risk for death from stage I breast cancer was highest for black women (6.2%) compared with white women (3.0%) (HR, 1.57 [95% CI, 1.40-1.75]; $P < .001$). After excluding women with triple-negative breast cancers, the age-adjusted HR for death for black women (vs white) did not decrease (4.6% vs 2.4%, respectively; HR, 1.73 [95% CI, 1.50-2.00]; $P < .001$). Asian women had a lower actuarial risk of death (1.9%) than white women (3.0%) (HR, 0.60 [95% CI, 0.49-0.73]; $P < .001$). In particular, the 7-year actuarial mortality was much lower for South Asian women (1.7%) than for non-Hispanic white women (3.0%) (HR, 0.48 [95% CI, 0.20-1.15]; $P = .10$). Of 885 South Asian women with stage I breast cancer, only 5 (0.6%; 95% CI, 0.2-1.3) were reported to have died.

Among all women with small-sized breast cancer tumors that were 2.0 cm or less (including node positive), the 7-year actuarial survival was 95.1% (95% CI, 94.9%-95.2%). The actuarial probability of a woman dying due to small-sized breast cancer tumors was significantly higher for black women (9.0%) compared with non-Hispanic white women (4.6%) (HR, 1.96 [95% CI, 1.82-2.12]; $P < .001$; **Table 5**). The higher risk of dying for black women vs non-Hispanic white women persisted when the model was adjusted for age, income, and ER status (HR, 1.56 [95% CI, 1.45-1.69]; $P < .001$). In the model adjusted for age and ER status alone, the HR for death was 1.53 (95% CI, 1.46-1.68) for black vs non-Hispanic white women ($P < .001$). When the model was adjusted for age and income alone, the HR for death was 1.86 (95% CI, 1.73-2.00; $P < .001$).

Discussion

The goal of cancer control programs is to increase the relative proportion of stage I breast cancers and thereby reduce cancer mortality. It is important to identify factors associated with the diagnosis of stage I breast cancers and the groups for whom the proportion of cancers detected at stage I is less than optimal. We found that probability of small-sized breast cancer tumors having spread to the regional lymph nodes or distantly varied between women with different racial/ethnic backgrounds and may reflect variations in the intrinsic biology of their tumors.

In all age groups, black race/ethnicity was associated with being diagnosed beyond stage I. This observation suggests that the stage disparity at diagnosis is not likely to be attributed to screening trends; rather, the paucity of stage I cancers appears to be explainable in large part by inherent biological factors. In support of this hypothesis, a black woman with small-sized breast cancer tumors was more likely to present with lymph node metastases, was more likely to have triple-negative cancer, and was more likely to present with distant metastases than a non-Hispanic white woman with tumors of similar size.

Black women are more likely to die due to breast cancer within 7 years compared with non-Hispanic white or Asian women. Previous data have shown that black women have a high risk of breast cancer recurrence regardless of age and tumor size[9,10] and that black ethnicity is an independent predictor of short survival.[18] In our study, this was not related to the high prevalence of triple-negative breast cancers in the black population. The adjusted HR for death due to stage I breast cancer among black women was similar with white women after triple-negative breast cancers were excluded from the analysis. Also, adjusting for income had little statistical effect on the HR, whereas adjusting for the ER status had a substantial reducing effect.

Biological factors may not entirely account for the association with early-stage diagnosis in all racial/ethnic groups. South Asian women were less likely to be diagnosed at stage I than were white women, but this association was significant only among women aged 40 years or older (ie, the target population for screening). Unlike the case for black women, the relatively advanced stage of presentation among South Asian women was not associated with other features of aggressive cancers. Among South Asian women, stage I cancers were particularly indolent, and fewer than 1% of the women died of their cancer during the 7-year follow-up period (Table 4). Among South Asian women with stage II breast cancers, the 7-year survival rate was 91.7%; this suggests that efforts should be made to increase breast cancer awareness in South Asian women.

The Asian category is a compilation of several subcategories. Among different Asian groups, Japanese women had the highest proportion of stage I breast cancers, whereas Indian/Pakistani women had the lowest percentage of stage I breast cancer at diagnosis. Studies suggest that Japanese women develop less aggressive breast cancers and exhibit a more vigorous host response, resulting in fewer tumors diagnosed at 2.0 cm or larger in diameter and fewer with lymph node metastases.[19-22] It is possible that dietary factors are relevant, such as the consumption of green tea, isoflavone, or soy

Table 4. Deaths Due to Stage I Breast Cancer at 7 Years

	Total No. of Patients (n = 179 414)	Deaths		Bivariable Analysis		Multivariable Analysis[a]	
		No.	% (95% CI)[b]	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Model 1[c]							
Age, y							
≤40	7151	152	2.1 (1.8-2.5)	1.24 (1.07-1.45)	<.001	1.02 (0.87-1.21)	.77
41-50	31 004	372	1.2 (1.1-1.3)	0.69 (0.62-0.76)	<.001	0.67 (0.60-0.75)	<.001
>50	141 259	2211	1.6 (1.5-1.6)	1 [Reference]		1 [Reference]	
Income/y, US $							
<50 000	41 499	797	1.9 (1.8-2.1)	1 [Reference]		1 [Reference]	
50 000-75 000	104 862	1566	1.5 (1.4-1.6)	0.76 (0.70-0.82)	<.001	0.84 (0.77-0.92)	<.001
>75 000	33 030	372	1.1 (1.0-1.2)	0.61 (0.55-0.68)	<.001	0.67 (0.59-0.76)	<.001
Estrogen receptor status							
Negative	26 554	1019	3.8 (3.6-4.1)	1 [Reference]	<.001	1 [Reference]	<.001
Positive	152 860	1716	1.1 (1.1-1.2)	0.32 (0.30-0.34)		0.32 (0.30-0.35)	
Race/ethnicity							
White	150 550	2217	1.5 (1.4-1.5)	1 [Reference]		1 [Reference]	
Black	14 302	387	2.7 (2.4-3.0)	1.95 (1.75-2.17)	<.001	1.57 (1.40-1.75)	<.001
Asian	11 948	95	0.8 (0.6-0.9)	0.57 (0.46-0.70)	<.001	0.60 (0.49-0.73)	<.001
Other ethnicity	2614	36	1.4 (0.9-2.0)	1.06 (0.77-1.48)	.71	1.10 (0.79-1.52)	.59
Model 2[c]							
Age, y							
≤40	7151	152	2.1 (1.8-2.5)	1.24 (1.05-1.46)	<.001	1.02 (0.86-1.20)	.83
41-50	31 004	372	1.2 (1.1-1.3)	0.70 (0.63-0.79)	.001	0.67 (0.60-0.75)	<.001
>50	141 259	2211	1.6 (1.5-1.6)	1 [Reference]		1 [Reference]	
Income/y, US $							
<50 000	41 499	797	1.9 (1.8-2.1)	1 [Reference]		1 [Reference]	
50 000-75 000	104 862	1566	1.5 (1.4-1.6)	0.76 (0.70-0.83)	<.001	0.84 (0.77-0.92)	<.001
>75 000	33 030	372	1.1 (1.0-1.2)	0.57 (0.51-0.65)	<.001	0.67 (0.59-0.75)	<.001
Estrogen receptor status							
Negative	26 554	1019	3.8 (3.6-4.1)	1 [Reference]	<.001	1 [Reference]	<.001
Positive	152 860	1716	1.1 (1.1-1.2)	0.31 (0.29-0.34)		0.30 (0.31-0.35)	
Race/ethnicity							
White							
Non-Hispanic	136 558	2002	1.5 (1.4-1.5)	1 [Reference]		1 [Reference]	
Hispanic	13 992	215	1.5 (1.3-1.7)	1.14 (0.99-1.31)	.07	1.13 (0.98-1.30)	.10
Black	14 302	387	2.7 (2.4-3.0)	1.97 (1.77-2.20)	<.001	1.57 (1.40-1.75)	<.001
Asian							
Chinese	2473	18	0.7 (0.4-1.1)	0.51 (0.32-0.82)	.005	0.55 (0.35-0.88)	.01
Japanese	2105	20	1.0 (0.6-1.5)	0.65 (0.42-1.01)	.05	0.69 (0.45-1.08)	.10
South Asian	885	5	0.6 (0.2-1.3)	0.46 (0.19-1.11)	.08	0.48 (0.20-1.15)	.10
Other Asian	6485	52	0.8 (0.6-1.0)	0.58 (0.44-0.77)	<.001	0.61 (0.46-0.80)	<.001
Other ethnicity	2614	36	1.4 (1.0-1.9)	1.08 (0.77-1.50)	.66	1.11 (0.80-1.54)	.54

Abbreviation: HR, hazard ratio.

[a] Included for age, income per year (US $), estrogen receptor status, and race/ethnicity.

[b] Percentages refer to actual proportions of women who died of breast cancer and are not the actuarial death rates used for the HRs.

[c] The difference between models 1 and 2 is the subcategorization of race/ethnicity in model 2.

products.[23-25] Various studies suggest that green tea consumption among Japanese women is associated with decreased nodal metastasis, increased expression of ERs, and a reduction in the risk of recurrence for stage I breast cancers (risk ratio, 0.56; 95% CI, 0.35-0.91).[23] Others have shown an inverse relationship between increased soy (isoflavone) consumption and the risk of breast cancer in Japanese women.[24-27] Further research in these areas is warranted.

Among white women, the proportion of stage I breast cancer was much lower for Hispanic than for non-Hispanic women. However, unlike the situation for black women, the 7-year breast cancer–specific survival for Hispanic white women was rela-

Table 5. Deaths Due to Breast Cancer Among Women With Small-Sized Tumors of 2.0 cm or Less

	Total No. of Patients (n = 223 895)	Deaths		Bivariable Analysis		Multivariable Analysis[a]	
		No.	% (95% CI)[b]	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age, y							
≤40	10 716	383	3.6 (3.2-3.9)	1.33 (1.20-1.48)	<.001	1.10 (0.99-1.22)	.08
41-50	41 306	896	2.2 (2.0-2.3)	0.81 (0.75-0.87)	<.001	0.77 (0.72-0.83)	<.001
>50	171 873	4255	2.5 (2.4-2.5)	1 [Reference]		1 [Reference]	
Income/y, US $							
<50 000	52 423	1633	3.1 (3.0-3.3)	1 [Reference]		1 [Reference]	
50 000-75 000	130 607	3107	2.4 (2.3-2.5)	0.75 (0.70-0.79)	<.001	0.82 (0.77-0.87)	<.001
>75 000	40 841	794	1.9 (1.8-2.1)	0.61 (0.56-0.66)	<.001	0.70 (0.64-0.76)	<.001
Estrogen receptor status							
Negative	34 256	2102	6.1 (5.9-6.4)	1 [Reference]	<.001	1 [Reference]	<.001
Positive	189 639	3432	1.8 (1.7-1.9)	0.31 (0.29-0.33)		0.32 (0.31-0.34)	
Race/ethnicity							
White							
Non-Hispanic	168 507	3971	2.4 (2.3-2.4)	1 [Reference]		1 [Reference]	
Hispanic	18 376	467	2.5 (2.3-2.8)	1.17 (1.06-1.29)	.001	1.14 (1.04-1.26)	.007
Black	19 031	820	4.3 (4.0-4.6)	1.96 (1.82-2.12)	<.001	1.56 (1.45-1.69)	<.001
Asian							
Chinese	3042	34	1.1 (0.8-1.6)	0.49 (0.35-0.68)	<.001	0.51 (0.36-0.72)	<.001
Japanese	2481	30	1.2 (0.8-1.6)	0.52 (0.36-0.74)	<.001	0.56 (0.39-0.81)	.002
South Asian	1156	17	1.5 (0.8-2.3)	0.74 (0.46-1.19)	.21	0.75 (0.46-1.20)	.23
Other Asian	8007	129	1.6 (1.3-1.9)	0.72 (0.61-0.86)	<.001	0.75 (0.63-0.89)	.001
Other ethnicity	3295	66	2.0 (1.5-2.5)	0.97 (0.76-1.24)	.79	0.99 (0.78-1.27)	.96

Abbreviation: HR, hazard ratio.

[a] Included age, income per year (US $), estrogen receptor status, and race/ethnicity.

[b] Percentages refer to actual proportions of women who died of breast cancer and are not the actuarial death rates used for the HRs.

tively good and was similar with non-Hispanic white women (96.5% vs 97.0%). The relatively low proportion of stage I breast cancers coupled with high survival rate suggests a need to improve breast cancer awareness and screening in the Hispanic population.

In our study, survival was associated with biological differences in tumor characteristics (eg, between black women and women of other ethnicities) but factors such as socioeconomic status, access to and use of health care, adherence to treatment, and comorbidity might also contribute to breast cancer disparities.[28,29] Recently, Silber et al[29] compared breast cancer survival in black and white women (all stages). After matching for demographic and social factors, the HR for death was 1.54 (95% CI, 1.46-1.62; $P < .001$) for black women. They estimated that the 5-year survival difference of 12.9% between black and white women could be attributable to breast cancer characteristics at presentation.

A high body mass index may adversely influence breast cancer-specific survival[30] and this association may help explain our results. Kwan et al[31] reported that the association of obesity with breast cancer mortality differed by ethnicity in the California Breast Cancer Survivorship Consortium study. In their study, a body mass index of 40 or higher (morbid obesity) was associated with a higher risk of breast cancer mortality in Hispanic and non-Hispanic white women, but not in black or Asian women.

Several important limitations need to be considered in evaluating this study. The SEER program covers only 28% of the entire US population. Some of the race/ethnicity groupings in our study may not be comprehensive. For example, South Asian ethnicity consisted of women of Indian or Pakistani origin but not women from other South Asian countries (eg, Bangladesh, Nepal, and Sri Lanka) who may be classified as other Asians. Differences in treatments received and patient comorbidities could influence differences in survival, but these variables were not available in the SEER database.

Other relevant limitations include migration of patients in and out of a specific SEER registry geographic area and missing data; these factors can potentially affect the accuracy of outcomes associated with long-term follow-up.[32]

Conclusions

Among US women diagnosed with invasive breast cancer, the likelihood of diagnosis at an early stage, and survival after stage I diagnosis, varied by race and ethnicity. Much of the difference could be statistically accounted for by intrinsic biological differences such as lymph node metastasis, distant metastasis, and triple-negative behavior of tumors.

ARTICLE INFORMATION

Author Contributions: Drs Iqbal and Sun had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Iqbal, Narod.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Iqbal, Ginsburg, Sun, Narod.
Critical revision of the manuscript for important intellectual content: Iqbal, Ginsburg, Rochon, Narod.
Statistical analysis: Sun, Narod.
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Study supervision: Ginsburg, Rochon, Narod.

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