Original Article

Higher Population-Based Incidence Rates of Triple-Negative Breast Cancer Among Young African-American Women

Implications for Breast Cancer Screening Recommendations

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BACKGROUND: Differences in the breast cancer burden of African-American women compared with white American women are well documented. Recent controversies have emerged regarding age-appropriate mammographic screening guidelines, and these surveillance recommendations may influence future breast cancer disparities. The objective of the current study was to evaluate age-specific breast cancer stage distributions and incidence rates of triple-negative breast cancer (TNBC) in a population-based tumor registry. **METHODS:** The authors analyzed breast cancers from the California Cancer Registry (CCR) that were diagnosed between 1988 and 2006. The results were stratified by age and race/ethnicity, with white Americans identified as non-Hispanic whites (NHWs) and African Americans identified as non-Hispanic blacks (NHBs). Breast cancer stage distributions and TNBC incidence rates also were analyzed. **RESULTS:** In total, 375,761 invasive breast cancers were evaluated (including 276,938 in NHWs and 21,681 in NHBs). NHBs and Hispanics tended to be younger than NHWs (median ages 57 years, 54 years, and 64 years, respectively). Lifetime incidence rates were higher for NHWs compared with NHBs and Hispanics; however, for women aged <44 years, incidence was highest among NHBs. NHBs also had higher incidence rates of stage III and IV disease and a higher incidence of TNBC in all age categories. **CONCLUSIONS:** Population-based data demonstrated that African-American women had a more advanced stage distribution for breast cancer compared with white American women and higher incidence rates for TNBC. These patterns were observed for women ages 40 to 49 years and for older women, and they suggest that mammographic screening for the early detection of breast cancer will be particularly relevant for younger African-American women. ***Cancer*** **2011;117:2747–53.** © *2011 American Cancer Society.*

More than 200,000 women are diagnosed with breast cancer each year in the United States, and it is projected that approximately 40,000 will die with the disease annually.[1] Breast cancer mortality rates have declined over the past 20 m years in the United States, and this improvement in outcome is largely explained by the combination of earlier detection and screening mammography coupled with the use of more effective systemic therapy.[2] Systemic therapy options for breast cancer are determined by the molecular marker expression of individual tumors. Therefore, the best outcomes are observed for cancers that are either detected early (ie, when the distant organ micrometastatic risk is low) or that have a marker pattern indicating a high likelihood of controlling micrometastases with targeted treatment, such as endocrine therapy for hormone receptor-positivite tumors and/or trastuzumab for tumors with human epidermal growth factor receptor 2 (HER2/*neu*) overexpression. Conversely, tumors that are detected at an advanced stage or that are negative for these markers are more likely to be associated with breast cancer mortality.

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Population-based data regarding the breast cancer burden of different subsets of the American female population have revealed several interesting (albeit incompletely understood) patterns. Most notably, African-American women have a lower lifetime risk of breast cancer, but their mortality rates are paradoxically higher compared with the rates among white American women.[1] The age-incidence curves also differ; among women aged <45 years, the incidence rates are higher for African Americans compared with white Americans. Furthermore, the frequency of breast tumors that are negative for the estrogen receptor (ER), the progesterone receptor (PR), and/or the HER2/*neu* marker also is increased among African-American women.[3]

Breast cancer screening with annual mammography beginning at age 40 years has been advocated since the mid-1990s by organizations such as the American Cancer Society, the American College of Surgeons, and the National Comprehensive Cancer Network. This recommendation was challenged recently by the US Preventive Services Task Force (USPSTF), which issued a published statement in November 2009 in support of deferring the initiation of mammography screening until age 50 years.[4] Presumably, this screening strategy could have a disproportionately adverse effect on women who face an increased risk of being diagnosed with early onset breast cancer, advanced-stage disease, and/or biologically more aggressive tumors. The objective of this project was to assess the potential implications of the USPSTF recommendation relative to African-American women by computing age-specific, population-based stage distributions for breast cancer as well as age-specific incidence rates of triple-negative breast cancer (TNBC). For these analyses, we relied on data from the population-based California Cancer Registry (CCR), which has provided valuable information regarding disparities in breast cancer related to racial/ethnic identity since 1988.[5-8]

MATERIALS AND METHODS

An analysis of CCR data from 1988 to 2006 was performed. Age-adjusted and age-specific invasive breast cancer incidence rates for the 3 major race/ethnic groups (non-Hispanic white [NHW], non-Hispanic black [NHB], and Hispanic) were computed using data from the CCR. The CCR is a population-based cancer registry that has monitored cancer incidence and mortality in California since 1988. The SEER*Stat software program (version 6.5.2; National Cancer Institute; Surveillance, Epidemiology, and End Results [SEER] Program, Bethesda, Md) was used to analyze the CCR database, including 95% confidence intervals.[9] Statistical significance testing was based on chi-square comparisons for categorical variables, and the Student *t* test was used to compare the mean values of continuous variables. *P* values <.05 were considered statistically significant.

The CCR database for breast cancer was analyzed according to disease stage at diagnosis (according to the American Joint Committee on Cancer Cancer Staging Manual, seventh edition) and stratified by age (categorized as ages <40 years, 40 to 49 years, 50 to 59 years, 60 to 74 years, and ≥75 years); then, comparisons were evaluated with respect to the racial/ethnic subsets of the California population. Racial/ethnic identity was assigned by self-report as documented by the tumor registries that contribute to the CCR program.

Staging information and positive versus negative hormone receptor (ER and PR) status also was assigned according to the information contributed by the CCR registrars. For HER2/*neu* expression, positive or negative status was based on documented immunohistochemistry and/or fluorescence in situ hybridization analysis. Statistics for TNBC incidence rates were limited to women who were diagnosed beginning in 2004. Documentation of HER2/*neu* status appeared to be more uniform and complete during this latter interval, when clinical trial results regarding the effectiveness of adjuvant trastuzumab for HER2/*neu*-overexpressing breast cancers were more widely available; therefore, this component of molecular marker information became more relevant on a routine basis for all women who were diagnosed with invasive breast cancer.[10,11]

RESULTS

In total, 375,761 women were newly diagnosed with invasive breast cancer as reported in the CCR from 1988 to 2006. Of these, there were 278,241 NHW women (74%), 21,716 NHB women (5.8%), and 45,523 Hispanic women (12.1%).

The median age at diagnosis was 64 years, 57 years, and 54 years for NHW, NHB, and Hispanic patients, respectively. The median age at diagnosis for patients with unknown racial/ethnic background was 61.5 years. The age-incidence rates listed in Table 1 and the age-incidence curves in Figure 1 demonstrate that the risk of breast cancer rose with increasing age for all racial/ethnic subsets that we evaluated. Figure 1 also indicates that, among

Table 1. California Cancer Registry Breast Cancer Incidence Rates by Stage and Age Category Among Non-Hispanic White, Non-Hispanic Black, and Hispanic Women Diagnosed During 1988 to 2006[a]

	Non-Hispanic Whites				Non-Hispanic Blacks				Hispanics			
Age, y	Rate, %	Lower CI	Upper CI	Count	Rate, %	Lower CI	Upper CI	Count	Rate, %	Lower CI	Upper CI	Count
Stage I												
<40	3.6	3.5	3.7	3299	2.9	2.6	3.2	393	1.8	1.6	1.9	967
40-49	60.7	59.7	61.7	14,969	40.1	37.8	42.4	1194	30.3	29.2	31.4	3043
50-59	130.5	128.9	132.2	24,576	75.5	71.7	79.4	1508	60	58.1	62	3545
60-74	221.9	219.9	223.9	46,806	122.5	117.4	127.6	2245	106.3	103.4	109.3	5114
≥75	210.6	208.2	213	29,303	115.6	108.6	122.9	1013	100	95.7	104.6	1972
Stage II												
<40	5.6	5.4	5.7	5166	6.3	5.9	6.8	860	4.5	4.3	4.6	2502
40-49	65.9	64.9	67	16,238	63.4	60.6	66.4	1895	47.9	46.5	49.2	4839
50-59	104.5	103.1	106	19,622	95.1	90.8	99.5	1897	68.2	66.1	70.4	4033
60-74	138.6	137	140.2	29,170	111	106.2	116	2033	84.7	82.1	87.3	4122
≥75	134.1	132.2	136.1	18,855	111.2	104.3	118.4	976	86.5	82.5	90.8	1698
Stage III												
<40	1.2	1.2	1.3	1131	1.9	1.7	2.1	255	1.4	1.3	1.5	795
40-49	13.1	12.6	13.5	3213	18.5	17	20.1	552	12.8	12.1	13.5	1298
50-59	20	19.3	20.6	3745	26.7	24.5	29.1	532	18.4	17.3	19.5	1087
60-74	21.7	21.1	22.4	4566	26.9	24.6	29.4	496	18.6	17.4	19.8	908
≥75	26.2	25.4	27.1	3745	34.9	31.1	39	307	20.3	18.3	22.4	396
Stage IV												
<40	0.5	0.4	0.5	433	0.9	0.8	1.1	124	0.5	0.4	0.5	275
40-49	5.5	5.2	5.8	1350	8.8	7.8	10	263	4.4	4	4.8	440
50-59	11.4	10.9	11.9	2149	17.3	15.5	19.2	345	8	7.3	8.7	472
60-74	17.3	16.8	17.9	3648	23.5	21.4	25.9	431	12.5	11.5	13.5	605
≥75	19	18.3	19.7	2695	25.6	22.4	29.2	225	12.8	11.2	14.4	249
NA/unstaged												
<40	2	1.9	2.1	1817	3	2.7	3.3	406	1.7	1.6	1.8	973
40-49	21.4	20.8	22	5266	27	25.2	28.9	806	16.4	15.6	17.2	1659
50-59	37	36.2	37.9	6961	43.3	40.4	46.3	864	26.3	25	27.6	1553
60-74	69.8	68.7	70.9	14,740	68	64.3	72	1238	39	37.3	40.8	1889
≥75	102.5	100.9	104.2	14,778	97	90.9	104	858	56.2	52.9	59.7	1089

CI indicates confidence interval; NA, not available.

[a] Rates are per 100,000 and were age-adjusted to the US 2000 standard population (19 age groups; US Census Bureau. Current Population Reports: P25-1130 Population Projections of the United States by Age, Sex, Race, and Hispanic Origin: 1995 to 2050. Washington, DC: US Census Bureau; 1996). CIs (Tiwari modification) are 95% for rates. Based on the January 2010 release of California Cancer Registry incidence data, National Center for Health Statistics estimates.

women aged <44 years, population-based incidence rates of breast cancer were highest for NHB women; for women aged >44 years, the incidence rates were highest for NHW women. Incidence rates were lowest for Hispanic women in all age categories. Incidence rates of stage I and II breast cancer were lower for NHB women compared with NHW women in all age categories; however, incidence rates for stages III and IV disease were higher for NHB women. Breast cancer incidence rates for any stage generally were lower for Hispanics women compared with NHW women in all age categories.

Figure 2 illustrates the incidence rates by disease stage for the study population subsets and demonstrates the shift toward more frequent detection of advanced-stage disease (stages III and IV) for NHB women compared with NHW and Hispanic women. Figure 3 indicates that most of the rising breast cancer incidence rates associated with increasing age were a consequence of increasing risk of non-TNBC. Incidence rates for TNBC were <50 per 100,000 population (for all race-ethnic groups combined) in all age categories, but these rates slowly rose with age and plateaued beyond the fifth decade of life.

Table 2 and Figure 4 demonstrate the increased risk of TNBC for NHB women in all age categories. The incidence of TNBC rose more steeply with increasing age for NHB women compared with NHW and Hispanic women, and those incidence rates were approximately

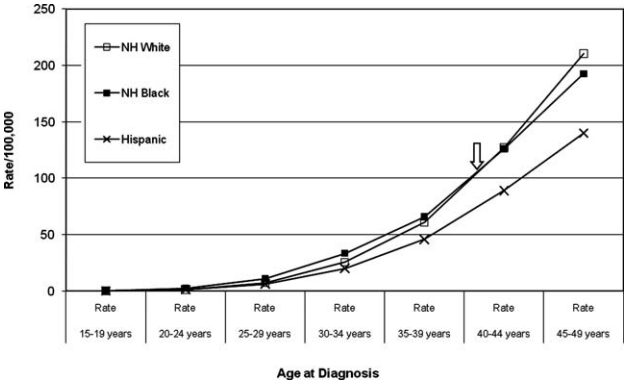

Figure 1. Age-specific breast cancer incidence rates are illustrated for women who were aged <50 years at diagnosis according to race/ethnicity from the California Cancer Registry. Note that crossover in the age-incidence curves between non-Hispanic (NH) whites and NH blacks occurred in the group ages 40 to 44 years (arrow), and the incidence rates were higher among younger NH blacks.

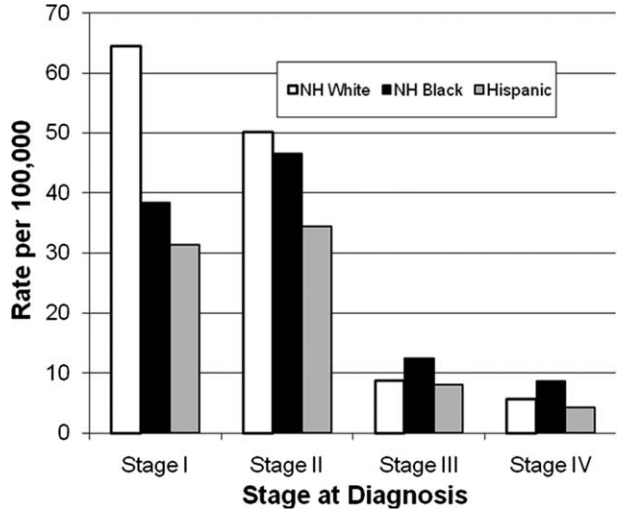

Figure 2. Age-adjusted incidence rates of breast cancer among women are illustrated according to race/ethnicity and disease stage at diagnosis from the California Cancer Registry. NH indicates non-Hispanic.

2-fold higher for NHB women compared with either of the other subsets in the groups ages 40 to 49 years and 50 to 59 years. The TNBC incidence rates peaked at 64.4 per 100,000 NHB women in the group ages 60 to 74 years.

DISCUSSION

Recent challenges to the traditional recommendations that American women initiate annual screening mammography at age 40 years have the potential for exerting a disproportionately adverse effect on African-American women because of the well documented younger age distribution for breast cancer in this population subset. Early detection of breast cancer is the most powerful determinant of outcome, and this will be particularly relevant for tumors that express phenotypes that cannot be controlled with targeted agents, such as endocrine therapy and/or trastuzumab. African-American women have higher mortality rates from breast cancer, and this is explained at least partially by the finding that they tend to present with more advanced stages compared with white American women. Therefore, they represent a community that has been the focus of many breast cancer awareness and screening/early detection programs. Our current study provides further evidence of the need to continue intensive breast cancer surveillance among African-American women ages 40 to 49 years. By studying data from the CCR, we observed higher population-based incidence rates of locally advanced breast cancer and TNBC among African-American women.

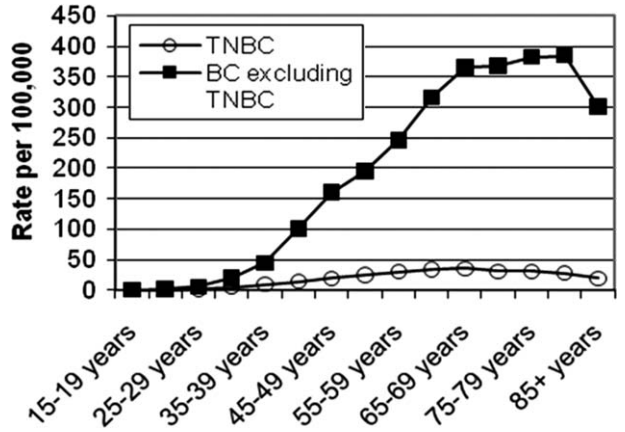

Figure 3. Triple-negative breast cancer (TNBC) incidence rates compared to incidence rates of all other breast cancers (BC). Incidence rates per 100,000 are illustrated by age from the California Cancer Registry.

Although the lifetime incidence rates of breast cancer are higher for white American women compared with African-American women, the SEER Program documents that, for women aged <45 years, population-based incidence rates are higher for African Americans.[12] Several investigators have demonstrated that the frequency of TNBC is higher for African-American patients with breast cancer compared their white American counterparts.[13-16] Furthermore, Carey et al[17] demonstrated that the risk of TNBC was particularly high among premenopausal African-American women based on an analysis of the Carolina Breast Cancer Study. By reporting on age-specific and race/ethnicity-specific patterns of disease in

Table 2. Triple-Negative Breast Cancer Incidence Rates per 100,000 by Age and Race From the California Cancer Registry[a]

	NHB		NHW		Hispanic	
Age, y	Incidence Rate	95% CI	Incidence Rate	95% CI	Incidence Rate	95% CI
0-39	4.1 ± 0.4	3.4-5.0	2.2 ± -0.1	2.0-2.5	2.1 ± 0.1	1.9-2.3
40-49	35.1 ± 2.2	31-39.6	16.8 ± 0.6	15.7-17.9	15.1 ± 0.7	13.7-16.5
50-59	54.9 ± 3.2	48.9-61.5	27.7 ± 0.8	26.2-29.2	24.9 ± 1.1	22.7-27.2
60-74	64.4 ± 3.8	57.1-72.4	36.3 ± 0.9	34.6-38.2	26.4 ± 1.4	23.8-29.3
≥75	49.9 ± 4.8	40.9-60.4	30.3 ± 1.0	28.3-32.3	19.3 ± 1.7	16.1-23.0

NHB indicates non-Hispanic black; NHW, non-Hispanic white; CI, confidence interval.
[a] Mean±standard deviation rates are per 100,000 US 2000 standard population. Confidence intervals (Tiwari modification) are 95% for rates.

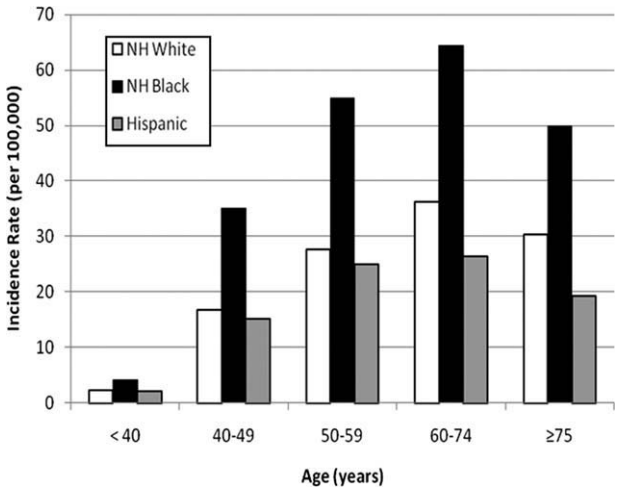

Figure 4. Triple-negative breast cancer incidence rates from the California Cancer Registry are shown by age and race (rates are per 100,000 and were age-adjusted to the 2000 US standard population [19 age groups; US Census Bureau. Current Population Reports: P25-1130 Population Projections of the United States by Age, Sex, Race, and Hispanic Origin: 1995 to 2050. Washington, DC: US Census Bureau; 1996]). Confidence intervals (Tiwari modification) are 95% for rates. NH indicates non-Hispanic.

the CCR, our study current provides powerful population-based evidence regarding the importance of aggressive screening for the early detection of breast cancer in young African-American women.

Reviews of data from the historic mammography screening trials were prepared by Nelson et al[18] and Mandelblatt et al on behalf of the Cancer Intervention and Surveillance Modeling Network (CISNET)[19] as background for the updated screening guidelines presented by the USPSTF in November 2009.[4] In summary, those investigators reported that, for women ages 40 to 49 years, approximately 1900 must be invited to mammographic screening to save 1 life; for women ages 50 to 59 years, approximately 1300 must be invited; and, for women ages 60 to 69 years, approximately 400 must be invited. Those reviewers also observed that the initiation of mammography screening at age 40 years rather than age 50 years resulted in an average gain of 33 life years per 1000 women screened. The CISNET authors commented that if the goal of a national screening program is to reduce mortality in the most efficient manner, then programs that screen biennially beginning at age 50 years are among the most efficient based upon the ratio of benefits to the number of screening examinations. CISNET also noted that, if the objective of the screening program is to maximize the number of life-years gained, then initiation of screening at age 40 years would be the preferred strategy.[19] The USPSTF opted to advocate in favor of supporting an efficiency-based screening model rather than a longevity-based program and they published a statement advising against routine screening mammography in average-risk women ages 40 to 49 years but recommended in favor of screening mammography every 2 years for women ages 50 to 74 years.[4] The CISNET authors also commented that none of the mammography screening models were likely to capture differences in outcome among specific population subsets, "such as women with *BRCA1* or *BRCA2* genetic susceptibility mutations, women who are healthier or sicker than average, or black women who seem to have more disease at younger ages than white women."[19] The USPSTF recommendation statement however, did not comment on the potential impact of their screening recommendations on race-ethnicity-associated breast cancer disparities.

Our study serves to inform the discussion regarding the relevance of mammography screening for African-American women ages 40 to 49 years. We observed that there was more advanced-stage disease at diagnosis in these younger African-American women, and we also observed higher incidence rates of TNBC for this population subset. Because mammography screening programs should improve early detection rates for breast cancer, and because the early detection of TNBC is critical for improving

Table 3. Published Studies of Estrogen Receptor-Negative/Progesterone Receptor-Negative/Human Epidermal Growth Factor Receptor 2-Negative (Triple-Negative) Breast Cancer Frequency by Race/Ethnic Identity

Study	Dataset	Sample Size Dataset	Proportion With TNBC, %		
			AA	WA	*P*
Carey 2006[17]	Carolina Breast Cancer Study	97 Premenopausal AA women; 164 premenopausal WA women	39	16	<.001
Morris 2007[13]	Thomas Jefferson University Hospital patients; SEER Program	2230 Thomas Jefferson University Hospital patients; 197,274 SEER patients	21%	10	<.001
Lund 2009[15]	Population-based cohort from Atlanta, Ga	116 AA patients; 360 WA patients	47	22	<.001
Lund 2008[14]	Grady Hospital; Atlanta, Ga	167 AA; 23 WA	29	13	.05
Moran 2008[16]	BCS patients from Yale University School of Medicine	99 AA; 968 WA	21	8	<.001
Parise 2009[5]	California Cancer Registry	3743 AA; 48,863 WA	28	12	NR
Stark 2010[30]	Henry Ford Hospital, Detroit, Mich	1008 WA; 581 AA	16	26	<.01

TNBC indicates triple-negative breast cancer; AA, African American; WA, white American; SEER, Surveillance, Epidemiology, and End Results; BCS, breast-conservation surgery; NR, not reported.

likelihood of its successful treatment, we believe that our current findings provide compelling evidence that screening mammography is particularly important for young African-American women. The USPSTF recommendation that routine screening mammography should not be initiated until age 50 years has the potential for widening the magnitude of breast cancer outcome disparities between African-American and white American women.

The CCR data on race/ethnicity-associated frequency of TNBC is consistent with other studies, as indicated in Table 3. The population-based incidence rates featured in our study serve to strengthen the validity of these observations. These rates indicate an inherently higher risk of TNBC for NHB/African-American women, refuting the argument that the larger proportion of TNBC in African-American women is an artifact of the "denominator" phenomenon (ie, African-American women appear to have more TNBC simply because they have fewer total breast cancers compared with white American women). Our data on women from California demonstrate an increased population-based risk of TNBC for NHB women.

This study is limited by our unfortunate inability to correlate mammography screening information with the age-specific and race/ethnicity-specific breast cancer incidence rates. Although the data regarding effectiveness of mammography in detecting TNBC (compared with detection rates for non-TNBC) are limited, the available published studies indicate that the frequency of mammographically occult breast tumors is similar for TNBC and non-TNBC. However, TNBC appears to be associated less frequently with microcalcifications and is more likely to be identified as a mass or asymmetric density.[20-23] Furthermore, Ma et al demonstrated that mammographic density (a common imaging finding among premenopausal women) is a risk factor for both TNBC and non-TNBC.[24]

Another noteworthy limitation of our current study is that the CCR (similar to the SEER Program) lacks detailed information on menstrual history and reproductive factors. Millikan et al[25] and other investigators[26] have suggested that childbearing patterns and lactation history may account for race/ethnicity-associated variation in breast cancer burden, although others have been unable to confirm those hypotheses.[27] Other investigators have reported an elevated risk of TNBC among contemporary populations of women in continental Africa,[28-30] suggesting that African ancestry may be associated with some heritable risk factor for TNBC.[31] Our population-based California dataset was unable to address any of these issues.

In summary, our data from California (which appear to be representative of national data) demonstrate an increased risk of advanced-stage breast cancer and TNBC for African-American women compared with white American and Hispanic-American women. These patterns are notably prominent for women aged <50 years, suggesting that mammography screening to improve the early detection of biologically aggressive patterns of breast cancer is particularly relevant for younger African-American women.

CONFLICT OF INTEREST DISCLOSURES

The collection of cancer incidence data used in this study was supported by the California Department of Public Health as part of the statewide cancer reporting program mandated by

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