Research Article

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Race-Specific Impact of Natural History, Mammography Screening, and Adjuvant Treatment on Breast Cancer Mortality Rates in the United States

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Abstract

Background: U.S. Black women have higher breast cancer mortality rates than White women despite lower incidence. The aim of this study is to investigate how much of the mortality disparity can be attributed to racial differences in natural history, uptake of mammography screening, and use of adjuvant therapy.

Methods: Two simulation models use common national race, and age-specific data for incidence, screening and treatment dissemination, stage distributions, survival, and competing mortality from 1975 to 2010. Treatment effectiveness and mammography sensitivity are assumed to be the same for both races. We sequentially substituted Black parameters into the White model to identify parameters that drive the higher mortality for Black women in the current time period.

Results: Both models accurately reproduced observed breast cancer incidence, stage and tumor size distributions, and breast cancer mortality for White women. The higher mortality for Black women could be attributed to differences in natural history parameters (26–44%), use of adjuvant therapy (11–19%), and uptake of mammography screening (7–8%), leaving 38% to 46% unexplained.

Conclusion: Black women appear to have benefited less from cancer control advances than White women, with a greater race-related gap in the use of adjuvant therapy than screening. However, a greater portion of the disparity in mortality appears to be due to differences in natural history and undetermined factors.

Impact: Breast cancer mortality may be reduced substantially by ensuring that Black women receive equal adjuvant treatment and screening as White women. More research on racial variation in breast cancer biology and treatment utilization is needed. *Cancer Epidemiol Biomarkers Prev; 20(1); 112–22. ©2011 AACR.*

Introduction

In 2009, an estimated 192,370 women in the United States were diagnosed with invasive breast cancer and approximately 40,170 women were expected to die of this disease (1). After remaining relatively constant for many years, breast cancer mortality in the United States decreased by 24% from 1990 to 2000 because of diffusion of mammography screening and improved adjuvant breast cancer treatment (2). However, trends show a growing disparity in breast cancer mortality between Black and White women. While the breast cancer mortality rates for White women steadily decreased from 1990 onward at an average annual rate of 2.4%, the rates in Black women have only decreased by 1.1% per year during this same period (3). The higher mortality rate for Black women (i.e., in 2006, 49 per 100,000 vs. 35 per 100,000 for White women 25 years and older) is particularly striking since breast cancer incidence is lower for Black than White women (3).

Several factors are thought to contribute to the observed race disparity in breast cancer mortality. Black women are more likely to present with breast cancer at a later stage than White women (4–6). This difference has been hypothesized to be due to low or irregular rates of use of mammography screening (7), delays in follow-up after an abnormal mammogram (8), and/or cultural beliefs and attitudes that may lead to delayed presentation of clinically diagnosed cases (9). Even within stage categories, Black women have significantly worse survival than White women after controlling for age and tumor

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markers (10). This racial difference in stage-specific survival has been hypothesized to be due to underuse of appropriate adjuvant therapy (11) and delays in treatment initiation (12–13). Also, higher rates of comorbidities, including cardiovascular disease and diabetes may affect Black women's ability to tolerate chemotherapy and lead to dose reductions that diminish treatment effectiveness (14). In addition, differences in tumor biology, such as higher rates of poor-prognosis triple-negative tumors in Blacks have been hypothesized to contribute to the Black–White disparities in breast cancer mortality (15–16).

In the present study, the impact of natural history, screening use and adjuvant therapy use on the disparity in breast cancer mortality between U.S. Black and White women is estimated using 2 established, independent population simulation models (17–18). Modeling provides an excellent "laboratory" for the evaluation of the separate contribution of these factors, because hypothetical scenarios can be simulated (e.g., changing 1 factor at a time). Our results are intended to inform health policy debates about the most effective strategies to reduce the disparity in breast cancer mortality between Black and White women and ultimately reduce the burden of breast cancer for all Americans.

Methods

Model overviews

MISCAN-Fadia (MIcrosimulation of SCreening ANalysis-Fatal diameter) and SPECTRUM (Simulating Population Effects of Cancer Control inTerventions-–Race and Understanding Mortality) are 2 simulation models developed within the Cancer Intervention and Surveillance Modeling Network (CISNET). CISNET is an international collaborative modeling effort funded by the National Cancer Institute (NCI). Collaborative modeling provides an opportunity to evaluate how model differences affect results.

The models have been described in detail elsewhere (17–18) and information about the models can be found online (19). Briefly, both models simulate breast cancer trends in the U.S. population in the absence of screening or adjuvant treatment and then overlay screening and adjuvant treatment diffusion over time. MISCAN-Fadia models tumor growth, where tumors can be detected once they are beyond a detection threshold and cured if the tumor diameter is below a fatal diameter. In SPECTRUM, tumors progress through stages, with screening effects due to age and stage shifts and adjuvant treatment reducing the hazard of death. In both models ductal carcinoma *in situ* (DCIS) is represented as a state that can regress, remain, and be diagnosed or progress to invasive cancer.

Model parameters

Race-specific common data inputs. MISCAN-Fadia and SPECTRUM use a common race-specific set of data inputs to model breast cancer mortality by race. The demographic characteristics of multiple birth cohorts of Black and White women born between 1890 and 1985 were based on historical data for number of births and deaths from the U.S. Census and the National Center for Health Statistics (NCHS; ref 20).

The background incidence of breast cancer in the absence of screening was estimated from the Connecticut Tumor Registry and Surveillance, Epidemiology and End Results (SEER) data with the use of an age-period-cohort (APC) model (21). The original APC model was used for White women and adapted for Black women using an age-specific relative risk of Black versus White incidence.

SEER data for stage distribution and breast cancer-specific survival from the period 1975 to 1979 were used to model the natural history of breast cancer in the absence of mammography screening and adjuvant therapy as these cancer control interventions did not begin to disseminate into the population in a substantial manner until after 1980.

The dissemination of mammography in the population was estimated using a 2-part model described elsewhere (22–23). The first component of the model involves estimating the distribution of age at first mammography and the second component estimates the interval between successive screenings. For both components, a race-specific variant has been used resulting in somewhat lower screening rates for Black women (24). For example, the screening rates were approximately 13% lower in Black than that in White women ageing 50 to 74 years in the period 1995 to 2005.

Age-, year-, AJCC (American Joint Committee on Cancer) stage-, estrogen receptor (ER), and human epidermal growth factor receptor 2 (HER2)-specific use of adjuvant therapy among Black and White women from 1975 to 2000 was estimated from data from the NCI's Patterns of Care (POC) studies (25–26) and updated through 2010 on the basis of data from patients presenting at National Comprehensive Cancer Network (NCCN) sites. Overall, Black women were 22% and 15% less likely to receive multiagent chemotherapy and hormonal therapy, respectively, than White women. These Black–White differences were applied to the adjuvant treatment dissemination curves from 1975 to 2010.

Non-race–specific inputs. Treatment effectiveness estimates are based on meta-analyses of randomized trial results from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG; refs 27–29). We assume that hormonal and chemotherapy regimens are equally effective in Black and White women (30).

The sensitivity of mammography screening is based on data from screening trials and Breast Cancer Surveillance Consortium (BCSC), and is assumed to be equal for both race groups. (D. Miglioretti, personal communication, January 2008.)

Model validation

SPECTRUM and MISCAN-Fadia have used several approaches to assess the internal reliability of the models

and the validity of the results against external data for the U.S. population (17–18). For the present study, we compared model predictions for incidence rates by race over time (1975–2006) with SEER data (31). Breast cancer incidence by race for women 25 years and older was directly age standardized to 2000 U.S. standard population. We also compared model predictions of the stage (SPECTRUM) and tumor size (MISCAN-Fadia) distribution by race (assuming observed race-specific dissemination of screening) with observed SEER data in the period 2004 to 2006 (the last year of publically available SEER data at the time of analysis).

Impact of screening and adjuvant therapy on breast cancer mortality

The models were used to estimate age-adjusted breast cancer mortality rates between 1975 and 2010 for Black and White women in the United States. We calculated percent mortality reductions by comparing the mortality in scenarios with screening, adjuvant treatment, and both with the background mortality predicted in the absence of screening and adjuvant treatment. Breast cancer mortality by race for women 25 years and older was directly age standardized to 2000 U.S. standard population. The predicted breast cancer mortality rates were compared to the observed rates by race (32).

Factors contributing to the observed mortality difference

We investigated the effect of the following factors on the difference between White and Black women in age-adjusted breast cancer mortality in a current period (the years 2004–2006): demography and breast cancer incidence, natural history (defined as the stage distribution and survival in the absence of screening and adjuvant treatment, and ER/HER2 distribution), screening use, and adjuvant treatment use. To this end, we sequentially substituted parameter values relating to these factors in the White version of each of the 2 models by corresponding values from the Black version and computed the fraction of the mortality difference between White and Black women explained by each factor.

Results

Model validation

From 1975 to 2006, the observed age-adjusted breast cancer incidence rates steadily rose from 173 to 249 per 100,000 in White women and from 144 to 227 per 100,000 in Black women. These trends were accurately reproduced by both models for both races (Fig. 1). The difference between the observed and predicted incidence was not more than 10% in either model in any year.

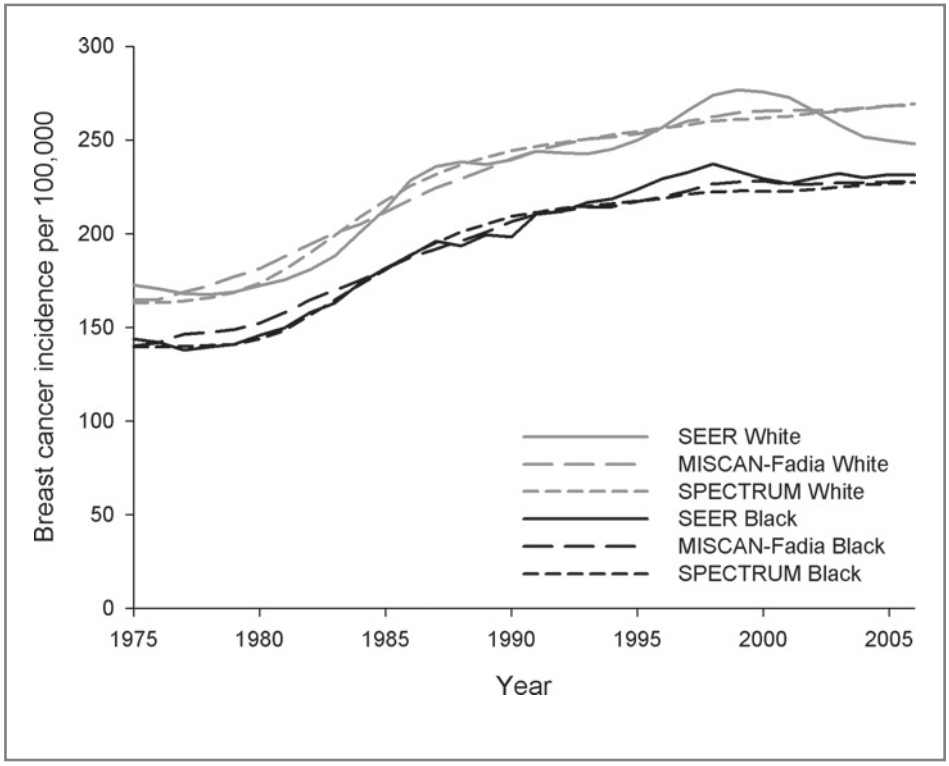

Figure 1. Age-adjusted incidence rates (3-year moving average) over time as observed (SEER) and predicted by MISCAN-Fadia and SPECTRUM for White and Black U.S. women 25 years and older.

The observed stage distribution at diagnosis for the period 2004 to 2006 was more favorable in White than in Black women (Fig. 2). This observation was reproduced by both models, with a more favorable tumor size distribution (MISCAN-Fadia) and stage distribution (SPECTRUM) for White than for Black women (Fig. 2A and B). However, for Black women, both models predicted a slightly more favorable stage or tumor size than actually observed.

Impact of screening and adjuvant therapy on breast cancer mortality

There have been different trends of age-adjusted breast cancer mortality observed over time (1975–2006) by race [Fig. 3A and B, i.e., (MISCAN-Fadia) and (SPECTRUM) for White and Fig. 4A and B, i.e., (MISCAN-Fadia) and (SPECTRUM) for Black women].

For White women, the model-predicted breast cancer mortality rates with screening and adjuvant treatment as disseminated in the population were similar to the observed rates. The difference between the observed and predicted rates was less than 8% for all years between 1975 and 2006 in both models. Both mammography screening (19–22% mortality reduction for MISCAN-Fadia and SPECTRUM, respectively) and adjuvant treatment (27–31% mortality reduction) contributed substantially to the observed reduction in breast cancer mortality among White women in both models (Table 1). The combination of mammography and adjuvant therapy is estimated to have resulted in substantially lower breast cancer mortality among White women in 2004 to 2006 (41–44% reduction) compared with a hypothetical situation without screening and adjuvant treatment.

For Black women, the model-predicted breast cancer mortality rates with screening and adjuvant treatment as disseminated in the population diverge from the observed rate. The observed breast cancer mortality decreases less and later than the predicted rates. The predicted mortality reductions in both models were somewhat lower than for White women: mammography screening (18–20% mortality reduction), adjuvant treatment (22–24% mortality reduction), and the combination of screening and treatment (38–39% mortality reduction; Table 1).

Factors contributing to the observed mortality difference

Table 2 compares observed age-adjusted breast cancer mortality in 2004 to 2006 among White women (36.1 per 100,000 women-years) and Black women (49.8 per 100,000) to predictions from a series of models with White parameter values sequentially replaced by Black values. The models for the White population predict mortality correctly (37.4 and 37.5 per 100,000 respectively, in MISCAN-Fadia and SPECTRUM). First, replacing demographic characteristics and breast cancer incidence lowered mortality predictions to 32.5 and 32.2 per 100,000, as a result of the lower incidence for Black women. Next, changing natural history parameters responsible for a less favorable stage distribution and survival in Black women raised predicted mortality to 36.9 and 40.1 per 100,000. The lower rate of screening among Black women raised mortality to 38.4 and 41.3 and the lower use of adjuvant therapy raised mortality to 40.3 and 42.0 per 100,000. Changing all parameters to Black values resulted in mortality predictions of 41.9 and 43.2 per 100,000 in MISCAN-Fadia and SPECTRUM, respectively. Of the difference between observed mortality and predicted mortality after taking into account the lower incidence among Blacks, natural history explained 26% (44%), screening use 8% (7%), and use of adjuvant therapy 19% (11%), leaving 46% (38%) unexplained in MISCAN-Fadia (SPECTRUM).

Discussion

To our knowledge, this is the first study using collaborative population modeling to evaluate the separate and combined impact of natural history, screening use, and adjuvant therapy use on race disparities in breast cancer mortality in the United States. Both models find that the majority of the Black–White disparities in mortality outcomes is attributable to variations in natural history and yet unknown factors, and to a lesser extent to differences in use of cancer screening or treatment services. In addition, the results suggest that racial differences in adjuvant treatment dissemination contribute to the racial disparity in breast cancer mortality to a greater extent than differences in screening uptake.

Our results indicate that breast cancer natural history parameters were a major driver of race-specific differences in mortality. Also, reduced screening and treatment use in Black women, which might be related to the higher proportion of un(der)insured Black women (33), contributed to the mortality disparity. However, the models also agree that a substantial part (38–46%) of the mortality difference by race remains unexplained, which is in line with previous work showing that several predictor variables contribute to, but do not fully explain, race differences in breast cancer survival (34).

Several factors might account for the unexplained part of the mortality difference. First, our assumptions about some inputs being equal for Blacks and Whites might be too optimistic for Black women (e.g., equal sensitivity of screening by race). Although the predicted incidence and stage distribution for Black women fit the observed data reasonably well, both models predict a slightly more favorable stage or tumor size distribution than observed for the period 2004 to 2006. This might indicate a somewhat reduced sensitivity of mammography screening for Black women, perhaps due to lower quality imaging or interpretation. In addition, the time interval between mammogram and follow-up might differ by race. For example, women who experienced a delay between the time of mammogram and diagnosis or last diagnostic test ruling out cancer were found to be more likely to be Black

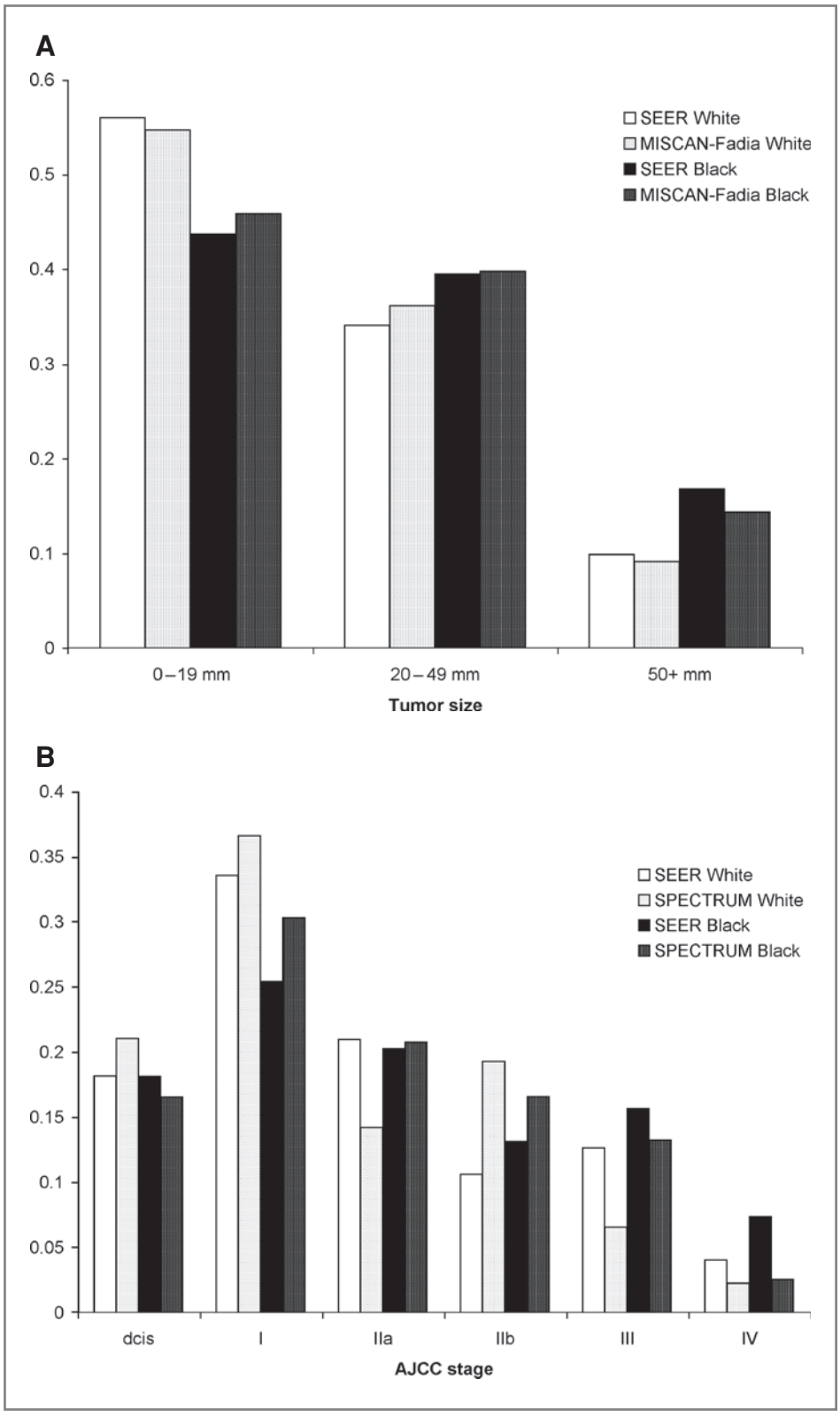

Figure 2. A, age-adjusted tumor size distribution of invasive breast cancers for White and Black U.S. women 25 years and older as observed and predicted by MISCAN-Fadia in 2004 to 2006. B, age-adjusted stage distribution for White and Black U.S. women 25 years and older as observed and predicted by SPECTRUM in 2004 to 2006.

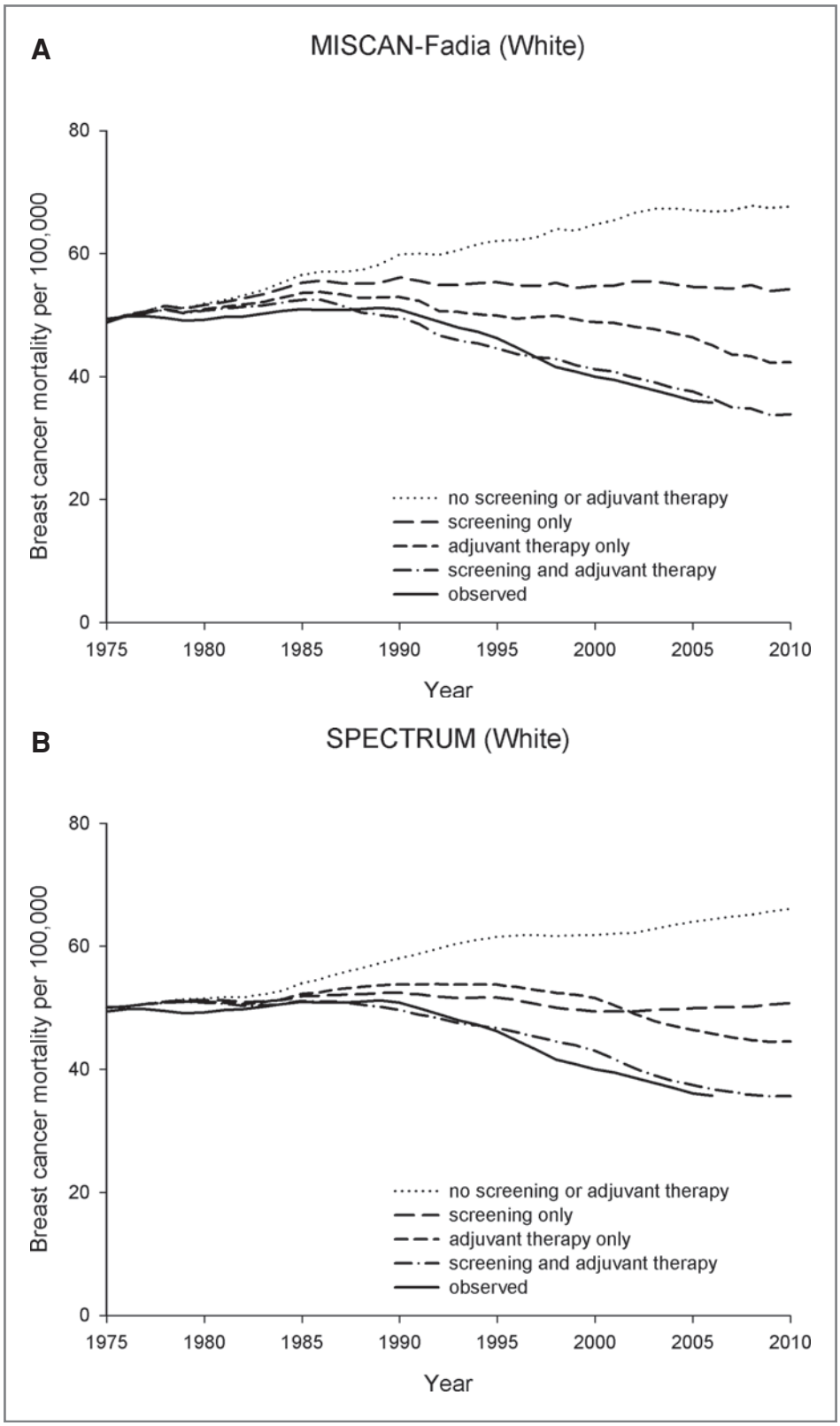

Figure 3. Age-adjusted breast cancer mortality rates (3-year moving averages) over time as observed and predicted in 4 scenarios for White women 25 years and older. A, MISCAN-Fadia; B, SPECTRUM.

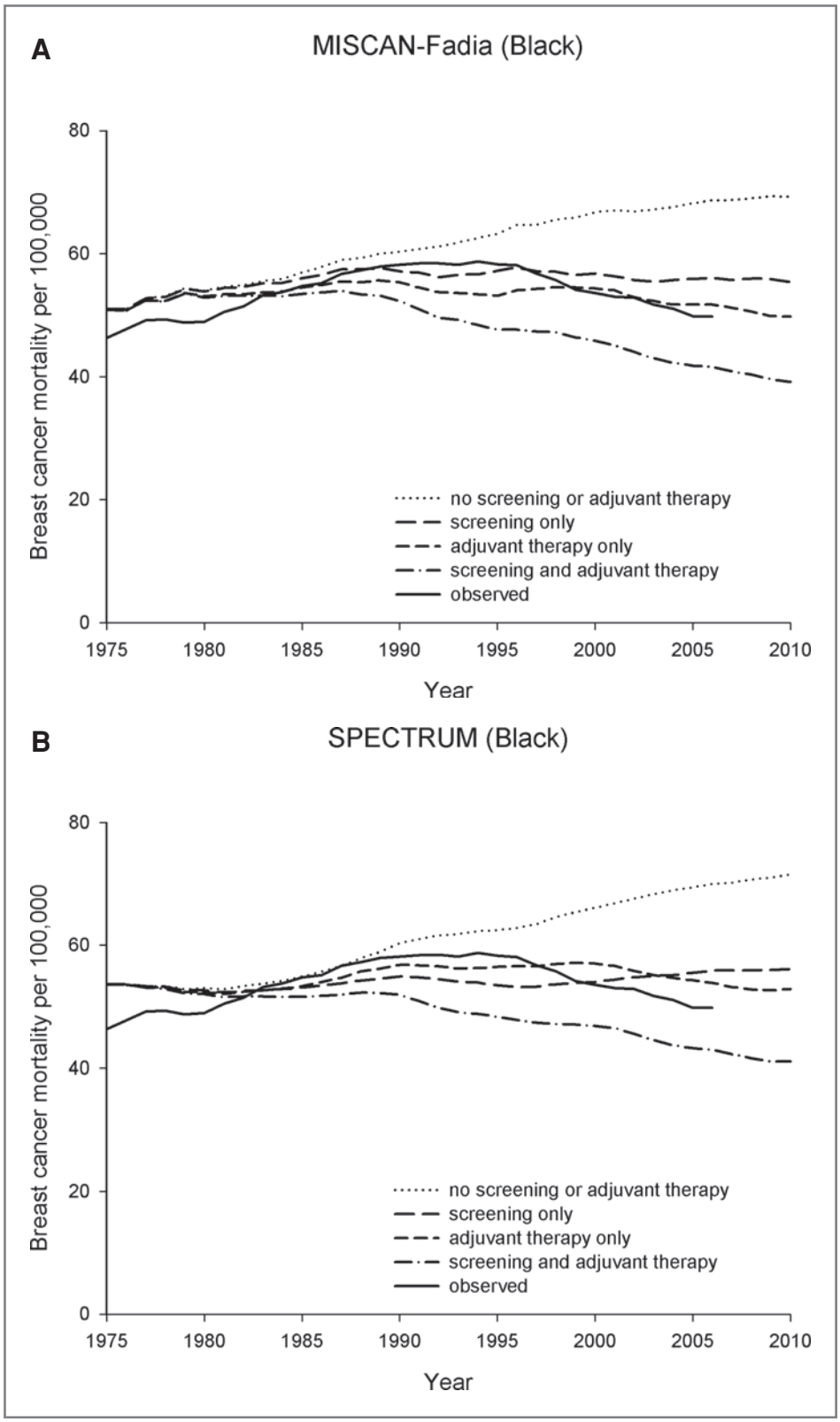

Figure 4. Age-adjusted breast cancer mortality rates (3-year moving averages) over time as observed and predicted in 4 scenarios for Black women 25 years and older. A, MISCAN-Fadia; B, SPECTRUM.

Table 1. Model predicted age-adjusted breast cancer mortality rates in 2004 to 2006 per 100,000 U.S. women 25 years and older

Scenarios	White				Black			
	MISCAN-Fadia		Spectrum		MISCAN-Fadia		Spectrum	
	Mortality rate per 100,000	Mortality reduction[a] %	Mortality rate per 100,000	Mortality reduction[a] %	Mortality rate per 100,000	Mortality reduction[a] %	Mortality rate per 100,000	Mortality reduction[a] %
No screening or adjuvant therapy	67.0	–	64.0	–	68.2	–	69.5	–
Screening only (as disseminated in the population)	54.6	18.6	49.9	22.0	55.9	18.1	55.5	20.1
Adjuvant therapy only (as disseminated in the population)	46.3	30.9	46.4	27.5	51.7	24.2	54.3	21.9
Screening and adjuvant therapy (as disseminated in the population)	37.5	44.0	37.4	41.4	41.9	38.6	43.2	37.8
Observed mortality rate	36.1				49.8			

[a]Mortality reductions (%) are calculated by comparing the predicted mortality to the background mortality in the scenario without screening and adjuvant therapy.

than White (odds ratio 1.45; 95% confidence interval = 1.13–1.85; ref 35).

Also, as observed in several randomized clinical trials, treatment efficacy was assumed to be equal for Blacks and Whites in our models (30). However, the higher prevalence of comorbidities for Black women might lead to dose reductions outside clinical trials, resulting in somewhat reduced treatment effectiveness in community practice. Also, Black women have been found to be less likely than White women to be treated at high-quality hospitals (36) and experience more delays between diagnosis and the beginning of treatment (37). In addition, Black women have been found to be more likely than White women to have no surgery (34), to discontinue treatment before completion of all courses (11% vs. 7%, respectively; $P = 0.07$; ref 38), and more likely to miss appointments (19% vs. 9%, respectively; $P = 0.0002$; ref 38). Those factors are not captured in our models, because high-quality data on the frequency of occurrence and effect on breast-cancer survival by race, age, stage, and calendar year were not available in this level of detail.

While we modeled racial differences in the distribution of known tumor prognostic markers (ER and HER2), an alternative explanation for our inability to explain the full mortality disparity is that Black women have experienced an increasing amount of aggressive tumor types over time based on less clearly defined prognostic markers. This might, for example, be related to racial differences in the prevalence of obesity in the United States, which have been increasing over the past 3 decades, with the most pronounced increases among Black women (39). Obesity affects breast cancer mortality rates in several ways (40). First, obesity may decrease treatment efficacy, because lower doses are delivered relative to what is recommended based on body surface area (41). In addition, obesity may influence breast cancer survival (42), mammography use (43), screening performance (44), and mammography follow-up [e.g., a higher frequency of obese women delayed return for mammography resolution compared with nonobese women (64.7% vs. 35.3%; ref 45)]. Including obesity directly in our models would help to partition the effect of race and obesity on the disparity in breast cancer mortality. More research on the race-specific types of tumor diagnosed over time will be critical to developing the knowledge base needed to refine the natural history components of our, and other, population surveillance models.

Both models indicate that both mammography screening and adjuvant treatment contributed substantially to the observed reduction in breast cancer mortality over the past several decades for both Black and White women. This result is consistent with conclusions from past modeling work for the overall U.S. female population (2). The predicted mortality reductions from the present study are somewhat larger than reported in past studies, probably due to greater penetration of screening in recent years and our inclusion of newer treatments (e.g., trastuzumab and aromatase inhibitors). Also, the percent mortality reductions depend somewhat on what age range is evaluated. For example, the percentages due to screening will be somewhat larger when a smaller age range excluding women unlikely to benefit from screening (25–40 year) is

Table 2. The effect of sequential replacement of parameters for Black women in the White model on the predicted breast cancer mortality rate for Black women 25 years and older for the period 2004 to 2006

	White value replaced with Black value (in bold)							
	Observed (White)	**None (White model)**	**Demography and incidence**	**Demography, incidence, and natural history**	**Demography, incidence, natural history, and screening**	**Demography, incidence, natural history, and treatment**	**All (Black model)**	**observed (Black)**
MISCAN-Fadia								
Mortality per 100,000	36.1	37.5	32.5	36.9	38.4	40.3	41.9	49.8
Difference, (obs–pred)			17.4	12.9	11.5	9.6	8.0	
% explained by replaced value[a]				26%	8%	19%	54%	
SPECTRUM								
Mortality per 100,000	36.1	37.4	32.2	40.1	41.3	42.0	43.2	49.8
Difference, (obs–pred)			17.6	9.8	8.5	7.8	6.6	
% explained by replaced value[a]				44%	7%	11%	62%	

[a]Calculated as the ratio of reduction of the difference between observed and predicted mortality rate and the *difference between observed and predicted mortality*, taken into account the lower incidence among Black women. So, in MISCAN-Fadia substituting Black natural history parameters into the White model explains 26% of the Black–White differences based on a reduction in the difference from 17.4 to 12.9 per 100,000, or 4.5 of the 17.4 per 100,000, that is, 26%.
obs, observed; pred, predicted.

evaluated. For Black women, the predicted percent mortality reductions were somewhat lower than that for White women, in particular the mortality reduction attributed to adjuvant treatment.

Our finding that treatment variations accounted for a greater amount of race variation in mortality than screening is consistent with previous research. For instance, an earlier modeling study showed that efforts to ensure that Black women receive the same treatment as White women was a more cost-effective approach to reducing their disproportionate mortality than investing in increased screening use (46). The finding that the effect of reduced screening use was relatively small (7–8%) is also consistent with previous work showing that the difference in screening rates between Black and White women is not very large (47). Previous work showed that differences in mammography use can explain 10–12% of excess late-stage breast cancer among Black women compared with White women (48–49).

The collaboration of 2 groups with different model assumptions and structure provides an excellent opportunity to cross-replicate modeling results, quantify uncertainty, and indicate which results are consistent across modeling approaches and therefore less dependent on unverifiable model assumptions. The resulting conclusions about race-specific differences in the impact of natural history, screening and adjuvant treatment on breast cancer mortality rates were similar across the 2 models and should provide greater credibility than inferences based on 1 model alone.

The most important limitation of the current study is the relative paucity of data on Black women, especially for the use of adjuvant treatment. Several studies that assessed the use of treatment by Black women in comprehensive cancer centers found no difference in treatment between races (50). However, data on treatment use in the population over time are sparse for Black women. In addition, the data that are available for Black women might suffer from selection bias, with Black women who participate in trials potentially not being representative of the overall Black population. In addition, although we used the best quality data available for Black and White women as input parameters for the models, this approach led to the use of several different data sources for different variables, with the potential problem of one (or more) of these data sources not being representative of the total Black (female) population. Next, while we portrayed known differences in biology by race and age (e.g., distribution of ER- and HER2-positive tumors), some aspects of the race-specific natural history of disease are not known and/or cannot be fully captured. Even with these acknowledged limitations, the 2 models demonstrate meaningful, qualitatively similar outcomes despite variations in structure and assumptions.

The findings of the current study have important policy implications. Our results indicate that breast cancer mortality may be reduced substantially by ensuring that Black women receive adjuvant treatment and mammography screening equal in quantity and quality to that which White women receive. However, a considerable portion

of the observed race differences in mortality remains unexplained. More research on racial variation in breast cancer biology, racial differences in actual treatment utilization, and responses to treatment is needed to refine optimal strategies for eliminating disparities and ensuring that all women benefit equally from medical advances and public health efforts to reduce the burden of breast cancer.

Disclosure of Potential Conflicts of Interest

Staff from NCI and BCSC provided some data and technical assistance. Model results are the sole responsibility of the authors. The funder did not have the right to pre-approve publication of the results.

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A list of the BCSC investigators and procedures for requesting BCSC data for research purposes are provided at: http://breastscreening.cancer.gov/.

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