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Variation in tumor natural history contributes to racial disparities in breast cancer stage at diagnosis

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Abstract

Background—Black women tend to be diagnosed with breast cancer at a more advanced stage than whites and subsequently experience elevated breast cancer mortality. We sought to determine whether there are racial differences in tumor natural history that contribute to these disparities.

Methods—We used the University of Wisconsin Breast Cancer Simulation Model, a validated member of the National Cancer Institute's Cancer Intervention and Surveillance Modeling Network, to evaluate the contribution of racial differences in tumor natural history to observed disparities in breast cancer incidence. We fit eight natural history parameters in race-specific models by calibrating to the observed race- and stage-specific 1975–2000 U.S. incidence rates, while accounting for known racial variation in population structure, underlying risk of breast cancer, screening mammography utilization, and mortality from other causes.

Results—The best fit models indicated that a number of natural history parameters must vary between blacks and whites to reproduce the observed stage-specific incidence patterns. The mean of the tumor growth rate parameter was 63.6% higher for blacks than whites (0.18, SE 0.04 vs. 0.11, SE 0.02). The fraction of tumors considered highly aggressive based on their tendency to metastasize at a small size was 2.2 times greater among blacks than whites (0.41, SE 0.009 vs. 0.019, SE 0.008).

Conclusion—Based on our simulation model, breast tumors in blacks grow faster and are more likely to metastasize earlier than tumors in whites. These differences suggest that targeted prevention and detection strategies that go beyond equalizing access to mammography may be needed to eliminate breast cancer disparities.

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Keywords

Breast Cancer Natural History; black women; white women; Simulation Model; Racial Disparities

Introduction

Disparities in breast cancer incidence and mortality between black and white women in the U.S. have long been a public health concern. Compared to whites, blacks have had higher breast cancer mortality rates despite lower incidence rates for almost thirty years [1,2]. The disparity in mortality continues to grow; in 2008, the breast cancer mortality rate for blacks was 40% higher than that for whites (31 vs. 22 per 100,000 women, respectively) [3].

The mortality disparity appears to stem primarily from the tendency for breast cancer in black women to be diagnosed at a more advanced stage (Fig. 1) and have more aggressive features [2,4–15]. These differences could potentially be due to racial variation in the natural history of the disease (e.g., growth rates), screening mammography utilization, and/or screening performance. Historically, blacks have trailed behind whites in utilization of screening mammography [16,17,12]. However, a number of studies have demonstrated that screening utilization has been comparable over the past fifteen years [2,18], and yet the difference in stage at diagnosis persists [2,8,4,6,7,9,12,15,14]. The sensitivity of screening mammography does not appear to be worse in blacks than among whites [19]. Additionally, several studies have observed that blacks are diagnosed with breast cancer at a later stage and are more likely to have tumors with poorer prognosis than whites independent of health care access or mammography [20]. These findings suggest that variation in the tumor natural history may be driving racial disparities in breast cancer outcomes [13,21–23].

The objective of this study was to evaluate whether racial differences in the natural history of breast cancer could explain the observed stage-specific incidence patterns among black and white women in the United States. We used the University of Wisconsin Breast Cancer Simulation Model (UWBCS) [24], a validated simulation model of the epidemiology of breast cancer, which was previously developed for the National Cancer Institute's Cancer Intervention and Surveillance Modeling Network (CISNET). The detailed natural history component of the UWBCS allows an evaluation of the role of racial variation of tumor growth and aggressiveness in breast cancer disparities within a framework that also considers racial variation in screening utilization and other important factors.

Methods

Overview

We modified the original UWBCS [24] to create race-specific models for blacks and whites. The original model structure was retained in each case, but race-specific inputs were developed for key components such as mammography utilization. The best fit natural history parameters were estimated separately for blacks and whites by calibrating to the observed 1975–2000 race-specific incidence data from the Surveillance, Epidemiology and End Results (SEER) Program of the National Cancer Institute.

UWBCS Model Overview

The UWBCS is a discrete-event, stochastic simulation model of breast cancer epidemiology in the U.S. female population and has previously been described in detail [24]. The model was designed to match age- and stage-specific breast cancer incidence rates and age-specific mortality rates in the U.S. female population between 1975 and 2000. It has been used to address a variety of questions including those related to the natural history of breast cancer

in the U.S. female population [24], the relative contributions of breast cancer screening and treatment improvements to the reduction in breast cancer mortality observed in the 1990's [25], the cost-effectiveness of different modes of screening mammography [26,27], and the comparative effectiveness of different screening strategies [21].

The original UWBCS model is not race-specific and is populated by about 3 million women, divided into birth cohorts to mimic the adult female population of the U.S. between 1975 and 2000. Individual women in the simulation experience four interacting stochastic processes which are modeled over time: the natural history of breast cancer from occult onset to breast cancer death or cure, breast cancer detection by screening mammography or clinical detection, the dissemination and effectiveness of breast cancer treatments over time, and death from non–breast cancer causes.

Breast cancer is modeled as a progressive disease. The natural history component of the UWBCS model assumes that invasive breast cancer originates from the progression of carcinoma in situ. Since the biologic onset of tumors is unobservable at first, its rate in the model is approximated using breast cancer incidence in the absence of screening at a later time point by utilizing an age-period-cohort (APC) model developed by Holford [28]. Over time, tumors progress in size and spread probabilistically to lymph nodes. Tumors grow according to a Gompertz-type function with a growth rate that follows a gamma distribution [29]. At the time of diagnosis, tumors are classified according to SEER historical stages (in situ, local, regional, or distant extent of disease). The heterogeneity in tumors in the population is approximated with four types of tumors: tumors with limited malignant potential (LMP), regular tumors, aggressive and highly aggressive tumors. Tumors with LMP are tumors in in situ or early localized stages of breast cancer that will never pose a lethal threat to the host women. Aggressive and highly aggressive tumors are tumors classified as regional or distant at a very small size of the focal primary tumor (particularly, at onset in the model). Depending on the effectiveness of treatments received in the model, uncontrolled growth and spread of invasive breast tumor may lead to death from breast cancer.

A statistical model described elsewhere [30,31] is used to describe mammography use and dissemination over time for 5-year birth cohorts of U.S. women. Screening initiation is assigned on the basis of birth year, and screening frequency (annual, biennial, or irregular) varies by birth year and age. Tumors can be detected by screening mammography or other means, and detection probabilities depend on the tumor size. Detected breast cancers are treated according to the year-specific prevalent clinical practice for a tumor in the given stage in a woman of a given age group [32]. Treatment effectiveness depends on the tumor stage at diagnosis and improves over time according to historical improvements.

The model parameters of the original model were calibrated to breast cancer incidence rates as reported by the SEER Program of the National Cancer Institute, hence the model results apply to the U.S. population.

Race-Specific Modifications of Model's Fixed Input Parameters

We modified four fixed inputs of the original UWBCS model to make them race-specific: the population age-structure, mortality from non-breast cancer causes, breast cancer incidence in the absence of screening, and mammography dissemination over time.

The race-specific population age-structure was estimated from Census data [33]. We estimated the cohort-specific mortality from non-breast cancer causes for each race using death rates reported in Berkeley Mortality Database for years 1968–1992 and the National

Center for Health Statistics (Centers for Disease Control and Prevention) for years 1900–1967 and 1993–2000 [34,35].

To estimate the background incidence of breast cancer in the absence of screening between 1975 and 2000 for white and black women separately, we adjusted the age-period-cohort model by Holford [28] for each race by utilizing SEER-reported race-, sex- and age-specific breast cancer incidence rates for years 1973 to 1981 when use of screening mammography was negligible [36]. We assumed that the age-specific ratio of breast cancer incidence in black versus white women would have remained constant between 1982 and 2000 if screening mammography had not been introduced.

As described in Cronin et al. (2009) [37], we used race-specific screening data from the Breast Cancer Surveillance Consortium (BCSC) regarding age at screening initiation and screening patterns to generate our race-specific mammography dissemination parameters.

Model Calibration and Race-Specific Input Parameters Fitted During Calibration

Eight parameters of the original UWBCS model which govern the tumor natural history properties were modified to allow race-specific values. These included:

1. *LMP Fraction*: The proportion of tumors with limited malignant potential.
2. *LMP Dwell Time*: The maximum sojourn time for LMP tumors, in years; after this time an undiagnosed tumor with limited malignant potential is no longer detectable by screening.
3. *Onset Proportion*: The ratio of age-specific biologic onset rate of tumors to age-specific incidence rate in the absence of screening. This parameter is used to estimate the unobservable biologic onset rates of tumors necessary to produce the observed incidence rates in the following years as dictated by the age-period-cohort (APC) model described elsewhere [28].
4. *APC Lag*: The number of years between biologic onset of tumors and their clinical surfacing in the absence of screening produced by the APC model [28]. This is a model-specific parameter used to represent the time between a tumor's biologic onset in the UWBCS and its possible discovery via self or clinical detection at a later time point in the APC model.
5. *Mean Growth*: The mean of the gamma distribution used in the Gompertz-type function that models tumor growth rate [29].
6. *Variance Growth:* The variance of the gamma distribution that is used in the Gompertz-type function that models tumor growth rate.
7. *Percent Aggressive*: The fraction of tumors classified as regional at a very small size of the focal primary tumor, that is, 2 mm in diameter. This parameter represents aggressive tumors that advance to regional cancer stage quickly and is included to avoid depleting the reservoir of tumors to be discovered at the regional stage under all reasonable screening regimens [24].
8. *Percent Highly aggressive*: analogous to the *Percent Aggressive* parameter, this represents the fraction of tumors classified as distant stage at a very small size of the focal primary tumor (2 mm in diameter).

For model calibration, we determined biologically plausible ranges for each natural history input parameter, partitioned those ranges (Table 1), and ran the model for all possible parameter combinations which totaled to 378,000 simulations for each race. We then determined the combinations of parameters for which the stage-specific age-adjusted

incidence rates among women over 20 years of age matched the U.S. observed rates as reported by SEER most closely.

Like in the original UWBCS model, to enforce the general trend in the incidence curves, we determined envelopes around the U.S. observed age-adjusted incidence rates of breast cancer for each of the four breast cancer stages in 1975–2000 [24]. We then evaluated the fit of the age-adjusted incidence rate curves produced by the model relative to the envelopes. A score between 0 and 104 was assigned to each curve based on the number of points it fell outside of the envelopes for all four stages of breast cancer in 1975–2000. The score of 0 implied that the produced incidence curves never fell outside of the envelopes; the score of 104 meant that they were completely outside of the envelopes, that is, in each year between 1975 and 2000 for all four breast cancer stages. As in the original UWBCS model calibration procedure [24], we considered the input vector to be acceptable if the incidence curves score of its output did not exceed 10; such input vectors we ranked for further analysis. The ranking was based on the probability of the age-specific breast cancer incidence in the corresponding output to match the observed incidence as reported in SEER for each year and stage of breast cancer; the higher the probability, the higher the rank. To calculate this probability, we assumed that the age- and stage-specific breast cancer incidence in each given year followed a Poisson distribution with parameter equal to the expected breast cancer incidence given the model. For each race, the set of input vectors within the top 100 ranks and an envelope score no greater than 10 formed a joint posterior distribution of acceptable model parameters.

Results

We found 69 acceptable natural history parameter vectors for black and 48 for white women. The mean stage-specific incidence curves produced by these acceptable parameter values are shown in Fig. 2 for each race. Both race-specific models demonstrated excellent matching to the observed stage-specific U.S incidence based on SEER data.

The posterior distributions of acceptable model input parameters are shown in Fig. 3 and their summary statistics (mean and standard error) are displayed in Table 2. *LMP Fraction*, *LMP Dwell Time* and *Onset Proportion* were similar for white and black women, although posterior uncertainty was greater for blacks. *APC Lag* was longer for blacks (2.65, SE 0.76) than whites (1.42, SE 0.82).

A number of aspects of tumor aggressiveness differed among blacks and whites. Compared to tumors among whites, tumors among blacks tended to grow at a faster rate (*Mean Growth*), had higher variation in their growth rates (*Variance Growth*), and were more likely to have spread to regional (*Percent Aggressive*) and distant (*Percent Highly aggressive*) sites while still at a small tumor size. The mean of the posterior distribution of the parameter governing tumor growth rate, *Mean Growth,* was 63.6% higher for blacks than whites (0.18, SE 0.04 vs. 0.11, SE 0.02, respectively), and the mean of the posterior distribution of the other tumor growth parameter, *Variance Growth,* was almost five-fold higher for blacks than whites (0.051, SE 0.024 vs. 0.009, SE 0.008). The fraction of tumors considered aggressive and highly aggressive based on their tendency to metastasize at a small size, *Percent Aggressive* and *Percent Highly aggressive*, was 33% and 2.2 times greater for black (0.032, SE 0.015 and 0.041, SE 0.009, respectively) than for white women (0.024, SE 0.017 and 0.019, SE 0.008, respectively).

However, since the differences between the separate posterior distributions from the two race models may reflect differences in the associated sampling distributions rather than substantive differences between the models, we also examined the posterior distributions for

the differences in parameters between the two race models. To this end, for each parameter from each race model, we generated random samples of size 1000 from the corresponding posterior distributions and calculated pairwise differences between the two samples, whites minus blacks. The posterior distribution for the difference in parameters between the race models are shown in Fig. 4; their means and 95% credible intervals (CI) are presented in Table 2. The 95% credible intervals were formed by the 2.5^{th} and 97.5^{th} percentiles of these posterior distributions [38].

The 95 % credible intervals for the mean differences between the posterior distributions for Mean Growth (Mean = −0.07, 95% CI −0.10, 0.00), Variance Growth (Mean = −0.041, 95% CI −0.064, 0.000), and Percent Highly Aggressive (Mean = −0.022, 95% CI −0.040, 0.000) support lower values of the parameter for whites than for blacks. The other credible intervals support no difference between the parameters for whites and blacks.

Discussion

We used a previously validated discrete-event stochastic simulation model of breast cancer epidemiology to evaluate differences in the natural history of breast cancer between black and white women. Model parameters were estimated for the two racial/ancestry groups while accounting for known differences in mammography utilization, and the resulting "best" models closely resembled the observed breast cancer rates as published by the SEER Program [36]. The best fit parameter estimates of our model indicated that the parameter governing tumor growth rates for blacks was almost two-fold higher than for whites, and a higher fraction of tumors in blacks had spread to a regional or distant stage at a very small size (one-third and over two-fold, respectively). The posterior distribution for the difference in parameters between the two race models also supported higher tumor growth rates in blacks and higher percent of highly aggressive tumors in blacks than in whites. This implies that, based on the model, tumors in blacks grow faster and tend to spread to advanced stages of breast cancer at a smaller size of the focal primary tumor compared to cancers among whites. These differences in natural history by race appear to drive the tendency for a more advanced stage distribution among black women.

One important consequence of these results is that with any given interval between two subsequent mammograms, our model suggests that breast cancer in blacks tends to progress to a more advanced stage than in whites. Thus, even with the same rate of adherence to breast cancer screening guidelines, we would expect a more advanced stage at diagnosis in black women. These findings are consistent with observational studies noting that blacks are diagnosed with breast cancer at a more advanced stage and are more likely to present with tumors of a more aggressive phenotype than whites [11,6–8,12,39], even with similar access to screening mammography [2,9,10]. Late stage at diagnosis is associated with poorer prognosis, and consequently higher breast cancer mortality in black women. Recently a group of investigators used two different simulation models to examine the potential impact of variation in natural history, mammography utilization, and adjuvant treatment on race-specific trends in breast cancer mortality [40]. They concluded that the majority of the disparities in breast cancer mortality between black and white women in the U.S. is attributable to differences in the natural history of the disease, while the differences in breast cancer screening and adjuvant treatment are weaker contributors [40]. Combined with our results regarding disparities in stage at diagnosis, these modeling studies provide consistent evidence that variation in tumor natural history by race is needed to explain the observed race-specific trends in both incidence and mortality.

Variation in tumor natural history could be due to differences in risk factor distributions by race, which in turn influence tumor biology. Blacks are more likely than whites to be

diagnosed with hormone receptor negative breast cancers [2,4,6,7,9–11,15,41] which have limited adjuvant treatment options. This variation in tumor subtypes could be due to differences in genetic predisposition or differences in the prevalence of risk factors such as postmenopausal hormone therapy, reproductive factors, or body mass index which may have differential influence on risk of tumor subtypes [42,9,43,11,13,44,45]. Specifically, the rapid increase in obesity rates observed in the U.S. over the period of time considered in the study disproportionately affected black women [46]. Obesity has shown to affect mammography utilization and effectiveness [47,48], which, in turn, may lead to more advanced stage at diagnosis and worse outcomes. However, the direct effect of obesity on the natural history of breast cancer remains unclear. In particular, while the version of the model used for this study did not account for individual risk factors, we are currently working on extending the model to account for individual risk factors including body mass index, breast density, postmenopausal hormone use, and family history of breast cancer. It is also possible that differences in tumor biology between black and white breast cancers are mostly or even completely due to different tumor subtype distributions [45]. In particular, a recent international study concluded that among women in West Africa, the founder population of most African-Americans, the proportion of tumors associated with poorer prognosis is much higher; specifically, hormone receptor-negative breast tumors were found to be predominant and the majority of breast tumors triple-negative [45]. The authors also noted that breast cancer subtypes are determined by both environmental exposures and genetic background. More research is needed to better understand differences in the tumor subtype distribution according to race and ethnicity, whether tumor subtypes are inherently different with respect to biology and tumor aggressiveness, and whether there are residual differences in tumor biology within a given tumor subtype according to race/ethnicity.

Differences in breast cancer treatment by race may also contribute to the observed disparities in breast cancer mortality between black and white women. Though some studies reported similar breast cancer treatment utilization for black and white women [49], others noted the existence of race-specific differences. In particular, black women were reported to receive suboptimal treatment for breast cancer, largely due to differential access to care [7] and being less likely to be treated at high-quality hospitals [50]. Blacks were more likely than whites to receive no surgery [51], less likely to receive appropriate surgery [6] and follow-up radiation therapy after undergoing breast conserving surgery [52,53], experienced greater delays between breast cancer diagnosis and treatment initiation [17,54,55], were about twice as likely to experience underuse of appropriate adjuvant therapy [56], and were more likely to terminate treatment prematurely and miss appointments [57,58]. Furthermore, obesity which is more prevalent in black women compared to white [46] may also decrease treatment efficacy [59]. Due to higher prevalence of obesity and other comorbidities, black breast cancer patients may receive lower adjuvant chemotherapy dose proportion and dose intensity [60,61]. However, we did not incorporate these factors into our model, largely due to the absence of appropriate high-quality data. A recent study using two other CISNET breast cancer simulation models who examined treatment-related parameters by race was not able to match breast cancer mortality, particularly in blacks, and concluded that the differences in mortality by race remained largely unexplained (38–46%) [40]. More research is needed that explores differences in breast cancer treatment by race as a contributor to disparities in breast cancer mortality.

The limitations of our study are driven by the modeling assumptions and accuracy of the data inputs and model calibration targets. Consequently, our study has the same limitations due to model assumptions as the non-race-specific UWBCS model [24]. The required inputs to the model had to be estimated from the available data, which often required manipulation to conform to the desired format (e.g., five- or ten-year aggregated or single-year data). The model inputs also relied on race-specific data over many years, and the precision of these

data for blacks was less robust than for whites due to smaller sample sizes, changes in methods for collecting race-specific data over time, and variation in how individuals report their race. Self-reported race information reflects race as a complex social construct rather than as an objective assessment of genetic predisposition such as could be provided by ancestral informative markers (AIM). One recent study suggested that self-reported race more than percent African ancestry as measured by AIMs is related to breast cancer tumor characteristics such as estrogen receptor status, stage at diagnosis and grade [62]. Social factors that, combined with inherited risk, influence whether women report their race as "white" or "black" are difficult to quantify. However, since we used the largest and highest quality data sources available, including SEER and the Breast Cancer Screening Consortium, we believe our race-specific data inputs were the best possible estimates.

Our sampling approach was constrained by the computational intensity of the project. Approximately 5 minutes were required to perform a single model run for a given parameter combination on a stand-alone computer. While we were unable to fully explore the parameter space in gaps between the constant step sizes and may have not adequately covered the parameter space for three parameters for blacks, namely, percent highly aggressive tumors, mean growth, and LMP dwell time, we used high throughput computing resources to sample over 378,000 input parameter combinations within the biologically plausible parameter space for each race. This detailed sampling provides a low likelihood that more optimal parameter value combinations were missed.

In conclusion, we used a simulation model to characterize potential differences in the natural history of breast cancer between black and white women in the United States that contribute to the observed disparities in breast cancer mortality. Our findings indicate that, on average, breast tumors in black women grow faster and are more often highly aggressive than those in whites. These factors drive the more advanced stage at diagnosis in black compared with white women which, in turn, is associated with higher breast cancer mortality. These results suggest that targeted breast cancer prevention and screening strategies that are sensitive to differences in tumor natural history may be needed to eliminate racial disparities in breast cancer outcomes in the United States.

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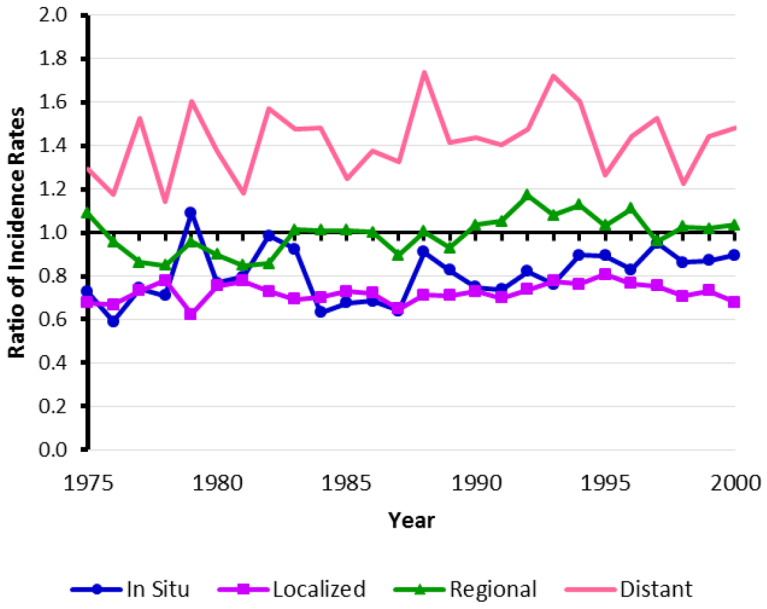

Fig. 1.

Ratio of U.S. observed age-adjusted incidence rates for blacks versus whites for each breast cancer stage. U.S. observed stage-specific incidence rates for women over 20 years of age were obtained from SEER and age-adjusted to the U.S. standard population in the year 2000.

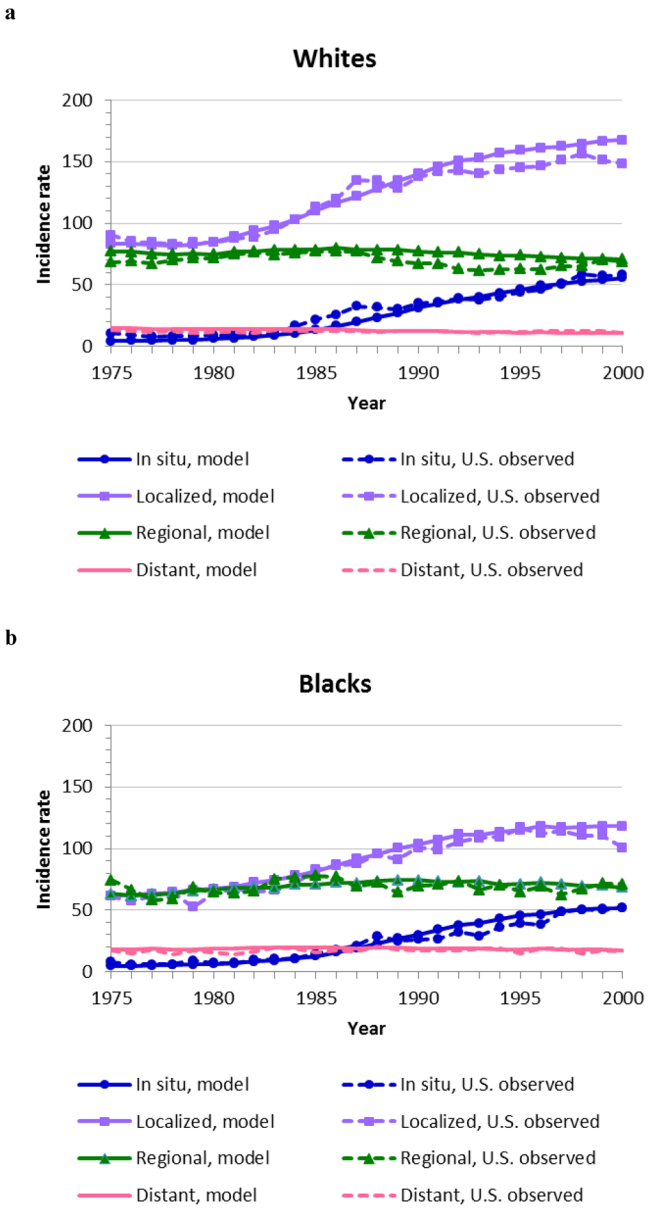

Fig. 2.

Model fit for the average of the joint posterior distribution of acceptable model input parameters: **(a)** for white women (W), **(b)** for black women (B). **Incidence rates** are given per 100,000 women over 20 years of age and age-adjusted to the U.S. standard population in the year 2000.

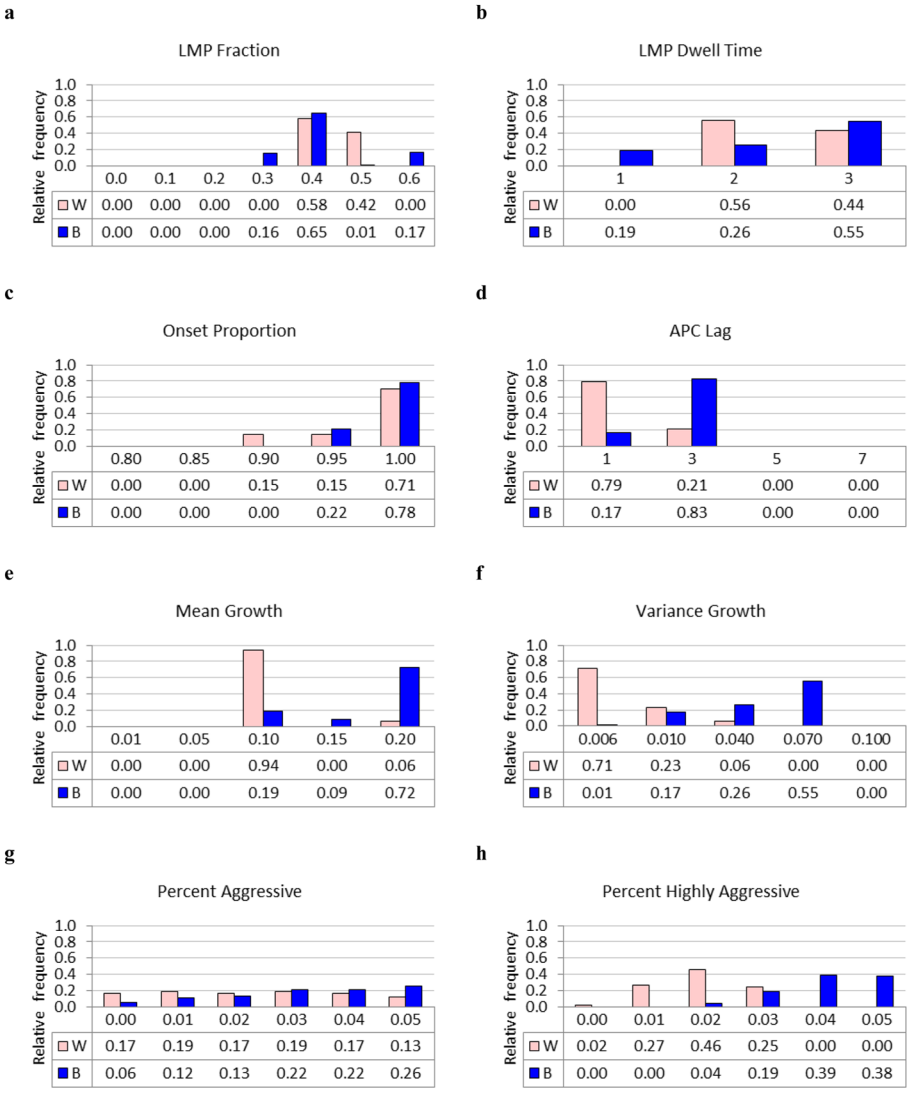

Fig. 3.

Joint posterior distribution of acceptable model parameters for black and white women. (**a**) *LMP Fraction*; (**b**) *LMP Dwell Time*; (**c**) *Onset Proportion*; (**d**) *APC Lag*; (**e**) *Mean Growth*; (**f**) *Variance Growth*; (**g**) *Percent Aggressive*; (**h**) *Percent Highly aggressive*. **Horizontal axes** represent parameter values.

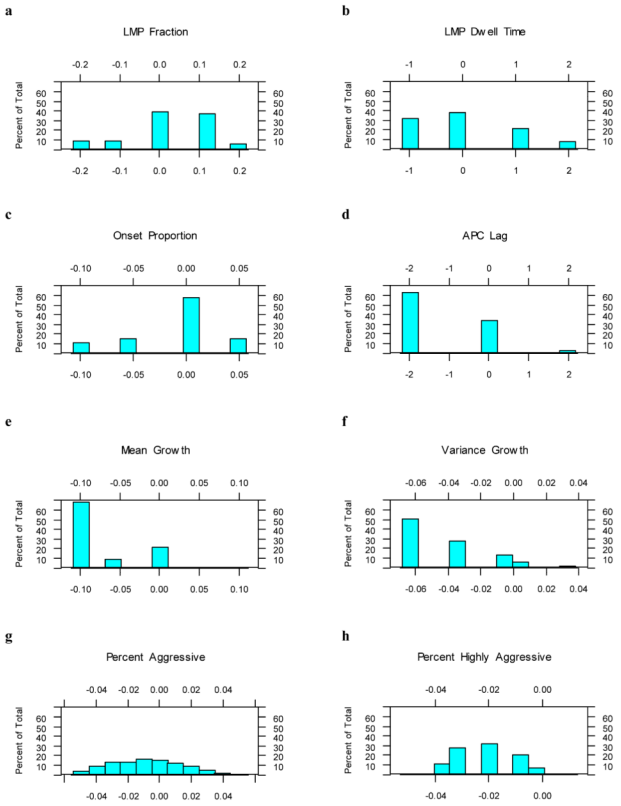

Fig. 4.

Histogram (percent of total) of the posterior distribution for the differences in parameters between the two race models (whites – blacks). (**a**) *LMP Fraction*; (**b**) *LMP Dwell Time*; (**c**) *Onset Proportion*; (**d**) *APC Lag*; (**e**) *Mean Growth*; (**f**) *Variance Growth*; (**g**) *Percent Aggressive*; (**h**) *Percent Highly aggressive*. **Horizontal axes** represent the difference in parameter values, whites minus blacks.

Table 1

Breast Cancer Natural History Input Parameters Used in UWBCS Model Calibration [24]

Parameter Name	Best fit in the original combined race UWBCS model	Sampled Parameter Values
LMP Fraction	0.42	0.00, 0.10, 0.20, 0.30, 0.40, 0.50, 0.60
LMP Dwell Time	2	1, 2, 3
Onset Proportion	0.90	0.80, 0.85, 0.90, 0.95, 1.00
APC Lag	3	1, 3, 5, 7
Mean Growth	0.12	0.01, 0.05, 0.10, 0.15, 0.20
Variance Growth	0.012	0.006, 0.010, 0.040, 0.070, 0.100
Percent Aggressive	0.01	0.00, 0.01, 0.02, 0.03, 0.04, 0.05
Percent Highly Aggressive	0.02	0.00, 0.01, 0.02, 0.03, 0.04, 0.05

Abbreviations: UWBCS, University of Wisconsin Breast Cancer Simulation; LMP, limited malignant potential; APC, Age-Period-Cohort

Table 2

Summary Statistics for Calibrated Input Parameters

Parameter	Whites		Blacks		Posterior Distribution of the Difference, (Whites-Blacks)*	
	Mean	SE	Mean	SE	Mean	95% Credible Interval
LMP Fraction	0.44	0.05	0.42	0.09	0.02	[−0.20, 0.20]
LMP Dwell Time	2.44	0.50	2.36	0.79	0.05	[−1.00, 2.00]
Onset Proportion	0.98	0.04	0.99	0.02	−0.01	[−0.10, 0.05]
APC Lag	1.42	0.82	2.65	0.76	−1.21	[−2.00, 2.00]
Mean Growth	0.11	0.02	0.18	0.04	−0.07	[−0.10, 0.00]
Variance Growth	0.009	0.008	0.051	0.024	−0.041	[−0.064, 0.000]
Percent Aggressive	0.024	0.017	0.032	0.015	−0.008	[−0.050, 0.030]
Percent Highly Aggressive	0.019	0.008	0.041	0.009	−0.022	[−0.040, 0.000]

*Based on the random sample (N=1,000) from the posterior distribution of the difference in the parameters, Whites – Blacks.

Abbreviations: LMP, limited malignant potential; APC, Age-Period-Cohort; SE, standard error