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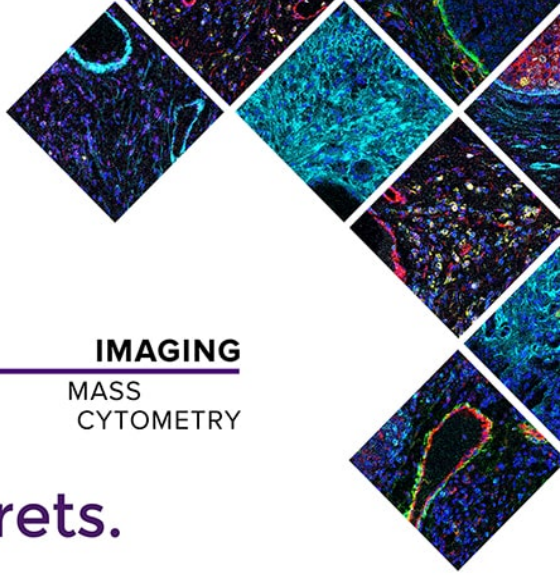

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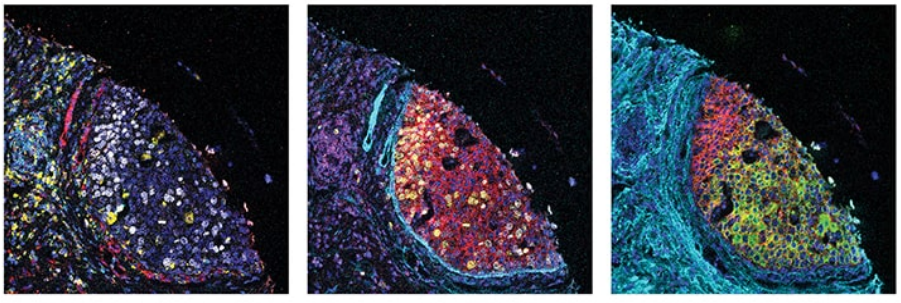

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Original Article

Performance of the IBIS/Tyrer-Cuzick Model of Breast Cancer Risk by Race and Ethnicity in the Women's Health Initiative

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BACKGROUND: The IBIS/Tyrer-Cuzick model is used clinically to guide breast cancer screening and prevention, but was developed primarily in non-Hispanic White women. Little is known about its long-term performance in a racially/ethnically diverse population. **METHODS:** The Women's Health Initiative study enrolled postmenopausal women from 1993-1998. Women were included who were aged <80 years at enrollment with no prior breast cancer or mastectomy and with data required for IBIS/Tyrer-Cuzick calculation (weight; height; ages at menarche, first birth, and menopause; menopausal hormone therapy use; and family history of breast or ovarian cancer). Calibration was assessed by the ratio of observed breast cancer cases to the number expected by the IBIS/Tyrer-Cuzick model (O/E; calculated as the sum of cumulative hazards). Differential discrimination was tested for by self-reported race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, Asian or Pacific Islander, and American Indian or Alaskan Native) using Cox regression. Exploratory analyses, including simulation of a protective single-nucleotide polymorphism (SNP), rs140068132 at 6q25, were performed. **RESULTS:** During follow-up (median 18.9 years, maximum 23.4 years), 6783 breast cancer cases occurred among 90,967 women. IBIS/Tyrer-Cuzick was well calibrated overall (O/E ratio = 0.95; 95% CI, 0.93-0.97) and in most racial/ethnic groups, but overestimated risk for Hispanic women (O/E ratio = 0.75; 95% CI, 0.62-0.90). Discrimination did not differ by race/ethnicity. Exploratory simulation of the protective SNP suggested improved IBIS/Tyrer-Cuzick calibration for Hispanic women (O/E ratio = 0.80; 95% CI, 0.66-0.96). **CONCLUSIONS:** The IBIS/Tyrer-Cuzick model is well calibrated for several racial/ethnic groups over 2 decades of follow-up. Studies that incorporate genetic and other risk factors, particularly among Hispanic women, are essential to improve breast cancer–risk prediction. ***Cancer*** **2021;0:1-9**.
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KEYWORDS: breast cancer, breast cancer risk, IBIS/Tyrer-Cuzick, model performance, race/ethnicity.

INTRODUCTION

Models that predict the risk of developing cancer are relevant for health policy and clinical decision-making. For breast cancer, guidelines for supplemental screening with magnetic resonance imaging and risk-reducing medications such as tamoxifen and aromatase inhibitors depend on risk estimates.[1,2] Widely used breast cancer–prediction models include the breast cancer risk-assessment tool (BCRAT or Gail model) and the BRCAPRO, BOADICEA/CanRisk, and IBIS/Tyrer-Cuzick models.[3-10] Of these, the IBIS/Tyrer-Cuzick and BOADICEA/CanRisk models have shown the best calibration and discrimination.[3,11-13] However, most prior studies of model performance had limited follow-up time or focused on women selected for family cancer history. Furthermore, all of these models were developed using data primarily from non-Hispanic White women.

It is increasingly recognized that race and ethnicity are imperfect proxies for social determinants of health.[14,15] However, breast cancer incidence and the distribution of breast cancer–risk factors vary between racial and ethnic groups within the United States (US),[16] and it is important to understand whether models that integrate this information to guide clinical decisions work well for everyone.

We evaluated the performance of the IBIS/Tyrer-Cuzick model among more than 90,000 women prospectively enrolled in the Women's Health Initiative (WHI) and followed for the development of breast cancer and other

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Additional supporting information may be found in the online version of this article.

DOI: 10.1002/cncr.33767, **Received:** May 5, 2021; **Revised:** May 28, 2021; **Accepted:** June 5, 2021, **Published online** Month 00, 2021 in Wiley Online Library (wileyonlinelibrary.com)

outcomes for 2 decades. We selected the IBIS/Tyrer-Cuzick model because its use is advised to inform breast cancer screening and prevention by multiple guideline organizations, including the National Comprehensive Cancer Network, the American Society of Clinical Oncology, and the American Cancer Society.[1,2,17,18] Although version 8 of the IBIS/Tyrer-Cuzick model, which incorporates mammographic density, is available for clinical use, we used the readily available version 7 that performs with similar accuracy because mammographic density data were not collected and available from WHI. We tested the hypothesis that IBIS/Tyrer-Cuzick would predict the risk of breast cancer among WHI participants and that the association between IBIS/Tyrer-Cuzick estimates and observed breast cancer development would not vary by race or ethnicity.

MATERIALS AND METHODS

The Women's Health Initiative

The WHI is a prospective study of morbidity and mortality among postmenopausal women who were randomized into 1 or more of 3 clinical trials or enrolled into an observational study. Details of WHI design, conduct, and follow-up have been published previously.[19-21] At enrollment, WHI participants were aged 49 to 81 years, were postmenopausal, and had an estimated life expectancy of at least 3 years. Participants were enrolled throughout the US from September 1993 through December 1998.

The analytic cohort for this study included women in the observational studies and clinical trials who had no prior history of breast cancer or mastectomy and had data available for the IBIS/Tyrer-Cuzick calculation. Women were excluded from analysis if they did not self-report race at baseline (which did not specifically ask about ethnicity but included non-Hispanic (NH) White or NH Black), were older than 80 years at enrollment, lacked follow-up data, or had an incident diagnosis of in situ without invasive breast cancer. Further details are provided in Supporting Figure 1.

Exposure Variables

Race, ethnicity, age, and risk factors used in the IBIS/Tyrer-Cuzick model (ages at menarche, first birth, and menopause; use of menopausal hormone therapy; and first- and second-degree–family cancer history) were collected prospectively from baseline questionnaires completed at WHI enrollment.[19-21] Height and weight to determine body mass index (BMI) were measured by clinic staff. An additional variable indicating country of origin (US-born vs foreign-born) was available for approximately half (47,221 of 90,967) of all participants.

Outcomes

For medical outcomes including breast cancer, WHI clinical trial participants were queried twice per year through 2005 and annually thereafter; observational study participants were queried annually. Breast cancer reports were verified by medical record and pathology report review by centrally trained physician adjudicators at the clinical centers, with final adjudication and staging per Surveillance Epidemiology and End Results program criteria at the WHI clinical coordinating center.[19-21]

The primary outcome was time from WHI enrollment to diagnosis of invasive breast cancer or censoring. Women were censored at the earliest of the following events: death, 85 years of age (the maximum age at which the IBIS/Tyrer-Cuzick model predicts breast cancer risk), or the end of calendar-time follow-up.

Risk Calculation

Version 7.0.2 of the IBIS/Tyrer-Cuzick model[4] was used to obtain estimates of remaining lifetime breast cancer risk. Age variables that were collected as categorical (ages of menarche, menopause, first birth, and breast cancer in relatives) were converted to single years for input into the IBIS/Tyrer-Cuzick model by taking the midpoint or using the rules described in Supporting Table 1. We used the model's default settings to specify baseline breast cancer–incidence rates from the United Kingdom's (UK's) Thames Cancer Registry and unknown results from genetic testing. No adjustments were made for competing mortalities.

Statistical Analysis

Analyses were conducted using R version 4.0.2 or higher.[22] *P* values were based on likelihood-ratio χ^2 test statistics unless otherwise noted. All *P* values are reported as 2-sided.

Model Calibration

We evaluated the IBIS/Tyrer-Cuzick model's calibration in terms of observed to expected (O/E) ratios. The observed number in these ratios was the total number of invasive breast cancer diagnoses from enrollment until either age 85 years or the end of follow-up. The expected number was the total cumulative hazard from the IBIS/Tyrer-Cuzick model that was accrued by

participants over the observation period. Exact 95% CIs for the population O/E ratio were computed assuming the observed number was Poisson-distributed with a mean equal to the expected number scaled by the population O/E ratio. An O/E ratio encompassing 1 was considered excellent, whereas a ratio of 0.9 to 1 was considered good. We compared the calibration between US-born and foreign-born Hispanic women with an exact test under the same assumptions.

Model Discrimination

Discrimination is frequently reported in terms of area under the curve, but is more appropriately tested through regression models.[23-26] We used Cox proportional hazards regression to test IBIS/Tyrer-Cuzick model discrimination in the overall cohort and to compare discrimination across racial and ethnic groups. In the full cohort, we predicted time to development of invasive breast cancer in terms of age at WHI enrollment and the log relative risk (RR) from the IBIS/Tyrer-Cuzick model. RR was calculated using the formula TC = 1 – (1 – B_0) ^ RR, where TC denotes remaining lifetime risk estimated from the IBIS/Tyrer-Cuzick model, and B_0 is the age-specific baseline breast cancer–incidence rate from the Thames Cancer Registry. We tested for differential discrimination across racial/ethnic groups by including an additional independent variable for race/ethnicity and a term for interaction between RR and race/ethnicity. Perfect discrimination by a model would correspond to HR = 2.72, such that ln(HR) = 1.

Exploratory Analysis: Optimizing Model Fit

We tested the hypothesis that racial and ethnic differences in breast cancer–incidence rates are explained by differences in the prevalence of the demographic, reproductive, and behavioral risk factors included in the IBIS/Tyrer-Cuzick model.[16,27] As an exploratory analysis, we tested whether risk factor variables in IBIS/Tyrer-Cuzick could be reweighted to better explain race/ethnicity–specific risks if combined in the most optimal manner possible for this cohort. Specifically, we fitted a Cox proportional hazards model with independent variables for race/ethnicity and each IBIS/Tyrer-Cuzick risk factor. Risk factors were coded as defined in the IBIS/Tyrer-Cuzick model[3] with exceptions to make some variables more consistent with the model's categorizations: height, age at first birth, and family history. Height (in meters) was coded as a 3-level variable (<1.6, 1.6-1.7, and ≥1.7 meters); age (in years) at first birth was coded as a 3-level variable (<20, 20-29, and ≥30 years); and family history of breast cancer was coded as a weighted count of relatives affected by breast cancer using 0.5 for first degree-relatives and 0.25 for second-degree relatives. A finding of statistical significance of race/ethnicity in this model with all IBIS/Tyrer-Cuzick risk factors optimized for this cohort would indicate that no simple combination of these risk factors can explain the race/ethnicity-specific differences in breast cancer risk. We further explored an extension of this model by including an independent variable for US-born versus foreign-born within the subset of Hispanic participants for whom birthplace information was available.

Exploratory Analysis: Simulating a Protective Single-Nucleotide Polymorphism

To explore a factor that could affect IBIS/Tyrer-Cuzick calibration in Hispanics, we simulated the frequency of a single-nucleotide polymorphism (SNP) rs140068132 on 6q25 in the estrogen receptor 1 (*ESR1*) gene, which is associated with a reduced risk of breast cancer development and is prevalent among Hispanics, but not in other racial/ethnic groups.[28] The simulation assumed a logistic regression model of the risk of developing breast cancer, with an odds ratio of 0.61 for the SNP and an intercept chosen to match the breast cancer incidence in that study.[28] The minor allele frequency was set to 0.07 among Hispanics,[28] 0.04 among American Indian/Alaskan Natives,[29,30] and 0 among other groups. Allele counts were simulated separately by race/ethnicity and breast cancer status, and the risk estimate from the IBIS/Tyrer-Cuzick model was adjusted using the formula $TC^* = 1 - (1 - TC) \text{ ^ } (0.61^X)$, where TC is the unadjusted estimate and X is the number of alleles (0-2).

RESULTS

Participant Characteristics

A total of 90,967 women met the inclusion criteria (Supporting Fig. 1). There were 80,260 NH White women, 5903 NH Black women, 2131 Asian or Pacific Islanders (API), 2368 Hispanics, and 305 American Indian or Alaskan Natives (AIANs; Table 1). The mean age at enrollment ranged from 59.9 years in Hispanics to 62.9 years in NH White women. AIANs had menopause earlier than APIs (mean 46 vs 48.7 years). BMI was higher in NH Black women than APIs (mean 30.9 vs 24.9 kg/m^2). NH Black women had earlier age at

TABLE 1. Participant Characteristics

	Non-Hispanic White N = 80,260	Non-Hispanic Black N = 5903	Asian or Pacific Islander N = 2131	Hispanic N = 2368	American Indian or Alaskan Native N = 305
	Mean or No. (%)	Mean or No. (%)	Mean or No. (%)	Mean or No. (%)	Mean or No. (%)
Age at WHI enrollment, y	62.9	60.8	62	59.9	61
Age at menarche, y	12.6	12.6	12.6	12.5	12.6
Age at menopause, y	48.4	46.5	48.7	47.8	46
Height (in.)	63.9	64.1	61.1	62.1	63.7
Weight (lbs)	159.8	180.2	132.5	156.6	171.3
Body mass index	27.5	30.9	24.9	28.6	29.7
Prior breast biopsy	17,401 (21.7)	1225 (20.8)	363 (17.0)	409 (17.3)	63 (20.7)
Parous	70,390 (87.7)	4965 (84.1)	1776 (83.3)	2038 (86.1)	279 (91.5)
Age at first birth, y	24.7	23.3	25.6	24.3	23.4
MH use: none	26,008 (32.4)	2745 (46.5)	612 (28.7)	854 (36.1)	101 (33.1)
MH use: past	10,553 (13.1)	802 (13.6)	246 (11.5)	263 (11.1)	50 (16.4)
MH use: current	43,699 (54.4)	2356 (39.9)	1273 (59.7)	1251 (52.8)	154 (50.5)
MH use duration, y	5.6	3.4	5.5	4.2	6.1
MH type: estrogen and progesterone	28,761 (35.8)	1013 (17.2)	877 (41.2)	739 (31.2)	88 (28.9)
MH type: estrogen only	25,491 (31.7)	2145 (36.3)	642 (30.1)	775 (32.7)	116 (38.0)
Family history of breast cancer	14,517 (18.1)	865 (14.7)	286 (13.4)	287 (12.1)	57 (18.7)
Birthplace information collected	45,270 (56.4)	2520 (42.7)	1143 (48.3)	1160 (54.4)	154 (50.5)
United States born vs foreign born	42,970 (94.9)	2453 (97.3)	763 (66.8)	884 (76.2)	151 (98.1)
Median follow-up time, y[a]	18.9	18.6	18.9	18.9	19.0

Abbreviations: MH, menopausal hormone; WHI, Women's Health Initiative.
[a]Median follow-up times were calculated by the reverse Kaplan-Meier method.

first birth than APIs (mean 23.3 vs 25.6 years), and shorter duration of menopausal hormone therapy use than AIANs (mean 3.4 vs 6.1 years). Family history of breast cancer was higher in AIANs than in Hispanics (18.7% vs 12.1%).

Breast Cancer Incidence by Race/Ethnicity

Over a median follow-up of 18.9 years (maximum 23.4 years), breast cancer developed in 6133 NH White (7.6%), 373 NH Black (6.3%), 140 API (6.6%), 115 Hispanic (4.9%), and 22 AIAN (7.2%) women (Fig. 1).

Model Calibration

IBIS/Tyrer-Cuzick calibration was evaluated for all 90,967 participants and in subsets by race/ethnicity (Fig. 1, Table 2). Overall, model calibration was good, with an O/E ratio of 0.95 (95% CI, 0.93-0.97). Calibration varied among racial/ethnic groups: The O/E ratio was 0.96 (95% CI, 0.93-0.98) in NH White women, 0.90 (95%CI, 0.83-0.97) in all racial/ethnic minority participants combined, 0.91 (95% CI, 0.82-1.0) in NH Black women, 0.75 (95% CI, 0.62-0.90) in Hispanic women, 1.01 (95% CI, 0.85-1.19) in API women, and 1.05 (95% CI, 0.66-1.59) in AIAN women. The O/E ratio in US-born Hispanic women was 0.94 (95% CI, 0.69-1.25) compared with 0.76 (95% CI, 0.45-1.21) in foreign-born Hispanic women, though the difference was not statistically significant ($P = .51$).

Model Discrimination

The IBIS/Tyrer-Cuzick model showed significant discrimination in the overall cohort with hazard ratio (HR) = 1.66, 95% CI, 1.59-1.73 ($P < 10^{-103}$). Significant discrimination was observed within each racial/ethnic group, except in AIAN women where statistical power was limited (Supporting Table 2). Discrimination did not differ significantly by race/ethnicity (P value for interaction = .24).

Exploratory Analysis: Optimizing Model Fit

Hispanic women had significantly lower risk than NH White women after optimally accounting for all IBIS/Tyrer-Cuzick risk factors. A slightly lower risk was observed among NH Black compared to NH White women. No other racial/ethnic group had risk differences unexplained by IBIS/Tyrer-Cuzick factors (Supporting Table 3).

We examined an additional independent variable, US-born vs foreign-born status, within 45,270 women for whom birthplace information was available, and it

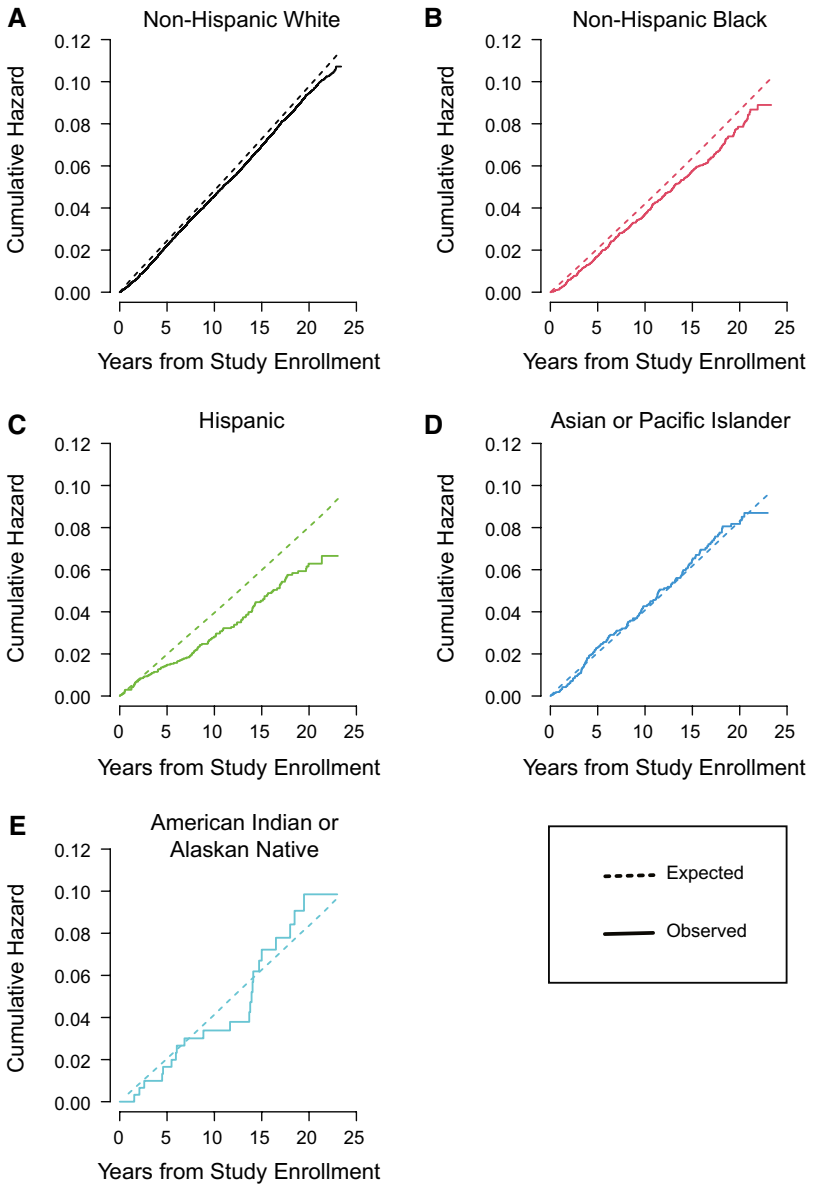

Figure 1. (A-E) Observed and expected cumulative breast cancer risk by race/ethnicity.

was not significantly associated with time to breast cancer diagnosis ($P = .58$). No racial/ethnic group had risk differences unexplained by the combination of US-born vs foreign-born status and IBIS/Tyrer-Cuzick factors. However, there were wide confidence intervals around estimates for some racial/ethnic groups (Supporting Table 4).

Exploratory Analysis: Simulating a Protective Single-Nucleotide Polymorphism

Simulating the prevalence and protective effect of the minor allele of rs140068132 at 6q25 suggested an improved O/E ratio for Hispanics of 0.80 (95% CI, 0.66-0.96). The O/E ratios for other racial/ethnic groups were unchanged because of the very low minor allele frequency of rs140068132 in these groups (Table 3).

DISCUSSION

In this study of more than 90,000 diverse women from the WHI with up to 23 years of follow-up time, we found good calibration of the IBIS/Tyrer-Cuzick model for prediction of breast cancer development in all racial/ethnic groups, with the exception of Hispanic women. An exploratory

TABLE 2. Calibration of the IBIS/Tyrer-Cuzick Model by Race/Ethnicity

Race/ethnicity	Total No.	Observed (O) Breast Cancers	Expected (E) Breast Cancers	O/E Ratio	Lower 95% CI	Upper 95% CI
Non-Hispanic White	80,260	6133	6408.6	0.96	0.93	0.98
All racial/ethnic minority groups	10,707	650	724.3	0.90	0.83	0.97
Black	5903	373	411	0.91	0.82	1.00
Hispanic	2368	115	153.2	0.75	0.62	0.90
United States-born Hispanic[a]	763	47	50.1	0.94	0.69	1.25
Foreign-born Hispanic[a]	380	18	23.6	0.76	0.45	1.21
Asian or Pacific Islander	2131	140	139.2	1.01	0.85	1.19
American Indian or Alaskan Native	305	22	20.9	1.05	0.66	1.59
Total	90,967	6783	7132.9	0.95	0.93	0.97

[a]As noted in Table 1, birthplace was reported for only 54.4% of Hispanic women.

TABLE 3. Exploratory Analysis of IBIS/Tyrer-Cuzick Model Simulating a Single-Nucleotide Polymorphism[a]

Race/Ethnicity	Total N	Observed (O) Cancers	Expected (E) Cancers	O/E Ratio	95% CI
Hispanic	2368	115	144.0	0.80	0.66-0.96
American Indian or Alaskan Native	305	22	20.9	1.05	0.66-1.59
Total	90,967	6783	7123.7	0.95	0.93-0.98

Results for other racial/ethnic groups were unchanged from those in Table 2.
[a]rs140068132 at 6q25: 0.07 frequency in Hispanics, 0.039 in American Indian or Alaskan Native; odds ratio 0.61 per allele.

analysis of the simulation of SNP rs140068132 at 6q25, which is associated with lower breast cancer risk, suggested improvement of IBIS/Tyrer-Cuzick model calibration for Hispanic women. To our knowledge, this is the largest, most diverse, and longest study examining the relationship between the IBIS/Tyrer-Cuzick model and the development of breast cancer. As newer risk models become available, clinical risk assessment stands to benefit from understanding how model performance may vary between racial and ethnic groups, potentially overestimating or underestimating breast cancer risk.

The IBIS/Tyrer-Cuzick model has performed as well as or better than other models in validation studies, contributing to its widespread adoption. The O/E ratio of 0.95 that we observed is consistent with prior publications. A 2003 analysis in a clinical sample of 1933 women in the UK found that the IBIS/Tyrer-Cuzick model had the best discriminatory accuracy in comparison with the BCRAT, Claus, and Ford models.[31] Recently, the IBIS/Tyrer-Cuzick model performed relatively well (O/E ratio = 0.84) and similar to the BRCAPRO and Breast Cancer Surveillance Consortium models in a US mammography screening cohort of 35,921 women.[32] In a study of the multinational Breast Cancer Prospective Family Study cohort enriched by women with a breast cancer family history or early-onset breast cancer (n = 18,856), the IBIS/Tyrer-Cuzick and BOADICEA/CanRisk models were better calibrated than the BRCAPRO and BCRAT models after 10 years of follow-up.[11] However, there are areas of suboptimal performance. Boughey et al reported overprediction by the IBIS/Tyrer-Cuzick model among women with atypical hyperplasia[33]; the model was revised to address this inaccuracy.[34] Valero et al found that the IBIS/Tyrer-Cuzick model overpredicted among women with lobular carcinoma in situ.[35] In the Nurses' Health Study cohort, the IBIS/Tyrer-Cuzick model overpredicted in higher-risk and older women and underpredicted in lower-risk women.[36] Coopey et al reported higher risk prediction with the IBIS/Tyrer-Cuzick model compared with the BCRAT and Claus models.[37]

Relatively few studies have evaluated model performance in racial/ethnic minority populations.[38-42] Despite large sample sizes of 15,000 to 35,000, recent studies have lacked statistical power to determine racial/ethnic differences in IBIS/Tyrer-Cuzick model performance.[11,32] The current study of 5 racial/ethnic groups thus fills an important gap. It is reassuring that model calibration was generally good to excellent, with CIs approaching or including 1.0. By contrast, however, the model overestimated risk in Hispanic women. Hispanics have lower breast cancer risk than NH White women,[16,43] with foreign-born Hispanic women having a lower risk than US-born Hispanic women.[44] A Hispanic-specific breast cancer–risk model was previously validated using the WHI data set; it was well calibrated for US-born Hispanics, but showed a trend toward overprediction in

foreign-born Hispanic women.[45] This may reflect the increase in breast cancer risk seen after migration to the US.[44,46] The current results are suggestive of improved IBIS/Tyrer-Cuzick model performance in US-born versus foreign-born Hispanic women, but are limited by the fact that only half of the participants had birthplace reported. The IBIS/Tyrer-Cuzick model may require an adjustment of risk estimates for effective use in Hispanic women, particularly those born outside the US.

Prior studies reported on augmenting models with data on emerging risk factors, including mammographic density.[47-49] Polygenic risk scores (PRSs), comprised of multiple SNPs, have been reported to improve performance of the BCRAT,[50] BOADICEA,[5] and IBIS/Tyrer-Cuzick models.[51-54] PRSs were developed using data primarily from NH White women; although recent studies suggest that PRSs may perform well in Hispanic and Asian women,[55,56] their addition to breast cancer–risk models has not yet been validated. We explored the possibility that inclusion of a potentially protective SNP common in Hispanics, rs140068132 at 6q25, might improve IBIS/Tyrer-Cuzick model calibration. The results of simulating this SNP suggested improvement in model calibration, which should be interpreted as hypothesis-generating. Incorporating race/ethnicity-specific PRS into cancer risk-prediction models should be a priority.

This study has limitations. We could not incorporate some factors shown to improve IBIS/Tyrer-Cuzick model performance, such as mammographic density because they were not routinely collected on WHI participants. Birthplace was not reported for all women, and the sample included postmenopausal women only. Mammographic screening rates may have differed across subgroups, which could lead to differences in breast cancer diagnosis. At the time of WHI enrollment in the 1990s, menopausal hormone therapy use and other risk factors (eg, obesity) had different prevalence than today; thus, it is possible that model performance might differ slightly among postmenopausal women in 2021. Study strengths include a large, diverse sample within the prospective WHI, up to 23 years of follow-up time, and confirmation of all cancer diagnoses. This ensured that participants were well characterized, that outcomes were carefully ascertained and adjudicated, and that all participants had uniform follow-up. These strengths increase the validity and generalizability of the study's results to postmenopausal women.

Implications for Patient Care

Breast cancer risk-prediction models are integral to clinical decision-making about optimal screening strategies and consideration of risk-reduction approaches. It is thus important that they perform as accurately as possible for all women. The current results suggest that use of the IBIS/Tyrer-Cuzick model version 7 is appropriate for most American postmenopausal women. However, newer models are becoming available, and it is essential to recognize that model performance may vary by race and ethnicity. Future studies that incorporate genetic and other risk factors, particularly for Hispanic women, are essential to improve breast cancer–risk prediction.

FUNDING SUPPORT

This study received support from Myriad Genetics, Inc; the Suzanne Pride Bryan Fund for Breast Cancer Research; the Jan Weimer Faculty Chair in Breast Oncology; and the BRCA Foundation. The Women's Health Initiative received funding from the National Heart, Lung, and Blood Institute, the National Institutes of Health, and the US Department of Health and Human Services (grant nos. HHSN268201600018C, HHSN268201600001C, HHSN268201600002C, HHSN268201600003C, and HHSN268201600004C).

CONFLICT OF INTEREST DISCLOSURES

Allison W. Kurian reports research funding to her institution from Myriad Genetics. Elisha Hughes, Ryan Bernhisel, Braden Probst, Stephanie Meek, Timothy Simmons, Jerry Lanchbury, Thomas P. Slavin, Susanne Wagner, and Alexander Gutin are employees of and have stock in Myriad Genetics. The other authors made no disclosures.

AUTHOR CONTRIBUTIONS

Allison W. Kurian: Conceptualization, funding acquisition, writing—original draft, and writing—review and editing. **Elisha Hughes:** Conceptualization, formal analysis, writing—original draft, and writing—review and editing. **Timothy Simmons:** Formal analysis and writing—review and editing. **Ryan Bernhisel:** Formal analysis and writing—review and editing. **Braden Probst:** Formal analysis and writing—review and editing. **Stephanie Meek:** Formal analysis, writing—original draft, and writing—review and editing. **Alexander Gutin:** Formal analysis and writing—review and editing. **Thomas E. Rohan:** Resources and writing—review and editing. **JoAnn Manson:** Resources and writing—review and editing. **Dorothy Lane:** Resources and writing—review and editing. **Rowan T. Chlebowski:** Resources and writing—review and editing. **Marcia Stefanick:** Conceptualization, resources, writing—original draft, and writing—review and editing.

DATA AVAILABILITY

The data underlying this article are available from the Women's Health Initiative.

REFERENCES

1. Visvanathan K, Fabian CJ, Bantug E, et al. Use of endocrine therapy for breast cancer risk reduction: ASCO clinical practice guideline update. *J Clin Oncol*. 2019;37:3152-3165.
2. Saslow D, Boetes C, Burke W, et al. American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. *CA Cancer J Clin*. 2007;57:75-89.
3. Brentnall AR, Cuzick J. Risk models for breast cancer and their validation. *Stat Sci*. 2020;35:14-30.
4. Tyrer J, Duffy SW, Cuzick J. A breast cancer prediction model incorporating familial and personal risk factors. *Stat Med*. 2004;23:1111-1130.

5. Lee A, Mavaddat N, Wilcox AN, et al. BOADICEA: a comprehensive breast cancer risk prediction modelincorporating genetic and nongenetic risk factors. *Genet Med*. 2019;21:1708-1718.
6. Lee AJ, Cunningham AP, Kuchenbaecker KB, Mavaddat N, Easton DF, Antoniou AC. BOADICEA breast cancer risk prediction model: updates to cancer incidences, tumour pathology and web interface. *Br J Cancer*. 2014;110:535-545.
7. Gail MH, Brinton LA, Byar DP, et al. Projecting individualized probabilities of developing breast cancer for White females who are being examined annually. *J Natl Cancer Inst*. 1989;81:1879-1886.
8. Berry DA, Parmigiani G, Sanchez J, Schildkraut J, Winer E. Probability of carrying a mutation of breast-ovarian cancer gene BRCA1 based on family history. *J Natl Cancer Inst*. 1997;89:227-238.
9. Berry DA, Iversen ES Jr, Gudbjartsson DF, et al. BRCAPRO validation, sensitivity of genetic testing of BRCA1/BRCA2, and prevalence of other breast cancer susceptibility genes. *J Clin Oncol*. 2002;20:2701-2712.
10. Antoniou AC, Pharoah PP, Smith P, Easton DF. The BOADICEA model of genetic susceptibility to breast and ovarian cancer. *Br J Cancer*. 2004;91:1580-1590.
11. Terry MB, Liao Y, Whittemore AS, et al. 10-year performance of four models of breast cancer risk: a validation study. *Lancet Oncol*. 2019;20:504-517.
12. Quante AS, Whittemore AS, Shriver T, Strauch K, Terry MB. Breast cancer risk assessment across the risk continuum: genetic and nongenetic risk factors contributing to differential model performance. *Breast Cancer Res*. 2012;14:R144.
13. Powell M, Jamshidian F, Cheyne K, Nititham J, Prebil LA, Ereman R. Assessing breast cancer risk models in Marin County, a population with high rates of delayed childbirth. *Clin Breast Cancer*. 2014;14:212-220.
14. Flanagin A, Frey T, Christiansen SL, Bauchner H. The reporting of race and ethnicity in medical and science journals: comments invited. *JAMA*. 2021;325:1049-1052.
15. Ioannidis JPA, Powe NR, Yancy C. Recalibrating the use of race in medical research. *JAMA*. 2021;325:623-624.
16. Kurian AW, Fish K, Shema SJ, Clarke CA. Lifetime risks of specific breast cancer subtypes among women in four racial/ethnic groups. *Breast Cancer Res*. 2010;12:R99.
17. Bevers TB, Helvie M, Bonaccio E, et al. Breast cancer screening and diagnosis, version 3.2018, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw*. 2018;16:1362-1389.
18. Bevers TB, Ward JH, Arun BK, et al. Breast cancer risk reduction, version 2.2015. *J Natl Compr Canc Netw*. 2015;13:880-915.
19. Curb JD, McTiernan A, Heckbert SR, et al. Outcomes ascertainment and adjudication methods in the Women's Health Initiative. *Ann Epidemiol*. 2003;13(9 suppl):S122-S128.
20. Anderson GL, Manson J, Wallace R, et al. Implementation of the Women's Health Initiative study design. *Ann Epidemiol*. 2003;13(9 suppl):S5-S17.
21. Hays J, Hunt JR, Hubbell FA, et al. The Women's Health Initiative recruitment methods and results. *Ann Epidemiol*. 2003;13(9 suppl):S18-S77.
22. R Core Team. R: a language and environment for statistical computing. R Foundation for Statistical Computing. Accessed February 22, 2021. https://www.R-project.org/
23. Austin PC, Steyerberg EW. Predictive accuracy of risk factors and markers: a simulation study of the effect of novel markers on different performance measures for logistic regression models. *Stat Med*. 2013;32:661-672.
24. Cook NR. Use and misuse of the receiver operating characteristic curve in risk prediction. *Circulation*. 2007;115:928-935.
25. Pepe MS, Kerr KF, Longton G, Wang Z. Testing for improvement in prediction model performance. *Stat Med*. 2013;32:1467-1482.
26. Vickers AJ, Cronin AM, Begg CB. One statistical test is sufficient for assessing new predictive markers. *BMC Med Res Methodol*. 2011;11:13.
27. National Cancer Institute, Surveillance Research Program. Surveillance, Epidemiology, and End Results (SEER) Program SEER*Stat Database: Populations— Total U.S. (1969-2018)—Linked to County Attributes—Total U.S., 1969-2018 Counties. Accessed February 23, 2021. www.seer.cancer.gov
28. Fejerman L, Ahmadiyeh N, Hu D, et al. Genome-wide association study of breast cancer in Latinas identifies novel protective variants on 6q25. *Nat Commun*. 2014;5:5260.
29. dbSNP. rs140068132. Accessed February 28, 2021. https://www.ncbi.nlm.nih.gov/snp/rs140068132#frequency_tab
30. Sherry ST, Ward M, Sirotkin K. dbSNP-database for single nucleotide polymorphisms and other classes of minor genetic variation. *Genome Res*. 1999;9:677-679.
31. Amir E, Evans DG, Shenton A, et al. Evaluation of breast cancer risk assessment packages in the family history evaluation and screening programme. *J Med Genet*. 2003;40:807-814.
32. McCarthy AM, Guan Z, Welch M, et al. Performance of breast cancer risk-assessment models in a large mammography cohort. *J Natl Cancer Inst*. 2020;112:489-497.
33. Boughey JC, Hartmann LC, Anderson SS, et al. Evaluation of the Tyrer-Cuzick (international breast cancer intervention study) model for breast cancer risk prediction in women with atypical hyperplasia. *J Clin Oncol*. 2010;28:3591-3596.
34. Cuzick J. IBIS breast cancer risk evaluation tool. Accessed March 2, 2021. https://ems-trials.org/riskevaluator/
35. Valero MG, Zabor EC, Park A, et al. The Tyrer-Cuzick model inaccurately predicts invasive breast cancer risk in women with LCIS. *Ann Surg Oncol*. 2020;27:736-740.
36. Glynn RJ, Colditz GA, Tamimi RM, et al. Comparison of questionnaire-based breast cancer prediction models in the Nurses' Health Study. *Cancer Epidemiol Biomarkers Prev*. 2019;28:1187-1194.
37. Coopey SB, Acar A, Griffin M, Cintolo-Gonzalez J, Semine A, Hughes KS. The impact of patient age on breast cancer risk prediction models. *Breast J*. 2018;24:592-598.
38. Adams-Campbell LL, Makambi KH, Frederick WA, Gaskins M, Dewitty RL, McCaskill-Stevens W. Breast cancer risk assessments comparing Gail and CARE models in African-American women. *Breast J*. 2009;15(1 suppl):S72-S75.
39. Adams-Campbell LL, Makambi KH, Palmer JR, Rosenberg L. Diagnostic accuracy of the Gail model in the Black Women's Health Study. *Breast J*. 2007;13:332-336.
40. Gail MH, Costantino JP, Pee D, et al. Projecting individualized absolute invasive breast cancer risk in African American women. *J Natl Cancer Inst*. 2007;99:1782-1792.
41. Sa-Nguanraksa D, Sasanakietkul T, O-Charoenrat C, Kulprom A, O-Charoenrat P. Gail model underestimates breast cancer risk in Thai population. *Asian Pac J Cancer Prev*. 2019;20:2385-2389.
42. Kurian AW, Gong GD, John EM, et al. Performance of prediction models for BRCA mutation carriage in three racial/ethnic groups: findings from the Northern California Breast Cancer Family Registry. *Cancer Epidemiol Biomarkers Prev*. 2009;18:1084-1091.
43. Power EJ, Chin ML, Haq MM. Breast cancer incidence and risk reduction in the Hispanic population. *Cureus*. 2018;10:e2235.
44. John EM, Phipps AI, Davis A, Koo J. Migration history, acculturation, and breast cancer risk in Hispanic women. *Cancer Epidemiol Biomarkers Prev*. 2005;14:2905-2913.
45. Banegas MP, John EM, Slattery ML, et al. Projecting individualized absolute invasive breast cancer risk in US Hispanic women. *J Natl Cancer Inst*. 2017;109:djw215.
46. Ziegler RG, Hoover RN, Pike MC, et al. Migration patterns and breast cancer risk in Asian-American women. *J Natl Cancer Inst*. 1993;85:1819-1827.
47. Brentnall AR, Cuzick J, Buist DSM, Bowles EJA. Long-term accuracy of breast cancer risk assessment combining classic risk factors and breast density. *JAMA Oncol*. 2018;4:e180174.
48. Tice JA, Cummings SR, Ziv E, Kerlikowske K. Mammographic breast density and the Gail model for breast cancer risk prediction in a screening population. *Breast Cancer Res Treat*. 2005;94:115-122.
49. Gabrielson M, Ubhayasekera KA, Acharya SR, et al. Inclusion of endogenous plasma dehydroepiandrosterone sulfate and mammographic density in risk prediction models for breast cancer. *Cancer Epidemiol Biomarkers Prev*. 2020;29:574-581.
50. Gail MH. Discriminatory accuracy from single-nucleotide polymorphisms in models to predict breast cancer risk. *J Natl Cancer Inst*. 2008;100:1037-1041.
51. Cuzick J, Brentnall AR, Segal C, et al. Impact of a panel of 88 single nucleotide polymorphisms on the risk of breast cancer in high-risk women: results from two randomized tamoxifen prevention trials. *J Clin Oncol*. 2017;35:743-750.

52. Evans DG, Brentnall A, Byers H, et al. The impact of a panel of 18 SNPs on breast cancer risk in women attending a UK familial screening clinic: a case-control study. *J Med Genet*. 2017;54:111-113.
53. van Veen EM, Brentnall AR, Byers H, et al. Use of single-nucleotide polymorphisms and mammographic density plus classic risk factors for breast cancer risk prediction. *JAMA Oncol*. 2018;4:476-482.
54. Brentnall AR, van Veen EM, Harkness EF, et al. A case-control evaluation of 143 single nucleotide polymorphisms for breast cancer risk stratification with classical factors and mammographic density. *Int J Cancer*. 2020;146:2122-2129.
55. Shieh Y, Fejerman L, Lott PC, et al. A polygenic risk score for breast cancer in US Latinas and Latin American Women. *J Natl Cancer Inst*. 2020;112:590-598.
56. Ho WK, Tan MM, Mavaddat N, et al. European polygenic risk score for prediction of breast cancer shows similar performance in Asian women. *Nat Commun*. 2020;11:3833.