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Journal of Cancer Immunology   **Review Article**

Performance of the Tyrer-Cuzick 8 Breast Cancer Risk Model Across Races: A Review

Melissa D Porterhouse, BS[1], Rosalinda Alvarado, MD[2,3*]

[1]Rush Medical College, Chicago, Illinois, USA

[2]Rush University Cancer Center, Chicago, Illinois, USA

[3]Department of Surgery, Division of Surgical Oncology, Rush University Medical Center, Chicago, Illinois, USA

[*]Correspondence should be addressed to Rosalinda Alvarado, Rosalinda_alvarado@rush.edu

Citation: Porterhouse MD, Alvarado R. Performance of the Tyrer-Cuzick 8 Breast Cancer Risk Model Across Races: A Review. J Cancer Immunol. 2022;4(2):47-51.

Abstract

Background: The Tyrer-Cuzick (TC) model is a breast cancer risk assessment tool that provides women with their risk of developing breast cancer based on genetic and personal factors. The most recent version of the TC model, TC8, is the first version to include breast density as a risk factor for breast cancer. Breast density is known to vary by race, leading to questions regarding the TC8 model's performance across races. Furthermore, recent findings have suggested that the TC8 model underestimates breast cancer risk in Black women. This review sought to summarize the current body of knowledge surrounding TC8 model validation across races and suggest future directions of study.

Findings: A review of the current literature yielded only four main studies validating the TC8 model. These studies found the TC8 model's performance to be adequate based on ratios of observed to expected breast cancer cases, Area Under the Curve (AUC) values, and c-index values. However, Black women were either underrepresented or not represented in all four studies. In fact, Black women represented less than five percent of the patient population in the studies identified. No studies validating the TC8 model in sufficiently diverse patient populations were identified.

Several studies assessing the performance of the TC7 model combined with breast density, a model similar to the TC8 model, were also identified during review of the literature. These studies found that the addition of breast density to the TC7 model improved its performance, although Black women were again underrepresented in these studies.

Conclusion: There is a lack of evidence regarding the TC8 model's performance in Black women. Further studies should be conducted to assess and validate the TC8 model in diverse populations that are representative of the overall United States population to ensure that Black women are receiving accurate breast cancer risk assessment.

Introduction

Breast cancer is a major cause of morbidity and mortality in the United States, affecting approximately 264,000 women annually and resulting in the death of nearly 16% of these women [1]. Given this detrimental impact of breast cancer, there has been a push in the past several decades to develop a breast cancer risk assessment model that provides women with an accurate estimation of their risk for developing breast cancer. Several risk models have been proposed for this purpose, but the Tyrer-Cuzick (TC) model has proven to be a preeminent and widely used option. Originally published in 2004, the TC model was one of the first breast cancer risk models to incorporate both personal and genetic factors to estimate a woman's risk of developing breast cancer [2]. Personal factors, such as medical and reproductive history,

and genetic factors, such as BRCA gene status and other low penetrance gene status, work together to give a more comprehensive assessment of breast cancer risk compared to other breast cancer risk models that rely on personal factors alone or genetic factors alone.

Since its initial development, the TC model has undergone several iterations to fine-tune its risk assessment as it has learned from real patient populations. Most recently, the TC model was adjusted to include breast density as a risk factor in its calculation of breast cancer risk. In this new model, denser breast tissue increases the breast cancer risk. While a previous version of the TC model (TC7) has been validated in a relatively diverse patient population [3], the TC8 model, the first TC model to include breast density as a risk factor, has yet to undergo validation studies in adequately diverse patient populations since its release in 2017. This is worrisome, as the TC model was originally developed using a predominantly White patient population [3]. With the inclusion of breast density in the new TC8 model, one must question whether the TC8 model performs equitably across all patient populations since it has been established that breast density varies by race, with White women having denser breast tissue and Black women have less dense breast tissue on average [4]. This is especially true in light of recent work suggesting the TC8 model underestimates breast cancer risk in Black women [5]. Seeing as TC8 scores are used by many institutions to guide important clinical decisions, such as whether to pursue supplemental breast cancer screening, it is essential that the model perform accurately in all patient populations. This review summarizes the current body of literature surrounding the TC8 model's performance across races and suggests plausible directions for future study.

Performance of TC8 Model Across Races

To date, no prospective studies have been conducted to validate the TC8 model's performance in sufficiently diverse populations and only a handful have been conducted to validate its performance at all (**Table 1**). One of the first studies to assess the TC8 model was conducted by Terry et al. in 2019

[6]. This study sought to validate four common breast cancer risk models, including the TC8 model, in a population of 15,732 women from the US, Canada, and Australia. The study found that the TC8 model was well-calibrated, producing a ratio of expected to observed cases of breast cancer of 1.03. These results show that the expected number of breast cancer cases were almost equal to the actual observed number of breast cancer cases in the study population. In other words, the model was found to be accurate at predicting breast cancer risk. However, the study was conducted in a mostly White patient population (79.5% of study patients identified as White). Specifically, the study included only 4.7% Black women, meaning Black women were underrepresented. Given this mostly homogenous study population, it cannot be determined from these results whether the TC8 model truly is well-calibrated in non-White patients.

Another study conducted by Choudhury et al. in 2019 also evaluated the TC8 model's performance [7]. This study was performed in a UK cohort of 64874 White patients. All non-White patients were excluded from the study. The TC8 model was again found to perform well in this study, producing an expected to observed ratio of 1.14 in women less than 50 years old and 1.13 in women 50 years old or greater. However, since this study included only White women, the results cannot be generalized to non-White populations.

In their 2019 study, Yala et al. examined the performance of the TC8 model alongside their own model in a cohort of US women [8]. In their full test set patient population, they found the TC8 model to produce an AUC value of 0.62. The test set population included only 4.8% Black women. In their risk test set patient population, the TC8 model was found to perform worse in Black patients than White patients, with an AUC value of 0.45 for Black patients compared to an AUC value of 0.62 for White patients. It is important to note that the risk test set included only 202 Black patients. Interestingly, another study conducted by Yala et al. in 2021 again produced an overall 5-year AUC value of 0.62 for the TC8 model [9]. However, this study also yielded a c-index of 0.64 for White patients and a c-index of 0.62 for Black patients, suggesting that the TC8

Table 1: Results of Studies Validating the TC8 Model.

Study Authors and Year	% Black Women Included in Study	Observed / expected ratio	AUC in Black Patients	AUC in White Patients	Overall AUC	C-index in Black Patients	C-index in White Patients
Terry et al. 2019 [6]	4.7%	1.03	-	-	-	-	-
Choudhury et al. 2019 [7]	0%	1.14 <50 y/o 1.13 ≥ 50 y/o	-	-	-	-	-
Yala et al. 2019 [8]	4.8%	-	0.45	0.62	0.62	-	-
Yala et al. 2021 [9]	4.7%	-	-	-	-	0.62	0.64

model performed similarly among Black and White patients. However, only 1204 (4.7%) Black women were included in this study. These two studies demonstrate the lack of consensus regarding the TC8 model's performance in Black women.

Finally, a recent analysis conducted by our team found that the TC8 model underestimated breast cancer risk in Black women [5]. In this study, only 10.7% of Black women were classified as high-risk based on their TC8 scores compared to 17.5% of White women (OR = 1.7). This was interpreted as an underestimation of risk for Black women given that Black women in America have greater breast cancer mortality rates than White women and only a slightly lower incidence of breast cancer [10]. This suggests that Black women should be classified as high-risk at least as often as White women, but this was not found to be the case. Further analysis suggested that lower rates of dense breasts among Black women played the most significant role in the lower rates of high-risk TC8 scores in this population. Seeing as this study included 37.9% Black women, it is currently the study that is most representative of the TC8 model's performance in Black women. However, while this study did provide important insight into rates of high-risk TC8 classifications across races, it was not a formal validation study and thus did not compare observed versus expected rates of breast cancer cases in the study population to formally validate the TC8 model.

Performance of TC7 Model Plus Breast Density Across Races

From the above review, it can be seen that there are few studies validating the TC8 model [6-9]. However, several studies have assessed whether adding breast density to the TC7 model improves its performance (**Table 2**). While these studies did not assess the TC8 model itself, the TC7 model plus breast density is similar to the TC8 model and thus may be a reasonable indicator of how the TC8 model functions. One of the first studies to assess the efficacy of adding breast

density to an existing TC model was conducted by Warwick et al. in 2014 [11]. This nested case-control study incorporated a cohort of 558 women at high-risk of breast cancer enrolled in the International Breast Cancer Intervention Study I. It was found that a risk model incorporating breast density in addition to the TC risk score was more accurate than the TC score alone (AUC of 0.62 for breast density plus TC model versus AUC of 0.51 for TC model alone). However, the authors do not include the racial distribution of patients in their report. It is thus not possible to know whether non-White women were adequately represented in this study. Additionally, this study only incorporated women at a higher-than-average risk of breast cancer, meaning the findings may not be generalizable to women with an average risk of developing breast cancer.

A similar study was conducted by Brentnall et al. in 2015 [12]. This study, conducted in a cohort of 50,628 patients from the UK, also found that adding breast density to the TC7 model allows for more accurate breast cancer risk prediction (AUC of 0.61 for breast density plus TC7 model versus AUC of 0.57 for TC model alone). However, this study was conducted using a mostly White patient population. Specifically, only 1.1% of the women in the study identified as Black. It therefore cannot be concluded that the model assessed in this study (breast density plus TC7 model) performs accurately in non-White patients.

An additional study conducted by Brentnall et al. in 2018 also assessed the function of the TC7 model plus breast density [13]. This cohort study was conducted in a population of 132,139 women from Washington, USA. The study found that a risk model including breast density plus the TC7 model was well-calibrated overall, with an observed/expected ratio of 1.02 for the TC7 model alone and an observed/expected ratio of 0.98 for the TC7 model plus breast density after a median follow up of 5.2 years. However, Black women were again underrepresented in this study, making up only 3.9% of the study population. Nonetheless, this model was subsequently

Table 2: Results of Studies Validating the TC7 Model Plus Breast Density.

Study Authors and Year	% Black Women Included in Study	AUC for TC7 Model Alone	AUC for TC7 Model Plus Breast Density	Observed/Expected Ratio for TC7 Model Alone	Observed/Expected Ratio for TC7 Model Plus Breast Density	Patients Classified as High-Risk Based on TC7 Score Alone	Patients Classified as High-Risk Based on TC7 Score Plus BI-RADS Breast Density
Warwick et al. 2014 [11]	Unknown	0.51	0.62	-	-	-	-
Brentnall et al. 2015 [12]	1.1%	0.57	0.61	-	-	-	-
Brentnall et al. 2018 [13]	3.9%	-	-	1.02	0.98	-	-
Brentnall et al. 2019 [14]	Unknown	-	-	-	-	4.8%	7.1%

employed in another study by Brentnall et al. in 2019 [14]. This case-control study, conducted in a US cohort of 2,717 patients, again found that breast density improves the accuracy of the TC model and allows for more accurate identification of women at high risk and at low risk for breast cancer. Specifically, 4.8% of the study population was found to be high-risk based on the TC7 model alone whereas 7.1% of the study population was classified as high-risk with the TC7 model plus BI-RADS breast density and 6.8% of patients were classified as high-risk with the TC7 model plus volumetric breast density. Furthermore, 12.1% of patients were classified as low-risk based on the TC7 model alone versus 21.0% with the TC7 model plus BI-RADS breast density and 17.5% with TC7 model plus volumetric breast density. This study was somewhat more inclusive than previous studies, including 10.6% non-White patients. However, the study does not further delineate the racial distribution of participants beyond White vs. non-White. It is therefore not possible to conclude whether Black patients were adequately represented in this study.

Conclusion and Future Directions of Study

Based on a review of the current literature, it is evident that there is a sparse amount of data evaluating the TC8 model's functioning, especially in diverse patient populations. In fact, our literature review produced no studies validating the TC8 model in a population that is representative of the overall United States population. Thus, the performance of the TC8 model across races remains largely unknown. While several studies have assessed the efficacy of the TC7 model combined with breast density [11-14], these studies cannot fully speak to the TC8 model's performance since other minor changes aside from breast density were also incorporated into the TC8 model [15]. Furthermore, these studies were also conducted with mostly White patient populations and therefore are not representative of the diverse populations served in reality. The importance of assessing the TC8 model's accuracy in varying populations was highlighted by our team's recent study finding that the TC8 model underestimates breast cancer risk in Black women [5]. Given the immense weight a woman's TC8 score can carry, it is imperative that further studies be conducted to evaluate and validate the TC8 model in diverse patient populations.

There are two initial starting points we believe would be particularly useful in assessing the TC8 model's performance. First, studies should be conducted to compare the observed number of breast cancer cases in a patient population to the expected number of breast cancer cases based off of TC8 predications for that patient population. Special care should be taken to ensure adequate inclusion of non-White patients. Second, studies reproducing our team's recent publication assessing the distribution of average-risk versus high-risk TC8 scores across races would be helpful in further evaluating the TC8 model's functioning in varying patient populations and delineating factors that may be causing racial disparities in TC8 scores [5]. These studies should pay particular attention to the role that breast density plays in the TC8 score seeing as the TC7 model, which does not include breast density, has been shown to perform well in Black patients while the TC8 model, which does include breast density, has been shown to underestimate risk in Black women [3,5]. Again, it is essential that these studies employ patient populations that are representative of the overall US population.

In conclusion, the limited amount of data regarding the TC8 model's performance in diverse populations combined with recent findings highlighting racial disparities in TC8 scores has caused concern that the TC8 model may not perform accurately in all patient populations [5]. Further studies should be conducted to validate the TC8 model's performance across races.

Conflicts of Interest

Funding Statement

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