



Not immune to inequity: minority under-representation in immunotherapy trials for breast and gynecologic cancers

Katherine V Grette , Aubrey L White, Eli K Awad, Jennifer M Scalici, Jennifer Young-Pierce, Rodney P Rocconi, Nathaniel L Jones

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University of South Alabama, Mobile, Alabama, USA

Correspondence to

Dr Katherine V Grette, University of South Alabama, Mobile, AL 36604, USA; kgrette@health.southalabama.edu

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HIGHLIGHTS

- Minority women are poorly represented in immunotherapy clinical trials for breast and gynecologic cancers.
- Enrollment of black women is especially low, accounting for only 5% of participants.
- Minority participation in clinical trials must increase to improve equity in health outcomes.

ABSTRACT

Objective To describe the participation of minority women in clinical trials using immunologic agents for breast and gynecologic cancers.

Methods A retrospective review of completed clinical trials involving immunotherapy for breast and gynecologic cancers was performed. Completed trials were examined for data on race, tumor type, and start year. Minority enrollment was stratified by tumor site. Based on Center for Disease Control and Prevention age-adjusted incidence for race, expected and observed ratios of racial participation were calculated and compared using χ^2 testing, $p \leq 0.05$.

Results A total of 53 completed immunotherapy clinical trials involving 8820 patients were reviewed. Breast cancer trials were most common ($n=24$) and involved the most patients ($n=6248$, 71%). Racial breakdown was provided in 41 studies (77%) for a total of 7201 patients. Race reporting was lowest in uterine ($n=4$, 67%) and cervical cancer trials ($n=6$, 67%), and highest in ovarian cancer trials ($n=12$, 86%). White patients comprised 70% ($n=5022$) of all the patients included. Only 5% of patients involved were black ($n=339$), and 83% of these patients ($n=282$) were enrolled in breast cancer trials. Observed enrollment of black women was 32-fold lower for ovarian, 19-fold lower for cervical, 15-fold lower for uterine, and 11-fold lower for breast cancer than expected. While all trials reported race between 2013 and 2015, no consistent trend was seen towards increasing race reporting or in enrollment of black patients over time.

Conclusion Racial disparities exist in clinical trials evaluating immunologic agents for breast and gynecologic cancers. Recruitment of black women is particularly low. In order to address inequity in outcomes for these cancers, it is crucial that significant attention be directed towards minority representation in immuno-oncologic clinical trials.

INTRODUCTION

Racial inequity in healthcare delivery and outcomes in the United States is well documented.^{1–9} Black women are disproportionately affected by a multitude of illnesses, including cardiovascular disease, diabetes, and most

cancer types.^{10–12} Disparities in breast and gynecologic malignancies are particularly striking, with lower rates of screening, higher rates of death, and lower 5-year survival among black women.^{1–3}

Although less likely to be diagnosed with breast cancer, black women are more likely to die of their disease.^{4 5} In ovarian cancer, black women have worse survival, lower rates of optimal debulking, and a higher likelihood of platinum-resistant disease.^{6 7} Perhaps the most striking difference is seen in cervical and endometrial cancers, where the risk of death is doubled for black women compared with white women.^{3 7 8} Black women are also less likely to be referred for genetic counseling or receive testing for cancer susceptibility syndromes.⁹

Despite initiatives by federal agencies, minority recruitment to clinical trials is poor.^{13 14} In 230 trials leading to US Food and Drug Administration (FDA) approval for oncologic therapies, black patients accounted for just 3% of over 100 000 patients involved, a trend that has improved little since 1985.^{15–17} In a series of previously published studies, our institution identified significant minority under-representation among Gynecologic Oncology Group (GOG) trials and phase I GOG trials in the United States.^{18 19}

Minority under-representation is especially important to address as our understanding of racial differences in pathophysiology grows. One emerging area in cancer research is differences in tumor biology with respect to ethnicity. Studies have begun to show a significant difference in tumor immunogenicity and host immune response between white and black women.^{20–22} In order to understand the efficacy and toxicity of immunomodulating agents in minority populations, it is critical that these patients are adequately represented in clinical trials.

We hypothesize that minority women are under-represented in immuno-oncologic clinical trials. Our goal is to describe the participation of minority women in clinical trials using immunologic agents for breast and gynecologic cancers.

Table 1 Completed immunotherapy trials and patient enrollment by cancer site

Cancer site	All completed trials		Race data available	
	Total trials	Total patients	Total trials	Total patients
Ovary	14	2087	12	2063
Cervix	9	319	6	245
Uterus	6	166	4	128
Breast	24	6248	19	4765
All	53	8820	41	7201

METHODS

A retrospective review of completed clinical trials involving immunotherapy for breast and gynecologic cancers was performed. Completed trials were identified on clinicaltrials.gov using the following search terms: immunotherapy, gynecologic cancers, gynecologic malignancies, uterine cancer, breast cancer, ovarian cancer, cervical cancer, and by individual drug name (eg, pembrolizumab). No limitations were placed on start year, type of trial, or country of origin. Single and multi-institutional trials were included. Trials were excluded when no immune modulating agents were studied, even when the word 'immunotherapy' was used by the investigators. Additionally, trials that included fewer than four patients with breast or a gynecologic cancer were excluded. Completed trials were cross-referenced with publications, when required, to obtain racial demographic data.

Two authors abstracted data on race, tumor type, and start year to minimize error. Minority enrollment was stratified by tumor site.

Based on Centers for Disease Control and Prevention (CDC) age-adjusted incidence for race, expected and observed ratios of racial participants were calculated and compared using a X^2 test. White patients were used as the comparison group for all other races. Statistical significance was set at $p \leq 0.05$. In accordance with the journal's guidelines, we will provide our data for the reproducibility of this study in other centers if such are requested.

RESULTS

A total of 53 completed immunotherapy clinical trials involving 8820 patients were identified (Table 1). One trial was excluded for involving fewer than four patients who had a breast or gynecologic cancer. Six additional trials were excluded from analysis of race data because racial breakdown was provided for the entire cohort, but not by cancer site. A complete list of trials included in the analysis can be found in the online supplemental material. Of the 53 trials reviewed, breast cancer trials were most common ($n=24$),

involving 71% of all enrolled patients. Race reporting was lowest in uterine ($n=4$, 67%) and cervical cancer trials ($n=6$, 67%), and highest in ovarian cancer trials ($n=12$, 86%).

Racial breakdown was provided in 41 studies (77%) for a total of 7201 patients (Table 1). Among trials that reported race, trials involving breast cancer were most common, representing 46% of trials ($n=19$), followed by ovarian at 29% ($n=12$), cervical at 15% ($n=6$), and uterine at 10% ($n=4$). Of the 7201 patients enrolled in trials where race was provided, 70% were white, 20% were Asian, 6% were 'other', and 5% were black (Table 2).

The highest proportion of black participants was observed in breast cancer trials (5.9%, $n=282$), and the lowest was in ovarian cancer trials (2%, $n=38$). Only 57 (2%) black women were enrolled in trials involving gynecologic malignancies. Asian and 'other' races exceeded black enrollment in 25 (61%) and 20 (49%) trials, respectively. Pembrolizumab was involved in 19 trials reporting race, for a total of 2462 patients, with 86% enrolled in breast cancer trials (Table 3). Only 7 (2%) black women out of 335 total patients were enrolled in the six trials evaluating pembrolizumab in gynecologic cancers.

Using CDC age-adjusted incidence, observed enrollment of black patients into all immunotherapy trials was significantly less than expected if accrual rates were equal across all races. Observed enrollment was 32-fold lower for ovarian, 19-fold lower for cervical, 15-fold lower for uterine, and 11-fold lower for breast cancer (Table 4).²³ Enrollment was also lower than expected for Asian women, but to a lesser degree: 3-fold lower for ovarian, 10-fold lower for cervical, 13-fold lower for uterine, and 2.5-fold lower for breast cancer (online supplementary table).²³ All trials reported race between 2013 and 2015, but no consistent trend was found toward increasing race reporting over time (Figure 1). Additionally, enrollment of Asian patients increased over time, but enrollment of black patients did not increase (online supplementary figure).

Table 2 Race of participants by cancer site

Site	White	Black	Asian	Other	All patients
Ovary	1555	38	416	54	2063
Cervix	202	12	17	14	245
Uterus	104	7	6	11	128
Breast	3161	282	997	325	4765
All Sites	5022 (70%)	339 (5%)	1436 (20%)	404 (6%)	7201

Table 3 Race of participants in pembrolizumab trials by cancer site

Site	Trials	White	Black	Asian	Other	All
Ovary	5	118	2	7	8	135
Cervix	2	100	2	12	8	122
Uterus	2	61	3	4	10	78
Breast	10	1427	115	451	134	2127
All gynecologic	9	279 (83%)	7 (2%)	23 (7%)	26 (8%)	335
All sites	19	1706 (69%)	122 (5%)	474 (19%)	160 (6%)	2462

DISCUSSION

Summary of Main Results

Clinical trials evaluate treatment efficacy and toxicity of therapeutic agents in specific populations of patients in order to inform treatment decisions and improve outcomes. Our results show that clinical use of immunologic agents is largely supported by data in white patients, with particularly low participation among black women. Pembrolizumab is one of the oldest and most well-studied immunologic agents, but only seven black patients contributed to our understanding of its function and approval for use in gynecologic malignancies.

Results in the Context of Published Literature

Minority women, particularly black women, have been under-represented in gynecologic oncology clinical trials, a trend that has improved little over time.^{15–18} As a result, there is very little evidence to inform conclusions regarding pharmacodynamics, toxicity, or efficacy in minority populations. Trials using immuno-oncologic agents for gynecologic and breast cancers are no exception. Emerging data indicate that race is associated with differences in immune composition and response to immunotherapy, suggesting that race may be an important consideration in choosing a therapeutic agent.

The precedent for race as a factor in management has been established in other areas of medicine. The American Heart Association now recommends calcium channel blockers and thiazide diuretics as first-line agents for antihypertensives in black patients, and recommends stricter control and a lower threshold to start an additional agent.²⁴ Prior to initiating carbamazepine, the FDA recommends genetic testing of Asian patients for alleles that might indicate risk for Stevens-Johnson syndrome and toxic epidermal necrolysis.²⁵ New research suggests warfarin dosing protocols should differ according to a patient's race.²⁶ In order to determine if similar racially influenced protocols are appropriate in cancer

therapy, minority women must be involved in the trials that determine efficacy, dosing, and toxicity of these medications.

Strengths and Weaknesses

The large number of patients included in this review strengthens our results. Additionally, our use of CDC incidence broken down by race allowed us to calculate an accurate expected number of minority patients for each cancer site. Our results are also clinically important: in the rapidly evolving field of immunotherapy, we have an opportunity to ensure equitable enrollment in ongoing and future trials to strengthen our understanding of racially influenced responses to treatment.

Unfortunately, inconsistencies in reporting of Hispanic, Alaskan Native, or American Indian heritage made it impossible to assess under-representation in these groups. Additionally, because of the relatively small numbers of non-white patients involved, outcomes could not be broken down by race. This only highlights the importance of achieving equitable enrollment. Without understanding how race impacts treatment, we cannot expect to solve disparities in outcomes.

Implications for Practice and Future Research

If enrollment inequity is not addressed, minority participation and outcome disparities will probably worsen over time. Under-representation in published trials may lead to eligibility criteria that differentially exclude minority women. As a result, new trials built from safety data established in white patients may have cut-off points that affect eligibility of minority patients to a greater degree, such as baseline creatinine level or diastolic blood pressure. Additionally, the racial composition of the United States is changing rapidly. The black population in the USA rose by more than 75% from 2000 to 2010, exceeding the total population growth during that time period.²⁷ Immunotherapy is likewise a rapidly growing

Table 4 Enrollment of black patients, expected versus observed

Site	Incidence per 100 000		Expected* black	Observed black	Difference	P value
	White patients	Black patients				
Ovary	10.4	8.1	1211	38	32-fold lower	<0.0001
Cervix	7.3	8.3	229	12	19-fold lower	<0.0001
Uterus	27.2	27.5	105	7	15-fold lower	<0.0001
Breast	125	121	3048	282	11-fold lower	<0.0001

*Calculated based on actual enrollment of white patients, and Center for Disease Control and Prevention incidence by cancer site for white and black patients.

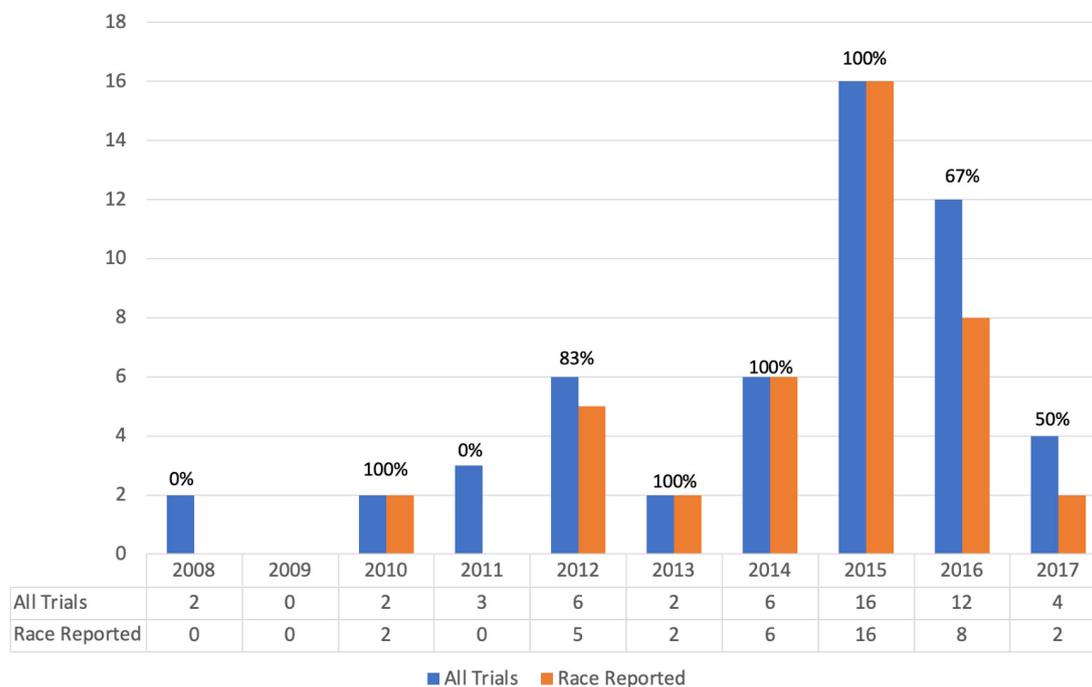


Figure 1 Completed trials reporting race by year.

field, with 30 new indications for immune modulating agents in 2019 alone.²⁸ Because of this, the number of black women treated with immunologic agents primarily shown to be effective and safe in white patients will continue to increase. Evidence-based strategies to achieve appropriate minority enrollment must be used to prevent the aggravation of disparities in this developing area of cancer care.

Improving recruitment of minority women to clinical trials requires an understanding of current barriers. Age, access to care, and socioeconomic status have all been implicated in a woman's decision to participate.^{29–31} However, a recent single institution prospective study investigated the effect of education on patients' willingness to participate in clinical research. Patients of all races were initially hesitant to enroll, but after education, white women were more likely to enroll than their minority peers.³² This suggests that the way in which we recruit our patients to clinical trial involvement is a potential target for change. In an ongoing study involving 1021 patients with endometrial cancer, our institution found that use of lay navigators whose demographics matched our patient population eliminated the racial disparity in enrollment, and also narrowed the disparity in progression-free survival between black and white women enrolled in clinical trials (manuscript in preparation). Adoption of these kinds of evidence-based strategies will help solve inequity in clinical trial enrollment and health outcomes.

CONCLUSIONS

Racial disparities exist in clinical trials evaluating the safety and efficacy of immunologic agents for breast and gynecologic cancers. Recruitment of black women is particularly low. In order to address inequity in outcomes for these cancers, it is crucial that significant attention be directed towards minority representation in immunologic clinical trials.

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ORCID iD

Katherine V Grette <http://orcid.org/0000-0002-9071-6170>

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