A Case-control Study Examining Disparities in Clinical Trial Participation among Breast Surgical Oncology Patients

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Conflicts of Interest to Disclose: None

Key words: breast cancer, clinical trials, health disparities, race/ethnicity, socioeconomic status, surgical oncology

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Abstract

Background

Clinical trial participation among racial/ethnic minorities remains low despite national efforts. We sought to determine how participation in clinical trials by breast surgical oncology patients has changed over time and what characteristics are associated with participation.

Methods

Women with breast cancer enrolled in NCI-sponsored, cooperative-group trials from 2000-2012 and who underwent oncologic surgery (n=17,125) were compared to trial-eligible women in the National Cancer Database diagnosed in 2000-2012 (n=792,719). Race-specific trial participation was plotted over time by income and reported as a proportion of the combined cohorts. Factors associated with trial participation were estimated using logistic regression; we report odds ratios (ORs) with 95% confidence intervals (CIs). p<0.05 was considered significant for all analyses.

Results

Participation declined across all groups over time due to a decrease in the scale and number of trials. In 2000-2003, Asian/Pacific-Islander (API, 7.17%), Hispanic (3.48%), and white (7.13%) patients from the highest income group had higher participation than their lower-income counterparts (API 3.95%, Hispanic 2.67%, white 5.96%), but by 2008-2012, only high-income white patients participated more than lower-income whites (0.32% vs 0.25%, all p<0.01). Black (OR 0.80, 95% CI 0.75-0.85) and Hispanic (OR 0.84, 95% CI 0.77-0.92) patients were less likely to participate than whites, but there were significant interactions between income and race/ethnicity, with high-income black patients being ~50% less likely to participate than lower-income blacks (all p<0.001).

Conclusions
Multifaceted interventions addressing the intersectionality of race/ethnicity and other patient characteristics are needed to address persistent disparities in trial participation among breast surgical oncology patients.
Manuscript

Introduction

In 1993, the United States (US) Congress enacted the National Institutes of Health (NIH) Revitalization Act, which was conceived to encourage the participation of women and racial/ethnic minority patients in NIH-sponsored research. Universal access to clinical studies has since become a top priority of the National Cancer Institute (NCI), but research comparing trial enrollment among minorities to their representation in state and national cancer registries has yielded conflicting results.

Duma et al.’s 2017 paper reviewing 14 years of clinical trial enrollment in cancer patients confirmed that trial participation among racial and ethnic minorities remained disproportionately low across most disease sites. But they reported near equal participation by race/ethnicity among breast cancer trials and offered them as an example of how racial parity in trial participation might ideally be achieved. Notably, however, this review specifically excluded trials for which a surgical intervention was being tested.

While there are breast cancer trials that examine the benefit of systemic therapy among patients who have also undergone surgery, it remains unclear whether the relative parity of participation seen among the breast cancer trials reviewed by Duma and colleagues would also be observed among trials in which oncologic surgery was the intervention being assessed or an important condition of enrollment. Furthermore, it is unknown to what extent socioeconomic factors might mediate racial/ethnic disparities in trial enrollment among breast surgical oncology patients given evidence that certain patient- and system-level factors – including access to postoperative rehabilitation and quality at the hospital level due to regionalization, respectively – might more specifically affect the treatment trajectory of patients who undergo oncologic surgery as compared to patients receiving medical therapy.
Accordingly, we sought to compare a contemporary cohort of breast surgical oncology patients, that is, patients for whom oncologic surgery is the intervention being tested or for which surgery is a criterion for participation, who were enrolled in clinical trials to a national sample of similar patients in order to (1) assess patterns of trial participation over time, (2) identify differences between trial participants and patients captured in institutional tumor registries, and (3) determine which patient characteristics are associated with likelihood of trial participation.

Methods

Cohort

We sought to examine clinical trial participation among patients with breast cancer who underwent oncologic surgery. In December 2014, clinicaltrials.gov was searched to identify trials conducted between 1999 and 2012 in the United States for patients ≥18 years old diagnosed with breast cancer. Filters were used to identify trials that (1) were conducted by oncology cooperative groups (American College of Surgeons Oncology Group [ACOSOG], Cancer and Leukemia Group B [CALGB], ECOG [Eastern Cooperative Oncology Group], North Central Cancer Treatment Group [NCCTG], National Surgical Adjuvant Breast and Bowel Project [NSABP], and Southwest Oncology Group [SWOG]); (2) were sponsored by the NCI; (3) were phase II or III; (4) included surgery as an intervention or treatment; and (5) were completed or terminated as of December 2014, resulting in a total of 47 clinical trials. Participant data for these trials were requested from NCI’s Cancer Therapy Evaluation Program (CTEP), which maintains patient-level information about individuals enrolled in NCI-sponsored, cooperative-group trials. Data for patients enrolled from 2000 to 2012 in 14 of the requested trials were provided by CTEP in June 2016.

Individual trial participant data – including age at diagnosis, year of trial enrollment, race, and ethnicity – were provided in a de-identified format except for zip code, which was used to link individual
participants to zip-code level, area-based socioeconomic indicators including annual median household (MH) income, proportion of residents with at least a high-school (HS) education, and geographic location. Trial inclusion criteria and final enrollment figures were cross-verified using both ClinicalTrials.gov and the respective journal publications in which trial results were ultimately published. All but two of the included trials excluded men, and of these, one enrolled one man (who was excluded from this study) and the other enrolled none.

Patients from the trial database enrolled in 2000-2012 were compared to women with breast cancer selected from the 1998-2012 National Cancer Data Base (NCDB) Participant User File who were diagnosed in 2000-2012 and were eligible for at least one trial. Because trial participation in the US is ~3%, it was assumed for the purpose of this study that patients in the NCDB did not participate in any trials. For both cohorts, race and ethnicity were combined into one variable with six categories: Asian/Pacific Islander (PI), Non-Hispanic black, Hispanic, Native American, Non-Hispanic white, and Other.

**Statistical Analysis**

Patient characteristics were summarized with N (%) for categorical variables and median (interquartile range [IQR]) for continuous variables. Chi-square and t-tests were used to compare categorical and continuous variables, as appropriate. Unadjusted trial participation rates within each of the 4 largest racial/ethnic groups (Asian/PI, Non-Hispanic black, Hispanic, and Non-Hispanic white) were plotted over time; the Breslow-Day procedure was used to test for homogeneity between income and trial participation while controlling for race, with a significant p-value of <0.05 indicating differences across racial groups. Multivariate logistic regression was performed for the binary outcome of trial participation (yes/no), while adjusting for age, race/ethnicity, number of trial enrollment slots per year (divided into 3 levels: <500, 500-1000, and >1000; this variable was included in place of year [of enrollment and diagnosis for trial and NCDB patients, respectively] to better capture how opportunity
for enrollment changed over time), area-based education, area-based MH income, and geographic location. Two-way and three-way interaction terms for race/ethnicity, income, education, and enrollment slots/year were estimated. Since payor information was not available for clinical trial participants, a subgroup regression analysis was performed on patients ≥65 years old to assess whether associations with trial participation in the full cohort would persist in a cohort of uniformly Medicare-eligible patients. Finally, a mediation analysis was performed for the full cohort to determine to what extent, interracial differences in trial participation were mediated by socioeconomic factors. We report odds ratios (ORs) and 95% confidence intervals (CIs) with a significance level of 0.05 for all analyses. Pairwise comparisons of odds ratios were conducted for significant interactions, and the Benjamini-Hochberg procedure was used to adjust for multiplicity. Only patients with available data were included in the regression models, and effective sample sizes are included in all tables. All statistical analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC) and R 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria). Our study was approved by the Duke University School of Medicine Institutional Review Board (IRB).

Results

Patient Characteristics

17,124 patients with breast cancer were included in our trial cohort, and 792,719 patients were included in the NCDB cohort (Table 1) based on eligibility for at least one of the 14 included trials, 7 of which specifically examined surgical interventions (Table 2, Supplemental Table 1). Within the NCDB control group, 469,111 patients (59.2%) were eligible for only one trial, 204,294 patients (25.8%) were eligible for two trials, and 119,314 patients (15.1%) were eligible for three trials. A higher proportion of trial participants were ≥65 years old (38.1% vs 27.9%), white (83.5% vs 73.7%), and from areas with higher levels of educational attainment (e.g., >93% HS education: 32.5% vs 27.4%) than the NCDB
controls (both p<0.001). Trial participants were also slightly younger (median 58 vs 60, p<0.001) and more likely to be from the Midwest (28.9% vs 25.4%). Among trial participants, we found that the median age of patients varied based on the Eastern Cooperative Oncology Group (ECOG) eligibility criteria for a given trial: the median age in trials for which ECOG scores were required to be ≤1 (an indicator of high functional status) was 51, while the median age of patients enrolled in trials with an ECOG cutoff of ≤2 was 59 and for those with no cutoff at all was 57.

After adjusting for known covariates, logistic regression demonstrated that higher level of area-based education (>93% vs ≤79% HS education: OR 2.55, 95% CI 2.37-2.75) and being from the Midwest (OR 1.33, 95% CI 1.27-1.40) or South (OR 1.15, 95% CI 1.09-1.21) were associated with greater likelihood of clinical trial participation relative to less education and being from the West (all p<0.001, Table 3). Patients <40 (OR 0.70, 95% CI 0.65-0.76) and ≥65 (OR 0.59, 95% CI 0.57-0.61) were less likely to participate than patients between the ages of 40 and 64 (p<0.001), and Hispanic (OR 0.84, 95% CI 0.77-0.92) and non-Hispanic black (OR 0.80, 95% CI 0.75-0.85) patients were less likely to participate than Non-Hispanic white patients (p<0.001). Patients from the highest area-based income bracket (≥$63,000) were less likely to participate than those from the lowest income bracket (<$38,000, OR 0.63, 95% CI 0.59-0.68), and likelihood of enrollment declined with increasing income (p<0.001, Table 3). Not surprisingly, having more opportunities to participate (>1000 slots/year: OR 20.03, 95% CI 18.88-21.24 and 500-1000 slots/year: OR 4.40, 95% CI 4.11-4.72) was also associated with higher likelihood of participation (vs <500 slots/year, p<0.001). Among Medicare-eligible patients (i.e., ≥65 years old), whites continued to constitute the largest proportion of both trial and NCDB patients, and, as observed in the full cohort, a higher proportion of the trial participants were white as compared to the NCDB controls (87.1 vs 78.7%, p<0.001, Supplemental Table 2). Also in keeping with the full cohort, higher area-level education and lower area-level income were associated with greater likelihood of trial participation (Supplemental Table 3).
To examine the association between lower area-based income and higher likelihood of trial participation, we plotted true, unadjusted trial participation rates by income group within each racial/ethnic group (Figure 1). A majority of trial participants were enrolled in the early 2000s, after which there was a decline in both the number and size of trials across all racial/ethnic groups and in relative participation rates across income groups (Figure 1, Table 1). In 2000-2003, when trial participation was the highest across all groups, Asian/PI (7.17%), Hispanic (3.48%), and white (7.13%) patients from the highest income group ($≥63,000) had greater trial participation than their counterparts in the lowest income group (<$38,000; Asian/PI 3.95%, Hispanic 2.67%, white 5.96%, p=0.003). However, by 2008-2012, participation had fallen drastically for all race/ethnicities (Figure 1); indeed, only white high-income patients had a higher unadjusted participation rate than their lower-income counterparts (0.32% vs 0.25%, p<0.001), a finding that was statistically significant but of questionable clinical significance. Among black patients, trial participation was higher among low-income patients than high-income patients in 2000-2003 (5.56% vs 4.45%) and 2004-2007 (2.59% vs 1.89%), but these rates were equal by 2008-2012 (0.35% for both income groups, Figure 1).

In keeping with these changing patterns in participation rates, we found significant interactions for race/ethnicity*education; income*education; slots/year*education; slots/year*race/ethnicity; income*race/ethnicity; slots/year*race/ethnicity; and income*race/ethnicity*slots/year of enrollment/diagnosis (p<0.001, Tables 4a-b). With decreased sample size for the Medicare-eligible population, estimation of interaction effects for this subgroup was not possible, so we only report the interactions for the full cohort.

Income-based interactions were incorporated into the final model, but the education-based interactions were not as their inclusion did not improve the overall fit of the model when AIC and BIC were considered together. As mentioned previously, likelihood of trial enrollment declined for all
racial/ethnic groups over time, but within racial/ethnic and income groups, there were significant differences.

After adjustment, when opportunity to participate was greatest (i.e., >1000 slots/year), low-income Hispanic patients (OR 0.53, CI 0.41-0.69) were still approximately 50% less likely to participate than low-income whites, and high-income Hispanic (OR 0.57, CI 0.44-0.73) and black (OR 0.66, CI 0.54-0.79) patients were approximately 45% and 35% less likely, respectively, to participate than high-income whites (all p<0.001, Table 4b).

Among blacks, patients with high area-based income were approximately 55% less likely to participate than low-income patients regardless of how great (>1000 slots/year: OR 0.48, CI 0.38-0.59) or small (<500 slots/year: 0.45, CI 0.28-0.74) the opportunity to participate, while high-income whites were only approximately 30-35% less likely to participate than low-income whites, again, regardless of how much opportunity there was to participate (>1000 slots/year: OR 0.68, CI 0.63-0.74; <500 slots/year: 0.64, CI 0.51-0.81, p<0.001 for all adjusted ORs, Table 4b). When opportunity to participate was low (<500 slots/year), high-income Hispanic patients were >80% less likely to participate than their low-income counterparts (OR 0.19, CI 0.12-0.29, p<0.001, Table 4b).

Our mediation analysis demonstrated that the effect of race was moderately reduced after adjusting for socioeconomic factors but remained significant (see Online Supplement), thus confirming that the effect of race on trial participation was partially mediated by socioeconomic factors.

Discussion

In our examination of trial participation by breast surgical oncology patients, we found that during the 12-year inclusion period, black and Hispanic patients were less likely to participate in clinical trials than whites – who constituted >80% of trial participants overall – and that trial participation has declined across all racial/ethnic groups over time. However, our study yielded a mixed picture on the
state of diversity with regards to trial participation among breast surgical oncology patients: area-based patient income was strongly associated with clinical trial participation but in varying ways and to different extents across racial/ethnic groups. Initially, high-income Asian/PI, Hispanic, and white patients had higher rates of participation than their lower income counterparts, but gains in participation appear to have been made among lower income members of these groups, to the point that low-income Asian/PI and Hispanic patients had higher rates of participation by the end of the study period relative to their higher income counterparts. But among black patients, lower area-based income (as compared to higher income) was associated with higher rates of trial participation throughout the study period, though this difference disappeared in later years, when participation across all racial/ethnic groups had declined to extremely low levels. In this context of much lower participation overall, improved participation among low-income, non-black patients resulted in a statistically significant association between declining area-based income and increased likelihood of participation, thereby suggesting that low income was associated with higher trial participation throughout the 12-year period of study, when in fact, this relationship was highly dynamic over time.

Our study is unique in demonstrating the complex interplay between race and income in a longitudinal assessment of disparities in clinical trial participation, and our results suggest the need for strategies to improve trial participation that account for the intersectionality of potential participants’ racial and socioeconomic characteristics. Based on these findings, one might conclude that efforts to diversify trial enrollment may have contributed to more low-income Asian/PI, white, and Hispanic patients enrolling in later years than in years past. The increased likelihood over time of non-black, low-income, racial/ethnic minority patients’ participating in trials relative to their white counterparts may also reflect the fact that poverty among whites tends to be concentrated in rural areas that are also remote from urban sites of trial participation. In contrast, recruitment strategies targeting black patients will need to address the unique barriers faced by not only by low-income blacks but also by...
their higher-income counterparts, who may have significant wariness of research participation as a result of having greater awareness of past wrongs and a greater desire and ability to exhibit choice in the type of care they receive.16 Finally, although Hispanic Americans represent the single largest growing demographic in the United States,17 their representation in clinical oncology trials remains low relative to their proportion of the population3,4,6,17,18 and can be ascribed to previously identified barriers including failure to provide translated education material as well as exclusions related to insurance status.18

But if clinical trial participation is to reflect the make-up of an increasingly diverse society whose members are living longer and with more co-morbidities, efforts must go beyond simply making trials more logistically accessible for patients. In our study, trials with more stringent requirements about patient functional status (as defined by ECOG score) had younger patients, raising concerns for systematic exclusion of older patients. Furthermore, exclusion criteria that include functional status and/or co-morbidities that are disproportionately found in people of color could further contribute to their under-representation in clinical trials.18 In much the same way that it is difficult and even dangerous to apply medications that are solely tested and developed in men to the treatment of women, structural features of trial design that contribute disproportionately to low inclusion of racial/ethnic minorities compromise our collective ability to apply the results of oncology innovation to diverse populations.

Over the course of our study period, trial participation declined sharply, and this phenomenon reflects both a shift to smaller and fewer trials over time and to the fact that the number of patients contributed to the NCDB increased over the period of study. Thus, the numerator for our trial participation rate decreased (Figure 1) while our control group and, accordingly, our denominator increased (Table 1), making the overall rates lower and lower over time. Nevertheless, we have little reason to believe that this increase in the size of the NCDB had a significant impact on our overall results.
because when we examined the racial and ethnic composition of the database, it remained fairly constant, with a small trend towards greater inclusion of non-white patients (23% of potentially trial-eligible patients in 2000-2003 vs 26% in 2008-2012) over time.

More significantly, the declining number of large trials reflects an evolution in our collective understanding of breast cancer, which is increasingly recognized to be a heterogeneous array of diseases that share an anatomic location rather than a single condition. Earlier trials in breast surgical oncology – such as the Z0010, Z0011, and NSABP-B32 trials, which all opened in 1999 – enrolled breast cancer patients with limited to no information on biomarker status and limited ability to tailor treatment according to the biology of the tumor and its susceptibility to available systemic treatment. Today, we know that extent of surgery (e.g., axillary lymph node sampling) can be tailored based not only on extent of disease but also on the anticipated efficacy of adjuvant therapy (e.g., radiation). Indeed, there is ongoing work to determine whether exceptional responders to neoadjuvant systemic therapy with HER2-enriched and triple-negative cancers can avoid surgery altogether. With increasingly narrow, subtype-specific inclusion criteria, future trials designed to help us refine and de-escalate breast cancer treatment will necessarily be smaller than the trials of the past. Thus, we must strive not so much to have ever more opportunities for trial participation but rather to make sure that the right patients find their way to the right trials. Specifically, we must prioritize the recruitment and inclusion of patients of color, who are disproportionately affected by some of the most aggressive breast cancer subtypes, lest we prevent these patients from being a part of the scientific process to which they would make important contributions and from which they can directly benefit.

**Limitations**

Our study had several limitations, including selection bias and an inability to account for patient preference, that are associated with conducting retrospective analyses of pooled cancer registries such
as the NCDB. We also acknowledge limitations related to the types of information included in the datasets that were available to us. We realize these limitations are only partially accounted for through statistical methodology, and we describe and address them in detail as part of the Online Supplement accompanying this manuscript. Finally, our study only included patients in NCI-sponsored clinical trials, the enrollment levels for which have declined over time while enrollment in non-NCI-sponsored (typically, industry-sponsored) oncologic clinical trials has increased. But with this increase in industry-sponsored investigations, we feel that the implications of our findings are especially important, as they can be applied to address concerns that industry-sponsored trials disproportionately target and enroll vulnerable groups who have limited or no other sources of healthcare.

Conclusions

In summary, our study demonstrated that racial and ethnic disparities persist with regards to trial participation among breast surgical oncology patients, with black and Hispanic patients’ being less likely to participate in trials than whites, but these differences are mediated by socioeconomic factors. We also found that likelihood of trial participation has declined across all racial/ethnic groups over time but that gains in participation among low-income Asian/PI, Hispanic, and white patients appear to have occurred. Black patients were the only group for whom lower income was consistently associated with higher rates of participation, but over time, participation rates have converged for all groups such that intra-racial, socioeconomic differences in participation have become smaller but also multidirectional. As a result, trial participation for the 12-year period of our study was associated with white race, higher levels of area-based education, and – most notably – lower levels of area-based income, belying the complex and dynamic relationship of these intersecting demographic characteristics over time. Thus, while racial and ethnic disparities in trial participation persist among breast surgical oncology patients,
interventions to ensure equitable trial access and participation will need to be similarly diverse and multifaceted.
Funding

This work is supported by the National Institutes of Health (Grant Number 1K08CA241390 [PI: Fayaju] to O.M.F.), the National Center for Advancing Translational Sciences of the National Institutes of Health (Grant Number 1KL2TR002554 [PI: Svetkey] to O.M.F.); the National Institutes of Health Building Interdisciplinary Research Careers in Women’s Health (Grant Number K12HD043446 [PI: Andrews] to R.A.G.); the National Institutes of Health Cancer Clinical Investigator Team Leadership Award at the Wake Forest University School of Medicine (Grant Number P30CA012197 [PI: Pasche] to J.H.S.); and the National Cancer Institute at the National Institutes of Health (P30CA014236 [PI: Kastan] to Duke Cancer Institute). The content of this manuscript is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Acknowledgements

None of the authors for this manuscript has any conflicts of interest, financial or otherwise, to disclose.

The National Cancer Data Base (NCDB) is a joint project of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society. The CoC’s NCDB and the hospitals participating in the CoC NCDB are the source of the de-identified data used herein; they have not verified and are not responsible for the statistical validity of the data analysis or the conclusions derived by the authors.
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Table 1. Characteristics of Breast Cancer Patients in NCI-sponsored Surgical Oncology Trials and Trial-eligible Controls from the National Cancer Data Base (NCDB), 2000-2012*†

|                        | All Patients | TDB      | NCDB       | P-Value |
|------------------------|--------------|----------|------------|---------|
| N                      | N = 809,843  | N= 17,124| N= 792,719 |         |
| (100%)                 | (2.1%)       | (97.9%)  |            |         |
| Age - Median (IQR)     | 60 (50 - 70) | 58 (50 - 66) | 60 (50 - 70) | <0.001  |
| Age Group              |              |          |            |         |
| <40                    | 45,125 (5.6%)| 44,273 (5.6%) | 852 (5%)  | <0.001  |
| 40-64                  | 457,895 (56.5%)| 446,406 (56.3%) | 11,489 (67.1%) |        |
| ≥65                    | 306,811 (37.9%)| 302,040 (38.1%) | 4,771 (27.9%) |        |
| Race                   |              |          |            |         |
| Non-Hispanic White     | 598,316 (73.9%)| 14,295 (83.5%) | 584,021 (73.7%) | <0.001  |
| Non-Hispanic Black     | 86,142 (10.6%)| 1,254 (7.3%) | 84,888 (10.7%) |        |
| Asian/PI               | 23,832 (2.9%)| 407 (2.4%)  | 23,425 (3%)  |        |
| Native American        | 2,044 (0.3%) | 34 (0.2%)  | 2,010 (0.3%) |        |
| Hispanic               | 40,395 (5%)  | 689 (4%)   | 39,706 (5%)  |        |
| Other                  | 51,392 (6.3%)| 445 (2.6%)  | 50,947 (6.4%) |        |
| MH Annual Income       |              |          |            |         |
| <$38,000               | 124,384 (15.4%)| 2,210 (12.9%) | 122,174 (15.4%) | <0.001  |
| $38,000-$47,999        | 170,293 (21%)| 3,387 (19.8%) | 166,906 (21.1%) |        |
| $48,000-$62,999        | 211,569 (26.1%)| 4,241 (24.8%) | 207,328 (26.2%) |        |
| ≥$63,000               | 287,846 (35.5%)| 5,648 (33%)  | 282,198 (35.6%) |        |
| HS Graduation          |              |          |            |         |
| ≤79%                   | 120,386 (14.9%)| 1,722 (10.1%) | 118,664 (15%) | <0.001  |
| 79.1-87%               | 189,540 (23.4%)| 3,060 (17.9%) | 186,480 (23.5%) |        |
| 87.1-93%               | 262,112 (32.4%)| 5,180 (30.2%) | 256,932 (32.4%) |        |
| >93%                   | 222,457 (27.5%)| 5,561 (32.5%) | 216,896 (27.4%) |        |
| Facility Location      |              |          |            |         |
| West                   | 141,946 (17.5%)| 2,728 (15.9%) | 139,218 (17.6%) |        |
| Midwest                | 206,308 (25.5%)| 4,948 (28.9%) | 201,360 (25.4%) | <0.001  |
| Northeast              | 174,716 (21.6%)| 2,397 (14%)  | 172,319 (21.7%) |        |
| South                  | 215,157 (26.6%)| 3,690 (21.5%) | 211,467 (26.7%) |        |
|                        | All Patients | TDB          | NCDB         | P-Value |
|------------------------|--------------|--------------|--------------|---------|
|                        | N = 809,843  | N=17,124     | N= 792,719   |         |
|                        | (100%)       | (2.1%)       | (97.9%)      |         |
| Unknown                | 71,716 (8.9%)| 3,361 (19.6%)| 68,355 (8.6%)|         |
| Year                   |              |              |              |         |
| 2000-2003              | 176,815 (21.8%)| 11,909 (69.5%)| 164,906 (20.8%)| <0.001 |
| 2004-2007              | 122,845 (15.2%)| 3,560 (20.8%) | 119,285 (15%) |         |
| 2008-2012              | 510,183 (63%) | 1,655 (9.7%)  | 508,528 (64.1%)|         |
| Trial Slots Open at Time of Diagnosis/Enrollment |              |              |              |         |
| <500                   | 411,188 (50.8%)| 1,286 (7.5%)  | 409,902 (51.7%)| <0.001 |
| 500-1000               | 179,111 (22.1%)| 2,443 (14.3%) | 176,668 (22.3%)|         |
| >1000                  | 219,544 (27.1%)| 13,395 (78.2%)| 206,149 (26%) |         |

* HS, high school. MH, median household. IQR, interquartile range. PI, Pacific Islander. TDB, trial database.
† t-tests and Chi-square tests were used to compare continuous and categorical characteristics, respectively, between groups.
Table 2. NCI-sponsored Cooperative-Group Trials with Breast Surgical Oncology Patients Enrolled between 2000-2012*

| Trial          | Phase | Surgical Intervention? | Year (Start-Completion Date/Published) | # Enrolled (Published) | # Enrolled (CTEP) | Age | cT | cN | cM | Receptor | Breast Surgery | Functional Status | Sex | Previous Malignancy Allowed |
|----------------|-------|------------------------|----------------------------------------|------------------------|-------------------|-----|----|----|----|----------|----------------|--------------------|-----|-----------------------------|
| ACOSOG-Z001022 | III   | Yes                    | 1999-2003                             | 5539                   | 5267              | ≥18 | 1-2|    |    |          | Lumpectomy       | ECOG≤2             | F   | Yes                         |
| ACOSOG-Z001123 | III   | Yes                    | 1999-2004                             | 891                    | 846               | ≥18 | 1-2|    |    |          | Lumpectomy       | ECOG≤2             | F   | No                          |
| ACOSOG-Z103122 | III   | No                     | 2006-2009 (Cohort A) 2009-2011 (Cohort B) | A: 377                 | 622               | ≥18 | 2-4e|    |    | ER+      | Lumpectomy       | All                | ECOG≤2             | F   | No                          |
| ACOSOG-Z104123 | III   | No                     | 2007-2011                             | 282                    | 282               | ≥18 | 0-4c|    |    | HER2+     | All              | All                | F   | No                          |
| ACOSOG-Z107124 | II    | Yes                    | 2009-2011                             | 756                    | 757               | ≥18 | 0-1| 1-2|    |          | Lumpectomy       | ECOG≤1             | F   | Yes                         |
| ACOSOG-Z107225 | II    | Yes                    | 2009-2013                             | 99                     | 99                | ≥18 | 1   |    |    |          | Lumpectomy       | ECOG≤2             | F   | No                          |
| ACOSOG-Z111026 | II    | Yes                    | 2012-2016                             | 223                    | 189               | ≥40 | 1-2|    |    |          | ER+ &/or PR+     | All                | ECOG≤1             | F   | Yes                         |
| CALGB-4090327  | III   | No                     | 2012-2016                             | 108                    | 105               | ≥18 | is/1mi |    |    |          | ER+ &/or PR+     | All                | ECOG≤1             | F   | Yes                         |
| ECOC-210828     | III   | Yes                    | 2011-2015                             | 383                    | 392               | ≥18 | All | All | 1   | All      | All              | ECOG≤1             | F   | Both                        |
| NCCTG-N03389    | II    | No                     | 2005-2007                             | 57                     | 57                | ≥18 | 2-4|    |    |          | ER+ &/or PR+     | All                | ECOG≤1             | F   | No                          |
| NSABP-B-3231    | III   | Yes                    | 1999-2004                             | 5611                   | 5474              | ≥18 | 1-3| 0   |    |          | ER+ &/or PR+     | All                | N/A               | F   | No                          |
| NSABP-B-3532    | III   | No                     | 2003-2006                             | 3104                   | 3104              | ≥18 | is | 0   |    |          | Lumpectomy       | ECOG≤2             | F   | No                          |
| SWOG-S001231    | III   | No                     | 2001-2005                             | 399                    | 399               | ≥18 | T3N0, |    |    |          | All              | All                | ECOG≤2             | F   | No                          |
| SWOG-S992333    | III   | No                     | 2000-2003                             | 98                     | 98                | ≥21 | 1-2|    |    |          | Mastectomy       | ECOG≤1             | F   | No                          |

*ACOSOG, American College of Surgeons Oncology Group. CALGB, Cancer and Leukemia Group B. ECOG, Eastern Cooperative Oncology Group. NCCTG, North Central Cancer Treatment Group. NSABP, National Surgical Adjuvant Breast and Bowel Project. SWOG, Southwest Oncology Group.
Table 3. Multivariate Logistic Regression on Likelihood of Trial Participation of Breast Surgical Oncology Trial Participants vs NCDB Controls, 2000-2012 *†

|                        | OR (95% CI) | P-Value | Overall P-Value |
|------------------------|-------------|---------|-----------------|
| Age Group              |             |         |                 |
| 40-64                  | -REF-       |         |                 |
| <40                    | 0.70 (0.65 – 0.76) | <0.001  |                 |
| ≥65                    | 0.59 (0.57 – 0.61) | <0.001  |                 |
| Race/Ethnicity         |             |         |                 |
| Non-Hispanic White     | -REF-       |         | <0.001          |
| Non-Hispanic Black     | 0.80 (0.75 - 0.85) | <0.001  |                 |
| Hispanic               | 0.84 (0.77 - 0.92) | <0.001  |                 |
| Asian/PI               | 0.93 (0.83 - 1.03) | 0.16    |                 |
| Native American        | 0.72 (0.50 - 1.04) | 0.08    |                 |
| Other                  | 0.26 (0.23 - 0.29) | <0.001  |                 |
| HS Graduation          |             |         |                 |
| ≤79%                   | -REF-       |         | <0.001          |
| 79.1-87%               | 1.21 (1.13 - 1.29) | <0.001  |                 |
| 87.1-93%               | 1.71 (1.60 - 1.82) | <0.001  |                 |
| >93%                   | 2.55 (2.37 - 2.75) | <0.001  |                 |
| MH Income              |             |         |                 |
| <$38,000               | -REF-       |         | <0.001          |
| $38,000-47,999         | 0.92 (0.86 - 0.97) | 0.005   |                 |
| $48,000-62,999         | 0.80 (0.75 - 0.85) | <0.001  |                 |
| ≥$63,000               | 0.63 (0.59 - 0.68) | <0.001  |                 |
| Facility Location      |             |         |                 |
| West                   | -REF-       |         | <0.001          |
| Midwest                | 1.33 (1.27 - 1.40) | <0.001  |                 |
| Northeast              | 0.74 (0.70 - 0.78) | <0.001  |                 |
| South                  | 1.15 (1.09 - 1.21) | <0.001  |                 |
| Unknown                | 1.44 (1.35 - 1.53) | <0.001  |                 |
| Slots/Year             |             |         |                 |
| <500                   | -REF-       |         | <0.001          |
| 500-1000               | 4.40 (4.11 - 4.72) | <0.001  |                 |
| >1000                  | 20.03 (18.88 - 21.24) | <0.001  |                 |

*HS, High School. MH, Median Household. PI, Pacific Islander.
†Trial participants = 15,483, NCDB eligible controls = 771,101, no interaction terms
Table 4a. Multivariate Logistic Regression on Likelihood of Trial Participation of Breast Surgical Oncology Trial Participants vs NCDB Controls, 2000-2012, with interaction terms*†‡

|                                | OR (95% CI) | P-Value | Overall P-Value |
|--------------------------------|-------------|---------|-----------------|
| **Age Group**                  |             |         |                 |
| 40-64                          | -REF-       |         |                 |
| <40                            | 0.71 (0.65 – 0.76) | <0.001 |                 |
| ≥65                            | 0.59 (0.56 – 0.61) | <0.001 |                 |
| **HS Graduation**              |             |         |                 |
| ≤79%                           | -REF-       | <0.001  |                 |
| 79.1-87%                       | 1.23 (1.16 – 1.32) | <0.001 |                 |
| 87.1-93%                       | 1.74 (1.63 – 1.86) | <0.001 |                 |
| >93%                           | 2.59 (2.40 – 2.79) | <0.001 |                 |
| **MH Income**                  |             |         |                 |
| <$38,000                       | -REF-       | <0.001  |                 |
| $38,000-47,999                 | 0.77 (0.59 – 0.99) | 0.04   |                 |
| $48,000-62,999                 | 0.74 (0.58 – 0.95) | 0.02   |                 |
| ≥$63,000                       | 0.64 (0.50 – 0.80) | <0.001 |                 |
| **Facility Location**          |             |         |                 |
| West                           | -REF-       | <0.001  |                 |
| Midwest                        | 1.33 (1.26 – 1.39) | <0.001 |                 |
| Northeast                      | 0.73 (0.69 – 0.77) | <0.001 |                 |
| South                          | 1.16 (1.10 – 1.22) | <0.001 |                 |
| Unknown                        | 1.44 (1.35 – 1.54) | <0.001 |                 |
| **Race/Ethnicity**             |             |         |                 |
| Non-Hispanic White             | -REF-       | <0.001  |                 |
| Asian/PI                       | 1.61 (0.51 – 5.09) | 0.42   |                 |
| Hispanic                       | 6.06 (4.45 – 8.25) | <0.001 |                 |
| Native American                | 2.95 (0.93 – 9.37) | 0.07   |                 |
| Non-Hispanic Black             | 1.30 (0.94 – 1.79) | 0.11   |                 |
| Other                          | 0.74 (0.36 – 1.52) | 0.41   |                 |
| **Slots/Year**                 |             |         |                 |
| <500                           | -REF-       | 0.99    |                 |
| 500-1000                       | 4.31 (3.34 – 5.55) | <0.001 |                 |
| >1000                          | 21.62 (17.47 – 26.77) | <0.001 |                 |
| **Income*Slots/Year**          |             |         |                 |
| Interaction a                  |             | 0.01    |                 |
| **Income* Race/Ethnicity**     |             |         |                 |
| Interaction a                  |             | <0.001  |                 |
| **Slots/Year * Race/Ethnicity**|             |         |                 |
| Interaction a                  |             | <0.001  |                 |
| **Income* Race/Ethnicity * Slots/Year** |     |         | <0.001 |
| Interaction a                  |             |         |                 |

*HS, High School. MH, Median Household. OR, odds ratio. PI, Pacific Islander.
†Trial participants = 15,483, NCDB eligible controls = 771,101, 3- and 2-way-interactions included
‡ORs for interactions are not shown. Select clinically relevant pairwise odds ratios are presented in Table 4b.
| Race/Ethnicity | MH Income | OR (95% CI) | P-Value | Adjusted P-Value |
|---------------|-----------|-------------|---------|-----------------|
| **Racial Difference at >1000 Slots/Year (Given Race vs. Non-Hispanic White)** | | | | |
| Asian/PI      | <$38,000  | 0.57 (0.29 - 1.12) | 0.10 | 0.13 |
|               | ≥$63,000  | 1.04 (0.88 - 1.23) | 0.62 | 0.62 |
| Hispanic      | <$38,000  | 0.53 (0.41 - 0.69) | <0.001 | <0.001 |
|               | ≥$63,000  | 0.57 (0.44 - 0.73) | <0.001 | <0.001 |
| Non-Hispanic Black | <$38,000 | 0.94 (0.84 - 1.06) | 0.30 | 0.35 |
|               | ≥$63,000  | 0.66 (0.54 - 0.79) | <0.001 | <0.001 |
| **MH Income Difference (≥$63,000 vs. <$38,000)** | | | | |
| Race/Ethnicity | Slots/Year | OR (95% CI) | P-Value | Adjusted P-Value |
| Asian/PI      | <500      | 0.27 (0.08 - 0.95) | 0.04 | 0.06 |
|               | >1000     | 1.24 (0.63 - 2.47) | 0.53 | 0.57 |
| Hispanic      | <500      | 0.19 (0.12 - 0.29) | <0.001 | <0.001 |
|               | >1000     | 0.73 (0.51 - 1.05) | 0.09 | 0.13 |
| Non-Hispanic Black | <500 | 0.45 (0.28 - 0.74) | 0.002 | 0.003 |
|               | >1000     | 0.48 (0.38 - 0.59) | <0.001 | <0.001 |
| Non-Hispanic White | <500 | 0.64 (0.51 - 0.81) | <0.001 | <0.001 |
|               | >1000     | 0.68 (0.63 - 0.74) | <0.001 | <0.001 |

* MH, Median Household. OR, odds ratio. PI, Pacific Islander.
† Derived from multivariate logistic regression model described in Table 4a; hundreds of pairwise ORs were generated but only those of greatest clinical relevance are displayed.
‡ Benjamini-Hochberg procedure was used to adjust p-values for multiple comparisons.
Figure 1a-d. Unadjusted Trial Participation Rates of Breast Cancer Patients in NCI-sponsored Surgical Oncology Trials, 2000-2012
| Race/Ethnicity         | 2000-2003 >=$63k | 2000-2003 <$38k | 2008-2012 >=$63k | 2008-2012 <$38k |
|-----------------------|------------------|----------------|------------------|-----------------|
| Asian/PI              | 7.17%            | 3.95%          | 0.23%            | 0.33%           |
| Hispanic              | 3.48%            | 2.67%          | 0.58%            | 1.39%           |
| Non-Hispanic Black    | 4.45%            | 5.56%          | 0.35%            | 0.35%           |
| Non-Hispanic White    | 7.13%            | 5.96%          | 0.32%            | 0.25%           |
| **Breslow-Day p-value** | 0.003            |                |                  | <0.001          |

Figure 1a-d
