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Socioeconomic and Clinical Factors Are Key To Uncovering Disparity in Accrual Onto Therapeutic Trials for Breast Cancer

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Abstract

To monitor and address disparity in accrual, patient participation in cancer clinical trials is routinely summarized by race/ethnicity. To investigate whether confounding obscures racial/ethnic disparity in participation, all women with breast cancer treated by medical oncologists at City of Hope Comprehensive Cancer Center from 2004 through 2009 were classified by birthplace and self-reported race/ethnicity, and followed for accrual onto therapeutic trials through 2010. Undetectable on univariate analysis, significantly reduced participation by subjects of African, Asian, Eastern European, Latin American, and Middle Eastern ancestries was revealed after accounting for age, socioeconomic factors, tumor and oncologist characteristics, and intrapractice clustering of patients.

Diversity among clinical research subjects is essential for ensuring that trial results are generalizable to the full population of patients.¹ In addition, trial participation may provide direct benefit to patients, who as subjects may receive more comprehensive care and access to experimental treatments not otherwise available. For these reasons, cancer centers routinely monitor disparity in accrual onto therapeutic trials by race/ethnicity and gender. This monitoring serves to inform institutional efforts to eliminate disparity in clinical trial participation.²

Studies of cooperative group trials^{3–5} have concluded that African American,^{3–5} Asian,^{4,5} and Hispanic^{3–5} patients are accrued at lower rates than non-Hispanic white patients. However, systematic reviews^{6,7} have concluded that the quality of studies on barriers to participation in cancer clinical trials is poor, with many threats to internal and external validity (eg, selection bias, poor survey design, hypothetical vs documented participation).⁷

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Uncontrolled confounding by socioeconomic factors threatens the validity of reported associations with race/ethnicity.³⁻⁶ According to a national study of patients with breast cancer aged 65 years or older,⁸ after age and county economic attributes are accounted for, African and Asian patients are no less likely and Hispanic patients are nearly 3 times more likely to participate in trials than Caucasian patients.

When evaluating disparities in clinical trial accrual, potential confounding factors are not limited to socioeconomic characteristics of the patient or her community. Clinical factors, such as younger age,^{9,10} more advanced stage of disease,^{9,10} newly diagnosed status,¹⁰ good performance status,¹⁰ and having an oncologist who is a principal investigator of breast cancer trials,¹¹ promote the likelihood that a patient with breast cancer will be offered a trial. The treatment setting also plays a role: centers with approved cancer programs (ie, comprehensive cancer centers) tend to promote accrual onto clinical trials more than other centers.⁵

To understand the extent to which socioeconomic and clinical factors may obscure disparity in accrual, the authors identified all women with breast cancer treated by medical oncologists at City of Hope Comprehensive Cancer Center in recent years; classified them per birthplace and self-reported race/ethnicity as primarily of African, Asian, Latin American, Eastern European, Middle Eastern, and other Caucasian ancestry; followed them for accrual onto therapeutic trials; and evaluated the association between ancestry and accrual, before and after accounting for socioeconomic and clinical factors.

Methods

Subjects

Because the study used deidentified data, the City of Hope Institutional Review Board granted a waiver of informed consent. Subjects were consecutive women with breast cancer (stage I-IV) first treated by a medical oncologist at the institution during 2004 through 2009, an era that was determined by the study cohort. (Patients seen only once for a second opinion were by definition never accrued onto a trial and thus were ineligible for the study. Out-of-state residents were too few [n=5] to permit their inclusion as a subgroup.) If a subject had synchronous breast tumors, only characteristics of the more advanced or hormone-negative tumor were studied. In cases of metachronous tumors, only characteristics of the first tumor were studied.

Definitions and Data Sources

The study's end point was accrual onto a trial of adjuvant, neoadjuvant, or nonadjuvant treatment for breast cancer from 2004 through 2010; this information was obtained from the center's protocol accrual database. Breast cancer trials were continuously available during the study. By definition, accrued subjects received at least one dose of assigned treatment. There was no matching of accrued and nonaccrued patients.

Self-reported data on race, Hispanic ethnicity, primary language, and birthplace were routinely collected on admission via written questionnaire. Infrequently, it was necessary to abstract missing data on subjects' primary language or place of birth from the medical

record (ie, from notation about self-reported nationality, linguistic preference, or use of a translator, such as staff or family member). From race, ethnicity, and birthplace, subjects were assigned a primary ancestry for this study using the following hierarchy: African (per primary racial identity), Asian (per primary racial identity), Middle Eastern (per birthplace), Eastern European (per birthplace), Latin American (per ethnicity), and the referent category of “other Caucasian” (per ethnicity [non-Hispanic], race [white], and birthplace [North America or Western Europe]). The few patients born abroad to non-Hispanic white parents in Asia or South Africa were classified as “other Caucasian.” No subject identified herself as Native American or Pacific Islander.

Zip code–level data on income and education were obtained from the United States Census Bureau’s American Community Survey, 2007–2011.¹² For “median household income during the past 12 months,” data were expressed in 2011-adjusted dollars. For educational attainment, percentage lacking a high school education among women aged 25 years or older of the subject’s own race/ethnicity was studied. Subjects (n=22) residing in zip codes that were too small to generate these data were assigned the sample’s median of “median household income” and the race/ethnicity-specific median of “percentage of adult females lacking high school education.”

Statistical Analysis

The study’s primary hypothesis was that accrual onto breast cancer trials varies by ancestry, the referent category being patients of “other Caucasian” ancestry. Covariates considered in the generalized estimating equations of binary outcome were characteristics relating to the patient (primary language, immigrant status, age at first visit, marital status, type of health insurance), zip code (distance to cancer center, median household income, race/ethnicity-specific percentage of adult women without high school education), tumor (stage, hormone [estrogen, progesterone] receptor status, HER2/neu status, calendar year of first visit, time since diagnosis), and the oncologist (status as principal investigator [PI] of any therapeutic trial of breast cancer treatment, time in practice at the institution, fluency in the patient’s primary language). The first model ignored all covariates; the second model took into account age and all covariates (tumor and oncologist characteristics, patient- and zip code–level socioeconomic factors, any interactions between covariates) that improved the model’s fit to the observed data. Both models took into account correlation among subjects treated by the same oncologist (intrapractice clustering of patients) using an independent type of correlation matrix structure. For each model, overall study error (potentially inflated from testing multiple types of ancestry) was maintained at less than 5% by using the Holm-Bonferroni adjustment to *P* values.¹³

Results

The subjects were 1482 women with breast cancer who presented for treatment at age 55.7 ± 12.4 years (Table 1). Of these, 446 (30.1%) were accrued onto a therapeutic trial during the observation period. Most subjects (70.0%) who participated in a trial were accrued onto relatively large trials (11 protocols that enrolled 10–126 current subjects each); 8 of those protocols offered informed consent documents in Spanish. In contrast, small-scale trials (55

protocols that enrolled 1–8 current subjects each) rarely obtained Spanish translations of consent documents.

Before any covariates were considered (Table 2, see column “Model Without Covariates”), accrual did not vary significantly by ancestry, except for a deficit among patients of Middle Eastern ancestry. In contrast, after accounting for socioeconomic and clinical covariates (Table 2, see column “Model With Covariates”), significant deficits in accrual became apparent for patients in all nonreferent categories of ancestry (African, Asian, Eastern European, Latin American, Middle Eastern). Moreover, these deficits differed from each other: for all possible contrasts between deficits, unadjusted *P* value was .02 or less. All socioeconomic and clinical covariates contributed to the model’s fit to the observed data except oncologist’s fluency in the patient’s primary language, which was the only covariate that was dropped from the final model.

Discussion

As demonstrated by the current study, disparity in accrual onto cancer clinical trials may go unrecognized unless socioeconomic and clinical factors are taken into account. In this study, adjustment for socioeconomic factors does not eliminate associations with race/ethnicity, as reported by others,^{8,14,15} but instead helps reveal ancestry-related disparities that otherwise would remain obscure. Also helpful to that end was statistical methodology that accounts for correlation among patients treated by the same oncologist.

The proportion of current subjects accrued onto a trial (30%) seems similar to reports of studies of patients with breast cancer at other comprehensive cancer centers (34%¹⁰ and 18%¹⁶). In all 3 studies, accrual onto trials varied by age; variation in age distribution across study samples makes direct comparisons between studies difficult.

Contrary to expectation, the authors found that lack of fluency in English alone does not constitute a barrier to accrual but instead exacerbates the barrier associated with increasing age at first visit. That age barrier displays no threshold corresponding to the elderly; instead, after age 40 years, age has a gradual adverse effect on accrual, suggesting that subjects are offered trials based on functional criteria without regard to chronologic age. Also contrary to expectation, the authors found that immigrant status promotes rather than deters accrual and that accrual does not vary based on whether the physician is able to speak the patient’s primary language.

Consistent with findings of an earlier report,¹¹ the authors found that accrual is enhanced when the subject’s physician is a PI for breast cancer trials. Contrary to previous reports of below-average⁸ or average⁵ accrual of Medicaid-insured patients, the authors observed their accrual to be heightened, but only when the oncologist was a PI. Otherwise-insured patients also experienced heightened accrual with PIs, whom the authors found to enroll subjects without regard for years since diagnosis. In contrast, non-PI oncologists enroll subjects without regard for their insurance status but do preferentially accrue patients who are at least 3 years beyond diagnosis.

Previous studies have associated accrual with higher income and other measures of socioeconomic status^{5,14} and inversely with local poverty and unemployment.⁸ Similarly, in the current study, accrual increases with median household income within the subject's zip code, but only in the upper half of the income distribution. At the same time, however, accrual in the current study is favorably associated with certain measures of socioeconomic disadvantage (Medicaid eligibility; low educational attainment among similar women in the subject's zip code), independent of income. These findings show that those socioeconomic factors apparently promote the offer and/or acceptance of a clinical trial.

According to the authors' analysis, the deficits in accrual currently observed by ancestry cannot be attributed to lack of fluency in English, language gap between physician and patient, or the other socioeconomic and clinical factors studied. Instead, a more likely explanation for disparity in accrual may be differing levels of health literacy, "the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions."¹⁷ Limited health literacy can result in less awareness of and/or willingness to participate in clinical trials; one or both of these factors have been associated with Asian, African American, and Hispanic ethnicity among patients attending oncology clinics.^{18,19} Additional patient characteristics that may contribute to disparity in trial accrual are belief that the disease's outcome is inevitable or "in God's hands,"¹⁵ preference against active decision-making²⁰ or against undergoing treatment,^{13,21} and weight given to perceived personal benefit versus altruism.^{13,22,23}

Limitations of the current study include its setting at a single cancer center, data on income and education being available for the patient's zip code rather than for the patient herself, and lack of data on comorbidities,¹⁴ performance status,¹⁰ and health literacy. In addition, offers and acceptances of trials were not tracked prospectively, and whether any subjects participated in therapeutic trials elsewhere could not be ascertained. Nevertheless, these limitations are routinely encountered when cancer centers monitor patient accrual onto therapeutic trials.

Further study is needed to identify and address the specific barriers to trial accrual that disproportionately affect "minority" women with breast cancer. From such research, clinical investigators may learn how to promote trial accrual among all eligible patients, regardless of their ancestry.

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Table 1

Characteristics of Patients With Breast Cancer at First Visit, by Trial Accrual Status

Characteristics	Total ^a (Column %)	Accrued ^b (Row %)	P ^c
Ancestry, per birthplace and self-reported race/ethnicity			.08
African	78 (5.3)	24 (30.8)	
Asian	242 (16.3)	66 (27.3)	
Eastern European	20 (1.3)	4 (20.0)	
Latin American	420 (28.3)	138 (32.9)	
Middle Eastern	96 (6.5)	18 (18.8)	
Other Caucasian ^d	626 (42.2)	196 (31.3)	
Primary language			.02
English	1246 (84.1)	377 (30.3)	
Spanish	138 (9.3)	50 (36.2)	
Other	98 (6.6)	19 (19.4)	
Immigrant			.60
Yes	570 (38.5)	167 (29.3)	
No	912 (61.5)	279 (30.6)	
Age (y)			<.0001
22–39	120 (8.1)	43 (35.8)	
40–49	362 (24.4)	125 (34.5)	
50–59	467 (31.5)	152 (32.6)	
60–69	330 (22.3)	98 (29.7)	
70–79	141 (9.5)	22 (15.6)	
80–95	62 (4.2)	6 (9.7)	
Health insurance			<.01
Medicaid/none	413 (27.9)	145 (35.1)	
Medicare or private insurance	1069 (72.1)	301 (28.2)	
Marital status			.16
Single	235 (15.9)	83 (35.3)	
Married	915 (61.7)	274 (30.0)	
Separated	30 (2.0)	11 (36.7)	
Divorced	155 (10.5)	45 (29.0)	
Widowed	143 (9.7)	32 (22.4)	
Unknown	4 (0.3)	1 (25.0)	
Median household income within zip code			.62
<\$45,500	214 (14.4)	68 (31.8)	
\$45,500–\$65,499	554 (37.4)	163 (29.4)	
\$65,500–\$85,499	487 (32.9)	140 (28.8)	
\$85,500	227 (15.3)	75 (33.0)	

Characteristics	Total ^a (Column %)	Accrued ^b (Row %)	P ^c
Percentage of race/ethnicity-matched women 25 y in zip code who lack high school education			.03
<5%	309 (20.9)	98 (31.7)	
5% to <30%	894 (60.3)	248 (27.7)	
30%	279 (18.8)	100 (35.8)	
Distance from zip code to cancer center			.13
<5 miles	105 (7.1)	25 (23.8)	
5 to <10 miles	261 (17.6)	79 (30.3)	
10 to <20 miles	447 (30.2)	140 (31.3)	
20 miles:			
Within Los Angeles or contiguous counties	620 (41.8)	194 (31.3)	
In more distant counties	49 (3.3)	8 (16.3)	
Tumor stage			<.0001
I	406 (27.4)	90 (22.2)	
II	589 (39.7)	162 (27.5)	
III	327 (22.1)	124 (37.9)	
IV	160 (10.8)	70 (43.8)	
ER status			<.0001
Positive	1092 (73.7)	296 (27.1)	
Negative	384 (25.9)	150 (39.1)	
Unavailable	6 (0.4)	0 (0)	
PR status			.02
Positive	906 (61.1)	249 (27.5)	
Negative	560 (37.8)	192 (34.3)	
Unavailable	16 (1.1)	5 (31.3)	
HER2 status			.13
Positive	336 (22.7)	116 (34.5)	
Negative	1020 (68.8)	295 (28.9)	
Unavailable	126 (8.5)	35 (27.8)	
ER/PR/HER2 status			.001
ER-, PR-, HER2-	206 (13.9)	76 (36.9)	
ER-, PR-, HER2 unavailable	157 (10.6)	62 (39.5)	
ER+ and/or PR+	1114 (75.2)	308 (27.5)	
ER, PR, HER2 all unavailable	5 (0.3)	0 (0)	
Years since diagnosis			.08
<1	460 (31.0)	126 (27.4)	
1	794 (53.6)	243 (30.6)	
2	68 (4.6)	17 (25.0)	

Characteristics	Total ^a (Column %)	Accrued ^b (Row %)	P ^c
3	160 (10.8)	60 (37.5)	
Calendar year			.003
2004	202 (13.6)	76 (37.6)	
2005	239 (16.1)	75 (31.4)	
2006	247 (16.7)	77 (31.2)	
2007	223 (15.1)	62 (27.8)	
2008	254 (17.1)	86 (33.9)	
2009	317 (21.4)	70 (22.1)	
Oncologist's role in breast cancer trials			<.0001
Principal investigator	769 (51.9)	297 (38.6)	
Not a principal investigator	713 (48.1)	149 (20.9)	
Duration of oncologist's practice at this institution			<.0001
<5 y	795 (53.6)	195 (24.5)	
5 y	687 (46.4)	251 (36.5)	
Oncologist fluent in patient's primary language			.95
Yes, English	1233 (83.2)	371 (30.1)	
Yes, language other than English	22 (1.5)	6 (27.3)	
No	227 (15.3)	69 (30.4)	

Abbreviations: ER, estrogen receptor; HER2, HER2/neu; PR, progesterone receptor.

^aN=1482.

^bN=446.

^cP value from univariate chi-square testing.

^dEnglish-speaking, non-Hispanic Caucasian patients born in the United States, Canada, Great Britain, Western Europe, or to such parents living in Asia or South Africa.

Table 2

Primary Ancestry as a Risk Factor for Accrual Onto a Therapeutic Trial for Breast Cancer (N=1482)

	Model Without Covariates		Model With Covariates	
	Odds Ratio (95% CI)	Holm-Adjusted P Value	Odds Ratio (95% CI)	Holm-Adjusted P-Value
Primary ancestry, per birthplace and self-reported race/ethnicity				
African	0.98 (0.80–1.19)	1.00	0.70 (0.54–0.92)	.011
Asian	0.82 (0.65–1.04)	.39	0.49 (0.42–0.58)	<.001
Eastern European	0.55 (0.25–1.19)	.39	0.27 (0.12–0.60)	0.003
Latin American	1.07 (0.84–1.38)	1.00	0.56 (0.42–0.76)	<.001
Middle Eastern	0.51 (0.33–0.78)	.01	0.35 (0.25–0.50)	<.001
Other Caucasian	1.00		1.00	
<i>Clinical Covariates:</i>				
Stage of tumor				
I			1.00	
II			1.24 (0.99–1.55)	
III			2.07 (1.57–2.74)	
IV			3.11 (2.31–4.19)	
Calendar year of first visit, by ER status ^a				
2004, any ER status			2.45 (1.73–3.48)	
2005–2007, any ER status			1.39 (1.07–1.80)	
2008, ER+			1.39 (1.07–1.80)	
2008, ER–			4.25 (2.94–6.15)	
2009, any ER status			1.00	
Physician's duration of practice at institution				
<5 y			0.82 (0.70–0.96)	
≥5 y			1.00	
Physician's role in breast cancer trials, by patient's health insurance and time since diagnosis ^a				
PI, Medicaid/uninsured patient, any time since diagnosis			3.52 (2.08–5.97)	
PI, Medicare/insured patient, any time since diagnosis			2.32 (1.66–3.25)	
Not a PI, any insurance status:				
Diagnosed ≥3 y before first visit to this center			2.27 (1.39–3.69)	
Diagnosed <3 y before first visit to this center			1.00	
<i>Socioeconomic Covariates:</i>				
Age at first visit to this center, by primary language ^a				

	Model Without Covariates		Model With Covariates	
	Odds Ratio (95% CI)	Holm-Adjusted <i>P</i> Value	Odds Ratio (95% CI)	Holm-Adjusted <i>P</i> -Value
Per (year of age beyond 39 y) ² /100, English			0.95 (0.93–0.97)	
Per (year of age beyond 39 y) ² /100, not English			0.87 (0.84–0.91)	
Immigrant				
Yes			1.34 (1.05–1.71)	
No			1.00	
Divorced				
Yes			0.75 (0.58–0.98)	
No			1.00	
Residential zip code				
Within the local or contiguous county			1.00	
Within a more distant county			0.33 (0.17–0.65)	
Median household income of zip code				
Per (\$1000 In Excess of \$66,000) ²			1.03 (1.02–1.05)	
Per (\$1000 In Excess of \$66,000) ² /100			0.95 (0.93–0.98)	
Educational attainment of race/ethnicity-matched women in zip code				
Per 1% of women >25 y lacking high school education			1.02 (1.00–1.03)	

Abbreviations: ER, estrogen receptor; PI, principal investigator.

^aThe categorization of risk factors was dictated by significant interaction between the variables listed.