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Research paper

How current reporting practices may mask differences: A call for examining cancer-specific demographic enrollment patterns in cancer treatment clinical trials

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ABSTRACT

Background: A lack of diversity among clinical trial (CT) participants remains a critical problem. Few studies have examined recruitment variability in cancer treatment CTs by cancer type. Given the increasing organ-specific specialization of oncologic care, an understanding of this variability may affect institutional recruitment practices.

Methods: This study examines three data sources from 2010 through 2014. The analyzed sample includes 3,580 CT participants identified in the institutional Clinical Trials Management System (CTMS) database and 20,305 incident cases of invasive cancer within a Comprehensive Cancer Center (CCC) institutional catchment area. A total of 341,114 incident cases of primary invasive cancer were identified through the California Cancer Registry (CCR). The primary study measurements were sociodemographic characteristics of the three populations (age, sex, race/ethnicity, and health insurance).

Results: Racial/ethnic disparities were observed, with more incident cases of Whites seen in cancer center (68%) and enrolled in CTs (72%) compared to incident cases in catchment area (67%) ($p < 0.001$) overall. More older adults (65) were enrolled in prostate cancer CTs (58%) than seen in cancer center (45%) ($p < 0.001$). Alternatively, fewer older adults were enrolled in breast and colorectal CTs than seen in cancer center ($p < 0.001$). Among colon ($p < 0.001$), breast ($p < 0.001$), and prostate ($p<0.001$) cancer types, insurance type significantly varied between incident cases in catchment area, cancer center, and among CT participants. For colorectal cancer, no difference in sex distribution was observed overall. A significant difference in insurance type within each cancer type was observed ($p < 0.001$).

Conclusions: These findings suggest that reporting overall recruitment frequencies may mask differences by cancer type.

1. Introduction

Well conducted and rigorous clinical trials are essential for cancer drug development. Accrual of racial/ethnic minorities, older adults, and patients from diverse sociodemographic backgrounds to cancer clinical trials is essential to increase the likelihood that trial results can be applied to all [1–3]. The Minority Health and Health Disparities Research Education Act of 2000 mandated the inclusion of minorities in clinical research and stressed the need for adequate sample sizes to make statistically supportable conclusions about causation [4]. Given the numerous challenges with accruing sufficient sample sizes of minorities and women, the new standard has evolved into being 'representative' of the underlying general population. In the era of precision medicine where therapies are tailored based on the clinical characteristics and particular biology of a tumor, the problem of underrepresentation (and under-sampling) in treatment clinical trials may further exacerbate

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inequalities in cancer treatment and outcomes, making it impossible to conclude the efficacy of novel therapies in minority groups [5,6]. To date, differences in accrual based on sex, age, and race/ethnicity persist, highlighting the inequities and potentially undermine the relevance of study finding to particular subpopulations [2,7–9].

In order to address this problem, National Cancer Institute designated Comprehensive Cancer Centers (NCI-CCC) across the United States are mandated to recruit racial/ethnic minorities and women to clinical trials proportionally to the population living in the catchment area and provide insight into potential variations to recruitment [10]. NCI-CCCs usually present overall results by sex and race/ethnicity as instructed in Cancer Center Support Grant (CCSG) Guidelines however the methodology for collecting these data have not been uniform across centers [10]. These reporting practices can mask important differences by clinic primary tumor site that may be indicators of drivers of cancer clinical trial participation disparities.

Disparities among cancer treatment clinical trial participants are well recognized [11–13]. Some studies have examined disparities within specific cancer types and identified the need for accruing representative patients within a tumor type [9]. The call for representation has largely endeavored to improve accrual of racial/ethnic minorities and women [14], however disparities in sex, age, and access also complicate the clinical trial recruitment landscape [15].

Given shifts in oncologic care to a more subspecialized model where medical oncologists practice within a cancer site-specific group, internal heterogeneity in recruitment practices ought to be examined. Disparity between the catchment area and cancer center reflects a need for targeted 'outreach' or activities to help bring patients to the CCC. On the other hand, a disparity between the types of patients seen at the cancer center and those accrued to cancer clinical trials reflects a need for improved 'in-reach' or internal recruitment efforts (Fig. 1). These categories of differences need to be determined in order to allocate recruitment efforts and resources in an appropriate manner.

This study had two main goals. First the study examined whether differences in recruitment were due to lack of outreach to the catchment areas or whether lack of representation of patients currently seeking care in the CCC. A secondary goal was to assess whether data presented at the overall level of the CCC masks differences within individual cancer types. This study compared the sociodemographic characteristics of patients enrolled in cancer treatment clinical trials (CTs) for breast, prostate and colorectal cancer from 2010 to 2014 at the Helen Diller Family Comprehensive Cancer Center (HDFCCC) at the University of California at San Francisco (UCSF), to all UCSF cancer patients, to, in turn all cancer patients living in the catchment area by cancer site. The conceptual model for this analysis is shown in Fig. 1. This analysis includes three selected cancer types (prostate, colorectal and breast) because these are common malignancies with a robust clinical trial infrastructure at the CCC.

2. Methods

2.1. Data collection

This study examined three data sources from 2010 through 2014. Specifically, data were queried from the institutional Clinical Trials Management System (CTMS) database for UCSF cancer interventional therapeutic clinical trial (CT) participant information regarding patients with prostate, breast, and colorectal cancers. A total of 3,580 CT participants were identified. All new ("incident") prostate, breast, and colorectal cancer cases treated at the HDFCCC through the UCSF institutional cancer registry were identified. A total of 20,305 CCC incident cases were identified. Finally, all incident invasive colon, breast, and prostate cancer diagnoses within the UCSF catchment area through the California Cancer Registry (CCR) were identified. The CCR is part of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program. The catchment area for the CCR is defined as the 48 Northern counties of California [16,17]. All new cases identified by autopsy were not included in the analysis. The total of 341,114 CA incident cases were examined in this study.

Sociodemographic information from all three data sources on age (less than 65; <65), race/ethnicity (White, Black, Asian American, and Pacific Islander [AAPI], Latino, and Other), sex, and insurance type at diagnosis (Medicaid, Medicare, Private, Veterans Affairs/Military, Other, Not insured) were collected. The following variables of interest were collected from the CTMS database: enrollment year for trial and cancer type.

All the research procedures were approved by the UCSF Committee on Human Research.

2.2. Statistical analysis

Sociodemographic and clinical characteristics were summarized by descriptive statistics. In general, frequency distribution and percentage were used to summarize categorical variables. Chi-square test was applied to test if the distributions of sociodemographic factors differed across the three populations and in pairwise comparison of populations. The statistical significance was declared at $P < 0.05$ and all the statistical analyses were computed by the statistical software STATA 15.0.

3. Results

3.1. All invasive cancers

The demographic distribution across all cancer types is summarized in Table 1. Among all cancer types, significantly more men were CT participants compared to women, a difference driven by more men being seen in the cancer center ($p < 0.001$). Age-based disparities were observed overall, and CT participants were significantly younger than incident cases in cancer center and catchment area ($p < 0.001$). The proportion of older adults was highest at 54% among the incident cases in the catchment area and lowest at 30% among CT participants. There was a significant difference in the distribution in race/ethnicity overall, with more White CT participants compared to incident cancer center cases and incident cases in catchment area (Fig. 2). The proportion of Whites increased from 67% among incident cases in catchment area to 68% in the cancer center to 72% among CT participants. While 20% of insurance was unknown among CT participants, insurance was observed to be significantly different overall ($p < 0.001$), and the proportion of Medicare insured decrease from incident cases in catchment area, cancer center and CT participants.

3.2. Patient characteristics in prostate, breast, and colorectal cancer

Among total incident cases in the catchment area for three cancer

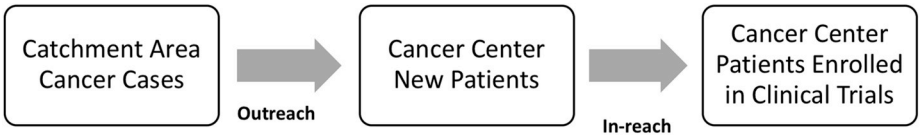

Fig. 1. CCC recruitment assessment conceptual model. 1. Catchment Area Cancer Cases; 2. Cancer Center New patients; 3. Cancer Center Patients Enrolled in Clinical Trials.

Table 1
Patient Characteristics for all cancer types.

Cancer Type	Characteristics		Catchment Area (CA) Incident Cases	CCC Incident Cases	CT Participants	*P* value (CA, CCC)	P value (CCC, CT)	Global P-value
All Cancer Types			No. (%)	No. (%)	No. (%)			
		Total	341,114	20,305	3580			
	Sex	Male	172,118 (50)	10,844 (53)	1,936 (54)	<0.001	0.457	<0.001
		Female	168,996 (50)	9,461 (47)	1,644 (46)			
	Age	00–64 years	157,208 (46)	12,879 (63)	2,506 (70)	<0.001	<0.001	<0.001
		65 + years	183,906 (54)	7,426 (37)	1,074 (30)			
	Race/Ethnicity	NH White	228,059 (67)	13,806 (68)	2,572 (72)	<0.001	<0.001	<0.001
		NH Black	19,565 (6)	1,078 (5)	145 (4)			
		Asian	40,026 (12)	2,811 (14)	449 (12)			
		Hispanic	45,063 (13)	2,227 (11)	350 (10)			
		Other	8,401 (2)	383 (2)	64 (2)			
	Insurance	Medicaid	23,498 (7)	2,894 (14)	273 (8)	<0.001	<0.001	<0.001
		Medicare	120,777 (35)	6,459 (32)	1,122 (31)			
		Private	156,737 (46)	9,702 (48)	1,437 (40)			
		Veterans Affairs/ Military	6,945 (2)	457 (2)	0 (0)			
		Other	16,906 (5)	619 (3)	15 (1)			
		Not insured	2,972 (1)	163 (1)	0 (0)			
		Unknown/Missing	13,279 (4)	11 (0)	733(20)			

types summarized in Table 2, 47% were male, 52% were ≥65 years (older adults), 35% were non-White, and 50% were privately insured. Among the 5,682 incident cases of invasive colon, breast, and prostate cancer in HDFCCC, 59% were male, 37% were older adults, 28% were non-White, and 54% were privately insured. Among the 1,326 cancer therapeutic clinical trial participants, 50% were male, 36% were older adults, 25% were non-White, and 42% were privately insured.

3.3. Cancer site-specific analysis

3.3.1. Prostate cancer

As seen in Table 2, prostate cancer CT participants (n = 345, 58%) were significantly older than the incident cases at the cancer center (n = 1,303, 45%, $p < 0.001$). However incident prostate cancer cases in the catchment area were significantly older than incident prostate cancer cases in cancer center ($p < 0.001$). Race/ethnicity differed across the three groups of men with prostate cancer ($p < 0.001$), driven by a larger percentage of White CT participants (81%) compared to incident prostate cancer cases among White men in catchment area (66%) ($p < 0.001$). Insurance differed across the three groups of men with prostate cancer ($p < 0.001$). The majority (51%) of CT participants were Medicare insured compared to 35% of incident cases in catchment area. The majority (55%) of incident cases in the cancer center had private insurance.

3.3.2. Breast cancer

Among patients with breast cancer, age varied significantly across the three groups ($p < 0.001$), where the proportion of older adults (≥65 years old) among incident cases in catchment area was significantly higher than cases observed in cancer center ($p < 0.001$). Race/ethnicity significantly differed across the three groups ($p < 0.001$), where 72% of CT participants were White compared to 66% of incident cases in catchment area ($p < 0.001$). Insurance type differed across the three groups overall ($p < 0.001$), and the majority of patients in all three groups were privately insured.

4.3.3. Colorectal cancer

No difference in sex distribution was observed between the three groups. Among patients with colon cancer, the age distribution was significantly different overall ($p < 0.001$), where older adults made up 23% of CT participants and 57% of incident cases in catchment area ($p < 0.001$). Race/ethnicity differed across all three groups, where 66% of CT participants were White compared to 65% of incident cases in catchment area ($p = 0.004$). Insurance type differed across the three groups ($p < 0.001$). The proportion of patients with Medicare insurance was observed to decrease across groups.

4. Discussion

This study found that disparities in race/ethnicity, age, and insurance type were observed across cancer types. Importantly, this study observed that different clinical practices for specific cancer types within a single CCC can lead to differential recruitment of underrepresented patients to cancer therapeutic clinical trials. To our knowledge, this is the first institutional-level analysis of disease-specific recruitment patterns.

Disparities based on age were observed to be both an outreach and in-reach problem at the CCC. However, the direction of disparities differed by cancer type. Specifically, in both breast and colorectal cancer, the incident cases in the cancer center and CT participants were younger than incident cases in catchment area, reflecting a need for both outreach and in-reach strategies to improve age-based disparities. However, for prostate cancer, the CT participants were older than incident cases in cancer center however closely reflected the patients living in the catchment area, demonstrating a need for outreach interventions among older adults with prostate cancer. For the race/ethnicity analysis, the data suggests that most of the effort for addressing disparities needs to be in outreach in order to better ensure that the incident cases in the cancer center reflect the incident cases at the catchment area.

This analysis suggests that CCCs should examine the heterogeneity of recruitment practices by cancer type in order to ensure equitable accrual of patients to cancer clinical trials overall. This analysis revealed that reporting practices of CCCs may mask differences observed in the individual level. There are limitations in this analysis. Given that these data were examined for a single site, similar cancer specific assessments will need to be performed at other CCCs to verify the trends observed. Additionally, given that three data sources were used in this study, timing of data capture may introduce bias in our observations. For example, the central registry records insurance type at time of initial diagnosis, however by the time a patient presents to a cancer center or enrolls in a clinical trial, the insurance type may change which is not accounted for in this study.

Despite these limitations, the findings have important implications for addressing CT recruitment disparities. CCCs are required to present overall data on recruitment and accrual among racial/ethnic minorities however assessing heterogeneity in practice within one clinical setting is not routinely performed. Overall, accrual assessments may suggest

Table 2
Disease programs patient demographics 2010–2014.

Cancer Type	Characteristics		Catchment Area (CA) Incident Cases	CCC Incident Cases	CT Participants	*P*- value (CA, CCC)	P- value (CCC, CT)	Global P-value
Prostate			No. (%)	No. (%)	No. (%)			
		Total	43,568	2,883	590			
	Age	00–64 years	18,003 (41)	1,580 (55)	245 (42)	<0.001	<0.001	<0.001
		65 + years	25,565 (59)	1,303 (45)	345 (58)			
	Race/Ethnicity	NH White	28,630 (66)	2,262 (79)	476 (81)	<0.001	0.564	<0.001
		NH Black	3,621 (8)	182 (6)	36 (6)			
		Asian	3,885 (9)	233 (8)	46 (8)			
		Hispanic	5,408 (12)	155 (5)	26 (4)			
		Other	2,024 (5)	51 (2)	6 (1)			
		Missing	0 (0)	0 (0)	0 (0)			
	Insurance	Medicaid	1,207 (3)	104 (4)	9 (2)	<0.001	<0.001	<0.001
		Medicare	15,270 (35)	1,041 (36)	302 (51)			
		Private	21,509 (49)	1,572 (55)	191 (32)			
		Veterans Affairs/ Military	1,578 (4)	67 (2)	0 (0)			
		Other	1,731 (4)	66 (2)	3 (1)			
		Not insured	216 (0)	33 (1)	0 (0)			
		Unknown/Missing	2,057 (5)	0 (0)	85 (14)			
Breast								
		Total	53,615	1,910	609			
	Sex	Male	372 (1)	9 (1)	0 (0)	0.247	0.090	0.062
		Female	53,243 (99)	1901 (99)	609 (100)			
	Age	00–64 years	30,326 (57)	1,421 (74)	512 (84)	<0.001	<0.001	<0.001
		65 + years	23,289 (43)	489 (26)	97 (16)			
	Race/Ethnicity	NH White	35,384 (66)	1,296 (68)	440 (72)	<0.001	0.171	<0.001
		NH Black	3,035 (6)	101 (5)	22 (4)			
		Asian	7,465 (14)	350 (18)	99 (16)			
		Hispanic	6,945 (13)	144 (8)	45 (7)			
		Other	786 (1)	19 (1)	3 (1)			
		Missing	0 (0)	0 (0)	0 (0)			
	Insurance	Medicaid	4,136 (8)	286 (15)	29 (5)	<0.001	<0.001	<0.001
		Medicare	15,372 (29)	468 (25)	169 (28)			
		Private	29,075 (54)	1091 (57)	315 (52)			
		Veterans Affairs/ Military	302 (1)	18 (1)	0 (0)			
		Other	2,578 (5)	38 (2)	1 (0)			
		Not insured	282 (1)	9 (0)	0 (0)			
		Unknown/Missing	1,870 (3)	0 (0)	95 (15)			
Colorectal								
		Total	29,832	889	127			
	Sex	Male	15,379 (52)	460 (52)	74 (58)	0.910	0.168	0.318
		Female	14,453 (48)	429 (48)	53 (42)			
	Age	00–64 years	12,835 (43)	578 (65)	98 (77)	<0.001	0.007	<0.001
		65 + years	16,997 (57)	311 (35)	29 (23)			
	Race/Ethnicity	NH White	18,721 (63)	554 (62)	84 (66)	<0.001	0.188	<0.001
		NH Black	1,925 (6)	58(7)	9 (7)			
		Asian	4,394 (15)	170 (19)	28 (22)			
		Hispanic	4,246 (14)	92 (10)	5 (4)			
		Other	546 (2)	15 (2)	1 (1)			
		Missing	0 (0)	0 (0)	0 (0)			
	Insurance	Medicaid	2,069 (7)	145 (16)	5 (4)	<0.001	<0.001	<0.001
		Medicare	11,267 (38)	269 (30)	25 (20)			
		Private	13,322 (45)	419 (47)	55 (43)			
		Veterans Affairs/ Military	500 (2)	13 (2)	0 (0)			
		Other	1,657 (6)	33 (4)	0 (0)			
		Not insured	310 (1)	10 (1)	0 (0)			
		Unknown/Missing	707 (2)	0 (0)	42 (33)			

equitable enrollment however a cancer-specific analysis may uncover inequitable accrual within a particular cancer type. Overall, this analysis informs a need for targeted in-reach and outreach practices by cancer type to achieve equitable accrual to cancer clinical trials.

6. Conclusions

Reporting overall accrual patterns by CCC may mask differences observed at individual cancer level. Given that academic research centers are important sites for cancer clinical trial accrual [18], a rigorous process of investigating cancer-specific recruitment trends within a broader catchment area is needed. If each cancer center investigated their own cancer-specific accrual patterns in the context of their larger community, targeted interventions applying in-reach and outreach strategies can be designed to improve accrual of underrepresented populations.

Conflict of interest disclosure

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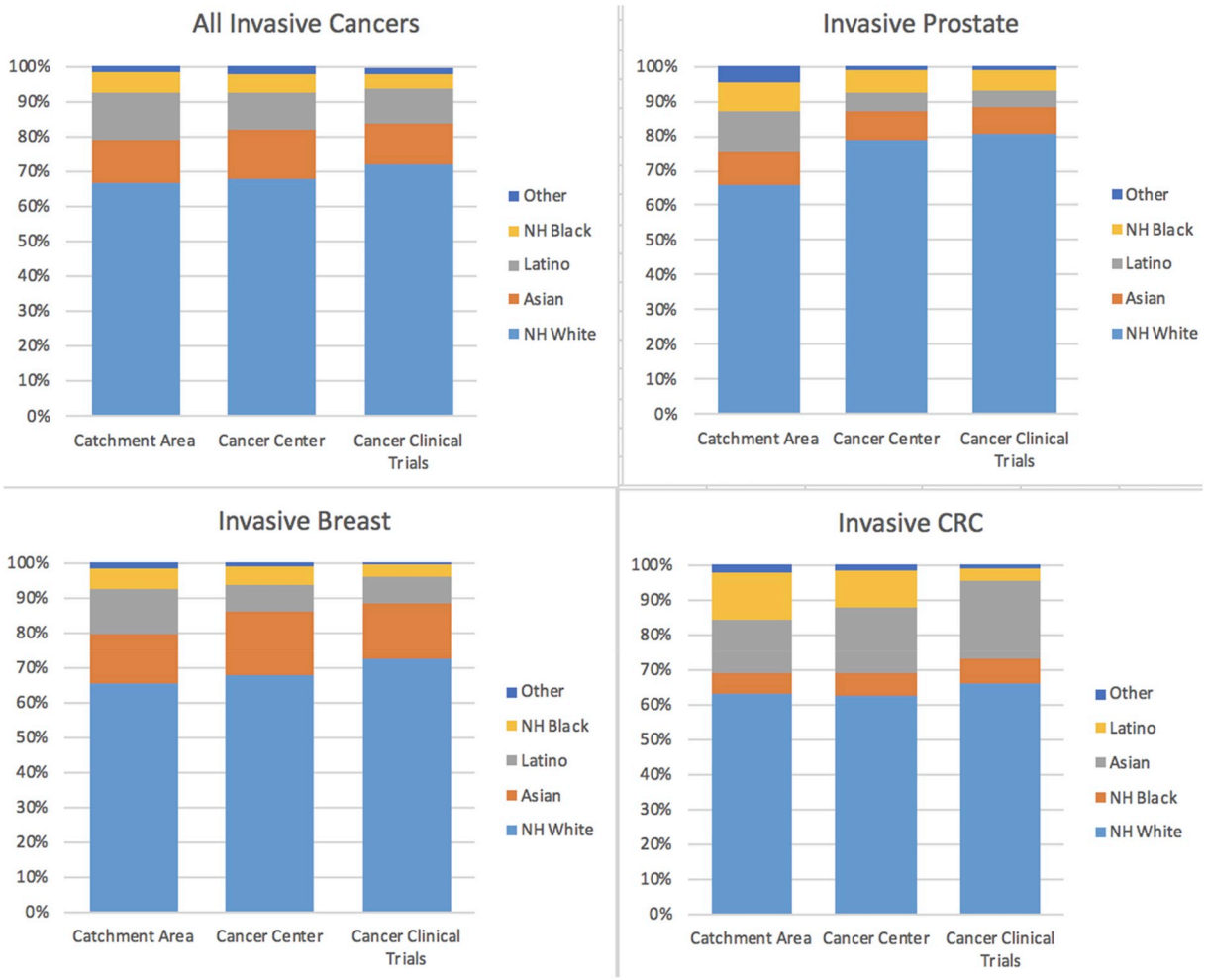

Fig. 2. Racial/ethnic distribution of patients within catchment area, seen at the cancer center, and enrolled in cancer clinical trials overall, and by disease type.

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