

Access Denied: Disparities in Thyroid Cancer Clinical Trials

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Abstract

For thyroid cancer clinical trials, the inclusion of participants from diverse patient populations is uniquely important given existing racial/ethnic disparities in thyroid cancer care. Since 2011, a paradigm shift has occurred in the treatment of advanced thyroid cancer with the approval of multiple systemic therapies by the US Food and Drug Administration based on their use in the clinical trials setting. Although these clinical trials recruited patients from up to 164 sites in 25 countries, the inclusion of racial/ethnic minority patients remained low. In this mini-review, we provide an overview of barriers to accessing cancer clinical trials, framed in the context of why patients with thyroid cancer may be uniquely vulnerable. Multilevel interventions and increased funding for thyroid cancer research are necessary to increase access to and recruitment of under-represented patient populations into thyroid cancer clinical trials.

Key Words: thyroid cancer, advanced thyroid cancer, disparities, clinical trial, cancer clinical trials, barriers to clinical trial enrollment

Abbreviations: FDA, US Food and Drug Administration; LEP, limited English proficiency; NIH, National Institutes of Health.

The outcomes of cancer clinical trials help to inform our understanding of novel therapeutics and have the potential to change clinical practice guidelines on what is standard of care in the treatment of patients with cancer. Thus, the inclusion of diverse and representative patient populations in cancer clinical trials is essential to improve the generalizability of trial results, including its efficacy and safety profile, to all patient populations who may use the drugs once approved by the US Food and Drug Administration (FDA) [1]. The National Institutes of Health (NIH) Revitalization Act of 1993 mandated the appropriate inclusion of women and racial/ethnic minorities in all NIH-funded clinical research [2]. Thirty years later, the participation of racial/ethnic minority patient populations in cancer clinical trials remains low [3–8]. Among its research goals, the National Institute on Minority Health and Health Disparities (NIMHD) aims to increase the overall proportion of participants from diverse populations included in NIH-funded clinical research to 40% by 2030 [9].

For thyroid cancer clinical trials, the inclusion of participants from diverse patient populations is uniquely important given existing racial/ethnic disparities in thyroid cancer care. Hispanic, Black, and Asian/Pacific Islander patients experience a disproportionate burden of disease and mortality related to thyroid cancer, which is the second most common cancer among Hispanic and Asian/Pacific Islander women in the United States [10, 11]. Studies have consistently found that non-White patients with thyroid cancer are more likely to be diagnosed at more advanced stage of thyroid cancer, more likely to experience postoperative complications from thyroid surgery, and less likely to receive guideline-concordant thyroid cancer care [12–18]. Likely related,

Hispanic and Asian/Pacific Islander women experience higher rates of mortality from thyroid cancer [19].

Historically, treatment options were so limited for patients with advanced thyroid cancer that access to thyroid cancer treatment often equated to access to a clinical trial. With the introduction of tyrosine kinase inhibitors for use as targeted therapy for thyroid cancer and advances in molecular genetic testing, new treatment options for advanced disease have become available. Since 2011, at least 10 systemic therapies have been approved by the FDA for treatment of advanced thyroid cancer based on its success in the clinical trial setting [20–27]. Although these clinical trials recruited patients from up to 164 sites in 25 countries, the final patient cohort was predominantly enrolled from European and North American sites. Furthermore, the non-White patient cohort ranged from 5% to 50% in each of these clinical trials, with 4% to 44% reported as Asian, 0% to 3% reported as Black, and 0% to 1% reported as Hispanic (Fig. 1) [20–31].

In this mini-review, we provide an overview of barriers to accessing cancer clinical trials, framed in the context of why patients with thyroid cancer may be uniquely vulnerable. In addition, we discuss potential strategies to improve access to thyroid cancer clinical trials for underrepresented patient populations in the United States.

Search Strategy

We searched PubMed using the key words “thyroid cancer,” “advanced thyroid cancer,” “disparities,” “clinical trial,” “cancer clinical trials,” and “barriers to clinical trial enrollment” to identify important themes, trends, and data described

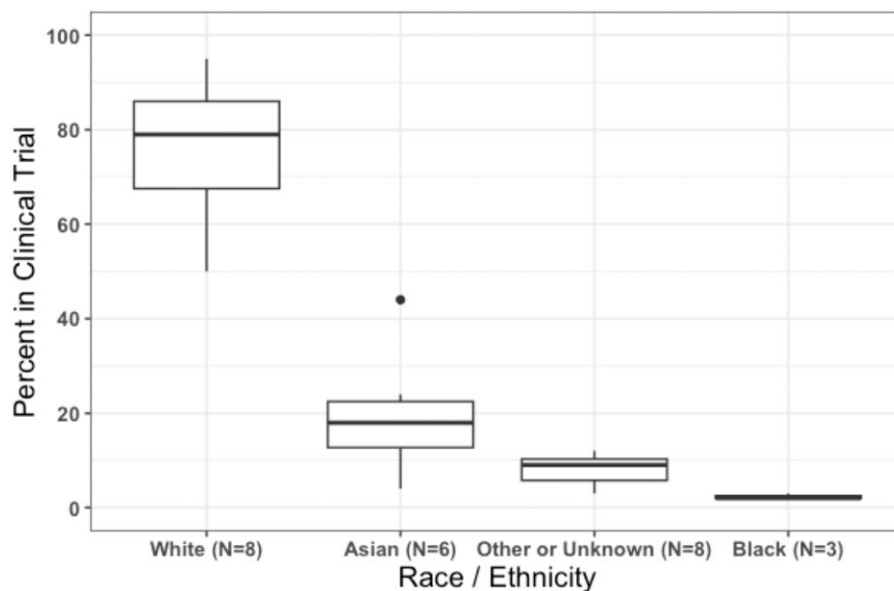


Figure 1. Race/ethnicity specific percentage reported in clinical trials that led to the US Food and Drug Administration (FDA)-approval of 10 systemic therapies for the treatment of advanced thyroid cancers. Only 8 of the clinical trials included any data on race/ethnicity: the phase 3 DECISION trial (sorafenib), phase 3 SELECT trial (lenvatinib), phase 3 ZETA trial (vandetanib), phase 3 COSMIC-311 trial (cabozantinib), phase 3 EXAM trial (cabozantinib), phase 1/2 LIBRETTO-001 study (selpercatinib), phase 1/2 ARROW study (pralsetinib), and the phase 2 ROAR basket study (dabrafenib/trametinib) [20-27]. The clinical trials that led to FDA approval of Entrectinib and Larotrectinib did not include race/ethnicity data on the patients with thyroid cancer who enrolled in the studies [28-31]. The EXAM trial and ZETA trial reported race as a dichotomous variable (White vs non-White, and White vs other race, respectively) [20, 26]—we included the latter categories in “other or unknown” in this figure.

in the current mini-review. Keywords were used alone or in combination with the “AND” term. We also searched the reference lists of articles identified by this search strategy and selected those that we judged relevant. Our reference list was also modified after comments from peer reviewers.

Barriers to Accessing Cancer Clinical Trial

Financial Barriers to Participating in Clinical Trials

Patients with thyroid and nonthyroid cancer are at risk for cancer-related financial hardship due to the burden of medical and nonmedical costs, missed work, job loss, and difficulty obtaining affordable health insurance [32-37]. Such financial hardship can influence cancer patients to become nonadherent to prescribed medications (ie, take less medication than prescribed, not fill or partially fill a prescription) and to forgo needed medical care [38]. Thus, patients who are at increased risk of cancer-related financial hardship, including low-income patients who are more sensitive to marginal financial expenses, may be less able to participate in cancer clinical trials [39, 40]. Although participation in a clinical trial is free, clinical trial participants are often required to invest a substantial amount of time (ie, time off from work, time traveling) and resources (ie, transportation and lodging cost, lost wages) to complete the trial protocol [33, 40]. In a single institutional study of patients who were eligible for participation in a cancer clinical trial, 13% declined because of the distance they would need to travel to get to the trial site [41]. Furthermore, some components of the clinical trial protocol (ie, laboratory studies and diagnostic testing) may be billed to patients' health insurance as standard of care for cancer treatment, with patients subsequently incurring routine care costs such as to copayments, coinsurance, and deductibles [33].

Patients with thyroid cancer, which is often diagnosed at a younger age than most other adult cancers [42], may be more

susceptible to cancer-related financial hardship compared to patients with nonthyroid cancers. Prior studies have found that younger age at time of cancer diagnosis is associated with increased likelihood of experiencing cancer-related financial hardship [43-46]. Barrows et al [44] reported that thyroid cancer survivors were more likely to report worry about having to pay large cancer-related medical bills compared to nonthyroid cancer survivors. Furthermore, a retrospective cohort analysis of individuals diagnosed with cancer between 1995 and 2009 in the western district of Washington state by Ramsey et al [47] found that the incidence rates for bankruptcy at 1 year after diagnosis was higher for individuals with thyroid cancer compared to those with lung, colorectal, breast, and prostate cancer. Studies of cancer survivors in general have also found that racial/ethnic minority patients are at increased risk of experiencing cancer-related financial hardship [45, 46, 48]. In a survey of 273 Hispanic women with differentiated thyroid cancer reported to the Los Angeles Surveillance Epidemiology and End Results (SEER) registry, Chen et al [49] found up to 38.0% of the cohort endorsed individual material measures of financial hardship due to thyroid cancer (38.0% had to use savings, 24.6% cut down on spending for food, 17.7% could not make payments on credit cards or other bills, 5.2% had to move out of their house or apartment because they could not afford to stay there, and 2.7% had their utilities turned off because the bill was not paid). In addition to race/ethnicity, thyroid cancer-related financial hardship appears to also be influenced by level of acculturation. In their survey of Hispanic women with thyroid cancer, Chen et al [49] also reported that while financial hardship decreased with age for high-acculturated women, financial hardship for low-acculturated women remained elevated across all age groups. Thus, given the higher risk of cancer-related financial hardship among patients with thyroid cancer and among racial/ethnic minority patients, the potential

financial burden associated with clinical trial participation remains a considerable barrier for racial/ethnic minority patient populations with thyroid cancer.

Structural Barriers Limits Enrollment of Diverse Patient Populations Into Clinical Trials

Despite the nearly 80% of cancer patients in general who receive their cancer care in community settings [50], most cancer clinical trials have traditionally been conducted at academic medical centers [51, 52]. In a meta-analysis of studies that examined the clinical trial decision-making pathway, Unger et al [53] found that 55.6% of cancer patients had zero cancer clinical trials available for their cancer type and stage at their treating medical center. The challenge with initiating clinical trials at nonacademic hospital sites is often related to structural barriers, including inadequate research infrastructure [53, 54]. A research infrastructure refers to the resources (ie, financial support, research staff, expertise, pool of patient participants from which to recruit, information technology systems, regulatory oversight committees, physical space, and facilities) and the coordination that is necessary to conduct a clinical trial [55]. In a Dallas safety-net hospital that cares for medically underserved patient populations, Gerber et al [56] found a substantial decrease in cancer clinical trial activation rates in the 2007 to 2014 period compared to the 1991 to 2006 period, with common reasons for nonactivation including an inability to perform the study procedure and the high startup costs. In semi-structured interviews, community oncologists noted

major barriers to patient enrollment in cancer clinical trials, including insufficient infrastructure support (ie, understaffed research personnel) and increased physician burden (ie, multiple competing factors resulting in limited physician time, knowledge, and awareness of trials) [50]. With racial/ethnic minority patient populations more likely to receive their thyroid cancer care at underresourced hospitals [57-59], the lack of diversity in cancer clinical trials likely reflects the substantial impact of inadequate research infrastructures.

Related to the lack of research infrastructure, racial/ethnic minority patients with thyroid cancer are at risk of being excluded from accessing cancer clinical trials as they are less likely to receive thyroid care by medical specialists and high-volume physicians. Using pooled data from the 2015 to 2018 Medical Expenditure Panel Survey (MEPS), Cai et al [60] found that even after accounting for several social determinants of access to care, racial/ethnic minority groups in general are significantly underrepresented in the outpatient practices of many medical and surgical specialties, including oncology and otolaryngology. Furthermore, in a population-based survey of patients with differentiated thyroid cancer, Radhakrishnan et al [61] found that patient-reported involvement of primary care physicians, endocrinologists, and surgeons in their thyroid cancer care varied by race/ethnicity. Non-White patients were more likely to report discussing thyroid cancer treatment with their primary care physicians and less likely to involve their surgeons. Thus, barriers to initiation of cancer clinical trials at nonacademic medical centers ultimately act to limit access to clinical trials for racial/ethnic minority patients, many of whom obtain their cancer care in the community setting.



Figure 2. Strategies to increase access to thyroid cancer clinical trials. To increase access to thyroid cancer clinical trials, interventions that address multilevel factors are necessary. At the level of the institution, health care executives and administrators need to prioritize the reduction of structural barriers to clinical trial participation. In addition, when designing clinical trial protocols, researchers should leverage existing technological advances in telemedicine to increase access to thyroid cancer clinical trials for underrepresented patient populations. Furthermore, for thyroid cancer clinical trials to be accessible to all patients regardless of socioeconomic status and English-language proficiency, funding agencies such as the National Institutes of Health and industry sponsors need to preemptively address financial and logistical barriers that may be relevant to patients with lower socioeconomic status and to racial/ethnic minority patient populations.

Language-based Barriers to Accessing Clinical Trials

In the United States, it is well documented that language barriers can lead to ineffective communication and negatively affect the quality of patients' health care [62-65]. Cancer patients with limited English proficiency (LEP) encounter similar challenges to accessing and participating in cancer clinical trials [66]. In a retrospective cohort study of patients with gynecologic cancers, Jorge et al [67] found that even after adjusting for ethnicity and insurance status, patients with LEP had 66% lower odds of participating in clinical trials than fluent English speakers. In addition, a survey of gynecologic research staff and providers identified the most significant barriers to research participation for patients with LEP to be the lack of translated consent forms and increased time needed to enroll patients with LEP [67]. This issue disproportionately affects community-based programs and underresourced health systems. Furthermore, cancer patients with LEP may be excluded from clinical trials on the basis of their language ability. Between 2019 and 2020, nearly 20% of US interventional clinical trials registered on ClinicalTrials.gov for adult populations in general required patients to have the ability to read, speak, and/or understand English [68].

For thyroid cancer, which has the highest mortality among Hispanic women and men and Asian/Pacific Islander women in the United States [19], language-based barriers to clinical trial participation may be especially relevant. In the United States, 35% of the Hispanic and Asian population have LEP [69]. Furthermore, about 1 in 5 Hispanic and Asian households are linguistically isolated, which the US Census Bureau defines as a household in which all adults speak

English less than “very well” [69]. For some patients with LEP, the barriers of clinical trial enrollment due to language discordance is magnified by literacy-related challenges during the informed consent process. Although it is generally recommended that consent forms be written at or below an eighth-grade reading level, most research-related documents are written at much higher reading levels [70-72]. However, 41% of the Hispanic population and 13% of the Asian population have below basic health literacy, which corresponds to being able to identify short straight-forward information in a text [73]. Thus, for Hispanic and Asian patients with thyroid cancer, language-based barriers may substantially limit their access to thyroid cancer clinical trials.

Strategies to Improve Access to Thyroid Cancer Clinical Trials

The lack of diversity and representation in cancer clinical trials is a decades-old issue. As such, nonthyroid cancer research has increasingly focused on multilevel strategies to overcome identified barriers to enhance the recruitment and retention of diverse patient populations. We next discuss potential strategies to increase access to thyroid cancer clinical trials for underrepresented patient populations (Fig. 2).

At the level of public policy, more funding for thyroid cancer research is needed to better understand barriers and facilitators to enrollment of underrepresented patient populations in thyroid cancer clinical trials. Although thyroid cancer is the seventh most common cancer in women [74], the second most common cancer in Hispanic and Asian/Pacific Islander women [10, 11], and was one of the most rapidly increasing cancers in the United States until recently [19], thyroid cancer research at the NIH continues to be underfunded relative to other cancer types. Despite the substantial clinical and economic burden associated with thyroid cancer [75], the National Cancer Institute allocated only \$13.5 million (ranked 28th) to thyroid cancer research in 2018 [76].

At the level of the institution, health care executives and administrators need to prioritize the reduction of structural barriers to clinical trial participation for vulnerable patient populations. This includes the development and strengthening of well-resourced research infrastructure in the community setting where racial/ethnic minority patient populations are more likely to obtain their cancer care [50, 53, 77]. In addition, the formation of targeted partnerships between community hospitals, including hospitals that are embedded in underserved communities, and academic medical centers is important to increase access to cancer clinical trials for underrepresented patient populations [78].

When designing clinical trial protocols, researchers can leverage existing technological advances to increase access to thyroid cancer clinical trials for underrepresented patient populations [79]. With the rapid adoption of telemedicine in cancer care delivery in recent years [80, 81], the incorporation of telehealth visits in cancer clinical trials may make it more accessible for patients by avoiding the inconvenience and expense of travel and time off from work [82, 83]. In addition, researchers may be able to leverage patient portals, which are associated with institutional electronic health records, to increase engagement with and recruitment of underrepresented patient populations.

For thyroid cancer clinical trials to be accessible to all patients regardless of socioeconomic status and English-language

proficiency, funding agencies such as the NIH and industry sponsors need to preemptively address financial and logistical barriers that may be relevant to patients with lower socioeconomic status and to racial/ethnic minority patient populations. Allocation of funds for financial reimbursement of trial-related expenditures (ie, for travel and/or lodging) would help to mitigate the financial burden of out-of-pocket expenses associated with clinical trial participation. Pilot studies of financial reimbursement programs for nonthyroid cancer clinical trials have yielded promising results [84-86]. Furthermore, since Hispanic and Asian/Pacific Islander patients with thyroid cancer are more likely to experience worse outcomes [10, 11], and both of these racial/ethnic groups have high rates of LEP [69], it may be beneficial to invest in the translation of clinical trial documents into non-English languages. In addition, the availability of patient information, both in English and non-English text, about thyroid cancer clinical trials in the ClinicalTrials.gov database would improve access through increased patient awareness of existing thyroid cancer clinical trials.

Conclusion

Since 2011, a paradigm shift has occurred in the treatment of advanced thyroid cancer with the recent FDA approval of multiple systemic therapies based on their use in the clinical trials setting. Thus, the lack of diversity in thyroid cancer clinical trials not only limits the generalizability of trial results, but also represents a disparity in access to high-quality thyroid cancer care. Multilevel interventions and increased funding for thyroid cancer research are necessary to increase access to and recruitment of underrepresented patient populations into thyroid cancer clinical trials.

Disclosures

The authors have nothing to disclose.

Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during the current study.

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