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# Chapter 2

## **Under-representation of racial minorities in prostate cancer studies submitted to the FDA to support potential marketing approval, 1993-2013**

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### **Abstract**

*Background:* United States (US) Food and Drug Administration (FDA) approval of new drugs depends on results from clinical trials that must be generalized to the US population. However, racial minorities are frequently under-represented in clinical studies. Enrollment of racial minorities was compared in key clinical studies submitted to the FDA in the last 10 years in support of potential marketing approval for prostate cancer (PCa) prevention or treatment.

*Methods:* Patient demographic data were obtained from archival datasets of large registration trials submitted to the FDA to support proposed PCa indications. Six countries/regions were analyzed: US, Canada, Australia, "Europe", United Kingdom and Eastern Europe. Background racial demographics were collected from national census data.

*Results:* Seventeen key PCa clinical trials were analyzed. These trials were conducted in the past twenty years, comprising 39,574 patients with known racial information. A majority of patients were enrolled in the US, but there appears to be a trend towards increased non-US enrollment over time. In all countries/regions, racial minorities were generally under-represented. There was no significant improvement in racial minority enrollment over time. The US enrolled the largest non-white population (7.1%).

*Conclusions:* Over the past twenty years, racial minorities were consistently under-represented in key PCa trials. There is a need for effective measures that will improve enrollment of racial minorities. With increased global enrollment, drug developers should aim to recruit a patient population which resembles the racial demographics of the patient population to which drug use will be generalized upon approval.

## Introduction

Prostate cancer (PCa) incidence and mortality rates vary among races. Between 2006 and 2010, the age-adjusted PCa incidence rates were 144.9, 228.5, 81.8 and 77.8 per 100,000 men in white, black, Asian and Native American men in the United States (US), respectively.<sup>1</sup> The age-adjusted PCa mortality rates were 21.2, 50.9, 10.1 and 20.7 per 100,000 men in the respective racial groups.<sup>1</sup> These results indicate that black people are most prone to PCa disease and death. In contrast, Asians are least likely to be diagnosed with and die from PCa. Comparing incidence rates to mortality rates, relative mortality is strikingly higher in black and Native American populations. In general, these patient groups present with more advanced disease and receive less aggressive treatment.<sup>2-6</sup> Furthermore, black patients diagnosed with very low-risk PCa may have more advanced PCa than white patients with the same diagnosis.<sup>7</sup> Multiple underlying factors may contribute to aforementioned epidemiological findings, such as genetic tumor alterations, differences in lifestyle, cultural and socioeconomic factors, distances needed to travel to the nearest hospital for treatment (which for multiple American Indian tribes can exceed 100 miles), variations in participation in population-based PSA screening, and non-conformity in clinical trial participation between racial groups.<sup>6, 8-15</sup>

Because the presentation of PCa disease differs amongst racial groups, the response to PCa therapies may also differ. Therefore, the US Food and Drug Administration (FDA) strongly recommends conducting clinical trials testing novel PCa drugs in a population that adequately represents the racial distribution of the US population that would receive the drug in a clinical setting. Nevertheless, minority accrual in clinical trials has been a challenge, as minorities are traditionally under-represented in clinical trials.<sup>14, 15</sup> Disparity between racial distribution in clinical trial populations compared to the average US population has been a factor in FDA decisions in the past. For example, during the Oncology Drug Advisory Committee meeting discussing finasteride and dutasteride for the chemoprevention of PCa in December 2010, the FDA noted that these studies lacked adequate enrollment of black patients, questioning how well the studies represented the average US PCa population. Therefore, minority accrual is of high importance in clinical studies with PCa patients.

In the current study, we report the enrollment of racial minorities in key clinical trials conducted in PCa patients submitted for FDA review in the past two decades. Minority accrual was compared across various countries/regions in the world. We further investigated whether minority accrual has changed over time.

## Methods

### *Data collection*

For the collection of demographic data, various statistical government resources, publicly available on the internet, were used. These included US 2010 census data, Canadian 2011

national household survey data, Australian 2011 census data, United Kingdom Census 2001 data, data from Institut Montaigne (French demographics) and data from the Czech Statistical Office (Český statistický úřad).

Key clinical trials submitted for FDA review in which patients were recruited between 1993 and 2013 were analyzed regardless of the marketing approval outcome. The proposed therapeutic indications were specific to PCa patients, i.e. drug or biologic products that sought approval for the treatment of bone metastases in cancer patients in general were not included in this study. Datasets from selected clinical trials were retrieved from FDA's archives. Anonymity was applied to non-public data.

### *Data analyses*

Data were analyzed for the following regions: globally, US, Canada, Australia, "Europe", United Kingdom and Eastern Europe. Countries in "Europe" included the 27 countries in the European Union (excluding Croatia) and the 4 countries forming the European Free Trade Association. Eastern European countries consisted of all countries in Europe east of the former Berlin wall, including Russia, but excluding Turkey. Turkey was considered part of West-Asia (the Middle East).

Eighteen key, or "pivotal", PCa clinical trials were identified during the time period specified in our analysis, 1993-2013. Of these, the key study supporting FDA approval of mitoxantrone was excluded from our analysis, as racial demographics of these patients had not been collected. The remaining 17 clinical trials, all included in our analysis, included key studies for review of abiraterone acetate, atrasentan hydrochloride, cabazitaxel, degarelix, denosumab, docetaxel, dutasteride, enzalutamide, finasteride, leuprorelin (six-month formulation), radium-223 dichloride, satraplatin, sipuleucel-T and triptorelin (six-month formulation).

On the basis of the initiation of patient enrollment, the 17 selected clinical trials were divided into two major time periods. In group 1, clinical trials were included that initiated enrollment between 1993 and 2004 (n=7); trials that initiated enrollment after 2004 were included in group 2 (n=10). Group 1 marks clinical trials that were designed before FDA approval of docetaxel, while clinical trials in group 2 were designed after docetaxel had been approved for its use in patients with castrate-resistant PCa.

US FDA guidelines recommend that investigators separately collect demographics regarding race and ethnicity in clinical trials.<sup>16</sup> In these guidelines, racial groups are divided into white, black, Asian, American Indian/Alaska Native, Pacific Islander, or other. Ethnicity is divided into Hispanic/Latino or non-Hispanic/Latino. In line with these guidelines, we divided race into white, black, Asian, native or other. White patients included people with European descent, the Middle East and Africa north of the Sahara. Black patients descended from sub-Saharan

Africa. Asian patients included all patients from Asian descent except for the Middle East and Russia. Natives were considered American Indians, Alaska Natives, Canadian Indians, Pacific Islanders and Aborigines. The race “other” primarily consisted of patients with a multiracial background.

A majority of studies in our analysis did not report Hispanics as a separate ethnicity, but as a race. All patients whose registered race was “Hispanic” were excluded from analyses, as only their ethnicity, but not their self-reported race, was known. Patients who did not have their race reported were also excluded from our analyses. In total, the race of  $\geq 90\%$  of patients was retrieved for analysis.

We calculated enrollment estimates for racial minorities that reflect the incidence and mortality of PCa amongst racial populations in the US to further explore whether minority representation was adequate in the clinical trials analyzed. To estimate projected patient enrollment in the US based on PCa incidence, we multiplied the age-adjusted incidence of PCa in each racial group by their proportion in the US population based on 2010 US census data. For each race, the calculated number was divided by the sum of all calculated numbers. This resulted in estimates of the percentage of each racial group needed in a PCa clinical trial to reflect the racial distribution of patients diagnosed with PCa. A similar procedure was used to estimate the projected patient minority enrollment in the US based on PCa mortality, which would approximately represent the racial distribution of patients who die from PCa.

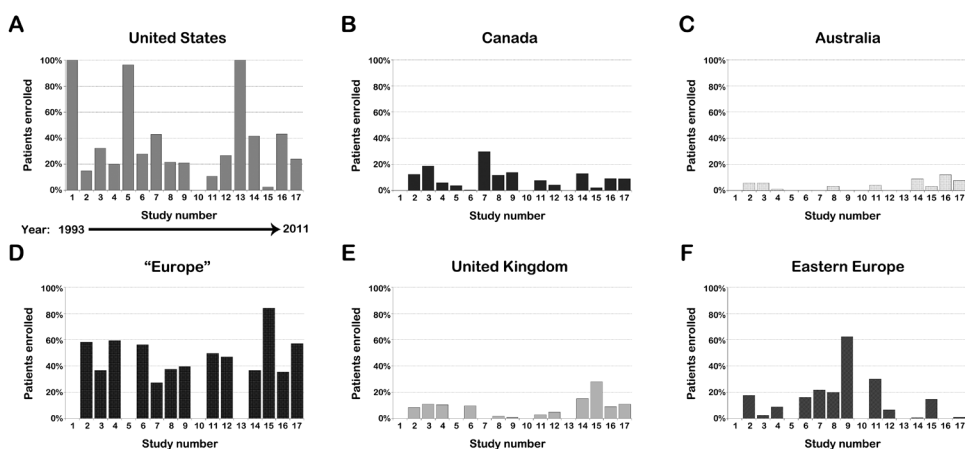
## Results

In total, 40,912 patients had been enrolled in selected clinical trials between October 1993 and February 2011. The race of 1,338 patients was unknown and were excluded. Of the remaining 39,574 patients, 60.2% were enrolled in the US, 26.5% in “Europe” (4.6% in the United Kingdom), 6.6% in Eastern Europe, 4.8% in Canada and 1.6% in Australia (Table 1).

**Table 1.** The percentage of patients enrolled per nation/region in key prostate cancer clinical trials analyzed in the current study.

Country/Region	Percentage of patients enrolled
United States	60.2%
Canada	4.8%
Australia	1.6%
“Europe”	26.5%
United Kingdom	4.6%
Eastern Europe	6.6%

Patients from the 17 trials were pooled together. Note that not all percentages add up to 100% because some studies enrolled patients in other countries/regions than listed, and because patients from the United Kingdom and parts of Eastern Europe are also counted in “Europe”.



**Figure 1.** Percentages of patients enrolled from selected nations/regions in key prostate cancer clinical trials.

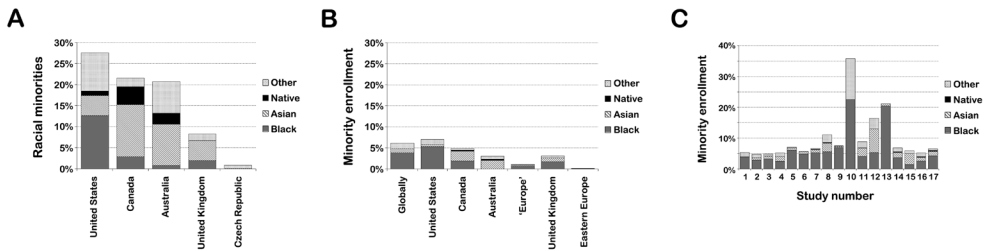
The percentage of patients enrolled in each analyzed country/region is displayed for all individual studies as shown in Figure 1, sorted by time of enrollment initiation. Patient enrollment varied widely between different studies: some studies completely enrolled patients in the US, while one recruited patients outside the US only.

Next we studied whether there was a difference in enrollment in countries between key PCa clinical trials initiated before or after 2005 (Table 2). Patient enrollment in the US had decreased. Enrollment in Canada was relatively low and slightly decreased post-2005. In contrast, patient enrollment in European countries was higher post-2005. Patient enrollment in Australia was also higher; however, this increase was driven mostly by the four most recent studies, in which up to 12% of patients were enrolled in Australia (Table 2, Fig. 1C). Although Eastern European enrollment was higher in group 2 compared to group 1, enrollment of Eastern Europeans decreased again in the most recent studies of group 2 (Fig. 1F).

**Table 2.** Average percentage of patients enrolled in key PCa clinical trials initiated before and after FDA docetaxel approval per analyzed nation/region.

Country/region	1993-2004	2005-2013
United States	47.7%	29.2%
Canada	10.1%	7.1%
Australia	1.8%	3.9%
"Europe"	34.0%	38.7%
United Kingdom	5.6%	7.4%
Eastern Europe	9.5%	13.5%

Percentages were calculated by dividing the sum of percentage enrollment in each individual study by the number of studies. Note that not all percentages add up to 100% because some studies enrolled patients in other countries/regions than listed, and because patients from the United Kingdom and parts of Eastern Europe are also counted in "Europe".



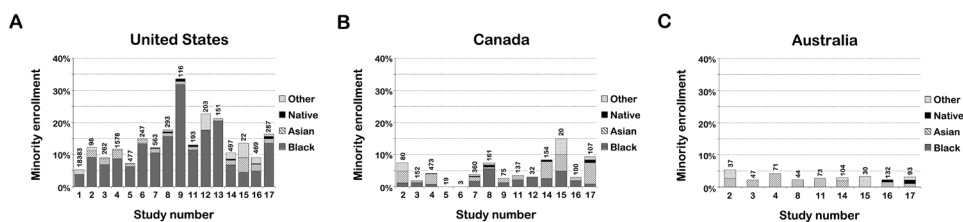
**Figure 2.** Racial minority demographics in Western nations/regions and enrollment of racial minorities in key PCa trials. A) Demographic distribution of racial minorities in a selection of Western nations. B) Global racial minority enrollment and racial minority enrollment in selected nations/regions. C) Global enrollment of racial minorities for each key PCa clinical trial.

In B), data was pooled from all 17 key PCa studies.

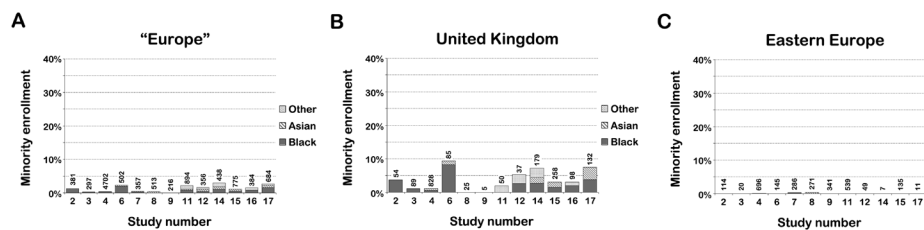
Our analyses further focused on enrollment of racial minorities in the selected PCa clinical trials in relation to national/regional racial minority population statistics. Studying national census data across the various countries, the non-white population was largest in the US (27.6%), while in Eastern European countries such as the Czech Republic less than 1% of the population consisted of non-whites (Fig. 2A). Pooling racial demographic data from all 17 studies and comparing enrollment between different nations/regions, enrollment of racial minorities was largest in the US (7.1%) (Fig. 2B); this population primarily consisted of black patients (5.3%). In other countries/regions, enrollment of racial minorities did not exceed 5%; minority accrual was virtually non-existent in Eastern Europe. Hence, comparing enrollment of racial minorities (Fig. 2B) to the expected pool of eligible patients based on census data (Fig. 2A), enrollment of racial minorities was appreciably lower across all nations/regions. Comparing global enrollment of racial minorities over time, enrollment of non-whites seemed to be consistent at approximately 5-10% (Fig. 2C). Exceptions were study 10, 12 and 13, which enrolled more than 15% of racial minorities. Study 10 was performed entirely outside the US. As this was a non-Western nation, it was not further analyzed. Study 13 was conducted completely in the US; study 12 had a large Asian population as this study had a higher enrollment in Asia compared to the other studies.

In the US, enrollment of racial minorities was higher across all studies as compared to global minority enrollment (compare Fig. 3A to Fig. 2C), possibly due to the large minority population in the US in general (Fig. 2A). Notably, enrollment of racial minorities was more than 20% in studies 9, 12 and 13 (Fig. 3A). In studies 12 and 13, Hispanic/Latino ethnicity was not collected as a separate category. Therefore, these patients may have been included in the racial groups 'black' and 'other', increasing minority enrollment as measured in this study compared to clinical trials in which the Hispanic population was excluded from analysis. The reported minority enrollment in study 9 excluded the 9% Hispanics from the analysis, as their race had not been collected separately from ethnicity.





**Figure 3.** Enrollment of racial minorities in key PCa clinical trials in A) the United States, B) Canada and C) Australia.



**Figure 4.** Enrollment of racial minorities in key PCa clinical trials in “Europe” (all countries of the European Union plus the European Free Trade Association), the United Kingdom, and Eastern Europe (all countries east of the former Berlin wall, including Russia but excluding Turkey).

Studies were excluded from graphs if no patient had been enrolled in the analyzed nation/region for that particular study. The total number of patients enrolled from the analyzed country/region (including white patients) is listed above each bar.

Racial minority enrollment did not exceed 15% in any Canadian (Fig. 3B) or Australian (Fig. 3C) study population. Comparing enrollment of racial minorities between Canada and Australia, which have a similar proportion of racial minorities in the population (Fig. 2A), Australia enrolled markedly fewer racial minorities.

In “Europe”, enrollment of racial minorities was relatively low (Fig. 4A). We further specified enrollment in the United Kingdom (Fig. 4B), a Western European country with an extensive colonial history, and in Eastern European countries (Fig. 4C). As one would expect based on the demographics (Fig. 2A), enrollment of racial minorities was higher in the United Kingdom, while virtually all patients enrolled in Eastern Europe were white. Similar results were found when analyzing minority enrollment of France separately: in line with its demographics, racial minority enrollment was higher in France compared to Eastern Europe, but slightly lower compared to the United Kingdom (data not shown).

## Discussion

Data from our study indicate that racial minorities are consistently under-represented in major clinical trials assessing novel PCa therapies, also relative to differences in population demographics by country. This finding is consistent with previous reports regarding PCa and other diseases.<sup>14, 15</sup> Treatment benefit may differ between racial groups due to variations

in tumor characteristics.<sup>9</sup> Therefore, the US FDA and other regulatory authorities strongly recommend registration of racial demographics for clinical studies.<sup>16</sup> Furthermore, studies have indicated that oncology patients who participated in clinical trials had better survival compared to non-participants.<sup>14, 17, 18</sup> These results may have been biased: patients with a worse prognosis may have been excluded from clinical trials, and physicians treating patients in a clinical trial may adhere more strictly to provided study protocols. For adjuvant breast cancer treatment, protocol adherence was strongly associated with improved survival.<sup>17</sup> Therefore, PCa survival may improve among minorities with increased participation in clinical trials.

In this study, we compared racial minority enrollment in PCa studies to the expected accrual based on census data. Our analysis has several important limitations. First, census data are self-reported and are only representative of people who respond to the questionnaires. Second, demographics were collected inconsistently: while in some studies Hispanics were reported under a separate category for ethnicity as recommended by US FDA guidelines,<sup>16</sup> in a majority of studies Hispanics were reported as a separate race. Third, to be able to adequately study the treatment effect in racial minorities, one could argue that enrollment of racial minorities should be increased even further. Fourth, data from the SEER database indicate that the incidence and mortality of PCa is higher in the black population than in the white population in the US.<sup>1</sup> Therefore, one could argue that adequate representation of the US PCa patients should include a higher percentage of black patients than reported in the census (12.6%). For example, we estimated that in studies performed in the general PCa population, evaluating a treatment in early stage disease (such as finasteride and dutasteride for PCa risk reduction), a representation of the US population would include 31.1% non-whites, and 18.9% black patients specifically. For therapies aimed at patients with late stage disease (such as enzalutamide for metastatic castrate-resistant PCa patients after docetaxel treatment), a stage at which most patients will eventually die from PCa, should include an estimated 26.1% black population due to the higher mortality rate in this racial group. The latter two examples further demonstrate that enrollment of racial minorities needs to be improved compared to current enrollment.

There are obvious limitations to grouping patients into broad phenotypic categories (white, black, Asian, native and other minorities). These racial groups are only very general predictors of biologic variations that may result in differences in PCa growth and therapy response. These biologic differences, in addition to environmental, socioeconomic and dietary variability, may be substantial between two populations categorized as the same race but from differing countries. E.g., while people from the Arabian Peninsula and North Africa are by consensus considered white in epidemiological studies, it is highly likely that substantial differences in environmental and genetic factors exist between these two

subgroups and Europeans within the same racial category. Similarly, significant differences may exist between Japanese patients living in Japan compared to those of Japanese ancestry who reside in the US. Despite these limitations, capturing racial demographics in clinical trials remains an important tool to ensure that the population enrolled more accurately approaches the general PCa population within a country. Furthermore, racial demographic data can identify potential challenges in clinical trial access, and reveal differences in the safety and efficacy of a therapy between racial subgroups, potentially aiding in the discovery of predictive biomarkers.

Although the need to increase minority accrual has universally been acknowledged, it remains a challenge as to how this goal can be achieved. Various efforts have had limited success in the past; for instance, efforts to increase enrollment of racial minorities in the PCPT study were fruitless.<sup>19</sup> The limited success of efforts to improve enrollment of racial minorities is reflected in our study results, as no significant improvement in minority recruitment has been made over the past two decades.

Previous research indicated that white and non-white patients have an equal interest in learning about clinical trials.<sup>20</sup> However, the investigators also found that the media used to collect information about clinical trials differed between racial groups in the US. While white patients used the internet and physicians more often as an information source, racial minorities more often relied on information provided by other patients. This is seemingly in contrast with a study by Markman et al., which suggested that the internet may be useful as a source to recruit minorities for participation in clinical trials.<sup>21</sup> Other studies have identified additional factors that may improve minority enrollment, such as approaching Asian patients by a more senior doctor, informing patients by staff and/or local leaders from the same ethnicity, and making use of written translations.<sup>22</sup> Furthermore, while most clinical trials are performed in university hospitals in major cities, rural minorities, particularly Native Americans in the US, would benefit if patients in community/peripheral hospitals would be recruited for studies too. Most importantly, studies concluded that the main factor influencing enrollment of racial minorities was level of trust.<sup>20, 22, 23</sup>

Despite the limited success of improving enrollment of racial minorities in oncology studies in general, some studies were more successful in recruiting minorities, such as study 9 in our analysis. Additional exploration indicated that enrollment of black patients was particularly high in one study site in Aventura, Florida. Here, 19 out of 29 patients enrolled in the study were classified as black; half of all black patients enrolled in this study were enrolled from this site. The population that this hospital served included a large population from the Caribbean, primarily indicated as “white/other, Hispanic” in the US census data. There seems to be discrepancy in reporting whether patients from the Caribbean are considered white (Hispanic), black or Native American (Puerto Rico). It is plausible that the investigator in that study registered patients from the Caribbean as black.

As a final note, our study results indicate that the majority of patients in PCa registration trials intended for US FDA review for marketing approval were enrolled in the US. However, our data also suggest a potential trend towards increased non-US enrollment. One key advantage of global clinical trial conduct is rapid enrollment, which can decrease the time needed to bring an effective treatment to the market. However, it also raises the question whether the results acquired from treating patients abroad properly reflect the efficacy and safety of the treatment in the average US population who will receive the treatment upon FDA approval. The current study underlines the importance of this question, as enrollment of racial minorities was lower in all studied nations/regions compared to the US, in particular in Eastern Europe. On the other hand, study 10, which globally had the highest enrollment of racial minorities, was conducted completely outside the US, in a country with a considerably higher non-white population. This indicates that adequate minority accrual is possible and there is not necessarily an objection to recruitment of patients outside the US or outside Western nations, provided that the rights, safety, and well-being of the subjects participating in those trials are ensured, there is compliance with good clinical practices, and that the results can be generalized to the US population. However, it must be acknowledged that biologic and socioeconomic characteristics of racial populations in the US may differ from such characteristics in the same racial population accrued in another country.

In conclusion, investigators and drug developers should take differences in racial demographics into account when selecting countries for clinical trials. In accordance with FDA's guidelines, sponsors are advised to classify racial demographics consistently and to consult the review division prior to study initiation about the estimated size of minority enrollment in their proposed trial.<sup>16</sup> While acknowledging that biologic and environmental differences may exist within the same racial category between countries, researchers should aim to improve enrollment of racial minorities during international trial conduct to accurately reflect demographics in countries for which they seek approval of their therapy. Inadequate minority enrollment may prevent achieving a full understanding of the benefit-risk profile of novel treatments in racial minorities. The trend toward increasing the number of non-US countries, including countries with a large white population, entails a trade-off of enhancing enrollment and time to trial completion versus enrolling a population that adequately represents the racial demographics of the average US population. Improved strategies to enhance minority accrual in such large multinational studies are needed.

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