Original Article

Assessment of Gender Representation in Clinical Trials Leading to FDA Approval for Oncology Therapeutics Between 2014 and 2019: A Systematic Review-Based Cohort Study

Kyle A. Dymanus, BS [1]; Mohit Butaney, MBBS[2,3]; Diana E. Magee, MD, MPH, MSc [4]; Amanda E. Hird, MD, MSc [4]; Amy N. Luckenbaugh, MD[5]; Merry W. Ma, MD, PhD[6]; Mary E. Hall, MD[5]; Heather L. Huelster, MD[5]; Aaron A. Laviana, MD, MBA[7]; Nancy B. Davis, MD[8]; Martha K. Terris, MD[6,9]; Zachary Klaassen, MD, MSc[6,9]; and Christopher J. D. Wallis, MD, PhD [5]

BACKGROUND: Ensuring representative data accrual in clinical trials is important to safeguard the generalizability of results and to minimize disparities in care. This study's goal was to evaluate differences in gender representation in trials leading to US Food and Drug Administration (FDA) cancer drug approvals. **METHODS:** An observational study was conducted from January 2014 to April 2019 using PubMed and the National Institutes of Health trials registry for primary trial reports. The National Cancer Institute's Surveillance, Epidemiology, and End Results program and US Census were consulted for national cancer incidence. The outcome was an enrollment incidence disparity (EID), which was calculated as the difference between male and female trial enrollment and national incidence, with positive values representing male overrepresentation. **RESULTS:** There were 149 clinical trials with 59,988 participants—60.3% and 39.7% were male and female, respectively—leading to 127 oncology drug approvals. The US incidence rates were 55.4% for men versus 44.6% for women. Gender representation varied by specific tumor type. Most notably, women were underrepresented in thyroid cancer (EID, +27.4%), whereas men were underrepresented in soft tissue cancer (EID, −26.1%). Overall, women were underrepresented when compared with expected incidence (EID, +4.9%; 42% of trials). **CONCLUSIONS:** For many specific tumor types, women are underrepresented in clinical trials leading to FDA oncology drug approvals. It is critical to better align clinical trial cohort demographics and the populations to which these data will be extrapolated. ***Cancer* 2021;127:3156-3162**. © *2021 American Cancer Society*.

LAY SUMMARY:

- This study assesses whether gender disparities exist in clinical trials leading to US Food and Drug Administration (FDA) cancer drug approvals. From January 2014 to April 2019, 149 clinical trials leading to FDA oncology drug approvals showed 60.3% and 39.7% of the enrollees were male and female, respectively.
- Gender representation varied by specific tumor when compared with the expected incidence rate of cancer in the United States, although women were more often underrepresented.
- Increased efforts are needed with regard to ensuring equitable representation in oncology clinical trials.

KEYWORDS: clinical trials, drug approval, health care disparities, medical oncology, sexism.

INTRODUCTION

Gender disparities in health care have influenced processes for appropriate diagnoses and treatment of many health conditions.[1] Among patients with cancer, these epidemiological variations have driven advancements to alleviate gender-specific differences in cancer susceptibility and mortality.[2,3] Clinical trials are essential for the development of novel cancer drug treatments and can benefit the medical community.[4] As a result of the evidence that women were underrepresented in important clinical trials, in 1993, the US National Institutes of Health (NIH) issued the Revitalization Act: a guideline for the evaluation of gender and minority differences in clinical trials for the full range of patients using the therapy.[5,6,7] In 2016, the European Association of Science Editors published the influential Sex and Gender Equity in Research guidelines to integrate sex and gender reporting into articles.[8] Currently, cancer clinical trials incorporate sex differences for a better understanding of the efficacy and toxicity of chemotherapeutics, as well as the roles of genetics and sex hormones.[9] However, trial populations may not always represent the population

Corresponding Author: Zachary Klaassen, MD, MSc, Assistant Professor, Division of Urology, Medical College of Georgia–Augusta University, Georgia Cancer Center, 1120 15th Street, BA-8414, Augusta, GA 30912 (zklaassen19@gmail.com).

[1]Department of Surgery, Medical College of Georgia, Augusta, Georgia; [2]Department of Surgery, Mayo Clinic, Rochester, Minnesota; [3]Department of Urology, Henry Ford Hospital, Detroit, Michigan; [4]Division of Urology, University of Toronto, Toronto, Ontario, Canada; [5]Department of Urology, Vanderbilt University Medical Center, Nashville, Tennessee; [6]Department of Surgery, Section of Urology, Medical College of Georgia–Augusta University, Augusta, Georgia; [7]Department of Surgery & Perioperative Medicine, University of Texas at Austin Dell Medical School, Austin, Texas; [8]Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee; [9]Georgia Cancer Center, Augusta, Georgia

Additional supporting information may be found in the online version of this article.

DOI: 10.1002/cncr.33533, **Revised:** February 3, 2021; **Accepted:** February 5, 2021, **Published online** June 23, 2021 in Wiley Online Library (wileyonlinelibrary.com)

that they are trying to emulate. It has been shown in several studies, in both oncology and nononcology clinical trial settings, that women may be underrepresented in clinical trials.[10-13] Although some reports refute this claim and a plethora of barriers exist to clinical trial participation and enrollment, there are known differences in the clinical outcome of medications, such as adverse drug reactions, which may be missed in underrepresented trials.[14-16] Physiologic variations may affect the pharmacokinetics and pharmacodynamics of these oncology drugs, so these differences need to be assessed for clinical relevance.[11] It is critical that trial data from men and women are not only available, but that they also effectively represent the treated population when decisions on safety, efficacy, side effects, and dosing of therapeutic agents are being made.[11]

Other studies have shown the existence of racial and age disparities in oncology clinical trials, but are less robust in assessing gender variation.[17,18] Mendis et al recently showed a slight female underrepresentation in hematological trials and a significant underrepresentation in solid organ malignancies using the International Agency for Research on Cancer and odds ratios for female trial enrollment.[13] The purpose of this study was to further clarify whether there is truly a gender disparity in clinical trials leading to cancer drug approvals using US Food and Drug Administration (FDA)-approved clinical trials from January 2014 to April 2019 by calculating enrollment incidence disparity (EID) using the National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER) program database. We hypothesized that many registration trials were not representative of the cancer patient population in the United States with respect to the age-adjusted incidence of the targeted cancer.

MATERIALS AND METHODS

Study Cohort

This study was exempt from institutional review board approval based on the public and deidentified nature of the work, following the standards of the Helsinki Declaration.

The FDA systematically identified and listed all oncology-specific drug approvals from the FDA drug archives database from January 2006 to April 2019.[19] We isolated those between January 2014 and April 2019 for our study. Based on these approvals, we identified the trials that formed the evidentiary base for the approval using FDA reviews, PubMed, and the NIH trials registry (ClinicalTrials.gov).[19,20] Notably, this approach to study identification has previously been used in other analyses examining disparities in clinical trials enrollment.[17] Among identified FDA approvals, we excluded those that were for male- or female-specific cancers (eg, prostate cancer or ovarian cancer), did not provide gender information for enrollees, could not be matched to cancers listed in the NCI SEER program database, had FDA drug-approval dates outside of the defined range, or did not fall under solid tumor or hematology-oncology categories. When multiple trials supported an FDA drug approval, each unique trial was included in the analysis.

To compare clinical trial demographics to national cancer statistics, the NCI SEER program database was consulted for specific cancer age-adjusted incidence rates per 100,000 by gender from 2014 to 2016.[21] Because the database did not include incidence rates from 2017 to 2019, they were estimated using 2016 SEER age-adjusted incidence rate values. Those values were correlated to the year's US Census population estimates to determine the approximate rate of increase or decrease in cancer incidence by gender.[22]

Analysis and Outcome Measures

First, each clinical trial was matched to the appropriate cancer category listed in the SEER program database based on the targeted organ and cancer type from histologic findings. We then analyzed the clinical trial data and identified the male and female enrollment percentages overall, as well as by specific cancer type. The total numbers of male and female trial participants for each cancer category were combined. Subsequently, the male and female enrollment percentage was calculated for each cancer type based on the combined value, allowing for a weighted average. For national cancer incidence between 2014 and 2019, the male and female age-adjusted rate per 100,000 was combined for each cancer category, and gender-specific incidence rate percentages were calculated.

We compared male and female clinical trial enrollment with national incidence data by calculating the EID. The EID was calculated as the difference between the male and female clinical trial enrollment and national incidence percentages. The EID values were calculated for the overall cancer population, as well as by specific cancer type. Positive values indicate an overrepresentation in males in clinical trials when compared with incidence, whereas negative values indicate an underrepresentation of males.

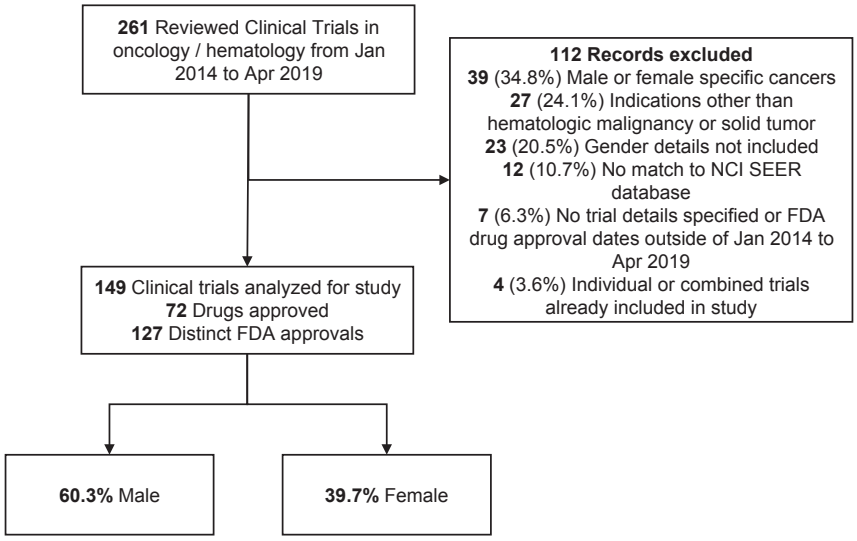

Figure 1. Breakdown of reviewed US Food and Drug Administration (FDA) approvals, exclusion criteria and number of trials used for gender analyses. The FDA approved 72 drugs in 127 distinct approvals based on 149 clinical trials included in this study. NCI indicates National Cancer Institute; SEER, Surveillance, Epidemiology, and End Results.

RESULTS

Baseline Approval and Trial Characteristics

The FDA approved 72 drugs in 127 distinct approvals based on 149 clinical trials included in this study (Supporting Table 1). A total of 261 trials were identified from our initial search. Based on exclusion criteria, 112 trials were excluded, leaving 149 included studies (Fig. 1). Notably, among the 112 trial excluded, 23 studies (20.5%) were excluded as gender details were not provided. The characteristics of the 149 clinical trials are shown in Table 1 and separated by year in Supporting Table 1. Most approvals were completed in 2017 (n = 40, 26.8%) and 2018 (n = 39, 26.2%). The majority of approvals were for lung and bronchus cancer (n = 34, 22.8%), followed by leukemia (n = 33, 22.1%), melanoma (n = 16, 10.7%), and non-Hodgkin lymphoma (n = 16, 10.7%). The trials were mostly multiple arm (n = 115, 77.2%) and phase 3 (n = 77, 51.7%) with between 100 and 500 participants enrolled (n = 84, 56.4%).

Gender Disparity Between Clinical Trials and the US Population by Cancer Type and Overall

A total of 59,988 patients were enrolled in the 149 included clinical trials. We assessed gender representation in clinical trials and national incidence rates across 14 specific cancer types (Table 2). Compared with population-based estimates, disparities in gender representation varied depending on specific cancer subtype. Most notably, women were underrepresented in thyroid and liver/intrahepatic bile duct cancers, whereas men were underrepresented in soft tissue and bladder cancers.

Using an assessment of EID indicative of disparities between trial enrollment and population-based incidence for specific cancer types (Table 2), 8 out of 14 cancer sites (57%) showed an overrepresentation of men. The largest disparities were seen in thyroid (men overrepresented EID, +27.4), soft tissue (men underrepresented EID, –26.1), bladder (men underrepresented EID, –10.8), and liver/intrahepatic bile duct (men overrepresented EID, +9.9) cancers.

Overall, 60.3% (n = 36,193) of the enrollees were male and 39.7% (n = 23,795) were female. Across all cancer types including sex-specific cancers, US population-based data show that men account for 55.4% of incident cancer diagnoses (age-adjusted rate per 100,000 = 762.78) versus 44.6% for women (age-adjusted rate per 100,000 = 614.46; Fig. 2). The EID showed an overrepresentation of men (EID, +4.9%; 42% of trials; Table 2).

DISCUSSION

In this study of clinical trials leading to approvals of oncology drugs by the FDA, we found that gender representation varied by specific cancer type with women being more often underrepresented when compared with national cancer incidence. To our knowledge, despite FDA guidelines and strategies to try to alleviate the differences in gender representation in oncology clinical trials, this

TABLE 1. Characteristics of US Food and Drug Administration Approvals/Trials for Hematology/Oncology, January 2014 to April 2019

Characteristics	No. (%)
Year of approval	
2014	17 (11.4)
2015	31 (20.8)
2016	16 (10.7)
2017	40 (26.8)
2018	39 (26.2)
2019	6 (4.0)
Specific disease for approval—all cancer sites combined	1 (0.7)
Solid tumor oncology	
Lung and bronchus	34 (22.8)
Melanoma	16 (10.7)
Urinary bladder	7 (4.7)
Kidney and renal pelvis	6 (4.0)
Colorectal	6 (4.0)
Stomach	5 (3.4)
Liver and intrahepatic bile duct	5 (3.4)
Thyroid	2 (1.3)
Soft tissue including heart	2 (1.3)
Pancreas	1 (0.7)
Hematology	
Leukemia	33 (22.1)
Non-Hodgkin lymphoma	16 (10.7)
Multiple myeloma	11 (7.4)
Hodgkin lymphoma	4 (2.7)
Trial characteristics	
Arms on trial	
Single	33 (22.1)
Multiple	115 (77.2)
Unknown	1 (0.7)
Phase of trial	
1	10 (6.7)
2	33 (22.1)
3	77 (51.7)
4	2 (1.3)
1/2	21 (14.1)
2/3	5 (3.4)
Unknown	1 (0.7)
Size of trial (number enrolled)	
<100	20 (13.4)
100-500	84 (56.4)
>500	45 (30.2)

is the first study to assess gender representation in these trials.[11] Guidelines in effect as of June 2015 require applicants to "explain how relevant biological variables, such as sex, are factored into research designs and analyses." Strong justification from the scientific literature, preliminary data, or other relevant consideration is required from researchers planning to study only one sex.[23] The data in this study suggest that these current guidelines and strategies have proven inadequate to address existing disparities.

Gender disparities in oncology clinical trials continue to be a concern with women more often underrepresented when compared with US incidence cancer rates. Additionally, similar trends are noted with EID in this study. Multiple studies are concordant with our findings and have emphasized the importance of gender representation in clinical trials.[11] Even after the US NIH Revitalization Act of 1993 was issued to require research on gender differences in clinical trials, the US Government Accountability Office released multiple statements further recommending improved study design to allow for results analysis by gender. Those reports recommended strategies like peer-reviewed publications and strong journal policies to monitor compliance, but unfortunately these policies have not resulted in significant increases in either accrual of women or reporting by sex.[7] Despite women being the major consumers of health care and prescription drugs and the primary decision-makers about health care for their families, this problem still persists.[24]

Across cancer subsets, the EID results varied with some underrepresentation of males and some of females. In particular, soft tissue malignancies and thyroid cancer show the greatest degree of gender incidence variation compared with other cancer subsets with male overrepresentation for thyroid (EID, +27.4) and female overrepresentation for soft tissue cancer (EID, –26.1). Postulation as to the causes underlying identified gender discrepancies in clinical trial enrollment is beyond the scope of the analysis undertaken. However, potential factors include trial inclusion/exclusion criteria, such as restriction to specific interventions, concurrent diagnoses or comorbidities, contraindicated medications, and funding; trial-related burdens including travel distance, additional out-of-pocket expenses, caregiver burdens, and family responsibilities that may differentially affect women; or potentially, though unproven, decreased willingness to go to treatment or participate.[25,26]

Other criteria such as the presence of industry funding, performance status, changing gender representation over time, and mortality were chosen to be excluded from this study, although some of these have been assessed in other studies.[17,18] Mortality was not assessed as incidence was deemed a better representation of clinical trial demographics and studies. Understanding any gender disparities that exist within oncology clinical trials is critical to continuing to address these concerns in medicine, especially with the number of cancer cases expected to increase by >20% and an increasing number of clinical trials every year.[27] The goal is to ensure that oncologic advancements resulting from these trials are applicable to all people with cancer, regardless of gender. However, given these results and others showing disparities based on age and race, it is clear that further work is required to ensure that trials informing oncology drug approvals are generalizable to the patient populations in which these agents will be used.[17,18] As an initial step, actions could include

TABLE 2. Relative Differences in Male and Female Enrollment in Clinical Trials and Incidence Rate by Specific Cancer Type

	Clinical Trials		Population-Based Incidence		
	Male (%)	Female (%)	Male (%)	Female (%)	EID
Colon and rectum	60.3	39.7	56.4	43.6	3.9
Digestive—stomach	72.1	27.9	64.4	35.6	7.7
Hodgkin lymphoma	57.0	43.0	55.4	44.6	1.6
Kidney cancer and renal pelvis	74.5	25.5	67.1	32.9	7.4
Leukemia	58.7	41.3	62.7	37.3	−4.0
Liver and intrahepatic bile duct	84.0	16.0	74.1	25.9	9.9
Lung and bronchus	59.1	40.9	55.8	44.2	3.2
Melanoma of the skin	56.4	43.6	62.1	37.9	−5.7
Myeloma	56.2	43.8	60.6	39.4	−4.3
Non-Hodgkin lymphoma	52.9	47.1	59.3	40.7	−6.4
Pancreas	56.8	43.2	56.0	44.0	0.8
Soft tissue including heart	33.2	66.8	59.3	40.7	−26.1
Thyroid	53.3	46.7	25.8	74.2	27.4
Urinary bladder	69.2	30.8	80.0	20.0	−10.8
Overall	60.3	39.7	55.4	44.6	4.9

Enrollment incidence disparity (EID) shows the gender disparity between clinical trials and US population by specific cancer type. Positive EID values indicate an overrepresentation of males (green color) in clinical trials when compared with incidence, whereas negative values indicate an underrepresentation of males (red color). Darker colors correlate to a stronger variation between the trials and the population.

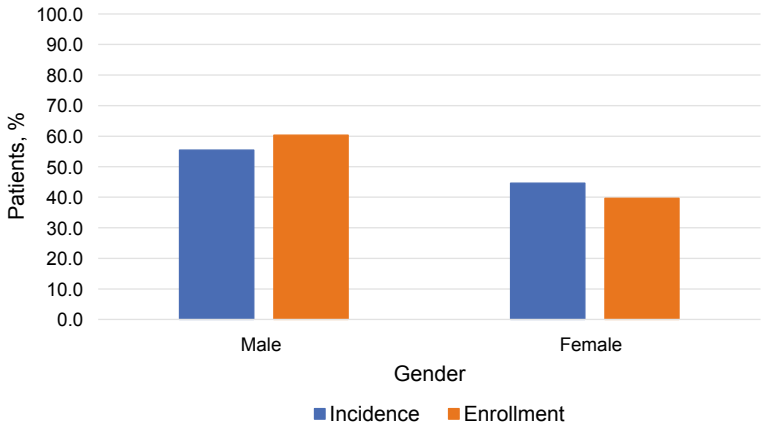

Figure 2. Comparison of male and female oncology clinical trial enrollment with US cancer incidence from 2014 to 2019.

implementing best practice recommendations, helping to establish gender-specific evidence-based guidance, ensuring analysis and reporting by gender, and encouraging further patient and researcher education.

Limitations

Several limitations should be considered with respect to this study. Trials were excluded that did not report the gender distribution of enrollees. Therefore, this analysis may either under- or overestimate the gender disparity in these oncology trials. We only examined studies leading to FDA drug approvals. Thus, these results cannot necessarily be extrapolated to phase 1 or 2 trials or those that did not lead to drug approval. Additionally, SEER disease-specific estimates for incidence may be a function of how disease-specific estimates were weighted and adjusted for using census data and thus may account for differences in estimations available in the current literature. Because the SEER program database used did not include incidence rates from 2017 to 2019, these were estimated using 2016 SEER age-adjusted incidence-rate values. We extrapolated our analysis to US Census population estimates, but did not adjust for global trial participation or changing mortality rates over time. Additionally, we combined the age-adjusted incidence rate per 100,000 for the years 2014 to 2019 for each cancer category and did not account for

change over time. We considered using a generalized least squares regression model with a recency decay factor but because the sample sizes were large enough over 5 years, we chose to use a pure average and did not account for variances by year. Furthermore, in the global assessment of cancer incidence—because of limitations in the SEER data set—we were unable to derive an estimate exclusive of sex-specific cancers; thus, these were included in the total incidence. Also, as the world population gender distribution is 1.01:1 male to female, some trials included large numbers of individuals from a single country outside the United States.[28] Therefore, we cannot assume the oncology demographics between males and females are consistent in every country because of differing treatment and screening practices and access to health care. It is worth noting that some clinical trials showed conflicting reports on how many men versus women were included in the trial depending on the source of the information (eg, PubMed vs. FDA vs. referenced study). Overall, the causes of gender disparity are complex, and the impact of biological, environmental, social, and financial factors should be acknowledged. Whether these potential disparities result in discrepant clinical outcomes remains to be seen and should be analyzed in future studies.

Overall, we found evidence of gender disparities in oncology clinical trials leading to drug approvals, with women more often underrepresented when compared with the US incidence cancer rates for specific tumor types. This offers an opportunity for additional targeted research and intervention for specific cancers, including thyroid and liver/intrahepatic bile duct cancers. Increased efforts are needed with regards to improving both female representation overall and equitable representation by individual cancer subset in oncology clinical trials. Future studies are needed to better understand the factors influencing the differences observed in this study and how best to move forward in addressing these differences with the goal of equal representation in modern cancer research. With the growing cancer burden in the aging population, eliminating the potential inequalities highlighted in this study is crucial to ensure the generalizability of future clinical trial results and optimal patient care.

FUNDING SUPPORT

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

CONFLICT OF INTEREST DISCLOSURES

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

AUTHOR CONTRIBUTIONS

Kyle A. Dymanus: Data curation, formal analysis, investigation, methodology, project administration, resources, validation, visualization, writing–original draft, and writing–review and editing. **Mohit Butaney:** Conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, supervision, validation, visualization, and writing–review and editing. **Diana E. Magee:** Formal analysis, investigation, methodology, validation, visualization, and writing–review and editing. **Amanda E. Hird:** Formal analysis, investigation, methodology, validation, visualization, and writing–review and editing. **Amy N. Luckenbaugh:** Formal analysis, investigation, methodology, validation, visualization, and writing–review and editing. **Merry W. Ma:** Formal analysis, investigation, methodology, validation, visualization, and writing–review and editing. **Mary E. Hall:** Formal analysis, investigation, methodology, validation, visualization, and writing–review and editing. **Heather L. Huelster:** Formal analysis, investigation, methodology, validation, visualization, and writing–review and editing. **Aaron A. Laviana:** Formal analysis, investigation, methodology, validation, visualization, and writing–review and editing. **Nancy B. Davis:** Formal analysis, investigation, methodology, validation, visualization, and writing–review and editing. **Martha K. Terris:** Formal analysis, investigation, methodology, validation, visualization, and writing–review and editing. **Zachary Klaassen:** Conceptualization, formal analysis, investigation, methodology, project administration, resources, supervision, validation, visualization, and writing–review and editing. **Christopher J. D. Wallis:** Conceptualization, formal analysis, investigation, methodology, project administration, resources, supervision, validation, visualization, and writing–review and editing.

DATA AVAILABILITY

The data are available in a public, open access repository:

1. We identified oncology drug approvals between January 2014 and April 2019 using the FDA drug archives database. Next, we reviewed PubMed and the NIH trials registry (ClinicalTrials.gov) to identify primary literature supporting each FDA drug approval. Websites: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm and https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm279174.htm
2. To compare clinical trial demographics to national cancer statistics, the NCI SEER program database was consulted for specific cancer age-adjusted incidence rates per 100,000 by gender from 2014 to 2016. Website: https://seer.cancer.gov/.

Because the database did not include incidence rates from 2017 to 2019, they were estimated using 2016 SEER age-adjusted incidence rate values. Those values were correlated to the year's US Census population estimates to determine the approximate rate of increase or decrease in cancer incidence by gender. Website: https://www.census.gov/

REFERENCES

1. Kent JA, Patel V, Varela NA. Gender disparities in health care. *Mt Sinai J Med*. 2012;79:555-559.
2. Dorak MT, Karpuzoglu E. Gender differences in cancer susceptibility: an inadequately addressed issue. *Front Genet*. 2012;3:268.
3. Cook MB, McGlynn KA, Devesa SS, Freedman ND, Anderson WF. Sex disparities in cancer mortality and survival. *Cancer Epidemiol Biomarkers Prev*. 2011;20:1629-1637.
4. Novitzke JM. The significance of clinical trials. *J Vasc Interv Neurol*. 2008;1:31.
5. U.S. Food and Drug Administration. Gender studies in product development: historical overview. 2018. Accessed November 24, 2019. https://www.fda.gov/science-research/womens-health-research/gender-studies-product-development-historical-overview
6. Holdcroft A. Gender bias in research: how does it affect evidence based medicine? *J R Soc Med*. 2007;100:2-3.
7. Geller SE, Koch AR, Roesch P, Filut A, Hallgren E, Carnes M. The more things change, the more they stay the same: a study to evaluate compliance with inclusion and assessment of women and minorities in randomized controlled trials. *Acad Med*. 2018;93:630-635.

8. Heidari S, Babor TF, De Castro P, Tort S, Curno M. Sex and gender equity in research: rationale for the SAGER guidelines and recommended use. *Res Integr Peer Rev*. 2016;1:2.
9. Kim HI, Lim H, Moon A. Sex differences in cancer: epidemiology, genetics and therapy. *Biomol Ther (Seoul)*. 2018;26:335-342.
10. Kwiatkowski K, Coe K, Bailar JC, Swanson GM. Inclusion of minorities and women in cancer clinical trials, a decade later: have we improved? *Cancer*. 2013;119:2956-2963.
11. Liu KA, Mager NA. Women's involvement in clinical trials: historical perspective and future implications. *Pharm Pract (Granada)*. 2016;14:708.
12. Uhl K, Parekh A, Kweder S. Females in clinical studies: where are we going? *Clin Pharmacol Ther*. 2007;81:600-602.
13. Mendis S, Anand S, Karasinska JM, et al. Sex representation in clinical trials associated with FDA cancer drug approvals differs between solid and hematologic malignancies. *Oncologist*. 2021;26:107-114.
14. Labots G, Jones A, de Visser SJ, Rissmann R, Burggraaf J. Gender differences in clinical registration trials: is there a real problem? *Br J Clin Pharmacol*. 2018;84:700-707.
15. Raz L, Miller VM. Considerations of sex and gender differences in preclinical and clinical trials. *Handb Exp Pharmacol*. 2012;:127-147.
16. Unger JM, Cook E, Tai E, Bleyer A. The role of clinical trial participation in cancer research: barriers, evidence, and strategies. *Am Soc Clin Oncol Educ Book*. 2016;35:185-198.
17. Loree JM, Anand S, Dasari A, et al. Disparity of race reporting and representation in clinical trials leading to cancer drug approvals from 2008 to 2018. *JAMA Oncology*. 2019;5:e191870.
18. Ludmir EB, Mainwaring W, Lin TA, et al. Factors associated with age disparities among cancer clinical trial participants. *JAMA Oncology*. 2019;5:1769-1773.
19. US Food and Drug Administration. Hematology/oncology (cancer) approvals & safety notifications. 2018. Accessed November 24, 2019. https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm279174.htm
20. US Food and Drug Administration. FDA approved drug products. 2019. Accessed November 24, 2019. https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm
21. National Cancer Institute. SEER*Stat database: incidence—SEER 9 regs research data, Nov 2018 Sub (1975-2016) <Katrina/rita population adjustment>—linked to county—total U.S., 1969-2017 counties. Surveillance, Epidemiology, and End Results (SEER) Program SEER*Stat Database: Incidence - SEER Research Data, 9 Registries, Nov 2018 Sub (1975-2016). Accessed September 4, 2019. https://seer.cancer.gov/
22. US Census Bureau. US Census 2018. Accessed September 3, 2019. https://www.census.gov/
23. National Institutes of Health. Consideration of sex as a biological variable in NIH-funded research. Notice Number: NOT-OD-15-1022015. National Institutes of Health.
24. Pinn VW. Sex and gender factors in medical studies: implications for health and clinical practice. *JAMA*. 2003;289:397-400.
25. Jones CW, Platts-Mills TF. Understanding commonly encountered limitations in clinical research: an emergency medicine resident's perspective. *Ann Emerg Med*. 2012;59:425-431, e411.
26. Garg R. Methodology for research I. *Indian J Anaesth*. 2016;60:640-645.
27. Weir HK, Thompson TD, Soman A, Moller B, Leadbetter S. The past, present, and future of cancer incidence in the United States: 1975 through 2020. *Cancer*. 2015;121:1827-1837.
28. Central Intelligence Agency. CIA Fact Book. 2018. Accessed November 24, 2019. https://www.cia.gov/library/publications/the-world-factbook/geos/xx.html