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Authors

Perera, Nirosha D
Bellomo, Tiffany R
Schmidt, Walker M
et al.

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Original Article

Analysis of Female Participant Representation in Registered Oncology Clinical Trials in the United States from 2008 to 2020

Nirosha D. Perera[1], Tiffany R. Bellomo[2], Walker M. Schmidt[3], Henry K. Litt[4], Margaret Shyu[5], MaKenna A. Stavins[6], Max M. Wang[7], Alexander Bell[8], Massoud Saleki[9], Katherine I. Wolf[10], Ruxandra Ionescu[6], Jacqueline J. Tao[11], Sunjong Ji[10], Ryan M. O'Keefe[12], Matthew Pun[10], Jordan M. Takasugi[6], Jecca R. Steinberg[13], Ronald S. Go[14], Brandon E. Turner[15,‡], Amit Mahipal[*,14,16,‡]

[1]Department of Medicine, Mayo Clinic, Rochester, MN, USA
[2]Department of Vascular Surgery, Massachusetts General Hospital Harvard Medical Center, Boston, MA, USA
[3]Alix School of Medicine, Mayo Clinic, Rochester, MN, USA
[4]Department of Medicine, University of California San Francisco, San Francisco, CA, USA
[5]Department of Medicine, Mount Sinai, New York, NY, USA
[6]School of Medicine, University of Washington, Seattle, WA, USA
[7]Feinberg School of Medicine, Northwestern, Chicago, IL, USA
[8]School of Medicine, University of California San Francisco, San Francisco, CA, USA
[9]Department of Medicine, University of Vermont, Burlington, VT, USA
[10]Department of Medicine, University of Michigan Medical Center, Ann Arbor, MI, USA
[11]Department of Medicine, New York-Presbyterian Weill Cornell, New York, NY, USA
[12]Department of Medicine, University of Pennsylvania, Philadelphia, PA, USA
[13]Department of Obstetrics & Gynecology, Northwestern, Chicago, IL, USA
[14]Department of Oncology, Mayo Clinic, Rochester, MN, USA
[15]Department of Radiation Oncology, Dana Farber Cancer Institute Harvard Medical Center, Boston, MA, USA
[16]Department of Oncology, University Hospitals, Case Western University, Cleveland, OH, USA

[*]Corresponding author: Amit Mahipal, MBBS, MPH, GI Oncology Program Leader, Department of Oncology, University Hospitals, Case Western University, 11100 Euclid Ave, Cleveland, OH 44106, USA. Tel: +1 216 910 4582; Fax: +1 216 844 5234; Email: amitmahipal@gmail.com
[‡]Contributed equally as co-senior authors.

Abstract

Background: Female underrepresentation in oncology clinical trials can result in outcome disparities. We evaluated female participant representation in US oncology trials by intervention type, cancer site, and funding.

Materials and Methods: Data were extracted from the publicly available Aggregate Analysis of ClinicalTrials.gov database. Initially, 270,172 studies were identified. Following the exclusion of trials using Medical Subject Heading terms, manual review, those with incomplete status, non-US location, sex-specific organ cancers, or lacking participant sex data, 1650 trials consisting of 240,776 participants remained. The primary outcome was participation to prevalence ratio (PPR): percent females among trial participants divided by percent females in the disease population per US Surveillance, Epidemiology, and End Results Program data. PPRs of 0.8-1.2 reflect proportional female representation.

Results: Females represented 46.9% of participants (95% CI, 45.4-48.4); mean PPR for all trials was 0.912. Females were underrepresented in surgical (PPR 0.74) and other invasive (PPR 0.69) oncology trials. Among cancer sites, females were underrepresented in bladder (odds ratio [OR] 0.48, 95% CI 0.26-0.91, $P = .02$), head/neck (OR 0.44, 95% CI 0.29-0.68, $P < .01$), stomach (OR 0.40, 95% CI 0.23-0.70, $P < .01$), and esophageal (OR 0.40 95% CI 0.22-0.74, $P < .01$) trials. Hematologic (OR 1.78, 95% CI 1.09-1.82, $P < .01$) and pancreatic (OR 2.18, 95% CI 1.46-3.26, $P < .01$) trials had higher odds of proportional female representation. Industry-funded trials had greater odds of proportional female representation (OR 1.41, 95% CI 1.09-1.82, $P = .01$) than US government and academic-funded trials.

Conclusions: Stakeholders should look to hematologic, pancreatic, and industry-funded cancer trials as exemplars of female participant representation and consider female representation when interpreting trial results.

Key words: oncology clinical trials; female participant representation; participation to prevalence ratio.

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Implications for Practice

Our cross-sectional study of 1650 US oncology trials registered on ClinicalTrials.gov from 2008 to 2020 showed female participants were underrepresented compared to their disease burden in surgical oncology, thyroid, bone/joint, kidney, bladder, stomach, and anal cancer trials. They were proportionately represented in medical and radiation oncology, industry-funded, hematologic, and pancreatic cancer trials. Female participant underrepresentation in oncology trials limits the generalizability of results and access to cutting-edge therapeutics. Our study highlights lessons learned from trial types that have achieved proportional female recruitment and retention, and spurs clinicians to interpret trial findings in the context of their characteristics and associations with female representation.

Introduction

Females have historically been underrepresented in biomedical research, including oncology clinical trials.[1-3] In 2002, a widely cited study found that females comprised only 34.7% of participants in cancer prevention and treatment trials from 1990 to 2001.[4] A 2013 updated study revealed continued sex gaps from 2000 to 2010.[5] The persistent failure to proportionally enroll female participants relative to their disease burden hinders the generalizability of cancer clinical trial findings and denies females access to novel therapeutics and potentially improved survival through trial participation.

As defined by the National Institutes of Health's (NIH) Office of Research on Women's Health (ORWH), "sex" refers to biological differences between females and males, including chromosomes, sex organs, and endogenous hormonal profiles. "Gender" refers to socially constructed and enacted roles and behaviors within the groups traditionally thought of as women and men, which occur in a historical and cultural context and vary across societies and over time.[6] In their efforts to encourage researchers to consider both sex and gender in their work, the NIH ORWH has developed a series of resources demonstrating how sex and gender can influence health.[7] For example, those with a biological sex of female are more likely than males to injure their knees when playing sports due to differences in knee and hip anatomy, imbalanced leg muscle strength, and looser tendons and ligaments, with knee injuries ultimately increasing a female's risk of knee osteoarthritis. Similarly, those with a gender of girl/woman are more likely to walk in high-heeled shoes which stresses the knee joint and can ultimately increase women's risk of knee osteoarthritis.[8] Similar examples have been shown in mental health, cardiovascular health, and smoking cessation,[8] suggesting that further research is needed to understand the interplay of these factors in other areas of health, such as cancer.

Epidemiologic data already suggest that sex plays a vital role in cancer incidence, prognosis, and mortality.[9] Data from the National Cancer Institute's Surveillance, Epidemiology, and End Results Program (SEER) from 2014 to 2016 indicate the lifetime probability of being diagnosed with an invasive cancer is slightly lower for females than males.[10] However, females suffer from lower cancer-specific 5-year survival rates.[11] Although overall cancer mortality has declined over the past 20 years, females trail behind males in mortality reduction.[12] Furthermore, sex may modulate cancer therapy efficacy and tolerability.[13-16] Recent research demonstrates sex-specific differences in response to systemic therapy agents,[16] radiotherapy,[17] and immunotherapy.[18] Females may be at higher risk of developing adverse drug reactions and toxicities.[13,19] Outcome variability may reflect differences in environmental exposures,[20,21] endogenous hormones,[22] access to care,[23] screening practices,[24] health literacy,[25] and complex interactions among these factors. Sufficient female enrollment for sex-specific analyses is necessary to better understand underlying mechanisms and develop solutions to sex-specific disparities.

Female enrollment in clinical trials should adequately reflect their disease burden in the general population. Although organizations such as the NIH have recently stated the need for female representation, the current state of sex bias within United States (US) oncology clinical trials remains unclear.[26] Therefore, we aimed to characterize female participant enrollment trends in US oncology trials registered on ClinicalTrials.gov from 2008 to 2020 and identify associations between proportional female participant representation and trial intervention type, cancer site, and funding.

Materials and Methods

We conducted a cross-sectional study of oncology interventional clinical trials registered on ClinicalTrials.gov between January 10, 2008 and September 3, 2020. Trials registered prior to 2007 were excluded to coincide with the Food and Drug Administration (FDA) Amendments Act, requiring most clinical trials involving FDA-regulated products and devices to submit registration.

Data Sources

All data were extracted via the Aggregate Analysis of ClinicalTrials.gov (AACT) database from publicly available records for all interventional studies (the term used by ClinicalTrials.gov for clinical trials) submitted to ClinicalTrials.gov from January 10, 2008 to September 3, 2020. Medical subject heading terms were applied to identify clinical trials relevant to oncology, using previously published protocols.[27-31] Trial title, abstract, description, and inclusion/exclusion criteria were manually reviewed to verify content and exclude non-oncology studies. Trials with a focus on reproductive or sex-specific organ cancers, incomplete study status, non-US location, or no report of participant sex data were excluded. As trials reported sex and not gender, we only explored patterns in female participant representation as opposed to women participant representation. Institutional Review Board approval/oversight was not required given publicly available data.

Variables

Oncology Intervention Type and Cancer Site

Oncology intervention type categories included: (1) radiation, (2) surgical, (3) other invasive (non-surgical and non-radiation procedures), (4) medical, and (5) other (physical therapy, counseling, or non-FDA approved therapies like traditional Chinese medicine). If a trial examined one intervention type, that type was assigned. If a trial compared 2 intervention

types in separate arms, both types were assigned. If a trial compared 2 or more intervention types, only those that varied among arms were assigned. If a trial examined multiple intervention types in a single arm, all involved types were assigned.

Cancer site was stratified into lung, brain and other nervous system (central nervous system [CNS]), hematologic, skin/melanoma, thyroid, bone/joint, head/neck, other soft tissue, colorectal, anal canal, stomach, liver/biliary tree, pancreas, esophagus, breast, cervix/uterus, ovaries, vulva/vagina, prostate, testicle/penis, kidney/renal pelvis, bladder, other, or unknown site. If a trial focused on multiple sites, all sites were assigned. If a trial focused on more than 7 sites or if no specific site was specified, "other" was assigned. If a trial mentioned a primary and metastasis site, both sites were assigned. If a trial mentioned the metastasis site but not the primary, or vice versa, only the explicitly mentioned site was assigned.

Sixteen medical student and resident physician researchers manually sorted trials into the above categories. All labelers achieved 90% or higher agreement in categorizing a training set of trials (correct categorization was pre-determined by co-senior author B.T.) before proceeding to the trials of interest. To ensure agreement, each labeler reviewed a subset (at least 10%) of another's categorizations.

Clinical Trial Characteristics

Twelve trial characteristics from the ClinicalTrials.gov database were extracted for analysis, including: (1) funding source, (2) phase, (3) number of participants, (4) submission date, (5) number of sites, (6) use of randomization, (7) oversight by a data-safety monitoring committee (DMC), (8) blinding, (9) recruitment status, (10) number of arms, (11) reported results, and (12) early discontinuation. "Early discontinuation" was noted if a study was defined by ClinicalTrials.gov as "terminated," "withdrawn," or "suspended." Only trials completed on or before September 30, 2017 were included in this portion of analysis to coincide with requirements to report results up to 3 years after completion. The ClinicalTrials.gov Protocol Registration Data Element Definitions for Interventional and Observational Studies was reviewed to understand missing automated data and labeling.[32]

Funding source was divided into 3 subcategories: (1) industry, (2) US government, and (3) academic, using the National Library of Medicine designations of sponsors and collaborators. "Industry" was defined as sponsorship/partnership by an industry agency. "U.S. government" was defined as sponsorship/partnership by the NIH or other federal agencies. The remaining trials represented sponsorship by academic institutions and, less so, by individuals, foundations, research institutes, and community-based associations. The heading "academic" was chosen due to prior analyses' findings that 90.1% of funding sources in this category was defined by US legal code as academic institutions.[33,34]

Exposures and Outcomes

Primary exposure variables were cancer site, intervention type, and funding source. Additional analyses compared trial characteristics including DMC presence, randomization, blinding, and status of results reported.

Primary outcome was proportional representation of female participants. Disease prevalence-corrected estimates for female participation were calculated as the percentage of females among trial participants divided by the percentage of females in the disease population per the November 2019 submission of the US SEER*Stat database (containing cancer prevalence data from 2000 to 2017).[35] For example, if 50% of females participated in a given clinical trial focusing on lung cancer and SEER data reported the disease prevalence for lung cancer in the United States as 50% female, the disease prevalence-corrected estimate would be 50 divided by 50, or 1. This calculation has been termed "participation to prevalence ratio" (PPR), with the range of 0.8-1.2 reflecting proportional or adequate female trial representation, as established in prior published protocols.[36-41]

Statistical Analysis

Statistical analyses were performed using R version 4.4.1 (r-project.org). Data extracted from the AACT database tool were merged with manually labeled trial characteristics using the National Clinical Trial identification number. 2017 SEER database cancer sites were matched to manually labeled trial cancer types. Participation to prevalence ratios were calculated for each cancer type that a trial included. As trials could be classified with multiple cancer or intervention types, these categories were not mutually exclusive. Therefore, category analyses resulted in a single trial's data repeated for each relevant intervention type. Descriptive statistics were calculated. Repeated measures general linear models were fit using the "ImerTest" package in R to test the association between trial characteristics and adequate representation. *P* values were calculated using Welch's modified *t* test from the "Basic Statistics and Data Analysis (BSDA)" package in R. Statistical significance was set at *P* value < .05.

Results

After exclusion of ineligible trials, 1650 trials (Table 1) composed of 240,776 participants met inclusion criteria and reported participant sex (Fig. 1). Females represented 46.9% of all participants (95% CI, 45.4-48.4), with an overall PPR of 0.912.

Representation by Cancer Site

Female participant representation varied by cancer site. Females were underrepresented compared to their population disease burden in anal canal (PPR 0.21, 4 trials), thyroid (PPR 0.57, 17 trials), stomach (PPR 0.68, 29 trials), kidney/renal pelvis (PPR 0.70, 38 trials), and bone/joint (PPR 0.79, 11 trials) cancer trials. Females were proportionately represented in head/neck (PPR 0.80, 73 trials), lung (PPR 0.84, 154 trials), bladder (PPR 0.85, 29 trials), skin/melanoma (PPR 0.88, 102 trials), pancreas (PPR 0.88, 73 trials), colon (PPR 0.90, 98 trials), hematologic (PPR 0.91, 406 trials), liver (PPR 1.01, 61 trials), CNS (PPR 1.03, 124 trials), soft tissue (PPR 1.05, 41 trials), and esophagus (PPR 1.05, 23 trials) cancer trials (Table 1). Females were not over-represented in any cancer site trial group (Fig. 2a, 2b).

When each cancer site was compared to all others, hematologic ([OR] 1.78, 95% CI 1.09-1.82, *P* < .01) and pancreatic (OR 2.18, 95% CI 1.46-3.26, *P* < .01) cancer trial focuses were significantly associated with higher odds of proportional female representation (with ORs reflecting the odds of a given trial type having a PPR 0.8-1.2, not to be confused with the PPR itself or indicating odds of having a higher PPR). Bladder (OR 0.48, 95% CI 0.26-0.91, *P* = .02), head/neck (OR 0.44, 95% CI 0.29-0.68, *P* < .01), stomach (OR 0.40, 95% CI 0.23-0.70, *P* < .01), and esophageal (OR 0.40 95% CI 0.22-0.74,

Table 1. Trial characteristics of all 1650 oncology trials with associated mean participation to prevalence ratios (PPR) and standard deviation (SD).[a]

	Number of trials	Mean PPR (SD)	Female proportion (%)
Trial site			
Lung	154	0.84 (0.16)	47
CNS	124	1.03 (0.21)	48
Heme	406	0.91 (0.13)	41
Skin/melanoma	102	0.88 (0.21)	40
Thyroid	17	0.58 (0.19)	51
Bone/joint	11	0.79 (0.21)	41
Head/neck	73	0.80 (0.16)	23
Soft tissue	41	1.05 (0.19)	45
Colorectal	98	0.90 (0.18)	46
Anal canal	4	0.21 (0.14)	22
Stomach	29	0.68 (0.14)	29
Liver	61	1.01 (0.17)	36
Pancreas	73	0.88 (0.11)	45
Esophagus	23	1.05 (0.15)	23
Kidney/renal pelvis	38	0.77 (0.14)	29
Bladder	29	1.00 (0.16)	20
Intervention type			
Radiation	196	0.83 (0.49)	42
Surgical	76	0.74 (0.25)	44
Invasive	40	0.69 (0.35)	38
Medicine	1948	0.82 (0.16)	46
Other	138	0.88 (0.33)	50
Phase			
I	10	1.39 (0.88)	52
II	1380	0.89 (0.37)	66
III	48	0.98 (0.37)	45
IV	18	0.83 (0.45)	54
Other	194	0.90 (0.45)	51
Funding source			
Industry	693	0.92 (0.35)	47
Academic	474	0.95 (0.38)	46
US Government	483	0.94 (0.43)	47
Blinding			
None/open-label	1439	0.90 (0.39)	45
Single	51	0.90 (0.51)	56
Double	76	0.88 (0.39)	51
Triple	36	0.90 (0.26)	55
Quadruple	45	0.90 (0.40)	52
NA	3	0.59 (0.25)	24
DMC			
Yes	921	0.90 (0.41)	45
No	566	0.89 (0.39)	47
NA	163	0.90 (0.32)	51
Randomized			
Yes	460	0.90 (0.41)	49
No	1184	0.90 (0.39)	45
NA	6	1.28 (0.63)	32
Results reported			
Yes	1504	0.90 (0.39)	47
No	146	0.88 (0.38)	44

[a]Description: trial characteristics of all 1650 trials. Proportional or adequate representation is defined as a PPR of 0.8-1.2. Since many trials focused on more than one cancer site and/or intervention type, the number of trials for these categories total greater than 1650.
Abbreviations: DMC, Data Safety Monitoring Committee; NA, not applicable.

$P < .01$) cancer had lower odds of adequate female representation when compared with all other cancer sites (Table 2).

Representation by Oncologic Intervention Type and Funding Source

Female participants were underrepresented in clinical trials of surgical (PPR 0.74, 76 trials) and other invasive (PPR 0.69, 40 trials) oncology trial types, but proportionately represented in radiation (PPR 0.83, 196 trials), medical (PPR 0.82, 1948 trials), and "other" (PPR 0.88, 138 trials) oncology trial types (Table 1). When compared with each other, oncology intervention types were not significantly associated with proportional representation of females (Table 2).

Less than half of the clinical trials were funded by industry (N = 693, 42%), followed by academic institutions (N = 474, 29%) and the US government (N = 483, 29%). Overall female representation was adequate across all funding sources (Table 1). Industry-funded trials had greater odds of proportional female representation (OR 1.41, 95% CI 1.09-1.82, P = .01) compared to government-funded counterparts (Table 2). Academic-funded trials did not show a statistically significant difference in odds of proportional female representation compared to government-funded trials (OR 1.27, 95% CI 0.96-1.67, P = .10; Table 2).

Representation by Trial Methodology

Females were over-represented within phase I trials as PPR was greater than 1.2 (PPR 1.39), and proportionally represented within phase II (PPR 0.89), phase III (PPR 0.98), phase IV (PPR 0.90), and trials without FDA-defined phases (PPR 0.90) (Table 1).

Female representation was proportional within all blinding categories: open-label trials PPR 0.90, single-blinded trials PPR 0.90, double-blinded trials PPR 0.88, triple-blinded trials PPR 0.90, and quadruple-blinded trials PPR 0.90 (Table 1). Compared to open-label trials, adequate representation was significantly associated with triple-blinded (OR 4.33, 95% CI 1.64-11.41, P < .01) and quadruple-blinded trials (OR 2.13, 95% CI 1.13-4.01, P = .02) (Table 2).

Regarding participant randomization, females were proportionately represented in randomized (PPR 0.90) and non-randomized trials (PPR 0.90) (Table 1). Female representation was also proportional in trials with (PPR 0.90) and without (PPR 0.89) DMC oversight (Table 1). The presence of a DMC was not significantly associated with increased odds of adequate representation.

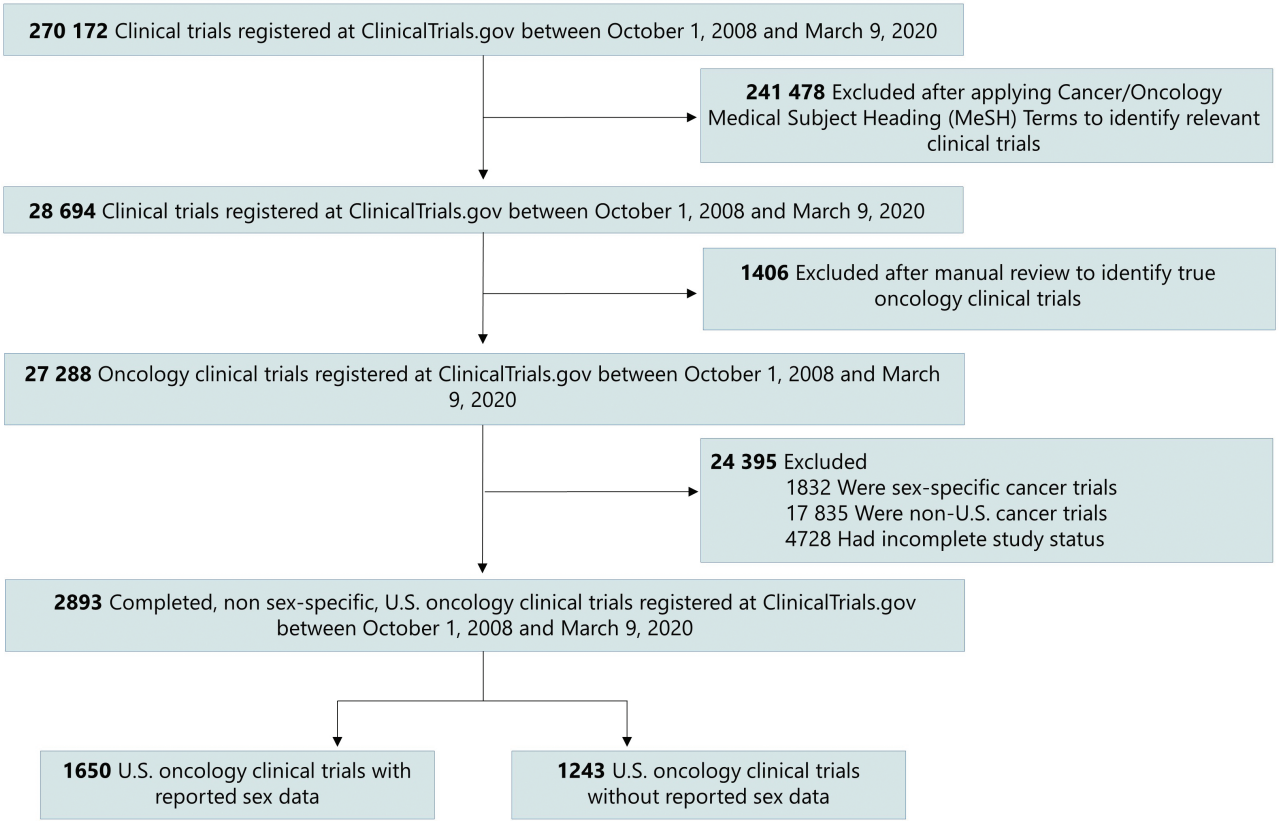

Figure 1. Flow diagram of clinical trials included in the analysis.

Association Between Representation, Trial Completion, and Results Reporting

Within our already strict inclusion criteria, no trials were discontinued early, and 1504 (of 1650 trials, 91%) reported results. PPR among trials reporting results was 0.90 compared to PPR 0.88 among trials not reporting results. Results reporting did not have statistically significant higher odds of proportional female representation compared to not reporting results (Table 2).

Representation Over Time

The overall number of clinical trials decreased from 1082 (2007-2012) to 568 (2013-2018). Female participant representation remained relatively static between 2007-2012 compared to 2013-2018 (PPR 0.89-0.91, $P = .51$). Over the same period, female representation remained without statistically significant change in medical (PPR 0.89-0.89, $P = .87$), surgical (PPR 0.73-0.82, $P = .45$), other invasive (PPR 0.71-0.75, $P = .84$), and radiation (PPR 0.89-0.83, $P = .55$) oncology trials. Female representation also remained stable in industry-funded (PPR 0.89-PPR 0.88, $P = .52$), academic-funded (PPR 0.92-0.93, $P = .84$), and US government-funded (PPR 0.87-0.91, $P = .86$) trials.

By cancer site, trials displayed statistically significant increases in female representation in stomach and esophageal cancer (PPR 0.55-0.86, $P = .02$ and PPR 0.64-1.52, $P = .01$, respectively). Trials in bone/joint and bladder cancer demonstrated non-statistically significant decreases in female representation (PPR 1.02-0.82, $P = .34$; PPR 0.92-0.79, $P = .45$, respectively).

Discussion

Despite decades of national efforts to increase female inclusion in US clinical trials and the known importance of proportionate representation for female health,[2,26] our study demonstrates continued female participant underrepresentation in certain oncology clinical trials. Although overall female enrollment in cancer clinical trials has increased compared to previous studies,[4,5] sex bias persists within trial subtypes. Specifically, females were underrepresented in surgical and other invasive oncology trials, with statistically significant sex gaps in bladder, head/neck, stomach, and esophageal cancers. Conversely, females were adequately represented in industry-funded, hematologic and pancreatic cancer trials.

The mean proportion of females enrolled in oncology trials in this study was 46.9% (95% CI, 45-48.4), modestly higher than the roughly 41% reported in 2 contemporary studies.[42,43] This demonstrates an upward trend in oncology clinical trial female enrollment, with previous studies documenting 34.7% enrollment in the 1990s and 38.6% in the 2000s.[4,5] However, our study reveals variations in female representation still exist among oncology intervention types, cancer sites, and funding sources, consistent with studies across other specialties: female enrollment varies among individual diseases and funding sources.[44,45] This lack of uniform proportional female representation challenges the ability of the medical field to move toward a culture of inclusivity and develop evidence-based recommendations to address disease-specific disparities.

Disease prevalence estimates in the general population were used to evaluate the number of females in the trial

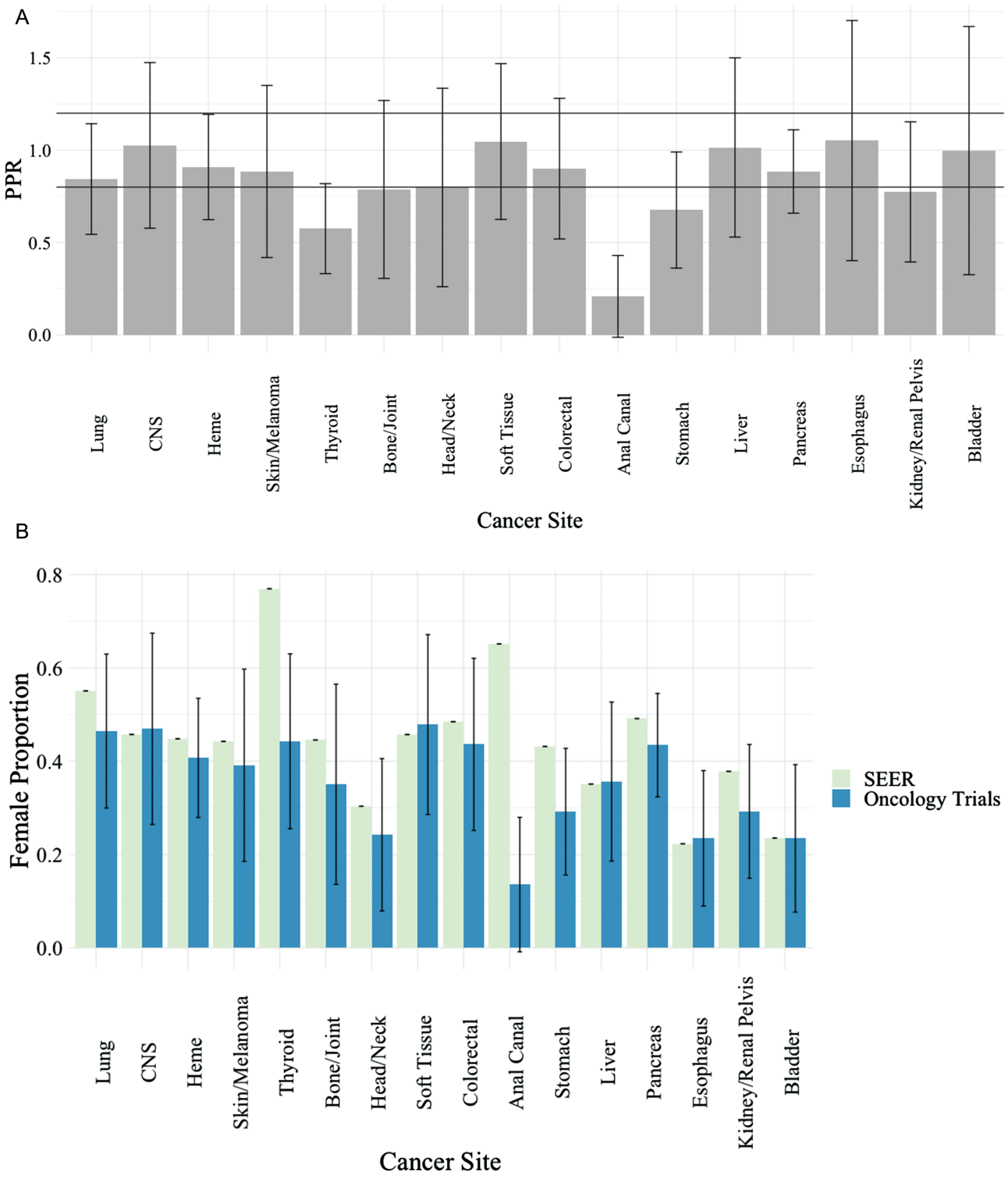

Figure 2. (**a**) Female representation as quantified by participation to prevalence ratio (PPR) for each cancer site. Description: horizontal lines represent the threshold and range for adequate representation of females defined as a PPR of 0.8-1.2. Vertical error bars represent 1 standard deviation from the mean PPR, as also listed in Table 1. (**b**) Female Proportion in Surveillance, Epidemiology, and End Results (SEER) Program population compared to female proportion in oncology clinical trials in this study.

compared to the number of females that should be enrolled, as opposed to simply providing a percentage of female participation without disease burden contextualization. According to these prevalence-corrected estimates, recent oncology trials overall were within the defined range for adequate representation of female participants, trending toward increased equity. However, deeper analysis is vital because overall adequate representation can result from over-representation in one area coupled with under-representation in another.[46,47] Overlooking sex-specific disparities within certain trial types or cancer types can negatively affect the millions of females living with cancer in the United States

Table 2. The association of multiple trial characteristics with adequate representation of females.[a]

	Odds ratio (95% CI)	*P* value
Intervention type		
Radiation	0.73 (0.49-1.10)	.13
Surgery	0.77 (0.42-1.43)	.41
Invasive	0.57 (0.23-1.41)	.23
Medicine	1.13 (0.88-1.45)	.32
Other	0.86 (0.54-1.39)	.55
Funding source		
Industry	1.41 (1.09-1.82)	.01
Academic	1.27 (0.96-1.67)	.10
Cancer site		
Lung	1.35 (0.95-1.91)	.09
CNS	0.85 (0.60-1.19)	.34
Hematologic	1.78 (1.42-2.25)	<.01
Skin/melanoma	0.73 (0.51-1.06)	.10
Thyroid	0.43 (0.17-1.10)	.08
Bone/joint	0.60 (0.20-1.76)	.35
Bladder	0.48 (0.26-0.91)	.02
Head/neck	0.44 (0.29-0.68)	<.01
Soft tissue	0.83 (0.47-1.46)	.52
Colorectal	1.35 (0.95-1.91)	.09
Anus	0.15 (0.02-1.23)	.08
Stomach	0.40 (0.23-0.70)	<.01
Liver	0.66 (0.43-1.02)	.06
Pancreas	2.18 (1.46-3.26)	<.01
Esophagus	0.40 (0.22-0.74)	<.01
Kidney/renal pelvis	0.62 (0.37-1.02)	.06
DMC		
Yes	0.94 (0.75-1.18)	.59
Randomization		
Yes	1.62 (1.30-2.01)	<.01
Blinding		
Single	0.90 (0.52-1.57)	.72
Double	1.26 (0.80-1.99)	.33
Triple	4.33 (1.64-11.41)	<.01
Quadruple	2.13 (1.13-4.01)	.02
Results reported		
Yes	1.00 (0.71-1.40)	.99

[a]The reference variable for each intervention type was all other intervention types. The reference variable for each funding source was funding by the United States government. The reference variable for each cancer site was all other cancer sites. The reference variable for data-safety monitoring committee (DMC) was trials without a DMC. The reference variable for randomization was all trials without randomization. The reference variable for blinding was open label trials. The reference variable for results reported was all trials without results reported. Significance is defined as *P* value < .05.
Abbreviations: CNS: central nervous system; DMC: data-safety monitoring committee.

Analysis by clinical trial type revealed that female representation was below the prevalence estimate for surgical and other invasive oncology intervention types, despite improvement since 2008. Females were also underrepresented in bladder, head/neck, stomach, and esophageal cancer trials, although representation in the latter 2 groups appears to be gradually improving. Improvements in representation are crucial as underrepresentation can contribute to outcome disparities. Previous studies demonstrate lower 5-year survival rates for females than males in anal canal and bladder cancer, with the latter seen especially following cystectomy.[48-50] Our study highlights female underrepresentation in bladder cancer relative to disease burden overall; improving representation in bladder cancer clinical trials could help evince strategies for reducing this mortality gap. Concerning bladder cancer particularly, one study cites a lack of targeted recruitment effort toward female participants despite well-known historical trial enrollment disparities, but does not provide reasoning on why this occured.[51] In non-sex-specific surgical oncology, a general paucity of research,[52] coupled with limited funding, training, and support for surgical clinical investigators specifically[53] may exacerbate female trial participation disparities. Previous studies on barriers to clinical trial participation have cited fear, transport difficulties, economic considerations, and interference with family responsibilities, with such barriers often disproportionately affecting women, as reasons for female participant underrepresentation.[54-56] There is a dearth of information to confidently identify the causes of participation disparities of females among non-sex-specific esophageal and stomach cancer trials, although it likely results from a combination of factors described above. Further research to understand the root causes of such disparities is necessary to aid the development of targeted solutions.

One potential solution to increase female participation and retention in trials would be the use of a skilled clinical trial team member to assist potential trial participants in identifying and negotiating barriers to care/participation. A 2020 pilot study found that trial participants heavily utilized these "trial navigators" to assist with logistical, housing, and transportation planning, as well as to provide referrals to relevant social, financial, and medical support systems that enabled their sustained trial participation and well-being during the trial.[57]

Clinical trials with industry funding or in hematologic and pancreatic cancer demonstrate these barriers can be overcome and can serve as potential models for fields with sex enrollment disparities. Addressing the above concerns with potential participants represents a path toward increased female recruitment and retention in oncology trials.

Of all funding sources, industry-funded trials most adequately represented female participants. This may speak to greater success in FDA regulations for nearly all industry-funded trials compared to NIH regulations for most government and academic-funded trials not overseen by the FDA.[58,59] Interestingly, the FDA does not mandate the participation of females in clinical trials, whereas the NIH has required female participation since 1986.[60] Although both organizations attempted to bolster female enrollment through various advocacy and outreach programs throughout the 1990s and 2000s, in 2013, the FDA alone was congressionally directed to investigate female participation in clinical trials and develop a plan for addressing barriers to female enrollment, which included increasing efforts to enroll cohorts who reflect disease prevalence and incidence.[61-64] Our study's finding of increased odds of proportional female representation in industry-funded trials compared to US government and academic trials suggests that relying on strict mandates for female participation has limited efficacy; resources may

be better spent identifying and addressing root causes of sex representation imbalance.

The only trial types with over-representation of female participants were phase I trials (PPR 1.4) and trials where randomization status was not applicable or not disclosed (PPR 1.28). This could raise the concern of whether female participants are shouldering an increased burden when it comes to evincing efficacy and side effects of newer/experimental treatments. However, these are also 2 of the smallest trial groups within our entire study, with 10 or less trials each, so we caution against over-interpretation of this trend.

This study has several strengths. Combining 12 years of ClinicalTrials.gov data with manual trial categorization, our study represents an extensive, verified data extraction and can therefore comment on both general and trial-subtype trends. Furthermore, recent research detailing statistically lower female enrollment rates in oncology trials[65] has drawn responses calling for representation analysis that considers not just enrollment rate, but also the different disease prevalence between males and females.[66] Our study does exactly that by utilizing PPR instead of percentages alone, rendering its conclusions more generalizable. Many cardiovascular disease studies started utilizing prevalence-corrected estimates in the form of PPR in the 2000s,[37-40] but the field of oncology has only more recently begun to utilize PPR.[46,47] To our knowledge, this study is among the first few in oncology to utilize PPR, hopefully paving the way for continued contextualized analysis. Although some studies in oncology note that incidence better reflects the individuals eligible for frontline therapy and thus they have opted not to use PPR,[47] our study aimed to examine not only novel therapy trials but also the many trials that focus on the quality of life/supportive interventions for patients already living with cancer and their loved ones, therapies for those who have relapsed, and the entire spectrum of those affected by oncologic disease. As we continue to make gains in life expectancy for patients diagnosed with cancer who continue to need evidence-based interventions and support, this broad spectrum of trial focus is better represented by a prevalence-based tool such as PPR.

This study has several limitations. ClinicalTrials.gov does not include all oncology trials. Despite amended recommendations by both the NIH and FDA, only 1650 of 2893 trials (57.0%) eligible for analysis reported participant sex, which is considerably lower than a similar study of US clinical trials across all specialties.[67] Of note, only NIH phase III clinical trials are required to report participant sex.[68] Additionally, our study does not include demographics such as participant age or race/ethnicity, which are often not reported and difficult to extract. Nor did we have access to individual patient-level data that might provide a more granular understanding of differences in sex-specific trial participation. Ideally, future research will investigate this and barriers that limit the participation of other underrepresented groups such as ethnic minorities, the elderly, and non-binary gender identities. As we did not have access to participant gender identity, we cannot comment on trends in the representation of trial participants who identify as women, which is of utmost importance to help further the field's understanding of how both sex and gender influence cancer care and outcomes. Similarly, sex data were provided by each trial's reporting investigator without the description of whether patients self-reported their sex or if sex was determined by other means, again limiting any discussion on sex versus gender in our study. Furthermore, our study does not factor in prognosis within each disease category. For example, females have lower 5-year cancer-specific mortality rates than males in stomach and esophageal cancer.[48] Perhaps this more favorable prognosis justifies the proportional underrepresentation of females in stomach and esophageal cancer trials that our study found. Lastly, ClinicalTrials.gov has several independent limitations in reporting, data change over time, and data entry enforcement.[69] One example is that clinical investigators are required to report participation only by biological sex rather than in combination with gender; this precludes examination of gender differences distinct from sex differences, a commonplace limitation throughout the literature.[70]

Sex differences should not be ignored when conducting clinical trials, especially with recent studies demonstrating sex differences in cancer risks, treatment response rates, and incidence of adverse drug reactions.[71] Our cross-sectional study shows that contemporary oncology trials underrepresent females compared to their disease burden in fields with sex-specific disparities in outcomes such as surgical oncology, bladder, head/neck, and stomach cancer trials. Fortunately, challenges to improve representation can be overcome, as seen in hematologic, pancreatic, and industry-funded trials, where mandates have been replaced with nuanced reviews and solutions to improve female representation. This data suggest that sex bias persists within oncology trials and calls for targeted and collaborative efforts to address this issue. Clinical researchers, industry, federal agencies, and patient-advocacy groups could cooperate to ensure representative patient populations are enrolled, enhancing our ability to provide informed, relevant, safe, and efficacious recommendations for every patient with cancer.

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Conflict of Interest

The authors have no conflicts of interest, financial or other, to disclose.

Author Contributions

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Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

References

1. Hawkes S, Haseen F, Aounallah-Skhiri H. Measurement and meaning: reporting sex in health research. *Lancet*. 2019;393(10171):497-499. https://doi.org/10.1016/s0140-6736(19)30283-1

2. Mazure CM, Jones DP. Twenty years and still counting: including women as participants and studying sex and gender in biomedical research. *BMC Womens Health*. 2015;15(26):94.
3. van der Graaf R, van der Zande ISE, den Ruijter HM, et al. Fair inclusion of pregnant women in clinical trials: an integrated scientific and ethical approach. *Trials*. 2018;19(1):78.
4. Swanson GM, Bailar JC, 3rd. Selection and description of cancer clinical trials participants--science or happenstance? *Cancer*. 2002;95(5):950-959.
5. 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(16):2956-2963. https://doi.org/10.1002/cncr.28168
6. National Institutes of Health: Office of Research on Women's Health. *Sex & Gender*. Accessed November 3, 2022. https://orwh.od.nih.gov/sex-gender#:~:text=%22Sex%22%20refers%20to%20biological%20differences,across%20societies%20and%20over%20time
7. National Institutes of Health: Office of Research on Women's Health. *How Sex/Gender Influence Health & Disease (A-Z)*. Accessed November 3, 2022. https://orwh.od.nih.gov/sex-gender/sexgender-influences-health-and-disease/how-sexgender-influence-health-disease-z
8. National Institutes of Health: Office of Research on Women's Health. *Infographic: How Sex/Gender Influence Health & Disease*. Accessed November 3, 2022. https://orwh.od.nih.gov/sex-gender/sexgender-influences-health-and-disease/infographic-how-sexgender-influence-health
9. Siegel RL, Miller KD, Fuchs HE, et al. Cancer statistics, 2021. *CA Cancer J Clin*. 2021;71(1):7-33.
10. Howlader N, Noone AM, Krapcho M, et al., eds. *SEER Cancer Statistics Review*. Bethesda, MD: National Cancer Institute; 1975-2016. https://seer.cancer.gov/csr/1975_2016/
11. *Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: incidence - SEER 9 Regs Research Data, Nov 2020 Sub (1975-2018), National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2021, based on the November 2020 submission*.
12. Centers for Disease Control and Prevention. *An Update on Cancer Deaths in the United States*. Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention, Division of Cancer Prevention and Control; 2021.
13. Rademaker M. Do women have more adverse drug reactions? *Am J Clin Dermatol*. 2001;2(6):349-351. https://doi.org/10.2165/00128071-200102060-00001
14. Anderson GD. Sex and racial differences in pharmacological response: where is the evidence? Pharmacogenetics, pharmacokinetics, and pharmacodynamics. *J Womens Health*. 2005;14(1):19-29.
15. Schmetzer O, Florcken A. Sex differences in the drug therapy for oncologic diseases. *Handb Exp Pharmacol*. 2012;(214):411-442.
16. Kim HI, Lim H, Moon A. Sex differences in cancer: epidemiology, genetics and therapy. *Biomol Ther*. 2018;26(4):335-342.
17. Luo HS, Xu HY, Du ZS, et al. Impact of sex on the prognosis of patients with esophageal squamous cell cancer underwent definitive radiotherapy: a propensity score-matched analysis. *Radiat Oncol*. 2019;14(1):74.
18. Wang S, Cowley LA, Liu XS. Sex differences in cancer immunotherapy efficacy, biomarkers, and therapeutic strategy. *Molecules*. 2019;24(18):3214. https://doi.org/10.3390/molecules24183214
19. Davidson M, Wagner AD, Kouvelakis K, et al. Influence of sex on chemotherapy efficacy and toxicity in oesophagogastric cancer: a pooled analysis of four randomised trials. *Eur J Cancer*. 2019;121:40-47. https://doi.org/10.1016/j.ejca.2019.08.010
20. Scarselli A, Corfiati M, Di Marzio D, et al. Gender differences in occupational exposure to carcinogens among Italian workers. *BMC Public Health*. 2018;18(1):413.
21. Syamlal G, Mazurek JM, Dube SR. Gender differences in smoking among U.S. working adults. *Am J Prev Med*. 2014;47(4):467-475. 10.1016/j.amepre.2014.06.013
22. Kotsopoulos J. Menopausal hormones: definitive evidence for breast cancer. *Lancet*. 2019;394(10204):1116-1118. https://doi.org/10.1016/s0140-6736(19)31901-4
23. Cameron KA, Song J, Manheim LM, et al. Gender disparities in health and healthcare use among older adults. *J Womens Health*. 2010;19(9):1643-1650.
24. Davis JL, Buchanan KL, Katz RV, et al. Gender differences in cancer screening beliefs, behaviors, and willingness to participate: implications for health promotion. *Am J Mens Health*. 2012;6(3):211-217.
25. Dumenci L, Matsuyama R, Riddle DL, et al. Measurement of cancer health literacy and identification of patients with limited cancer health literacy. *J Health Commun*. 2014;19(Suppl 2):205-224. https://doi.org/10.1080/10810730.2014.943377
26. Clayton JA, Collins FS. Policy: NIH to balance sex in cell and animal studies. *Nature*. 2014;509(7500):282-283. 10.1038/509282a
27. Espinoza M, Hsieh A, Hsiehchen D. Systematic characterization of gastrointestinal clinical trials. *Dig Liver Dis*. 2016;48(5):480-488. https://doi.org/10.1016/j.dld.2016.01.003
28. Turner B, Rajeshuni N, Tran EM, et al. Characteristics of ophthalmology trials registered in ClinicalTrials.gov, 2007-2018. *Am J Ophthalmol*. 2020;211:132-141. https://doi.org/10.1016/j.ajo.2019.11.004
29. Steinberg JR, Weeks BT, Reyes GA, et al. The obstetrical research landscape: a cross-sectional analysis of clinical trials from 2007-2020. *Am J Obstet Gynecol MFM*. 2021;3(1):100253.
30. Magnani CJ, Steinberg JR, Harmange CI, et al. Clinical trial outcomes in urology: assessing early discontinuation, results reporting and publication in ClinicalTrials.Gov Registrations 2007-2019. *J Urol*. 2021;205(4):1159-1168. https://doi.org/10.1097/ju.0000000000001432
31. Jia JL, Turner BE, Azad AD, et al. Characteristics of dermatology clinical trials 2007-2018: insights from a systematic analysis of ClinicalTrials.gov. *J Am Acad Dermatol*. 2022;86(3):685-688. https://doi.org/10.1016/j.jaad.2021.02.078
32. *ClinicalTrials.gov Protocol Registration Data Element Definitions for Interventional and Observational Studies*. Accessed October 8, 2021. https://prsinfo.clinicaltrials.gov/definitions.html
33. U.S. Code Title 20. *Education: U.S. Code 1001 - General Definition of Institution of Higher Education*. Accessed October 8, 2021. https://www.law.cornell.edu/uscode/text/20/1001
34. U.S. Code Title 20. *Education: U.S. Code 1681 - Sex*. Accessed October 8, 2021. https://uscode.house.gov/view.xhtml?req=granuleid:USC-prelim-title20-section1681&num=0&edition=prelim
35. *Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: incidence - SEER Research Data, 18 Registries, Nov 2019 Sub (2000-2017) - Linked To County Attributes - Time Dependent (1990-2017) Income/Rurality, 1969-2018 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, released April 2020, based on the November 2019 submission*.
36. Poon R, Khanijow K, Umarjee S, et al. Participation of women and sex analyses in late-phase clinical trials of new molecular entity drugs and biologics approved by the FDA in 2007-2009. *J Womens Health*. 2013;22(7):604-616.
37. Scott PE, Unger EF, Jenkins MR, et al. Participation of women in clinical trials supporting FDA approval of cardiovascular drugs. *J Am Coll Cardiol*. 2018;71(18):1960-1969. https://doi.org/10.1016/j.jacc.2018.02.070
38. Khan MS, Shahid I, Siddiqi TJ, et al. Ten-year trends in enrollment of women and minorities in pivotal trials supporting recent US Food and Drug Administration approval of novel cardiometabolic drugs. *J Am Heart Assoc*. 2020;9(11):e015594.
39. Chen S, Li J. Participation of black US residents in clinical trials of 24 cardiovascular drugs granted FDA approval, 2006-2020. *JAMA Netw Open*. 2021;4(3):e212640. https://doi.org/10.1001/jamanetworkopen.2021.2640

40. Khan SU, Khan MZ, Raghu Subramanian C, et al. Participation of women and older participants in randomized clinical trials of lipid-lowering therapies: a systematic review. *JAMA Netw Open*. 2020;3(5):e205202. https://doi.org/10.1001/jamanetworkopen.2020.5202
41. Eshera N, Itana H, Zhang L, Soon G, Fadiran EO. Demographics of clinical trials participants in pivotal clinical trials for new molecular entity drugs and biologics approved by FDA from 2010 to 2012. *Am J Ther*. 2015;22(6):435-455. https://doi.org/10.1097/mjt.0000000000000177
42. Duma N, Vera Aguilera J, Paludo J, et al. Representation of minorities and women in oncology clinical trials: review of the past 14 years. *J Oncol Pract*. 2018;14(1):e1-e10.
43. Sosinsky AZ, Rich-Edwards JW, Wiley A, et al. Enrollment of female participants in United States drug and device phase 1-3 clinical trials between 2016 and 2019. *Contemp Clin Trials*. 2022;115:106718. https://doi.org/10.1016/j.cct.2022.106718
44. Jin X, Chandramouli C, Allocco B, et al. Women's participation in cardiovascular clinical trials from 2010 to 2017. *Circulation*. 2020;141(7):540-548. https://doi.org/10.1161/circulationaha.119.043594
45. Mansukhani NA, Yoon DY, Teter KA, et al. determining if sex bias exists in human surgical clinical research. *JAMA Surg*. 2016;151(11):1022-1030. https://doi.org/10.1001/jamasurg.2016.2032
46. Varma T, Wallach JD, Miller JE, et al. Reporting of study participant demographic characteristics and demographic representation in premarketing and postmarketing studies of novel cancer therapeutics. *JAMA Netw Open*. 2021;4(4):e217063. https://doi.org/10.1001/jamanetworkopen.2021.7063
47. Jenei K, Meyers DE, Prasad V. Use of participation to prevalence ratio for evaluating the representation status of women in oncology clinical trials—reply. *JAMA Oncol*. 2022;8(3):480-480. https://doi.org/10.1001/jamaoncol.2021.6971
48. Cook MB, McGlynn KA, Devesa SS, Freedman ND, Anderson WF. Sex disparities in cancer mortality and survival. *Cancer Epidemiol Biomarkers Prev*. 2011;20(8):1629-1637. https://doi.org/10.1158/1055-9965.epi-11-0246
49. Otto W, May M, Fritsche HM, et al. Analysis of sex differences in cancer-specific survival and perioperative mortality following radical cystectomy: results of a large German multicenter study of nearly 2500 patients with urothelial carcinoma of the bladder. *Gend Med*. 2012;9(6):481-489. https://doi.org/10.1016/j.genm.2012.11.001
50. Schmid M, Shariat SF, Soave A, et al. Contemporary gender-specific outcomes in Germany after radical cystectomy for bladder cancer. *Curr Urol Rep*. 2014;15(6):409.
51. Javier-DesLoges J, Nelson TJ, Murphy JD, et al. An evaluation of trends in the representation of patients by age, sex, and diverse race/ethnic groups in bladder and kidney cancer clinical trials. *Urol Oncol*. 2022;40(5):199 e15-199 e21.
52. Wong BO, Perera ND, Shen JZ, et al. Analysis of registered clinical trials in surgical oncology, 2008-2020. *JAMA Netw Open*. 2022;5(1):e2145511. https://doi.org/10.1001/jamanetworkopen.2021.45511.
53. Naredi P, La Quaglia MP. The future of trials in surgical oncology. *Nat Rev Clin Oncol*. 2015;12(7):425-431. https://doi.org/10.1038/nrclinonc.2015.72
54. Brown DR, Fouad MN, Basen-Engquist K, Tortolero-Luna G. Recruitment and retention of minority women in cancer screening, prevention, and treatment trials. *Ann Epidemiol*. 2000;10(Suppl_8):S13-S21. https://doi.org/10.1016/s1047-2797(00)00197-6.
55. Borno HT, Zhang L, Siegel A, et al. At what cost to clinical trial enrollment? A retrospective study of patient travel burden in cancer clinical trials. *Oncologist*. 2018;23(10):1242-1249.
56. 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(2):107-114.
57. Cartmell KB, Bonilha HS, Simpson KN, et al. Patient barriers to cancer clinical trial participation and navigator activities to assist. *Adv Cancer Res*. 2020;146:139-166.
58. U.S. Food and Drug Administration. Investigational new drug applications and new drug applications. *Fed Regist*. 1998;63(28):6854-6862.
59. National Institutes of Health: Department of Health and Human Services. *Monitoring Adherence to the NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical Research Fiscal Year 2009-2010*.
60. U.S. Code Title 42. *Public Health and Welfare: U.S. Code 289a-2 - Inclusion of Women and Minorities in Clinical Research*. Accessed February 16, 2022. https://www.govinfo.gov/content/pkg/USCODE-2011-title42/pdf/USCODE-2011-title42-chap6A-subchapIII-partH-sec289a-2.pdf
61. National Institute of Health. *Inclusion of Women and Minorities as Participants in Research Involving Human Subjects. NIH Central Resource for Grants and Funding Information*. Accessed February 16, 2022. https://grants.nih.gov/policy/inclusion/women-and-minorities.htm
62. U.S. Food and Drug Administration. *Understanding Sex Differences at the FDA*. Accessed February 16, 2022. https://www.fda.gov/science-research/womens-health-research/understanding-sex-differences-fda
63. U.S. Food and Drug Administration. *Collection, Analysis, and Availability of Demographic Subgroup Data for FDA-Approved Medical Products*. Accessed February 16, 2022. https://www.fda.gov/media/86561/download
64. U.S. Food and Drug Administration. *FDA's Action Plan for FDASIA Section 907: Questions and Answers*. Accessed February 16, 2022. https://www.fda.gov/regulatory-information/food-and-drug-administration-safety-and-innovation-act-fdasia/fdas-action-plan-fdasia-section-907-questions-and-answers
65. Jenei K, Meyers DE, Prasad V. The inclusion of women in global oncology drug trials over the past 20 years. *JAMA Oncol*. 2021;7(10):1569-1570. https://doi.org/10.1001/jamaoncol.2021.3686
66. Chen S, Li J, Shu M. Use of participation to prevalence ratio for evaluating the representation status of women in oncology clinical trials. *JAMA Oncol*. 2022;8(3):479-480. https://doi.org/10.1001/jamaoncol.2021.6968
67. Steinberg JR, Turner BE, Weeks BT, et al. Analysis of female enrollment and participant sex by burden of disease in US clinical trials between 2000 and 2020. *JAMA Netw Open*. 2021;4(6):e2113749. https://doi.org/10.1001/jamanetworkopen.2021.13749
68. National Institutes of Health. *Amendment: NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research*. Accessed October 8, 2021. https://grants.nih.gov/grants/guide/notice-files/NOT-OD-18-014.html
69. Tse T, Fain KM, Zarin DA. How to avoid common problems when using ClinicalTrials.gov in research: 10 issues to consider. *BMJ*. 2018;361:k1452.
70. Clayton JA, Tannenbaum C. Reporting sex, gender, or both in clinical research? *JAMA*. 2016;316(18):1863-1864. https://doi.org/10.1001/jama.2016.16405
71. Lee E, Wen P. Gender and sex disparity in cancer trials. *ESMO Open*. 2020;5(Suppl_4):e000773. https://doi.org/10.1136/esmoopen-2020-000773