HHS Public Access

Author manuscript

J Natl Compr Canc Netw. Author manuscript; available in PMC 2023 February 08.

Published in final edited form as:

J Natl Compr Canc Netw. 2022 July ; 20(7): 792–799.e4. doi:10.6004/jnccn.2022.7017.

Potential impact of revised NCI eligibility criteria guidance: prior malignancy exclusion in breast cancer clinical trials

Matthew Perez, MD[1,*], **Caitlin C. Murphy, PhD**[2], **Sandi L. Pruitt, PhD**[3,4], **Sawsan Rashdan, MD**[4,5], **Asal Rahimi, MD**[4,5], **David E. Gerber, MD**[3,4,5]

[1]School of Medicine, UT Southwestern Medical Center, Dallas TX

[2]School of Public Health, University of Texas Health Science Center at Houston (UTHealth), Houston TX

[3]Department of Population and Data Sciences, UT Southwestern Medical Center, Dallas TX

[4]Harold C. Simmons Comprehensive Cancer Center, UT Southwestern Medical Center, Dallas TX

[5]Department of Internal Medicine, UT Southwestern Medical Center, Dallas TX

Abstract

Background: Many individuals with cancer have survived a prior cancer and for this reason may have been excluded from clinical trials. Recent National Cancer Institute (NCI) guidance recommends including these individuals, especially when the risk of the prior malignancy interfering with either safety or efficacy endpoints is very low. Using breast cancer as an example, we determined the potential effect this policy change may have on clinical trial accrual.

Patients and Methods: We reviewed protocols of NCI-sponsored breast cancer clinical trials activated 1991–2016. We quantified prevalence of prior cancer-related exclusion criteria and assessed the association with trial characteristics using Fisher's exact tests. Using NCI Surveillance Epidemiology and End Results (SEER) data, we estimated the prevalence and timing of prior primary (non-breast) cancer diagnoses among patients with breast cancer.

Results: Among 87 clinical trials (total target enrollment 137,253 patients), 77% excluded individuals with prior cancer, most commonly (79%) within the preceding five years. Among trials with radiographic response or toxicity endpoints, 69% excluded prior cancer. In SEER data, the prevalence of a prior (non-breast) cancer diagnosis ranged 5.7–7.7%, depending on breast cancer stage, of which 39% occurred within five years of the incident breast cancer. For trials excluding prior cancer, the estimated proportion of patients excluded for this reason ranged from 1.3–5.8%, with estimated number of excluded patients ranging from 1–288.

Address for Correspondence: David E. Gerber, MD, Division of Hematology-Oncology, Harold C. Simmons Comprehensive Cancer Center, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd., Mail Code 8852, Dallas, TX 75230-8852, USA, Phone: 214-648-4180, Fax: 214-648-1955, david.gerber@utsouthwestern.edu.

*Dr. Perez is currently at University of Washington Affiliated Hospitals

Contributions to Study and/or Manuscript:

Concept and design (S.L.P., D.E.G.), data collection (M.P.), statistical analysis (C.C.M., S.L.P.), data interpretation (C.C.M., S.L.P., S.R., A.R., D.E.G.), manuscript drafting (M.P., C.C.M., S.L.P., D.E.G.), final manuscript approval (M.P., C.C.M., S.L.P., S.R., A.R., D.E.G.)

Conflicts of Interest/Competing Interests: No relevant conflicts of interests.

Discussion: More than three-fourths of NCI-sponsored breast cancer clinical trials exclude patients with prior cancer, including almost 70% of trials with response or toxicity endpoints. As more than 5% of breast cancer patients have a history of prior cancer, in large phase 3 trials this practice may exclude hundreds of patients.

Conclusion: Following recent NCI eligibility guidance, the inclusion of patients with prior cancer on breast cancer trials may have a meaningful impact on accrual.

Keywords

accrual; clinical research; enrollment; eligibility; epidemiology; oncology

1.0 Background

In December 2021, the National Cancer Institute (NCI) issued revised guidance on eligibility criteria for cancer clinical trials.[1] Based on 2017/2021 recommendations from the American Society of Clinical Oncology (ASCO) and Friends of Cancer Research (Friends),[2–4] the document addresses several aspects of eligibility, including brain metastases, HIV and viral hepatitis infection, organ function, concomitant medications, performance status, and prior or concurrent malignancies. For this last category, NCI specifically recommends including patients with prior or concurrent malignancies, especially when the risk of malignancy interfering with either safety or efficacy endpoints is very low. This approach resembles that put forth in recent U.S. Food and Drug Administration (FDA) guidance, which recommends including patients with prior or concurrent malignancies if the natural history or treatment do not have the potential to interfere with safety or efficacy assessment of the investigational drug. In particular, FDA recommends including such patients in initial dose finding, preliminary activity-estimating, or proof-of-concept studies.[5]

In recent years, the number of cancer survivors in the U.S. has increased dramatically, from fewer than 4 million in 1977, to 18 million in 2022, to a projected 26 million in 2040.[6,7] These individuals are living longer. Whereas only half of cancer survivors in the 1970s were beyond 5 years of diagnosis, that proportion now exceeds two-thirds, with almost half beyond 10 years of diagnosis.[6] As a result, the number of persons diagnosed with multiple cancers has increased.[8–10] Given these trends, to estimate the impact of prior cancer diagnoses on clinical trial enrollment and the potential effect of recent NCI guidance, we determined the (1) prevalence and nature of prior cancer-related eligibility criteria in NCI-sponsored breast cancer clinical trials, and (2) the estimated proportion and numbers of patients excluded from these trials due to a prior cancer diagnosis.

2.0 Methods

2.1 Protocol Identification and Data Abstraction

This study was approved by the UT Southwestern Medical Center Institutional Review Board. We requested protocol documents for breast cancer clinical trials activated 1991–2016 directly from the sponsoring National Clinical Trials Network (NCTN) group (Alliance, ECOG-ACRIN, NRG, SWOG). We developed and pre-tested a data abstraction form to collect relevant data from trial protocols. The form was implemented in REDCap

(Research Electronic Data Capture), a secure web-based application designed to support data capture for research studies.[11]

Our abstraction form (Supplemental Table 1) collected data related to trial phase, disease stage, primary endpoint, primary treatment modality, sponsoring NCI Network group, and year of activation. For trials comprising multiple phases (eg, phase I/II), we characterized the trial according to the highest phase. For trials including patients with multiple stages of breast cancer (eg, included patients with stage II or III disease), we characterized the trial according to the most advanced stage as the most conservative approach because rates of prior cancer are higher for earlier stage breast cancer. For trials with multiple primary endpoints, we categorized by a single endpoint using the following hierarchy: survival>progression>recurrence >other. For trials with multiple treatment modalities, we characterized according to which treatment modality represented the primary research question. We recorded whether protocols excluded patients with (1) prior cancer (including type, time-frame, and exceptions); and (2) prior cancer treatment (including type and time-frame). We recorded separately whether protocols included “guidance” statements related to prior cancer; in these cases, the enrollment of participants with a history of prior cancer was cautioned but ultimately left to the discretion of the enrolling clinician. For this analysis, prior cancer diagnosis and prior cancer treatment related to earlier breast cancer were not included.

Primary data abstraction was performed by a single investigator (M.P.). For quality assurance, a senior clinical investigator (D.E.G.) reviewed all fields of data abstraction for the first 10 protocols entered and reviewed fields related to exclusion of prior cancer diagnoses and prior cancer treatment for all protocols.

2.2 SEER Data

We analyzed data from the Surveillance Epidemiology and End Results (SEER-9) program of population-based cancer registries. We included women aged 18 years or older diagnosed with breast cancer (SEER behavior code 3, AJCC 7th edition stages 0-IV) between 2016 and 2017. We excluded male breast cancer because of its rarity (<1% of all breast cancers) and because the prevalence and timing of prior cancers may differ according to patient sex.[12,13] We defined prior cancer as any primary cancer of a different type (inclusive of women with different type prior cancers only and women with a different type prior cancer and a same type [breast cancer] prior cancer) using the *sequence number* variable as previously described.[13] For women diagnosed with more than one breast caner during 2016–2017, we used sequence number and year of diagnosis to select the most recent breast cancer as the index case.

2.3 Statistical Analysis

We reported the time frame and other characteristics of prior cancer-related exclusion criteria using descriptive statistics (number, percent) and qualitatively assessed similarities and differences in the wording of these criteria. We used Fisher’s exact tests to explore associations between trial characteristics and prior cancer-related exclusion criteria. We estimated the proportion and number of patients excluded due to a prior cancer diagnosis

from clinical trials through the following steps. First, we determined the proportion of patients with prior non-breast cancer diagnoses in SEER according to the breast cancer stage under study in the clinical trial. Second, we multiplied this proportion by the proportion of prior cancer cases occurring within the time-frame specified in the clinical trial (e.g., within 5 years). Third, we used the resulting modified proportion to estimate the number of patients expected to be excluded due to prior cancer as follows: (% of targeted breast cancer population by stage with prior cancer diagnosis x proportion of prior cancer diagnoses within specified time frame) / 100. Lastly, for each trial we estimated the absolute number of patients excluded due to prior cancer by using the trial target sample size and the estimated proportion excluded as follows: {target enrollment / [1 − (% excluded/100)]} − target enrollment. For trials excluding patients with “current” or “active” cancer, we estimated the proportion of affected patients by using the ≤ 2 years’ time frame.

Statistical analyses were performed using Stata 15.1.[14]

3.0 Results

In total, 87 trials (representing a combined target enrollment of 137,253 patients) were included in the analysis. All trials were phase II or III, 74 (85%) focused on medical therapies, and 4 (5%) had an overall survival primary endpoint. Additional trial characteristics are listed in Table 1.

Overall, 67 trials (77%) excluded individuals with a history of prior cancer. Among these trials, the most common time frame for exclusion was within five years of enrollment (79%). Notably, four trials (6%) excluded patients regardless of when prior cancers were diagnosed. Additionally, five trials included “guidance” statements, of which only one also had criteria explicitly excluding prior cancer diagnoses. These statements, which addressed only eligibility related to prior cancer diagnoses, cautioned against enrollment of patients with prior cancer unless the investigator believed the likelihood of recurrence of the prior cancer was below a specified threshold (most commonly 30%). All trials excluding prior cancer mentioned certain exceptions to the exclusion; nearly all (93%) applied two or more exceptions. Exceptions included non-melanoma skin cancer (75%), *in situ* cervical cancer (68%), other *in situ* cancers (15%), and other (8%). Sample wording for prior cancer-related exclusion and guidance are presented in Table 2.

Breast cancer stage, endpoint, treatment modality, year of activation, and trial phase were not associated with exclusion of prior cancer (Table 3). NCI network group was statistically significantly associated with prior cancer exclusion; for example, all 18 NRG trials excluded patients with prior cancer; fewer Alliance trials applied this exclusion (65%). Furthermore, 16 of the 18 NRG trials (88%) employed the same prior cancer exclusion time-frame (5 years). Forty-six trials (53%) excluded prior cancer treatment. There was a nearly statistically significant correlation between exclusion of prior cancer treatment and prior cancer diagnosis (P=0.08). Of note, 8% of trials that excluded prior cancer treatment did not exclude prior cancer diagnoses, while 32% of trials that excluded prior cancer diagnoses did not exclude prior cancer treatment (Figure 1). Among the 46 trials that excluded prior cancer treatment, 44 (96%) excluded prior treatment at any time-point. Categorizing prior cancer

treatment as either surgery, radiation therapy, chemotherapy, or other medical therapy (eg, targeted therapy, hormonal therapy), 33 (72%) excluded one treatment category, 9 (20%) excluded two treatment categories, and 4 (9%) excluded three treatment categories. The most commonly excluded treatment category was chemotherapy (65%), followed by other medical therapy (43%), radiation therapy (24%), and surgery (4%).

We identified 46,824 women with breast cancer in SEER. We determined the prevalence of prior non-breast cancer diagnoses overall and according to breast cancer stage among the 45,294 women with available stage (Table 4a). We also determined the timing of prior cancer among the 3,008 women with available year of diagnosis of the prior non-breast cancer (Table 4b). In general, we observed numerically higher rates of prior cancer among earlier stage breast cancer stages. Among prior non-breast cancers, 39% occurred within the five years preceding the lung cancer diagnosis, representing the most common time frame of prior cancer exclusion in the protocols we examined.

Using the stage of breast cancer under study, the time-frame of prior breast cancer exclusion, and the prevalence and timing of prior non-breast cancers in the SEER registry, we estimated the proportion and absolute number of patients excluded from the 87 protocols included in our analysis (Table 5 and Supplemental Table 2). Among all trials, which had a total target enrollment of 137,253 patients, we estimated that 3,018 (2.2%) would be excluded due to a prior cancer diagnosis. For 10 trials, we estimated that more than 100 patients would be excluded due to prior cancer. All 10 trials were phase 3 and had a primary endpoint of recurrence. For trials excluding prior cancer, the estimated proportion of patients excluded for this reason ranged from 1.3–5.8%, with estimated number of excluded patients ranging from 1–288. For the 20 trials that did not exclude prior cancer, total target enrollment was 19,633 and estimated number of patients with prior cancer was 1,127 (5.7%).

4.0 Discussion

With the goal of achieving diverse and representative populations in future clinical trials, recent NCI guidance recommends broadening cancer clinical trial eligibility criteria across numerous categories, including prior or concurrent malignancies. In the present study, we analyzed NCI-sponsored breast cancer clinical trial protocols to determine how this policy change might affect trial enrollment. We found that more than three-quarters of clinical trials excluded patients with prior non-breast cancer, most commonly if the prior cancer was diagnosed within five years of the incident breast cancer. When we applied the prevalence and timing of prior cancer in the SEER dataset, we estimated that in some trials this practice results in excluding 5.8 percent of potential patients; in 11 percent of trials, it excludes more than 100 potential patients. Based on these findings, it seems likely that the recent NCI guidance could have a meaningful impact on trial accrual.

Excluding patients with a prior cancer diagnosis from cancer clinical trials appears to be a common practice. For instance, over 80 percent of NCI-sponsored lung cancer clinical trials exclude patients with prior cancer.[15] To reconsider this longstanding practice, one must consider and critically appraise the motivations that underlie it. One possible concern is that treatment of prior cancer will interfere with assessment of the intervention under

study for the current breast cancer. Prior treatment could hypothetically render patients at greater risk for toxicity. Alternatively, exposure to prior treatment could alter the breast cancer's sensitivity to the experimental therapy. To address these possibilities, trials could instead exclude prior cancer *treatment.* About half of the trials in the present analysis took this approach, usually excluding specific cytotoxic or targeted agents evaluated in the clinical trial. Other trials excluded prior treatment only if it exceeded a specific threshold of cumulative dose of number of administered cycles. Importantly, in women with breast cancer, almost two-thirds of non-breast prior cancers are in situ or localized stage, and fewer than 10 percent of prior cancers are metastatic.[16] Thus it seems unlikely that only a minority of prior cancers would require any systemic therapy.

Another potential concern is the effect of a prior cancer on survival of women with breast cancer. In the SEER-Medicare population, almost 10 percent of breast cancer patients with a prior cancer diagnosis die from the previous cancer and a prior cancer diagnosis is associated with increased risk of death in stage I-III breast cancer.[16] However, overall survival is rarely employed as a primary endpoint in breast cancer clinical trials, representing only five percent of protocols in the present analysis. Presumably, these factors would be less relevant to trials with non-survival endpoints (particularly response or toxicity endpoints). Nonetheless, more than three-quarters of such trials in the present study excluded patients with a prior cancer diagnosis.

Even in the most recent years, the majority of trial protocols exclude patients with previous cancer. Efforts to mitigate the detrimental impact on enrollment are apparent through the multiple exceptions (most commonly non-melanoma skin cancer and *in situ* cancers) and "guidance" statements. These clauses request that clinicians to estimate an individual patient's likelihood of prior cancer recurrence to determine eligibility, a challenging directive fraught with uncertainty. As further evidence of the general confusion surrounding the potential concerns related to prior cancer impact on trial conduct or outcomes, our analysis demonstrates widely varying interpretations. Time-frames for excluded prior cancer diagnoses range from as short as only concurrently active cancers to a prior cancer diagnosis at any point in the patient's life. The most common interval—employed by more than three-quarters of trials with prior cancer exclusion—was five years, a recommendation that was previously made, but is no longer recommended, by the National Cancer Institute.[15,17] Indeed, despite representing diverse breast cancer stages, endpoints, and treatment modalities, all but two of the NRG protocols in the present study used the five-year interval, suggesting that exclusion criteria may be copied from prior trials without clear reasoning.

Excluding patients with prior cancer from breast cancer clinical trials may have a disproportionate effect on older individuals. Similar to other cancers,[18] in breast cancer populations the prevalence of prior cancer increases with patient age. For patients ages <65 years, 5% have prior cancer, compared to 6% for 66–70 years and 10% for ages >85 years.[13,19] Indeed, this phenomenon may contribute to age disparities in cancer clinical trials, where subjects are more than six years younger than general oncology populations. Notably, this imbalance is greater for industry-sponsored trials (which were not included in the present study) and is increasing over time.[20] Failure to meet protocol eligibility or not

receiving information about potential trials appear to drive this disparity, and most elderly individuals demonstrate interest in trial participation when provided the opportunity.[21–25]

Can observations from this study be generalized to other breast cancer trials, such as those sponsored by pharmaceutical companies? Among a sample of lung cancer trials, those with pharmaceutical industry sponsors have similar rates of prior cancer exclusion than do NCI-sponsored studies.[15] Regardless of sponsor type, the practice of excluding prior cancer likely persists due to historical precedent and inertia. Over time, clinical trial protocols tend to accumulate new eligibility criteria while rarely discarding those no longer relevant. For example, many immunotherapy clinical trials have added new eligibility criteria related to history of autoimmune disease, organ transplantation, and immunosuppressant use, but have not removed or relaxed eligibility criteria less relevant to these new therapies (such as strict minimum blood counts required for safe administration of conventional chemotherapy).[26]

Complex, poorly justified, inconsistent, and overly restrictive trial eligibility criteria may limit access to novel therapies, hinder trial recruitment and completion, and limit generalizability of trial results. To simplify eligibility, facilitate searches for appropriate trials, and harmonize trial populations to support comparisons of treatment effects, clinicians, representatives from the pharmaceutical industry, and international regulators have drafted a recommended eligibility criteria framework to guide investigators and sponsors in the design of cancer clinical trials.[27] The forthcoming FDA Draft Guidance for Industry, “Eligibility for Non-Small Cell Lung Cancer Trials,” serves as a prototype, with guidance for other cancer types under development. By connecting diverse stakeholders and incorporating public input, these efforts may provide opportunities to revise longstanding approaches to trial eligibility, including those related to prior cancer diagnoses.

There are caveats to the interpretation of our findings. The definition of “active” cancer as a cancer diagnosed within two years of the incident breast cancer fails to account for the possibility that cancers within this time-frame are no longer clinically active, or that prior cancers diagnosed earlier might remain clinically active. We recognize that prior cancer diagnoses may accompany other comorbidities or frailty.[16] Accordingly, some patients with prior cancer diagnoses may still not meet protocol eligibility even if the prior cancer no longer excludes them. The age discrepancy between general oncology and clinical trial populations is unlikely to have a major effect on our findings because (a) by using SEER data, we include all patient ages; and (b) based on earlier epidemiologic studies,[13,19] the difference in prior cancer prevalence between these populations is likely to be minimal.

In conclusion, more than three quarters of NCI-sponsored breast cancer clinical trials exclude individuals with prior cancer, a proportion that has not declined over time. This restriction is applied variably, with different time-frames and exceptions across trials, suggesting that the rationale and justification for the practice remains unclear. Given the large number of trials and population burden of breast cancer, this restriction alone could potentially exclude tens of thousands of women over time. Overly stringent eligibility criteria may limit trial enrollment, leading to prolonged study accrual and/or premature study closure.[28–30] Despite repeated calls to simplify these criteria, they have continued to increase in number and complexity over time.[26,31] If incorporated into future trial protocols,

recent NCI guidance recommending broader eligibility criteria may reverse these trends, enhancing trial accrual, completion, and generalizability.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

The authors thank Helen Mayo, MLS (UT Southwestern Medical Library) for assistance with literature searches, Ms. Dru Gray for assistance with manuscript preparation, Dr. Aniruddha B. Rathod for assistance with SEER analysis, and Ms. Jessica Philips for assistance obtaining the trial protocols. Study data were collected and managed using REDCap electronic data capture tools hosted at UT Southwestern and supported by UT Southwestern Academic Information Systems; and CTSA Grant UL1TR001105 provided by the National Center for Advancing Translational Sciences of the National Institutes of Health at the NIH.

Funding:

This work was supported by National Cancer Institute (NCI) Midcareer Investigator Award in Patient-Oriented Research (K24 CA201543-01, to D.E.G.) and R01CA229834-02 (to S.L.P.).

References:

1. National Cancer Institute (NCI) Cancer Therapy Evaluation Program (CTEP). Broadening/ Modernizing Eligiblity Criteria for National Cancer Institute (NCI) Sponsored Clinical Trials. 2021. chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/viewer.html?pdfurl=https%3A%2F%2Fctep.cancer.gov%2FprotocolDevelopment%2Fdocs%2FCTEP_Broadened_Eligibility_Criteria_Guidance.pdf&clen=431762&chunk=true.) Accessed January 13, 2022.
2. Lin NU, Prowell T, Tan AR, et al. Modernizing Clinical Trial Eligibility Criteria: Recommendations of the American Society of Clinical Oncology-Friends of Cancer Research Brain Metastases Working Group. J Clin Oncol 2017;35:3760–73. [PubMed: 28968165]
3. Uldrick TS, Ison G, Rudek MA, et al. Modernizing Clinical Trial Eligibility Criteria: Recommendations of the American Society of Clinical Oncology-Friends of Cancer Research HIV Working Group. J Clin Oncol 2017;35:3774–80. [PubMed: 28968173]
4. Lichtman SM, Harvey RD, Damiette Smit MA, et al. Modernizing Clinical Trial Eligibility Criteria: Recommendations of the American Society of Clinical Oncology-Friends of Cancer Research Organ Dysfunction, Prior or Concurrent Malignancy, and Comorbidities Working Group. J Clin Oncol 2017;35:3753–9. [PubMed: 28968172]
5. U.S. Food and Drug Administration. Oncology Center of Excellence, Center for Biologics Evaluation and Research, Center for Drug Evaluation and Research. Cancer Clinical Trial Eligibility Criteria: Patients with Organ Dysfunction or Prior or Concurrent Malignancies. 2020. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cancer-clinical-trial-eligibility-criteria-patients-organ-dysfunction-or-prior-or-concurrent. Accessed March 30, 2022.
6. de Moor JS, Mariotto AB, Parry C, et al. Cancer survivors in the United States: prevalence across the survivorship trajectory and implications for care. Cancer Epidemiol Biomarkers Prev 2013;22:561–70. [PubMed: 23535024]
7. Bluethmann SM, Mariotto AB, Rowland JH. Anticipating the “Silver Tsunami”: Prevalence Trajectories and Comorbidity Burden among Older Cancer Survivors in the United States. Cancer Epidemiol Biomarkers Prev 2016;25:1029–36. [PubMed: 27371756]
8. Glicksman AS, Fulton JP. Metachronous cancer. R I Med J (2013) 2013;96:41–4.
9. Ye Y, Neil AL, Wills KE, Venn AJ. Temporal trends in the risk of developing multiple primary cancers: a systematic review. BMC Cancer 2016;16:849. [PubMed: 27814758]
10. Weir HK, Johnson CJ, Thompson TD. The effect of multiple primary rules on population-based cancer survival. Cancer Causes Control 2013;24:1231–42. [PubMed: 23558444]

11. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. Journal of Biomedical Informatics 2009;42:377–81. [PubMed: 18929686]
12. Anderson WF, Jatoi I, Tse J, Rosenberg PS. Male breast cancer: a population-based comparison with female breast cancer. J Clin Oncol 2010;28:232–9. [PubMed: 19996029]
13. Murphy CC, Gerber DE, Pruitt SL. Prevalence of Prior Cancer Among Persons Newly Diagnosed With Cancer: An Initial Report From the Surveillance, Epidemiology, and End Results Program. JAMA Oncology 2018;4:832–6. [PubMed: 29167866]
14. Milas L, Mason KA, Ang KK. Epidermal growth factor receptor and its inhibition in radiotherapy: in vivo findings. Int J Radiat Biol 2003;79:539–45. [PubMed: 14530163]
15. Gerber DE, Laccetti AL, Xuan L, Halm EA, Pruitt SL. Impact of prior cancer on eligibility for lung cancer clinical trials. J Natl Cancer Inst 2014;106.
16. Pruitt SL, Zhu H, Heitjan DF, et al. Survival of women diagnosed with breast cancer and who have survived a previous cancer. Breast Cancer Res Treat 2021.
17. National Cancer Institute, Cancer Therapy Evaluation Program. Guidelines Regarding the Inclusion of Cancer Survivors and HIV-positive Individuals on Clinical Trials http://ctep.cancer.gov/protocolDevelopment/policies_hiv.htm. Accessed January 13, 2022.
18. Laccetti AL, Pruitt SL, Xuan L, Halm EA, Gerber DE. Effect of prior cancer on outcomes in advanced lung cancer: implications for clinical trial eligibility and accrual. J Natl Cancer Inst 2015;107.
19. Pruitt SL, Zhu H, Heitjan DF, et al. Survival of women diagnosed with breast cancer and who have survived a previous cancer. Breast Cancer Res Treat 2021;187:853–65. [PubMed: 33620590]
20. Ludmir EB, Mainwaring W, Lin TA, et al. Factors Associated With Age Disparities Among Cancer Clinical Trial Participants. JAMA Oncology 2019;5:1769–73. [PubMed: 31158272]
21. Shenoy P, Harugeri A. Elderly patients' participation in clinical trials. Perspect Clin Res 2015;6:184–9. [PubMed: 26623388]
22. Hutchins LF, Unger JM, Crowley JJ, Coltman CA Jr., Albain KS. Underrepresentation of patients 65 years of age or older in cancer-treatment trials. N Engl J Med 1999;341:2061–7. [PubMed: 10615079]
23. Lee PY, Alexander KP, Hammill BG, Pasquali SK, Peterson ED. Representation of elderly persons and women in published randomized trials of acute coronary syndromes. JAMA 2001;286:708–13. [PubMed: 11495621]
24. Comis RL, Miller JD, Aldige CR, Krebs L, Stoval E. Public attitudes toward participation in cancer clinical trials. J Clin Oncol 2003;21:830–5. [PubMed: 12610181]
25. Townsley CA, Chan KK, Pond GR, Marquez C, Siu LL, Straus SE. Understanding the attitudes of the elderly towards enrolment into cancer clinical trials. BMC Cancer 2006;6:34. [PubMed: 16466574]
26. Garcia S, Bisen A, Yan J, et al. Thoracic Oncology Clinical Trial Eligibility Criteria and Requirements Continue to Increase in Number and Complexity. J Thorac Oncol 2017;12:1489–95. [PubMed: 28802905]
27. Gerber DE, Singh H, Larkins E, et al. Standardizing eligibility criteria: a new approach to simplifying and harmonizing cancer clinical trials JAMA Oncology 2022. In press.
28. Kotwall CA, Mahoney LJ, Myers RE, DeCoste L. Reasons for non-entry in randomized clinical trials for breast cancer: a single institutional study. J Surg Oncol 1992;50:125–9. [PubMed: 1593883]
29. Lee JY, Breaux SR. Accrual of radiotherapy patients to clinical trials. Cancer 1983;52:1014–6. [PubMed: 6883268]
30. Simon MS, Du W, Flaherty L, et al. Factors associated with breast cancer clinical trials participation and enrollment at a large academic medical center. J Clin Oncol 2004;22:2046–52. [PubMed: 15082724]
31. Fuks A, Weijer C, Freedman B, Shapiro S, Skrutkowska M, Riaz A. A study in contrasts: eligibility criteria in a twenty-year sample of NSABP and POG clinical trials. National Surgical

Adjuvant Breast and Bowel Program. Pediatric Oncology Group. J Clin Epidemiol 1998;51:69–79. [PubMed: 9474067]

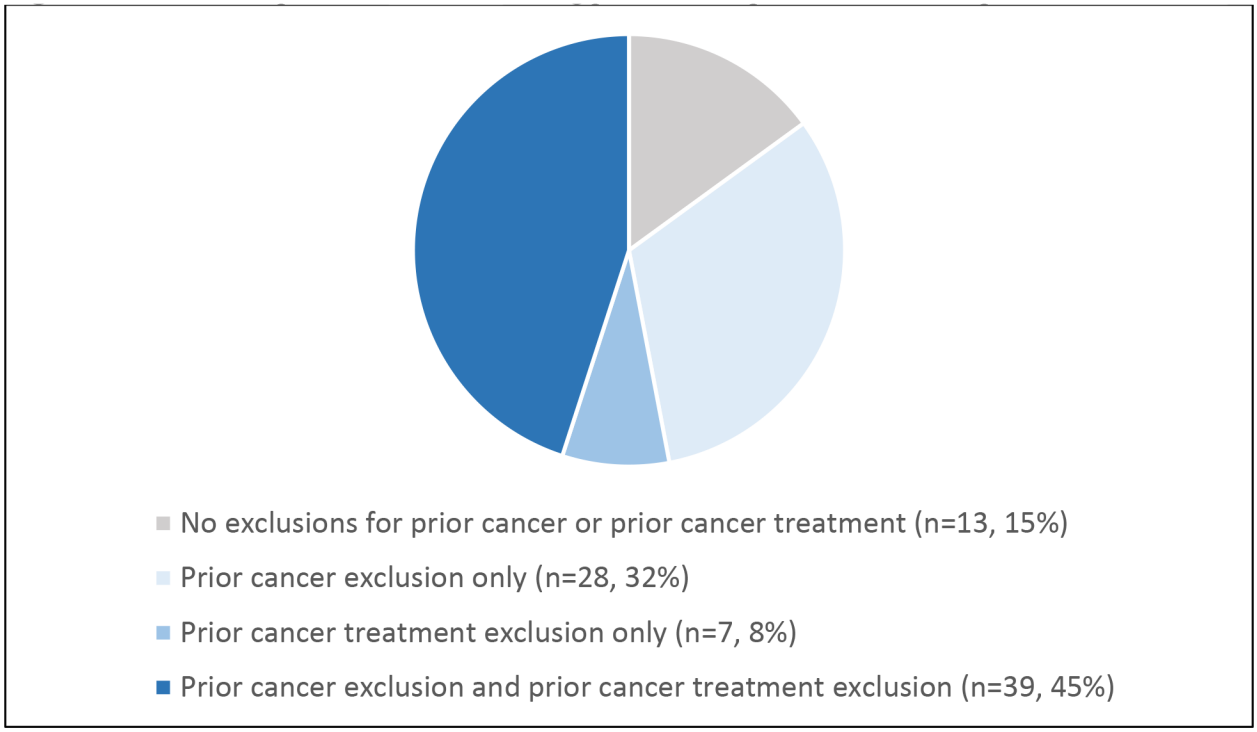

Figure 1.
Number and percent of trials excluding patients with prior cancer and/or prior cancer treatment

Table 1.

Trial characteristics

	Total (n=87)	Trials with prior cancer exclusion (n=67)	Trials with prior cancer treatment exclusion (n=46)
	Number (%)		
Breast cancer stage [a]			
0,1	7 (8)	5 (7)	4 (9)
2	6 (7)	5 (7)	4 (9)
3	46 (53)	33 (49)	22 (48)
4	28 (32)	24 (36)	16 (35)
Primary endpoint			
Response / toxicity	29 (33)	20 (30)	18 (39)
Survival	4 (5)	4 (6)	0
Progression	14 (16)	11 (16)	7 (15)
Recurrence	35 (40)	28 (42)	20 (43)
Other[b]	5 (6)	4 (6)	1 (2)
Primary treatment modality			
Surgery	5 (6)	3 (4)	3 (7)
Radiation therapy	3 (4)	3 (4)	3 (7)
Chemotherapy	25 (29)	20 (30)	13 (28)
Hormonal therapy	13 (15)	11 (16)	4 (9)
Targeted therapy	21 (24)	17 (25)	16 (35)
Other medical therapy[c]	15 (17)	9 (13)	7 (15)
Other, non-treatment trials	5 (6)	4 (6)	0
Year of activation			
1991–1999	18 (21)	15 (22)	9 (20)
2000–2009	41 (47)	30 (45)	24 (52)
2010–2016	28 (32)	22 (33)	13 (28)
Trial phase [a]			
2	25 (29)	19 (28)	17 (37)
3	59 (68)	45 (67)	29 (63)
Other[d]	3 (4)	3 (4)	0
Network group			
Alliance	28 (32)	18 (27)	14 (30)
ECOG-ACRIN	32 (37)	24 (36)	15 (33)
NRG	18 (21)	18 (27)	14 (30)
SWOG	9 (10)	7 (10)	3 (7)

[a] Some trials included individuals with multiple cancer stages or multiple phases; trials were recoded to the most advanced stage or phase

[b] Includes detection rate, imaging findings, pregnancy outcome, weight loss

[c] Includes immunotherapy, multiple medical therapies, other medical therapies

[d] Includes cohort or cross-sectional study, pregnancy outcome

Table 2.

Prior cancer-related exclusion criteria

Trial protocols excluding patients with prior cancer		
Exclusion time frame	**Sample wording**	**Number (%*) of trials**
Active	Patients may not have a “currently active” second malignancy other than non-melanoma skin cancers. Patients are not considered to have a “currently active” malignancy if they have completed therapy and are considered by their physician to be at less than 30% risk of relapse	3 (4)
2–4 years	No prior invasive malignancy (except non-melanomatous skin cancer, curatively resected thyroid papillary carcinoma, and invasive and non-invasive cancers related to the breast cancer) unless disease free for a minimum of 3 years	4 (6)
≤ 5 years	No other malignancy within 5 years of registration with the exception of basal cell or squamous cell carcinoma of the skin treated with local resection only or carcinoma in situ of the cervix.	53 (79)
≤ 10 years	Patients with a history of a malignant neoplasm aside from breast carcinoma are ineligible except for patients with curatively treated basal or squamous cell cancer of the skin or carcinoma in situ of the cervix. Patients who are > 10 years since any other curatively treated neoplasm will be eligible.	3 (4)
Ever	Patients must have no history of other malignant neoplasms, except curatively treated basal cell or squamous cell carcinoma of the skin or carcinoma of the cervix in-situ.	4 (6)
Trial protocols with guidance wording about the inclusion of patients with prior cancer		
Guidance	The following guidelines are to assist physicians in selecting patients for whom protocol therapy is safe and appropriate: Patients with a “currently active” second malignancy other than non-melanoma skin cancers are not to be registered. Patients are not considered to have a “currently active” malignancy if they have completed therapy and considered by their physician to be at less than 30% risk of relapse.	5

*Among the 67 trials excluding prior cancer.

Table 3.

Association of selected trial characteristics with prior cancer exclusion

Characteristic	Trials without prior cancer exclusion (n=20) N (%)	Trials with prior cancer exclusion (n=67) N (%)	*P* value[a]
Breast cancer stage [b]			
0,1	2 (10)	5 (7)	.55
2	1 (5)	5 (7)	
3	13 (65)	33 (49)	
4	4 (20)	24 (36)	
Primary endpoint			
Response/toxicity/complications	9 (45)	20 (30)	.70
Survival	0 (0)	4 (6)	
Progression/survival	3 (15)	11 (16)	
Recurrence	7 (35)	28 (42)	
Other	1 (5)	4 (6)	
Primary treatment modality			
Surgery	2 (10)	3 (4)	.61
Radiation therapy	0 (0)	3 (4)	
Chemotherapy	5 (25)	20 (30)	
Hormonal therapy	2 (10)	11 (16)	
Targeted therapy	4 (20)	17 (25)	
Other medical therapy[c]	6 (30)	9 (13)	
Other, non-treatment trials	1 (5)	4 (6)	
Year of activation			
1990–1999	3 (15)	15 (22)	.80
2000–2009	11 (55)	30 (45)	
2010–2017	6 (30)	22 (33)	
Trial phase [b]			
2	6 (30)	19 (28)	1.00
3	14 (70)	45 (67)	
Other	0 (0)	3 (4)	
Network group			
Alliance	10 (50)	18 (27)	.02
ECOG	8 (40)	24 (36)	
NRG	0 (0)	18 (27)	
SWOG	2 (10)	7 (10)	

[a] P value from Fisher's exact test

[b] Some trials included individuals with multiple cancer stages or multiple phases; trials were recoded to the most advanced stage or phase

Table 4.

Prevalence of cancer diagnoses prior to breast cancer overall and by stage of breast cancer **(a)** and timing **(b)** of non-breast cancer diagnoses prior to breast cancer among breast cancer patients in SEER 9 registry.

a.

	Cases n	No prior cancer n (%)	Prior breast cancer only n (%)	Prior non-breast cancer * n (%)	Prior cancer, unknown site n (%)
All women	46,824	37,143 (79.3)	3,954 (8.4)	3,008 (6.4)	2,719 (5.8)
Breast cancer stage					
0	104	83 (79.8)	5 (4.8)	8 (7.7)	8 (7.7)
I	23,904	18,321 (76.6)	2,339 (9.8)	1,670 (7.0)	1,574 (6.6)
II	14,621	12,171 (83.2)	901 (6.2)	839 (5.7)	710 (4.9)
III	4,186	3,473 (83.0)	255 (6.1)	238 (5.7)	220 (5.3)
IV	2,479	1,977 (79.8)	228 (9.2)	144 (5.8)	130 (5.2)

b.

Cases N=3008		Cumulative cases N=3008	
Time frame	**n (%)**	Time frame	**n (%)**
≤2 years	708 (23.5)	≤2 years	708 (23.5)
>2 – 3 years	178 (5.9)	≤3 years	886 (29.5)
>3 – ≤5 years	299 (9.9)	≤5 years	1185 (39.4)
>5 – ≤ 10 years	649 (21.6)	≤10 years	1834 (61.0)
>10 years	1174 (39.0)	Total	3008 (100)

* includes cases with prior non-breast cancer only and those with both prior non-breast cancer and prior breast cancer

Table 5.

Estimated proportion and number of patients excluded from breast clinical trials due to prior cancer diagnosis.

Estimated exclusion	Number (%) of protocols
Proportion of patients (%)	
0	20 (23)
1–3	60 (69)
>3–5	3 (3)
>5	4 (5)
Number of patients (n)	
0	20 (23)
1–25	38 (44)
26–100	20 (23)
>100	10 (11)