

BRIEF COMMUNICATION

Exclusion of Male Patients in Breast Cancer Clinical Trials

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Men make up an estimated 1% of patients diagnosed with breast cancer in the United States each year (1). This analysis examined the inclusion and representation of men in breast cancer trials between January 1, 2000, and April 31, 2017. On ClinicalTrials.gov, 426 trials were identified and evaluated for inclusion and recruitment of male breast cancer patients. Of these, 277 trials (65%) excluded male breast cancer patients in their enrollment criteria. Overall, 0.42% of trial participants were men, with the lowest enrollment rates in hormonal and targeted therapy trials (0.1% and 0.1%, respectively). No men were included in the 70 trials studying neoadjuvant therapies. Future trials should take extra measures to recruit male participants to adequately understand the efficacy and safety of new regimens in this subset of patients.

In 2018, 2550 new cases of invasive breast cancer will be diagnosed in men (1). Recent studies have identified differences in clinical and biological features between male and female breast cancer, highlighting the importance of inclusion of both sexes in clinical trials (2). The goal of our analysis was to methodically define the representation of men in breast cancer trials.

ClinicalTrials.gov was queried on May 1, 2017, for all therapeutic breast cancer trials from January 1, 2000, to April 31, 2017. Search terms included breast cancer and studies with results and interventional trials ($n = 721$ trials). Trials with unknown recruitment status or without status verification in 12 months were excluded. As the registry does not include personal identifiers, this analysis received a waiver for the informed consent requirement.

For the analysis, exclusion of male patients was classified as "strict exclusion" vs "allowed" and treated as a binary variable. We used logistic regression models to test the association between male patients' exclusion and trial characteristics. All statistical tests were two-tailed, and a P value of less than .05 was considered statistically significant. Data analysis was performed using SPSS statistical software.

Our initial search yielded 721 trials, 295 of which were later excluded (Figure 1). In the final analysis, 426 trials were

included. Only five studies designed to include men were completed; two of these were observational studies (NCT00773669 and NCT00666731). To our knowledge, none of these studies have been peer-reviewed and published in manuscript form (3,4). Table 1 summarizes trial characteristics. During the study period, 31 clinical trials in male breast cancer were early terminated and 11 were withdrawn; none of these were included in our analysis.

A total of 106 353 patients were enrolled. Out of 426 breast cancer trials, 277 trials (65%) excluded male breast cancer patients and 28 trials (7%) did not address male patients' inclusion/exclusion in their criteria.

Men represented 0.42% of the trial participants ($n = 452$). Hormonal and targeted therapy trials had the lowest male enrollment rates (0.1% and 0.1%, respectively). Despite chemotherapy trials having the highest proportion of male enrollment (0.2%), the number of male participants was only 234 (Table 1). Further, 70 trials (16%) studied neoadjuvant therapies, and no men were recruited into any of these trials. After dividing trials by phase, 67% of phase I trials included male patients compared with 22% of phase III trials.

In univariate analyses, hormonal trials and trials designed for metastatic disease had higher odds of excluding men (odds ratio [OR] = 4.17, 95% CI = 1.14 to 15.23, $P < .03$; OR = 2.28, 95% CI = 1.08 to 4.81, $P < .03$, respectively). University cooperative group-sponsored trials had lower odds of excluding men than those sponsored by the pharmaceutical industry and National Cancer Institute (NCI)-sponsored trials (OR = 0.55, 95% CI = 0.27 to 0.98, $P < .05$). However, none of these associations remained statistically significant in multivariable analysis.

Most of the trials included in our analysis were completed between 2011 and 2016 (83%). No changes were seen in the representation of male breast cancer patients over time.

Multiple efforts have been spearheaded by the NCI and other institutions to improve the recruitment of men in breast cancer trials. Despite these efforts, we observed that the recruitment of

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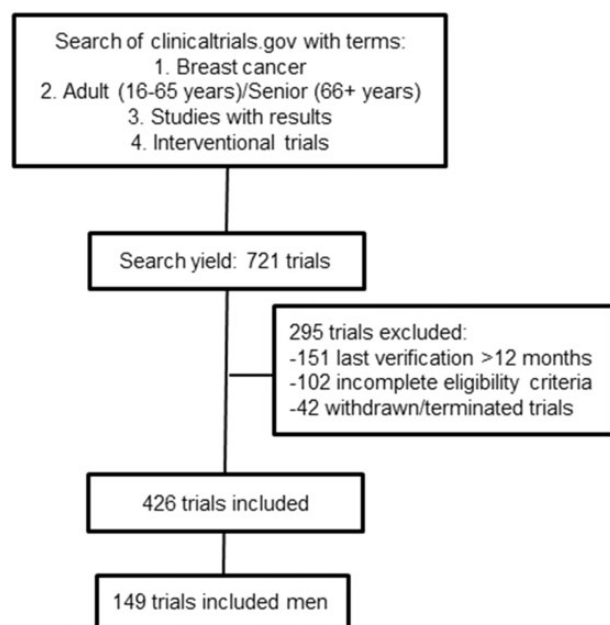


Figure 1. Consort diagram depicting the criteria used to identify trials used in the analysis.

male patients remains low. Out of 106 353 trial participants, only 452 were men.

In our analysis, the extent of exclusion varied by certain clinical trial characteristics. Hormonal trials were more likely to exclude men; this may be due to the fact that gonadotropin-releasing hormone agonists appear to be needed to safely treat men with aromatase inhibitors (5,6), increasing trial complexity and cost. Also, multiple trials designed to study hormonal therapy in men have been prematurely closed due to poor accrual (eg, S0611, Goserelin and anastrozole in men with recurrent/metastatic breast cancer; NCT 00217659).

The lowest recruitment of men was seen in neoadjuvant trials. One possible explanation is a perceived lesser benefit of neoadjuvant therapy in men, who usually opt for mastectomy (7). However, the CREATE-X trial (8) demonstrated that response to neoadjuvant therapy can guide adjuvant treatment decisions; improving accrual of men to neoadjuvant trials will allow investigators and regulatory agencies understand the safety and efficacy of experimental regimens in this unique group of patients.

There are several limitations to our analysis. First, frequent amendments to protocols occur, and these can result in changes to inclusion/exclusion criteria that may not have been captured. Next, the trials we evaluated were weighted heavily toward those from the United States and may not be generalizable to the rest of the world. Finally, additional factors likely played into the recruitment of male breast cancer patients beyond those we observed.

In the absence of a clear rationale for exclusion, male breast cancer patients should be included in all breast cancer clinical trials. Longer accrual periods and adequate budgets to support community outreach are necessary to improve recruitment. Patient navigation and educational programs that target both patients and medical providers on the availability and benefits of clinical trials have been proven to be effective in improving the recruitment of underrepresented groups and could be utilized in breast cancer trials (9).

Table 1. Trial characteristics*

Trial characteristics	No. (%)
Phase	
Phase 1	18 (4)
Phase 1b-2	87 (20)
Phase 2	270 (63)
Phase 3	51 (12)
Sponsor	
University-Cooperative group	158 (37)
Industry	209 (49)
NCI	59 (14)
Location	
Asia	43 (10)
Europe only	64 (15)
United States only	187 (44)
International	95 (22)
Other	37 (9)
Treatment	
Chemotherapy	184 (43)
Chemotherapy and targeted therapy	50 (12)
Hormonal therapy	117 (27)
Targeted therapy	33 (8)
Other	42 (10)
Line of therapy	
First	162 (38)
Second	72 (17)
Third	21 (5)
Various lines of therapy	171 (40)
Recruitment sites	
Single	177 (42)
Multiple sites	249 (58)
Other	
Neoadjuvant trials	70 (16)
Metastatic/recurrent cancer	288 (68)

*NCI = National Cancer Institute.

Cardoso et al. (5) have demonstrated the importance of international collaborations with the creation of an international registry, allowing further characterization of male breast cancer. Hence, the German Breast Group is also leading efforts to improve the understanding of endocrine treatment options for male breast cancer patients, with preliminary data reporting that all three treatment strategies were well tolerated. We await the final results for this trial as an opportunity to learn from their recruitment strategies (4).

Randomized trials including female and male breast cancer patients should be designed carefully, with recruitment targets, tailored inclusion/exclusion criteria, and individual analyses by sex. Understanding of the requirements and limitations of male breast cancer trials is necessary to avoid early termination and withdrawal of future clinical trials.

In conclusion, we found that most clinical trials excluded male breast cancer patients from participating. Future trials should aim to increase male patient participation, especially in neoadjuvant and hormonal therapy trials where most of the data is lacking.

Notes

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