Title

Lessons from the Failure to Complete a Trial of Denosumab in Women With a Pathogenic BRCA1/2 Variant Scheduling Risk-Reducing Salpingo-Oophorectomy.

Journal

Cancer Prevention Research, 15(11)

Authors

Trivedi, Meghna
Arber, Nadir
Friedman, Eitan
et al.

Publication Date

2022-11-01

DOI

10.1158/1940-6207.CAPR-22-0051

Peer reviewed

HHS Public Access

Author manuscript

Cancer Prev Res (Phila). Author manuscript; available in PMC 2023 August 21.

Published in final edited form as:

Cancer Prev Res (Phila). 2022 November 01; 15(11): 721–726. doi:10.1158/1940-6207.CAPR-22-0051.

Lessons from the Failure to Complete a Trial of Denosumab in Women With a Pathogenic *BRCA1/2* Variant Scheduling Risk-Reducing Salpingo-Oophorectomy

Meghna S. Trivedi[1], **Nadir Arber**[2], **Eitan Friedman**[3], **Judy E. Garber**[4], **Kevin Holcomb**[5], **Neil S. Horowitz**[4], **Jason D. Wright**[1], **J. Jack Lee**[6], **Lana A. Vornik**[6], **Saba Abutaseh**[6], **Tawana Castile**[6], **Edward R. Sauter**[7], **Eileen Dimond**[7], **Brandy M. Heckman-Stoddard**[7], **Margaret House**[7], **Goli Samimi**[7], **Powel H. Brown**[6], **Katherine D. Crew**[1]

[1]Columbia University Irving Medical Center, New York, New York.

[2]Tel Aviv Sourasky Medical Center, Tel Aviv, Israel.

[3]Chaim Sheba Medical Center, Tel-Aviv University Medical School, Tel Aviv, Israel.

[4]Dana-Farber Cancer Institute, Boston, Massachusetts.

[5]Weill Cornell Medical Center, New York, New York.

[6]University of Texas MD Anderson Cancer Center, Houston, Texas.

[7]Division of Cancer Prevention, National Cancer Institute, Rockville, Maryland.

Abstract

Female carriers of pathogenic/likely pathogenic (P/LP) *BRCA1/2* variants are at increased risk of developing breast and ovarian cancer. Currently, the only effective strategy for ovarian cancer risk reduction is risk-reducing bilateral salpingo-oophorectomy (RR-BSO), which carries adverse effects related to early menopause. There is ongoing investigation of inhibition of the RANK ligand (RANKL) with denosumab as a means of chemoprevention for breast cancer in carriers of *BRCA1* P/LP variants. Through the NCI Division of Cancer Prevention (DCP) Early Phase Clinical Trials Prevention Consortia, a presurgical pilot study of denosumab was developed in premenopausal carriers of P/LP *BRCA1/2* variants scheduled for RR-BSO with the goal of collecting valuable data on the biologic effects of denosumab on gynecologic tissue. The study was terminated early due to the inability to accrue participants. Challenges which impacted the conduct of this study included a study design with highly selective eligibility criteria and requirements and the COVID-19 pandemic. It is critical to reflect on these issues to enhance the successful completion of future prevention studies in individuals with hereditary cancer syndromes.

Corresponding Author: Meghna S. Trivedi, Department of Medicine, Division of Hematology/Oncology, Columbia University Medical Center, 161 Fort Washington Avenue, New York, NY 10032. mst2134@cumc.columbia.edu.

Introduction

Female carriers of pathogenic/likely pathogenic (P/LP) *BRCA1/2* variants have an elevated lifetime risk of developing breast and ovarian cancer. High-grade serous carcinoma (HGSC) is the most common and fatal ovarian cancer histologic subtype and P/LP *BRCA1/2* variants are found in 17% of HGSC cases (1). Although there are effective nonsurgical risk management options for breast cancer, including enhanced breast cancer screening and chemoprevention, options for ovarian cancer risk management are limited.

There is no effective method of screening for ovarian cancer (2). Instead risk-reducing bilateral salpingo-oophorectomy (RR-BSO) is typically recommended for women with P/LP *BRCA1* variants between the ages of 35 to 40, but can be delayed until 40 to 45 for women with P/LP *BRCA2* variants due to on average later onset of ovarian cancer (3). RR-BSO is associated with a significant reduction in ovarian cancer risk, ovarian cancer-specific mortality, and all-cause mortality (4). However, RR-BSO is also associated with clinically significant adverse effects related to premature menopause, including osteoporosis, cardiovascular disease, cognitive impairment, and increased anxiety (5). There is a large unmet need for an ovarian cancer chemopreventive agent given the high risk for ovarian cancer in this population, high mortality associated with diagnosis, and limited options for ovarian cancer prevention and screening.

Receptor activator of RANK ligand (RANKL) is an osteoclast differentiation factor that is essential for the development and activation of osteoclasts. In the breast, RANKL is secreted by progesterone receptor (PR)-positive epithelial cells in response to progesterone and acts as a paracrine factor on estrogen receptor (ER)-negative/PR-negative progenitor cells through its receptor RANK. There is significantly increased RANK expression in progenitor cells from carriers of P/LP *BRCA1* variants when compared with *BRCA1* wild-type (WT) controls (6). In mouse models, RANK signaling has been shown to promote mammary tumor formation and progression (7, 8). The RANK/RANKL pathway may also play a role in tumor progression and recurrence based on preclinical data (9).

Denosumab is a mAb that inhibits RANKL and is approved for prevention of fractures in patients with osteoporosis and bone metastases from solid tumor malignancies (10, 11). In a study of carriers of P/LP *BRCA1/2* variants, investigators demonstrated that treatment with 120 mg denosumab monthly for 3 months resulted in decreased proliferation in breast tissue as measured by Ki67 staining (6). There is an ongoing phase III international trial investigating the use of denosumab as chemoprevention for breast cancer in premenopausal women with P/LP *BRCA1* variants (clinicaltrials.gov identifier NCT04711109). In addition, there are trials investigating the effect of denosumab on breast density (NCT04067726) and on early-stage breast cancer in the presurgical setting (NCT02900469), both of which are not limited to carriers of P/LP *BRCA1/2* variants.

Although these studies show the potential promise for RANKL inhibition as a breast cancer prevention strategy in carriers of P/LP *BRCA1/2* variants, there are limited data on the effect of RANKL inhibition on gynecologic tissues. Progesterone has a protective effect in ovarian cancer and endometrial cancer (12, 13); however, the mechanism by which it renders

protection and the involvement of the RANK/RANKL pathway is still unclear (14). Wieser and colleagues demonstrated that RANK, RANKL, and osteo-protegerin (OPG) mRNA expressions are elevated in ovarian cancer tissue and RANKL expression is particularly elevated in *BRCA1/2* mutated ovarian cancer (15). In addition, in a cohort of 192 patients with ovarian cancer ($N = 44$ with *BRCA1/2* P/LP variants), high RANKL expression was found to be an independent prognostic factor for PFS (HR, 1.42; $P = 0.017$) and overall survival (HR, 1.70; $P = 0.007$; ref. 15). Three ovarian cancer cell lines (OVCAR3, SKOV6, and HTB77) were treated with denosumab, but this did not have an effect on proliferation as evaluated by MTT assays and by expression analyses of cell the cycle proteins G_1–S-specific cyclin-E (CCNE) and transcription factor E2F3a (*E2F3A*; ref. 15). If denosumab is shown to be beneficial for breast cancer prevention in the setting of a *BRCA1* P/LP variant, it is critical to determine whether it would have biologic effects on gynecologic tissues and potentially also decrease the risk of ovarian and endometrial cancer risk in this population.

Within the NCI Division of Cancer Prevention (DCP) Early Phase Clinical Trials Prevention Consortia, we developed a presurgical, window-of-opportunity pilot study with the purpose of assessing the anti-proliferative effects of denosumab on gynecologic tissues in premenopausal carriers of P/LP *BRCA1/2* variants scheduled for RR-BSO. After 2 years, the trial was terminated early without the accrual of any participants. A challenge to successful participant enrollment was the study design and strict eligibility criteria for the trial. The COVID-19 global pandemic exacerbated the recruitment challenge as enrollment to cancer control and prevention trials decreased more than to therapeutic clinical trials (16, 17).

Main Text

Study design

We conducted a multicenter, open-label randomized controlled trial of presurgical administration of denosumab versus no treatment among 60 premenopausal women with P/LP variants in *BRCA1* or *BRCA2* undergoing RR-BSO, with or without hysterectomy (Fig. 1). The primary trial endpoint was to compare Ki67 proliferation index in fallopian tube fimbrial epithelial cells after denosumab treatment versus no treatment. Details on the study design can be found online (18). This study was approved by the NCI Central Institutional Review Board (CIRB).

The study was open for patient accrual at four sites, which were selected due to being high volume academic centers with expertise in delivering preventive care to patients with hereditary breast and ovarian cancer syndromes: Columbia University Irving Medical Center (CUIMC), Weill-Cornell Medical Center (WCMC), Dana Farber Cancer Institute and Brigham and Women’s Hospital (DFCI), and Tel Aviv Sourasky Medical Center/Chaim Sheba Medical Center (TASMC).

Recruitment methods

Given the anticipated challenges in identifying this select population, extensive efforts were made in pre-screening and screening potential participants. Pre-screens were defined as meeting team-defined high-level eligibility criteria (women with a known P/LP *BRCA1* or *BRCA2* variant) and were thus qualified for continued eligibility screening. A waiver of consent to pre-screen patients was obtained by the NCI CIRB. Study staff utilized electronic health records, clinic schedules, and preexisting databases to identify women meeting pre-screen criteria. We also developed a social media campaign and partnerships with patient advocacy groups.

Once subjects were identified through pre-screen, further review was done to determine if a subject was eligible for contact. If a subject was determined to be eligible, an attempt was made to contact the subject or her treating physician. All pre-screening and screening data were collected by research staff and entered into the Accrual Quality Improvement Program (AQuIP) On-line Accrual Reporting System (OARS) developed within the NCI DCP to promote clinical trial accrual efficiency and improve study recruitment and retention (19).

Study timeline

A site was deemed to be activated once it had the ability to enroll and treat participants per protocol. The study was activated on March 14, 2019, at CUIMC. DFCI was activated in April 2019. WCMC and TASMC were activated in January 2020. The global pandemic began affecting the sites in March 2020, resulting in cancellation of elective surgeries and pause of clinical trial enrollment. By March 2021, due to no participant enrollment and the ongoing global pandemic, the study closed to enrollment.

Recruitment efforts

A total of 372 subjects were pre-screened for participation in this trial. A total of 238 subjects were not eligible for contact; the reasons for noncontact are shown in Table 1. Of the 134 subjects deemed to be eligible for contact for further screening, 89 subjects could not be contacted. A total of 42 subjects were contacted and declined to sign consent for the study (Fig. 2). Three subjects at TASMC were contacted and signed consent but were not randomized. The reasons for not being randomized were that two subjects failed their initial screening after signing the consent (one was breastfeeding and one was on letrozole) and one subject was unable to start due to COVID-19 lockdown restrictions.

Discussion

We aimed to enroll 60 premenopausal carriers of P/LP *BRCA1/2* variants planning to undergo RR-BSO to a randomized pilot study of presurgical denosumab versus no treatment to evaluate the agent's effect on tissue and blood biomarkers. After approximately 2 years, no participants were randomized, and the trial was terminated. There were challenges in the conduct of this trial related to study design and further exacerbated by the global COVID-19 pandemic. We will discuss the impact of these challenges on the conduct of the trial, how we attempted to overcome these challenges, and how these insights can inform the development and conduct of future trials.

Challenges due to study design

We believe the study design posed the greatest challenge to the successful completion of this trial. The strict eligibility criteria of the trial, which were scientifically necessary, limited the pool of potential participants. The prevalence of *BRCA1/2* pathogenic variants is 1:400 in the general population and 1:40 among those of Ashkenzai Jewish descent. The number of eligible subjects is further decreased when considering only premenopausal women within the recommended age group for RR-BSO. We attempted to overcome this challenge by working with patient advocacy groups and using clinical and research databases to identify potential participants. We recruited patients from multiple clinics, including gynecologic oncology, breast oncology, genetics, and HBOC clinics; however, effectively screening multiple different clinics was challenging, particularly in the setting of understaffed clinical and research teams. Even with large numbers of subjects prescreened, only about one third met initial screening criteria and even fewer were available for contact or participation. Prior literature showed that on average, only 10% of women at high risk for breast cancer enrolled for participation in chemoprevention trials (20). The number who signed consent to participate this study (3/45,7%) is consistent with prior chemoprevention studies that recruited women at increased risk for breast cancer.

In addition, we found that timing the intervention with RR-BSO was a barrier to recruitment. Starting the intervention between day 1 and 3 of the menstrual cycle and performing surgery during the luteal phase of the menstrual cycle were unique challenges in the design of this trial. Timing with the menstrual cycle was indicated given the changes in tissue and serum biomarkers based on menstrual phase. Of the 45 women approached for participation in the trial, the most common reason for nonparticipation was the timing of surgery (N = 10), particularly the unwillingness to delay RR-BSO. This prompted an amendment to the protocol in July 2020 to decrease the number of presurgical doses of denosumab from three to four doses to one to two doses, thereby decreasing the presurgical intervention period from 12 to 16 weeks to 4 to 6 weeks.

Challenges due to the COVID-19 pandemic

Another barrier to the completion of this trial was the COVID-19 global pandemic, which began shortly after the final sites were activated in January 2020. The COVID-19 pandemic affected this trial in three ways: (i) reduction in preventive procedures, including screening and health maintenance; (ii) hold on elective surgical procedures; (iii) pause in clinical trial enrollment and prioritization of cancer treatment trials.

Preventive procedures, such as cancer screening and routine health maintenance visits, were drastically reduced over the course of the pandemic due to guidelines recommending the delay of nonessential procedures and visits to minimize infection risk and maximize resource utilization. Furthermore, patients themselves were hesitant to seek medical care for nonurgent procedures and testing due to fear of COVID-19 exposure, as well as due to employment changes, transportation issues, and childcare challenges (21–23). For example, prostate-specific antigen (PSA) testing decreased by 36.4% from pre-pandemic (January 2018-February 2020) to early-pandemic (March 2020–May 2020) and average number of monthly prostate biopsies decreased by 37.9% from pre-pandemic to early-pandemic (24).

Screening tests for breast and colorectal cancer were decreased by 89.2% and 84.5%, respectively, during the period of January 2020 to April 2020 compared with the period of January 2019 to April 2019 (25). Even as the cases of COVID-19 decreased, re-initiation of preventive care was challenged by the limited resources and workforce and backlog of more essential medical activities (21). In the early phase of the pandemic, we observed a decrease in elective surgeries, such as RR-BSO, given concerns about conserving resources and personal protective equipment. During later stages of the pandemic, the study sites did not see an increase in numbers of RR-BSO performed, likely due to the decrease in preventive care and increased patient hesitancy described above.

Finally, clinical trial conduct and enrollment was significantly decreased over the course of the pandemic. In a survey of clinical cancer programs, about 60% of programs stopped screening and/or enrollment for certain clinical trials over the course of the pandemic (26). In the denosumab trial, during the period of March 2020 to June 2020, pre-screening at the US sites dropped off substantially due to COVID-19 restrictions. In addition, there was prioritization of trials based on different factors, including patients' needs, safety, and disease severity, potential patient and site burdens, and available resources (26). On the basis of data from the SWOG Cancer Research Network, although enrollment to both treatment and cancer control and prevention clinical trials decreased significantly in the early weeks of the pandemic, enrollment to cancer control and prevention trials decreased significantly more than treatment trials (OR, 0.38; 95% CI, 0.29–0.50; $P < 0.001$; ref. 16). One year after the start of the COVID-19 pandemic, cancer treatment trials were able to regain enrollments (91% of expected enrollments) but the same was not seen with cancer control and prevention trials, where actual enrollments were 54% of expected enrollments (17, 27).

Conclusions and Lessons Learned

The COVID-19 pandemic further complicated the conduct of a trial already challenged to enroll participants. Although the COVID-19 pandemic was a factor outside of the control of the study team, it is important to consider how other factors in the trial could be modified in future research.

Structural, clinical, and attitudinal barriers to clinical trial enrollment are well documented. These challenges are amplified in the prevention setting, where a healthy individual is asked to participate in a trial requiring additional visits, testing, and often drug interventions to prevent a disease rather than treat a disease. Furthermore, window of opportunity trials utilize a short-term intervention and are primarily proof-of-principle studies without direct benefit to patients. Future trials should consider participant acceptability of use of drugs for cancer risk reduction; for example, considering whether an injectable agent is less preferable to an oral or topical agent in the prevention setting. Studies investigating an oral contraceptive in the pre-RR-BSO setting have been completed in the *BRCA1/2* population (NCT02155777) as well as in a non-*BRCA1/2* selected population (NCT00445887), both of which also had less restrictive eligibility criteria than our study. A study investigating aspirin in the pre-RR-BSO setting is also underway (NCT03480776) in the *BRCA1/2* population. If injection is the only option, consideration should be given to the minimum number of doses needed for adequate systemic drug levels to achieve biologic effect. The presurgical study

design and the acceptability of delay to risk-reducing surgery to participate in a clinical trial should also be considered.

In addition, perhaps less stringent eligibility criteria, without scientific compromise, would allow for a larger pool of potential participants. Conducting research in those at highest risk for cancer, specifically those with inherited cancer predisposition syndromes, is critical even though the population pools may be limited. It was evident from this study that the number needed to pre-screen and screen to get a single participant to sign consent was larger than anticipated (~1:100) and as such, additional pre-screening resources and research staff may be needed for the conduct of these trials. There has been successful accrual in prior preventive trials for hereditary cancer syndromes. For example, in a phase Ib, placebo-controlled, randomized trial of naproxen for colorectal cancer chemoprevention, 80 participants with Lynch Syndrome, which has an estimated prevalence of 1:279 (28), were enrolled from four academic centers over approximately 4 years (29). Despite a limited population pool and only four academic centers, this study was able to complete accrual, perhaps due to the acceptability of the intervention and less restrictive eligibility criteria. Consideration should be given as to whether there may be issues unique to *BRCA1/2* that make it challenging to conduct chemoprevention trials. Ovarian and breast cancer prevention interventions in female carriers of P/LP *BRCA1/2* variants would typically occur during years when childbearing is an important issue. If RR-BSO is indicated between ages 35 and 45, women may be attempting to complete childbearing and breastfeeding prior to that time, making it difficult or impossible to participate clinical trials. In addition, it is estimated that only 10% to 20% of all P/LP *BRCA1* and *BRCA2* carriers in the United States have been identified, making the pool for potential prevention trial participants even lower (30). Efforts to identify of carriers of P/LP *BRCA1/2* variants, and thus increase the pool of potential participants, may facilitate accrual to such prevention trials in the future. If identification of *BRCA1/2* status occurs at cancer diagnosis, the opportunity for prevention is lost.

Several solutions to designing prevention trials for successful completion should be considered. First, trials in this setting should consider taking the team science approach. Including many sites through a research consortium, and additionally providing adequate resources and funding for recruitment effort, will allow for screening large numbers of potential participants and subsequently more enrolled participants. Second, involve patient advocates and advocacy groups, particularly in the inherited cancer syndrome space, which will ensure that the approach is acceptable to potential participants and increase awareness of the trial. Third, close monitoring of recruitment activities and barriers to enrollment during the conduct of the study is also essential, as it can allow for early implementation of protocol modifications to enhance accrual, such as reduction in number of doses or broadening of eligibility criteria for a more pragmatic trial design. Finally, focused efforts on testing of family members of carriers of P/LP variants (cascade testing) and increased awareness of risk factors for carrying P/LP variants in the primary care setting may enhance the identification of carriers thereby allowing more unaffected individuals to participate in prevention trials in the future. Trials for identification of carriers of P/LP variants should be conducted in parallel with prevention trials to achieve success in hereditary cancer syndromes. As new prevention studies are developed and ongoing, these factors should be taken into consideration for the successful completion of these trials.

Acknowledgments

We thank Amgen for providing agent for this study. We would like to acknowledge Ellen Richmond MS, GNP-BC for her work in developing Accrual Quality Improvement Program (AQuIP) Online Accrual Reporting System (OARS). We would like to thank CCS Associates for regulatory support and MRI Global for agent repository support. This study was funded by HHSN261201200034I (MD Anderson).

Authors' Disclosures

M.S. Trivedi reports grants from NCI during the conduct of the study. J.E. Garber reports other support from Amgen during the conduct of the study; and Co-PI of a DOD grant supporting a clinical trial of denosumab for breast cancer risk reduction in *BRCA1* carriers. K. Holcomb reports other support from Johnson and Johnson outside the submitted work. J.D. Wright reports grants from Merck and personal fees from UpToDate outside the submitted work. G. Samimi reports other support from National Cancer Institute during the conduct of the study. P.H. Brown reports Genetex (<1% of total stock, not publicly traded). No disclosures were reported by the other authors.

References

1. Alsop K, Fereday S, Meldrum C, deFazio A, Emmanuel C, George J, et al. BRCA mutation frequency and patterns of treatment response in BRCA mutation-positive women with ovarian cancer: a report from the Australian Ovarian Cancer Study Group. J Clin Oncol 2012;30: 2654–63. [PubMed: 22711857]
2. Evans DG, Gaarenstroom KN, Stirling D, Shenton A, Maehle L, Dorum A, et al. Screening for familial ovarian cancer: poor survival of BRCA1/2 related cancers. J Med Genet 2009;46:593–7. [PubMed: 18413372]
3. National Comprehensive Cancer Network. Guidelines; c2022 [cited 2022 July 25]. Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic; [about 2 screens]. Plymouth Meeting (PA). Available from: https://www.nccn.org/guidelines/guidelines-detail?category=2&id1503.
4. Finch AP, Lubinski J, Moller P, Singer CF, Karlan B, Senter L, et al. Impact of oophorectomy on cancer incidence and mortality in women with a BRCA1 or BRCA2 mutation. J Clin Oncol 2014;32:1547–53. [PubMed: 24567435]
5. Dowdy SC, Stefanek M, Hartmann LC. Surgical risk reduction: prophylactic salpingo-oophorectomy and prophylactic mastectomy. Am J Obstet Gynecol 2004;191:1113–23. [PubMed: 15507929]
6. Nolan E, Vaillant F, Branstetter D, Pal B, Giner G, Whitehead L, et al. RANK ligand as a potential target for breast cancer prevention in BRCA1-mutation carriers. Nat Med 2016;22:933–9. [PubMed: 27322743]
7. Zoi I, Karamouzis MV, Adamopoulos C, Papavassiliou AG. RANKL signaling and ErbB receptors in breast carcinogenesis. Trends Mol Med 2016;22:839–50. [PubMed: 27567286]
8. Schramek D, Leibbrandt A, Sigl V, Kenner L, Pospisilik JA, Lee HJ, et al. Osteoclast differentiation factor RANKL controls development of progestin-driven mammary cancer. Nature 2010;468:98–102. [PubMed: 20881962]
9. Dougall WC. Molecular pathways: osteoclast-dependent and osteoclast-independent roles of the RANKL/RANK/OPG pathway in tumorigenesis and metastasis. Clin Cancer Res 2012;18:326–35. [PubMed: 22031096]
10. Stopeck AT, Lipton A, Body JJ, Steger GG, Tonkin K, de Boer RH, et al. Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: a randomized, double-blind study. J Clin Oncol 2010;28:5132–9. [PubMed: 21060033]
11. Cummings SR, Martin JS, McClung MR, Siris ES, Eastell R, Reid IR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med 2009;361:756–65. [PubMed: 19671655]
12. Kotsopoulos J, Lubinski J, Gronwald J, Cybulski C, Demsky R, Neuhausen SL, et al. Factors influencing ovulation and the risk of ovarian cancer in BRCA1 and BRCA2 mutation carriers. Int J Cancer 2015;137:1136–46. [PubMed: 25482078]

13. Ho SM. Estrogen, progesterone and epithelial ovarian cancer. Reprod Biol Endocrinol 2003;1:73. [PubMed: 14577831]
14. Monzo-Miralles A, Martin-Gonzalez V, Smith-Ballester S, Iglesias-Miguel V, Cano A. The RANKL/RANK system in female reproductive organ tumors: A preclinical and clinical overview. Adv Clin Exp Med 2021;30:879–83. [PubMed: 34435475]
15. Wieser V, Sprung S, Tsibulak I, Haybaeck J, Hackl H, Fiegl H, et al. Clinical impact of RANK signalling in ovarian cancer. Cancers 2019; 11:791. [PubMed: 31181781]
16. Unger JM, Blanke CD, LeBlanc M, Hershman DL. Association of the coronavirus disease 2019 (COVID-19) outbreak with enrollment in cancer clinical trials. JAMA Netw Open 2020;3: e2010651. [PubMed: 32478845]
17. Unger JM, Xiao H, LeBlanc M, Hershman DL, Blanke CD. Cancer clinical trial participation at the 1-year anniversary of the outbreak of the COVID-19 pandemic. JAMA Netw Open 2021;4:e2118433. [PubMed: 34323986]
18. ClinicalTrials.gov. Identifier NCT03382574, Pilot Study of Denosumab in BRCA1/2 Mutation Carriers Scheduled for Risk-Reducing Salpingo-Oophorectomy; Bethesda (MD): National Library of Medicine (US). Feb 29, 2000. 2017 December 26 [cited 2022 July 25]; [about 11 p.]. Available from: https://clinicaltrials.gov/ct2/show/NCT03382574.
19. National Cancer Institute Division of Cancer Prevention. 2012 Consortia for Early Phase Prevention Trials. Rockville (MD): Clinical Trials Management; c2000 [cited 2022 July 25]; [about 5 screens]. Available from: https://prevention.cancer.gov/clinical-trials/clinical-trials-management/2012-consortia-early-phase.
20. Recruitment of women to clinical trials. Lancet 2001;358:853. [PubMed: 11567694]
21. Basu P, Alhomoud S, Taghavi K, Carvalho AL, Lucas E, Baussano I. Cancer screening in the coronavirus pandemic Era: Adjusting to a new situation. JCO Glob Oncol 2021;7:416–24. [PubMed: 33784177]
22. DuBois RN. COVID-19, cancer care and prevention. Cancer Prev Res 2020;13:889–92.
23. Carethers JM, Sengupta R, Blakey R, Ribas A, D'Souza G. Disparities in cancer prevention in the COVID-19 Era. Cancer Prev Res 2020;13: 893–6.
24. Kaufman HW, Chen Z, Niles JK, Radcliff J, Fesko Y. Patterns of Prostate-specific antigen testing and prostate biopsies during the COVID-19 pandemic. JCO Clin Cancer Inform 2021;5:1028–33. [PubMed: 34648367]
25. London JW, Fazio-Eynullayeva E, Palchuk MB, Sankey P, McNair C. Effects of the COVID-19 pandemic on Cancer-related patient encounters. JCO Clin Cancer Inform 2020;4:657–65. [PubMed: 32716647]
26. Waterhouse DM, Harvey RD, Hurley P, Levit LA, Kim ES, Klepin HD, et al. Early Impact of COVID-19 on the conduct of oncology clinical trials and Long-term opportunities for transformation: findings from an American Society of Clinical Oncology Survey. JCO Oncology Practice 2020;16:417–21. [PubMed: 32396491]
27. Samimi G, House M, Benante K, Bengtson L, Budd T, Dermody B, et al. Lessons learned from the impact of COVID-19 on NCI-sponsored Cancer Prevention Clinical Trials: moving toward Participant-centric study designs. Cancer Prev Res 2022;15:279–84.
28. Win AK, Jenkins MA, Dowty JG, Antoniou AC, Lee A, Giles GG, et al. Prevalence and penetrance of major genes and polygenes for colorectal cancer. Cancer Epidemiol Biomarkers Prev 2017;26:404–12. [PubMed: 27799157]
29. Reyes-Uribe L, Wu W, Gelincik O, Bommi PV, Francisco-Cruz A, Solis LM, et al. Naproxen chemoprevention promotes immune activation in Lynch syndrome colorectal mucosa. Gut 2021;70:555–66. [PubMed: 32641470]
30. Nitecki R, Moss HA, Watson CH, Urbauer DL, Melamed A, Lu KH, et al. Facilitated cascade testing (FaCT): a randomized controlled trial. Int J Gynecol Cancer 2021;31:779–83. [PubMed: 33443030]

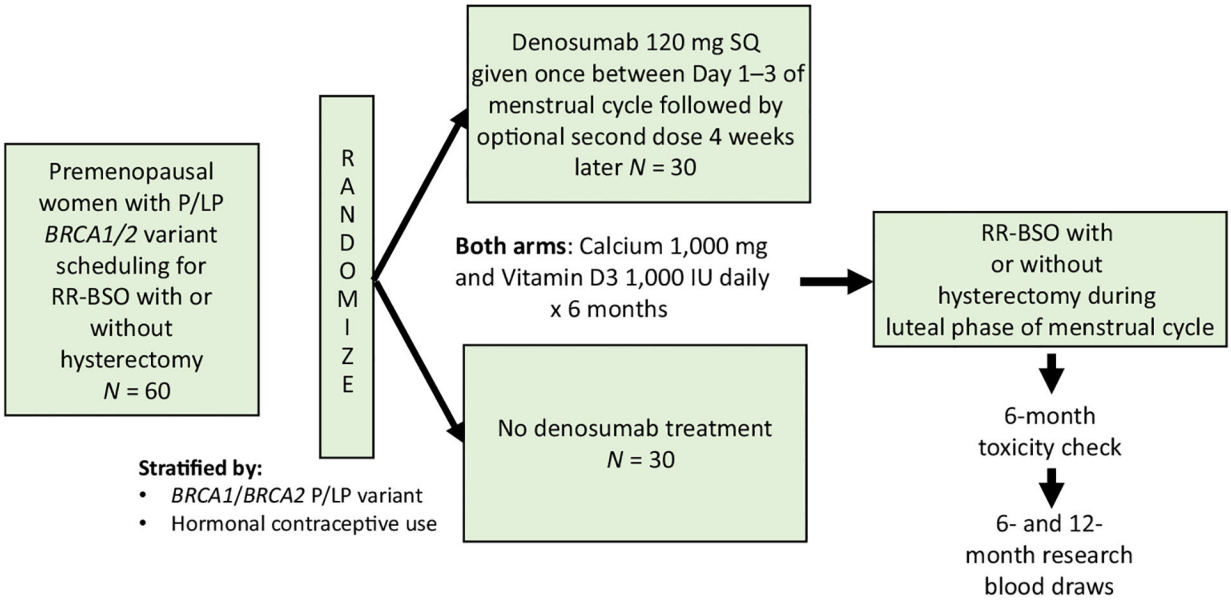

Figure 1.

Trial study schema. Premenopausal women with a pathogenic/likely pathogenic (P/LP) *BRCA1/2* variant scheduling for risk-reducing bilateral salpingo-oophorectomy (RR-BSO) with or without hysterectomy were planned to be randomized to receive presurgical denosumab for 1–2 doses or no denosumab treatment prior to surgery. All participants were to take calcium and vitamin D3 supplements. RR-BSO would occur during the luteal phase of the menstrual cycle. Details on the study design can be found online (18).

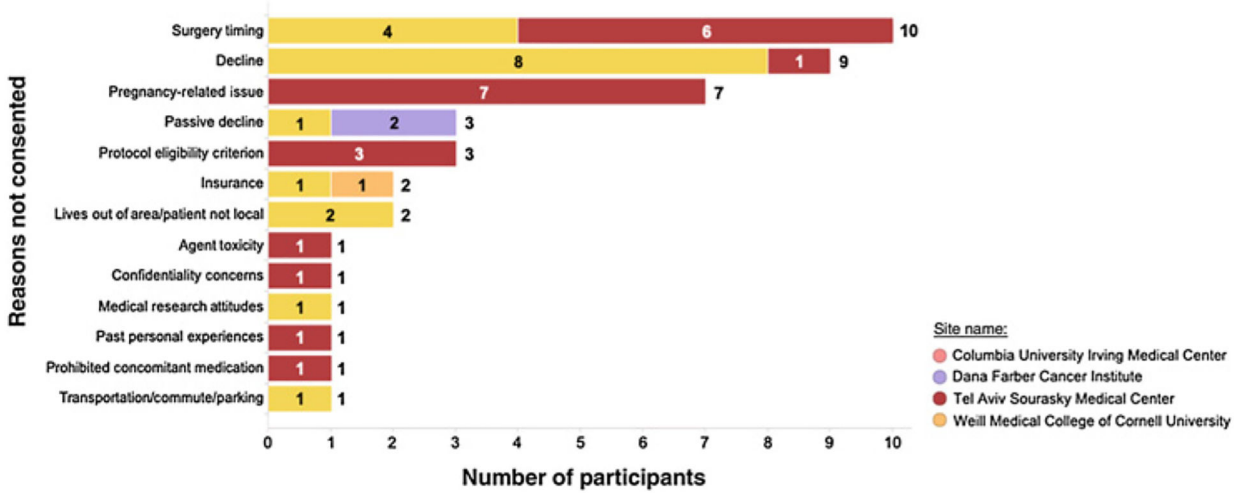

Figure 2.

Reasons for not signing consent to study. Forty two subjects were contacted to participate in the study but declined to sign consent. The most common reason for not signing consent was the timing of surgery ($N = 10$).

Table 1.

Reasons for non-contact of pre-screened subjects.

Reason for non-contact	Number (%)
Already had RR-BSO	85 (35.7)
Not planning for surgery in near future	41 (17.2)
Pre-existing cancer diagnosis within 6 months or on active treatment for cancer	
Breast cancer	18 (7.6)
Ovarian cancer	8 (3.4)
Unspecified cancer diagnosis	5 (2.1)
COVID restrictions	17 (7.1)
Pregnant or breast feeding	15 (6.3)
Post-menopausal	14 (5.9)
Surgery timing	9 (3.8)
Unable to commit to trial due to time, financial, or location constraints	9 (3.8)
No follow up in clinic	8 (3.4)
On another clinical trial	5 (2.1)
Non-cancer co-morbidity	2 (0.8)
Only wants salpingectomy	1 (0.4)
Language barrier	1 (0.4)
Total	238 (100)