Future Research Needs To Reduce the Risk of Primary Breast Cancer in Women was available for public comment from September 29, 2010, to October 25, 2010. In response to questions and suggestions received, revisions were made in this version to clarify that no incentives were offered to stakeholders to participate. Additional background was included on development of the two questionnaires. A note was added to Table 1 to explain that variations in the stakeholder perspective preassigned and the perspective self-identified by the participants led to differences in the numbers reported for allocation of participants. Table B was added to the Executive Summary to highlight priority research areas and potential study designs.

Future Research Needs Paper

Number 5

Future Research Needs To Reduce the Risk of Primary Breast Cancer in Women

Identification of Future Research Needs from Comparative Effectiveness Review No. 17

Prepared for:
Agency for Healthcare Research and Quality
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The information in this report is intended to help health care researchers and funders of research make well-informed decisions in designing and funding research and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of scientific judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical research and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances.

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Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the Children's Health Insurance Program (CHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting comparative effectiveness reviews (CERs) of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see http://effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that CERs will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that consumers who make decisions about their own and their family's health can benefit from the evidence.

As part of a new effort in 2010, AHRQ has supported EPCs to work with various stakeholders, including patients, to further develop and prioritize the future research needed by decisionmakers. The Future Research Needs products are intended to inform and support researchers and those who fund research to ultimately enhance the body of comparative effectiveness evidence so that it is useful for decisionmakers.

Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an email list to learn about new program products and opportunities for input. Comparative effectiveness reviews will be updated regularly.

Acknowledgments

First, we thank the stakeholders who devoted their time to this project and whose participation made this report possible. We thank our colleagues at the Oregon Evidence-based Practice Center, David Buckley, M.D., M.P.H., Evelyn Whitlock, M.D., M.P.H., and Carrie Patnode, Ph.D., M.P.H., for drafting the initial proposal of this project. The authors also thank Lillian Nail, R.N., Ph.D., F.A.A.N., Heidi Nelson, M.D., M.P.H., and Xiangshu Xiao, Ph.D., M.S., for their expertise and thoughtful contributions during informational interviews. We acknowledge the contributions of AHRQ Task Order Officer, Christine Chang, M.D., M.P.H. and Scientific Resource Center Research Associate, Howard Balshem, M.S. We would like to thank Leah Williams, B.S., for editorial support and Sasha Walia, B.S., for administrative support. Finally, we thank Mark Helfand, M.D., M.P.H. for his insights, editorial review and continued support.

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Contents

Tables

Figures

Appendixes

Executive Summary

The Effective Health Care Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its comparative effectiveness reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders, including consumers.

The full report and this summary are available at www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Background

Breast cancer is the second most commonly diagnosed cancer and the second most common cause of cancer-related death in women with more than 200,000 new cases of invasive breast cancer expected in women in 2010 and more than 40,000 breast cancer-related deaths expected this year in the United States.[1] Despite U.S. Food and Drug Administration (FDA) approval and clinical endorsement for the use of selective estrogen receptor modulators (SERMs) to reduce the risk of breast cancer, less than 1 percent of U.S. women use tamoxifen citrate as preventive therapy.[2,3,4] The 2009 comparative effectiveness review (CER) on the effectiveness of medications to reduce the risk of primary breast cancer in women without preexisting cancer demonstrated the efficacy of two SERMs, tamoxifen citrate (RR, 0.70; 95% CI, 0.59 to 0.82; 4 trials) and raloxifene (RR, 0.44; CI, 0.27 to 0.71; 2 trials).[5,6] However, the CER also outlined many adverse effects and unknowns about the medications. The objective of this pilot project was to engage stakeholders to develop and prioritize a list of research questions to address the research gaps related to the CER. First, our goal was to provide sufficient detail—including population, intervention, comparator, and outcome (PICO)—for researchers and funders to use in the development of research proposals and solicitations, respectively.[7] Second, this project was intended to identify a feasible and effective approach to identify and prioritize future research from systematic reviews in general.

Methods

A national sample of stakeholders, including clinicians, consumer advocates, research funders, researchers, and policymakers were invited to participate in a project to develop a research agenda to reduce the risk of primary breast cancer. Recruitment of stakeholders began June 11 and final questionnaire responses were received July 27, 2010.

Stakeholders were invited to participate in an informational Webinar and to complete a research prioritization questionnaire. No financial incentives were offered for stakeholders to participate. Two questionnaires were developed to evaluate the research priorities for breast cancer prevention: one for consumers/policymakers (Questionnaire I) and another for clinicians, research funders, and researchers (Questionnaire II). The questionnaires were constructed from information gaps identified in the CER, through informational interviews with the lead investigator for the CER, and through informational interviews with basic science and clinical

researchers. The questionnaire used open-ended and structured questions to identify high priority research topics.

Narrative responses were categorized according to questionnaire. Four investigators independently reviewed responses and narratives, identified research themes, and coded each theme as population, intervention, comparator, outcome, and influencing factors (PICO). Investigators met to compare codes and themes and reconciled inconsistencies. The top 10 research priorities (see Table A) were then listed and compared by questionnaire type.

Results

Twenty-one of 40 (53%) invited stakeholders completed the questionnaire. Nine consumers and policymakers completed Questionnaire I, and 12 clinicians, research funders (including 3 federal employees) and researchers completed Questionnaire II. Based on the answers to open-ended questions, stakeholders agreed that a priority for future research should be placed on understanding which populations are at greatest risk for breast cancer and those most likely to benefit from preventive therapies. However, while consumers and policymakers focused on demographic factors, such as age, race, and ethnicity of the population, clinicians, research funders, and researchers focused on examining risk based on genetics and biomarkers. As a whole, stakeholders were highly interested in nonmedical interventions, such as lifestyle changes, diet, and exercise, while clinicians, research funders, and researchers wanted not only more information on the effectiveness of individual lifestyle changes but also direct comparisons of medical vs. nonmedical treatments. Similarly, stakeholders agreed that research is needed to identify and evaluate methods to ensure that health care providers were up to date in their knowledge and to promote informed decisionmaking. Compared with researchers, clinicians, and funders, consumers, and policymakers were more likely to want additional research on patient–provider communication and how to communicate risks to patients.

Looking across all structured questions, at least 50 percent of respondents in both Questionnaire I and Questionnaire II groups (consumer/policymaker and researcher/research funder/clinician, respectively) rated the following five questions as highest priority by PICO:

Population: Studies of how age affects the benefits and/or harms of interventions to reduce the risk of breast cancer (78%; 75%)
Intervention: Prescription medications: tamoxifen, raloxifene (50%; 55%)
Outcome: Evaluation of how long the beneficial effects of therapy last (100%; 67%)

Influencing Factors: Studies of how to communicate benefits and risk to patients (78%; 83%) and Research on predicting risk of breast cancer (89%; 75%)

Additionally, 100 percent of consumers, policymakers, research funders, researchers, and clinicians reported that patients would use a prediction model to assist in their decisionmaking if a current model were available.

The table below summarizes the top 10 priority research areas by highest rank, grouped according to questionnaire type.

Table A. Top 10 priority research areas to reduce the risk of primary breast cancer

Questionnaire I: Consumer/Policymaker	% High Priority[a]	Rank	Questionnaire II: Clinician/Research Funder/Researcher	% High Priority[a]	Rank
Persistent effect of preventive therapy	100%	**1**	How to communicate benefits and risks to patients	83.3%	**1**
Reporting harmful effects of preventive therapy	88.9%	**2**	Predicting risk of breast cancer	75.0%	**2**
Predicting risk of breast cancer	88.9%	**2**	Understanding which populations of women would optimally benefit from medications to reduce the risk of breast cancer	75.0%	**2**
Studies of how to communicate benefits and risks to patients	77.8%	**4**	How clinicians are weighing the risks and benefits to preventive therapy	75.0%	**2**
Studies of what populations optimally benefit from medications to reduce the risk of breast cancer	77.8%	**4**	Persistent effect of preventive therapy	66.7%	**5**
Complementary and alternative therapies	66.7%	**6**	Patient attitudes toward prescribing medications to reduce breast cancer risk	66.7%	**5**
Studies of how race and/or ethnicity affect interventions to reduce the risk of breast cancer	66.7%	**6**	Studies of clinicians' attitudes toward prescribing medications	58.3%	**7**
Molecular targeted drugs specific to cancer pathways	62.5%	**8**	Aromatase Inhibitors	54.5%	**8**
What factors influence a woman's decisionmaking to take medications to reduce breast cancer risk	55.6%	**9**	SERMs	54.5%	**8**
SERMs	50.0%	**10**	Gene-based drugs	54.5%	**8**
Combination therapies: i.e., prescription medications plus diet	50.0%	**10**			

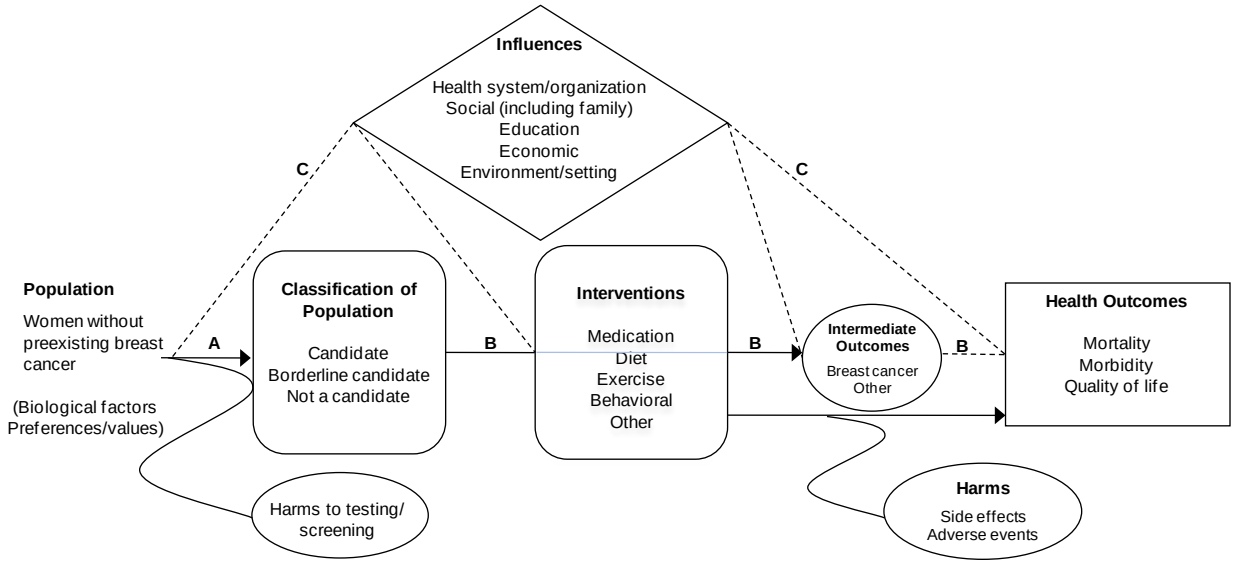
Abbreviations: SERM=selective estrogen receptor modulator.

[a] Percentages indicate a priority ranking of "high" by respondents from choices of "high," "medium," or "low."

Conclusions

We developed a conceptual framework to illustrate national priorities for future research to reduce the risk of primary breast cancer in women (see Figure A).

Figure A. Conceptual framework, future research needs to reduce the risk of primary breast cancer



According to stakeholders, the highest priority research areas for the prevention of breast cancer are:

(1) Population—understanding which populations are at highest risk of breast cancer, most likely to experience benefit, and least likely to be harmed by therapy (Question A).
(2) Intervention—broadening the scope of investigation beyond medications to include factors such as lifestyle, diet and exercise (Question B).
(3) Influencing factors—understanding influences such as health system factors, communication, education, dissemination of high quality information into clinical practice and to patients, and decisionmaking on initiation, continuation, and responses to preventive therapies (Question C).
(4) Integration of biological markers across the spectrum of research relating to breast cancer to understand populations that are most likely to benefit from therapy and to monitor response to therapy (integrated in Questions A, B, and C).

In Table B, we present potential study designs to address priority research gaps identified by stakeholders (see Table 7 of the main report for referenced table). Two of these priority topic areas, additional interventions such as diet (Question B) and influencing factors (Question C) are largely outside the scope of the original CER, and an evidence review could help delineate what is known and guide research in these areas. Preliminary searches indicate there is likely to be a sufficient literature for both.

Table B. Future research agenda for breast cancer prevention

Framework Question(s)	Priority Research Area (Question)	Research Needs and Potential Study Designs
Question A: What women are most susceptible to benefits versus harms of breast cancer risk reduction treatment? A1: What is the most effective method to identify appropriate candidates for treatment (classification of population)? A2: What markers (including biomarkers) and tests are useful in classifying people as candidates for treatment? A3: What is the most effective method to determine a woman's risk for breast cancer?	Studies of how race and/or ethnicity affect interventions to reduce the risk of breast cancer	Actively recruit minorities to gather sufficient power in ongoing studies
		Meta-analysis pooling data from all published studies
	Predicting risk of breast cancer	Genomic models for individual risk prediction
		Updated risk models
		Intervention studies to gather data and store blood specimens for analysis of possible serum markers for breast cancer risk
		Identification of factors (including biomarkers) that predict women who develop breast cancer and more aggressive types of breast cancer
		Registry to examine factors
		Cohorts such The Nurses' Health Study I & II
	Studies of what populations optimally benefit from medication to reduce the risk of breast cancer	Continued followup of current studies (ensure variables of interest are followed)
		Ensuring trials/analyses are consistently stratifying by relevant populations
		Analyze serum from women in intervention studies to determine if there are biomarkers that predict which women are most likely to benefit from medications to reduce the risk of breast cancer
		Development of risk models to predict who is most likely to benefit from medications to reduce the risk of breast cancer
		Meta-analysis of pooled data from studies
		Target specific subpopulations (e.g. mammographic density, menopausal status) and exposures (e.g., DES)
		Basic science (e.g., animal studies)
Question B: What interventions are most effective to reduce the risk of breast cancer and improve short and long term outcomes? B1: What interventions are most effective to reduce the risk of the most aggressive types of breast cancer? B2: What are the mechanisms of action of interventions? B3: What surveillance mechanisms and intervals optimize short and long term outcomes?	Lifestyle, diet, weight loss, exercise modification	Randomized controlled trials of diet, exercise, weight loss
		Basic science
		Ecological studies among communities with differing diet, exercise habits
		Other (e.g., observational studies, reviews)
	Complementary and alternative therapies (CAM)	Randomized controlled trials of complementary and alternative therapies
		Basic science
		Other (e.g., observational studies, reviews)
	Aromatase Inhibitors	Randomized controlled trials
		Basic science
		Other (e.g., observational studies, reviews)
	SERMs (focus of original CER)[e]	Randomized controlled trials
		Basic science
		Other (e.g., observational studies, reviews)
	Metformin	Randomized controlled trials
		Observational studies
	Gene-based drugs and molecular targeted drugs specific to cancer pathways	Randomized controlled trials
		Drug development
	Combination therapies: e.g., medications + diet; medications + aspirin	Randomized controlled trials
		Basic science

Framework Question(s)	Priority Research Area (Question)	Research Needs and Potential Study Designs
		Observational studies
	CAM vs. medications Diet modification vs. medications	Basic science
		Randomized controlled trial
	Persistent effect of preventive therapy, is cancer prevented or delayed?	Long-term followup of current intervention studies
		Other (e.g., observational studies, reviews)
	Understand appropriate surveillance windows	Long-term followup of current intervention studies with imaging, biomarker, histology and surveillance
	Oversampling for subgroups to assess who is most likely to benefit	Long-term followup of current intervention studies
	Reporting harmful effects of preventive therapy	Long-term followup of current intervention studies
		Short-term adverse event studies
		Basic science
		Reviews, case-control studies, and case reports
Question C: What factors influence the acceptability and effectiveness of breast cancer risk reduction treatment? C1: What factors magnify or reduce risk? C2: What factors influence patient and clinician decisionmaking? a) What is the effective method for providers to communicate risks to patients? b) What is the most effective method for patients and clinicians obtain current, high-quality most evidence to inform their decisions? C3: What factors improve/reduce effectiveness of breast cancer risk reduction treatment? C4: What factors improve or worsen outcomes from breast cancer risk reduction treatment?	Studies of what factors influence a women's decision-making to take preventive therapy	Focus groups/interviews of patients
		Questionnaires of patients
		Decision aids and decision modeling
		Patient navigators
		Observational studies
	Studies of clinicians/patient attitudes toward prescribing medications to reduce the risk of breast cancer	Questionnaires of clinicians and patients
		Case-based decisionmaking varying certain features
		Focus groups/interviews
		Survey medical decisions on case paradigms of varying degree
	Studies of how clinicians are weighing risks and benefits of preventive therapy	Questionnaires of clinicians
		Modeling of series of patient cases presented to clinician, then decisionmaking analyzed with respect to varying factors
	Studies of how to communicate benefits and risks to patients	One-on-one interviews of how information presented vs. perceived
		Focus groups with clinicians/patients
		Randomized control trial of decision aid
		Qualitative research (e.g. videotaping counseling sessions)
		Different techniques of communication randomized and evaluated for effectiveness
	Studies focused on effective education & dissemination strategies for clinicians and patients of prevention strategies	Content evaluation of printed materials
		Decision aid

Abbreviations: CAM, complementary and alternative medicine; DES, diethylstilbestrol; SERM, selective estrogen receptor modulator.
[e] Research focus of original CER.

We found that the traditional analytic framework used to structure reviews does not adequately address future research needs. We present a conceptual framework for future research that emphasizes high priority research domains and depicts "influencing factors" that are important to stakeholders and integral to patient-centered care.[8,9,10] The prominence of influencing factors among stakeholder priorities suggests that they should be depicted in CER frameworks and added to PICO as I PICO.

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Background

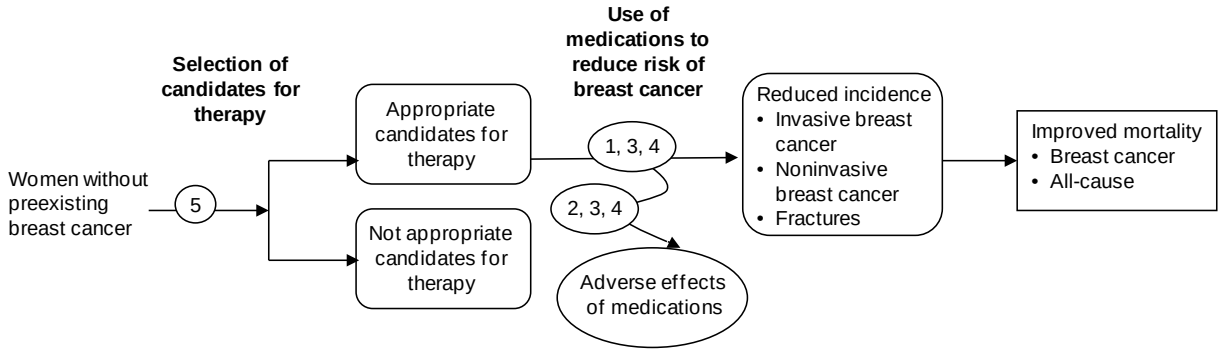
Breast cancer is the second most commonly diagnosed cancer in women in the United States, with over 200,000 new cases of invasive breast cancer expected in women in 2010.[1] It is the second most common cause of cancer-related death in women, killing over 40,000 women each year.[1] Tamoxifen was approved by the U.S. Food and Drug Administration (FDA) in 1999 as a preventive strategy for women at high risk of developing breast cancer. Data from the 2000 National Health Interview Survey estimated that 10 million U.S. women ages 35 to 79 years of age were candidates for tamoxifen preventive therapy and for 2.4 million of these women, the benefits would outweigh the harms.[2] However, despite its approval for more than a decade, less than one percent of women use tamoxifen as a preventive therapy.[3] In 2007, the FDA approved the use of raloxifene hydrochloride for reduction in the risk of invasive breast cancer in postmenopausal women with osteoporosis and/or at high risk for invasive breast cancer.[4]

In 2008, the Agency for Healthcare Research and Quality (AHRQ) commissioned the Oregon Evidence-based Practice Center (Oregon EPC) to conduct a comparative effectiveness review (CER) on the effectiveness of medications to reduce the risk of primary breast cancer in women.[2,3] Briefly, the five key questions addressed by the review were:

(1) In adult women without preexisting breast cancer, what is the comparative effectiveness of selective estrogen receptor modulators (SERMs) tamoxifen and raloxifene, and the selective tissue estrogenic activity regulator (STEAR) tibolone, when used to reduce risk for primary breast cancer on improving short-term and long-term outcomes?
(2) What is the evidence for harms?
(3) How do outcomes vary by heterogeneity in subpopulations?
(4) What is the evidence that harms or secondary potential benefits affect treatment choice, concordance, adherence, and persistence to treatment?
(5) What methods, such as clinical risk-assessment models, have been used to identify women who could benefit from medications to reduce risk of breast cancer?

Figure 1 depicts the analytic framework for the target population, interventions, and outcomes of the CER.

Figure 1. CER analytic framework



Note: Numbers refer to key questions.

The CER found that two selective estrogen receptor modulators (SERMs), tamoxifen citrate (RR, 0.70; 95% CI, 0.59 to 0.82; 4 trials) and raloxifene (RR, 0.44; CI, 0.27 to 0.71; 2 trials), were effective to reduce the risk of invasive breast cancer in women without preexisting cancer. However, the CER also found that the medications have important adverse effects.

Research Gaps

The CER identified a number of research gaps and limitations (Appendix A).[2,3] These are summarized below, and categorized according to the most applicable element of the population, intervention, comparator, and outcome (PICO) framework:[4]

Population

- Evaluation in population subgroups (e.g., nonwhite women, premenopausal women, and women who have comorbid conditions or are taking additional medications for other indications)
- Determination of the optimal candidates for risk-reduction medications
- Evaluation of clinical risk instruments to identify high-risk women who are most likely to benefit from risk reducing interventions
- Clearer identification of the characteristics of patients who experience specific adverse effects.

Intervention

- Determination of optimal doses, duration of treatment, timing of medication use, and adherence to treatment
- Additional evaluation of tibolone
- Trials of other emerging medications to reduce breast cancer risk, such as aromatase inhibitors and retinoids
- Trials of strategies to optimize benefits and minimize harms, such as the concurrent use of a SERM and an anticoagulant
- Controlled trials of lifestyle modification interventions to reduce risk for breast cancer, such as weight loss and exercise.

Comparator

- Head-to-head comparison trials, including trials with tibolone

Outcome

- Evaluation of persistence of effects after treatment
- Long-term tracking of outcomes
- Further analysis of currently available trial data to evaluate differences in the net impact (risk/benefit) for women of various ages and risk groups
- Adequate ascertainment and power to detect statistical differences in adverse outcomes.

Other

- Understanding the physician and patient decisionmaking process, including optimal methods for communicating risk and attitudes.

Objective

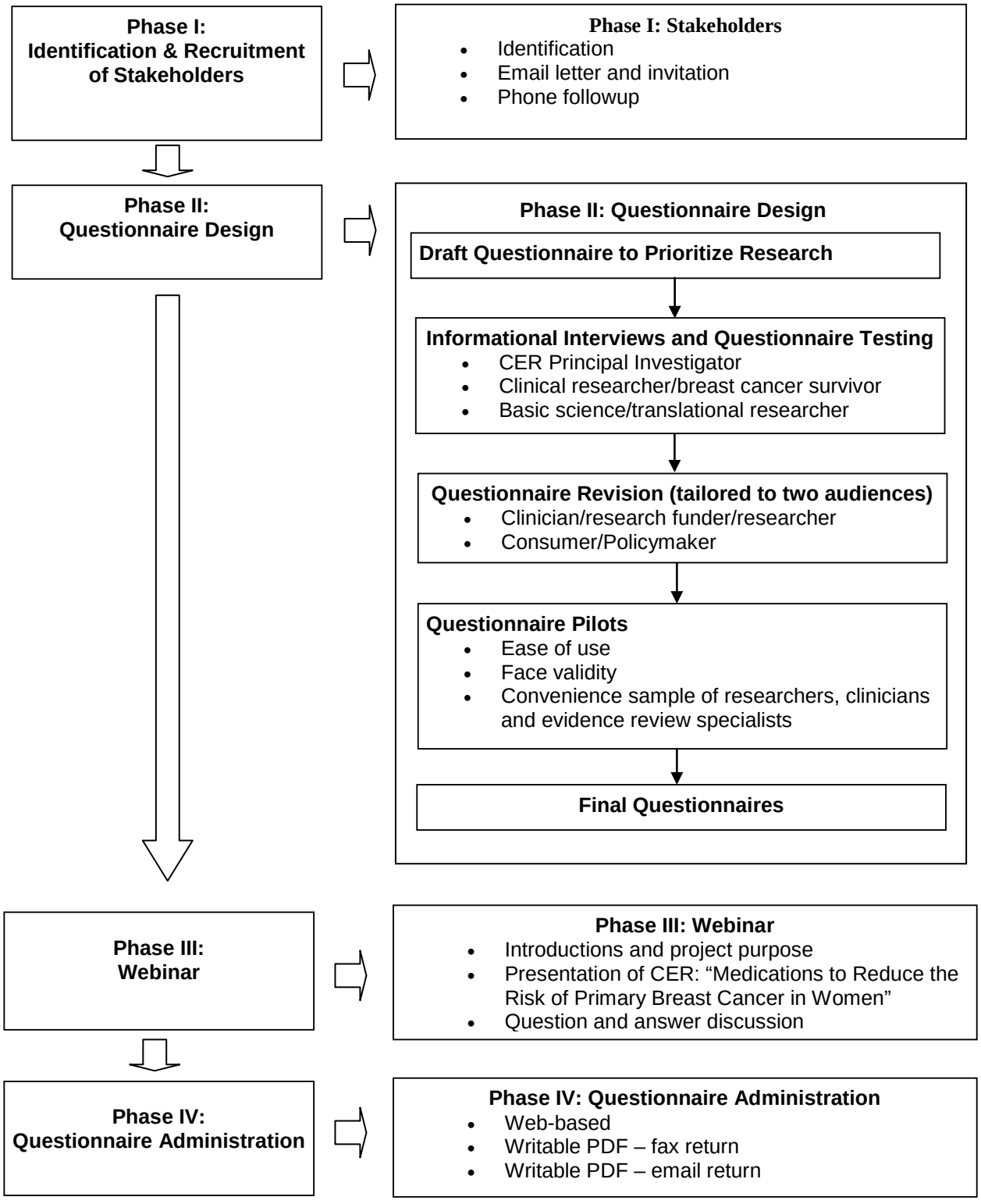
The objective of this pilot project was to engage stakeholders to develop and prioritize a list of research questions to reduce the risk of primary breast cancer. Our goal was to provide sufficient detail—including population, intervention, comparator, and outcome (PICO)—for researchers and funders to use in the development of research proposals and solicitations,

respectively. Secondarily, this project was intended to identify a feasible and effective approach to identify and prioritize future research from systematic reviews in general.

Methods

The identification of research needs and prioritization processes was based upon our experience and that of others with similar future research prioritization projects.[5,6-9] The study design combined qualitative and quantitative methods.[5,6-9] A national sample of stakeholders including clinicians, consumer advocates, policymakers, research funders, and researchers were invited to participate in an informational Webinar and research prioritization questionnaire. Figure 2 presents the phases of the project.

Figure 2. Study design



Oregon Health & Science University and Kaiser Permanente Center for Health Research Institutional Review Boards determined that the project did not meet the definition of human subject research per 45 CFR 46.102.

Identification and Recruitment of Stakeholders

A list of stakeholder groups consisting of clinicians, consumer advocates, research funders, researchers, and policymakers with interests in breast cancer prevention research was generated by the research team *a priori*. We identified participants through requests to directors of major research, professional, and advocacy organizations known to have interest in breast cancer prevention and/or treatment; searching DIRLINE, the National Library of Medicine's on-line directory of health of organizations; individual recommendations from the project team and Oregon EPC leadership; recommendations from researchers in the field; members of the CER technical expert panel; and snowball sampling (chain referral sampling). Efforts were made during recruitment to ensure representation of relevant identified stakeholder groups. No financial incentives were offered for stakeholders to participate.

Invitation letters were sent electronically with followup phone calls as necessary to 40 organizations and individuals and included 17 consumer advocates and policymakers and 23 clinicians, research funders, and researchers. Consumer advocates (10) were recruited from private and public organizations specific to women's health, minority health, and breast cancer. Policymakers (7) contacted included professional medical societies as well as public health and federal organizations. Clinicians (8) invited were from a broad range of disciplines (family practice to surgery) in university, health maintenance, and rural and private practice settings. Researchers (9) invited had expertise in the social sciences, basic/clinical research, and breast cancer. Finally, research funders (6) invited were from federal funding agencies and private foundations.

For purposes of questionnaire mailing, stakeholders were divided into two distinct groups: consumers/policymakers (10 accepted the invitation, including one from a federal organization) and clinicians/research funders/researchers (12 accepted the invitation, including 3 from federal funding agencies). Recruitment was conducted from June 11 to July 2, 2010. Stakeholders were informed that the project would involve participation in a 90-minute Webinar and completion of a questionnaire. Organizations and individuals unable to participate in the live Webinar were offered an option to watch the taped Webinar online and complete the questionnaire. Participants were contacted no more than three times. Stakeholders who agreed to participate were sent the EPC Conflict of Interest Disclosure Form to be completed and returned prior to the Webinar.

Disclosure and Evaluation of Conflicts of Interest

Each stakeholder completed an "EPC Conflict of Interest Disclosure Form" prior to viewing the Webinar and receiving the questionnaire. Of the 22 participants who agreed to complete the questionnaire, 15 declared no conflicts, two provided information on financial and professional/business interests, and four provided information on professional/business interests. One additional stakeholder returned a disclosure form declaring business/professional interests, but did not respond to the questionnaire. The research team reviewed all conflict statements and concluded that no disclosed conflicts precluded participation in the project.

Questionnaire Development and Refinement

In order to enroll sufficient numbers of stakeholders, obtain comparable data, and abide by the Paperwork Reduction Act in forming the stakeholder group, which disallows government contract work to administer standard survey questions to greater than nine non-Federal employees without prior OMB approval, we developed two self-administered research prioritization questionnaires, one tailored to consumers and policymakers (Questionnaire I; Appendix B), and a second tailored to clinicians, research funders, and researchers (Questionnaire II; Appendix C) to evaluate research priorities for breast cancer prevention research among stakeholders. The questionnaires were constructed from information gaps identified in the CER and through informational interviews with the lead investigator for the CER and researchers.

Informational Interviews

We interviewed researchers to understand the current status and focus of breast cancer research. Because breast cancer research involves both clinical and basic sciences, we interviewed researchers from both disciplines. Interviews were recorded with the permission of the key informants and were transcribed. Interview transcripts were reviewed for key content and common themes using principles of grounded theory.[10] Each interview began with a summary of the major findings of the evidence review and the objectives of this project.

Researchers were asked to describe the kind of research that they do relating to breast cancer. The questions included, "Thinking from your area of research, what do you believe are the most important research needs relating to medications to reduce the risk of breast cancer?" "What alternatives to medications are most important to study or most promising?" "Would an analytic framework describing future research needs be useful to basic and clinical researchers?" The researchers emphasized the importance of molecular biomarkers (such as PARP inhibitors and sonic hedgehog) to every aspect of breast cancer extending from identification of high risk populations, to monitoring responses to therapies and to the development of molecularly targeted drugs.

Furthermore, they discussed the importance of genetics, biology, and understanding the mechanisms of action of breast cancer and interventions to prevent breast cancer. They emphasized the importance of understanding breast cancer beyond estrogen, progesterone, and HER2/neu receptor status, and focused on the need to understand and prevent triple negative breast cancer and the most aggressive breast cancers. They mentioned the importance of lifestyle interventions including diet, exercise, weight loss, and alcohol on risk and also mentioned the use of complementary and alternative medications to either reduce the risk of breast cancer or to treat side effects of other medications as combined therapy. Regarding risk models, the main question they wanted to know was if a current breast cancer risk prediction model were available, would clinicians routinely use it in practice? Input from these researchers led to the addition of questions to the questionnaires reflecting these priorities. The questionnaires were organized into six sections: Introduction, Populations of Interest, Interventions, Comparators, Outcomes, and Additional Items.

Research Prioritization Questionnaire

The research prioritization questionnaires used open-ended and structured questions to identify priority research topics. The open-ended question asked stakeholders, "What do you

believe are the most important research questions in preventing breast cancer?" Stakeholders were asked to respond with at least three questions that they thought were highest priority for research. This question was intentionally asked in the Introduction section prior to the itemized listing to elicit the initial impressions of stakeholders as well as at the end of the questionnaire (in the Additional Items section of Appendices B and C) to allow us to assess if their research priorities changed after they answered all of the questions.

Thirty-six structured questions with room for narratives were organized according to PICO. For each of the structured questions, stakeholders were asked (1) to indicate whether the topic was low, medium, or high priority for future research, (2) to provide narrative text to indicate the criteria they used to prioritize the topic, and (3) to detail the types of research they recommended. The two questionnaires differed in terminology depending on the population. Questionnaire I was oriented towards general readers while Questionnaire II used terminology familiar to clinicians and researchers. The questionnaires were reviewed by the three key informants and the AHRQ Task Order Officer (TOO), and the resulting questionnaires were piloted with a convenience sample of researchers, clinicians, and evidence review staff for ease of use, readability, face validity, and to provide time estimates for completion (Figure 2). Web-based questionnaires were created and administered via Survey Monkey (© 1999-2010, San Jose, CA).

Webinar and Questionnaire Administration

Stakeholders participated in a 90-minute Webinar entitled, "Developing a Future Research Agenda to Reduce the Risk of Primary Breast Cancer in Women" on Friday July 9, 2010, from 12:00-1:30 p.m. (Eastern Time). The Webinar described the purpose of the project, summarized the findings and future research gaps identified from the CER, and concluded with a 30 minute question and answer and discussion session. The Webinar was conducted via Adobe Connect (Adobe Systems © 2010, San Jose, CA), moderated by Dr. Jeanne-Marie Guise, and evidence was presented by Dr. Heidi Nelson, lead author of the CER. Immediately following the Webinar, participants were electronically mailed the link to the Web-based questionnaire, a writeable PDF of the research prioritization questionnaire, and the presentation slides from the Webinar (Appendices B and C). Participants who were unable to attend the live Webinar received a Web-based link to the taped Webinar and questionnaire. Participants were asked to complete the questionnaire by July 16. Up to three electronic reminders (and followup phone calls when necessary) were sent reminding participants to complete the questionnaire.

Analysis

Data were entered into Excel (© 2007, Microsoft, Seattle, Washington). Distributions (frequency and percentage) of research prioritization were analyzed overall by questionnaire (Questionnaire I: Consumer/Policymaker and Questionnaire II: Clinician/Research Funder/Researcher) and by self-reported stakeholder perspective. Narrative texts were categorized according to questionnaire and priority type and were analyzed for recurring themes. Four investigators independently reviewed responses and narratives; identified research themes; and coded each theme as population, intervention, comparator, outcome, and influencing factors (PICO). The investigators met to compare codes and themes and reconciled inconsistencies.

For the structured questions, responses were also stratified by questionnaire. For each question, the number and proportion of high, medium, and low priority responses was calculated and also grouped by PICO and influencing factors. To determine the top 10 research priorities,

each question was ranked by the proportion of high priority responses (e.g. a question with 100 percent of responses ranking it a high priority received the highest rank (1). The top 10 research priorities were then compared between the two questionnaires to describe differences in research prioritization by the two strata of stakeholders (consumer/policymakers and clinician/research funder/researcher). The high priority research questions from both open-ended and structured responses are listed with suggestions for potential study designs to address the question and listings of related ongoing and completed research. Finally, to identify stakeholder's preferred method to receive of future research documents, the number and proportion of responses for each format by questionnaire was calculated.

Identification of Ongoing Studies

In order to add context to the final research needs, we conducted searches of research funding, ongoing research, and recently completed research. Ongoing studies were identified through stakeholder questionnaires and formal searches. The original search strategies from the CER were re-searched from January 2009 to July 14, 2010 in MEDLINE, the Cochrane Central Registry of Controlled Trials, and the Cochrane Database of Reviews of Effects (DARE) via OVID. Citation searches were performed to identify published materials citing the CER in Scopus, Google Scholar, and the Annals of Internal Medicine Web site. Unpublished materials were identified by searching clinical trial registries (ClinicalTrials.gov, Current Controlled Trials, Clinical Trial Results, WHO Trial Registries) and grant databases (NIHRePORTER, HSRProj, AHRQ GOLD), as well as individual funders' Web sites (See Appendix D for details). Titles, abstracts, dates, and text were reviewed to evaluate whether the research was directly related to the CER or whether it filled information gaps identified from the review. Identified studies were matched with stakeholder identified research priorities to provide further details for future research needs.

Results

Stakeholders

Twenty-two of 40 stakeholders (55%), representing consumer advocates and policymakers (9), and clinicians, research funders, and researchers (12, including 3 federal employees), (Table 1) agreed to participate, and 21 of 40 invited completed the questionnaire (53%).

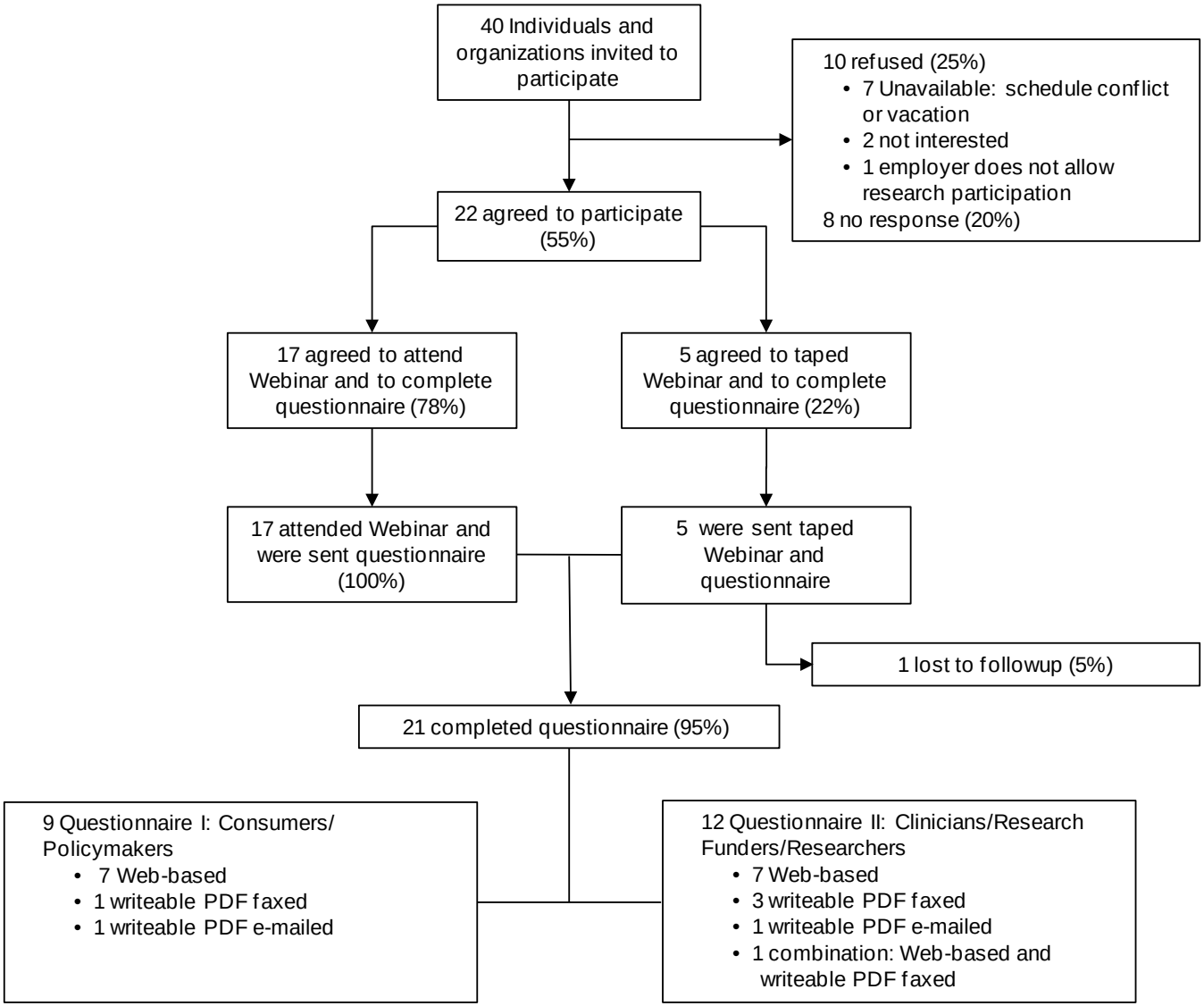
Table 1. Participants and organizations

Stakeholders	Total Invited	Participated[a]	Percent Participation	Participating Organizations And Individuals
Consumer Advocates	10	6	60%	Breast Cancer Action, Susan G. Komen Foundation, Northwest Portland Indian Health Board, Our Bodies Ourselves, Young Survival Coalition, and National Partnership for Women and Families
Policymakers	7	2	29%	American College of Obstetricians and Gynecologists, AHRQ
Clinicians	8	4	50%	Family physician, naturopathic physician, breast cancer surgeons (2)
Research Funders	6	4	67%	National Cancer Institute (2), National Institutes of Health, Office of Research in Women's Health, and American Cancer Society
Researchers	9	5	56%	University/ Academic Medical Centers (4) and the National Comprehensive Cancer Network
Total	**40**	**21**	**53%**	

[a]Variations in the stakeholder perspective we assigned and the perspective self-identified by the participants led to differences in the numbers reported for allocation of participants to Questionnaire I or II (Figure 3) and the numbers of participants by stakeholder category (Table 1).

Research funders (67%) were most likely to participate of all stakeholders, while policymakers were least likely to participate (29%). Among consumer advocates, researchers, and clinicians, 60%, 56%, and 50%, respectively, participated. Participants were not substantially different from non-participants. Ultimately, of the 21 stakeholders, 29% were consumer advocates, 24% researchers, 19% clinicians, 19% research funders, and 9% policymakers (Figure 3).

Figure 3. Recruitment and participation



Reasons for refusal included: not interested in the project (2), unavailable due to a vacation/schedule conflict (7) and one clinician declined because the employer, a federal organization, does not allow participation in research (Figure 3).

Also shown in Figure 3, stakeholders varied in their preference for questionnaire completion. Three stakeholders initially submitted incomplete questionnaires and were contacted by the study team to review and to complete missing sections. Reasons for incomplete questionnaires were technical difficulties (trouble with internet connection) and accidental omission of a section of the PDF questionnaire. One-third of the stakeholders completed the questionnaire in more than one sitting.

Stakeholders were asked to self report their perspective(s) and these were compared to the primary perspectives assigned by the research team (Table 2). Among respondents, stakeholder perspectives were correctly assigned by the research team in 20 of 21 cases (95%). The one discrepancy was a member of a policymaking body that self-identified as clinician, research funder, and researcher. Interestingly, 38 percent of stakeholders reported that they were responding from multiple perspectives.

Table 2. Team-assigned and self-identified perspectives of stakeholders

Respondent	Perspective Assigned	Perspective Chosen
1	Clinician	Clinician, Consumer Advocate
2	Clinician	Clinician
3	Clinician	Clinician
4	Clinician	Clinician
5	Clinician	Clinician
6	Consumer Advocate	Consumer Advocate
7	Consumer Advocate	Consumer Advocate, Clinician
8	Consumer Advocate	Consumer Advocate
9	Consumer Advocate	Consumer Advocate
10	Consumer Advocate	Consumer Advocate
11	Consumer Advocate	Consumer Advocate
12	Policymaker	Clinician, Research Funder, Researcher
13	Policymaker	Clinician, Policymaker
14	Policymaker	Clinician, Researcher
15	Research Funder	Clinician, Research Funder, Researcher
16	Research Funder	Research Funder
17	Research Funder	Clinician, Research Funder, Researcher Policymaker
18	Researcher	Researcher
19	Researcher	Researcher, Clinician
20	Researcher	Researcher
21	Researcher	Researcher

Research Priorities

Two distinct methods were used to obtain future research ideas and priorities: (1) an open-ended question asking stakeholders to write in at least three questions that they thought were highest priority for research and (2) prioritization and comments from structured questions. Frequencies with which each item was listed as high priority were calculated and items presented from highest to lowest frequency.

Research Priorities According To Open-Ended Questions

Stakeholders were asked, "What do you believe are the most important research questions in preventing breast cancer?" This question was intentionally asked prior to the itemized listing to acquire the initial impressions of stakeholders. Table 3 summarizes narrative themes by questionnaire group.

Table 3. Research priorities from open-ended questions

Questionnaire I: Consumer/Policymaker	Questionnaire II: Clinician/Research Funder/Researcher
Population	***Population***
1) What group is at highest risk for breast cancer? a. Race/ethnicity/community/exposures/ genetics/menopausal status 2) What group is most likely to benefit from treatment? a. Genetics 3) Risk assessment tools a. Accuracy b. Tailored to racial/ethnic groups c. Tailored to individual conditions 4) Distribution of receptor types among racial/ethnic minorities, as well as within subgroups	1) What group is at highest risk for breast cancer? a. Biomarkers 2) What group is most likely to benefit from medical over lifestyle treatment? a. Genetics b. Biomarkers c. More than just ER status (ER tumors are heterogenous) 3) Risk assessment tools a. More accurately predict risk b. More accurately predict who is likely to benefit from treatment c. Tailored to racial ethnic groups d. Including molecular/genetic biomarkers e. Tailored to individual conditions 4) How can we prevent ER-negative breast cancer?
Intervention	***Intervention***
1) Interventions suggested a. Behavioral b. Environmental c. Ingestible substances d. Specific recommendations (Indian diet) 2) Best timing in breast cancer life cycle for intervention 3) Interventions targeting a. Highest risk b. Aggressive and lethal types of breast cancer c. ER-negative breast cancer 4) What substances ingested by women (in food, air, water) increase the risk of breast cancer?	1) Identifying more effective medications to reduce the risk of breast cancer 2) Interventions suggested a. Fish oil b. DIM c. Green tea d. Diet/weight control e. Vegetables (type & amount) f. Fruit (type & amount) g. Lifestyle i. Exercise ii. Stress management h. Metformin i. Aromatase inhibitors 3) Studying specific interventions in specific populations (effect of diet, exercise, and weight control on breast cancer risk among African American and Hispanic women) 4) Intervention studies need to bank serum for biomarkers/cytokines to understand response and for potential monitoring
Comparators	***Comparators***
None	1) Diet/lifestyle modifications vs. medications a. Tamoxifen/aromatase vs. lifestyle vs. combined b. What groups more likely to benefit from each

Questionnaire I: Consumer/Policymaker	Questionnaire II: Clinician/Research Funder/Researcher
Outcomes	***Outcomes***
1) Long-term followup a. Is cancer 'prevented' or delayed? b. Harms - what are the long-term effects of taking raloxifene for 10 or more years? 2) Target more aggressive types of breast cancer	1) Long-term followup a. Efficacy for tamoxifen and raloxifene 2) Molecular/genetic predictors of response to treatment a. Understanding phenotype of responders vs. nonresponders b. Biomarkers to shorten clinical trials time 3) Screening/surveillance intervals 4) Risk/benefit ratio of treatments
Influencing Factors	***Influencing Factors***
1) Decisionmaking a. Patient - how do women weigh the benefits/harms of chemoprophylaxis? b. Provider - how can providers best support a person's decisionmaking process? c. Who is considering preventive care? d. Tailored to race/ethnic background 2) Education a. How can we ensure the provider is up to date on the latest research? 3) Communication a. How providers communicate information in a way patients understand? b. What opportunities are important for patients to ask questions for information, guidance and support? c. What is best method to communicate risks? 4) Influences a. Differences in systems of care (increased coverage of prevention activities from health plans) b. What factors influence a women's decision to use chemoprophylaxis?	1) Decisionmaking a. Tools to improve decisionmaking and communication b. Individualized risks 2) Education a. Better strategies to disseminate information (especially aromatase inhibitors) b. How can we ensure the provider is up to date on the latest research? c. How can we ensure the patient is up-to-date on the latest research? 3) Compliance a. Patient - understanding why more patients do not use SERMs b. Provider - barriers for physicians prescribing SERMs 4) Influences a. Social b. Economic c. Medical barriers preventing high-risk women from using chemopreventive agents

Abbreviations: ER=estrogen receptor; DIM=diindolylmethane; SERM=selective estrogen receptor modulator.

While all stakeholders agreed that a priority for future research should be placed on understanding which populations are at highest risk for breast cancer and which are most likely to benefit from preventive therapies, consumers and policymakers focused on demographic factors such as age, race, and ethnicity. Researchers and funders, on the other hand, focused on examining risk based upon genetics and biomarkers. As a whole, stakeholders consistently were highly interested in non-medical interventions such as lifestyle changes including diet, and exercise, with clinicians, funders, and researchers wanting not only more information on the effectiveness of individual changes but also direct comparisons of medical vs. non-medical (e.g., lifestyle) treatments. Similarly, both stakeholder groups thought research is needed to identify and evaluate methods to ensure that providers were up to date in their knowledge and to promote decisionmaking. Compared with researchers, clinicians, and funders, consumers and policymakers were more likely to want additional research on patient-provider communication strategies and how to communicate risks to patients.

Research Priorities According to Structured Questions

Table 4 details responses for each questionnaire question by stakeholder group.

Table 4. Detailed responses to structured priority questions

Consumer/Policymaker Question	High (%) (n)	Medium (%) (n)	Low (%) (n)	Clinician/Research Funder/Researcher Question	High (%) (n)	Medium (%) (n)	Low (%) (n)
Population				**Population**			
Q5. Studies of how age affects the benefits and/or harms of interventions to reduce the risk of breast cancer.	44.4% (4)	55.6% (5)	0 (0)	Q4. Studies to understand the differences of benefits and/or adverse effects by age.	50.0% (6)	25.0% (3)	25.0% (3)
Q6. Studies of how race and/or ethnicity affect the interventions to reduce the risk of breast cancer.	66.7% (6)	33.3% (3)	0 (0)	Q5. Studies to understand the differences of benefits and/or adverse effects by race and/or ethnicity.	33.3% (4)	33.3% (4)	33.3% (4)
Q7. Studies to understand which populations of women would optimally benefit from medications to reduce their risk of breast cancer.	77.8% (7)	11.1% (1)	11.1% (1)	Q6. Studies to understand which populations of women would optimally benefit from medications to reduce their risk of breast cancer. Please include recommendations (i.e., study types, populations).	75.0% (9)	16.7% (2)	8.3% (1)
Intervention/Comparators (Comparisons)				**Intervention/Comparators (Comparisons)**			
Q8. Prescription medications: Tamoxifen, Raloxifene	50.0% (4)	50.0% (4)	0 (0)	Q9. Tamoxifen citrate and raloxifene (SERMs: Selective Estrogen Receptor Modulators)	54.5% (6)	18.2% (2)	27.3% (3)
Q9. Prescription medication: Tibolone (this medication is not currently approved in the US)	25.0% (2)	62.5% (5)	12.5% (1)	Q7. Tibolone (STEAR: Selective Tissue Estrogenic Activity Regulator)	20.0% (2)	40.0% (4)	40.0% (4)
Q10. Vitamin A derived medications (e.g. retinols)	42.9% (3)	42.9% (3)	14.3% (1)	(Question not asked of Clinician/Research funder/Researcher)			
(Question not asked of Consumer/Policymaker)				Q8. Aromatase inhibitors	54.5% (6)	9.1% (1)	36.4% (4)
Q11. Drugs based on a person's genetics	37.5% (3)	50.0% (4)	12.5% (1)	Q12. Gene-based drugs	54.5% (6)	9.1% (1)	36.4% (4)
Q12. Drugs that target specific molecular cancer pathways	62.5% (5)	37.5% (3)	0 (0)	Q13. Molecularly targeted agents	40.0% (4)	50.0% (5)	10.0% (1)
Q13. Complementary and alternative therapies	66.7% (6)	33.3% (3)	0 (0)	Q10. Complementary and alternative therapies	36.4% (4)	9.1% (1)	54.5% (6)
Q15. Weight loss as therapy	22.2% (2)	44.4% (4)	33.3% (3)	Q14. Weight loss as therapy	50.0% (6)	16.7% (2)	33.3% (4)
Q16. Exercise as therapy	33.3% (3)	44.4% (4)	22.2% (2)	Q15. Exercise as therapy	50.0% (6)	16.7% (2)	33.3% (4)
Q17. Diet as therapy	22.2% (2)	55.6% (5)	22.2% (2)	Q16. Diet as therapy	50.0% (6)	25.0% (3)	25.0% (3)
Q19. Combination therapies (e.g., aspirin + prescription medication)	50.0% (3)	33.3% (2)	16.7% (1)	Q18. Combination therapies (e.g., aspirin + tamoxifen)	27.3% (3)	36.4% (4)	36.4% (4)
Q20. Other lifestyle modifications	37.5% (3)	50.0% (4)	12.5% (1)	Q20. Other lifestyle modifications	16.7% (2)	33.3% (4)	50.0% (6)

Consumer/Policymaker Question	High (%) (n)	Medium (%) (n)	Low (%) (n)	Clinician/Research Funder/Researcher Question	High (%) (n)	Medium (%) (n)	Low (%) (n)
Outcomes				**Outcomes**			
Q24. Reporting all harmful effects of medications prescribed to reduce breast cancer risk.	88.9% (8)	11.1% (1)	0 (0)	Q24. Ascertainment of adverse effects of medications prescribed to reduce breast cancer risk (please discuss which are most important and how you recommend they be studied).	41.7% (5)	25.0% (3)	33.3% (4)
Q25. Evaluation of how long the beneficial effects of therapy last.	100% (9)	0 (0)	0 (0)	Q25. Evaluation of the persistent effect of breast cancer risk reduction treatment.	66.7% (8)	25.0% (3)	8.3% (1)
Additional Items				**Additional Items**			
Q27. Studies of doctors' attitudes toward prescribing medications to reduce breast cancer risk.	33.3% (3)	33.3% (3)	33.3% (3)	Q27. Studies of clinicians' attitudes toward prescribing medications to reduce breast cancer risk.	58.3% (7)	16.7% (2)	25.0% (3)
Q28. Studies of how doctors are weighing the risks and benefits of medications to reduce breast cancer risk.	44.4% (4)	33.3% (3)	22.2% (2)	Q28. Studies of how clinicians are weighing the risks and benefits of prescribing medications to reduce breast cancer risk.	75.0% (9)	16.7% (2)	8.3% (1)
Q29. Studies of doctors' attitudes toward recommending non-medication-related interventions to reduce breast cancer risk.	22.2% (2)	33.3% (3)	44.4% (4)	Q29. Studies of clinicians' attitudes towards prescribing non-medication-related interventions to reduce breast cancer risk.	33.3% (4)	25.0% (3)	41.7% (5)
Q30. Studies of patients' attitudes toward taking medications to reduce breast cancer risk.	44.4% (4)	44.4% (4)	11.1% (1)	Q30. Studies of patients' attitudes toward prescribing medications to reduce breast cancer risk.	66.7% (8)	16.7% (2)	16.7% (2)
Q31. Studies of what factors influence a woman's decision-making about medications to reduce breast cancer risk.	55.6% (5)	44.4% (4)	0 (0)	(Question not asked of Clinician/Research funder/Researcher)			
Q32. Studies of how to communicate benefits and risk to patients.	77.8% (7)	22.2% (2)	0 (0)	Q31. Studies of how to communicate benefits and risks to patients.	83.3% (10)	8.3% (1)	8.3% (1)
Q33. Studies of how doctors and patients are working together to decide if medications to reduce risk of breast cancer should be prescribed.	22.2% (2)	66.7% (6)	11.1% (1)	Q32. Studies of how clinicians and patients are working together to decide if medications to reduce risk of breast cancer should be prescribed.	33.3% (4)	41.7% (5)	25.0% (3)
Q34. Research on predicting risk of breast cancer.	88.9% (8)	11.1% (1)	0 (0)	Q33. Research on risk prediction models (please specify and recommend areas of improvement).	75.0% (9)	25.0% (3)	0 (0)
Q35. If a current breast cancer risk prediction model were available, do you think patients would use it to help make decisions about therapy? Why or why not?	Yes; 100% (7)	No; 0 (0)		Q34. If a current breast cancer risk prediction model were available, would you routinely use it in your practice?	Yes 100% (11)	No; 0 (0)	

Looking across all structured questions, at least 50 percent of respondents in both Questionnaire I and II groups (consumer/policymaker and researcher/research funder/clinician, respectively) rated the following five questions as highest priority by PICO:

Population: Studies of how age affects the benefits and/or harms of interventions to reduce the risk of breast cancer (78%; 75%)
Intervention: Prescription medications: tamoxifen, raloxifene (50%; 55%)
Outcomes: Evaluation of how long the beneficial effects of therapy last (100%; 67%)
Other: Studies of how to communicate benefits and risk to patients (78%; 83%) and Research on predicting risk of breast cancer (89%; 75%)

Additionally, 100 percent of consumers, policymakers, clinicians, research funders, and researchers reported that patients would use a prediction model to assist in their decisionmaking if a current model were available. Compared with researchers, consumer advocates and policymakers were more interested in future research relating to the harms of therapy (89% vs. 42%). Narratives provided interesting differences in the criteria used for prioritization. Narratives from researchers indicated that harms of medications were either already known or that it was assumed they would be measured, as illustrated by this researcher who rated measurement of harms as low priority: "Already well documented. What is important is being able to predict who is most likely to have an adverse event and what can be done to prevent it." This is in contrast to the comment from a policymaker that emphasizes the importance of looking for unintended consequences of recommendations: "Hate to possibly prescribe a drug to prevent breast cancer and she dies of a stroke or pulmonary embolism."

Looking at narratives regarding the long-term beneficial effects of therapy, there was general agreement among all stakeholders that this was a priority though the rationale differed slightly. Consumers and policymakers commented that knowing the long-term beneficial effects of therapy would help them balance benefits and harmful effects and would motivate decisions to consider preventive therapy (implying prioritization of decisionmaking – influencing factor). On the other hand, researchers, funders, and clinicians commented that current studies have relatively short-term followup, and that long-term benefits such as survival are important to optimize duration of therapy (emphasizing outcome and intervention). Table 5 summarizes the top 10 priority research areas by rank order grouped according to questionnaire type.

Table 5. Top 10 priority research areas

Questionnaire I: Consumer/Policymaker[a]	% High Priority[a]	Rank	Questionnaire II: Clinician/Research Funder/Researcher[a]	% High Priority[a]	Rank
Persistent effect of preventive therapy	100%	**1**	How to communicate benefits and risks to patients	83.3%	**1**
Reporting harmful effects of preventive therapy	88.9%	**2**	Predicting risk of breast cancer	75.0%	**2**
Predicting risk of breast cancer	88.9%	**2**	Understanding which populations of women would optimally benefit from medications to reduce the risk of breast cancer	75.0%	**2**
Studies of how to communicate benefits and risks to patients	77.8%	**4**	How clinicians are weighing the risks and benefits to preventive therapy	75.0%	**2**
Studies of what populations optimally benefit from medications to reduce the risk of breast cancer	77.8%	**4**	Persistent effect of preventive therapy	66.7%	**5**
Complementary and alternative therapies	66.7%	**6**	Patient attitudes toward prescribing medications to reduce breast cancer risk	66.7%	**5**
Studies of how race and/or ethnicity affect interventions to reduce the risk of breast cancer	66.7%	**6**	Studies of clinicians' attitudes towards prescribing medications	58.3%	**7**
Molecular targeted drugs specific to cancer pathways	62.5%	**8**	Aromatase Inhibitors	54.5%	**8**
What factors influence a woman's decision-making to take medications to reduce breast cancer risk	55.6%	**9**	SERMs	54.5%	**8**
SERMs	50.0%	**10**	Gene-based drugs	54.5%	**8**
Combination therapies: i.e., prescription medications + diet	50.0%	**10**			

Abbreviations: SERM= selective estrogen receptor modulator.

[a] Percentages indicate a priority ranking of "high" by respondents from choices of "high," "medium," or "low."

According to the ranking of responses to the structured list, consumers and policymakers more frequently rated studies of interventions as high priority, followed by population, influencing factors, and outcomes, whereas researchers, research funders, and clinicians more frequently rated other factors highest, followed by intervention studies, and then outcomes.

Preferences for Future Research Dissemination

Lastly, we asked stakeholders to indicate how they would like to receive results from this national research stakeholder prioritization process (Table 6). Clinicians, researchers, and funders unanimously preferred to receive the document as a journal article whereas consumers and policymakers unanimously preferred a standalone document.

Table 6. Preferred format to receive future research documents

Questionnaire I: Consumer/Policymaker		**Questionnaire II: Clinician/Research Funder/Researcher**	
Format	***Percent (n)***	***Format***	***Percent (n)***
Chapter in an evidence report	25% (2)	Chapter in an evidence report	8.3% (1)
Magazine article	25% (2)	Journal article	100% (12)
Stand alone document	100% (8)	Standalone document	33.3% (4)
Webinar	25% (2)	Webinar	25% (3)
Podcast	0%	Podcast	8.3% (1)
Other (please specify) Publication in a highly visible journal with links to online document	12.5% (1)	Other (please specify) Summary email with links	8.3% (1)

Discussion

Discussion of Process Issues or Recommendations

Engaging stakeholders to shape research so that it is more responsive to what consumers, patients, clinicians, and decision-makers need is a national priority. Because this practice is relatively new, there is no clear guidance for the optimal methods of stakeholder engagement or distribution of stakeholders. While approximately half of invited stakeholders agreed to participate in this project, we were still able to achieve adequate participation within each stakeholder group. We were able to accomplish this because we defined the optimal stakeholder groups before extending invitations and then carefully monitored acceptance and refusals, adjusting recruitment accordingly. Through this process, we documented our *a priori* stakeholder groups, compared them with our final participation, and ensured participation of all five major stakeholder groups. Ultimately, through close monitoring of recruitment, 29 percent of participants were consumer advocates, followed by researchers (24%), clinicians (19%), funders (19%), and policymakers (9%). Factors that may have negatively influenced response rates include short time frame between invitation and Webinar, summer vacations, and transitions to other professional positions. Processes that facilitated stakeholder engagement included personal contact with organizations and individuals, existing relationships with individuals, and stakeholders being so invested in the topic that they either wanted to participate themselves or personally recommended others. This personal championship not only encouraged engagement but also created momentum around the dissemination of the final product.

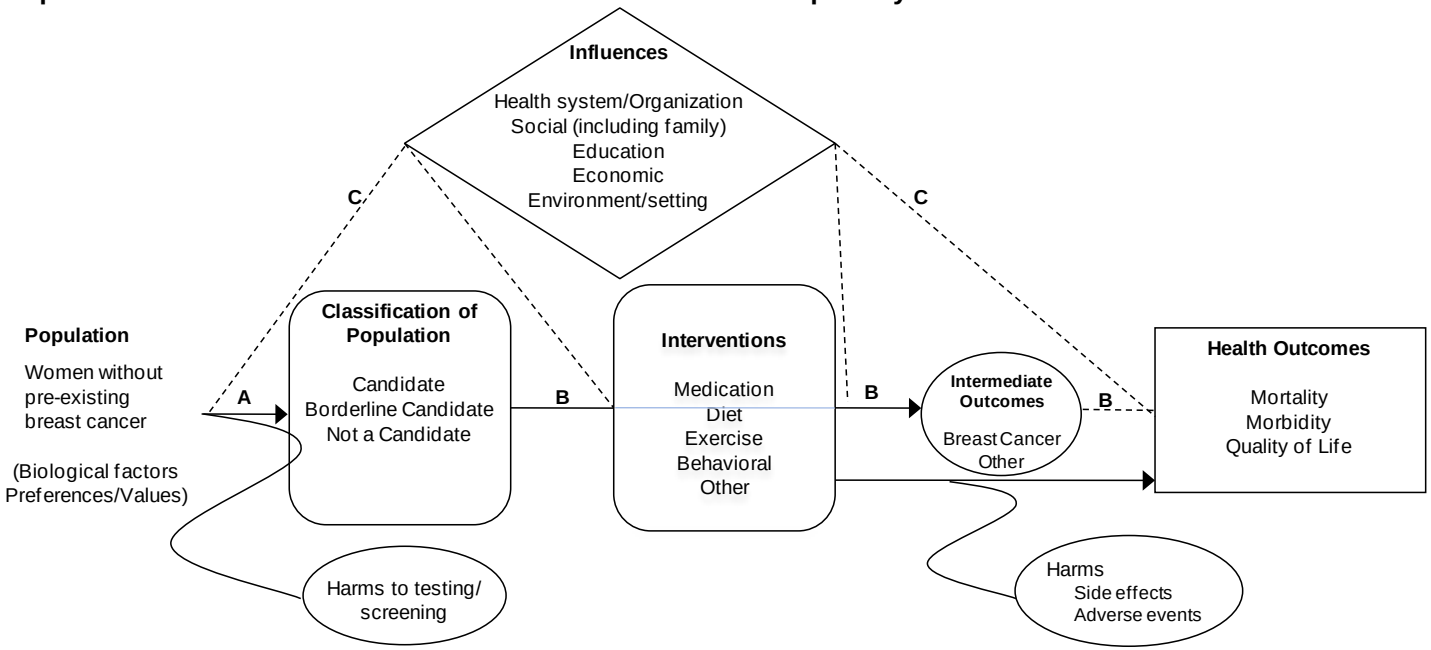
The goal of this project was to prioritize research relating to the prevention of primary breast cancer. Quantitative methods such as questionnaires, Delphi processes, and voting are frequently used as efficient and equitable processes to obtain priorities. In this project we asked all stakeholders to rate items as high, medium, or low priority to determine the top ten priorities in rank order based upon the frequency that individual stakeholders rated the item as high priority. We plan to compare these results to priorities by stakeholder group to have a deeper understanding of whether and how stakeholders differ in their priorities. When using a questionnaire, offering different administration formats for the questionnaire (choice of email delivery of PDF form or Web-based form) may have promoted broader participation as two-thirds of stakeholders chose the Web-based option and 1/3 chose either electronic completion of PDF sent by email or printed PDF returned by fax.

Framework for Future Research and Reflections on CERs

Analytic frameworks have been used to structure reviews but were not designed to guide discussions of future research. In the usual format for an analytic framework, interventions and actions are represented by arrows and events are represented in boxes. This format facilitates discussion of outcomes, but it makes it very difficult to focus attention on the range and choice of interventions. For future research discussions, graphical frameworks need to clearly communicate ideas, linkages, and assumptions in an organized way that demonstrates that the research proposed is well-integrated, well-reasoned, and appropriately designed to advance a field of research.

Figure 4 presents a conceptual framework for future research in the primary prevention of breast cancer. Similar to analytic frameworks of CERs the framework is read from left to right starting with the population of interest on the left and ending with health outcomes on the right. Arrows are used to indicate actions and squares to indicate health outcomes. Circular symbols (circles and ovals) are used to indicate events, whether benefits (e.g., intermediate outcomes) or harms. We have used rounded boxes to highlight important topics for future research discussion and we have added the diamond that has been used (e.g., behavioral intervention[11] and Vaginal Birth After Caesarean frameworks[6,12]) to indicate influencing factors.

Figure 4. Conceptual framework: future research needs to reduce the risk of primary breast cancer



Key Research Questions

Overall: Which interventions are most effective to reduce risk of breast cancer for which patients under what circumstances?

A. What women are most susceptible to benefits versus harms of breast cancer risk reduction treatment?
   - A1: What is the most effective method to identify appropriate candidates for treatment (classification of population)?
   - A2: What is the most effective method to determine a woman's risk for breast cancer?
   - A3: What markers (including biomarkers) and tests are useful in classifying people as candidates for treatment?

B. What interventions are most effective to reduce the risk of breast cancer and improve short and long term outcomes?
   - B1: What interventions are most effective to reduce the risk of the most aggressive types of breast cancer?
   - B2: What are the mechanisms of action of interventions?
   - B3: What surveillance mechanisms and intervals optimize short and long term outcomes?

C. What factors influence the acceptability and effectiveness of breast cancer risk reduction treatment?
   - C1: What factors magnify or reduce risk?
   - C2: What factors influence patient and clinician decision making?
     - What is the most effective method for providers to communicate risks to patients?
     - What is the most effective method for patients and clinicians obtain current , high-quality evidence to inform their decisions?
   - C3: What factors improve/reduce effectiveness of breast cancer risk reduction treatment?
   - C4: What factors improve or worsen outcomes from breast cancer risk reduction treatment?
   - C5: Do risk prediction models or decision support or other tools improve C1-C4?

The future research needs framework demonstrates the three major areas for future research in the primary prevention of breast cancer. Stakeholders consistently agreed that one of the highest priorities is answering the question: **Who is at highest risk for developing breast cancer and most likely to benefit from preventive therapies (Future Research Question A)?** This question combines risk for breast cancer and susceptibility to benefits and harms of therapies. See Table 7 for details on research gaps identified by stakeholders and corresponding study designs. Investigations in this area could include determining all the possible markers and tests that should be considered to classify women regarding their candidacy for preventive therapies. Specifically, which molecular, genetic, and demographic characteristics and/or blood or imaging tests predict who is at highest risk of developing the most aggressive forms of breast cancer? Stakeholders frequently mentioned wanting more epidemiological research in premenopausal women. We are aware of a study underway that combines literature synthesis and epidemiological methods to examine which factors increase a premenopausal woman's (ages 40-49) risk for primary breast cancer and the magnitude of these risk factors.[13] For example, the study will estimate a woman's risk of primary breast cancer if she has a history of smoking.

Another suggestion was to conduct intervention studies in special populations. For example, intervention studies among women with hyperplasia in breast biopsy and repeated biopsy to see if the tissue changes. Which factors predict who is most susceptible to harms of therapy vs. benefits? In general, the two groups of stakeholders emphasized different features of the population. Consumers and policymakers emphasized demographic features of the population that may reflect access to care and create additional vulnerabilities that worsen prognosis, whereas researchers, funders, and clinicians were interested in the molecular and genetic basis that places a woman at higher risk, causes the development of more aggressive disease, and/or predicts better response to therapies. One informational interview mentioned that the Gail model, which is often used to calculate risk, does not predict risk for special populations such as the Puerto Rican population in New York City and Mexican-American population on the west coast.

Researchers highlighted that SERMs do not completely prevent even estrogen receptor-positive cancers and they have considerable side effects and adverse events. They felt that molecular biomarkers such as PARP inhibitors offered promise to both target the most lethal types of breast cancer and focus the medications. Stakeholders' comments such as, "Would prefer identification of molecular or genetic predictors of response to chemopreventive interventions as this would enable a more individualized approach to women at increased risk of breast cancer," demonstrate the importance of these features in individuals and populations of individuals for patient-centered care.

Moreover, researchers suggested using stored biologic samples from participants in the SERM trials who had events vs. those who did not to explore the genetic (SNPs) and molecular characterization to better predict risk and benefit. While biological factors may be implicit in the model, the emphasis of stakeholders on their importance not only to discovery but to individualized care caused us to highlight these items in the population. The wide range of factors thought to contribute to population risks require a wide range of investigator skills ranging from basic science to epidemiology to clinical researchers.

Progressing through the framework, the next major research question is: **What interventions are most effective to reduce the risk of breast cancer and improve short and long-term outcomes (Future Research Question B)?** Overall, when discussing interventions, the I (intervention), C (comparison), and O (outcome) of PICO were often inextricably

intertwined in the responses of stakeholders such that it was not possible to accurately distinguish the relative priority of the benefits (outcomes) of an intervention from the intervention itself. While the scope of the CER focused on traditional medications to prevent breast cancer, stakeholders' interests in interventions were much broader, extending to lifestyle changes, diet, exercise, dietary supplements, and other interventions.

> "This [weight loss as therapy] is an intervention that carries essentially no harm and great preventive/therapeutic benefits for many diseases"
>
> "I like this idea [weight loss as therapy] because of the huge public health burden of the obesity epidemic and the biologically plausible effectiveness without drugs."
>
> "The evidence for this is weak and varies by menopausal status and too many confounders."
>
> "Wow!!! If this works we could have labels on some foods "eating this may be hazardous to your breast"'
>
> "Exercise and dietary modification may be interesting to study in young females (children and adolescents)."
>
> "One published paper in African American women . . . none for Hispanic women. The challenge for this . . . lies in the fact that longitudinal studies like the Women's Healthy Eating and Living Project (experimental design) are needed to adequately address these areas. The potential benefits and long term health care savings would far outweigh the costs of doing the studies."
>
> "This (exercise as therapy) is an intervention that carries essentially no harm and great preventive/therapeutic benefits for many diseases. Better understanding the benefits of exercise on breast cancer prevention would provide clinicians with additional rationale for recommending it and would motivate more women to be active."
>
> "I'm ready for a trial--but the logistics of a trial and its size make this a hard sell. I do not know any evidence from other trials of exercise (which is always confounded by weight loss) that did show cancer reduction. The Women's Health Initiative diet arm did cause weight loss but no cancer risk changes were observed. I think the weight and exercise trial should be combined, given the known difficulty of sustaining weight loss without increasing physical activity"

Several stakeholders wanted a study comparing lifestyle changes to medications. Comparisons mentioned from questionnaire responses included tamoxifen or aromatase inhibitors compared with diet/exercise and an arm combining medications and lifestyle changes. A basic science researcher commented on research in other fields demonstrating that exercise up-regulated certain gene expressions (for example in depression) and that it would be good to understand at a physiological level whether exercise has similar effects on breast cancer genes. However, as mentioned in questionnaires and informational interviews, diet and exercise are complicated interventions and it is important to understand what specific factors are necessary for the intervention. For these reasons, an evidence review that would review the literature on the effectiveness of lifestyle interventions to reduce the risk of primary breast cancer may be particularly helpful both to inform current patient decisionmaking and future research in this

area. Such a review could evaluate the effectiveness of multiple lifestyle interventions (weight loss, exercise, diet, green tea, and fish oil) that were mentioned by stakeholders and suggest promising interventions to reduce the risk of primary breast cancer. The findings could help in the design of the interventions as well as study designs by highlighting important limitations in prior work, barriers, and specifying individual or combination therapies to be considered in future studies. A preliminary search of the literature found there are likely to be sufficient studies to inform a systematic review of the effectiveness of non-medication based interventions to prevent breast cancer with over 800 abstracts and a handful of comparative studies.

The third high priority research question for the prevention of breast cancer is: **What factors influence the acceptability and effectiveness of risk reduction treatment (Research Question C)?** The biggest difference between the CER analytic framework and the future conceptual framework is the addition of a diamond (used in behavioral intervention frameworks) to represent influencing factors, with action arrows extending both to the arrow between the population and intervention and the intervention and outcomes. Influencing factors, such as patient-provider communication and decisionmaking, attitudes and prescribing practices, insurance status, community, and exposures on risk and availability and susceptibilities to treatment were consistently among the highest priority items mentioned among stakeholders and were the leading priority for clinicians, research funders, and researchers.

Some stakeholders mentioned wanting to understand what barriers prevented providers from prescribing SERMs and patients from taking them. The results of such research would be helpful not only for existing medications but also for upcoming medications such as aromatase inhibitors. While we identified a questionnaire of family medicine providers, obstetrician/ gynecologists, and internal medicine primary care providers regarding their practices for breast cancer prevention screening and prescribing SERMs, the study has a number of methodological limitations.[14] Providers were asked to self- report to questions specific to screening for breast cancer and prescribing SERMs. The degree to which providers were prescribing SERMs specifically for breast cancer prevention compared with osteoporosis was not discussed. Given the inclination to provide positive responses (e.g. higher prescribing of SERMs), creative scenario-based questioning or questionnaires that combine characteristics of the patient or prevention conditions might provide a better understanding of providers' behaviors and attitudes towards the use of SERMS to reduce the risk of breast cancer. This also presents an area where an evidence review may be helpful to inform and guide future research as well as clinical practice. Furthermore, stakeholders wanted to know about the best strategies to communicate risks to patients, how to have discussions about harms and benefits of preventive therapies, and how to ensure that both patients and providers were up to date on current research. We conducted a preliminary search which identified 400 abstracts relating to breast cancer and communication and attitudes.

Consumers and policymakers were particularly interested in the degree to which environmental, economic, community, and social factors influenced decisionmaking, options, and outcomes. Stakeholder comments such as below reflect that influencing factors are critical to patient-centered care and comparative effectiveness research.

> "We need studies that go beyond racial and ethnic disparities. As we all know, disparities just means "difference." What matters is what leads to those differences and is often social and economic and racial inequities. Studies should

look at what societal changes would have most impact on risk reduction in communities of color."

"What social, economic, medical barriers prevent high risk women from using chemo-preventive agents?"

"I wonder if you want to do studies about other influences…because I just personally feel that clinicians aren't that influential anymore. It's more CNN and my neighbor and my cousin and my mom with cancer… the social network theory around health and disease. Social networks have a lot to do with how we do things."

"How can physicians or other health care providers best support a persons' decisionmaking process who is considering preventive care for breast cancer. How can we ensure the provider is up-to-date on the latest research, that he/she has explained that information to a patient in a way he/she will understand and then provide an opportunity for the patient to ask questions and seek additional information, guidance and support?"

"The provider-patient communication dynamic is imperative to good decision-making. If we can understand this better, then we can find those populations where communication can be improved."

"There is a primary disconnect between patient and physician understanding/perception of risk-benefit rations for chemoprevention agents that is both poorly documented and clearly not understood. Well designed studies are needed that integrate health literacy and communication and target patients AND physicians."

"Even more critical would be the development of tools that would facilitate this communication in a busy primary care practice. Such tools should communicate the patient's breast cancer risk, the benefits and harms of risk reduction therapy and lead the patient through a decision-making process."

As demonstrated by comments above, clinicians, consumer, research funders, researchers and policymakers were concerned about how to best disseminate information to ensure that patients and clinicians were able to make informed decisions based on high-quality evidence. They also wanted to understand the patient-provider communication process and the most effective method for communicating risks and facilitating decisionmaking. Because they are important to stakeholders and integral to patient-centered care, we believe that influencing factors should be depicted when appropriate in CER frameworks. Depicting influencing factors in frameworks encourages the reviewers to look for related evidence, and raises the readers' awareness of their importance. For those reasons, we propose the addition of "Influencing factors (I)" to PICO as I PICO. The paradigm of research embodied in this framework promotes interdisciplinary and translational research teams that have been endorsed nationally.

Future Research Study Designs

To activate and inform future research, Table 7 lists all priority research topics that arose from narrative and structured responses, ongoing and completed research relating to that topic,

and potential study designs for future research in that area organized according to the conceptual framework. From searches described above (See Methods: Identification of Ongoing Studies), the research team identified approximately 200 ongoing, recently completed, and/or funded studies from clinical trial registries, grant databases, and individual funders' Web sites. These studies were listed according to stakeholder identified priorities.

Table 7. Future research agenda for breast cancer prevention

Framework Question(s)	Priority Research Area (Question)	Research Needed And Potential Study Design	Ongoing Research[a,b,c]	Completed Research[a,b,c]	Completed Research[b,c,d]	I PICO Category
Question A: What women are most susceptible to benefits vs. harms of breast cancer risk reduction treatment? A1: What is the most effective method to identify appropriate candidates for treatment (classification of population)? A2: What is the most effective method to determine a woman's risk for breast cancer? A3: What markers (including biomarkers) and tests are useful in classifying people as candidates for treatment?	Studies of how race and/or ethnicity affect interventions to reduce the risk of breast cancer	Actively recruit minorities to gather sufficient power in ongoing studies				P
		Meta-analysis pooling data from all published studies				
	Predicting risk of breast cancer	Genomic models for individual risk prediction		15	16-31	P
		Updated risk models	13, 32, 33		29, 34-43	
		Intervention studies to gather data and store blood specimens for analysis possible serum markers for breast cancer risk	44-64	65		
		Identification of factors (including biomarkers) that predict women who develop, breast cancer, more aggressive types of breast cancer, and/ or triple negative breast cancer	66-75	76	19, 22, 77-96	
		Registry to examine factors	59, 97-100			
		Cohorts such as Women's Health Initiative, The Nurses' Health Study I & II	73, 75, 100-103		104	
	Studies of what populations optimally benefit from medication to reduce the risk of breast cancer	Continued followup of current studies (ensure variables of interest are followed)	64, 66, 105, 106			P
		Ensuring trials/analyses are consistently stratifying by relevant populations				
		Analyze serum from women in intervention studies to determine if there are biomarkers that predict which women are most likely to benefit from medications to reduce the risk of breast cancer	107, 108	109, 110		
		Development of risk models to predict who is most likely to benefit from medications to reduce the risk of breast cancer	111	109, 112	113	
		Meta-analysis of pooled data from studies				

Framework Question(s)	Priority Research Area (Question)	Research Needed And Potential Study Design	Ongoing Research[a,b,c]	Completed Research[a,b,c]	Completed Research[b,c,d]	I PICO Category
		Target specific subpopulations (e.g. mammographic density, age, menopausal status and exposures (e.g., DES)	97, 114-116	117	118-125	
		Basic science (e.g., animal studies)	126-128			
Question B: What interventions are most effective to reduce the risk of breast cancer and improve short and long term outcomes? B1: What interventions are most effective to reduce the risk of the most aggressive types of breast cancer? B2: What are the mechanisms of action of interventions? B3: What surveillance mechanisms and intervals optimize short and long term outcomes?	Lifestyle, diet, weight loss, exercise modification	Randomized controlled trials of diet, exercise, weight loss	58, 61, 62, 129, 130	131-136		I
		Basic science	137			
		Ecological studies among communities with differing diet, exercise habits				
		Other (e.g., observational studies, reviews)	138		27, 139-148	
	Complementary and alternative therapies	Randomized controlled trials of complementary and alternative therapies	44, 45, 54-57, 63, 149-163	136, 164-166		I
		Basic science	162, 167-180			
		Other (e.g., observational studies, reviews)	53, 168, 181-183		27, 184-185	
	Aromatase Inhibitors	Randomized controlled trials	46, 47, 60, 106, 186-190	65, 191-193		I
		Basic science				
		Other (e.g., observational studies, reviews)			185, 194, 195	
	SERMs (focus of original CER)[e]	Randomized controlled trials	49, 63, 196-201	192, 202-207	208-210	I
		Basic science	211-213		121, 214-218	
		Other (e.g., observational studies, reviews)			28, 185, 219-222	
	Metformin	Randomized controlled trials				I
		Observational studies			223	
	Gene-based drugs	Randomized controlled trials				I
		Drug development	224			
	Molecular targeted drugs specific to cancer pathways	Randomized controlled trials				I
		Drug development	74, 224, 225			
	Combination therapies: e.g., medications + diet; medications + aspirin	Randomized controlled trials	52, 63, 226, 227	192, 228, 229	210	I
		Basic science	230, 231		232	
		Observational studies				
	CAM vs. medications	Randomized controlled trial	63			C
	Diet modification vs.					C

Framework Question(s)	Priority Research Area (Question)	Research Needed And Potential Study Design	Ongoing Research[a,b,c]	Completed Research[a,b,c]	Completed Research[b,c,d]	I PICO Category
	medications: tamoxifen/ AI vs. lifestyle vs. combined	Basic science				
	Persistent effect of preventive therapy, is cancer prevented or delayed?	Long-term followup of current intervention studies	197, 233	204	234	O
		Other	99			
	Understand appropriate surveillance windows	Long-term followup of current intervention studies with imaging, biomarker, histologic etc, surveillance	114		144, 235	O
	Oversampling for subgroups to assess who is most likely to benefit					
	Reporting harmful effects of preventive therapy	Long-term followup of current intervention studies	48, 106, 236-239	110, 192, 204, 205, 207, 228, 229, 240-244	245, 246	O
		Short-term adverse event studies	247		248, 249	
		Basic science			250-257	
		Reviews, case-control studies, and case reports			17, 28, 144, 185, 194, 209, 220, 222, 245, 248, 253, 258-290	
Question C: What factors influence the acceptability and effectiveness of breast cancer risk reduction treatment? C1: What factors magnify or reduce risk? C2: What factors influence patient and clinician decisionmaking? c) What is the effective method for providers to	Studies of what factors influence a women's decision-making to take preventive therapy	Focus groups/interviews of patients			291-295	Influencing factors
		Questionnaires of patients			296-302	
		Decision aids and decision modeling	303, 304		305, 306	
		Patient navigators	307-311			
		Other (e.g., observational)	233		312-315	
	Studies of clinicians/patient attitudes toward prescribing medications to reduce the risk of breast cancer	Questionnaires of clinicians/patients			14, 316-320	Influencing factors
		Case based decisionmaking varying certain features			321	
		Focus groups/interviews			294, 322	
		Survey medical decisions on case paradigms of varying degree				
		Other (e.g., observational)			305, 314, 315, 323	
	Studies of how	Questionnaires of clinicians			324	Influencing

Framework Question(s)	Priority Research Area (Question)	Research Needed And Potential Study Design	Ongoing Research[a,b,c]	Completed Research[a,b,c]	Completed Research[b,c,d]	I PICO Category
communicate risks to patients? d) What is the most effective method for patients and clinicians obtain current, high-quality most evidence to inform their decisions? C3: What factors improve/reduce effectiveness of breast cancer risk reduction treatment? C4: What factors improve or worsen outcomes from breast cancer risk reduction treatment?	clinicians are weighing risks and benefits of preventive therapy	Modeling of series of patient cases presented to physician, then decisionmaking analyzed with respect to varying factors				factors
	Studies of how to communicate benefits and risks to patients	One-on-one interviews of how information presented vs. perceived				Influencing factors
		Focus groups				
		Randomized control trial of decision aid				
		Qualitative research			325-327	
		Different techniques of communication randomized and evaluated for effectiveness	328, 329	330		
	Studies focused on effective education & dissemination strategies for clinicians and patients of prevention strategies	Content evaluation of printed materials			331	Influencing factors
		Decision aid	332			

Abbreviations: CAM=complementary and alternative medicine; DES=diethylstilbestrol; SERM=selective estrogen receptor modulator.

[a] Results from clinical trials registries (e.g., clinical trials.gov) and grant agencies (e.g., NIH reporter).

[b] Numbers denote citations (see References).

[c] Blank cells denote no studies found.

[d] For Framework Questions A and B, results are from published literature since CER (January 2009 - July 14, 2010). For Framework Question C, results are from published literature from inception through July 14, 2010.

[e] Research focus of original CER.

Ongoing and completed studies still remain underpowered to assess the differential risk and effectiveness of preventive therapies based upon race or ethnicity. Similarly, while there are several studies of biomarkers, intervention studies do not appear to be collecting biomarker data which could advance our understanding of responses to treatment. In general, ongoing and completed studies focus on short-term intermediate outcomes such as mammographic density changes, hormone levels and precancerous lesions. Recognizing this limitation, some large interventions studies such as the STAR trial have added long-term followup. This is critical to understanding benefits and risks, to understand whether therapy prevents or delays the development of breast cancer, and to understand which population is most likely to accrue benefits rather than harms.

Conclusions

We developed a conceptual framework to illustrate national priorities for future research to reduce the risk of primary breast cancer in women (see Figure 4). According to stakeholders, the highest priority research areas for the prevention of breast cancer are:

(1) Population—understanding which populations are at highest risk of breast cancer, most likely to experience benefit, and least likely to be harmed by therapy (Question A).
(2) Intervention—broadening the scope on interventions (beyond medications) and comparative effectiveness research to include factors such as lifestyle, diet and exercise (Question B).
(3) Influencing factors—understanding influences such as health system factors, communication, education, dissemination of high quality information into clinical practice and to patients, and decisionmaking on initiation, continuation, and responses of preventive therapies (Question C).
(4) Integration of biological markers across the spectrum of research relating to breast cancer, understanding populations that are most likely to benefit from therapy, and monitoring response to therapy (integrated in Questions A, B, and C).

For two of these high-priority topics—intervention (Question B) and influencing factors (Question C)—an evidence review could help inform and guide research in these areas, and preliminary searches indicate there is likely to be a sufficient literature.

In general, we found that the traditional analytic framework used to structure reviews does not adequately address future research needs. However, with some adjustments to highlight major areas for research and the addition of biological and influencing factors, we were able to develop a conceptual framework to illustrate national priorities for future research.

Secondarily, we learned important lessons regarding stakeholder engagement. For various reasons, not all stakeholders will be able or willing to participate in a future research needs investigation. Having a list of multiple stakeholders for each stakeholder category is important to ensure sufficient numbers of responses in each category. Other important approaches to successful stakeholder recruitment and engagement include: making personal connections with stakeholders, stakeholders acting as advocates and recruiters for the project contacting potential stakeholders through multiple venues, and being persistent in outreach, referral requests, and followup.

Due to time constraints, we were unable to follow up with stakeholders to verify summary results. The results presented are the high-priority areas for research captured from responses in questionnaires similar to the Institute of Medicine CER priority list,[333] and they require further development to be actionable research protocols. While questionnaires are effective methods to equitably represent priorities, they are not an optimal format for the creative process of research study design and development. In-person discussions through meetings, focus groups, and panels where conversations and options could be explored and developed are more conducive to study design and protocol development. The information from this report, particularly the conceptual framework and Table 7 (Future Research Agenda for Breast Cancer Prevention) provides a solid foundation for such discussions to expand and detail the specific research needs to advance this field of study.

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Abbreviations

Acronym/Abbreviation	Definition
AHRQ	Agency for Healthcare Research and Quality
CER	Comparative Effectiveness Review(s)
DIM	Diindolylmethane
ER	Estrogen receptor
EPC	Evidence-based Practice Center
I PICO	Influencing factors, Population, Intervention, Comparator, Outcome
NIH	National Institutes of Health
PICO	Population, Intervention, Comparator, Outcome
SERM	Selective estrogen receptor modulator
SNP	Single nucleotide polymorphism
STAR	Study of Tamoxifen and Raloxifene
STEAR	Selective tissue estrogenic activity regulator

Appendix A. CER Section on Future Research Needs

Excerpted from:
Nelson H, Fu R, Humphrey L, Smith M, Griffin J, Nygren P. Comparative effectiveness of medications to reduce risk of primary breast cancer in women. Comparative Effectiveness Review No. 17. Rockville, MD: Agency for Healthcare Research and Quality; 2009.

Although several essential questions have been addressed by current studies, many more remain. More research is needed on tibolone's role in reducing risk for breast cancer and its harms. Although tibolone is not currently approved for use in the United States, it is widely used elsewhere and may be approved in the future. To avoid increasing risk for stroke, future trials of tibolone will need to focus on younger women. Future trials could confirm results of the LIFT trial and compare tibolone's efficacy in head-to-head trials with other medications. More research is needed to further evaluate findings from other studies of tibolone and determine their relevance to women using it for breast cancer risk reduction. For example, a recent multi-center trial of 3,148 breast cancer patients with vasomotor symptoms was stopped early because women using tibolone had higher breast cancer recurrence rates compared with placebo (HR 1.40;1.14,1.70). The Tibolone Histology of the Endometrium and Breast Endpoints Study (THEBES) comparing tibolone and continuous combined conjugated equine estrogen plus medroxyprogesterone acetate indicated that tibolone did not cause endometrial hyperplasia or carcinoma in postmenopausal women and had a more favorable vaginal bleeding profile.

Trials of other emerging medications to reduce breast cancer risk, such as aromatase inhibitors and retinoids, will be needed as these are developed. Well designed and powered head-to-head trials could contribute much needed information on outcomes, duration and timing of treatment, and identification of optimal candidates. Controlled trials of lifestyle modification interventions to reduce risk for breast cancer, such as weight loss and exercise, should also be explored. These interventions could be incorporated into comparative trials that also include medications.

While the efficacy of tamoxifen, raloxifene, and tibolone has been demonstrated for women in randomized controlled trials, it is not clear which women in clinical practice would optimally benefit from risk reducing medications. Inclusion criteria for three of the placebo-controlled tamoxifen trials (NSABP P-1, IBIS, Royal Marsden) and STAR included an assessment of risk for breast cancer, and only women reaching a specified threshold were enrolled. However, for the other raloxifene and tibolone trials, no breast cancer risk assessment was performed and women of all risk groups were included. Despite these differences, trials of all the medications demonstrated efficacy in reducing invasive breast cancer. Our further analysis by various population subgroups, such as by age, menopausal status, and others, also indicated no major differences, suggesting that everyone would benefit. Future research to determine the optimal candidates for these medications would help focus risk reducing efforts. Applying these findings to clinical selection criteria would improve identification of candidates in practice settings.

In addition to improving our understanding of which women are optimal candidates, research is needed to further evaluate clinical risk instruments to identify high-risk women who are most likely to benefit from risk reducing interventions. Current research indicates that prediction models that include breast density offer marginal improvement in diagnostic accuracy.

Addition of other factors such as diet, alcohol use, physical activity, smoking status, and height offer little improvement in diagnostic accuracy. The use of previously acknowledged risk factors, such as prior postmenopausal hormone therapy, needs to be reconsidered as new research indicating no associations with breast cancer are reported. New models need to build on research findings from older models, and research needs to expand beyond diagnostic accuracy studies. Models need to be evaluated in relevant clinical settings and populations to 48 determine their effectiveness in identifying high-risk women for clinical decisionmaking. Effective models should also be validated in various racial and ethnic populations, among non- English speakers, and across multiple age groups. This work should include research regarding optimal methods for communicating risks and benefits to women.

The results of trials indicate that adverse effects differ between medications and may drive decisions for risk reducing medications as much or more than benefits. Further research to more clearly identify characteristics of individuals experiencing specific adverse effects would guide physicians and patients to regimens that cause the least harm. Strategies could be tested that optimize benefits and minimize harms. For example, the effects of adding aspirin in conjunction with tamoxifen or raloxifene could improve the benefit/harm balance for women by reducing risks of thromboembolic adverse events, stroke, and possibly breast cancer itself. Further analysis of data from the MORE and RUTH trials could address this question because a large proportion of subjects were using aspirin in these trials. Future trials could evaluate the benefits and harms of using tamoxifen or raloxifene with an anticoagulant such as warfarin, heparin, or low molecular weight heparin.

Primary prevention trials need to be continually evaluated for long-term and unanticipated outcomes. For example, tamoxifen users in the NSABP P-1 trial who developed estrogen receptor negative breast cancer had shorter times to diagnosis and were more likely to be detected by routine mammograms than placebo users who developed estrogen receptor negative breast cancer. Additional research to assess the use of raloxifene since its recent FDA approval for reducing risk for breast cancer will also be useful.

Evaluating the timing of medication use may also lead to effective clinical strategies. Results of current trials suggest that breast cancer risk reduction persists after treatment while some harms diminish. It is important to understand these changes over time. Use of medication for risk reduction at younger ages (45 to 55 years) could provide better long-term benefit and short-term harm for individuals at lower risk of thromboembolism or stroke than use at older ages (>60 years). Further analysis of data from currently available trials could compare risk/benefit profiles for women of various ages and risk groups. Additional analysis could also indicate optimal treatment durations. Shortening treatment duration would reduce harms, but also could compromise efficacy.

Despite prior recommendations to identify women at high-risk for breast cancer and offer medications to reduce their risks, and the availability of two SERMs for this purpose, use is believed to be low in the United States. This contrasts sharply with the use of statin medications to reduce cholesterol levels and cardiovascular disease. Understanding the differences and similarities in these approaches to risk reduction would be useful for clinicians. This requires research regarding the attitudes of physicians toward recommending 5 years of medication therapy to reduce risk as well as attitudes of patients regarding receptivity to this recommendation and adherence over time. Research on the physician and patient decision making process could identify factors important for selecting use of medications to reduce breast cancer risk beyond empirical risk.

Appendix B. Future Research Agenda Questionnaire I: Consumer/Policymaker

Future Research Agenda: Reducing the Risk of Breast Cancer

The purpose of this project is to develop and prioritize a future research agenda to close evidence gaps identified from the Evidence-based Practice Center systematic review entitled, "Medications to Reduce Risk of Primary Breast Cancer in Women."*

*Nelson HD, Fu R, Humphrey L, Smith ME, Griffin JC, Nygren P. Comparative Effectiveness of Medications To Reduce Risk of Primary Breast Cancer in Women. Comparative Effectiveness Review No. 17. (Prepared by Oregon Evidence-based Practice Center under Contract No. 290-2007-10057-1.) Rockville, MD: Agency for Healthcare Research and Quality. September 2009.

Page 1

Future Research Agenda: Reducing the Risk of Breast Cancer

Section I: Introduction

* 1. What perspective(s) are you representing (please check all that apply)?

- ☐ Consumer Advocate
- ☐ Clinician
- ☐ Policymaker
- ☐ Researcher
- ☐ Funder of Research

* 2. Please fill out the information below.

Name:	
Organization:	
Address:	
Address 2:	
City/Town:	
State:	
ZIP:	
Country:	
Email Address:	
Phone Number:	

3. What would you/your organization most like to know about preventing breast cancer?

Page 2

Future Research Agenda: Reducing the Risk of Breast Cancer

4. What do you believe are the most important research questions that need to be addressed in preventing breast cancer? Please list at least three.

Page 3

Future Research Agenda: Reducing the Risk of Breast Cancer

Section II: Populations

The following items reflect the research gaps identified from breast cancer researchers and the evidence report. **Please prioritize each item in the questions/statements below**. You may want to consider the following criteria in your prioritization (burden of disease, high public interest, vulnerable populations, utilization of existing resources, potential impact, etc). **Please use narrative as much as possible in the space below to help us understand the types of research that you believe are most important**.

1. Studies of how age affects the benefits and/or harms of interventions to reduce the risk of breast cancer.

- ◯ High
- ◯ Medium
- ◯ Low

Please provide prioritization (thoughts on why this is/isn't important) AND research comments (details of what kinds of research you suggest).

2. Studies of how race and/or ethnicity affect the interventions to reduce the risk of breast cancer.

- ◯ High
- ◯ Medium
- ◯ Low

Please provide prioritization (thoughts on why this is/isn't important) AND research comments (details of what kinds of research you suggest).

Future Research Agenda: Reducing the Risk of Breast Cancer

3. Studies to understand which populations of women would optimally benefit from medications to reduce their risk of breast cancer.

- ◯ High
- ◯ Medium
- ◯ Low

Please provide prioritization (thoughts on why this is/isn't important) AND research comments (details of what kinds of research you suggest).

Future Research Agenda: Reducing the Risk of Breast Cancer

Section III: Intervention Studies/Comparisons

The following items reflect the research gaps identified from breast cancer researchers and the evidence report. **Please prioritize each item in the questions/statements below**. You may want to consider the following criteria in your prioritization (burden of disease, high public interest, vulnerable populations, utilization of existing resources, potential impact, etc). **Please use narrative as much as possible in the space below to help us understand the types of research that you believe are most important**.

1. Prescription medications: Tamoxifen, Raloxifene

- ◯ High
- ◯ Medium
- ◯ Low

Please provide prioritization (thoughts on why this is/isn't important) AND research comments (details of what kinds of research and comparison groups you suggest).

2. Prescription medication: Tibolone (this medication is not currently approved in the US)

- ◯ High
- ◯ Medium
- ◯ Low

Please provide prioritization (thoughts on why this is/isn't important) AND research comments (details of what kinds of research and comparison groups you suggest).

Future Research Agenda: Reducing the Risk of Breast Cancer

3. Vitamin A derived medications (e.g. retinols)

- ◯ High
- ◯ Medium
- ◯ Low

Please provide prioritization (thoughts on why this is/isn't important) AND research comments (details of what kinds of research and comparison groups you suggest).

4. Drugs based on a person's genetics

- ◯ High
- ◯ Medium
- ◯ Low

Please provide prioritization (thoughts on why this is/isn't important) AND research comments (details of what kinds of research and comparison groups you suggest).

Future Research Agenda: Reducing the Risk of Breast Cancer

5. Drugs that target specific molecular cancer pathways

- ◯ High
- ◯ Medium
- ◯ Low

Please provide prioritization (thoughts on why this is/isn't important) AND research comments (details of what kinds of research and comparison groups you suggest).

6. Complementary and alternative therapies

- ◯ High
- ◯ Medium
- ◯ Low

Please provide prioritization (thoughts on why this is/isn't important) AND research comments (details of what kinds of research and comparison groups you suggest).

7. Please specify complementary and alternative therapies:

Future Research Agenda: Reducing the Risk of Breast Cancer

8. Weight loss as therapy

- ◯ High
- ◯ Medium
- ◯ Low

Please provide prioritization (thoughts on why this is/isn't important) AND research comments (details of what kinds of research and comparison groups you suggest).

9. Exercise as therapy

- ◯ High
- ◯ Medium
- ◯ Low

Please provide prioritization (thoughts on why this is/isn't important) AND research comments (details of what kinds of research and comparison groups you suggest).

Future Research Agenda: Reducing the Risk of Breast Cancer

10. Diet as therapy

- ◯ High
- ◯ Medium
- ◯ Low

Please provide prioritization (thoughts on why this is/isn't important) AND research comments (details of what kinds of research and comparison groups you suggest).

11. Please specify diet therapies:

12. Combination therapies (e.g., aspirin + prescription medication)

- ◯ High
- ◯ Medium
- ◯ Low

Please provide prioritization (thoughts on why this is/isn't important) AND research comments (details of what kinds of research and comparison groups you suggest).

Future Research Agenda: Reducing the Risk of Breast Cancer

13. Other lifestyle modifications

- ◯ High
- ◯ Medium
- ◯ Low

Please provide prioritization (thoughts on why this is/isn't important) AND research comments (details of what kinds of research and comparison groups you suggest).

14. Please specify lifestyle modifications:

15. Which of the medications and/or therapies would you like to see compared directly with one another (please list all)?

Future Research Agenda: Reducing the Risk of Breast Cancer

16. Are there any emerging areas of breast cancer risk reduction or prevention not included in this questionnaire (please list)?

Page 12

Future Research Agenda: Reducing the Risk of Breast Cancer

Section IV: Outcomes

The following items reflect the research gaps identified from breast cancer researchers and the evidence report. **Please prioritize each item in the questions/statements below**. You may want to consider the following criteria in your prioritization (burden of disease, high public interest, vulnerable populations, utilization of existing resources, potential impact, etc). **Please use narrative as much as possible in the space below to help us understand the types of research that you believe are most important**.

1. Reporting all harmful effects of medications prescribed to reduce breast cancer risk.

- ◯ High
- ◯ Medium
- ◯ Low

Please provide prioritization (thoughts on why this is/isn't important) AND research comments (details of what kinds of research you suggest).

2. Evaluation of how long the beneficial effects of therapy last.

- ◯ High
- ◯ Medium
- ◯ Low

Please provide prioritization (thoughts on why this is/isn't important) AND research comments (details of what kinds of research you suggest).

Future Research Agenda: Reducing the Risk of Breast Cancer

3. What other outcomes are important to study?

Future Research Agenda: Reducing the Risk of Breast Cancer

Section V: Additional Items

The following items reflect the research gaps identified from breast cancer researchers and the evidence report. **Please prioritize each item in the questions/statements below**. You may want to consider the following criteria in your prioritization (burden of disease, high public interest, vulnerable populations, utilization of existing resources, potential impact, etc). **Please use narrative as much as possible in the space below to help us understand the types of research that you believe are most important**.

1. Studies of doctors' attitudes toward prescribing medications to reduce breast cancer risk.

- ◯ High
- ◯ Medium
- ◯ Low

Please provide prioritization (thoughts on why this is/isn't important) AND research comments (details of what kinds of research you suggest).

2. Studies of how doctors are weighing the risks and benefits of medications to reduce breast cancer risk.

- ◯ High
- ◯ Medium
- ◯ Low

Please provide prioritization (thoughts on why this is/isn't important) AND research comments (details of what kinds of research you suggest).

Future Research Agenda: Reducing the Risk of Breast Cancer

3. Studies of doctors' attitudes toward recommending non-medication-related interventions to reduce breast cancer risk.

- ◯ High
- ◯ Medium
- ◯ Low

Please provide prioritization (thoughts on why this is/isn't important) AND research comments (details of what kinds of research you suggest).

4. Studies of patients' attitudes toward taking medications to reduce breast cancer risk.

- ◯ High
- ◯ Medium
- ◯ Low

Please provide prioritization (thoughts on why this is/isn't important) AND research comments (details of what kinds of research you suggest).

Future Research Agenda: Reducing the Risk of Breast Cancer

5. Studies of what factors influence a woman's decision-making about medications to reduce breast cancer risk.

- ◯ High
- ◯ Medium
- ◯ Low

Please provide prioritization (thoughts on why this is/isn't important) AND research comments (details of what kinds of research you suggest).

6. Studies of how to communicate benefits and risk to patients.

- ◯ High
- ◯ Medium
- ◯ Low

Please provide prioritization (thoughts on why this is/isn't important) AND research comments (details of what kinds of research you suggest).

Future Research Agenda: Reducing the Risk of Breast Cancer

7. Studies of how doctors and patients are working together to decide if medications to reduce risk of breast cancer should be prescribed.

- ◯ High
- ◯ Medium
- ◯ Low

Please provide prioritization (thoughts on why this is/isn't important) AND research comments (details of what kinds of research and you suggest).

8. Research on predicting risk of breast cancer.

- ◯ High
- ◯ Medium
- ◯ Low

Please provide prioritization (thoughts on why this is/isn't important) AND research comments (details of what kinds of research and you suggest).

Future Research Agenda: Reducing the Risk of Breast Cancer

9. If a current breast cancer risk prediction model were available, do you think patients would use it to help make decisions about therapy? Why or why not?

- ◯ Yes
- ◯ No

Please explain:

10. Please describe any research you are involved in or know of that is related to this project.

11. Reflecting on your responses, what do you believe are the top three research priorities?

Future Research Agenda: Reducing the Risk of Breast Cancer

12. Additional suggestions/comments?

Page 20

Future Research Agenda: Reducing the Risk of Breast Cancer

Section VI: Future Research Needs Communication

This pilot project is designed to involve stakeholders in determining and prioritizing future research needs based on the findings of a systematic evidence review to produce a future research document.

1. What information would you want this document to include?

2. How would you use this document?

3. How would you like to receive this information (please check all that apply)?

- ☐ Chapter in an evidence report
- ☐ Magazine article
- ☐ Standalone document
- ☐ Webinar
- ☐ Podcast
- ☐ Other (please specify)

Future Research Agenda: Reducing the Risk of Breast Cancer

Thank you for your participation. You have completed the survey.

Appendix C. Future Research Agenda Questionnaire II: Clinician/Research Funder/Researcher

Future Research Agenda: Reducing the Risk of Breast Cancer

The purpose of this project is to develop and prioritize a future research agenda to close evidence gaps identified from the Evidence-based Practice Center systematic review entitled, "Medications to Reduce Risk of Primary Breast Cancer in Women."*

*Nelson HD, Fu R, Humphrey L, Smith ME, Griffin JC, Nygren P. Comparative Effectiveness of Medications To Reduce Risk of Primary Breast Cancer in Women. Comparative Effectiveness Review No. 17. (Prepared by Oregon Evidence-based Practice Center under Contract No. 290-2007-10057-1.) Rockville, MD: Agency for Healthcare Research and Quality. September 2009.

Page 1

Future Research Agenda: Reducing the Risk of Breast Cancer

Section I: Introduction

* 1. What perspective(s) are you representing (please check all that apply)?

- [ ] Consumer Advocate
- [ ] Clinician
- [ ] Policymaker
- [ ] Researcher
- [ ] Funder of Research

* 2. Please fill out the information below:

Name:
Company:
Address:
Address 2:
City/Town:
State:
ZIP:
Email Address:
Phone Number:

3. Thinking of your area of expertise, what do you believe are the most important research questions in preventing breast cancer? Please list at least three.

Future Research Agenda: Reducing the Risk of Breast Cancer

Section II: Populations of Interest

The following items reflect the research gaps identified from breast cancer researchers and the evidence report. **Please prioritize each item in the questions/statements below**. You may want to consider the following criteria in your prioritization (burden of disease, high public interest, vulnerable populations, utilization of existing resources, potential impact, etc). **Please use narrative as much as possible in the space below to help us understand the types of research that you believe are most important**.

1. Studies to understand the differences of benefits and/or adverse effects by age.

- ◯ High
- ◯ Medium
- ◯ Low

Please provide prioritization (thoughts on why this is/isn't important) AND research comments (details of what kinds of research you suggest).

2. Studies to understand the differences of benefits and/or adverse effects by race and/or ethnicity.

- ◯ High
- ◯ Medium
- ◯ Low

Please provide prioritization (thoughts on why this is/isn't important) AND research comments (details of what kinds of research you suggest).

Future Research Agenda: Reducing the Risk of Breast Cancer

3. Studies to understand which populations of women would optimally benefit from medications to reduce their risk of breast cancer. Please include recommendations (i.e., study types, populations).

- ◯ High
- ◯ Medium
- ◯ Low

Please provide prioritization (thoughts on why this is/isn't important) AND research comments (details of what kinds of research you suggest).

Future Research Agenda: Reducing the Risk of Breast Cancer

Section III: Intervention Studies/Comparators

The following items reflect the research gaps identified from breast cancer researchers and the evidence report. **Please prioritize each item in the questions/statements below**. You may want to consider the following criteria in your prioritization (burden of disease, high public interest, vulnerable populations, utilization of existing resources, potential impact, etc). **Please use narrative as much as possible in the space below to help us understand the types of research that you believe are most important**.

1. Tibolone (STEAR: Selective Tissue Estrogenic Activity Regulator)

- ◯ High
- ◯ Medium
- ◯ Low

Please provide prioritization (thoughts on why this is/isn't important) AND research comments (details of what kinds of research and comparators you suggest).

2. Aromatase inhibitors

- ◯ High
- ◯ Medium
- ◯ Low

Please provide prioritization (thoughts on why this is/isn't important) AND research comments (details of what kinds of research and comparators you suggest).

Future Research Agenda: Reducing the Risk of Breast Cancer

3. Tamoxifen citrate and raloxifene (SERMs: Selective Estrogen Receptor Modulators)

- ◯ High
- ◯ Medium
- ◯ Low

Please provide prioritization (thoughts on why this is/isn't important) AND research comments (details of what kinds of research and comparators you suggest).

4. Complementary and alternative therapies

- ◯ High
- ◯ Medium
- ◯ Low

Please provide prioritization (thoughts on why this is/isn't important) AND research comments (details of what kinds of research and comparators you suggest).

5. Please specify complementary and alternative therapies you would recommend

Future Research Agenda: Reducing the Risk of Breast Cancer

6. Gene-based drugs

- ◯ High
- ◯ Medium
- ◯ Low

Please provide prioritization (thoughts on why this is/isn't important) AND research comments (details of what kinds of research and comparators you suggest).

7. Molecularly targeted agents

- ◯ High
- ◯ Medium
- ◯ Low

Please provide prioritization (thoughts on why this is/isn't important) AND research comments (details of what kinds of research and comparators you suggest).

Future Research Agenda: Reducing the Risk of Breast Cancer

8. Weight loss as therapy

- ◯ High
- ◯ Medium
- ◯ Low

Please provide prioritization (thoughts on why this is/isn't important) AND research comments (details of what kinds of research and comparators you suggest).

9. Exercise as therapy

- ◯ High
- ◯ Medium
- ◯ Low

Please provide prioritization (thoughts on why this is/isn't important) AND research comments (details of what kinds of research and comparators you suggest).

Future Research Agenda: Reducing the Risk of Breast Cancer

10. Diet as therapy

- ◯ High
- ◯ Medium
- ◯ Low

Please provide prioritization (thoughts on why this is/isn't important) AND research comments (details of what kinds of research and comparators you suggest).

11. Please specify diet therapies

12. Combination therapies (e.g. aspirin + tamoxifen)

- ◯ High
- ◯ Medium
- ◯ Low

Please provide prioritization (thoughts on why this is/isn't important) AND research comments (details of what kinds of research and comparators you suggest).

Future Research Agenda: Reducing the Risk of Breast Cancer

13. Please specify combination therapies you would recommend

14. Other lifestyle modifications

- ◯ High
- ◯ Medium
- ◯ Low

Please provide prioritization (thoughts on why this is/isn't important) AND research comments (details of what kinds of research and comparators you suggest).

15. Please specify lifestyle modifications

16. Which of the medications and/or therapies would you like to see compared in a head-to-head trial (please list all)?

Future Research Agenda: Reducing the Risk of Breast Cancer

17. Are there any areas of research to reduce the risk of breast cancer not included in this questionnaire (please describe)?

Future Research Agenda: Reducing the Risk of Breast Cancer

Section IV: Outcomes

The following items reflect the research gaps identified from breast cancer researchers and the evidence report. **Please prioritize each item in the questions/statements below**. You may want to consider the following criteria in your prioritization (burden of disease, high public interest, vulnerable populations, utilization of existing resources, potential impact, etc). **Please use narrative as much as possible in the space below to help us understand the types of research that you believe are most important**.

1. Ascertainment of adverse effects of medications prescribed to reduce breast cancer risk (please discuss which are most important and how you recommend they be studied).

- ◯ High
- ◯ Medium
- ◯ Low

Please provide prioritization (thoughts on why this is/isn't important) AND research comments (details of what kinds of research you suggest).

2. Evaluation of the persistent effect of breast cancer risk reduction treatment.

- ◯ High
- ◯ Medium
- ◯ Low

Please provide prioritization (thoughts on why this is/isn't important) AND research comments (details of what kinds of research you suggest).

Future Research Agenda: Reducing the Risk of Breast Cancer

3. What other outcomes are important to study?

Future Research Agenda: Reducing the Risk of Breast Cancer

Section V: Additional Items

The following items reflect the research gaps identified from breast cancer researchers and the evidence report. **Please prioritize each item in the questions/statements below**. You may want to consider the following criteria in your prioritization (burden of disease, high public interest, vulnerable populations, utilization of existing resources, potential impact, etc). **Please use narrative as much as possible in the space below to help us understand the types of research that you believe are most important**.

1. Studies of clinicians' attitudes toward prescribing medications to reduce breast cancer risk.

- ◯ High
- ◯ Medium
- ◯ Low

Please provide prioritization (thoughts on why this is/isn't important) AND research comments (details of what kinds of research you suggest).

2. Studies of how clinicians are weighing the risks and benefits of prescribing medications to reduce breast cancer risk.

- ◯ High
- ◯ Medium
- ◯ Low

Please provide prioritization (thoughts on why this is/isn't important) AND research comments (details of what kinds of research you suggest).

Future Research Agenda: Reducing the Risk of Breast Cancer

3. Studies of clinicians' attitudes towards prescribing non-medication-related interventions to reduce breast cancer risk.

- ◯ High
- ◯ Medium
- ◯ Low

Please provide prioritization (thoughts on why this is/isn't important) AND research comments (details of what kinds of research you suggest).

4. Studies of patients' attitudes toward prescribing medications to reduce breast cancer risk.

- ◯ High
- ◯ Medium
- ◯ Low

Please provide prioritization (thoughts on why this is/isn't important) AND research comments (details of what kinds of research you suggest).

Future Research Agenda: Reducing the Risk of Breast Cancer

5. Studies of how to communicate benefits and risks to patients.

- ◯ High
- ◯ Medium
- ◯ Low

Please provide prioritization (thoughts on why this is/isn't important) AND research comments (details of what kinds of research you suggest).

6. Studies of how clinicians and patients are working together to decide if medications to reduce risk of breast cancer should be prescribed.

- ◯ High
- ◯ Medium
- ◯ Low

Please provide prioritization (thoughts on why this is/isn't important) AND research comments (details of what kinds of research and you suggest).

Future Research Agenda: Reducing the Risk of Breast Cancer

7. Research on risk prediction models (please specify and recommend areas of improvement).

- ◯ High
- ◯ Medium
- ◯ Low

Please provide prioritization (thoughts on why this is/isn't important) AND research comments (details of what kinds of research and you suggest).

8. If a current breast cancer risk prediction model were available, would you routinely use it in your practice?

- ◯ Yes
- ◯ No

Why or why not?

9. Please describe research you are involved in and/or are aware of related to this project.

Future Research Agenda: Reducing the Risk of Breast Cancer

10. Reflecting on your responses, what do you believe are the top three research priorities?

11. Additional suggestions/comments?

Future Research Agenda: Reducing the Risk of Breast Cancer

Section VI: Future Research Needs Dissemination

This pilot project is designed to involve stakeholders in determining and prioritizing future research needs based on the findings of a systematic evidence review to create a future research document.

1. What information would you want this document to include?

2. How would you use this document?

3. How would you like to receive such information (please check all that apply)?

- ☐ Chapter in an evidence report
- ☐ Journal article
- ☐ Standalone document
- ☐ Webinar
- ☐ Podcast
- ☐ Other (please specify)

Future Research Agenda: Reducing the Risk of Breast Cancer

Thank you for your participation. You have now completed the survey.

Appendix D. Search Strategy for Ongoing Studies

Clinical Trials, Searched 7/14/2010

ClinicalTrials.gov
(breast cancer risk [DISEASE] AND (tamoxifen OR raloxifene OR tibolone) [TREATMENT]) OR (breast cancer chemoprevention [ALL-FIELDS]) (81 results)
searched 7/14/2010
breast cancer prevention [ALL-FIELDS] (316 results)

Current Controlled Trials
breast cancer chemoprevention (one result)
tamoxifen (35 results only 2 related to breast cancer risk reduction)
ralozifene (no unique results)
tibolone (no unique results)
searched 7/14/2010
breast cancer prevention (one unique result)

Clinical Study Results
[no results for tamoxifen, raloxifene or tibolone]
searched 7/14/2010
breast cancer prevention [no results]

WHO Clinical Trials
(tamoxifen OR raloxifen OR tibolone) AND breast cancer risk (319 results, only 7 unique items related to breast cancer risk reduction were added)
searched 7/14/2010
breast cancer prevention (26 results, 2 unique items)

Citation Search to find articles that have cited the review—Searched 7/14/2010

Scopus—3 articles found
Google Scholar—5 articles found (2 unique)
Annals of Internal Medicine Website—2 articles found (1 unique)

Reproduction of original search—Searched from January 2009 to current

MEDLINE 1996 to June Week 4 Searched 7/7/2010

#	Searches	Results
1	(ovar$ adj5 (cancer$ or tumor$ or malignan$ or carcino$ or neoplas$)).mp.	33906
2	exp tamoxifen/	9988
3	exp raloxifene/	1818

4	2 or 3	9988
5	1 and 4	270
6	limit 5 to humans	245
7	limit 6 to yr="2009 -Current"	21

#	Searches	Results
1	exp tamoxifen/	9988
2	exp raloxifene/	1818
3	1 or 2	9988
4	exp tamoxifen/ae, po, to	1821
5	exp raloxifene/ae, po, to	230
6	4 or 5	1821
7	exp genital diseases, female/ci, ep, et	30430
8	exp genital diseases, female/	130131
9	6 and 8	630
10	3 and 7	645
11	9 or 10	724
12	3 and 8	1044
13	12 not 11	320
14	limit 13 to yr="2009 -Current"	23

#	Searches	Results
1	tamoxifen/ae, po, to	1635
2	exp raloxifene/ae, po, to	230
3	1 or 2	1801
4	exp uterine diseases/	49051
5	exp uterus/	29657
6	4 or 5	70631
7	3 and 6	610
8	exp hysterectomy/	8836
9	3 and 8	37
10	7 or 9	616

11	limit 10 to (english language and humans)	528
12	limit 11 to yr="2009 -Current"	15

#	Searches	Results
1	selective estrogen receptor modulators/ or raloxifene/ or tamoxifen.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	13705
2	exp breast neoplasms/pc	6517
3	1 and 2	1021
4	primary prevention/	8310
5	(primar$ adj2 prevent$).mp.	14372
6	exp breast neoplasms/	101219
7	1 and 4 and 6	34
8	chemoprevention/	2678
9	chemoprevent$.mp.	11095
10	1 and 6 and 9	411
11	1 and 5 and 6	77
12	10 or 11	457
13	(prevent$ adj3 (breast$ adj2 (neoplas$ or tumor$ or cancer$ or malignan$))).mp.	1668
14	1 and 13	675
15	6 and 14	594
16	12 or 15	855
17	limit 16 to humans	847
18	limit 17 to english language	795
19	limit 17 to abstracts	701
20	18 or 19	831
21	limit 20 to yr="2009 -Current"	36

#	Searches	Results
1	tibolone.mp.	787
2	exp breast neoplasms/	101219

3	exp breast/	12793
4	2 or 3	106836
5	1 and 4	150
6	1 not 5	637
7	limit 6 to yr="2009 -Current"	44

#	Searches	Results
1	exp tamoxifen/ae, po, ct, to	1827
2	exp raloxifene/ae, ct, to	231
3	selective estrogen receptor modulators/ae, co, to, po	376
4	1 or 2 or 3	1948
5	exp cardiovascular diseases/mo, ci, co, ep, et	334514
6	exp stroke/mo, co, ci, ep, et	25812
7	exp cardiovascular system/pp, de	97774
8	5 or 6 or 7	414246
9	4 and 8	177
10	exp cardiovascular system/	355700
11	exp cardiovascular diseases/	718165
12	10 or 11	895463
13	exp tamoxifen/	9988
14	exp raloxifene/	1818
15	selective estrogen receptor modulators/	2594
16	13 or 14 or 15	10910
17	4 and 12	197
18	8 and 16	560
19	17 or 18	580
20	limit 9 to humans	176
21	limit 19 to humans	432
22	21 not 20	256
23	12 and 16	846
24	limit 23 to humans	618
25	24 not 21	186

26	(2009$ or 2010$).ed.	1054711
27	12 and 16	846
28	26 and 27	71

#	Searches	Results
1	exp breast neoplasms/	101219
2	exp risk/	455470
3	1 and 2	13514
4	exp risk assessment/	108692
5	1 and 4	3271
6	limit 5 to humans	3262
7	exp breast neoplasms/ep, et	10531
8	4 and 7	1164
9	exp breast neoplasms/pc, eh	7858
10	exp breast neoplasms/ge	18582
11	4 and 9	669
12	4 and 10	840
13	exp disease susceptibility/	65653
14	7 and 13	893
15	9 and 13	564
16	8 or 11 or 14 or 15	2664
17	limit 16 to english language	2517
18	(model$ or valid$).mp.	1332255
19	17 and 18	711
20	seer.mp.	2733
21	17 and 20	47
22	19 or 21	739
23	limit 22 to yr="2009 -Current"	107

#	Searches	Results
1	tibolone.mp.	787
2	exp breast neoplasms/	101219

3	exp breast/	12793
4	2 or 3	106836
5	1 and 4	150
6	limit 5 to yr="2009 -Current"	10

#	Searches	Results
1	exp tamoxifen/	9988
2	exp raloxifene/	1818
3	1 or 2	9988
4	exp tamoxifen/ae, po, to	1821
5	exp raloxifene/ae, po, to	230
6	4 or 5	1821
7	exp genital diseases, female/ci, ep, et	30430
8	exp genital diseases, female/	130131
9	6 and 8	630
10	3 and 7	645
11	9 or 10	724
12	3 and 8	1044
13	12 not 11	320
14	limit 13 to yr="2009 -Current"	23

EBM Reviews—Cochrane Central Register of Controlled Trials 2nd Quarter 2010 Searched 7/7/2010

#	Searches	Results
1	tibolone.mp.	368
2	limit 1 to yr="2009 -Current"	12

#	Searches	Results
1	((tamoxifen or raloxifene) adj5 (endometri$ or uterine or uterus or hysterec$)).mp.	198
2	limit 1 to yr="2009 -Current"	6

#	Searches	Results
1	tamoxifen.mp.	2634
2	raloxifene.mp.	460
3	placebo$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]	118412
4	1 and 2	31
5	1 and 3	337
6	2 and 3	252
7	4 or 5 or 6	592
8	((breast$ or mammar$) adj5 (cancer$ or tumor$ or carcino$ or adenocarcin$ or neoplas$ or malignan$)).mp.	11674
9	7 and 8	302
10	limit 9 to yr="2009 -Current"	12

EBM Reviews—Cochrane Database of Systematic Reviews 2005 to May 2010 Searched 7/7/2010

#	Searches	Results
1	tamoxifen.mp.	54
2	raloxifene.mp.	9
3	placebo@.mp.	3999
4	1 and 2	3
5	1 and 3	37
6	2 and 3	9
7	4 or 5 or 6	43
8	((breast$ or mammar$) adj5 (cancer$ or tumor$ or carcino$ or adenocarcin$ or neoplas$ or malignan$)).mp.	239
9	7 and 8	19
10	limit 9 to last 2 years	11

#	Searches	Results
1	tibolone.mp.	11
2	limit 1 to last 2 years	6

#	Searches	Results
1	((tamoxifen or raloxifene) adj5 (endometri$ or uterine or uterus or hysterect$)).mp.	7
2	limit 1 to last 2 years	4

EBM Reviews—Database of Abstracts of Reviews of Effects 2nd Quarter 2010 Searched 7/7/2010

#	Searches	Results
1	((tamoxifen or raloxifene) adj5 (endometri$ or uterine or uterus or hysterect$)).mp.	5
2	limit 1 to last 2 years	5

#	Searches	Results
1	tamoxifen.mp.	52
2	raloxifene.mp.	15
3	placebo$.mp.	2557
4	1 and 2	7
5	1 and 3	16
6	2 and 3	9
7	4 or 5 or 6	22
8	((breast$ or mammar$) adj5 (cancer$ or tumor$ or carcino$ or adenocarcin$ or neoplas$ or malignan$)).mp.	376
9	7 and 8	16
10	limit 9 to last 2 years	16

#	Searches	Results
1	tibolone.mp.	6
2	limit 1 to last 2 years	6

Grants—searched 7/14/2010

NIH RePORTER
breast cancer chemoprevention (136 results)
breast cancer risk reduction (112 results)

HSRProj
breast cancer chemoprevention (8 results)

AHRQ GOLD
breast cancer (no unique results)

The following Web sites of funding agencies were searched directly on 7/14/2010 & 7/15/2010

Alaska Run for Women
http://www.akrfw.org/grants_10.htm

American Association for Cancer Research
http://www.aacr.org/home/scientists/research-funding--fellowships.aspx

American Cancer Society
http://www.cancer.org/Research/index

American Society of Clinical Oncology
http://www.asco.org/ASCOv2/Research+Resources/Grants+%26+Awards

ASCO Cancer Foundation
http://www.ascocancerfoundation.org/TACF/Grants/Grant+Recipients/Young+Investigator+Award

Avon Foundation
http://www.avonfoundation.org/funding-and-grants/avon-foundation-funding-history.html

Baldwin Breast Cancer Research Fund, Inc., Carol M.
http://www.findacure.org/grants_awarded.html

Blue Cross and Blue Shield of North Carolina Foundation
http://www.bcbsncfoundation.org/grants/

Breast Cancer Research Foundation
http://www.bcrfcure.org/

DTIC Online—Public Scientific & Technical Information
http://www.dtic.mil/

Flight Attendant Medical Research Institute, Inc.
http://www.famri.org/researchers/awards_history.html

Foundation, Mary Kay
http://www.mkacf.org/Pages/GrantRecipients_2009.aspx

HealthCare Foundation for Orange County, The
http://www.hfoc.org/index.jsp

Howard Hughes Medical Institute
http://www.hhmi.org/research/search.html

Komen Foundation
http://ww5.komen.org/researchgrantsawarded.aspx?id=16252

Dr. Susan Love Research Foundation
http://www.dslrf.org/breastcancer/content.asp?L2=1&L3=2&SID=125

National Cancer Institute
http://www.cancer.gov/clinicaltrials/search

Noreen Fraser Foundation
http://www.noreenfraserfoundation.org/about/grants/

Premera CARES Program
https://www.premera.com/stellent/groups/public/documents/xcpproject/abt_giving_wa.asp

Rosenberg Foundation, Inc., Henry and Ruth Blaustein, The
http://www.blaufund.org/foundations/henryruthgrant_2009.html#3

Wawa, Inc. Corporate Giving Program
http://www.wawa.com/wawaweb/Charity.aspx

Wellcome Trust
http://www.wellcome.ac.uk/Funding/Grants-awarded/index.htm

Women's Funding Alliance
http://www.wfalliance.org/impact/recentgrants.php