



Complete Summary

GUIDELINE TITLE

Chemoprevention of breast cancer: recommendations and rationale.

BIBLIOGRAPHIC SOURCE(S)

U.S. Preventive Services Task Force. Chemoprevention of breast cancer: recommendations and rationale. Ann Intern Med 2002 Jul; 137(1):56-8. [13 references]

COMPLETE SUMMARY CONTENT

SCOPE
METHODOLOGY - including Rating Scheme and Cost Analysis
RECOMMENDATIONS
EVIDENCE SUPPORTING THE RECOMMENDATIONS
BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS
QUALIFYING STATEMENTS
IMPLEMENTATION OF THE GUIDELINE
INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT
CATEGORIES
IDENTIFYING INFORMATION AND AVAILABILITY

SCOPE

DISEASE/CONDITION(S)

Breast cancer

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Prevention

CLINICAL SPECIALTY

Family Practice
Internal Medicine
Obstetrics and Gynecology
Oncology
Preventive Medicine

INTENDED USERS

Advanced Practice Nurses
Allied Health Personnel
Health Care Providers
Nurses
Physician Assistants
Physicians

GUIDELINE OBJECTIVE(S)

To summarize the current U.S. Preventive Services Task Force (USPSTF) recommendations and supporting scientific evidence on chemoprevention of breast cancer

TARGET POPULATION

Women with no previous history of breast cancer

INTERVENTIONS AND PRACTICES CONSIDERED

1. Tamoxifen
2. Raloxifene

Note: Currently, only tamoxifen is approved by the U.S. Food and Drug Administration (FDA) for the specific indication of breast cancer chemoprevention. Although there are biological reasons to suspect that raloxifene should have similar benefits, trial data currently are limited to one study in which the primary outcome was fracture prevention. Additional trials to further evaluate this drug's efficacy for breast cancer chemoprevention are under way, including a trial comparing efficacy and safety of raloxifene and tamoxifen. Raloxifene is approved by the U.S. Food and Drug Administration for preventing and treating osteoporosis.

MAJOR OUTCOMES CONSIDERED

- Mortality from breast cancer
- Incidence of breast cancer
- Adverse effects of chemoprevention
- Beneficial effects of chemoprevention

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The Evidence-based Practice Center (EPC) staff searched for English-language articles included in the MEDLINE database from 1966 to December 2001, the Cochrane Collaboration Library, and practice guidelines to identify studies evaluating chemoprevention to prevent breast cancer among women who have never had breast cancer.

Search Strategy

The search strategy involved two phases. The first phase of searching used broad search terms and review criteria. The following MeSH terms were used: "breast neoplasms;" "Tamoxifen;" "estrogen antagonists;" "raloxifene;" "keoxifene;" and "selective estrogen receptor modulator." The searches were limited to humans and female, and the following review criteria were included: "controlled clinical trial;" "randomized controlled trials;" "random allocation;" "single-blind method;" and "double-blind method." The searches yielded 700 articles (635 from MEDLINE and 65 from reference lists of reviews, the Cochrane Collaboration Library, and practice guidelines.) The aim of this phase was to maximize the probability that all articles that could be useful in any way were found.

The second phase used more stringent review criteria to focus on papers that most directly answered the following key questions:

1. Do chemopreventive agents reduce mortality from breast cancer?
2. Do chemopreventive agents reduce the incidence of breast cancer?
3. Do chemopreventive agents have other beneficial effects?
4. Do chemopreventive agents increase the risk of adverse effects?
5. What are the costs associated with chemoprevention of breast cancer?

A total of 70 articles were examined in phase 2.

Inclusion and Exclusion Criteria

Since no clinical trial has been large enough to examine the impact of chemoprevention on mortality from breast cancer (Key Question #1 above), the review of evidence focused on key question 2 through 5. The Evidence-based Practice Center required randomized controlled trials of chemoprevention agents in populations of women without breast cancer in which the outcome measures included breast cancer incidence and/or mortality for key questions 2 through 4. The Evidence-based Practice Center staff also specifically searched for studies with selective estrogen-receptor modulators (SERMs).

The Evidence-based Practice Center staff used the following general inclusion criteria:

- Articles found only in MEDLINE
- Articles written only in English
- Articles evaluating only humans
- Articles with randomized controlled trial designs (all other designs, such as, cost-effectiveness, systematic reviews, meta-analysis, were examined separately)

Four Evidence-based Practice Center staff independently reviewed the titles and abstracts and excluded those that they agreed clearly did not meet eligibility criteria. When the initial reviewers disagreed or were uncertain, the articles were carried forward to the next review stage in which Evidence-based Practice Center team members reviewed the full articles and made a final decision about inclusion or exclusion by consensus.

Only 4 studies met all inclusion criteria from phase 2 (see the National Guideline Clearinghouse Guideline Summary field labeled "Source Documents" below).

NUMBER OF SOURCE DOCUMENTS

700 articles from MEDLINE and other searches.

70 articles retrieved for more detailed evaluation.

Four articles met inclusion criteria. These articles were randomized controlled trials evaluating the benefits of chemoprevention of breast cancer for women without previous breast cancer (3 trials using tamoxifen; 1 trial using raloxifene).

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

The U.S. Preventive Services Task Force (USPSTF) grades the quality of the overall evidence on a 3-point scale (good, fair, or poor).

Good

Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes.

Fair

Evidence is sufficient to determine effects on health outcomes, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; generalizability to routine practice; or indirect nature of evidence on health outcomes.

Poor

Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

Note: See the companion document titled "Current Methods of the U.S. Preventive Services Task Force: a Review of the Process" (Am J Prev Med 2001 Apr; 20[3S]:21-35) for a more detailed description of the methods used to assess the quality and strength of the evidence for the three strata at which the evidence was reviewed.

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Note from the National Guideline Clearinghouse (NGC): A systematic evidence review was prepared by the Research Triangle Institute-University of North Carolina Evidence-based Practice Center (EPC) for the Agency for Healthcare Research and Quality (AHRQ) for use by the U.S. Preventive Services Task Force (USPSTF) (see the "Companion Documents" field).

The Evidence-based Practice Center staff entered study design and outcomes data from the articles on chemoprevention for breast cancer into an electronic database (Microsoft Access). They also constructed evidence tables in Microsoft Word.

To characterize the quality of the included studies, the staff rated the internal and external validity for each article in the evidence table using criteria developed by the U.S. Preventive Services Task Force (USPSTF) Methods Work Group. The staff then rated the aggregate internal validity and external validity as well as the coherence (consistency or agreement of the results of the individual studies for each of the key questions in the analytic framework).

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Balance Sheets
Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

When the overall quality of the evidence is judged to be good or fair, the U.S. Preventive Services Task Force (USPSTF) proceeds to consider the magnitude of net benefit to be expected from implementation of the preventive service. Determining net benefit requires assessing both the magnitude of benefits and the magnitude of harms and weighing the two.

The USPSTF classifies benefits, harms, and net benefits on a 4-point scale: "substantial," "moderate," "small," and "zero/negative."

"Outcomes tables" (similar to 'balance sheets') are the USPSTF's standard resource for estimating the magnitude of benefit. These tables, prepared by the topic teams for use at USPSTF meetings, compare the condition specific outcomes

expected for a hypothetical primary care population with and without use of the preventive service. These comparisons may be extended to consider only people of specified age or risk groups or other aspects of implementation. Thus, outcomes tables allow the USPSTF to examine directly how the preventive services affects benefits for various groups.

When evidence on harms is available, the topic teams assess its quality in a manner like that for benefits and include adverse events in the outcomes tables. When few harms data are available, the USPSTF does not assume that harms are small or nonexistent. It recognizes a responsibility to consider which harms are likely and judge their potential frequency and the severity that might ensue from implementing the service. It uses whatever evidence exists to construct a general confidence interval on the 4-point scale (e.g., substantial, moderate, small, and zero/negative).

Value judgments are involved in using the information in an outcomes table to rate either benefits or harms on the USPSTF's 4-point scale. Value judgments are also needed to weigh benefits against harms to arrive a rating of net benefit.

In making its determinations of net benefit, the USPSTF strives to consider what it believes are the general values of most people. It does this with greater confidence for certain outcomes (e.g., death) about which there is little disagreement about undesirability, but it recognizes that the degree of risk people are willing to accept to avert other outcomes (e.g., cataracts) can vary considerably. When the USPSTF perceives that preferences among individuals vary greatly, and that these variations are sufficient to make trade-off of benefits and harms a 'close-call', then it will often assign a C recommendation (see the "Recommendation Rating Scheme" field). This recommendation indicates the decision is likely to be sensitive to individual patient preferences.

The USPSTF uses its assessment of the evidence and magnitude of net benefit to make recommendations. The general principles the USPSTF follows in making recommendations are outlined in Table 5 of the companion document cited below. The USPSTF liaisons on the topic team compose the first drafts of the recommendations and rationale statements, which the full panel then reviews and edits. Recommendations are based on formal voting procedures that include explicit rules for determining the views of the majority.

From: Harris RP, Helfand M, Woolf SH, Lohr KN, Mulrow, CD, Teutsch SM, Atkins D. Current methods of the U.S. Preventive Services Task Force: a review of the process. Methods Work Group, Third U.S. Preventive Services Task Force. *Am J Prev Med* 2001 Apr;20(3S):21-35.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

The U.S. Preventive Services Task Force (USPSTF) grades its recommendations according to one of five classifications (A, B, C, D, or I), reflecting the strength of evidence and magnitude of net benefit (benefits minus harms).

A

The U.S. Preventive Services Task Force (USPSTF) strongly recommends that clinicians provide [the service] to eligible patients. (The USPSTF found good evidence that [the service] improves important health outcomes and concludes that benefits substantially outweigh harms.)

B

The U.S. Preventive Services Task Force (USPSTF) recommends that clinicians provide [the service] to eligible patients. (The USPSTF found at least fair evidence that [the service] improves health outcomes and concludes that benefits outweigh harms.)

C

The U.S. Preventive Services Task Force (USPSTF) makes no recommendation for or against routine provision of [the service]. (The USPSTF found at least fair evidence that [the service] can improve health outcomes but concludes that the balance of benefits and harms is too close to justify a general recommendation.)

D

The U.S. Preventive Services Task Force (USPSTF) recommends against routinely providing [the service] to asymptomatic patients. (The USPSTF found at least fair evidence that [the service] is ineffective or that harms outweigh benefits.)

I

The U.S. Preventive Services Task Force (USPSTF) concludes that the evidence is insufficient to recommend for or against routinely providing [the service]. (Evidence that [the service] is effective is lacking, of poor quality, or conflicting and the balance of benefits and harms cannot be determined.)

COST ANALYSIS

Two well-conducted cost-effectiveness studies, based on Breast Cancer Prevention Trial (BCPT) data, have been published. Using different methods and different assumptions, both examined the incremental cost effectiveness of chemoprevention for cohorts of women similar to those in the BCPT. For high-risk women ages 35-49, they calculated estimates of \$41,372 to \$46,619 per additional life-year gained; for women ages 60-69, estimates were \$74,981 to \$122,401 per additional life-year gained. In sensitivity analyses, cost-effectiveness ratios were more favorable under assumptions of 10 as opposed to 5 years of benefit from tamoxifen, and with previous hysterectomy, but in each case the ratios were most favorable for younger women.

From: Kinsinger LA, Harris, R, Lewis C, Woolf, SH, Sox, HC, Lohr, KN. Chemoprevention of breast cancer: a summary of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med* 2002 Jul; 137(1):59-67 (see the "Companion Documents" field).

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Peer Review. Before the U.S. Preventive Services Task Force (USPSTF) makes its final determinations about recommendations on a given preventive service, the Evidence-based Practice Center (EPC) and the Agency for Healthcare Research and Quality (AHRQ) send a draft systematic evidence review to 4 to 6 external experts and to federal agencies and professional and disease-based health organizations with interests in the topic. They ask the experts to examine the review critically for accuracy and completeness and to respond to a series of specific questions about the document. After assembling these external review comments and documenting the proposed response to key comments, the topic team presents this information to the Task Force in memo form. In this way, the Task Force can consider these external comments and a final version of the systematic review before it votes on its recommendations about the service. Draft recommendations are then circulated for comment from reviewers representing professional societies, voluntary organizations and Federal agencies. These comments are discussed before the whole U.S. Preventive Services Task Force before final recommendations are confirmed.

Recommendations of Others. Recommendations for chemoprevention of breast cancer from the following groups were discussed:

- American College of Obstetricians and Gynecologists
- American Society of Clinical Oncology
- Canadian Task Force on Preventive Health Care

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

The U.S. Preventive Services Task Force (USPSTF) grades its recommendations (A, B, C, D, or I) and the quality of the overall evidence for a service (good, fair, poor). The definitions of these grades can be found at the end of the "Major Recommendations" field.

- The U.S. Preventive Services Task Force recommends against the routine use of tamoxifen or raloxifene for the primary prevention of breast cancer in women at low or average risk of breast cancer. (See "Clinical Considerations", below, for a discussion of risk.) D recommendation (see Appendix Table 1 in the original guideline document).

The U.S. Preventive Services Task Force found fair evidence that tamoxifen and raloxifene may prevent some breast cancers in women at low or average risk of breast cancer, based on extrapolation from studies of women at higher risk. The U.S. Preventive Services Task Force concluded, however, that the potential harms of chemoprevention may outweigh the potential benefits in women who are not at high risk of breast cancer.

- The U.S. Preventive Services Task Force recommends that clinicians discuss chemoprevention with women at high risk for breast cancer and at low risk for adverse effects of chemoprevention. (See "Clinical Considerations", below, for a discussion of risk.) Clinicians should inform patients of the potential benefits and harms of chemoprevention. B recommendation (see Appendix Table 1 in the original guideline document).

The U.S. Preventive Services Task Force found fair evidence that treatment with tamoxifen can significantly reduce the risk of invasive estrogen-receptor--positive breast cancer in women at high risk for breast cancer and that the likelihood of benefit increases as the risk of breast cancer increases. The U.S. Preventive Services Task Force found consistent but less abundant evidence for the benefit of raloxifene. The U.S. Preventive Services Task Force found good evidence that tamoxifen and raloxifene increase the risk of thromboembolic events (for example, stroke, pulmonary embolism, and deep venous thrombosis) and symptomatic side effects (for example, hot flashes) and that tamoxifen, but not raloxifene, increases the risk of endometrial cancer. The U.S. Preventive Services Task Force concluded that the balance of benefits and harms may be favorable for some high-risk women but will depend on breast cancer risk, risk of potential harms, and individual patient preferences.

Clinical Considerations

- Clinicians should consider both the risk for breast cancer and the risk for adverse effects when identifying women who may be candidates for chemoprevention.

Risk of breast cancer: Older age; a family history of breast cancer in a mother, sister, or daughter; and a history of atypical hyperplasia on a breast biopsy are the strongest risk factors for breast cancer. Table 1 of the original guideline document indicates how the estimated benefits of tamoxifen vary depending on age and family history. Other factors that contribute to risk include race, early age at menarche, pregnancy history (nulliparity or older age at first birth), and number of breast biopsies. The risk for developing breast cancer within the next 5 years can be estimated using risk factor information by completing the National Cancer Institute Breast Cancer Risk Tool (the "Gail model," available at the [National Cancer Institute Web site](#) or 1-800-4-CANCER). Clinicians can use this information to help individual patients considering tamoxifen therapy estimate the potential benefit. However, the validity, feasibility, and impact of using the Gail model to identify appropriate candidates for chemoprevention has not been tested in a primary care setting. The Gail model does not incorporate estradiol levels or estrogen use, factors that some studies suggest may influence the effectiveness of tamoxifen.

Risk of adverse effects. Women are at lower risk for adverse effects from chemoprevention if they are younger; have no predisposition to thromboembolic events such as stroke, pulmonary embolism, or deep venous thrombosis; or do not have a uterus.

- In general, the balance of benefits and harms of chemoprevention is more favorable for (1) women in their 40s who are at increased risk for breast

cancer and have no predisposition to thromboembolic events and (2) women in their 50s who are at increased risk for breast cancer, have no predisposition to thromboembolic events, and do not have a uterus. For example, a woman who is 45 years of age and has a mother, sister, or daughter with breast cancer would have approximately an 1.6% risk of developing breast cancer over the next 5 years (see Table 1 of the original guideline document). On average, treating such women with tamoxifen for 5 years would prevent about three times as many invasive cancers (8 per 1000) as the number of serious thromboembolic complications caused (1 stroke and 1 to 2 pulmonary emboli per 1000). Among women 55 years of age, benefits exceed harms only for those who are not for risk of endometrial cancer; and the margin of benefit is small unless risk of breast cancer is substantially increased (for example, 4% over 5 years).

- Women younger than 40 years of age have a lower risk for breast cancer, and thus will not experience as large an absolute benefit from breast cancer chemoprevention as older women. Women 60 years of age and older, who have the highest risk of breast cancer also have the highest risk of complications from chemoprevention with a less favorable balance of benefits and harms.
- The U.S. Preventive Services Task Force found more evidence for the benefits of tamoxifen than for the benefits of raloxifene. Currently, only tamoxifen is approved by the U.S. Food and Drug Administration (FDA) for the specific indication of breast cancer chemoprevention. Although there are biological reasons to suspect that raloxifene should have similar benefits, trial data currently are limited to one study in which the primary outcome was fracture prevention. Additional trials to further evaluate this drug's efficacy for breast cancer chemoprevention are under way, including a trial comparing efficacy and safety of raloxifene and tamoxifen. Raloxifene is approved by the U.S. Food and Drug Administration for preventing and treating osteoporosis.

Definitions:

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D

The U.S. Preventive Services Task Force (USPSTF) recommends against routinely providing [the service] to asymptomatic patients. (The USPSTF found at least fair evidence that [the service] is ineffective or that harms outweigh benefits.)

I

The U.S. Preventive Services Task Force (USPSTF) concludes that the evidence is insufficient to recommend for or against routinely providing [the service]. (Evidence that [the service] is effective is lacking, of poor quality, or conflicting and the balance of benefits and harms cannot be determined.)

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Good

Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes.

Fair

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Poor

Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of evidence supporting each recommendation is identified in the "Major Recommendations" field.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Potential Benefits of Chemoprevention

The use of agents to prevent the development of breast cancer was suggested by trials of breast cancer treatment with tamoxifen, a compound with both estrogen-like and anti-estrogen properties (a selective estrogen receptor modulator). A meta-analysis of 55 studies evaluating tamoxifen for the treatment of women with breast cancer found that the drug was associated with an approximately 50% reduction in the risk for developing new cancers in the opposite breast among women who took the drug for 5 years.

The U.S. Preventive Services Task Force (USPSTF) found and evaluated 4 randomized controlled trials (RCTs) of breast cancer chemoprevention in women who had never had breast cancer. Three of these trials used tamoxifen as the chemopreventive agent; 1 trial used raloxifene, another selective estrogen receptor modulator.

Of the 3 randomized controlled trials of tamoxifen, the largest (the Breast Cancer Prevention Trial-BCPT), with 13,388 women enrolled, found a risk reduction of invasive cancer of 49% among women at high risk for breast cancer (estimated 5-year risk of 1.66% or greater). Over the course of the Breast Cancer Prevention Trial, a total of 264 women were diagnosed with invasive breast cancer: 175 in the placebo group and 89 in the tamoxifen group (risk reduction [RR], 0.51; 95% confidence interval [CI], 0.39-0.66). The absolute risk reduction was 21.4 cases per 1,000 women over 5 years.

The 2 other tamoxifen randomized controlled trials did not show a similar benefit. The relative risk reduction for breast cancer was 0.94 (95% CI 0.59 -1.43) for the Royal Marsden Hospital study and 0.87 (95% CI 0.62-2.14) for the Italian Tamoxifen Prevention Study. Although the reasons for these discrepant results are not definitively established, possible explanations include differences in the duration of therapy and differences between women enrolled in each study. The average duration of therapy was shorter in the European trials and, compared with the women enrolled in the Breast Cancer Prevention Trial, the women in these trials were younger, had more estrogen-receptor-negative cancers, and were more likely to be taking hormone replacement therapy or to have had an oophorectomy.

The study evaluating raloxifene in postmenopausal women with osteoporosis found a 76% risk reduction (RR 0.24, 95% CI 0.13-0.44) in the development of invasive breast cancer. After a median follow-up of 40 months, the absolute risk reduction among women taking raloxifene was 7.9 cases per 1,000 women (number needed to treat, 126).

When effective, both raloxifene and tamoxifen were effective only against estrogen receptor-positive tumors.

Subgroups Most Likely to Benefit:

Women at high risk for developing breast cancer, including:

- Older age
- Family history of breast cancer in a mother, sister, or daughter
- History of atypical hyperplasia on breast biopsy
- Race
- Early age at menarche
- Pregnancy history (nulliparity or older age at first birth)
- Number of breast biopsies

[The risk of developing breast cancer within the next 5 years can be estimated using risk factor information by completing the National Cancer Institute Breast Cancer Risk Tool (the "Gail model") available at the [National Cancer Institute Web site](#) or 800-4-CANCER]

In general, the balance of benefits and harms of chemoprevention is more favorable for:

1. Women in their 40s who are at increased risk for breast cancer and have no predisposition to thromboembolic events; and,
2. Women in their 50s who are at increase risk for breast cancer, have no predisposition to thromboembolic events, and do not have a uterus.

POTENTIAL HARMS

Potential Harms of Chemoprevention

Both tamoxifen and raloxifene increase the risk for thromboembolic events and hot flashes; tamoxifen increases the risk for endometrial cancer. The number of total thromboembolic events in all 4 randomized controlled trials was small and differences in specific complication rates between the treatment and placebo arms were statistically significant only for pulmonary embolism. Among women aged 50 and older, for whom the potential harms of tamoxifen and raloxifene are more common than they are for younger women, the Breast Cancer Prevention Trial reported that after a median of 55 months of use, tamoxifen increased the rate of stroke from 1.3 cases/1000 women in the placebo group to 2.2 cases/1000 women in the study group (RR 1.75, 95% CI 0.98-3.20); increased the rate of pulmonary embolism from 0.3 cases/1000 women in the placebo group to 1.0 cases/1000 women in the study group (RR 3.19%, 95% CI 1.12-11.15); increased the rate of deep vein thrombosis from 0.9 cases/1000 women in the placebo group to 1.5 cases/1000 women in the study group (RR 1.71, 95% CI 0.85-3.58).

Fewer thromboembolic events occurred among women younger than 50, and the trial found no significant difference in incidence between the tamoxifen and placebo groups in this age group. The relative risk increase in venous

thromboembolism from tamoxifen or raloxifene appears similar to the risk for venous thromboembolism from oral contraceptives or hormone replacement therapy.

Among women aged 50 and older in the Breast Cancer Prevention Trial, participants who received tamoxifen, compared with those who took placebo, had a 4.0 times greater risk (95% CI 1.70-10.90) of developing Stage 1 endometrial cancer (0.8 cancers/1000 women taking placebo versus 3.1 cancers/1000 women taking tamoxifen for a median of 55 months). Among women younger than 50, the Breast Cancer Prevention Trial found no significant difference in endometrial cancer rates between the two groups. No deaths attributed to endometrial cancer occurred in the trial. Raloxifene has not been associated with an increase in endometrial cancer.

The Breast Cancer Prevention Trial reported that women in the tamoxifen group were at increased risk of developing cataracts and having cataract surgery compared with placebo (RR 1.14 [95% CI 1.01-1.29] and 1.57 [95% CI 1.16-2.14], respectively).

Quality of life issues have also been of concern and were addressed in the Breast Cancer Prevention Trial. Women in the Breast Cancer Prevention Trial reported increased rates of bothersome hot flashes (45.7% in the tamoxifen group versus 28.7% in the placebo group) and bothersome vaginal discharge (12.4% in the tamoxifen group versus 4.5% in the placebo group). Women given raloxifene also noted higher rates of hot flashes than women given placebo (10.7% in the raloxifene group versus 6.4% in the placebo group).

Although long-term adherence for highly motivated women was about 80% in the Breast Cancer Prevention Trial and about 90% in the raloxifene trial, adherence rates in the general population are unknown.

Subgroups Most Likely to be Harmed:

The potential harms of tamoxifen and raloxifene are more common for women aged 50 and older than they are for younger women.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

The authors of this article are responsible for its contents, including any clinical or treatment recommendations. No statement in this article should be construed as an official position of the Agency for Healthcare Research and Quality, the U.S. Department of Defense or the U.S. Department of Health and Human Services.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

The experiences of the first and second U.S. Preventive Services Task Force (USPSTF), as well as that of other evidence-based guideline efforts, have highlighted the importance of identifying effective ways to implement clinical recommendations. Practice guidelines are relatively weak tools for changing clinical practice when used in isolation. To effect change, guidelines must be coupled with strategies to improve their acceptance and feasibility. Such strategies include enlisting the support of local opinion leaders, using reminder systems for clinicians and patients, adopting standing orders, and audit and feedback of information to clinicians about their compliance with recommended practice.

In the case of preventive services guidelines, implementation needs to go beyond traditional dissemination and promotion efforts to recognize the added patient and clinician barriers that affect preventive care. These include clinicians' ambivalence about whether preventive medicine is part of their job, the psychological and practical challenges that patients face in changing behaviors, lack of access to health care or of insurance coverage for preventive services for some patients, competing pressures within the context of shorter office visits, and the lack of organized systems in most practices to ensure the delivery of recommended preventive care.

Neither the resources nor the composition of the U.S. Preventive Services Task Force equip it to address these numerous implementation challenges, but a number of related efforts seek to increase the impact of future U.S. Preventive Services Task Force reports. The U.S. Preventive Services Task Force convened representatives from the various audiences for the [Guide](#) ("Put Prevention Into Practice. A Step-by-Step Guide to Delivering Clinical Preventive Services: A Systems Approach") - clinicians, consumers and policy makers from health plans, national organizations and Congressional staff - about how to modify the content and format of its products to address their needs. With funding from the Robert Wood Johnson Foundation, the U.S. Preventive Services Task Force and Community Guide effort have conducted an audience analysis to further explore implementation needs. The [Put Prevention into Practice](#) initiative at the Agency for Healthcare Research and Quality (AHRQ) has developed office tools such as patient booklets, posters, and handheld patient mini-records, and a new implementation guide for state health departments.

Dissemination strategies have changed dramatically in this age of electronic information. While recognizing the continuing value of journals and other print formats for dissemination, the Agency for Healthcare Research and Quality will make all U.S. Preventive Services Task Force products available through its [Web site](#). The combination of electronic access and extensive material in the public domain should make it easier for a broad audience of users to access U.S. Preventive Services Task Force materials and adapt them for their local needs. Online access to U.S. Preventive Services Task Force products also opens up new possibilities for the appearance of the third edition of the Guide to Clinical Preventive Services. Freed from having to serve as primary repository for all of U.S. Preventive Services Task Force work, the next Guide may be much slimmer than the almost 1000 pages of the second edition.

To be successful, approaches for implementing prevention have to be tailored to the local level and deal with the specific barriers at a given site, typically requiring

the redesign of systems of care. Such a systems approach to prevention has had notable success in established staff-model health maintenance organizations, by addressing organization of care, emphasizing a philosophy of prevention, and altering the training and incentives for clinicians. Staff-model plans also benefit from integrated information systems that can track the use of needed services and generate automatic reminders aimed at patients and clinicians, some of the most consistently successful interventions. Information systems remain a major challenge for individual clinicians' offices, however, as well as for looser affiliations of practices in network-model managed care and independent practice associations, where data on patient visits, referrals and test results are not always centralized.

RELATED QUALITY TOOLS

- [Pocket Guide to Good Health for Adults](#)
- [A Step-by-Step Guide to Delivering Clinical Preventive Services: A Systems Approach](#)
- [Breast Cancer Chemoprevention. What's New from the USPSTF.](#)

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Staying Healthy

IOM DOMAIN

Effectiveness
Patient-centeredness
Safety

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

U.S. Preventive Services Task Force. Chemoprevention of breast cancer: recommendations and rationale. *Ann Intern Med* 2002 Jul; 137(1):56-8. [13 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

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2002 Jul

GUIDELINE DEVELOPER(S)

United States Preventive Services Task Force - Independent Expert Panel

GUIDELINE DEVELOPER COMMENT

The U.S. Preventive Services Task Force (USPSTF) is a Federally-appointed panel of independent experts. Conclusions of the U.S. Preventive Services Task Force do not necessarily reflect policy of the U.S. Department of Health and Human Services (DHHS) or U.S. Department of Health and Human Services agencies.

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GUIDELINE COMMITTEE

U.S. Preventive Services Task Force (USPSTF)

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

The U.S. Preventive Services Task force has an explicit policy concerning conflict of interest. All members and evidence-based practice center (EPC) staff disclose at each meeting if they have an important financial conflict for each topic being discussed. Task Force members and EPC staff with conflicts can participate in discussions about evidence, but members abstain from voting on recommendations about the topic in question.

From: Harris RP, Helfand M, Woolf SH, Lohr KN, Mulrow, CD, Teutsch SM, Atkins D. Current methods of the U.S. Preventive Services Task Force: a review of the process. Methods Work Group, Third U.S. Preventive Services Task Force. Am J Prev Med 2001 Apr;20(3S):21-35.

GUIDELINE STATUS

This is the current release of the guideline.

An update is not in progress at this time.

GUIDELINE AVAILABILITY

Electronic copies: Available from the [U.S. Preventive Services Task Force \(USPSTF\) Web site](#). Also available from the [Annals of Internal Medicine Online](#) and the [National Library of Medicine's Health Services/Technology Assessment Text \(HSTAT\) Web site](#).

Print copies: Available from the Agency for Healthcare Research and Quality Publications Clearinghouse. For more information, go to <http://www.ahrq.gov/news/pubsix.htm> or call 1-800-358-9295 (U.S. only). (Outside the United States: 1-410-381-3150; Toll-free TDD service; hearing impaired only: 888-586-6340.)

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

Evidence Reviews:

- Kinsinger LA, Harris, R, Lewis C, Woolf, SH, Sox, HC, Lohr, KN. Chemoprevention of breast cancer: a summary of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med* 2002 Jul; 137(1):59-67. Electronic copies are available from the [U.S. Preventive Services Task Force \(USPSTF\) Web site](#) and the [Annals of Internal Medicine Online](#).
- Kinsinger LA, Harris R, Lewis C, Wooddell M. Chemoprevention of breast cancer. Rockville (MD): Agency for Healthcare Research and Quality; 2002 Jul (in process).

Background Articles:

- Woolf SH, Atkins D. The evolving role of prevention in health care: contributions of the U.S. Preventive Services Task Force. *Am J Prev Med* 2001 Apr; 20(3S):13-20.
- Harris RP, Helfand M, Woolf SH, Lohr KN, Mulrow, CD, Teutsch SM, Atkins D. Current methods of the U.S. Preventive Services Task Force: a review of the process. Methods Work Group, Third U.S. Preventive Services Task Force. *Am J Prev Med* 2001 Apr; 20(3S):21-35.
- Saha S, Hoerger TJ, Pignone MP, Teutsch SM, Helfand M, Mandelblatt. The art and science of incorporating cost effectiveness into evidence-based recommendations for clinical preventive services. Cost Work Group of the Third U.S. Preventive Services Task Force. *Am J Prev Med* 2001 Apr; 20(3S):36-43.

Electronic copies: Available from [U.S. Preventive Services Task Force \(USPSTF\) Web site](#).

Additional Implementation Tools:

- A step-by-step guide to delivering clinical preventive services: a systems approach. Rockville (MD): Agency for Healthcare Research and Quality (AHRQ), 2001. 189 p. (Pub. No. APPIP01-0001). Electronic copies available from the [AHRQ Web site](#).

Print copies: Available from the Agency for Healthcare Research and Quality Publications Clearinghouse. For more information, go to <http://www.ahrq.gov/news/pubsix.htm> or call 1-800-358-9295 (U.S. only).

- The Preventive Services Selector, an application for Palm Pilots and other PDA's, is also available from the [AHRQ Web site](#).
- Breast cancer chemoprevention. What's new from the third USPSTF. Rockville (MD): Agency for Healthcare Research and Quality; 2002 Jun. Electronic copies: Available from [USPSTF Web site](#).

PATIENT RESOURCES

The following is available:

- The Pocket Guide to Good Health for Adults. Rockville (MD): Agency for Healthcare Research and Quality (AHRQ); 2003.

Electronic copies: Available from the [U.S. Preventive Services Task Force \(USPSTF\) Web site](#). Copies also available in Spanish from the [USPSTF Web site](#).

Print copies: Available from the Agency for Healthcare Research and Quality (AHRQ) Publications Clearinghouse. For more information, go to <http://www.ahrq.gov/news/pubsix.htm> or call 1-800-358-9295 (U.S. only).

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC STATUS

This NGC summary was completed by ECRI on June 25, 2002. The information was verified by the guideline developer as June 27, 2002.

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