

# Chemoprevention of Breast Cancer: A Summary of the Evidence for the U.S. Preventive Services Task Force

Linda S. Kinsinger, MD, MPH; Russell Harris, MD, MPH; Steven H. Woolf, MD, MPH; Harold C. Sox, MD; and Kathleen N. Lohr, PhD

**Purpose:** Chemoprevention offers promise as a strategy for reducing morbidity and mortality from breast cancer in women. This review examined the evidence for the effectiveness of chemoprevention in women without a history of breast cancer.

**Data Sources:** MEDLINE (1966 to December 2001).

**Study Selection:** English-language, randomized, controlled trials (RCTs) of chemoprevention of breast cancer in women without a previous diagnosis of breast cancer were examined, and 4 relevant trials, 3 involving tamoxifen and 1 involving raloxifene, were selected. Trials that provided data on the harms of tamoxifen or raloxifene, studies of the costs of chemoprevention, and studies of risk assessment were also reviewed.

**Data Extraction:** Four reviewers independently abstracted data on key variables, including study population, sample size, randomization, treatment, and outcomes.

**Data Synthesis:** The largest of the RCTs of tamoxifen reported a 49% reduction in relative risk (0.51 [95% CI, 0.39 to 0.66]) for

invasive cancer among women with an estimated 5-year breast cancer risk of at least 1.66%. The other tamoxifen trials did not observe a statistically significant benefit, but only a few women in each trial took tamoxifen during the entire study period. The raloxifene study of postmenopausal women with osteoporosis found a 76% reduction in relative risk (0.24 [CI, 0.13 to 0.44]) for invasive breast cancer. Tamoxifen and raloxifene were effective only against estrogen receptor-positive tumors. Both drugs increased risk for venous thromboembolic disease and hot flashes; tamoxifen increased risk for endometrial cancer and stroke.

**Conclusions:** Tamoxifen and raloxifene reduce the incidence of estrogen receptor-positive breast cancer in women. The relative risk reduction seems similar across all breast cancer risk groups. The absolute risk reduction varies by risk factors for breast cancer, however, and must be balanced against the potential harms to judge the appropriateness of treatment for individual women.

*Ann Intern Med.* 2002;137:59-67.

www.annals.org

See related article on pp 56-58 and editorial comment on pp 52-54.

Despite improvements in the rates of screening and early detection, treatment advances, and healthier lifestyles, breast cancer remains the most common nonskin cancer among women in the United States. In 2002, it will account for an estimated 203 500 new cases of invasive cancer and 54 300 cases of in situ cancer (1). Although mortality rates for some groups of women have modestly decreased in recent years, 39 600 women are expected to die of breast cancer in 2002 (1-3). The strongest risk factors for breast cancer—increasing age, family history, and hormonal factors (age at menarche and menopause)—are not easily modifiable (4-12). Although obesity and alcohol intake are associated with increased risk, prospective studies have not yet shown that modifying these risk factors prevents the disease. Thus, other preventive strategies must be considered.

Evidence that chemopreventive drugs might be able to prevent breast cancer first came to light in trials testing tamoxifen as adjuvant chemotherapy in women with breast cancer (13). Tamoxifen is a compound with both estrogen-like and antiestrogen properties (known as a selective estrogen-receptor modulator). A meta-analysis of 55 studies of adjuvant tamoxifen therapy demonstrated that it reduced the risk for new cancer in the opposite breast by 47% ( $P < 0.001$ ) among women who took the drug for 5 years, suggesting a potential role in primary prevention (14). Tamoxifen also reduces the occurrence of invasive breast cancer in women with ductal carcinoma in situ (15). Another selective estrogen-receptor modulator, raloxifene, has also been studied as a possible chemopreventive agent. Al-

though vitamin A analogues, such as fenretinide, have been investigated as potential drugs for chemoprevention, trial results have been disappointing (16).

Staff members of the Research Triangle Institute—University of North Carolina Evidence-based Practice Center, together with two members of the U.S. Preventive Services Task Force (USPSTF), reviewed the scientific evidence on issues related to the benefits and harms of chemoprevention of breast cancer in women without a history of breast cancer. This review was performed to assist the USPSTF in making recommendations for clinicians about chemoprevention for breast cancer (17).

## METHODS

Using USPSTF methodology, we first developed an analytic framework and a set of key questions to guide the search (18). (Details about the framework, key questions, and search strategy are available at [www.annals.org](http://www.annals.org).) In general, we focused on evidence from randomized, controlled trials (RCTs) on the effectiveness of chemopreventive agents in reducing incidence of and death from breast cancer, as well as other potential beneficial and adverse effects. We also examined studies of the cost-effectiveness of these agents. Briefly, our search strategy involved two phases. The first used broad search terms and review criteria to maximize the probability of identifying all potentially relevant articles, and the second applied more stringent review criteria to focus on studies directly applicable to the key questions. We limited the search to English-language

Table 1. Summary of Four Randomized, Controlled Trials of Breast Cancer Chemoprevention\*

Study (Reference)	Patients Age		Agent Dose	Median Follow-up	Breast Cancer Type	Cases of Breast Cancer		Breast Cancer Rate per 1000 Woman-Years		P Value	Relative Risk (95% CI)			
	n	y				mo	n	%	Placebo Group			Treatment Group	Placebo Group	Treatment Group
Royal Marsden (19)	2471	30–70	Tamoxifen, 20 mg/d	70	All	36	34	5.0†	4.7†	>0.2	0.94 (0.59–1.43)			
Italian Study (21, 23)	5408	35–70	Tamoxifen, 20 mg/d	46	All	22	19	2.3†	2.1†	>0.2	0.87 (0.62–2.14)‡			
					ER+	10	8	NA	NA	NA	NA			
Breast Cancer Prevention Trial (20)	13 388	≥35	Tamoxifen, 20 mg/d	81.2	All	45	34	NA	NA	>0.2	0.75 (0.48–1.18)§			
				54.6	Invasive	175	89	6.8†	3.4†	<0.001	0.51 (0.39–0.66)			
					ER+	130	41	NA	NA	NA	0.31 (0.22–0.45)			
Multiple Outcomes of Raloxifene Evaluation (22, 24)	7705	66.5 (median)	Raloxifene, 60 mg/d or 120 mg/d	40	All	69	35	2.7†	1.4†	<0.002	0.50 (0.33–0.77)			
					Invasive	32	22	4.3	1.5	<0.001	0.35 (0.21–0.58)			
					ER+	27	13	3.6	0.9	<0.001	0.24 (0.13–0.44)			
					ER+	20	4	NA	NA	NA	0.10 (0.04–0.24)			
					48	All	44	33	NA	NA	NA	0.38 (0.24–0.58)		
					Invasive	39	22	NA	NA	NA	0.28 (0.17–0.46)			
	ER+	31	10	NA	NA	NA	0.16 (0.09–0.30)							

\* ER+ = estrogen receptor-positive; NA = not available.  
 † Data obtained from reference 23.  
 ‡ Calculated by the current authors.  
 § Value given is a hazard ratio, the estimate of relative risk at a given time.

articles included in MEDLINE from 1966 to December 2001. Two authors and two other staff members from the Evidence-based Practice Center independently reviewed the titles and abstracts of articles identified by this search strategy and excluded those that they agreed clearly did not meet eligibility criteria. The authors fully reviewed articles that met the criteria.

This research was funded by the U.S. Agency for Healthcare Research and Quality. Agency staff and USPSTF members participated in the initial design of the study and reviewed interim analyses and the final manuscript.

**RESULTS**

Four RCTs examined the benefits of chemoprevention of breast cancer for women without previous breast cancer (19–22) (Table 1). Three trials used tamoxifen (20 mg/d) as the chemopreventive agent: the Royal Marsden Hospital (United Kingdom) Tamoxifen Chemoprevention Trial (19); the Italian Tamoxifen Prevention Study (21); and the National Surgical Adjuvant Breast and Bowel Project P-1 Study, known as the Breast Cancer Prevention Trial (BCPT) (20). One trial, the Multiple Outcomes of Raloxifene Evaluation (MORE) (22), studied raloxifene. All four trials were well designed and conducted; all were double-blind, used concealed allocation to intervention and control groups, based their study size on calculations of statistical power, had defined study outcomes and data monitoring boards, and used intention-to-treat analysis.

**Effectiveness of Chemoprevention**

Neither of the two European tamoxifen trials found a reduction in overall breast cancer incidence. The Royal Marsden Trial (19) included 2471 women between 30 and 70 years of age with at least one first-degree relative who developed breast cancer before 50 years of age, one first-degree relative with bilateral breast cancer, or one affected first-degree relative of any age plus another first-degree or second-degree relative with the disease. In an interim analysis (median follow-up, almost 6 years), the Royal Marsden investigators found that 34 cases of breast cancer had been detected in the tamoxifen group and 36 in the placebo group (relative risk [RR], 0.94 [95% CI, 0.59 to 1.43]).

The Italian Tamoxifen Prevention Study (21, 23) enrolled 5408 women aged 35 to 70 years who had had a hysterectomy for an indication other than cancer. Almost 67% of these women had also had bilateral (48.3%) or unilateral (18.6%) oophorectomy before menopause. At a median follow-up of almost 4 years, 41 cases of breast cancer had been diagnosed, 19 in the tamoxifen group and 22 in the placebo group (P > 0.2). Because relative risk was not provided, we calculated it to be 0.87 (CI, 0.62 to 2.14). After 6.75 years of follow-up, this study reported a nonstatistically significant trend toward a reduction in breast cancer incidence for all trial participants (hazard ratio [HR], 0.75 [CI, 0.48 to 1.18]). For the 29% of women (similar in each group) who took hormone replacement

therapy during the trial, the difference was statistically significant (HR, 0.36 [CI, 0.14 to 0.91]) (23).

In contrast to the European trials, the BCPT (21) found that the incidence of invasive breast cancer decreased by 50% over a median follow-up of 54.6 months. The BCPT, the largest chemoprevention trial, enrolled 13 388 women aged 35 years and older who had an estimated 5-year risk for breast cancer of at least 1.66%. This risk was calculated by applying a multivariate logistic regression model developed by Gail and colleagues (25) from data from a large cohort study of breast cancer screening. The factors that determine risk in this model include age, number of first-degree female relatives with breast cancer, nulliparity or age at first birth, number of breast biopsies, pathologic diagnosis of atypical hyperplasia, and age at menarche. Participants were stratified by age (35 to 49 years, 50 to 59 years, and  $\geq 60$  years) and estimated 5-year risk for breast cancer (<2.5%, 2.5% to 3.9%, and  $\geq 4.0\%$ ).

Over the course of the BCPT, a total of 264 women (175 in the placebo group and 89 in the tamoxifen group) received a diagnosis of invasive breast cancer (RR, 0.51 [CI, 0.39 to 0.66]). The absolute risk reduction was 21.4 cases per 1000 women over 5 years. The number of women who would need to be treated with tamoxifen for 5 years to prevent one case of breast cancer (number needed to treat for benefit [NNT<sub>B</sub>]) was 47. The BCPT found 69 cases of noninvasive breast cancer in the placebo group and 35 in the tamoxifen group (RR, 0.50;  $P < 0.002$ ). The absolute risk reduction was 8.2 cases per 1000 women (NNT<sub>B</sub>, 122). The relative risk reduction was similar across all age groups and all risk levels. The drug was effective only against estrogen receptor–positive tumors (130 placebo cases vs. 41 tamoxifen cases) (RR, 0.31 [CI, 0.22 to 0.45]); it did not reduce the incidence of estrogen receptor–negative tumors (31 placebo cases vs. 38 tamoxifen cases). Given the relatively short follow-up, few deaths from breast cancer occurred in any of these trials. No study found statistically significant differences in mortality between study groups.

The MORE trial (22) was designed primarily to examine the effect of raloxifene on osteoporosis fracture risk; breast cancer incidence was also assessed. It involved 7705 women with osteoporosis or previous vertebral fractures who were at least 2 years past menopause and were no older than 80 years of age (median age, 66.5 years). Participants were randomly assigned to receive raloxifene or placebo. Although the MORE investigators did not formally calculate breast cancer risk, the study groups were balanced in such breast cancer risk factors as age, body mass index, alcohol intake, and family history. After a median follow-up of 40 months, 40 cases of invasive breast cancer were confirmed: 13 cases in the 5129 women assigned to raloxifene and 27 in the 2576 women assigned to placebo (RR, 0.24 [CI, 0.13 to 0.44]). The absolute risk reduction was approximately 7.9 cases per 1000 women over 40 months (NNT<sub>B</sub>, 126). Raloxifene reduced the incidence of estrogen receptor–positive cancer by 90% (RR, 0.10 [CI, 0.04 to 0.24]) but had no effect on estrogen receptor–negative tumors (RR, 0.88 [CI, 0.26 to 3.00]) or on 12 cases of ductal carcinoma in situ. Data from longer follow-up (48 months) continued to show a substantial decrease in total incidence of invasive breast cancer (RR, 0.28 [CI, 0.17 to 0.46]) and incidence of estrogen receptor–positive cancer (RR, 0.16 [CI, 0.09 to 0.30]) but no effect on estrogen receptor–negative tumors (RR, 1.13 [CI, 0.35 to 3.66]) (24).

We compared the studies in terms of factors that might explain their discrepant results: family history of breast cancer among the participants, estrogen receptor status of the detected cases of breast cancer, use of hormone replacement therapy, loss to follow-up, and premature discontinuation of the assigned study medication (Table 2). These factors varied. Discontinuation of study drugs was problematic in all four trials. At the time the reports were published, only a few women in the Royal Marsden study ( $n = 79$  [6.3%]) and in the Italian study ( $n = 77$  [2.9%]) had taken tamoxifen for the full study period (8 years and 5 years, respectively); 2424 (36.9%) women took tamoxifen for at least 5 years in the BCPT. In the later report

Table 2. Comparison of Randomized, Controlled Trials of Breast Cancer Chemoprevention\*

Study (Reference)	Women with a Family History of Breast Cancer	Women with ER+ Tumors	Women Who Used HRT	Women Who Were Lost to Follow-up	Women Who Discontinued the Study Drug		Women Who Took Tamoxifen for $\geq 5$ Years
					Placebo Group	Treatment Group	
							n (%)
Royal Marsden (19)	100	63	26	11	31	40	79 (6.3)
Italian Study (21, 23)†	21	43	14	0.6	25	28	77 (2.9)
Breast Cancer Prevention Trial (20)	21	Unknown	29	Not available	34	36	2462 (45)
Multiple Outcomes of Raloxifene Evaluation (22)	76	71	0	1.6	20	24	2424 (36.9)
	12	60	10	Not available	25†	22†	Not applicable

\* ER+ = estrogen receptor–positive; HRT = hormone replacement therapy.

† Cumulative withdrawal at 36 months (includes women lost to follow-up).

‡ First line refers to initial results published in 1998; second line refers to results with longer follow-up published in 2002.

Table 3. Adverse Events in Four Randomized, Controlled Trials of Breast Cancer Chemoprevention\*

Outcome	Study (Reference)	Events, n		Cumulative Rate per 1000 Women, %		Relative Risk (95% CI)
		Placebo Group	Treatment Group	Placebo Group	Treatment Group	
Endometrial cancer	BCPT (20)	15	36	0.91	2.30	2.53 (1.35–4.97)
	<50 y	8	9	1.09	1.32	1.21 (0.41–3.60)
	≥50 y	7	27	0.76	3.05	4.01 (1.70–10.90)
	RMH (19)	1	4	NA	NA	NA
	MORE (22)	4	6	NA	NA	0.8 (0.2–2.7)
Stroke	BCPT (20)	24	38	0.92	1.45	1.59 (0.93–2.77)
	<50 y	4	3	0.39	0.30	0.76 (0.11–4.49)
	≥50 y	20	35	1.26	2.20	1.75 (0.98–3.20)
	Italian (21)	0	5	NA	NA	NA
Pulmonary embolism	BCPT (20)	6	18	0.23	0.69	3.01 (1.15–9.27)
	<50 y	1	2	0.10	0.20	2.03 (0.11–119.62)
	≥50 y	5	16	0.31	1.00	3.19 (1.12–11.15)
	RMH (19)	2	3	NA	NA	NA
	Italian (21)	1	1	NA	NA	NA
	MORE (22)	3	10	NA	NA	3.1 (1.5–6.2)†
Deep venous thrombosis	BCPT (20)	22	35	0.84	1.34	1.60 (0.91–2.86)
	<50 y	8	11	0.78	1.08	1.39 (0.51–3.99)
	≥50 y	14	24	0.88	1.51	1.71 (0.85–3.58)
	RMH (19)	2	4	NA	NA	NA
	Italian (21)	3	6	NA	NA	NA
	MORE (22)	5	18	NA	NA	3.1 (1.5–6.2)†

\* BCPT = Breast Cancer Prevention Trial; Italian = Italian Tamoxifen Prevention Study; MORE = Multiple Outcomes of Raloxifene Evaluation; NA = data not available; RMH = Royal Marsden Hospital Tamoxifen Chemoprevention Trial.

† Results reported for pulmonary embolism and deep venous thrombosis combined.

from the Italian trial, 45% of women had taken tamoxifen for 5 years (23). Previous studies of breast cancer treatment with tamoxifen have shown that 5 years of therapy was more effective than shorter periods (13, 14).

**Other Potential Benefits of Chemoprevention**

Before the BCPT and the MORE trial, evidence suggested that tamoxifen and raloxifene had favorable effects on blood lipid levels and therefore might be expected to reduce cardiovascular events (26, 27). In the BCPT, rates of cardiovascular events did not differ between the tamoxifen and placebo groups. A recent report from the MORE trial found no difference between the raloxifene and placebo groups for all participants. However, among women with high cardiovascular risk, the raloxifene group had a 40% reduction (RR, 0.60 [CI, 0.38 to 0.95]) in cardiovascular events (28). This result must be considered preliminary because cardiovascular events were a secondary outcome and were assessed by self-report.

The BCPT and the MORE trial also examined the effect of these drugs on bone fractures. The BCPT found a nonstatistically significant trend toward a reduction in hip, spine, and Colles fractures (RR, 0.81 [CI, 0.63 to 1.05] for all fractures combined) in the tamoxifen group. The MORE trial found a 30% to 50% reduction in vertebral fractures (RR, 0.7 [CI, 0.5 to 0.8] for 60 mg of raloxifene per day and 0.5 [CI, 0.4 to 0.7] for 120 mg/d) in the raloxifene group but no difference between groups in non-vertebral fractures (29).

**Harms of Chemoprevention**

Only the BCPT and the MORE trial were large enough to evaluate statistically significant differences in the

incidence of adverse consequences between women taking tamoxifen or raloxifene and women taking placebo (Table 3). Risk for endometrial cancer was 2.53 (CI, 1.35 to 4.97) times greater in participants who received tamoxifen in the BCPT than in those who received placebo (absolute risk increase, 7.6 per 1000 women over 4.5 years) (20). On subgroup analysis, the risk increase was statistically significant for women 50 years of age and older (RR, 4.01 [CI, 1.70 to 10.90]). Women younger than 50 years of age who were assigned to tamoxifen had no increased risk. All cases of endometrial cancer in the tamoxifen group were stage 1, and no women died of endometrial cancer. In the MORE study (22), raloxifene was not associated with an excess incidence of endometrial cancer (RR, 0.8 [CI, 0.2 to 2.7]).

Investigators also followed participants for the occurrence of thromboembolic events (Table 3). In the BCPT, women in the tamoxifen group were at increased risk for stroke, pulmonary embolism, and deep venous thrombosis. However, only the difference for pulmonary embolism reached statistical significance (RR, 3.01 [CI, 1.15 to 9.27]) (20). The increased risk was concentrated in women 50 years of age and older; the relative risks for women younger than 50 years of age were smaller than those for older women (Table 3). In the MORE study, women in the raloxifene groups had approximately a threefold increased risk for pulmonary embolism and deep venous thrombosis compared with those in the placebo groups (RR, 3.1 [CI, 1.5 to 6.2]) (19, 22); the study did not report stroke rates. The total number of thromboembolic events in all four trials was small. The BCPT reported an increased risk for cataracts and having cataract surgery in

women assigned to the tamoxifen group (RR, 1.14 [CI, 1.01 to 1.29] and 1.57 [CI, 1.16 to 2.14], respectively) (20).

Researchers also examined the incidence of unpleasant side effects that influence quality of life. Women in the BCPT reported increased rates of “quite a bit” or “extremely” bothersome hot flashes (45.7% in the tamoxifen group vs. 28.7% in the placebo group; statistical significance not given) and “quite a bit” or “extremely” bothersome vaginal discharge (12.4% in the tamoxifen group vs. 4.5% in the placebo group; statistical significance not given) (20). On a health-related quality of life questionnaire, the mean percentage of women reporting a problem on four measures of sexual function (for example, lack of sexual interest) was approximately 1 percentage point greater in the tamoxifen group than in the placebo group. Although these differences were statistically significant, they are probably not clinically important (30). Participants in the MORE trial who were assigned to raloxifene also noted higher rates of hot flashes than did participants assigned to placebo (10.7% vs. 6.4%;  $P < 0.001$ ) (22).

## DISCUSSION

The weight of the evidence favors a substantial effect of tamoxifen and raloxifene in reducing the incidence of estrogen receptor–positive breast cancer. Three separate lines of evidence lead us to this statement: 1) the large magnitude of effect of tamoxifen in the BCPT, 2) the large magnitude of effect of raloxifene in the MORE trial, and 3) the significant reduction in contralateral breast cancer seen in the adjuvant tamoxifen treatment trials (13, 14, 31–33).

### Understanding Discrepancies in the Evidence

Results for tamoxifen in the two European trials seemingly contradict this conclusion. The failure of these trials to demonstrate a significant benefit in overall breast cancer incidence might suggest that tamoxifen is ineffective. Alternatively, these results might be consistent with other hypotheses. First, tamoxifen may be effective for some but not all women, and differences in study results may be attributable to differences in the study populations. Second, the differences in trial results may be attributable to differences in trial design and conduct.

Because tamoxifen is effective only for estrogen receptor–positive breast cancer, any factor that reduces the risk for this type of cancer makes it more difficult to demonstrate a drug effect. Some literature suggests that such factors as stronger family history (34–36) (as in the Royal Marsden trial) or younger age and lower estrogen levels from oophorectomy (34, 35) (as in the Italian trial) may be less strongly associated with estrogen receptor–positive breast cancer than with estrogen receptor–negative breast cancer; however, this association has not been definitively established. If further research shows that the women in the European trials were at lower risk for estrogen receptor–positive breast cancer because of such differences, this

factor may help explain the lack of consistency between the results of these trials and those of the BCPT.

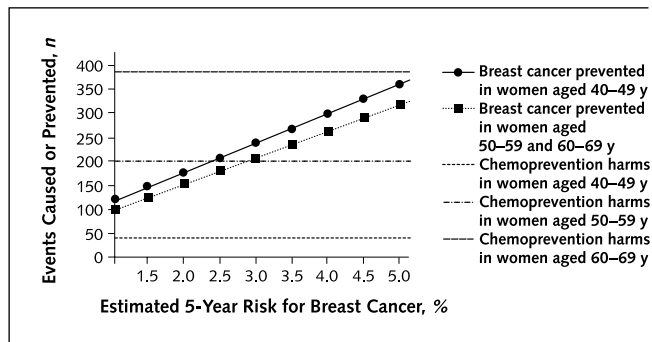
Some evidence already suggests that this was the case. The proportion of estrogen receptor–positive breast cancer was distinctly lower in the Italian trial than in the other trials (43% vs. 60% to 71%) (Table 2). The reduction in breast cancer incidence among women in the Italian study who took hormone replacement therapy (23), as well as a subsequent analysis from the MORE trial indicating that raloxifene’s effect was seen primarily among women with higher levels of estradiol (37), also indicates that estrogen is important in the action of these drugs. A follow-up analysis of the BCPT results among women with inherited mutations of *BRCA1* and *BRCA2* found that 83% of *BRCA1* tumors were estrogen receptor–negative and were not affected by tamoxifen. Seventy-six percent of *BRCA2* tumors were estrogen receptor–positive, and there was a nonstatistically significant trend toward a reduction with tamoxifen therapy (38). The women in the three tamoxifen trials differed in several characteristics other than breast cancer risk that may help explain the differences among the trial results.

At least two design and implementation issues, statistical power and duration of therapy, may be relevant. The trials have limited power to detect a statistically significant difference in the incidence of breast cancer if only a few cases of cancer are detected. Fewer cases of cancer were detected in the Italian study (41 cases in the initial report and 79 in the second report) and in the Royal Marsden study (70 cases) than in the BCPT (264 cases), a difference influenced by the larger number of women enrolled in the BCPT and their higher risk for breast cancer.

However, the lack of a strong trend favoring tamoxifen in overall breast cancer incidence in the European trials (3 fewer cases of cancer in the initial Italian report, 11 fewer in the second Italian report, and 2 fewer in the Royal Marsden study) and the strong effect seen in the BCPT indicate that an inadequately powered study design probably does not fully explain the different results. The 95% CIs for the BCPT and the two European trials overlap only minimally (Table 1). Because factors other than power must account for the findings, we did not combine the three primary prevention tamoxifen trials to obtain a summary measure of tamoxifen effect.

The mean duration of tamoxifen therapy, which is influenced by both attrition and nonadherence, may account for at least part of the difference in results across the trials. Duration of therapy is important because data from the BCPT and the adjuvant breast cancer therapy trials (13) indicate that the effect of tamoxifen on the incidence of breast cancer becomes apparent only after a year of treatment and increases with time up to 5 years of treatment. Therefore, a larger proportion of patients taking tamoxifen for a short period would dampen the observed benefit of the drug. The larger BCPT included a larger proportion (37%) of women who took tamoxifen long enough to re-

**Figure.** Benefits and harms of chemoprevention with tamoxifen per 10 000 women in three age groups.



Harms include endometrial cancer, stroke, and pulmonary embolism combined. Adapted from reference 49.

ceive the full potential benefit, whereas fewer women in the European trials (3% to 6%) took tamoxifen for a full 5 years (Table 2). Among women in the Italian trial who followed the treatment assignment for longer than 1 year, those assigned to tamoxifen had a nonstatistically significant trend toward decreased breast cancer incidence compared with those who received placebo (11 cases vs. 19 cases;  $P = 0.16$  [RR not given]). Among women in the second Italian report, who took the assigned treatment for a longer period, tamoxifen reduced breast cancer incidence compared with no tamoxifen among those who also received hormone replacement therapy.

In summary, several features of the European studies and their participants probably reduced the observed effect of tamoxifen compared with the BCPT. Whether these characteristics fully account for the discrepancy among the studies is not clear. We found the evidence from the BCPT sufficiently convincing to conclude that tamoxifen confers substantial benefit.

For raloxifene, the primary concern with a conclusion of effectiveness is the fact that only one RCT, albeit large and well conducted, has been done. The strength of this trial, the care with which the end point of breast cancer was ascertained, and the similarity of mechanism of action of raloxifene and tamoxifen (39) make it reasonable to conclude that raloxifene is also effective in reducing the incidence of breast cancer.

### Considerations of Risk for Breast Cancer

The relative risk reduction for estrogen receptor–positive breast cancer is similar for all risk groups. The 1.66% risk level used as an inclusion criterion in the BCPT has no apparent biological significance to suggest that chemoprevention would convey a smaller relative risk reduction for lower-risk women. This level of risk was based on a statistical power calculation to determine the number of women needed for recruitment into the study (40).

Given a constant relative risk reduction across breast cancer risk groups, the absolute risk reduction derived from taking a chemopreventive agent increases directly with a

patient's probability of developing estrogen receptor–positive breast cancer (Figure). At present, the most commonly used tool for calculating risk for breast cancer is the Gail model (25, 41), although it cannot specify a risk for only estrogen receptor–positive cancer. Three studies that examined the validity of the Gail model in predicting invasive breast cancer (estrogen receptor–positive and estrogen receptor–negative combined) have found it to be generally accurate in predicting risk among women who undergo regular screening mammography (42–44). It overestimates risk among younger women not undergoing routine mammography (45). The 95% CI is approximately 1.6% to 2.5% for a Gail model risk of 2% and is narrower for risks lower than 2% (46).

Perhaps the biggest problem with the Gail model is its lack of discriminative ability. A “high-risk” woman has a 5-year risk of 1.66%, meaning that more than 98 of every 100 women in this group will not develop invasive breast cancer. Thus, the model only roughly separates women who will develop breast cancer from those who will not (47, 48). A more discriminating approach to estimating the risk for estrogen receptor–positive breast cancer, rather than all breast cancer, would be useful in targeting chemoprevention to women who would benefit most (37).

Using the Gail model and the relative risk reduction found in the BCPT, Gail and colleagues (49) calculated the cases of invasive (both estrogen receptor–positive and estrogen receptor–negative) and noninvasive breast cancer that would be prevented by 5 years of tamoxifen therapy. These calculations for total cases of cancer prevented (invasive and noninvasive combined) are depicted in the Figure. The number of cases of cancer prevented is slightly higher among younger women because slightly more noninvasive cases of cancer would be prevented. The U.S. National Cancer Institute used the Gail model to develop a breast cancer risk assessment calculating tool (<http://bcra.ncl.nih.gov/brc/>) (41) and distributed it to approximately 9200 health care professionals. Use of the tool in clinical practice has not been well studied. Whether clinicians will regularly use this or other similar risk assessment tools has yet to be determined.

### Considerations of Harm

Few prospective population-based studies provide information on the incidence of thromboembolic events in women not taking tamoxifen or the degree to which that risk varies in the presence of such factors as ethnicity, increasing age, smoking, and hypertension (50–56). Because thromboembolic events (stroke, pulmonary embolus, and deep venous thrombosis) were small in the BCPT and MORE trials (Table 3), the CIs around the increase in relative risk were wide. Thus, we are uncertain about both the baseline absolute risk for thromboembolic events in the community and the relative risk by which the baseline risk is multiplied for tamoxifen users. The increase in relative risk for venous thromboembolism conferred by tamoxifen

or raloxifene therapy does not seem to differ much from that seen with oral contraceptives (57) or hormone replacement therapy (58).

### Weighing Benefits and Harms

Using the best available community baseline data and relative risks from the BCPT, Gail and colleagues calculated the number of excess adverse events for hypothetical populations of various ages who received tamoxifen for 5 years (49). Because of uncertainties regarding data from the Gail model and baseline risk in community groups, these numbers should be viewed as rough approximations. The number of adverse events, for example, would probably be higher in women with hypertension or other risk factors for thromboembolic events or with a family history of endometrial cancer. Adverse events would be lower in women with no predisposition to thromboembolic events and in women who have had hysterectomies.

The **Figure** is useful, however, to show general trends. Younger women, on average, have a lower incidence of chemoprevention harms, so the benefit-to-harm ratio is more favorable for younger than older women. Benefit increases with higher breast cancer risk: The benefit-to-harm ratio becomes more favorable for higher-risk women than for lower risk women. Thus, the group with the most favorable benefit-to-harm profile is younger women with higher breast cancer risk, probably a small percentage.

Although the **Figure** provides estimates of the probability that chemoprevention will prevent cancer or cause harms, the weight attached to these outcomes depends on individual values. The level of risk at which expected benefits begin to outweigh expected harms will be different for different women. These estimates of benefits and harms should be applied only to white women because the chemoprevention trials included very few women of other ethnicities (59, 60). In general, the tradeoff between benefits and harms seems to be less favorable for African-American women because they have a lower risk for breast cancer (3) and higher background rates of adverse events (50, 56).

Two well-conducted cost-effectiveness studies (61, 62), based on BCPT data, have been published. Using different methods and different assumptions, both studies examined the incremental cost-effectiveness of chemoprevention for cohorts of women similar to those in the BCPT. For high-risk women aged 35 to 49 years, the studies calculated estimates of \$41 372 to \$46 619 per additional life-year gained; for women aged 60 to 69 years, 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 years of benefit as opposed to 5 years of benefit from tamoxifen, and assumptions of previous hysterectomy, but in each case the ratios were most favorable for younger women.

The U.S. Food and Drug Administration has approved the use of tamoxifen, but not raloxifene, for breast

cancer risk reduction in women who are 35 years of age or older and have a 5-year risk of at least 1.67% (60, 63).

### Future Research

Many questions remain about chemoprevention of breast cancer (64). First, we need to learn more about the effects of the drugs. We need better information about the optimal dose, the duration of effect, the presence and magnitude of any reduction in breast cancer mortality rates, and the magnitude of known and unknown adverse or beneficial effects (65, 66). Studies in women with breast cancer indicate that treatment with tamoxifen for longer than 5 years confers no additional benefit. It is not known what happens to incidence of breast cancer once women stop taking a chemopreventive drug. Studies of adjuvant tamoxifen use for breast cancer treatment have found that the benefit lasts at least another 5 years and probably longer after the 5-year treatment period (67, 68). Whether the same holds true for chemoprevention is not known.

Second, we need to learn how best to use tamoxifen and raloxifene. This includes finding better ways to select women most likely to benefit and least likely to be harmed, as well as determining better ways to counsel them about the effects of chemoprevention (69, 70). How many eligible women will choose to take tamoxifen or raloxifene for 5 years is uncertain.

Further clinical trials are needed to answer these and other questions. Because many women in the BCPT placebo group began taking tamoxifen after the study results were made public, the BCPT is unlikely to provide further information on chemoprevention. The International Breast Cancer Intervention Study, based in the United Kingdom, Europe, and Australia, is an ongoing placebo-controlled study of breast cancer chemoprevention with tamoxifen (71). The National Cancer Institute has launched a study, the Study of Tamoxifen and Raloxifene (STAR) trial, that will directly compare tamoxifen and raloxifene (72). Results are anticipated by 2006. Another RCT, the Raloxifene Use for the Heart (RUTH) study, will assess the effects of raloxifene compared with placebo on both coronary heart disease and breast cancer (73). An important question is whether the RUTH trial will corroborate the MORE finding of a beneficial cardiovascular effect of raloxifene.

Although current evidence suggests that the tradeoff between benefits and harms may be acceptable for relatively few women, these studies of tamoxifen and raloxifene signal a new and promising direction for research in the control of breast cancer. We should pursue this direction energetically.

### APPENDIX: METHODS

The Research Triangle Institute–University of North Carolina Evidence-based Practice Center (EPC), together with members of the current U.S. Preventive Services Task Force (USPSTF), sought to clarify issues concerning che-

moprevention to prevent breast cancer by performing a systematic review of the relevant scientific literature.

### Analytic Framework

The systematic evidence review (available on the Agency or Healthcare Research and Quality Web site at [www.ahrq.gov/clinic/uspstfix.htm](http://www.ahrq.gov/clinic/uspstfix.htm)) examines the evidence supporting the use of chemoprevention to prevent breast cancer among women who have never had the disease. **Appendix Figure 1** presents a comprehensive analytic framework for this topic. For the variable, "Population at risk for breast cancer," several populations should be considered: 1) premenopausal women at average risk for breast cancer, 2) premenopausal women at high risk for breast cancer, 3) postmenopausal women at average risk for breast cancer, and 4) postmenopausal women at high risk for breast cancer. In addition, because of the effect of tamoxifen or other chemopreventive agents on other potentially serious conditions, women with particularly increased (or decreased) risk for thromboembolic events, bone fractures, or endometrial cancer should be considered separately. Some of the adverse effects of tamoxifen or raloxifene ("Adverse effects/costs" of chemoprevention) are deep venous thromboembolism, pulmonary embolism, stroke, endometrial cancer, hot flashes, and cataracts. Possible benefits from tamoxifen or raloxifene chemoprevention ("Other beneficial effects") include reduced risk for heart disease and bone fractures. "Health outcomes" include mortality or morbidity from breast cancer. We also consider "Incidence of breast cancer" to be a health outcome worthy of consideration in its own right. "Adverse effects/costs" of treatment include adverse effects of chemotherapy, surgery, and radiation therapy used to treat breast cancer.

### Key Questions

The primary, overarching question is: 1) Do chemopreventive agents reduce mortality from breast cancer? The secondary questions (that is, linkage questions) are: 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 for adverse effects? and 5) What are the costs associated with chemoprevention of breast cancer? No clinical trial has been large or long enough to examine the impact of chemoprevention on death from breast cancer (key question 1). In addition, the effectiveness of treatment for breast cancer is clear and has been examined in a continuing rigorous meta-analysis. The adverse effects of treatment are also well documented. Therefore, this review focuses on key questions 2 through 5. In these questions, we consider evidence about issues of dose and duration of chemoprevention.

### Inclusion and Exclusion Criteria

We prospectively established inclusion and exclusion criteria for the key questions. For key questions 2 through 4, we required randomized, controlled trials of chemopreventive agents in populations of women without breast

cancer in which the outcome measures included breast cancer incidence, mortality, or both. Because the only agents we found that met these criteria were selective estrogen-receptor modulators, we specifically searched for studies of these agents.

### Literature Search and Review of Abstracts and Articles

We used the inclusion and exclusion criteria to develop the search criteria provided in **Appendix Table 1**. Study selection is detailed in **Appendix Figure 2**. We searched MEDLINE for studies of the appropriate design in humans. Our search strategy yielded 635 potentially useful articles (**Appendix Table 2**). We added another 65 articles by searching reference lists of reviews, the Cochrane Library, and guidelines. Our evaluation strategy involved two phases. The first phase used broad search terms and review criteria for all 700 article abstracts; the aim was to maximize the probability that all articles that could be useful in any way came to our attention (**Appendix Table 3**). Four EPC staff independently reviewed the titles and abstracts of the 700 articles identified by the literature searches 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 EPC team members reviewed the full articles and made a final decision about inclusion or exclusion by consensus. A total of 70 articles were examined in phase 2 (**Appendix Table 4**). The second phase used more stringent review criteria for full review of the articles themselves to focus our attention on papers that most directly answered the key questions (**Appendix Table 3**). Only four studies met all inclusion criteria from phase 2 (**Appendix Table 4**). We abstracted these four studies into an evidence table, evaluating their quality in detail. Where appropriate in the other parts of the review, we cite articles that are not in the evidence tables; these studies or materials may not directly address the key questions but assist in interpretation of the articles in the evidence tables. To characterize the quality of the included studies, we rated the internal and external validity for each article in the evidence table by using criteria developed by the USPSTF Methods Work Group. We 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. In all of these steps, EPC staff collaborated with two members of the USPSTF who acted as liaisons for this topic. The collaboration took place chiefly by e-mail and conference calls. Steps in the development of the systematic evidence review on this topic were presented at USPSTF meetings in May and September 1999 and February 2000. At these meetings, the EPC staff and Task Force liaisons also were able to discuss the analytic framework and key questions, literature search strategy, results, and implications of the findings.

From Cecil G. Sheps Center for Health Services Research, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; Virginia Commonwealth University, Fairfax, Virginia; American College of Physicians—American Society of Internal Medicine, Philadelphia, Pennsylvania; and Research Triangle Institute, Research Triangle Park, North Carolina.

**Disclaimer:** 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 U.S. Agency for Healthcare Research and Quality, the U.S. Department of Defense, or the U.S. Department of Health and Human Services.

**Acknowledgments:** The authors thank David Atkins, MD, MPH, Director; Dana Best, MD, MPH; and Eve Shapiro of the Agency for Healthcare Research and Quality Clinical Prevention Program. They thank Carmen Lewis, MD, MPH, and Margaret Wooddell, MA, for assistance in reviewing the studies of tamoxifen and raloxifene cited in this paper; Audrina J. Bunton, BA, and Lynn Whitener, MSLS, DrPH, of University of North Carolina, and Sonya Sutton, BSPH, and Loraine Monroe of the Research Triangle Institute; and Bahjat Qaqish, MD, PhD, for statistical assistance.

**Grant Support:** This study was developed by the Research Triangle Institute—University of North Carolina Evidence-based Practice Center under contract to the Agency for Healthcare Research and Quality (Contract No. 290-97-0011), Rockville, Maryland.

**Requests for Reprints:** Reprints are available from the AHRQ Web site at [www.ahrq.gov](http://www.ahrq.gov) (click on Preventive Services) and in print through the AHRQ Publications Clearinghouse (800-358-9295).

Current author addresses, the appendix, appendix figures, and appendix tables are available at [www.annals.org](http://www.annals.org).

**Current Author Addresses:** Dr. Kinsinger: Program on Prevention, CB# 7508, Wing D, Room 383, University of North Carolina School of Medicine, Chapel Hill, NC 27599-7508. Dr. Harris: Cecil G. Sheps Center for Health Services Research, CB# 7590, University of North Carolina at Chapel Hill, 725 Airport Road, Chapel Hill, NC 27599-7590. Dr. Woolf: Department of Family Practice, Virginia Commonwealth University, 3712 Charles Stewart Drive, Fairfax, VA 22033. Dr. Sox: American College of Physicians—American Society of Internal Medicine, 190 N. Independence Mall West, Philadelphia, PA 19106-1572. Dr. Lohr: Research Triangle Institute, 3040 Cornwallis Road, Research Triangle Park, NC 27709-2194.

## References

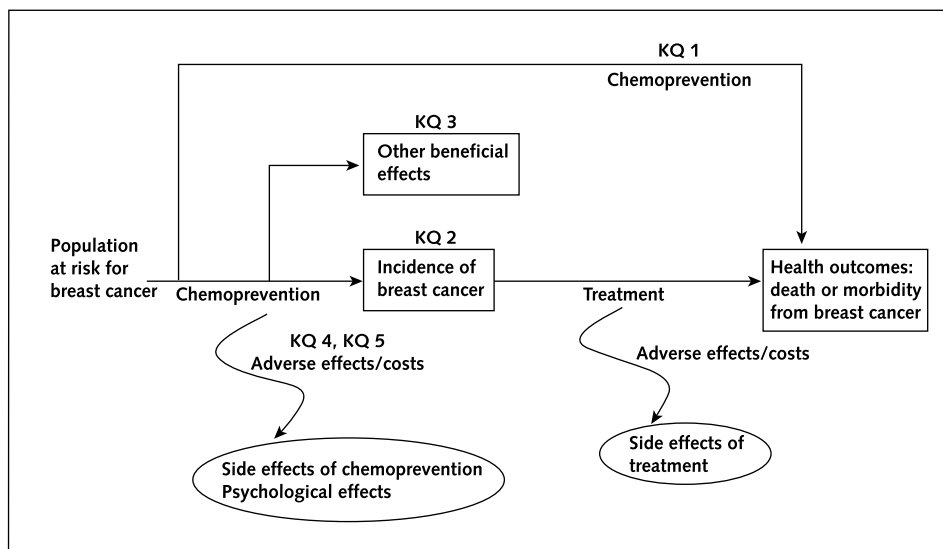
- Jemal A, Thomas A, Murray T, Thun M. Cancer statistics, 2002. *CA Cancer J Clin.* 2002;52:23-47. [PMID: 11814064]
- Recent trends in mortality rates for four major cancers, by sex and race/ethnicity—United States, 1990-1998. *MMWR Morb Mortal Wkly Rep.* 2002; 51:49-53. [PMID: 11843259]
- Chu KC, Tarone RE, Kessler LG, Ries LA, Hankey BF, Miller BA, et al. Recent trends in U.S. breast cancer incidence, survival, and mortality rates. *J Natl Cancer Inst.* 1996;88:1571-9. [PMID: 8901855]
- Kelsey JL, Bernstein L. Epidemiology and prevention of breast cancer. *Annu Rev Public Health.* 1996;17:47-67. [PMID: 8724215]
- Kelsey JL, Gammon MD, John EM. Reproductive factors and breast cancer. *Epidemiol Rev.* 1993;15:36-47. [PMID: 8405211]
- Verloop J, Rookus MA, van der Kooy K, van Leeuwen FE. Physical activity and breast cancer risk in women aged 20-54 years. *J Natl Cancer Inst.* 2000;92:

- 128-35. [PMID: 10639514]
7. Hankinson SE, Willett WC, Manson JE, Colditz GA, Hunter DJ, Spiegelman D, et al. Plasma sex steroid hormone levels and risk of breast cancer in postmenopausal women. *J Natl Cancer Inst.* 1998;90:1292-9. [PMID: 9731736]
8. Cauley JA, Lucas FL, Kuller LH, Stone K, Browner W, Cummings SR. Elevated serum estradiol and testosterone concentrations are associated with a high risk for breast cancer. Study of Osteoporotic Fractures Research Group. *Ann Intern Med.* 1999;130:270-7. [PMID: 10068384]
9. Toniolo PG, Levitz M, Zeleniuch-Jacquotte A, Banerjee S, Koenig KL, Shore RE, et al. A prospective study of endogenous estrogens and breast cancer in postmenopausal women. *J Natl Cancer Inst.* 1995;87:190-7. [PMID: 7707406]
10. Zmuda JM, Cauley JA, Ljung BM, Bauer DC, Cummings SR, Kuller LH, et al. Bone mass and breast cancer risk in older women: differences by stage at diagnosis. *J Natl Cancer Inst.* 2001;93:930-6. [PMID: 11416114]
11. Zhang Y, Kiel DP, Kreger BE, Cupples LA, Ellison RC, Dorgan JF, et al. Bone mass and the risk of breast cancer among postmenopausal women. *N Engl J Med.* 1997;336:611-7. [PMID: 9032046]
12. Hulka BS, Stark AT. Breast cancer: cause and prevention. *Lancet.* 1995;346: 883-7. [PMID: 7564675]
13. Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy. 133 randomised trials involving 31,000 recurrences and 24,000 deaths among 75,000 women. Early Breast Cancer Trialists' Collaborative Group. *Lancet.* 1992;339:1-15. [PMID: 1345950]
14. Tamoxifen for early breast cancer: an overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. *Lancet.* 1998;351:1451-67. [PMID: 9605801]
15. Fisher B, Dignam J, Wolmark N, Wickerham DL, Fisher ER, Mamounas E, et al. Tamoxifen in treatment of intraductal breast cancer: National Surgical Adjuvant Breast and Bowel Project B-24 randomised controlled trial. *Lancet.* 1999;353:1993-2000. [PMID: 10376613]
16. Veronesi U, De Palo G, Marubini E, Costa A, Formelli F, Mariani L, et al. Randomized trial of fenretinide to prevent second breast malignancy in women with early breast cancer. *J Natl Cancer Inst.* 1999;91:1847-56. [PMID: 10547391]
17. Kinsinger L, Harris R, Lewis C, Wooddell M, Woolf S, Sox H, et al. Chemoprophylaxis of Breast Cancer. Systematic Evidence Review. Rockville, MD: Agency for Healthcare Research and Quality; 2001 [In press].
18. Harris RP, Helfand M, Woolf SH, Lohr KN, Mulrow CD, Teutsch SM, et al. Current methods of the US Preventive Services Task Force: a review of the process. *Am J Prev Med.* 2001;20:21-35. [PMID: 11306229]
19. Powles T, Eeles R, Ashley S, Easton D, Chang J, Dowsett M, et al. Interim analysis of the incidence of breast cancer in the Royal Marsden Hospital tamoxifen randomised chemoprevention trial. *Lancet.* 1998;352:98-101. [PMID: 9672274]
20. Fisher B, Costantino JP, Wickerham DL, Redmond CK, Kavanah M, Cronin WM, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *J Natl Cancer Inst.* 1998;90:1371-88. [PMID: 9747868]
21. Veronesi U, Maisonneuve P, Costa A, Sacchini V, Maltoni C, Robertson C, et al. Prevention of breast cancer with tamoxifen: preliminary findings from the Italian randomised trial among hysterectomised women. Italian Tamoxifen Prevention Study. *Lancet.* 1998;352:93-7. [PMID: 9672273]
22. Cummings SR, Eckert S, Krueger KA, Grady D, Powles TJ, Cauley JA, et al. The effect of raloxifene on risk of breast cancer in postmenopausal women: results from the MORE randomized trial. Multiple Outcomes of Raloxifene Evaluation. *JAMA.* 1999;281:2189-97. [PMID: 10376571]
23. Veronesi U, Maisonneuve P, Sacchini V, Rotmensz N, Boyle P. Tamoxifen for breast cancer among hysterectomised women. *Lancet.* 2002;359:1122-4. [PMID: 11943263]
24. Cauley JA, Norton L, Lippman ME, Eckert S, Krueger KA, Purdie DW, et al. Continued breast cancer risk reduction in postmenopausal women treated with raloxifene: 4-year results from the MORE trial. Multiple outcomes of raloxifene evaluation. *Breast Cancer Res Treat.* 2001;65:125-34. [PMID: 11261828]
25. Gail MH, Brinton LA, Byar DP, Corle DK, Green SB, Schairer C, et al. Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. *J Natl Cancer Inst.* 1989;81:1879-86. [PMID: 2593165]
26. Walsh BW, Kuller LH, Wild RA, Paul S, Farmer M, Lawrence JB, et al. Effects of raloxifene on serum lipids and coagulation factors in healthy postmeno-

- pausal women. *JAMA*. 1998;279:1445-51. [PMID: 9600478]
27. Love RR, Newcomb PA, Wiebe DA, Surawicz TS, Jordan VC, Carbone PP, et al. Effects of tamoxifen therapy on lipid and lipoprotein levels in postmenopausal patients with node-negative breast cancer. *J Natl Cancer Inst*. 1990;82:1327-32. [PMID: 2199681]
  28. Barrett-Connor E, Grady D, Sashegyi A, Anderson PW, Cox DA, Hoszowski K, et al. Raloxifene and cardiovascular events in osteoporotic postmenopausal women: four-year results from the MORE (Multiple Outcomes of Raloxifene Evaluation) randomized trial. *JAMA*. 2002;287:847-57. [PMID: 11851576]
  29. Ettinger B, Black DM, Mitlak BH, Knickerbocker RK, Nickelsen T, Genant HK, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. *JAMA*. 1999;282:637-45. [PMID: 10517716]
  30. Day R, Ganz PA, Costantino JP, Cronin WM, Wickerham DL, Fisher B. Health-related quality of life and tamoxifen in breast cancer prevention: a report from the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *J Clin Oncol*. 1999;17:2659-69. [PMID: 10561339]
  31. Stewart HJ. The Scottish trial of adjuvant tamoxifen in node-negative breast cancer. Scottish Cancer Trials Breast Group. *J Natl Cancer Inst Monogr*. 1992;11:117-20. [PMID: 1320920]
  32. Rutqvist LE, Cedermark B, Glas U, Mattsson A, Skoog L, Somell A, et al. Contralateral primary tumors in breast cancer patients in a randomized trial of adjuvant tamoxifen therapy. *J Natl Cancer Inst*. 1991;83:1299-306. [PMID: 1886157]
  33. Fisher B, Redmond C. Systemic therapy in node-negative patients: updated findings from NSABP clinical trials. National Surgical Adjuvant Breast and Bowel Project. *J Natl Cancer Inst Monogr*. 1992;11:105-16. [PMID: 1627417]
  34. Stanford JL, Szklo M, Brinton LA. Estrogen receptors and breast cancer. *Epidemiol Rev*. 1986;8:42-59. [PMID: 3533584]
  35. Habel LA, Stanford JL. Hormone receptors and breast cancer. *Epidemiol Rev*. 1993;15:209-19. [PMID: 8405205]
  36. Potter JD, Cerhan JR, Sellers TA, McGovern PG, Drinkard C, Kushi LR, et al. Progesterone and estrogen receptors and mammary neoplasia in the Iowa Women's Health Study: how many kinds of breast cancer are there? *Cancer Epidemiol Biomarkers Prev*. 1995;4:319-26. [PMID: 7655325]
  37. Cummings SR, Duong T, Kenyon E, Cauley JA, Whitehead M, Krueger KA, et al. Serum estradiol level and risk of breast cancer during treatment with raloxifene. *JAMA*. 2002;287:216-20. [PMID: 11779264]
  38. King MC, Wieand S, Hale K, Lee M, Walsh T, Owens K, et al. Tamoxifen and breast cancer incidence among women with inherited mutations in BRCA1 and BRCA2: National Surgical Adjuvant Breast and Bowel Project (NSABP-P1) Breast Cancer Prevention Trial. *JAMA*. 2001;286:2251-6. [PMID: 11710890]
  39. MacGregor JI, Jordan VC. Basic guide to the mechanisms of antiestrogen action. *Pharmacol Rev*. 1998;50:151-96. [PMID: 9647865]
  40. Fisher B, Costantino J. Highlights of the NSABP Breast Cancer Prevention Trial. *Cancer Control*. 1997;4:78-86. [PMID: 10763006]
  41. Breast Cancer Risk Assessment Tool. National Cancer Institute (NCI) and National Surgical Adjuvant Breast and Bowel Project (NSABP). Accessed at <http://bcra.nci.nih.gov/brc/> on 8 February 2002.
  42. Spiegelman D, Colditz GA, Hunter D, Hertzmark E. Validation of the Gail et al. model for predicting individual breast cancer risk. *J Natl Cancer Inst*. 1994;86:600-7. [PMID: 8145275]
  43. Bondy ML, Lustbader ED, Halabi S, Ross E, Vogel VG. Validation of a breast cancer risk assessment model in women with a positive family history. *J Natl Cancer Inst*. 1994;86:620-5. [PMID: 8003106]
  44. Costantino JP, Gail MH, Pee D, Anderson S, Redmond CK, Benichou J, et al. Validation studies for models projecting the risk of invasive and total breast cancer incidence. *J Natl Cancer Inst*. 1999;91:1541-8. [PMID: 10491430]
  45. Armstrong K, Eisen A, Weber B. Assessing the risk of breast cancer. *N Engl J Med*. 2000;342:564-71. [PMID: 10684916]
  46. Benichou J, Gail MH, Mulvihill JJ. Graphs to estimate an individualized risk of breast cancer. *J Clin Oncol*. 1996;14:103-10. [PMID: 8558184]
  47. Rockhill B, Spiegelman D, Byrne C, Hunter DJ, Colditz GA. Validation of the Gail et al. model of breast cancer risk prediction and implications for chemoprevention. *J Natl Cancer Inst*. 2001;93:358-66. [PMID: 11238697]
  48. Gail MH, Costantino JP. Validating and improving models for projecting the absolute risk of breast cancer [Editorial]. *J Natl Cancer Inst*. 2001;93:334-5. [PMID: 11238688]
  49. Gail MH, Costantino JP, Bryant J, Croyle R, Freedman L, Helzlsouer K, et al. Weighing the risks and benefits of tamoxifen treatment for preventing breast cancer. *J Natl Cancer Inst*. 1999;91:1829-46. [PMID: 10547390]
  50. Sacco RL, Hauser WA, Mohr JP. Hospitalized stroke in blacks and Hispanics in northern Manhattan. *Stroke*. 1991;22:1491-6. [PMID: 1962322]
  51. Broderick JP, Phillips SJ, Whisnant JP, O'Fallon WM, Bergstralh EJ. Incidence rates of stroke in the eighties: the end of the decline in stroke? *Stroke*. 1989;20:577-82. [PMID: 2718196]
  52. Silverstein MD, Heit JA, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ 3rd. Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. *Arch Intern Med*. 1998;158:585-93. [PMID: 9521222]
  53. Whisnant JP, Wiebers DO, O'Fallon WM, Sicks JD, Frye RL. A population-based model of risk factors for ischemic stroke: Rochester, Minnesota. *Neurology*. 1996;47:1420-8. [PMID: 8960721]
  54. Rosamond WD, Folsom AR, Chambless LE, Wang CH, McGovern PG, Howard G, et al. Stroke incidence and survival among middle-aged adults: 9-year follow-up of the Atherosclerosis Risk in Communities (ARIC) cohort. *Stroke*. 1999;30:736-43. [PMID: 10187871]
  55. Manolio TA, Kronmal RA, Burke GL, O'Leary DH, Price TR. Short-term predictors of incident stroke in older adults. The Cardiovascular Health Study. *Stroke*. 1996;27:1479-86. [PMID: 8784116]
  56. Kuller L, Fisher L, McClelland R, Fried L, Cushman M, Jackson S, et al. Differences in prevalence of and risk factors for subclinical vascular disease among black and white participants in the Cardiovascular Health Study. *Arterioscler Thromb Vasc Biol*. 1998;18:283-93. [PMID: 9484995]
  57. Leblanc ES, Laws A. Benefits and risks of third-generation oral contraceptives. *J Gen Intern Med*. 1999;14:625-32. [PMID: 10571709]
  58. Daly E, Vessey MP, Hawkins MM, Carson JL, Gough P, Marsh S. Risk of venous thromboembolism in users of hormone replacement therapy. *Lancet*. 1996;348:977-80. [PMID: 8855852]
  59. Taylor AL, Adams-Campbell LL, Wright JT Jr. Risk/benefit assessment of tamoxifen to prevent breast cancer—still a work in progress? [Editorial] *J Natl Cancer Inst*. 1999;91:1792-3. [PMID: 10547378]
  60. Lippman SM, Brown PH. Tamoxifen prevention of breast cancer: an instance of the fingerpost. *J Natl Cancer Inst*. 1999;91:1809-19. [PMID: 10547388]
  61. Noe LL, Becker RV 3rd, Gradishar WJ, Gore M, Trotter JP. The cost effectiveness of tamoxifen in the prevention of breast cancer. *Am J Manag Care*. 1999;5:389-406. [PMID: 10538851]
  62. Grann VR, Sundararajan V, Jacobson JS, Whang W, Heitjan DF, Antman KH, et al. Decision analysis of tamoxifen for the prevention of invasive breast cancer. *Cancer J Sci Am*. 2000;6:169-78. [PMID: 10882333]
  63. Rockhill B, Colditz G, Kaye J. Re: tamoxifen prevention of breast cancer: an instance of the fingerpost [Letter]. *J Natl Cancer Inst*. 2000;92:657-9. [PMID: 10772687]
  64. Bruzzi P. Tamoxifen for the prevention of breast cancer. Important questions remain unanswered, and existing trials should continue [Editorial]. *BMJ*. 1998;316:1181-2. [PMID: 9552991]
  65. Radmacher MD, Simon R. Estimation of tamoxifen's efficacy for preventing the formation and growth of breast tumors. *J Natl Cancer Inst*. 2000;92:48-53. [PMID: 10620633]
  66. Ganz PA, Desmond KA, Leedham B, Rowland JH, Meyerowitz BE, Belin TR. Quality of life in long-term, disease-free survivors of breast cancer: a follow-up study. *J Natl Cancer Inst*. 2002;94:39-49. [PMID: 11773281]
  67. Fisher B, Dignam J, Bryant J, DeCillis A, Wickerham DL, Wolmark N, et al. Five versus more than five years of tamoxifen therapy for breast cancer patients with negative lymph nodes and estrogen receptor-positive tumors. *J Natl Cancer Inst*. 1996;88:1529-42. [PMID: 8901851]
  68. Stewart HJ, Prescott RJ, Forrest AP. Scottish adjuvant tamoxifen trial: a randomized study updated to 15 years. *J Natl Cancer Inst*. 2001;93:456-62. [PMID: 11259471]
  69. Kinsinger L, Harris R. Breast cancer screening discussions for women in their forties. *Breast Disease*. 2001;13:21-31.

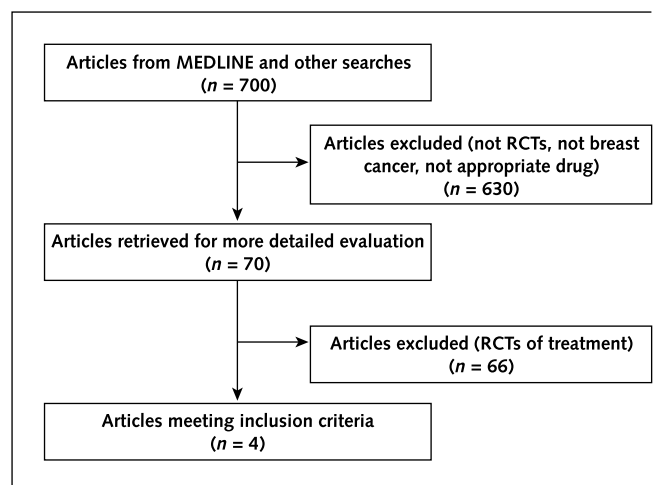
70. Cancer risk communication: what we know and what we need to learn. December 10-11, 1998. *J Natl Cancer Inst Monogr.* 1999;25:1-185. [PMID: 10854446]
71. Cuzick J. A brief review of the International Breast Cancer Intervention Study (IBIS), the other current breast cancer prevention trials, and proposals for future trials. *Ann N Y Acad Sci.* 2001;949:123-33. [PMID: 11795344]
72. Prevention Study of Tamoxifen and Raloxifene (STAR) in Postmenopausal Women at Increased Risk for Invasive Breast Cancer. National Cancer Institute (NCI) and National Surgical Adjuvant Breast and Bowel Project (NSABP). Available at [www.nsabp.pitt.edu/STAR/Index.html](http://www.nsabp.pitt.edu/STAR/Index.html). Accessed 8 February 2002.
73. Barrett-Connor E, Wenger NK, Grady D, Mosca L, Collins P, Kornitzer M, et al. Coronary heart disease in women, randomized clinical trials, HERS and RUTH [Editorial]. *Maturitas.* 1998;31:1-7. [PMID: 10091198]

Appendix Figure 1. Analytical framework.



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

Appendix Figure 2. Article selection.



RCTs = randomized, controlled trials.

**Appendix Table 1. Breast Cancer Chemoprevention: Inclusion and Exclusion Criteria**

Category	Inclusion Criteria	Exclusion Criteria
Databases	MEDLINE	Other databases
Languages	English only	Other languages
Populations	Humans only	Animals
Study design	Randomized, controlled trials; other designs examined separately (cost-effectiveness studies, systematic reviews, meta-analyses)	Letters, editorials, and nonsystematic reviews without original data

**Appendix Table 4. Summary Results from Literature Searches and Reviews**

Variable	Studies, n
Phase 1: abstract reviews	
Obtained from literature search	635
Obtained from supplemental search	65
Excluded at abstract review phase	630
Included for full article review	70
Phase 2: full article review	
Excluded after full review	66
Included in evidence tables	4

**Appendix Table 2. Search Strategy Results for Breast Cancer Chemoprevention**

Steps	Search Strategy	Studies, n
1	Explode breast neoplasms	90 662
2	Limit 1 to (human and female)	70 714
3	Explode tamoxifen	6743
4	Explode estrogen antagonists or raloxifene	10 229
5	Explode estrogen antagonists or keoxifen	10 206
6	Selective estrogen-receptor modulator	32
7	3 or 4 or 5 or 6	10 230
8	2 and 7	3756
9	Limit 8 to controlled clinical trials	45
10	Limit 8 to randomized, controlled trials	447
11	Explode randomized, controlled trials	12 678
12	Explode random allocation	38 532
13	Explode single-blind method	4241
14	Explode double-blind method	55 099
15	11 or 12 or 13 or 14	98 408
16	8 and 15	349
17	9 or 10 or 16	635

**Appendix Table 3. Review Criteria for Abstracts and Articles in Breast Cancer Chemoprevention**

Review criteria for abstracts
Randomized, controlled trial
Either primary prevention or treatment of patients with breast cancer
Difference between arms of trial is tamoxifen or raloxifene
Outcome is incidence, mortality, recurrence, or disease-free interval
Review criteria for articles
Randomized, controlled trial
Primary prevention only
Tamoxifen or raloxifene vs. placebo
Outcome is incidence of or death from breast cancer