Chemoprevention of Breast Cancer: A Summary of the Evidence

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Epidemiology

Despite improvements in the rates of screening and early detection, treatment advances, and healthier lifestyles, breast cancer remains the most common non-skin 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 declined in recent years, 39,600 women are expected to die from 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 an increased risk of breast cancer, 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 the context of trials testing the use of tamoxifen as adjuvant chemotherapy in women with breast cancer.[13] Tamoxifen is a compound with both estrogen-like and anti-estrogen properties (known as a selective estrogen-receptor modulator [SERM]). A meta-analysis of 55 studies of adjuvant tamoxifen therapy demonstrated that it reduced the risk of new cancers in the opposite breast by 47% (P <0.00001) 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 (DCIS).[15] Another SERM, raloxifene, has also been studied as a possible chemopreventive agent. Although Vitamin A analogs, such as fenretinide, have been investigated as potential drugs for chemoprevention, trial results are disappointing to date.[16]

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The USPSTF recommendations based on this evidence review can be found in Chemoprevention of Breast Cancer: Recommendations and Rationale (which precedes this chapter), available on the AHRQ Web site and through the AHRQ Publications Clearinghouse.

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reviewed the scientific evidence on issues related to the benefits and harms of chemoprevention of breast cancer in women without a previous history of breast cancer 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 can be found in the appendix). In general, we focused on randomized controlled trial (RCT) evidence of the effectiveness of chemopreventive agents in reducing incidence and mortality from breast cancer and other potential beneficial and adverse effects. We also examined studies of the cost-effectiveness of these agents. Briefly, our search strategy involved 2 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 articles included in the MEDLINE database from 1966 to December 2001.

Two authors and 2 other RTI–UNC EPC staff 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 reviewed in full those articles meeting the criteria.

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Results

Four RCTs examined the benefits of chemoprevention of breast cancer for women without previous breast cancer (Table 1).[19-22] Three trials used tamoxifen (20 mg/d) as the chemopreventive agent: the Royal Marsden Hospital (UK) 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 studied raloxifene: the Multiple Outcomes of Raloxifene Evaluation trial (MORE).[22] All 4 trials were well designed and conducted: all were double-blinded, 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 2 European tamoxifen trials found a reduction in overall breast cancer incidence. The Royal Marsden study[19] included 2,471 women between 30 and 70 years of age with a family history of at least 1 first-degree relative under age 50 years with breast cancer, 1 first-degree relative with bilateral breast cancer, or 1 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% confidence interval [CI], 0.59-1.43).

The Italian Tamoxifen Prevention Study[21,23] enrolled 5,408 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 either a bilateral (48.3%) or unilateral (18.6%) oophorectomy before menopause. At a median follow-up period of almost 4 years, 41 cases of breast cancer had been diagnosed: 19 in the tamoxifen group and 22 in the placebo group (P=0.64). A relative risk was not given in the paper; we calculated it to be 0.87 (95% CI, 0.62-2.14). After 6.75 years of follow-up, this study reported a non-statistically significant trend toward a reduction in breast cancer incidence for all trial participants (hazard ratio [HR], 0.75; 95% CI, 0.48-1.18); for

Table 1. Summary of 4 randomized controlled trials of breast cancer chemoprevention

Study (n)	Agent, dose	Median follow-up (mo.)	Breast cancer types	Cases of breast cancer (n)		Breast cancer rate/1,000 woman years			Relative risk (95% CI)
				Placebo	Treatment	Placebo	Treatment	*P* value	
Royal Marsden[19] (n=2,471, ages 30-70)	Tamoxifen, 20 mg/d	70	All types	36	34	5.0*	4.7*	0.8	0.94 (0.59-1.43)
Italian study[21,23] (n=5,408, ages 35-70)	Tamoxifen, 20 mg/d	46	All types	22	19	2.3*	2.1*	0.64	0.87† (0.62-2.14)
			ER+	10	8	NA	NA	NA	NA
		81.2	All types	45	34	NA	NA	0.215	HR‡ 0.75 (0.48-1.18)
Breast cancer prevention trial[20] (n=13,388, ages 35+)	Tamoxifen, 20 mg/d	54.6	Invasive	175	89	6.8*	3.4*	<0.00001	0.51 (0.39-0.66)
			ER+	130	41	NA	NA	NA	0.31 (0.22-0.45)
			Noninvasive	69	35	2.7*	1.4*	<0.002	0.50 (0.33-0.77)
Multiple outcomes of Raloxifene evaluation[22,25] (n=7,705, median age 66.5)	Raloxifene, 60 or 120 mg/d	40	All types	32	22	4.3	1.5	<0.001	0.35 (0.21-0.58)
			Invasive	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 types	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)

*Data from reference (23).

†Calculated by authors.

‡HR, hazard ratio, the estimate of relative risk at a given time.

Note: CI indicates Confidence Interval; ER+, estrogen-receptor positive; NA, Data not available.

the 29% of women (similar in each group) who took hormone replacement therapy (HRT) during the trial, the difference was statistically significant (HR, 0.36; 95% CI 0.14-0.91).[23]

In contrast to the European trials, the U.S. BCPT[20] found a halving of the incidence of invasive breast cancer over a median follow-up time of 54.6 months. The BCPT, the largest chemoprevention trial, enrolled 13,388 women aged 35 and older who had an estimated 5-year risk of breast cancer of at least 1.66%. This risk was calculated by applying a multivariate logistic regression model developed by Gail et al[24] 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 (35-49, 50-59, and >60) and estimated 5-year risk of breast cancer (<2.5%, 2.5 to 3.9%, and >4.0%).

Over the course of the BCPT, a total of 264 women were diagnosed with invasive breast cancer: 175 in the placebo group and 89 in the tamoxifen group (RR, 0.51; 95% CI, 0.39-0.66). The absolute risk reduction was 21.4 cases per 1,000 women over 5 years. The number of women who would need to be treated with tamoxifen for 5 years to prevent 1 case of breast cancer (NNT) 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 1,000 women (NNT, 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 versus 41 tamoxifen cases (RR, 0.31; 95% CI, 0.22-0.45); it produced no reduction in estrogen receptor-negative tumors (31 placebo cases, 38 tamoxifen cases).

Given the relatively short period of follow-up, few breast cancer deaths occurred in any of these trials. No study found statistically significant differences in mortality between study arms.

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 7,705 women with osteoporosis or previous vertebral fractures who were at least 2 years postmenopausal and no older than 80 years (median age 66.5 years). Participants were randomly assigned to 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 of breast cancer. After a median follow-up of 40 months, 40 cases of invasive breast cancer were confirmed: 13 cases in the 5,129 women assigned to raloxifene and 27 in the 2,576 women assigned to placebo (RR, 0.24; 95% CI, 0.13-0.44). The absolute risk reduction was about 7.9 cases per 1,000 women over 40 months (NNT, 126). Raloxifene reduced the incidence of estrogen-receptor positive cancers by 90% (RR, 0.10; 95% CI, 0.04-0.24) but had no effect on estrogen-receptor negative tumors (RR, 0.88; 95% CI, 0.26-3.00) or on the 12 cases of DCIS. Data from longer follow-up (48 months) continue to show a substantial decrease in total invasive breast cancer incidence (RR, 0.28; 95% CI, 0.17-0.46) and in the incidence of estrogen receptor-positive cancers (RR, 0.16; 95% CI, 0.09-0.30), but no effect on estrogen receptor-negative tumors (RR, 1.13; 95% CI, 0.35-3.66).[25]

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 breast cancers, HRT use, loss to follow-up, and premature discontinuation of the assigned study medication (Table 2). These factors varied among the trials. Discontinuation of study drugs was problematic in all 4 trials. At the time the reports were published, only a few women in the Royal Marsden study (79 [6.3%]) and in the Italian study (77 [2.9%]) had taken tamoxifen for the full study period (8 years and 5 years, respectively); 2,424 (36.9%) women took tamoxifen for at least 5 years in the BCPT. In the later report 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]

Table 2. Comparison of randomized controlled trials of breast cancer chemoprevention

Study	Family history (%)	ER+ tumors* (%)	HRT use† (%)	Loss to follow-up (%)	Discontinuation of study drug (%)		Women who took Tamoxifen for ≥ 5 years (n[%])
					Placebo	Treatment	
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)
	21	Unk§	29	NA	34	36	2,462 (45)
Breast cancer prevention trial[20]	76	71	0	1.6	20	24	2,424 (36.9)
Multiple outcomes of Raloxifene evaluation[22]	12	60	10	NA	25‖	22‖	Not applicable

*ER+, estrogen receptor-positive.

†HRT, hormone replacement therapy.

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

§Unk, unknown; NA, data not available.

‖Cumulative withdrawal at 36 months (includes loss to follow-up).

Other Potential Benefits of Chemoprevention

Before the BCPT and MORE studies, evidence suggested that tamoxifen and raloxifene had favorable effects on blood lipids and thus might be expected to reduce cardiovascular (CV) events.[26,27] In the BCPT, rates of CV events did not differ between the tamoxifen and placebo arms. A recent report from the MORE trial found no difference between the raloxifene and placebo groups for all participants, but among women with high CV risk, the raloxifene group had a 40% reduction (RR, 0.60; 95% CI 0.38-0.95) in CV events.[28] This result must be considered preliminary because CV events was a secondary outcome and was assessed by self-report.

Both the BCPT and MORE trials also examined the impact of these drugs on bone fractures. The BCPT found a non-statistically significant trend toward a reduction in hip, spine, and Colles' fractures (RR, 0.81 for all fractures combined; 95% CI, 0.63-1.05) in the tamoxifen group. MORE found a 30% to 50% reduction in vertebral fractures (RR, 0.7; 95% CI, 0.5-0.8 for 60 mg/d of raloxifene; RR, 0.5; 95% CI, 0.4-0.7 for 120 mg/d) in the raloxifene group, but no difference between groups in nonvertebral fractures.[29]

Harms of Chemoprevention

Only the BCPT and MORE studies were large enough to evaluate statistically significant differences in the incidence of adverse consequences between women taking tamoxifen or raloxifene and women taking placebo (see Table 3). BCPT participants in the tamoxifen arm had a 2.53 (95% CI, 1.35-4.97) times greater risk of developing endometrial cancer than those in the placebo group (absolute risk increase 7.6 per 1,000 women over 4.5 years).[20] On subgroup analysis, the risk increase was statistically significant for women aged 50 and older (RR, 4.01; 95% CI, 1.70-10.90). Women under age 50 assigned to tamoxifen had no increased risk. All cases of endometrial cancer in the tamoxifen arm were Stage 1; there were no deaths due to endometrial cancer. In the MORE study,[22]

Table 3. Adverse events in 4 randomized controlled trials of breast cancer chemoprevention

Outcomes	Study	No. of events (n)		Cumulative rate/ 1,000 women		Relative risk (95% CI)
		Placebo	Treatment	Placebo	Treatment	
Endometrial cancer	BCPT	15	36	0.91	2.30	2.53 (1.35-4.97)
	<50 y old	8	9	1.09	1.32	1.21 (0.41-3.60)
	≥50 y old	7	27	0.76	3.05	4.01 (1.70-10.90)
	RMH	1	4	NA	NA	NA
	MORE	1	4	NA	NA	0.8 (0.2-2.7)
Stroke	BCPT	24	38	0.92	1.45	1.59 (0.93-2.77)
	<50 y old	4	3	0.39	0.30	0.76 (0.11-4.49)
	≥50 y old	20	35	1.26	2.20	1.75 (0.98-3.20)
	Italian	0	5	NA	NA	NA
Pulmonary embolism	BCPT	6	18	0.23	0.69	3.01 (1.15-9.27)
	<50 y old	1	2	0.10	0.20	2.03 (0.11-119.62)
	≥50 y old	5	16	0.31	1.00	3.19 (1.12-11.15)
	RMH	2	3	NA	NA	NA
	Italian	1	1	NA	NA	NA
	MORE	3	10	NA	NA	3.1 (1.5-6.2)*
Deep vein thrombosis	BCPT	22	35	0.84	1.34	1.60 (0.91-2.86)
	<50 y old	8	11	0.78	1.08	1.39 (0.51-3.99)
	≥50 y old	14	24	0.88	1.51	1.71 (0.85-3.58)
	RMH	2	4	NA	NA	NA
	Italian	3	6	NA	NA	NA
	MORE	5	18	NA	NA	3.1 (1.5-6.2)*

*Results reported for pulmonary embolism and deep vein thrombosis combined.

Note: BCPT indicates the Breast Cancer Prevention Trial[20]; CI, Confidence Interval; Italian, the Italian Tamoxifen Prevention Study[21]; MORE, the Multiple Outcomes of Raloxifene Evaluation[22]; NA, Data not available; RMH, the Royal Marsden Hospital Tamoxifen Chemoprevention Trial.[19]

raloxifene was not associated with an excess of endometrial cancers (RR, 0.8; 95% CI, 0.2-2.7).

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 vein thrombosis, although only the difference for pulmonary embolism reached statistical significance (RR, 3.01; 95% CI, 1.15-9.27).[20] The increased risk was concentrated in women aged 50 and older; the relative risks for women younger than age 50 were smaller than those for older women (Table 3). In the MORE study, women in the raloxifene groups had approximately a 3-fold increased risk of pulmonary embolism and deep vein thrombosis compared with those in the placebo groups (RR, 3.1; 95% CI, 1.5-6.2)19,22; it did not report stroke rates. The total number of thromboembolic events in all 4 trials was small.

The BCPT also reported an increased risk of developing cataracts and having cataract surgery for women assigned to the tamoxifen group (RR, 1.14 [95% CI, 1.01-1.29] and 1.57 [95% CI, 1.16-2.14], 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, 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, 4.5% in the placebo group, statistical significance not given).[20] On a health-related quality of life questionnaire, the mean percentages of women reporting a problem on 4 different sexual functioning measures (eg, lack of sexual interest) was about 1 percentage point greater in the tamoxifen group than in the placebo group; although the differences were statistically significant, they are not likely clinically important.[30] MORE participants assigned to raloxifene also noted higher rates of hot flashes than did women 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 2 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: (a) tamoxifen is effective for some but not all women, and differences in study results are attributable to differences in the study populations; or (b) the differences in trial results are attributable to differences in how the trials were designed and conducted.

Different Groups of Women

Because tamoxifen is effective only for estrogen receptor-positive breast cancer, any factor that reduces the risk for this type of cancer makes it harder to demonstrate a drug effect. Although not established, 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 associated with less estrogen receptor-positive than estrogen receptor-negative breast cancer. If further research shows that, given differences such as these, the women in the European trials were at lower risk of estrogen receptor-positive breast cancer, 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. In the Italian trial, the proportion of all breast cancers that were estrogen receptor-positive (43%) was distinctly lower than in the other trials (60% to 71%) (Table 2). The reduction in breast cancer incidence among women in the Italian study who took HRT,[23] and 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 decreased by tamoxifen; 76% of *BRCA2* tumors were estrogen receptor-positive and there was a nonstatistically significant trend toward a reduction with tamoxifen.[38]

The women in the tamoxifen trials differed on several characteristics other than breast cancer risk that may help explain the differences in the 3 trials.

Differences in the Design and Conduct of the Trials

At least 2 design and implementation issues may be relevant: statistical power and duration of therapy. The power of the trials to find a statistically significant difference in the incidence of breast cancer is limited if the number of cancers detected during the study is small. The numbers of cancers in the Italian (41 in initial report and 79 in the second report) and Royal Marsden (70 cancers)

studies were smaller than that of the BCPT (264), a difference influenced by both the larger number of women enrolled and their higher risk for breast cancer.

Still, the lack of a strong trend favoring tamoxifen in overall breast cancer incidence in the European trials (3 fewer cancers 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 BCPT means that an inadequately powered study design is likely not the full explanation for the differences in the results. The 95% confidence intervals for the BCPT and the 2 European trials overlap only minimally (Table 1). Because factors other than power must account for the findings, we did not combine the 3 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 noncompliance, 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; the effect increases with time up to 5 years of treatment. Thus, a larger proportion of subjects taking the drug for a short period of time would dampen the observed benefit of the drug. The larger BCPT included a larger proportion (37%) of women who took tamoxifen long enough to receive 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 assignment for longer than 1 year, those assigned to tamoxifen had a nonstatistically significant trend toward decreased breast cancer incidence than those on placebo (11 cases vs 19 cases, P=0.16, RR not given); among women in the second Italian report, who took assigned treatment for a longer time, tamoxifen reduced breast cancer incidence (compared to no tamoxifen) among those who also took HRT.

In summary, several features of the European studies and their participants likely reduced the observed effect of tamoxifen relative to BCPT effects; whether these characteristics fully account for the discrepancy between the studies is not clear. We found the evidence from the BCPT sufficiently convincing to conclude that there is substantial benefit from tamoxifen.

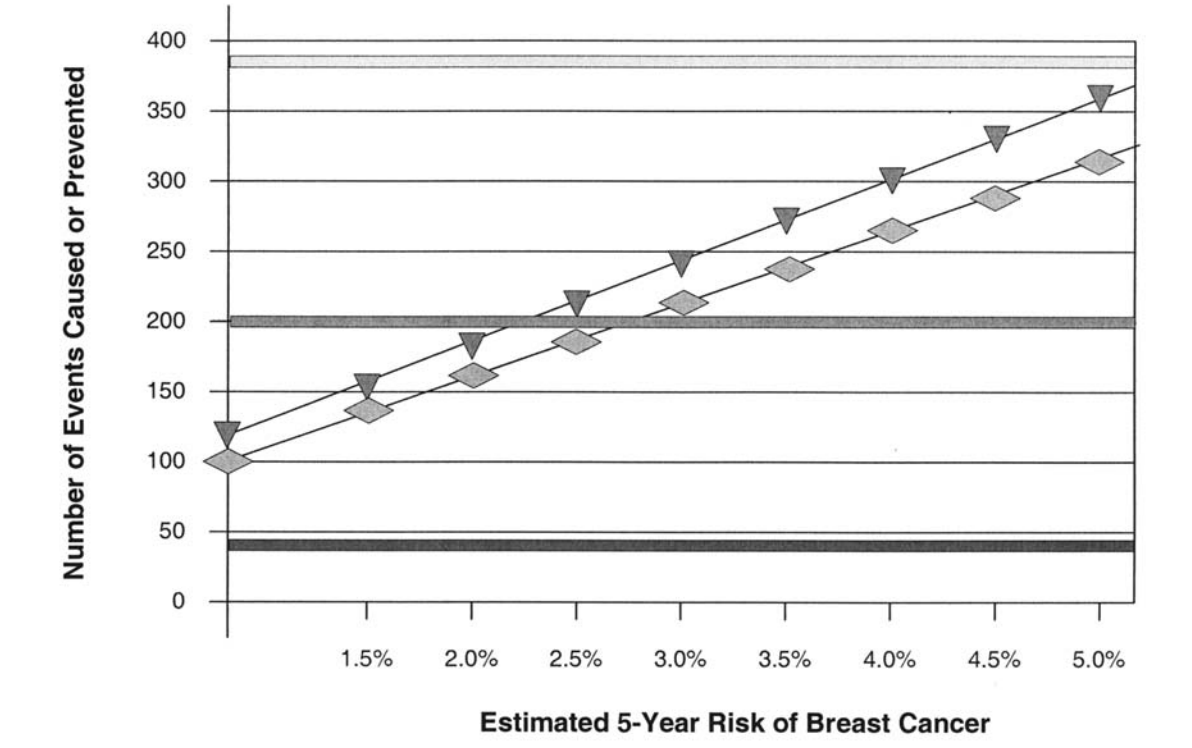
For raloxifene, the primary concern with a conclusion of effectiveness is the fact that only 1 RCT, albeit large and well-conducted, has been done. The strength of this trial, the care with which the endpoint of breast cancer was ascertained, and the similarity of mechanism of action of raloxifene and tamoxifen[39] make it reasonable to conclude that raloxifene is also effective in reducing the incidence of breast cancer.

Considerations of Risk of Developing 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 biologic significance to suggest that chemoprevention would convey a smaller relative risk reduction for women with lower risk. 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 from taking a chemopreventive agent increases directly with the individual's probability of developing estrogen receptor-positive breast cancer (Figure 1). At present, the most commonly used tool for calculating risk of developing breast cancer is the Gail model,[24,41] although it cannot specify a risk just for estrogen receptor-positive cancer. Three studies to examine the validity of the Gail model to predict 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 mammographic screening.[42-44] It overestimates risk among younger

Figure 1. Benefits and harms* of chemoprevention with Tamoxifen per 10,000 women in 3 age groups†



* Harms include endometrial cancer, stroke, and pulmonary embolism combined

† Adapted from Gail et al, 1999[49]

women not undergoing routine mammography.[45] At a Gail model risk of 2%, the 95% confidence interval is approximately 1.6% to 2.5%; the CI is narrower for risks less 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 of 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 et al[49] calculated the number of invasive (both estrogen receptor-positive and estrogen receptor-negative) and noninvasive breast cancers that would be prevented by 5 years of tamoxifen therapy. These calculations for total cancers prevented (invasive and noninvasive combined) are depicted in Figure 1. The number of cases of cancer prevented is slightly higher among younger women because of a slightly higher number of non-invasive cancers prevented.

The National Cancer Institute (NCI) used the Gail model to develop a breast cancer risk assessment calculating tool ("risk disk," available at http://bcra.nci.nih.gov/brc/)[41] and distributed it to about 9,200 health care professionals. Use of the "risk disk" 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 the numbers of thromboembolic events (ie, stroke, pulmonary embolus, and deep vein thrombosis) in the BCPT and MORE trials were small (Table 3), the confidence intervals around the increase in relative risk are wide. Thus, we are uncertain about both the baseline absolute risk of thromboembolic events in the community and the relative risk by which the baseline risk is multiplied for tamoxifen users. The relative risk increase in venous thromboembolism from tamoxifen or raloxifene does not appear to differ much from that of oral contraceptives[57] or HRT.[58]

Weighing Benefits and Harms

Using the best available community baseline data and relative risks from the BCPT, Gail et al calculated the number of excess adverse events for hypothetical populations of various ages taking tamoxifen for 5 years.[49] Because of uncertainties for data from both 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 likely 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 subgroups 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 women with higher breast cancer risk than for women with lower risk. Thus, the group with the most favorable benefit-to-harm profile is younger women with higher breast cancer risk. This is likely to be a small percentage of women.

Although Figure 1 provides estimates of the probability that chemoprevention will prevent cancers or cause harms, the weight attached to these outcomes depends on individual values. The level of breast cancer 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 color.[59,60] In general, the trade-off between benefits and harms appears to be less favorable for African American women because they have a lower risk of developing 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 examined the incremental cost effectiveness of chemoprevention for cohorts of women similar to those in the BCPT. For high-risk women aged 35-49, they calculated estimates of $41,372 to $46,619 per additional life-year gained; for women aged 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.

The 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, and the magnitude of the known and any 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. Not known is what happens to the incidence of breast cancer once women stop the chemopreventive drug. Studies of adjuvant tamoxifen use for the treatment of breast cancer 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 those women most likely to benefit and least likely to be harmed, and 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. Many women in the BCPT placebo group began taking tamoxifen after the study results were made public. Thus, the BCPT is unlikely to provide further information on the many unanswered questions of chemoprevention. The International Breast Cancer Intervention Study (IBIS), 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 that will directly compare tamoxifen and raloxifene, the Study of Tamoxifen and Raloxifene (STAR) trial (NSABP P-2).[72] Results are anticipated by 2006. Another RCT, the Raloxifene Use for the Heart study (RUTH), will assess the effectiveness of raloxifene compared with placebo on both coronary heart disease and breast cancer.[73] An important question is whether RUTH will corroborate the MORE finding of a beneficial CV effect of raloxifene.

Although the trade-off between benefits and harms for the present drugs, given current evidence, may be acceptable for a relatively small number of women, the findings from the 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.

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Appendix: Methods

The RTI-UNC Evidence-based Practice Center (EPC), together with members of the current U.S. Preventive Services Task Force (USPSTF), sought to clarify issues concerning chemoprevention to prevent breast cancer by performing a systematic review of the relevant scientific literature on this topic.

Analytic Framework

The systematic evidence review (SER) on this topic (available on the AHRQ Web site at www.ahrq.gov/clinic/serfiles.htm) examines the evidence for chemoprevention to prevent breast cancer among women who have never had breast cancer. Figure 1 in this appendix presents a comprehensive analytic framework for this topic.

The analytic framework begins on the left side with the population at risk. Several different populations should be considered:

1. premenopausal women with "average" risk of breast cancer;
2. premenopausal women with "high" risk of breast cancer;
3. postmenopausal women with "average" risk of breast cancer;
4. postmenopausal women with "high" risk of breast cancer.

In addition, because of the effect of tamoxifen or other chemopreventive agents on potentially serious conditions other than breast cancer, women with particularly increased (or decreased) risk of thromboembolic events, bone fractures, or endometrial cancer should be considered separately.

Moving to the right in the analytic framework, the "chemoprevention" arrow points to a box labeled "incidence of breast cancer." Moving downward from the chemoprevention arrow is an "adverse effects/costs" arrow. Some of the adverse effects of tamoxifen or raloxifene are deep vein thromboembolism, pulmonary embolism, stroke, endometrial cancer, hot flashes, and cataracts.

Possible benefits from tamoxifen or raloxifene chemoprevention include reduced risk of heart disease and bone fractures. These are listed together in a separate box: "other beneficial effects."

Farther to the right is a "treatment" arrow, leading to a box labeled "health outcomes," which includes mortality and/or morbidity from breast cancer. We also consider "incidence of breast cancer" to be a health outcome worthy of consideration in its own right.

Leading downward from the "treatment" arrow is another "adverse effects/costs" arrow. Included here are adverse effects from chemotherapy, surgery, and radiation therapy used to treat breast cancer.

Finally, an "overarching" arrow for chemoprevention leads directly to reduced mortality and morbidity from breast cancer.

Key Questions

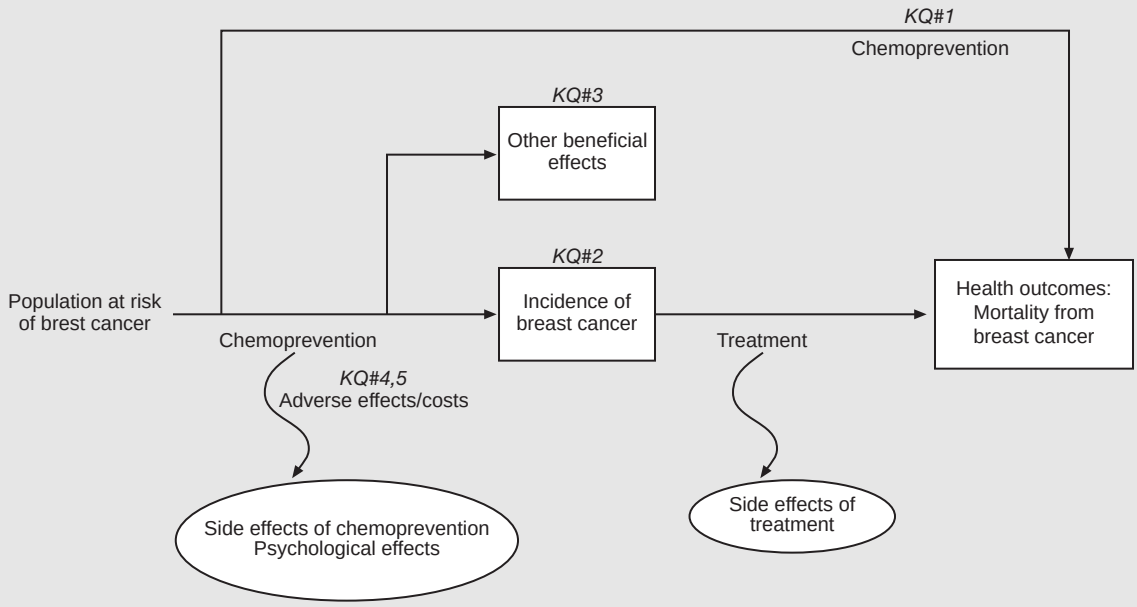
The primary, overarching question, shown as the topmost line in Figure 1, is the following:

1. Do chemopreventive agents reduce mortality from breast cancer?

The secondary questions (ie, linkage questions), shown in the body of Figure 1, are the following:

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?

Appendix Figure 1. Analytic framework: chemoprevention of breast cancer



Key Questions (KQ): (1) Do chemoprevention 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?

No clinical trial has been large or long enough to examine the impact of chemoprevention on mortality 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. We consider in these questions evidence about issues of dose and duration of chemoprevention.

Inclusion/Exclusion Criteria

We prospectively established inclusion and exclusion criteria for the key questions. For key questions 2-4, we required randomized controlled trials (RCTs) of chemoprevention agents in populations of women without breast cancer in which the outcome measures included breast cancer incidence and/or mortality. Because the only agents we found that met these criteria were selective estrogen-receptor modulators (SERMs), we specifically searched for studies of these agents.

Literature Search and Review of Abstracts/Articles

We operationalized the inclusion and exclusion criteria into the search criteria given in Appendix Table 1. We searched the MEDLINE database for studies of the appropriate study design in humans. Our search strategy yielded 635 potentially useful articles (Appendix Table 2). We added another 65 articles from searching reference lists of reviews, the Cochrane library, and guidelines.

Our evaluation strategy involved 2 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

Appendix Table 1. Breast cancer chemoprevention: inclusion and exclusion criteria

Category	Inclusion	Exclusion
General inclusion and exclusion criteria		
Databases	MEDLINE	Other databases
Languages	English only	Other languages
Populations	Humans only	Animal studies
Study Design	Randomized controlled trials; other designs examined separately (cost-effectiveness, systematic reviews, meta-analyses)	Letters, editorials, and non-systematic reviews that have no original data

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 those papers that most directly answered the key questions (Appendix Table 3). Only 4 studies met all inclusion criteria from phase 2 (Appendix Table 4). We abstracted these 4 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 they do 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

Appendix Table 2. Breast cancer chemoprevention: search strategy results

Search strategy for breast cancer chemoprevention		
1	Explode breast neoplasms	90,662
2	Limit 1 to (human and female)	70,714
3	Explode Tamoxifen	6,743
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	3,756
9	Limit 8 to controlled clinical trial	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	4,241
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

for each article in the evidence table 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 these steps, EPC staff collaborated with 2 members of the USPSTF who acted as liaisons for this topic. The collaboration took place chiefly by electronic mail and conference calls. Steps in the development of the SER on this topic were presented at USPSTF meetings in May and September 1999 and February 2000 where 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.

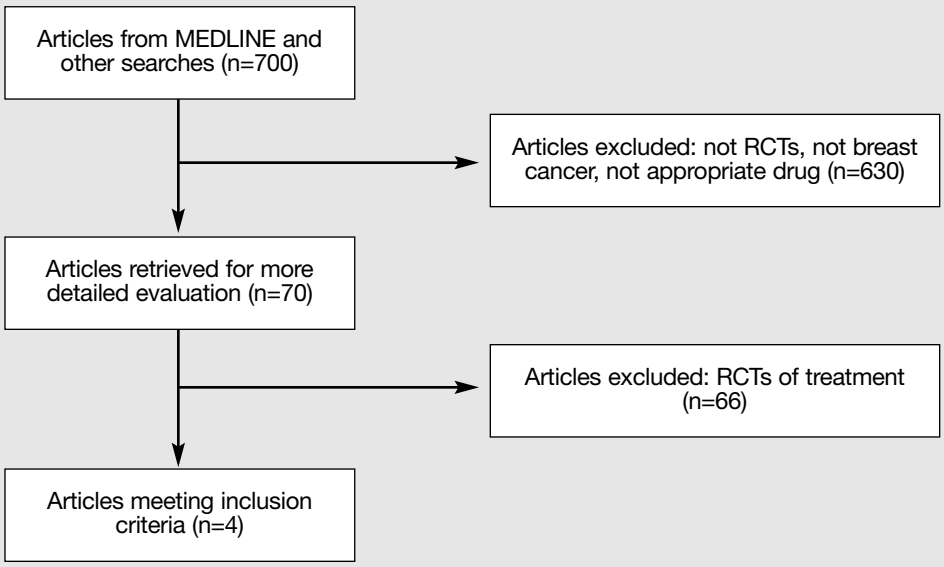
Appendix Table 3. Breast cancer chemoprevention: review criteria for abstracts and articles

Review criteria for breast cancer chemoprevention
Review criteria for abstracts
i. randomized controlled trial;
ii. either primary prevention or treatment of patients with breast cancer;
iii. difference between arms of trial is tamoxifen or raloxifene; and
iv. outcome is incidence, mortality, recurrence, or disease-free interval.
Review criteria for articles
i. randomized controlled trial;
ii. primary prevention only;
iii. tamoxifen/raloxifene versus placebo; and
iv. outcome is incidence of or mortality from breast cancer.

Appendix Table 4. Summary results from literature searches and reviews

Search and review results	
Phase 1: Abstract reviews	
From literature search	635
From supplemental search	65
Excluded at abstract review phase	630
Included for full article review	70
Phase 2: Full article reviews	
Excluded after full review	66
Included in evidence tables	4

Appendix Figure 2. Selecting articles for chemoprevention of breast cancer



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