American Society of Clinical Oncology Technology Assessment of Pharmacologic Interventions for Breast Cancer Risk Reduction Including Tamoxifen, Raloxifene, and Aromatase Inhibition

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Objective: To update an evidence-based technology assessment of chemoprevention strategies for breast cancer risk reduction.

Potential Interventions: Tamoxifen, raloxifene, aromatase inhibition, and fenretinide.

Outcomes: Outcomes of interest include breast cancer incidence, breast cancer–specific survival, overall survival, and net health benefit.

Evidence: A comprehensive, formal literature review was conducted for relevant topics. Testimony was collected from invited experts and interested parties. The American Society of Clinical Oncology (ASCO) prescribed technology assessment procedure was followed.

Values: More weight was given to published randomized trials.

Benefits/Harms: A woman's decision regarding breast cancer risk reduction strategies is complex and will depend on the importance and weight attributed to information regarding both cancer- and noncancer-related risks and benefits.

Conclusions: For women with a defined 5-year projected breast cancer risk of $\geq 1.66\%$, tamoxifen (at 20 mg/d for 5 years) may be offered to reduce their risk.

Risk/benefit models suggest that greatest clinical benefit with least side effects is derived from use of tamoxifen in younger (premenopausal) women (who are less likely to have thromboembolic sequelae and uterine cancer), women without a uterus, and women at higher breast cancer risk. Data do not as yet suggest that tamoxifen provides an overall health benefit or increases survival. In all circumstances, tamoxifen use should be discussed as part of an informed decision-making process with careful consideration of individually calculated risks and benefits. Use of tamoxifen combined with hormone replacement therapy or use of raloxifene, any aromatase inhibitor or inactivator, or fenretinide to lower the risk of developing breast cancer is not recommended outside of a clinical trial setting. This technology assessment represents an ongoing process and recommendations will be updated in a timely matter.

Validation: The conclusions were endorsed by the ASCO Health Services Research Committee and the ASCO Board of Directors.

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THE WORKING group (Appendix) reviewed the literature and, in a series of meetings and conference calls, considered recommendations from the original 1999 technology assessment.[1] The technology assessment was limited to breast cancer chemoprevention. By this definition, surgical and lifestyle interventions were excluded from consideration but have been reviewed elsewhere.[2,3]

METHODS

The technology assessment followed previously described procedures.[1] A comprehensive literature review incorporated MEDLINE, Cancer Lit, PubMed, and scientific Internet sites (selected by link frequency). References were searched for the period from the last technology assessment (June 1999) through March 2002 using the following search terms: tamoxifen, raloxifene, aromatase inhibitors, retinoids and breast cancer, breast cancer risk reduction, and breast cancer risk communication. Of the 3,733 references identified and reviewed at least by title, 119 are referenced in the current report. Published information was updated by including key investigators in the Working Group and inviting corporate entities to provide emerging evidence (see Acknowledgment).

RESULTS

Conclusions of this technology assessment are outlined below (Table 1).

Tamoxifen

For women with a 5-year projected breast cancer risk of $\geq 1.66\%$, tamoxifen (at 20 mg/d for 5 years) may be offered to reduce risk. Consideration of tamoxifen is appropriate for the goal of lowering the short-term risk of developing breast cancer. Risk/benefit models suggest that greatest clinical

Table 1. Conclusions

Tamoxifen

For women with a 5-year projected breast cancer risk of ≥ 1.66%, tamoxifen (at 20 mg/d for 5 years) may be offered to reduce risk. Consideration of tamoxifen is appropriate for the goal of lowering the short-term risk of developing breast cancer. Risk/benefit models suggest that greatest clinical benefit with least side effects are derived from use of tamoxifen in younger (premenopausal) women (who are less likely to have thromboembolic sequelae and uterine cancer), women without a uterus, and women at higher breast cancer risk. Data do not as yet suggest that tamoxifen provides overall health benefit or increases survival.

Risk/benefit calculation for tamoxifen use is challenging with no simple scale to weigh the disparate clinical outcomes that vary in their morbidity and mortality risk. To inform potential tamoxifen users, the relative risk of all outcomes under tamoxifen influence need to be translated into absolute terms for each woman, considering outcomes under tamoxifen influence. In all circumstances, tamoxifen use should be discussed as part of an informed decision-making process with careful consideration of risks and benefits.

Raloxifene

Use of raloxifene to lower breast cancer risk is not recommended. Raloxifene should be reserved for its approved indication to prevent or treat bone loss in postmenopausal women.

Aromatase inhibitor/inactivators

Use of any aromatase inhibitor or aromatase inactivator to lower breast cancer risk is not recommended.

Retinoids

Use of frenretinide to lower breast cancer risk is not recommended.

Other issues

Clinical trials evaluating potential chemoprevention agents either alone or in combination are encouraged.

Placebo controls are appropriate for breast cancer risk reduction trials since no intervention has been demonstrated to favorably impact net health or survival.

Use of tamoxifen in combination with hormone replacement therapy outside of a clinical trial setting is not recommended given uncertainty regarding long-term side effects of the combination and the association of hormone replacement therapy with increased breast cancer risk in observational studies.

Use of tamoxifen for risk reduction in combination or sequentially with other agents (such as raloxifene or aromatase inhibitors) has either not been studied or studies have not yet been reported.

This technology assessment represents an ongoing process, and we will continue to monitor data and update recommendations in a timely manner.

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benefit with least side effects are derived from use of tamoxifen in younger (premenopausal) women (who are less likely to have thromboembolic sequelae and uterine cancer), women without a uterus, and women at higher breast cancer risk. Data do not as yet suggest that tamoxifen provides an overall health benefit or increases survival.

Risk/benefit calculation for tamoxifen use is challenging. There is no simple scale to weigh the disparate clinical outcomes that vary in their morbidity and mortality risk. To inform potential tamoxifen users, the relative risk of out-

comes under tamoxifen influence needs to be translated into absolute terms for each woman. In all circumstances, tamoxifen use should be discussed as part of an informed decision-making process with careful consideration of risks and benefits.

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Use of raloxifene to lower breast cancer risk is not recommended. Raloxifene should be reserved for its approved indication to prevent or treat bone loss in postmenopausal women.

Aromatase Inhibitor/Inactivators

Use of any aromatase inhibitor or aromatase inactivator to lower breast cancer risk is not recommended.

Retinoids

Use of fenretinide to lower breast cancer risk is not recommended.

Other Issues

Clinical trials evaluating potential chemoprevention agents either alone or in combination are encouraged. Use of tamoxifen in combination with hormone replacement therapy (HRT) is not recommended outside of a clinical trial setting, given the uncertainty regarding long-term side effects of the combination and the association of HRT with increased breast cancer risk in observational studies. Use of tamoxifen in combination or sequentially with raloxifene or aromatase inhibitors for breast cancer risk reduction has either not been studied or studies have yet to be reported. Placebo controls are appropriate for breast cancer risk reduction trials since no intervention has been demonstrated to have a favorable impact on net health or survival.

This technology assessment represents an ongoing process, and the Working Group will continue to monitor data and update recommendations in a timely manner. The basis for these recommendations follow. Clinical evidence is reviewed by chemopreventive agent.

TAMOXIFEN

Clinical Evidence Relevant to Tamoxifen's Effect on Breast Cancer Risk Reduction

Tamoxifen's influence on breast cancer in risk reduction trials. Tamoxifen is the only agent approved by the United States Food and Drug Administration (FDA) for breast cancer risk reduction. Four randomized trials are prospectively evaluating tamoxifen (Nolvadex; AstraZeneca, Wilmington, DE) for breast cancer risk reduction.[4-7] At the last technology assessment, three trials had reported

Table 2. Randomized, Prospective Trials of Tamoxifen for Primary Breast Cancer Risk Reduction

	Eligibility			Characteristics of Study Population			
Trial	Age Range (years)	Included	Excluded	Median Age (years)	Concurrent HRT Use (%)	Breast CA Family History (% with 1st degree relative)	Prior Breast Diagnosis
NSABP P1	≥ 35 and judged to have ≥ 10-year life expectancy	Age ≥ 60 or 35-59 with 5-year breast CA risk of ≥ 1.66% (Gail model) or prior LCIS	Current HRT, prior DVT or PE, HRT or oral contraceptive for 3 months prior, prior DCIS	52	HRT use was study exclusion	75	7% with LCIS; 10% with ADH; total 17% with LCIS or ADH
IBIS-1	35-70	Increased breast CA risk by comprehensive model	Any prior cancer, DVT or PE, DCIS	51	40	96	5% with LCIS or ADH
Royal Marsden	30-70	Increased breast CA risk, with involved 1st-degree relative	Any prior cancer, DVT or PE	47	42	100	11 women with DCIS entered; all excluded from analysis; none with LCIS or ADH
Italian	35-70	Hysterectomy required; increased breast CA risk not required	Prior DVT or PE	51	19	21	None with LCIS or ADH

NOTE. Total cancers include invasive breast cancers and ductal carcinoma-in-situ but excludes lobular cancer-in-situ. Active, blinded follow-up continues for all but NSABP P1. The Royal Marsden trial involves 8 years of tamoxifen therapy; all others involve 5 years of therapy.

Abbreviations: NSABP, National Surgical Adjuvant Breast and Bowel Project; IBIS, International Breast Cancer Intervention Study; CA, cancer; Tam, tamoxifen; OR, odds ratio; 95% CI, 95% confidence interval; LCIS, lobular carcinoma-in-situ; HRT, hormone replacement therapy; DVT, deep venous thrombosis; PE, pulmonary embolism; DCIS, ductal carcinoma-in-situ; ADH, atypical ductal hyperplasia; NR, not reported.

outcome with 479 breast cancers observed. A meta-analysis of these studies, of which the National Surgical Breast and Bowel Project (NSABP) P-1 trial contributed the largest proposition of entered patients, identified a significant 42% reduction in relative risk (RR) of developing breast cancer associated with tamoxifen use (RR, 0.58; 95% confidence interval [CI], 0.38 to 0.84).[8]

The absolute risk reduction in these trials was less than 2 per 100 women given tamoxifen for 5 years. The absolute risk reduction anticipated in an individual woman depends on her calculated breast cancer risk, with women at higher risk having greater potential benefit. For instance, the average 65-year-old woman with no family history has an anticipated risk reduction of 1 per 100, while a 50-year-old woman with two affected siblings and two prior biopsies but no germline mutation has an anticipated risk reduction of approximately 2.5 per 100.

The initial report of the International Breast Cancer Intervention Study (IBIS-1) comparing tamoxifen with placebo and updates of the two other European chemoprevention tamoxifen trials[7] substantially increase information regarding tamoxifen's influence on breast cancer risk (Tables 2 and 3). Currently, 738 breast cancers have been reported in the four randomized tamoxifen trials, 54% more than available at the last technology assessment.

The IBIS-1 trial randomized 7,154 women at increased breast cancer risk to tamoxifen or placebo. The primary end point was breast cancer development (invasive and ductal carcinoma-in-situ) and the secondary end point was development of endometrial and other cancers. A relatively young population (median age, 50.8 years) at increased breast cancer risk that was identified using a newly developed risk assessment tool was randomized to tamoxifen (20 mg/d for 5 years) or placebo. Tamoxifen significantly decreased the risk of breast cancer development (odds ratio, 0.67; 95% CI, 0.49 to 0.91; $P = .01$), based on distribution of 169 breast cancers.

Concurrent HRT use was permitted in the IBIS-1 study, was used by over 40% of participants, and had no detrimental effect on tamoxifen-associated breast cancer risk reduction. As in P-1, tamoxifen use in IBIS-1 reduced only receptor-positive breast cancers and had no influence on the receptor-negative cancers seen. A recent observational study reporting a tamoxifen-associated increase in receptor-negative breast cancers[9] will require further evaluation.

A meta-analysis[7] now including the four randomized tamoxifen trials with updated results[10] from all three European trials identified a 38% reduction in breast cancer with tamoxifen (odds ratio, 0.62; 95% CI, 0.42 to 0.89). These results support a significant influence of tamoxifen on

Table 2.   (Cont'd)

No. Randomized		No. of Breast Cancers by Type						For Total Cancers	
		Invasive CA		Noninvasive CA		Total CA			
Placebo	Tam	Placebo	Tam	Placebo	Tam	Placebo	Tam	OR	95% CI
6,707	6,681	175	89	69	35	244	124	0.51	0.39-0.66
3,701	3,709	85	63	16	5	101	68	0.67	0.49-0.91
1,244	1,250	64	54	7	7	75	62	0.83	0.58-1.16
2,708	2,700	NR	NR	NR	NR	45	34	0.76	0.47-1.60

reducing short-term breast cancer risk, with a magnitude of effect somewhat smaller than seen in the P-1 trial.

Tamoxifen's influence on survival in risk reduction trials. None of the four tamoxifen trials was designed to assess tamoxifen's influence on survival. Available data do not yet suggest that tamoxifen favorably influences overall health or survival in the risk reduction setting. Currently, the number of deaths are closely comparable in the tamoxifen and control arms of the prevention trials.[7] All three European trials continue blinded follow-up and will provide additional information on tamoxifen and breast cancer development, carry-over effects after tamoxifen discontinuation, and breast cancer–specific survival and overall survival in the future.

Tamoxifen use with HRT. There is increasing experience with combined tamoxifen and HRT for breast cancer risk reduction. The Royal Marsden Hospital Trial included 523 women using both tamoxifen and HRT; subgroup analysis found no interaction on breast cancer development.[5] In the Italian study,[6] a subgroup analysis found tamoxifen significantly reduced breast cancer risk only in women receiving HRT, an analysis based on only nine cancers. The large IBIS-1 trial reported comparable tamoxifen-associated risk reduction in women with or without concurrent HRT use. In IBIS-1, combined HRT and tamoxifen was not associated with a greater short-term increase in endometrial cancer or vascular events compared with tamoxifen alone.[7]

Although no interaction between HRT and tamoxifen on breast cancer was identified, the association of HRT with increased breast cancer risk in observational studies[11,12] and uncertainties regarding long-term effects of combined HRT and tamoxifen use argue against routine use of such a combination in a risk reduction setting. However, further evaluation of combined HRT and tamoxifen use remains an active area of investigation.

Tamoxifen's influence on contralateral breast cancer in adjuvant trials. In the last published Early Breast Cancer Trialists Cooperative Group (EBCTCG) analysis of adjuvant trials,[13] a 47% reduction in relative risk of contralateral breast cancer was associated with 5 years of tamoxifen use (RR, 0.53; SD, 0.09; $P < .00001$), providing further support for a tamoxifen effect on new breast cancer development.

The EBCTCG 2000 update identified 553 contralateral breast cancers and reported that contralateral breast cancer risk reduction was seen only in women who had an initial receptor-positive tumor.[14] Supporting this observation is a recent report that women who develop receptor-negative breast cancer are likely to develop receptor-negative contralateral breast cancer.[15]

Tamoxifen duration for risk reduction. In the P-1 and IBIS trials, which provide the most evidence on risk reduction, the duration of tamoxifen use was 5 years.[4,7] Indirect information on tamoxifen duration in this setting comes from follow-up of the NSABP B-14 trial in adjuvant disease, which found no additional benefit on contralateral breast cancer for continued tamoxifen use beyond 5 years.[16]

Tamoxifen's effects on benign breast disease. A concern that tamoxifen's effect on breast cancer risk may only reflect early therapy of invasive disease has been addressed

Table 3. Quantity of Data Relevant to Breast Cancer Risk Reduction by Chemoprevention Agents

	Tamoxifen	Raloxifene	Anastrozole	Fenretinide
No. of risk reduction randomized prospective trials	4 (all reported)	2 (none reported)	None	1
No. of breast cancers reported in prospective, randomized risk reduction trials	738	0	0	0
No. of breast cancers reported in randomized trials from secondary analyses	N/A	77*	N/A	N/A
Effect of interventions on breast cancer risk				
OR	0.62	0.35	N/A	N/A
95% CI	0.42-0.89	0.21-0.58	N/A	N/A
No. of adjuvant breast cancer trials reported	33	0	1	1
No. of new contralateral breast cancers reported in adjuvant trials	553	N/A	62	41
Effect of intervention on contralateral breast cancer risk				
OR	0.53†	N/A	0.42	0.92
95% CI	0.37-0.78	N/A	0.22-0.79	0.66-1.29
Maximum follow-up available for toxicity information, years	20	4	2.5	2.5

Abbreviation: N/A, not available.

NOTE. Breast cancer in these reports includes both invasive breast cancer and ductal carcinoma-in-situ but excludes lobular carcinoma-in-situ.

*Results from a secondary analysis of a randomized osteoporosis trial.

†Based on Early Trialist report (Early Trialist 1998) for 5 years of tamoxifen use with 252 breast cancers seen.

by an analysis of benign breast disease in the P-1 trial. In this setting, tamoxifen was associated with a significant reduction in both the total number of biopsies and in the proportion of specimens from these biopsies showing atypical hyperplasia, typical hyperplasia, adenosis, cysts, and metaplasia.[17]

Tamoxifen's effects in women with BRCA1/BRCA2 *mutations.* The NSABP has evaluated the effect of tamoxifen on breast cancer risk in P-1 participants with inherited *BRCA1* or *BRCA2* mutations.[18] Of 288 women who developed breast cancers, 19 had either *BRCA1* or *BRCA2* mutations. Tamoxifen reduced breast cancer risk in women with *BRCA2* mutations, in whom tumors were largely receptor-positive (RR, 0.38; 95% CI, 0.06 to 1.56), but not in women with *BRCA1* mutations (RR, 1.67; 95% CI, 0.32 to 10.70), in whom tumors were more commonly receptor-negative. However, a matched case-control study reported significant protection against contralateral breast cancer in carriers of *BRCA1* mutations treated with tamoxifen (odds ratio, 0.38; 95% CI, 0.19 to 0.74), while contralateral cancers in *BRCA2* mutation carriers were less influenced (odds ratio, 0.63; 95% CI, 0.20 to 1.50).[19]

The extremely limited number of subjects in these reports and the mixed results seen preclude reliable assessment of tamoxifen effects in this setting. Given the overall number of identified mutation carriers, this important issue is unlikely to be resolved by further analyses of completed trials.

Tamoxifen's effects in women with prior breast disease. Women with a history of ductal carcinoma-in-situ[20] or lobular carcinoma-in-situ are at recognized increased breast cancer risk and are reasonable candidates for tamoxifen use.[4] Women with prior receptor-positive invasive breast cancer who have either not received tamoxifen or received tamoxifen for less than 5 years are also at increased breast cancer risk and can potentially benefit from tamoxifen.[21,22]

Tamoxifen in African-American women. Tamoxifen's effectiveness in breast cancer risk reduction in African-American women has been inferred from a retrospective analyses involving 58 contralateral breast cancers seen in NSABP adjuvant trials,[23] where a 52% reduction in relative risk of contralateral breast cancer was observed (RR, 0.48; 95% CI, 0.34 to 0.89).

Other Positive and Negative Effects of Tamoxifen Use

New information on tamoxifen has emerged from the NSABP P-1 study, the EBCTCG 2000 update, and meta-analyses of published literature.[24,25] The effects of tamoxifen reflect more than 20 years of clinical trial use.

Tamoxifen's carry-over effects. The EBCTCG updated results from trials comparing 5 years of tamoxifen use to no therapy in more than 8,000 women with early breast cancer.[14] Although not published, presented results informed the National Cancer Institute's Adjuvant Breast Cancer Consensus Conference.[26] In the EBCTCG update, time-dependent effects of tamoxifen use were identified. Five years of tamoxifen substantially reduced the risk for

breast cancer recurrence and contralateral cancer that persisted for 5 to 10 years after termination of tamoxifen use. In addition, increased endometrial cancer risk was also persistent, supporting a previously identified trend.[13,25,27] Publication of the EBCTG update is needed to fully evaluate these observations.

Tamoxifen and quality of life, depression, and cognition. Tamoxifen use is associated with more frequent hot flashes and vaginal discharge.[4] Development of cataracts also is more frequent (RR, 1.14; 95% CI, 1.01 to 1.29) with tamoxifen use, with the absolute risk increasing by 3 per 1,000 women.[4]

Tamoxifen did not adversely influence questionnaire-assessed depression risk,[28] quality of life,[29] or several other psychosocial or social functions.[30,31] Other risk reduction trials have yet to report on these parameters.

Tamoxifen's effects on cognition are not resolved. A neuroimaging study compared levels of myoinositol (a glial marker) in women receiving tamoxifen, HRT, or no hormonal treatments. A significant time-dependent reduction in myoinositol was seen with tamoxifen, consistent with agonist action on brain predictive of a favorable neuroprotective effect.[32,33] In a cross-sectional study of nursing home residents, women who reported past tamoxifen use had less frequent Alzheimer's disease and greater activities of daily living compared with women who had never used tamoxifen.[34] However, in an observational study using mailed questionnaires, current users complained of somewhat more memory problems,[35] although no decrease in cognitive function was seen. Additional studies using sensitive methodologies that delineate memory and recall abilities are addressing this issue.

Tamoxifen and cardiovascular events. In the NSABP P-1 trial, cardiovascular events, including myocardial infarctions, were similar in women receiving tamoxifen or placebo regardless of pre-existing coronary heart disease.[36]

Tamoxifen and vascular events. Vascular events include deep venous thrombosis, pulmonary embolism, stroke, and transient ischemic attack. A recent meta-analysis of published tamoxifen trials found the incidence of both venous thromboembolic events and strokes to be significantly greater in women receiving tamoxifen.[24] The EBCTG update confirmed prior estimates of tamoxifen-associated excess mortality related to vascular events, largely pulmonary emboli of approximately one death per 1,000 postmenopausal women treated for 5 years.[14] Since nearly half of thromboembolic events seen in the IBIS trial occurred within 3 months of surgery or fracture,[7] tamoxifen use should be carefully re-evaluated in women using tamoxifen in a risk reduction setting after such events. Given common protocol exclusions for vascular events (Table 2)

and identified risk, tamoxifen use for breast cancer risk reduction is relatively contraindicated and not recommended in women with a history of deep vein thrombosis, pulmonary embolus, stroke, or transient ischemic attack.

Tamoxifen and endometrial cancer. Tamoxifen increases endometrial cancer risk in postmenopausal women with a uterus by approximately two- to four-fold.[4,7] In the EBCTG update, tamoxifen-associated excess mortality related to endometrial cancer was approximately one death per 1,000 postmenopausal women with a uterus treated.[14] New information on tamoxifen-related endometrial cancers comes from a case-control study with 309 endometrial cancers. Long-term tamoxifen users who developed endometrial cancer had a relatively unfavorable prognosis related to histology (more common malignant mixed mesodermal tumors or sarcomas of the endometrium) and higher stage.[37] Endometrial cancer risk with tamoxifen was increased by prior estrogen use and obesity.[38] Despite ongoing trials, use of progestins to mitigate tamoxifen's effects on the endometrium, as widely used in HRT regimens, is not recommended given progestin's activity as a breast mitogen.[39,40]

Prospective evaluation did not support the routine use of either endometrial biopsy[41] or transvaginal ultrasound[42] in ongoing monitoring for women with history of breast cancer receiving tamoxifen. Recommended follow-up for women receiving tamoxifen includes a yearly gynecologic examination and timely work-up of vaginal bleeding.

Tamoxifen and gastrointestinal cancers. Although a meta-analysis of randomized trials identified increased gastrointestinal and colorectal malignancies associated with tamoxifen use,[24] a nested case-control study found no increase in colorectal cancer among tamoxifen users,[43] so this issue remains unsettled.

Tamoxifen and fractures. Tamoxifen use was associated with a modest, nonsignificant reduction in fractures compared with placebo in the P-1 trial[4] and with significantly fewer fractures compared with anastrozole in an adjuvant trial.[44] Whether the latter represents a positive tamoxifen effect, a negative aromatase inhibitor effect, or some combination remains to be determined.

RALOXIFENE

Clinical Evidence Relevant to Raloxifene's Effect on Breast Cancer Risk Reduction

Two ongoing, randomized, prospective trials are evaluating raloxifene (Evista; Lilly, Indianapolis, IN) and breast cancer risk,[45,46] but neither has reported clinical outcome.

Data on raloxifene's influence on breast cancer come almost exclusively from the Multiple Outcomes of Ralox-

Table 4. Status of Selected Ongoing Randomized Trials for Primary Breast Cancer Risk Reduction With Clinical Outcome End Points

Study	Entry	Intervention	Target Accrual	Current Accrual	Year Results Anticipated	Reference
Raloxifene for Use in the Heart (RUTH)	Increased heart disease risk; breast CA risk assessed	Raloxifene 60 mg/d × 5 years v Placebo × 5 years	10,000	10,011 (completed)	2005	Mosca 2001
Study of Tamoxifen and Raloxifene (STAR)	Increased breast CA risk	Tamoxifen 20 mg/d × 5 years v Raloxifene 60 mg/d × 5 years	22,000	12,868	2008	Vogel 2001
Hormone Replacement Therapy Opposed by Low-Dose Tamoxifen (HOT)	Increased breast CA risk	All receive HRT Tamoxifen 5 mg/d × 5 years v Placebo × 5 years	8,500	Accrual started	Later	Decensi 2002
International Breast Intervention Study-2 (IBIS-2)	Increased breast CA risk	Anastrozole 1 mg/d × 5 years v Placebo × 5 years	10,000	Proposed	Later	Cuzick 2002
Aromasin Prevention Study (ApreS)	BRCA1/2 mutation carriers	Exemestane 25 mg/d × 5 years v Placebo × 5 years	666	Proposed	Later	Bevilacqua 2001

NOTE. Studies with these agents for women with ductal carcinoma-in-situ are not included.

ifene Evaluation (MORE) study, in which 7,705 postmenopausal women with osteoporosis were randomized to raloxifene at 60 or 120 mg/d or placebo for 4 years and monitored for breast cancer development from the safety database. At the last technology assessment, a total of 54 breast cancers (39 invasive) were reported. The MORE study has been updated[47-49] with the most recent report, including 77 verified breast cancers of which 59 were invasive.[49] Raloxifene use (combining both dosage arms) continues to be associated with a significant reduction in relative risk of developing invasive breast cancers (RR, 0.28; 95% CI, 0.09 to 0.30), especially estrogen receptor–positive breast cancers. The absolute reduction in risk of developing breast cancer was 1.4 per 100 women given raloxifene for 5 years' duration.

The MORE study continues to follow women under an amended design. Reconsented participants have been continued on the original treatment assignment, with those on the 120-mg/d arm receiving a reduced dose of 60 mg/d (the FDA-approved osteoporosis dose). Clinical outcome will be evaluated at 6 and 8 years after entry.

Cautions regarding interpretation of the raloxifene data expressed in the previous technology assessment are still applicable. A meta-analysis of several randomized trials with 10,575 women (including the MORE trial) previously reported a smaller (55%) relative reduction in breast cancer risk in the raloxifene arms.[50] The current status of an updated report of breast cancer development in these raloxifene randomized trials is not available.

In an intriguing subgroup analysis conducted in 7,290 of the MORE participants, the placebo group women with baseline estradiol levels greater than 10 pmol/L had a 6.8-fold higher rate of breast cancer than women with undetectable levels ($P = .005$ for trend).[47] In addition, the raloxifene-associated reduction in breast cancer risk was largely in women with the highest baseline estradiol levels, which suggests that individualized stratification for breast cancer risk reduction interventions may be possible. This hypothesis will require prospective confirmation.

Study of Tamoxifen and Raloxifene and Raloxifene for Use in the Heart: Definitive raloxifene outcome trials. Definitive assessment of raloxifene's influence on breast cancer awaits the results from two ongoing randomized trials (Table 4). The Study of Tamoxifen and Raloxifene (STAR) trial has randomized more than 13,000 women of a 22,000 recruitment target and is scheduled to report outcome in 2008 or 2009.[45] The Raloxifene for Use in the Heart (RUTH) study has completed recruitment with 10,011 postmenopausal women and has added breast cancer to cardiac disease as a second primary study end point.[46] The RUTH trial, with baseline breast cancer risk assessment, periodic serial mammography, and randomization to either raloxifene 60 mg/d or placebo, will report breast cancer outcomes in 2005 after completion of the fourth-year mammograms.

Pending results of the outcome trials (Table 4), there is currently insufficient evidence to support routine use of raloxifene for breast cancer risk reduction.

Raloxifene use in women with resected breast cancer. Raloxifene reduces mammographic breast density[51] and breast cancer proliferative indices.[52] However, as raloxifene has limited activity against advanced breast cancer when

used after tamoxifen[53] and does not decrease and may increase hot flash frequency,[54] there is no basis for substituting raloxifene for tamoxifen in the treatment of adjuvant breast cancer patients experiencing menopausal symptoms.

Currently, there are no published data regarding sequential tamoxifen and raloxifene use or use of raloxifene with HRT. Preclinical studies demonstrating raloxifene stimulation of tamoxifen-resistant breast cancers in athymic mice[55] and raloxifene cross-resistance with tamoxifen[53] suggest caution in raloxifene use in women with resected breast cancer who have completed tamoxifen adjuvant therapy.

Other Positive and Negative Effects of Raloxifene Use

Raloxifene's toxicity profile remains largely as previously described.[1] Published information on raloxifene is based on 4 years of use and is limited to postmenopausal women. Emerging reports regarding raloxifene effects are summarized below.

Raloxifene and fracture risks. The FDA approved raloxifene 60 mg/d for osteoporosis prevention and therapy in postmenopausal women.[56] The disproportionately greater decrease in vertebral fractures relative to bone density increase seen with raloxifene[57] supports use of clinical outcomes rather than intermediate markers for definitive evaluation of interventions.

Raloxifene and other effects. Raloxifene did reduce cardiovascular events when examined as a secondary end point in the previously mentioned MORE trial.[58] Raloxifene is associated with a three-fold increase in potentially life-threatening vascular events (RR, 3.1; 95% CI, 1.5 to 6.2 for venous thrombolic events),[59] comparable to the risk of these events with either tamoxifen or HRT use.[60]

The suggestion from preclinical and early clinical trials[61] that raloxifene will have little influence on the endometrium awaits determination of endometrial cancer rates in ongoing longer-term randomized clinical trials. Raloxifene reduced uterine leiomyomas in one randomized trial[62] and may reduce risk of pelvic floor surgery as well.[63]

Given the preclinical studies consistent with neuroprotection,[64] raloxifene's influence on cognition has received preliminary evaluation, with a trend toward less decline in tests of verbal memory and attention.[65]

AROMATASE INHIBITORS/INACTIVATORS

Clinical Evidence Relevant to the Effect of Aromatase Inhibition on Breast Cancer Risk Reduction

No full-scale randomized trials evaluating aromatase inhibitor use for primary breast cancer risk reduction have been conducted. A comprehensive comparative review of this class of agents is beyond the scope of this technology assessment, but they have been reviewed elsewhere.[66,67] Anastrazole, letrozole, and exemestane are all in randomized trials for adjuvant breast cancer therapy. Information from these studies will inform future comparative assessments.

There is interest in evaluating aromatase inhibitors for breast cancer risk reduction because estrogen levels are strongly related to higher breast cancer risk in postmenopausal women[68] and estrogen levels are greatly reduced by aromatase inhibitors.[66]

The Anastrazole, Tamoxifen Alone and Combined trial. Relevant to breast cancer risk reduction are results from an adjuvant trial involving the aromatase inhibitor anastrozole (Arimidex; AstraZeneca). The Anastrazole, Tamoxifen alone and Combined (ATAC) trial[44] is an international, multicenter, randomized, double-blind trial that randomized 9,366 patients with early-stage breast cancer to three treatment arms: tamoxifen 20 mg/d, anastrazole 1 mg/d, or the combination for 5 years. Primary study end points included disease-free survival and safety/tolerability; new (contralateral) breast cancer primary tumors were a secondary end point. Anastrazole, but not the anastrazole plus tamoxifen combination, was superior to tamoxifen in disease-free survival after a median follow-up of 33.4 months (discussed extensively by Winer et al[69]).

In the ATAC trial, anastrazole use was also associated with a significant 58% reduction in new contralateral breast primary tumors (RR, 0.42 and 95% CI, 0.22 to 0.79 for anastrazole compared with tamoxifen groups; $P < .0068$). The absolute reduction in risk of developing a new contralateral breast cancer associated with anastrozole compared with tamoxifen was less than 1%. Currently, 62 new invasive contralateral breast cancers have occurred in the ATAC trial. In comparison, the tamoxifen-associated relative risk reduction of 49% in contralateral cancers reported in the NSABP B-14 adjuvant trial, which provided strong impetus for the P-1 trial, was based on the distribution of 83 contralateral cancers.[70] In the ATAC trial, women on the anastrozole arm had significantly fewer vascular and endometrial events[71] but more musculoskeletal events and fractures compared with those on the tamoxifen arm.[44,71]

Because there are no data on the long-term effects of aromatase inhibitor therapy, these agents should not be used in primary prevention for breast cancer outside of a research study.

Proposed breast cancer risk reduction trials of aromatase inhibition. The effects of aromatase inhibitors (anastrozole, letrozole) and inactivators (exemestane) in advanced breast cancer[66] and the emerging effects of anastrozole on contralateral breast cancer risk[44] support

further evaluation of anastrazole and other agents in this class for breast cancer risk reduction (Table 4).

RETINOIDS

Fenretinide's influence on contralateral breast cancer risk has been evaluated in one randomized, prospective trial in nearly 3,000 women with early-stage breast cancer. Although fenretinide had no effect on contralateral breast cancer development in the overall study population, a posthoc analysis suggested reduced contralateral breast cancer risk in premenopausal women.[72] The agent was well tolerated, with diminished dark-vision adaption and dermatologic disorders being the most common adverse events.[73] A fenretinide and tamoxifen combination is currently being evaluated.[73,74]

EXOGENOUS ESTROGEN AND CHRONIC DISEASE RISK

A practical issue when considering tamoxifen for breast cancer risk reduction is how to balance tamoxifen use against the potential benefits of HRT on chronic disease risk and overall mortality. Issues related to combined tamoxifen and HRT use have been discussed previously (see "Tamoxifen use with HRT" section, above).

No full-scale randomized clinical trials of HRT have prospectively evaluated HRT's influence on primary prevention of coronary heart disease or either coronary heart disease–associated mortality or all-cause mortality.

More recent observational studies suggest an association with HRT use and an increase in breast cancer risk of approximately 30%,[12] especially for longer use (> 5 years) and for regimens with progestins.[11,39] Translated into absolute risk, approximately six excess breast cancers would be anticipated in 1,000 women using HRT for 10 years.[75] Use of HRT is associated with an approximate three-fold increase in life-threatening vascular events and, when used without progestins, increased endometrial cancer risk.[76]

The approved indications for estrogens used as HRT include symptoms associated with moderate to severe menopause and prevention and management of osteoporosis. Although HRT is often proposed for improving overall health and reducing mortality, recent estimates of HRT's influence on mortality are largely based on purported effects on cardiac events stemming from observational study results and lipid profile influence.[77,78] The established effects of HRT in preventing osteoporosis have a relatively small impact on mortality because life-threatening fractures tend to occur later in life.

A favorable effect of HRT on cognition has been predicted from preclinical and observational studies,[79] but the data are somewhat mixed. A meta-analysis of observational studies identified a risk of dementia in estrogen users of 0.71 (95% CI, 0.53 to 0.96) compared with nonusers.[65] However, a randomized trial of estrogen therapy for mild to moderate Alzheimer's disease showed no effect of 1 year of therapy on disease progression or on global, cognitive, or functional outcomes.[80] The Women's Health Initiative Memory Study will address the question of HRT's effect on cognitive function in a large population of healthy postmenopausal women.[81]

Observational findings on HRT and epithelial ovarian cancer are mixed, but a recent large case-control study associated users of HRT regimens with estrogen alone or sequentially added progestins with increased ovarian cancer risk.[82]

A full discussion of the risks and benefits of HRT is beyond the scope of the current technology assessment. Observational studies suggest an association with long-term HRT use and an approximate 35% reduction in primary cardiovascular events.[76] However, randomized prospective clinical trials have recently evaluated HRT's influence on clinical end points, including cardiac and vascular events. In these trials, HRT use did not result in secondary prevention of coronary vascular disease (CVD) or cerebral vascular events.[83,84] In the large population (> 27,000) of generally healthy postmenopausal women randomized to HRT or placebo in the ongoing Women's Health Initiative, interim analysis found an increase in the number of myocardial infarctions, strokes, and thromboembolic events in the initial years for women receiving HRT as compared with placebo.[85] Continued follow-up of such trials will provide definitive assessment of HRT's influence on CVD and overall mortality. Results from the Women's Health Initiative are anticipated in 2005.[86]

Review of this emerging body of information has led several agencies, including the American Heart Association, to alter their recommendations regarding HRT. The Association's recommendations for HRT and CVD now state that "firm recommendations for primary prevention await randomized clinical trial results and there is insufficient data to suggest that HRT should be initiated for the sole purpose of primary prevention of CVD."[87]

This technology assessment takes no position regarding HRT use in postmenopausal women. However, recommendation of HRT use for cardiovascular disease risk reduction and overall health or survival benefit should be approached using the same risk/benefit algorithm outlined for tamoxifen.

BREAST CANCER RISK ASSESSMENT

Assessment of breast cancer risk is the first step in considering tamoxifen use.[3,78,88] The most useful model

available for breast cancer risk assessment[89] was developed by Gail et al[90] (the Gail model) and adjusted to take into consideration the lower breast cancer risk of Hispanic women. Rockhill et al[91] used data from white women in the Nurses Health Study to address this Gail model's validity. In their analyses, the model did well in predicting breast cancer risk in subgroups of women ("calibration") but had only modest ability to discriminate whether an individual woman would or would not develop breast cancer ("discriminatory accuracy"). Since tamoxifen's influence on breast cancer risk is limited to receptor-positive disease, development of improved approaches to more accurately assess an individual woman's risk of developing receptor-positive tumors is a priority research issue.

The Gail model does not incorporate information needed to assess germline mutation carrier status or several other high-breast-cancer-risk situations, such as prior thoracic radiation.[92] Thus, additional information must be collected to determine whether use of the Gail model is appropriate.

Issues related to genetic susceptibility testing and, in particular, evaluation for *BRCA1* and *BRCA2* are reviewed elsewhere.[78,88] Factors related to having 10% or greater risk of germline mutation include the following: known *BRCA1* and *BRCA2* family mutation, breast and ovarian cancer in the same family member, two or more family members under age 50 with breast cancer, male breast cancer, one or more family members under age 50 with breast cancer plus Ashkenazi ancestry, ovarian cancer plus Ashkenazi ancestry, and breast cancer before age 40. Women whose history suggests breast cancer germline mutation are not appropriate candidates for use of the Gail model, as their risk would be underestimated. Such women are candidates for genetic counseling referral.

For women without prior breast cancer or who are not at increased risk for *BRCA1*/*BRCA2*, use of the Gail model is appropriate as long as there are no family members with breast cancer diagnosed before age 50. In those circumstances, the Claus model tables, which incorporate detailed family history, should be used.[93]

Information on breast cancer risk for both medical and nonmedical personnel is available from the Internet at the National Cancer Institute's PDQ breast cancer prevention site, http://www.cancer.gov/cancer_information/.

With regard to breast cancer risk assessment in the future, additional diagnostic and laboratory tests are being evaluated for breast cancer risk assessment. They include bone density, mammographic breast density, circulatory estradiol levels, and breast cells collected by a variety of techniques.[94] The role of these procedures in clinical practice is beyond the scope of the present technology assessment.

COMPARISON OF QUANTITATIVE APPROACHES FOR TAMOXIFEN RISK/BENEFIT ESTIMATION

Survey research has identified some reluctance of women to favorably consider tamoxifen for breast cancer risk reduction.[95,96] The current status of methods to communicate risk and benefits of tamoxifen in a risk reduction setting are outlined below in a discussion of approaches to estimate positive and negative effects of tamoxifen. The global effects of tamoxifen use for breast cancer risk reduction have been estimated using approaches that differ in clinical outcomes considered, assumed duration of tamoxifen effect, the perspective of analysis (individual *v* society *v* third-party payer), assigned values of risks and benefits, and methodologies used for integrating outcomes (Table 5).

Gail Model to Estimate Positive and Negative Effects of Tamoxifen for Individuals

The only model currently available in a format allowing calculation of an individual risk/benefit assessment for tamoxifen use was developed by Gail et al.[97] Using information from a variety of sources, this model generates tabular estimates of net benefit and risk of tamoxifen use in groups of women according to 5-year breast cancer risk, age, presence or absence of uterus, and race. The number of health outcomes either induced or prevented by 5 years of tamoxifen use was estimated. A net benefit/risk index was derived by assigning weights to each clinical event and summing the benefits and harms.

Because models make assumptions about potential benefit (greatest in women with high risk of breast cancer) and greatest risk (generally older women who are at more jeopardy for thromboembolism and uterine cancer), these models predict that young women should experience a better benefit/risk ratio. Such studies do not factor in other sequelae, such as menopausal symptoms or sexual dysfunction, that may be more problematic in younger women.

Application of the Gail model suggests that tamoxifen is most beneficial in younger women at higher breast cancer risk and those without a uterus. African-American women are anticipated to have less tamoxifen benefit based largely on increased risk of a vascular event and lower fracture risk.[98]

Although clinically useful, the Gail model predicted outcomes only in the 5-year treatment period, the assumptions in developing the risk/benefit index have not been validated, and some results are sensitive to minor changes in weights assigned to utilities. The weights assigned to the clinical outcomes were neither empirically derived nor preference-based and do not reflect differences in mortality, morbidity, or timing of occurrence. In addition, the likeli-

Table 5. Summary of Analytic Approaches to Weighing the Risks and Benefits of Tamoxifen

Reference	Analytic Approach	Perspective	Outcomes Considered in Addition to Breast Cancer	Time Horizon After Initiation of Tamoxifen	Comments	Principal Outcome
Schrag 1997	Markov model	Individual patient	None	NA	Tamoxifen not included as a strategy	Life expectancy
NCI Risk Disk	Statistical logistic regression model	Individual patient	None	NA	Predicts only breast cancer risk	5 year and lifetime breast cancer risk
Gail 1999	Lifetables	Individual patient	Endometrial cancer, hip fracture, stroke, VTE*	5 years	Breast, endometrial cancer, stroke, and hip fracture assigned equal value	Net benefit risk index (sum of total no. of events)
Smith 2000	Spreadsheet	Health service payer	Endometrial cancer, hip fracture, stroke, TIA, VTE	5 years	No distinction between pre- and postmenopausal risks	Cost per life-year gained
Hershman 2002 Grann 2000	Markov model	Health service payer	Endometrial cancer, hip fracture, VTE, cataracts	5 years	Unconventional utility assessment; no distinction between women with and without a uterus	Quality-adjusted life expectancy and cost-effectiveness
Will 2001	Simulation model	Individual patient	Endometrial cancer, all fractures, CHD, stroke, DVT	Explored alternative assumptions	Assumed no mortality associated with DVT	Life expectancy
Col 2002	Markov model	Individual patient	Endometrial cancer, hip fractures, VTE, stroke	Explored alternative assumptions out to 15 years	Only applicable to postmenopausal women; no costs or utilities	Life expectancy
Duffy 2002	Meta-analysis	Individual patient	None	Not specified	Assumes that the effect of tamoxifen is dependent on ER status; impact of tamoxifen on BRCA1/2 is inferred based on ER status	Relative risk according to BRCA1/2 status

Abbreviations: CHD, coronary heart disease; VTE, venous thrombotic events, including both pulmonary embolism (PE) and deep venous thrombosis (DVT); ER, estrogen receptor; TIA, transient ischemic attacks.

*Other clinical outcomes were included but assigned a weight of zero, which effectively excluded them from the benefit-risk index.

hood of incurring most adverse effects except for endometrial cancer was based only on age not individual disease risk. Despite these concerns, the Gail model provides the best available beginning framework for risk calculation.

New strategies and decision aids that incorporate mortality estimates and carry-over effects of tamoxifen are under development[99] and are described below.

Other Models to Estimate Positive and Negative Effects of Tamoxifen

Smith and Hillner,[100] in a cost-effectiveness analysis based on tamoxifen effects seen in P-1 over 5 years, found tamoxifen use to be cost-effective overall, considering all medical event–related costs compared with no tamoxifen use. Duffy and Nixon[101] used meta-analytic techniques to estimate the impact of tamoxifen among *BRCA1/BRCA2* carriers, finding tamoxifen to be more effective among *BRCA2* carriers (27% risk reduction) than among *BRCA1* carriers (no significant reduction). The impact of tamoxifen on *BRCA1/BRCA2* carriers was inferred by assuming that the effect of tamoxifen is dependent on estrogen receptor status, determining the proportion of estrogen receptor–positive tumors among *BRCA1* and *BRCA2* mutation carriers, and computing a weighted average for *BRCA1/BRCA2* carriers.

Markov Modeling of Clinical Outcomes In Markov modeling, each clinical outcome is valued according to its survival or quality-adjusted survival impact, with time-dependent rates and utilities assigned to each outcome.[102] Survival projections involve extrapolation based on assumptions concerning long-term effects of treatment (where information is often limited). Differences between the various published Markov models exploring tamoxifen impact are outlined below.

The models of Hershman et al[103] and Grann et al[104] predict that tamoxifen use increases life expectancy of higher-risk women by 69 days for 35-year-olds and 27 days for 60-year-olds. The practical application of the predictions of quality-adjusted survival in this model is limited by the assignment of utilities (hip fracture was assigned a lower utility than metastatic breast cancer). Women with and without a uterus were treated equally, precluding determinations involving endometrial cancer risk.

Will et al,[105] using data from Canadian cancer registries and vital statistics to simulate effects of tamoxifen under a range of assumptions, incorporated all P-1 outcomes and calculated that tamoxifen would extend life expectancy among women whose 5-year predicted risk was 3.32% or greater.

Col et al[99] used a Markov model to address the impact of tamoxifen among postmenopausal women at varying levels of risk for breast and endometrial cancer and hip fracture. This model incorporates individual risk factors for both the benefits and principal harms of tamoxifen and is the only published model to include residual impact of tamoxifen based on the most recent EBCTCG update.[14] This model predicts that tamoxifen use in 50-year-old women without a uterus results in an increased life expectancy of 1 to 4 months, whereas women with a uterus have gains only if they are at higher breast cancer risk. Tamoxifen carry-over effects on breast and endometrial cancer risk have a strong impact on the benefit/risk survival profile.

These Markov models are complex and are constrained by the quality of the informing data. Despite the limitations, each model adds insight into assessing the risks and benefits of tamoxifen. None of the Markov models described has been assessed for validity or is available in a format allowing for individual patient data entry. Attempts are underway to develop such programs for routine clinical use.

CHALLENGES IN COMMUNICATING TAMOXIFEN'S RISKS AND BENEFITS

To make informed decisions regarding breast cancer risk reduction, women need to understand the risks and benefits of any proposed intervention. Limited publications have emerged since the last review concerning communication of risk to women who are at moderate breast cancer risk.

Women typically overestimate their risk of breast cancer,[106] emphasizing the importance of effective communication of breast cancer risk in this setting. Relative risk describes the ratio of the risk of disease in one group compared with that in another, does not take into consideration a person's baseline risk, and does not describe the magnitude of the absolute risk. Absolute risk varies according to baseline level of risk and could be very small when the disease is uncommon. Overall, women should be given information that presents the risks and benefits of any intervention using both absolute and relative terms.[107]

How risk information is presented,[108-110] worded,[107] and framed[111,112] may affect its interpretation.[113] Framing the benefits (ie, gains) of treatment in relative rather than absolute terms can affect a patient's perception of a therapy's effectiveness,[114] making the benefits of a treatment appear more favorable[115] or, conversely, emphasizing its risks (ie, losses).[116]

Most framing studies have focused on a treatment's effect on a single outcome over a single time horizon.[112] Women deciding on tamoxifen therapy need to consider its effects (both beneficial and harmful) on several outcomes over an extended time horizon. A study examining patient preferences for communicating complex risk information[117] found that patients preferred risk estimates framed in absolute rather than relative terms, graphical and textual explanations provided together, and risk estimates given over more than one time horizon. In addition, use of contextual and graphical displays may improve understanding of numerical risk/benefit information.[110] Efforts are underway to develop such platforms for general clinical use.

In sum, the communication of tamoxifen's risks and benefits should include both absolute and relative information over a relevant time period. Attention should be paid to how the information is framed and presented.

CONCORDANCE WITH OTHER AGENCY RECOMMENDATIONS

The recommendations of this technology assessment update regarding tamoxifen and raloxifene are in substantive agreement with two recently published guidelines from other agencies generated under slightly different time frames.[118,119]

ACKNOWLEDGMENT

APPENDIX

The appendix listing the members of the ASCO Risk Reduction Update Working Group is available online at www.jco.org.

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