Chemoprevention of Breast Cancer: Recommendations and Rationale: U.S. Preventive Services Task Force

United States Preventive Services Task Force

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Abstract

Figure 4

Agency for Healthcare Research and Quality

Figure 2

US Department of Health and Human Services

SUMMARY OF RECOMMENDATIONS

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

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

CLINICAL CONSIDERATIONS

Risk for breast cancer: Older age; a family history of breast cancer in a mother, sister, or daughter; and a history of atypical hyperplasia on a breast biopsy are the strongest risk factors for breast cancer. Table 1 indicates how the estimated benefits of tamoxifen vary depending on age and family history. Other factors that contribute to risk include race, early age at menarche, pregnancy history (nulliparity or older age at first birth), and number of breast biopsies. The risk for developing breast cancer within the next 5 years can be estimated using risk factor information by completing the National Cancer Institute Breast Cancer Risk Tool (the “Gail model,” available at http://cancer.gov/bcrisktool/ or 800-4-

CANCER). Clinicians can use this information to help individual patients considering tamoxifen therapy estimate the potential benefit. However, the validity, feasibility, and impact of using the Gail model to identify appropriate candidates for chemoprevention has not been tested in a primary care setting. The Gail model does not incorporate estradiol levels or estrogen use, factors that some studies suggest may influence the effectiveness of tamoxifen.

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

Figure 3

Table !:Predicted Benefits and Harms of 5 Years of Tamoxifen Therapy according to Age and Family History*

Variable‡	Women 45 Years of Age	Women 55 Years of Age	Women 65 Years of Age	Women 75 Years of Age
Predicted 5-year risk of breast cancer, %^				
No Family history	0.7	1.1	1.5	1.6
Family history	1.6	2.3	3.2	3.4
Benefits per 1000 women over 5 y of tamoxifen therapy				
Cases of invasive breast cancer avoided, *n*				
No Family history	3-4	5-6	7-8	8
Family history	8	11-12	16	17
Cases of noninvasive breast cancer avoided, *n*				
No family history	1-2	2	2-3	2-3
Family history	2-3	3-4	4-5	5-6
Hip fractures avoided, *n*†	<1	3	5	15
Harms per 1000 women over 5 y of tamoxifen therapy				
Cases of endometrial cancer caused, *n*†	1-2	12	21	22
Strokes caused, *n*†	1	3	9	20
Pulmonary emboli caused, *n*†	1-2	4-5	9	18
Cases of deep venous thrombosis caused, *n*†	1-2	1-2	3	4

* These estimates are based on the Gail model, outcomes from the Breast Cancer Prevention Trial, and baseline rates of harms from Gail et al (13). ‡ No family history = no first-degree relatives with breast cancer; family history = 1 first-degree relative with breast cancer. ^ Based on menarche at 12 years of age, first birth at 22 years of age, and no history of breast biopsy, as calculated from the Gail model. † Modified from Gail et al (13). [13]

SCIENTIFIC EVIDENCE

EPIDEMIOLOGY AND CLINICAL CONSEQUENCES

Breast cancer is the most common non-skin cancer in women. An estimated 203,500 new cases of invasive breast cancer will be diagnosed in 2002, and 39,600 women will die from the disease.[3] Although the USPSTF concluded that early detection of breast cancer through mammography has reduced deaths from breast cancer, the effectiveness of mammography is limited. Another approach to reducing breast cancer deaths is chemoprevention for primary prevention of cancer.

POTENTIAL BENEFITS OF CHEMOPREVENTION

The use of agents to prevent the development of breast cancer was suggested by trials of breast cancer treatment with tamoxifen, a compound with both estrogen-like and anti-estrogen properties (a selective estrogen receptor modulator).[4] A meta-analysis of 55 studies evaluating tamoxifen for the treatment of women with breast cancer found that the drug was associated with an approximately 50% reduction in the risk for developing new cancers in the opposite breast among women who took the drug for 5 years.[5]

The USPSTF found and evaluated 4 randomized controlled trials (RCTs) of breast cancer chemoprevention in women who had never had breast cancer.4 Three of these trials used tamoxifen as the chemopreventive agent[6,7,8]; 1 trial used raloxifene, another selective estrogen receptor modulator.[9]

Of the 3 RCTs of tamoxifen, the largest (the Breast Cancer Prevention Trial — BCPT), with 13,388 women enrolled, found a risk reduction of invasive cancer of 49% among women at high risk for breast cancer (estimated 5-year risk of 1.66% or greater).7 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 2 other tamoxifen RCTs did not show a similar benefit. The relative risk reduction for breast cancer was 0.94 (95% CI, 0.59 -1.43) for the Royal Marsden Hospital study6 and 0.87 (95% CI, 0.62-2.14) for the Italian Tamoxifen Prevention Study.8 Although the reasons for these discrepant results are not definitively established, possible explanations include differences in the duration of therapy and differences between women enrolled in each study.1 The average duration of therapy was shorter in the European trials and, compared with the women enrolled in BCPT, the women in these trials were younger, had more estrogen-receptor-negative cancers, and were more likely to be taking hormone

replacement therapy or to have had an oopherectomy.[1]

The study evaluating raloxifene in postmenopausal women with osteoporosis found a 76% risk reduction (RR, 0.24; 95% CI, 0.13-0.44) in the development of invasive breast cancer.9 After a median follow-up of 40 months, the absolute risk reduction among women taking raloxifene was 7.9 cases per 1,000 women (number needed to treat, 126).9 When effective, both raloxifene and tamoxifen were effective only against estrogen receptor-positive tumors.1

POTENTIAL HARMS OF CHEMOPREVENTION

Both tamoxifen and raloxifene increase the risk for thromboembolic events and hot flashes; tamoxifen increases the risk for endometrial cancer.1 The number of total thromboembolic events in all 4 trials was small, and differences in specific complication rates between the treatment and placebo arms were statistically significant only for pulmonary embolism.1 Among women aged 50 and older, for whom the potential harms of tamoxifen and raloxifene are more common than they are for younger women, the BCPT reported that after a median of 55 months of use, tamoxifen increased the rate of stroke from 1.3 cases/1,000 women in the placebo group to 2.2 cases/1,000 women in the study group (RR, 1.75; 95% CI, 0.98-3.20); increased the rate of pulmonary embolism from 0.3 cases/1,000 women in the placebo group to 1.0 cases/1,000 women in the study group (RR, 3.19%; 95% CI, 1.12-11.15); increased the rate of deep vein thrombosis from 0.9 cases/1,000 women in the placebo group to 1.5 cases/1,000 women in the study group (RR, 1.71; 95% CI, 0.85-3.58).7

Fewer thromboembolic events occurred among women younger than 50, and the trial found no significant difference in incidence between the tamoxifen and placebo groups in this age group.7 The relative risk increase in venous thromboembolism from tamoxifen or raloxifene appears similar to the risk for venous thromboembolism from oral contraceptives or hormone replacement therapy.1

Among women aged 50 and older in the BCPT, participants who received tamoxifen, compared with those who took placebo, had a 4.0 times greater risk (95% CI, 1.70-10.90) of developing Stage 1 endometrial cancer (0.8 cancers/1,000 women taking placebo vs 3.1 cancers/1,000 women taking tamoxifen for a median of 55 months).7 Among women younger than 50, the BCPT found no significant difference in endometrial cancer rates between the two groups. No deaths attributed to endometrial cancer occurred in the trial.7 Raloxifene has not been associated with an increase in endometrial cancer.9

The BCPT reported that women in the tamoxifen group were at increased risk for developing cataracts and having cataract surgery compared with placebo (RR, 1.14 [95% CI, 1.01-1.29] and 1.57 [95% CI, 1.16-2.14], respectively).7

Quality of life issues have also been of concern and were addressed in the BCPT. Women in the BCPT reported increased rates of bothersome hot flashes (45.7% in the tamoxifen group vs 28.7% in the placebo group) and bothersome vaginal discharge (12.4% in the tamoxifen group vs 4.5% in the placebo group).7 Women given raloxifene also noted higher rates of hot flashes than women given placebo (10.7% in the ralixifene group vs 6.4% in the placebo group).9

Although long-term adherence for highly motivated women was about 80% in the BCPT trial and about 90% in the raloxifene trial, adherence rates in the general population are unknown.[2]

RECOMMENDATIONS OF OTHERS

The American College of Obstetricians and Gynecologists emphasizes the importance of clinician judgment and recommends that any decision to use tamoxifen be made on an individual basis after consideration of the patient's medical history, risk assessment, and preferences, and with attention to the ability to manage complications of therapy.[10] The American Society of Clinical Oncology suggests that women with a 5-year projected risk for breast cancer greater than or equal to 1.66% may be offered tamoxifen to reduce their risk. They also recommend that raloxifene use should be reserved for treatment of osteoporosis in postmenopausal women.[11] The Canadian Task Force on Preventive Health Care recommends that clinicians counsel women at high risk for breast cancer (Gail index 1.66% for 5 years) about the potential benefits and harms of breast cancer prevention with tamoxifen.[12]

APPENDIX A
U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS AND RATINGS

The Task Force grades its recommendations according to one of 5 classifications (A, B, C, D, I) reflecting the strength of evidence and magnitude of net benefit (benefits minus harms):

A. The USPSTF strongly recommends that clinicians routinely provide [the service] to eligible patients. The USPSTF found good evidence that [the service] improves important health outcomes and concludes that benefits substantially outweigh harms.

B. The USPSTF recommends that clinicians routinely provide [the service] to eligible patients. The USPSTF found at least fair evidence that [the service] improves important health outcomes and concludes that benefits outweigh harms.

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

D. The USPSTF recommends against routinely providing [the service] to asymptomatic patients. The USPSTF found at least fair evidence that [the service] is ineffective or that harms outweigh benefits.

I. The USPSTF concludes that the evidence is insufficient to recommend for or against routinely providing [the service]. Evidence that the [service] is effective is lacking, of poor quality, or conflicting and the balance of benefits and harms cannot be determined.

APPENDIX B
U.S. PREVENTIVE SERVICES TASK FORCE STRENGTH OF OVERALL EVIDENCE

The USPSTF grades the quality of the overall evidence for a service on a 3-point scale (good, fair, poor):

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

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

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

{image:4}

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http://www.ahrq.gov/

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