CER # 17:
Comparative Effectiveness of Medications To Reduce Risk of Primary Breast Cancer in Women

Original release date:
September 14, 2009

Surveillance Report:
October 2011

Key Findings:
• 2 of 6 conclusions for Key Question 1, 1 of 7 conclusions for Key Question 2, and 1 of 5 conclusions for Key Question 3 are probably out of date due to longer term followup of a major trial and the availability of new drugs for this indication.
• All conclusions for Key Questions 4 and 5 are considered still valid.
• There are no new significant safety concerns.

Summary Decision

This CER’s priority for updating is Medium
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Appendixes cited in this report are available at:
http://www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=179
Comparative Effectiveness of Medications To Reduce Risk of Primary Breast Cancer in Women

1. Introduction

Comparative Effectiveness Review (CER) # 17, Comparative Effectiveness of Medications to Reduce Risk of Primary Breast Cancer in Women was originally released on September 14, 2009. It was therefore due for a surveillance assessment in March, 2010. When the Surveillance program began in Summer 2010 this CER was therefore selected to be in the first wave of reports for surveillance.

2. Methods

2.1 Literature Searches

We conducted a limited literature search for the years 2008-2011 using the identical search strategy used for the original report. This search included five high-profile general medical interest journals (Annals of Internal Medicine, British Medical Journal, Journal of the American Medical Association, Lancet, and the New England Journal of Medicine) and four specialty journals (American Journal of Obstetrics and Gynecology, Clinical Cancer Research, Journal of Bone Mineral Research, and the Journal of the National Cancer Institute). The specialty journals were those most highly represented among the references for the original report. Appendix A includes the search methodology for this topic.

2.2 Study selection

In general we used the same inclusion and exclusion criteria as the original CER. However, we also accepted for review studies of new agents for primary prevention of breast cancer.

2.3 Expert Opinion

We shared the conclusions of the original report with 12 experts in the field (including the original project leader, suggested field experts, original technical expert panel (TEP) members) for their assessment of the need to update the report and their recommendations of any relevant new studies; four subject matter experts responded. Appendix C shows the questionnaire matrix that was sent to the experts.

2.4 Check for qualitative and quantitative signals

Since this CER did not contain meta-analyses, all signals are qualitative.
2.5 Compilation of Findings and Conclusions

For this assessment we constructed a summary table that included the key questions, the original conclusions, and the findings of the new literature search, the expert assessments, and any FDA reports that pertained to each key question. To assess the conclusions in terms of the evidence that they might need updating, we used a 4-category scheme:

- Original conclusion is still valid and this portion of the CER does not need updating
- Original conclusion is possibly out of date and this portion of the CER may need updating
- Original conclusion is probably out of date and this portion of the CER may need updating
- Original conclusion is out of date

In making the decision to classify a CER conclusion into one category or another, we used the following factors when making our assessments:

- If we found no new evidence or only confirmatory evidence and all responding experts assessed the CER conclusion as still valid, we classified the CER conclusion as still valid.
- If we found some new evidence that might change the CER conclusion, and/or a minority of responding experts assessed the CER conclusion as having new evidence that might change the conclusion, then we classified the CER conclusion as possibly out of date.
- If we found substantial new evidence that might change the CER conclusion, and/or a majority of responding experts assessed the CER conclusion as having new evidence that might change the conclusion, then we classified the CER conclusion as probably out of date.
- If we found new evidence that rendered the CER conclusion out of date or no longer applicable, we classified the CER conclusion as out of date. Recognizing that our literature searches were limited, we reserved this category only for situations where a limited search would produce prima facie evidence that a conclusion was out of date, such as the withdrawal of a drug or surgical device from the market, a black box warning from FDA, etc.

2.6 Determining Priority for Updating

We used the following two criteria in making our final conclusion for this CER:

- How much of the CER is possibly, probably, or certainly out of date?
- How out of date is that portion of the CER? For example, would the potential changes to the conclusions involve refinement of original estimates or do the potential changes mean some therapies are no longer favored or may not exist? Is the portion of the CER that is probably or certainly out of date an issue of safety (a drug withdrawn from the market, a black box warning) or the availability of a new drug within class (the latter being less of a signal to update than the former)?
3. Results

3.1 Search

The literature search identified 102 titles. After title and abstract review, we further reviewed the full text of 19 journal articles. The remaining 83 titles were rejected because they were editorials, letters, or did not include topics of interest. In addition to the searches, we also reference-mined articles of interest and retrieved 11 articles. Further, three additional articles were reviewed and added at the suggestion of the experts.

Through literature searches, reference mining, and expert recommendations, 33 articles went on to full text review. 14 articles were rejected because they had already been included in the earlier report or did not include a comparison of interest. Of the 19 that were further reviewed, three were abstracted into an evidence table<sup>3-5</sup> (Appendix B).

3.2 Identifying qualitative and quantitative signals

Table 1 shows the original key questions, the conclusions of the original report, the results of the literature and drug database searches, the experts’ assessments, the recommendations of the Southern California Evidence-based Practice Center (SCEPC) regarding the need for update, and qualitative signal.
Table 1: Summary Table

<table>
<thead>
<tr>
<th>Conclusions From CER Executive Summary</th>
<th>RAND Literature Search</th>
<th>FDA</th>
<th>Expert Opinion EPC Investigator Other Experts</th>
<th>Conclusion from SCEPC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Key Question 1: In adult women without preexisting breast cancer, what is the comparative effectiveness of selective estrogen receptor modulator (SERMs) tamoxifen citrate, and the selective tissue estrogenic activity regulator (STEAR) tibolone, when used to reduce risk for primary breast cancer on improving short-term and long-term outcomes including invasive breast cancer, noninvasive breast cancer, including ductal carcinoma <em>in situ</em> (DCIS), breast cancer mortality, all-cause mortality, and osteoporotic fractures?</td>
<td>The STAR head-to-head follow-up (median of 81 months) showed tamoxifen is superior to raloxifene at reducing invasive breast cancer. Examestane, an aromatase inhibitor was found to significantly reduce invasive breast cancer in postmenopausal women who were at moderately increased risk for breast cancer compared to placebo.</td>
<td>No new data</td>
<td>Three experts thought this conclusion was still valid, but one expert noted that there are important NEW SERMs and aromatase inhibitors that are important. One expert thought this conclusion was out of date.</td>
<td>Conclusion is probably out of date and this portion of the CER may need updating. Consider adding aromatase inhibitors, (examestane, anastrozole, and letrozole) which have been studied in previous trials (ATAC, Italian, BIG, ARNO/ABCSG, IES). New literature on lasofoxifene (non-FDA approved, and Pfizer NOT pursuing FDA approval) has come out that shows that a 0.5 mg dose appears to reduce the risks of both total and ER-positive invasive breast cancer in postmenopausal women with osteoporosis. Another non-FDA approved drug, arzoxifene was shown to decrease the incidence of invasive breast cancer. Further development of this drug by Lilly as been dropped.</td>
</tr>
<tr>
<td>Eight large randomized controlled trials provide data on breast cancer risk reduction in women without pre-existing breast cancer. These include one good-quality head-to-head trial of tamoxifen and raloxifene and seven fair- and good-quality placebo-controlled trials (four tamoxifen, two raloxifene, and one tibolone). Results on placebo controlled trials cannot be directly compared between types of medications because of important differences between study subjects. Tamoxifen (risk ratio [RR] 0.70; 0.59, 0.82; four trials), raloxifene (RR 0.44; 0.27, 0.71; two trials), and tibolone (RR 0.44; 0.27, 0.71; two trials), and tibolone (RR 0.32; 0.13, 0.80; one trial) reduce the incidence of invasive breast cancer in midlife and older women by approximately 30 percent to 68 percent. Tamoxifen and raloxifene had similar effects in the STAR (Study of Raloxifene and Tamoxifen) head-to-head trial.</td>
<td></td>
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</tr>
<tr>
<td>Reduction of invasive breast cancer continued at least 3 to 5 years after discontinuation of</td>
<td>The STAR head-to-head follow-up (median of 81 months) showed continued reduction of</td>
<td>No new data</td>
<td>Three experts thought this conclusion was still valid.</td>
<td>Conclusion is still valid and this portion of the CER does not need updating.</td>
</tr>
<tr>
<td>Conclusions From CER Executive Summary</td>
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<td>Conclusion from SCEPC</td>
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<tr>
<td>tamoxifen in the two trials providing post-treatment follow-up data.</td>
<td>invasive breast cancer at least 1 to 2 years after discontinuation of both tamoxifen and raloxifene, with superiority of tamoxifen over raloxifene.</td>
<td>One expert thought this conclusion was out of date.</td>
<td>Three experts thought this conclusion was still valid.</td>
<td>Conclusion is still valid and this portion of the CER does not need updating.</td>
</tr>
<tr>
<td>Tamoxifen (RR 0.58; 0.42, 0.79; four trials) and raloxifene (RR 0.33; 0.18, 0.61; two trials) reduced estrogen receptor positive invasive breast cancer, but not estrogen receptor negative invasive breast cancer, in placebo-controlled trials. They had similar effects in the STAR head-to-head trial.</td>
<td>Examestane, an aromatase inhibitor, was found to significantly reduce estrogen receptor positive invasive breast cancer but not estrogen receptor negative invasive breast cancer in postmenopausal women who were at moderately increased risk for breast cancer compared to placebo.</td>
<td>No new data</td>
<td>Three experts thought this conclusion was still valid.</td>
<td>Conclusion is still valid and this portion of the CER does not need updating.</td>
</tr>
<tr>
<td>Tamoxifen and raloxofine did not significantly reduce noninvasive breast cancer, including DCIS, in meta-analysis of four placebo-controlled trials, although noninvasive breast cancer was significantly reduced in the NSABP P-1 (National Surgical Adjuvant Breast and Bowel Project) tamoxifen trial (RR 0.63; 0.45, 0.89). The STAR head-to-head trial indicated non statistically significant differences between raloxifene and tamoxifen (RR 1.40; 0.98, 2.00).</td>
<td>The STAR head-to-head follow-up (median of 81 months) showed no statistical significant difference in noninvasive breast cancer between tamoxifen and raloxifene. Examestane, an aromatase inhibitor, did not significantly reduce DCIS compared to placebo.</td>
<td>No new data</td>
<td>Three experts thought this conclusion was still valid.</td>
<td>Conclusion is still valid and this portion of the CER does not need updating.</td>
</tr>
<tr>
<td>All-cause mortality is similar for women using raloxifene and those using tamoxifen, and also similar for tamoxifen, raloxifene, or tibolone compared with placebo, although followup times in most trials were short. Tamoxifen does not reduce</td>
<td>The STAR head-to-head follow-up (median of 81 months) showed no statistical significant difference in all-cause mortality or specific causes of death between tamoxifen and raloxifene.</td>
<td>No new data</td>
<td>All experts agreed this conclusion was still valid.</td>
<td>Conclusion is still valid and this portion of the CER does not need updating.</td>
</tr>
<tr>
<td>Conclusions From CER Executive Summary</td>
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<tr>
<td>breast cancer mortality compared to placebo.</td>
<td>All cause mortality was similar for women using exemestane compared with placebo.</td>
<td></td>
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<tr>
<td>Tamoxifen and raloxifene had similar effects on fractures at multiple sites in the STAR head-to-head trial. In placebo-controlled trials, raloxifene (RR 0.61; 0.54, 0.69; two trials) and tibolone (RR 0.55; 0.41, 0.74; one trial) reduced vertebral fractures; tamoxifen (RR 0.66; 0.45, 0.98; one trial) and tibolone (RR 0.74; 0.58, 0.93; one trial) reduced nonvertebral fractures; and tibolone reduced wrist (RR 0.54; 0.35, 0.82; one trial) but not hip fractures.</td>
<td>Examestane, an aromatase inhibitor, did not significantly reduce skeletal fracture compared to placebo.</td>
<td>No new data</td>
<td>All experts agreed this conclusion was still valid.</td>
<td>Conclusion is still valid and this portion of the CER does not need updating.</td>
</tr>
</tbody>
</table>

**Key Question 2. What is the evidence for harms of tamoxifen citrate, raloxifene, and tibolone when used to reduce risk for primary breast cancer?**

| Raloxifene caused fewer thromboembolic events (RR 0.70; 0.54, 0.91) than tamoxifen in the STAR head-to-head trial. Tamoxifen (RR 1.93; 1.41, 2.64; four trials) and raloxifene (RR 1.60; 1.15, 2.23; two trials) cause more thromboembolic events than placebo. Risk returned to normal after discontinuation of tamoxifen in the two trials providing post-treatment data. Tibolone does not increase risk for thromboembolic events, although data are limited. | The STAR head-to-head follow-up (median of 81 months) showed raloxifene caused fewer thromboembolic events than tamoxifen. | No new data | Three experts agreed this conclusion was still valid. One expert thought this was not true for tibolone but did not reference a study. | Conclusion is still valid and this portion of the CER does not need updating. |

<p>| Tamoxifen, raloxifene, and tibolone do not increase risk for coronary heart disease events, although data for tibolone are limited. | Examestane, an aromatase inhibitor, did not significantly increase risk for coronary heart disease compared to placebo. | No new data | Three experts agreed this conclusion was still valid. One expert thought this was not true for tibolone but did not reference a study. | Conclusion is still valid and this portion of the CER does not need updating. |</p>
<table>
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</tr>
</thead>
<tbody>
<tr>
<td>Tibolone causes more strokes than placebo (RR 2.19; 1.14, 4.23); tamoxifen and raloxifene do not increase risk for stroke.</td>
<td>No new data</td>
<td>No new data</td>
<td>All experts agreed this conclusion was still valid. One expert noted that tibolone has a black box warning for stroke.</td>
<td>Conclusion is still valid and this portion of the CER does not need updating.</td>
</tr>
<tr>
<td>In the STAR head-to-head trial, raloxifene caused fewer cases of endometrial hyperplasia (RR 0.16; 0.09, 0.29) and was associated with fewer hysterectomies (RR 0.44; 0.35, 0.56) than tamoxifen, but differences for endometrial cancer were not statistically significant (RR 0.62; 0.35, 1.08).</td>
<td>The STAR head-to-head follow-up (median of 81 months) showed raloxifene caused fewer cases of invasive uterine cancer, fewer cases of endometrial hyperplasia, and fewer hysterectomies than tamoxifen.</td>
<td>No new data</td>
<td>Two experts thought this conclusion was out of date. Two experts thought this was still valid.</td>
<td>Conclusion is probably out of date and this portion of the CER may need updating.</td>
</tr>
<tr>
<td>Tamoxifen causes more cases of endometrial cancer than placebo (RR 2.13; 1.36, 3.32; three trials); raloxifene does not increase risk for endometrial cancer or uterine bleeding, and tibolone does not increase risk for endometrial cancer in clinical trials but was associated with more cases of endometrial cancer in a large cohort study (RR 1.79; 1.43, 2.25).</td>
<td>No new data</td>
<td>No new data</td>
<td>All experts agreed this conclusion was still valid.</td>
<td>Conclusion is still valid and this portion of the CER does not need updating.</td>
</tr>
<tr>
<td>Raloxifene caused fewer cataracts (RR 0.79; 0.68, 0.92) and cataract surgeries (RR 0.82; 0.68, 0.99) than tamoxifen in the STAR head-to-head trial. Tamoxifen was associated with more cataract surgeries than placebo in the NSABP P-1 trial (RR 1.57; 1.16, 2.14). Raloxifene does not increase risk for cataracts or cataract surgery.</td>
<td>The STAR head-to-head follow-up (median of 81 months) showed raloxifene caused fewer cataracts and cataract surgeries than tamoxifen.</td>
<td>No new data</td>
<td>All experts agreed this conclusion was still valid.</td>
<td>Conclusion is still valid and this portion of the CER does not need updating.</td>
</tr>
</tbody>
</table>
In head-to-head comparisons, women using raloxifene reported more musculoskeletal problems, dyspareunia, and weight gain, while those using tamoxifen had more gynecological problems, vasomotor symptoms, leg cramps, and bladder control symptoms. Most common side effects for tamoxifen are hot flashes and other vasomotor symptoms, vaginal discharge, and other vaginal symptoms such as itching or dryness; for raloxifene, vasomotor symptoms and leg cramps; and for tibolone, vaginal bleeding and reduced number and severity of hot flashes.

Key Question 3: How do outcomes for tamoxifen citrate, raloxifene, and tibolone when used for primary prevention of breast cancer vary by heterogeneity in subpopulations?

<table>
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<tr>
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<tr>
<td>In head-to-head comparisons, women using raloxifene reported more musculoskeletal problems, dyspareunia, and weight gain, while those using tamoxifen had more gynecological problems, vasomotor symptoms, leg cramps, and bladder control symptoms. Most common side effects for tamoxifen are hot flashes and other vasomotor symptoms, vaginal discharge, and other vaginal symptoms such as itching or dryness; for raloxifene, vasomotor symptoms and leg cramps; and for tibolone, vaginal bleeding and reduced number and severity of hot flashes.</td>
<td>Women using exemestane, an aromatase inhibitor, reported more hot flashes, fatigue, sweating, insomnia, diarrhea, nausea, arthritis, joint pain, and muscle pain compared to placebo.</td>
<td>No new data</td>
<td>All experts agreed this conclusion was still valid.</td>
<td>Conclusion is still valid and this portion of the CER does not need updating.</td>
</tr>
</tbody>
</table>

The STAR head-to-head follow-up (median of 81 months) showed that the point estimate for invasive breast cancer was higher in the raloxifene arm than in the tamoxifen arm for all categories of participant characteristics, with statistical significance for no history of lobular carcinoma in situ, history of atypical hyperplasia, and a 5-year predicted breast cancer risk of > 5.01

No new data

Two experts thought this conclusion was out of date.

Two experts thought this conclusion was still valid.

Conclusion is probably out of date and this portion of the CER may need updating.

Tamoxifen reduces breast cancer outcomes in subgroups evaluated in prevention trials based on age, menopausal status, estrogen use, family history of breast cancer, and history of lobular carcinoma in situ or atypical hyperplasia. In

No new data

No new data

All experts agreed this conclusion was still valid.

Conclusion is still valid and this portion of the CER does not need updating.
### Conclusions From CER Executive Summary

<table>
<thead>
<tr>
<th>RAND Literature Search</th>
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</tr>
</thead>
<tbody>
<tr>
<td>the NSABP P-1 trial, cancer rates were highest and risk reduction greatest among women in the highest modified Gail model risk category and among women with prior atypical hyperplasia.</td>
<td>No new data</td>
<td>No new data</td>
<td>All experts agreed this conclusion was still valid. Conclusion is still valid and this portion of the CER does not need updating.</td>
</tr>
<tr>
<td>Raloxifene reduces breast cancer outcomes in subgroups evaluated in prevention trials based on age, age at menarche, parity, age at first live birth, and body mass index. Estimates from subgroups based on prior estrogen use, family history of breast cancer, and prior hysterectomy or oophorectomy are limited by smaller numbers of subjects.</td>
<td>No new data</td>
<td>No new data</td>
<td>All experts agreed this conclusion was still valid. Conclusion is still valid and this portion of the CER does not need updating.</td>
</tr>
<tr>
<td>Thromboembolic events and endometrial cancer were more common in older (&gt;50) than younger women in the NSABP P-1 trial.</td>
<td>No new data</td>
<td>No new data</td>
<td>All experts agreed this conclusion was still valid. Conclusion is still valid and this portion of the CER does not need updating.</td>
</tr>
<tr>
<td>Tibolone causes more strokes in older (&gt;70 years) than younger women.</td>
<td>No new data</td>
<td>No new data</td>
<td>Two experts thought this conclusion was still valid. Two experts did not know. Conclusion is still valid and this portion of the CER does not need updating.</td>
</tr>
</tbody>
</table>

**Key Question 4.** What is the evidence that harms or secondary potential benefits listed above affect treatment choice, concordance, adherence, and persistence to treatment with tamoxifen citrate, raloxifene, and tibolone when used for primary prevention of breast cancer?

Comparisons of adherence and persistence rates across medications in prevention trials are limited because few trials report treatment duration, completion rates, or other measures of adherence and persistence, and trials were designed for different treatment
| No new data | No new data | Three experts agreed this conclusion was still valid. One expert commented that there was no good information on adherence. Conclusion is still valid and this portion of the CER does not need updating. |


### Conclusions From CER

- **Executive Summary**

  - **RAND Literature Search**
    - Discontinuation rates for tamoxifen or raloxifene are generally higher than placebo. In the few trials reporting discontinuation rates, the difference between treatment and placebo groups was <2 percent for adverse events and <4 percent for nonprotocol-specified events.

  - **FDA**
    - No new data

  - **Expert Opinion**
    - All experts agreed this conclusion was still valid.

  - **Conclusion from SCEPC**
    - Conclusion is still valid and this portion of the CER does not need updating.

  - **EPC Investigator Other Experts**

- **Women make decisions to use tamoxifen for risk reduction based on their concern for adverse effects as well as their risk for breast cancer, according to small descriptive studies.**

  - **No new data**

  - **No new data**

  - **Three experts agreed this conclusion was still valid.**

  - **One expert did not know.**

  - **Conclusion is still valid and this portion of the CER does not need updating.**

- **Women weigh their physicians’ recommendations highly when deciding whether to take tamoxifen for risk reduction, according to descriptive studies of concordance.**

  - **No new data**

  - **No new data**

  - **Three experts agreed this conclusion was still valid.**

  - **One expert did not know.**

  - **Conclusion is still valid and this portion of the CER does not need updating.**

- **Studies of treatment choice and concordance for raloxifene and tibolone for breast cancer risk reduction are lacking.**

  - **No new data**

  - **No new data**

  - **Two experts agreed this conclusion was still valid.**

  - **Two experts did not know.**

  - **Conclusion is still valid and this portion of the CER does not need updating.**

### Key Question 5. What methods, such as clinical risk-assessment models, have been used to identify women who could benefit from medications to reduce risk of breast cancer?

- **Nine risk stratification models that predict an individual’s risk for developing breast cancer have been evaluated for use in clinical settings. Models consider multiple risk factors for breast cancer.**

  - **Cummings, et al, report a systematic review of all the breast cancer risk models with the inclusion of breast density. They suggest a risk stratification model with breast density retained good calibration and slightly improved discriminatory.**

  - **No new data**

  - **Two experts agreed this conclusion was still valid.**

  - **Two experts did not know, one of whom suggested that the surveillance project from National Breast Cancer Surveillance project showed**

  - **Conclusion is still valid and this portion of the CER does not need updating. The only new article was excluded from inclusion, given that breast density is not something that can be used in the clinical setting in a primary care office.**
<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Risk stratification models demonstrate good calibration, with the expected number of breast cancer cases in a study population closely matching the number of breast cancer cases observed.</td>
<td>No new data</td>
<td>No new data</td>
<td>Three experts agreed this conclusion was still valid. One expert did not know.</td>
<td>Conclusion is still valid and this portion of the CER does not need updating.</td>
</tr>
<tr>
<td>All models have low discriminatory accuracy in predicting the probability of breast cancer in an individual. Most models perform only slightly better than age alone as a risk predictor.</td>
<td>No new data</td>
<td>No new data</td>
<td>Two experts agreed this conclusion was still valid. One expert did not know.</td>
<td>Conclusion is still valid and this portion of the CER does not need updating.</td>
</tr>
<tr>
<td>A Gail score of $\geq 1.66$ percent has been used as a risk threshold in prevention trials and in Food and Drug Administration approval of tamoxifen and raloxifene for breast cancer prevention. However, this threshold has low discriminatory accuracy in predicting breast cancer in an individual.</td>
<td>No new data</td>
<td>No new data</td>
<td>All experts agreed this conclusion was still valid.</td>
<td>Conclusion is still valid and this portion of the CER does not need updating.</td>
</tr>
</tbody>
</table>

Legend: ATAC =Arimidex, Tamoxifen, Alone or in Combination; ARNO/ABCSG=Arimidex-Nolvadex/Austrian Breast Cancer Study Group; BIG=Breast International Group; DCIS=ductal carcinoma in situ; FDA=Federal Drug Association; IES=Intergroup Examestane Study; NSABP=National Surgical Adjuvant Breast and Bowel Project; SCEPC=Southern California Evidence-based Practice Center; STAR=Study of Tamoxifen and Raloxifene; RR=risk ratio;
References


Appendixes

Appendix A: Search Methodology

Appendix B: Evidence Table

Appendix C: Questionnaire Matrix
Appendix A. Search Methodology

CER SURVEILLANCE – BREAST CANCER SEARCH METHODOLOGY

DATABASE SEARCHED & TIME PERIOD COVERED:
Medline on OVID – 2008-7/6/2011

ALL MEDLINE SEARCHES LIMITED TO THE FOLLOWING JOURNALS:
GENERAL BIOMEDICAL:
Annals of Internal Medicine
British Medical Journal
Journal of the American Medical Association
Lancet
New England Journal of Medicine

SPECIALTY JOURNALS:
American Journal of Obstetrics & Gynecology
Clinical Cancer Research
Journal of Bone Mineral Research
Journal of the National Cancer Institute

Search 1A
1 selective estrogen receptor modulators/ or raloxifene/ or tamoxifen.mp.
2 exp Breast Neoplasms/pc
3 1 and 2
4 exp Primary Prevention/
5 (primar$ adj2 prevent$).mp.
6 exp Breast Neoplasms/
7 1 and 4 and 6
8 exp Chemoprevention/
9 chemoprevent$.mp.
10 1 and 6 and 9
11 1 and 5 and 6
12 10 or 11
13 (prevent$ adj3 (breast$ adj2 (neopl$ or tum$ or canc$ or malignan$))).mp.
14 1 and 13
15 6 and 14
16 12 or 15
17 limit 16 to humans
18 limit 17 to english language
19 limit 18 to abstracts
Search 1B (Revision at recommendation of librarian who ran original search):
1 selective estrogen receptor modulators/ or raloxifene/ or tamoxifen.mp.
2 exp Breast Neoplasms/pc
3 1 and 2
4 exp Primary Prevention/
5 (primar$ adj2 prevent$).mp.
6 exp Breast Neoplasms/
7 1 and 4 and 6
8 exp Chemoprevention/
9 chemoprevent$.mp.
10 1 and 6 and 9
11 1 and 5 and 6
12 10 or 11
13 (prevent$ adj3 (breast$ adj2 (neoplas$ or tumor$ or cancer$ or malignan$))).mp.
14 1 and 13
15 6 and 14
16 12 or 15
17 (chemoprevent$ adj3 (breast$ adj2 (neoplas$ or tumor$ or cancer$ or malignan$))).mp.
18 (prevent$ adj3 (mammar$ adj2 (neoplas$ or tumor$ or cancer$ or malignan$))).mp.
19 (chemoprevent$ adj3 (mammar$ adj2 (neoplas$ or tumor$ or cancer$ or malignan$))).mp.
20 13 or 17 or 18 or 19
21 1 and 20
22 6 and 21
23 12 or 22
24 23 not 16

NOTE – THIS REVISION YIELDED ONE ADDITIONAL REFERENCE

Search 2:
1 exp tamoxifen/ae, po, to
2 exp Raloxifene/ae, to, po
3 exp Placebos/ or placebo$.mp.
4 exp Breast Neoplasms/
5 1 and 2
6 1 and 3
7 2 and 3
8 4 and 5
9 4 and 6
10 4 and 7
11 random$.mp.
12 exp Randomized Controlled Trials/
13 randomized controlled trial.pt.
14 rct$.mp.
15 11 or 12 or 13 or 14
16 8 and 15
17 9 and 15
18 10 and 15
19 16 or 17 or 18
20 exp Cardiovascular Diseases/ep, et
21 exp Endometrial Neoplasms/ep, et
22 exp tamoxifen/
23 exp raloxifene/
24 20 or 21
25 22 and 23
26 3 and 22
27 3 and 23
28 25 or 26 or 27
29 24 and 28
30 15 and 29
31 19 or 30 1
32 limit 31 to yr="2008 - 2011"

NUMBER OF RESULTS: 24
NUMBER WHEN LIMITED TO SPECIFIED JOURNALS: 2

Search 3
1 exp breast neoplasms/pc
2 exp ovarian neoplasms/pc
3 1 or 2
4 (family adj5 histor$).mp.
5 exp genetic predisposition to disease/
6 brca.mp.
7 (brca1 or brca2).mp.
8 4 or 5 or 6 or 7
9 selective estrogen receptor modulators/ 2
10 exp selective estrogen receptor modulators/
11 (serm or serms or tamoxifen or raloxifene).mp.
12 10 or 11
13 3 and 8 and 12
14 exp contraceptives, oral/
15 3 and 8 and 14
16 13 or 15
17 limit 16 to yr="2008 - 2011"

NUMBER OF RESULTS: 30
NUMBER WHEN LIMITED TO SPECIFIED JOURNALS: 0
Search 4a:
1 exp tamoxifen/
2 exp raloxifene/
3 1 or 2
4 exp tamoxifen/ae, po, to
5 exp raloxifene/ae, po, to
6 4 or 5
7 exp genital diseases, female/ci, ep, et
8 exp genital diseases, female/
9 6 and 8
10 3 and 7
11 9 or 10
12 limit 11 to yr="2008 - 2011"

NUMBER OF RESULTS: 86
NUMBER WHEN LIMITED TO SPECIFIED JOURNALS: 3

SEARCH 4b - COMPARISON SEARCH ON PUBMED:
Date limitation: 2008-7/20/2011

tamoxifen OR raloxifene
AND
NOT
animal* NOT (human OR humans)

NUMBER OF RESULTS: 323
NUMBER OF RESULTS AFTER REMOVING DUPLICATES FROM OVID MEDLINE SEARCH & LIMITING TO SPECIFIED JOURNALS: 5

Search 5:
1 exp tamoxifen/ae, po, to
2 exp raloxifene/ae, po, to
3 exp uterine diseases/
4 exp uterus/
5 1 or 2
6 3 or 4
7 5 and 6
8 exp hysterectomy/
9 5 and 8
10 7 or 9
11 limit 10 to (english language and humans)
12 limit 11 to yr="2008 - 2011"

NUMBER OF RESULTS: 55
NUMBER WHEN LIMITED TO SPECIFIED JOURNALS: 0
Search 6:
1 (ovar$ adj5 (cancer$ or tumor$ or malignan$ or carcino$ or neoplas$)).mp.
2 exp tamoxifen/
3 exp raloxifene/
4 2 or 3
5 1 and 4
6 limit 5 to humans
7 limit 6 to yr="2008 - 2011"

NUMBER OF RESULTS: 55
NUMBER WHEN LIMITED TO SPECIFIED JOURNALS: 3

Search 7 (NOTE – terms not in boldface were searched but not included in the final strategy):
1 exp tamoxifen/ae, po, ct, to
2 exp raloxifene/ae, ct, to
3 selective estrogen receptor modulators/ae, co, to, po
4 1 or 2 or 3
5 exp cardiovascular diseases/mo, ci, co, ep, et
6 exp stroke/mo, co, ci, ep, et
7 exp cardiovascular system/pp, de
8 5 or 6 or 7
9 4 and 8
10 exp cardiovascular system/
11 exp cardiovascular diseases/
12 10 or 11
13 exp tamoxifen/
14 exp raloxifene/
15 selective estrogen receptor modulators/
16 13 or 14 or 15
17 4 and 12
18 8 and 16
19 17 or 18
20 limit 19 to humans
21 9
22 limit 21 to humans
23 20 not 22
24 12 and 16
25 limit 24 to humans
26 25 not 20
27 limit 26 to (humans and yr="2008 - 2011")
28 25
29 limit 28 to (humans and yr="2008 - 2011")

NUMBER OF RESULTS: 126
NUMBER WHEN LIMITED TO SPECIFIED JOURNALS: 11
Search 8:
1 exp tamoxifen/
2 exp raloxifene/
3 selective estrogen receptor modulators/
4 1 or 2 or 3
5 ((heart$ or myocardi$ or cardi$ or atria$ or ventric$) adj5 (fibril$ or arrhythm$ or abnormal$ adj2 rhythm$)).mp.
6 4 and 5
7 (tamoxifen or raloxifene).mp.
8 5 and 7
9 6 or 8
10 limit 9 to yr="2008 - 2011"

NUMBER OF RESULTS: 6
NUMBER WHEN LIMITED TO SPECIFIED JOURNALS: 0

Search 9:
1 exp biliary tract/
2 exp biliary tract diseases/
3 1 or 2
4 exp tamoxifen/
5 exp raloxifene/
6 selective estrogen receptor modulators/
7 4 or 5 or 6
8 3 and 7
9 8
10 limit 9 to humans
11 (gallstone$ or gall stone$ or gallbladder$ or gall bladder$ or bile duct$ or biliary tract$ or cholelith$ or cholecyst$ or choledocholith$).mp.
12 7 and 11
13 limit 12 to humans
14 10 or 13
15 14
16 limit 15 to yr="2008 - 2011"

NUMBER OF RESULTS: 5
NUMBER WHEN LIMITED TO SPECIFIED JOURNALS: 1

Search 10:
1 exp breast neoplasms/
2 tibolone.mp.
3 exp breast/
4 1 or 3
5 2 and 4
6 limit 5 to yr="2008 - 2011"

NUMBER OF RESULTS: 33
NUMBER WHEN LIMITED TO SPECIFIED JOURNALS: 3
Search 11:
1 exp breast neoplasms/
2 exp risk/
3 1 and 2
4 exp risk assessment/
5 1 and 4
6 limit 5 to humans
7 exp breast neoplasms/ep, et
8 4 and 7
9 exp breast neoplasms/pc, eh
10 exp breast neoplasms/ge
11 4 and 9
12 4 and 10
13 exp disease susceptibility/
14 7 and 13
15 9 and 13 7
16 8 or 11 or 14 or 15
17 limit 16 to (english language and humans)
18 (model$ or valid$).mp.
19 17 and 18
20 seer.mp.
21 17 and 20
22 19 or 21
23 17 not 22
24 limit 23 to yr="2008 - 2011"

NUMBER OF RESULTS: 602
NUMBER WHEN LIMITED TO SPECIFIED JOURNALS: 49

DATABASE SEARCHED & TIME PERIOD COVERED;
Cochrane databases (Systematic Reviews, Database of Abstracts of Reviews of Effects, CENTRAL Register of Clinical Trials) – 2008-7/14-7/20/2011

Search #1
Cochrane CENTRAL Register of Clinical Trials
#1 (tamoxifen.mp.)
#2 (tamoxifen.mp.)
#3 (tamoxifen):ti,ab,kw
#4 (raloxifene):ti,ab,kw
#5 (placebo*):ti,ab,kw
#6 (#3 AND #4)
#7 (#3 AND #4)
#8 (#3 AND #5)
#9 (#4 AND #5)
#10 (#7 OR #8 OR #9)
#11 (breast* OR mammar*) AND (cancer* OR tumor* OR carcino* OR adenocarcin* OR neoplas* OR malignan*):ti,ab,kw
#12 (#10 AND #11)  
#13 (#12), from 2008 to 2011

**NUMBER OF RESULTS: 38**

Search #2  
**Cochrane CENTRAL Register of Clinical Trials**  
#6 (tamoxifen OR raloxifene):ti,ab,kw and (endometri* OR uterine OR uterus OR hysterect*):ti,ab,kw

**NUMBER OF RESULTS: 28**

Search #3:  
**DATABASE:**  
Cochrane Database of Systematic Reviews  
"tamoxifen OR raloxifene in Title, Abstract or Keywords and endometri* OR uterine OR uterus OR hysterect* in Title, Abstract or Keywords"

**NUMBER OF RESULTS: 4**

Search #4  
**DATABASE:**  
Cochrane Database of Abstracts of Reviews of Effects  
"tamoxifen OR raloxifene in Title, Abstract or Keywords and endometri* OR uterine OR uterus OR hysterect* in Title, Abstract or Keywords"

**NUMBER OF RESULTS: 0**

Search #5:  
**DATABASE:**  
Cochrane CENTRAL Register of Clinical Trials  
#10 (tibolone):ti,ab,kw

**NUMBER OF RESULTS: 49**

Search 6:  
**DATABASE:**  
Cochrane Database of Systematic Reviews  
(tibolone):ti,ab,kw

**NUMBER OF RESULTS: 2**

Search 7:  
**DATABASE:**
Cochrane Database of Abstracts of Reviews of Effects
"tibolone in Title, Abstract or Keywords

NUMBER OF RESULTS: 0
### Appendix B. Evidence Table

<table>
<thead>
<tr>
<th>Article ID, Author, year</th>
<th>Trial</th>
<th>n</th>
<th>Subjects</th>
<th>Primary Outcome</th>
<th>Duration</th>
<th>Study Quality/Applicability</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Key Question 1:</strong> In adult women without preexisting breast cancer, what is the comparative effectiveness of selective estrogen receptor modulator (SERMs) tamoxifen citrate, raloxifene, and the selective tissue estrogenic activity regulator (STEAR) tibolone, when used to reduce risk for primary breast cancer on improving short-term and long-term outcomes including invasive breast cancer, noninvasive breast cancer, including ductal carcinoma <em>in situ</em> (DCIS), breast cancer mortality, all-cause mortality, and osteoporotic fractures?</td>
<td></td>
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<tr>
<td><strong>Tamoxifen vs Raloxifene</strong></td>
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</tr>
<tr>
<td>Vogel, 2010a³</td>
<td>STAR Update</td>
<td>19,490 -tamoxifen (20 mg/day): 9,736 -raloxifene (60 mg/day): 9,754</td>
<td>Postmenopausal women age ≥ 35 years, with a 5- year predicted breast cancer risk of 1.66% based on the modified Gail model. Mean age 58.5 years; 94% white; 52% post hysterectomy; none using estrogen.</td>
<td>Invasive Breast Cancer</td>
<td>Subject took medication for 5 years with median follow-up of 81 months</td>
<td>Good/Good</td>
<td>RR Raloxifene:Tamoxifen -Invasive breast cancer: 1.24 (1.05-1.47) -Non-invasive breast cancer: 1.22 (0.95-1.59)</td>
</tr>
<tr>
<td>Vogel, 2010b⁴</td>
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<tr>
<td><strong>Examestane vs Placebo</strong></td>
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</tr>
<tr>
<td>Goss, 2011⁵</td>
<td>NCIC Clinical Trials Group Mammary Prevention Trial P-3</td>
<td>4560 -examestane (25 mg) alone or with celecoxib: 2285 -placebo: 2275</td>
<td>Postmenopausal women age ≥ 35 with one of the following factors: a 5- year predicted breast cancer risk of 1.66% based on the modified Gail model; age ≥ 60; prior atypical ductal or lobular hyperplasia or lobular carcinoma in situ.; ductal carcinoma in situ with mastectomy. Mean age 62.5 years; 93% white;</td>
<td>Invasive Breast Cancer</td>
<td>Subject took examestane for median time of 10.2 months with a median follow-up of 35 months</td>
<td>Good/Good</td>
<td>RR Examestane:Placebo -Invasive breast cancer: 0.34 (0.17-0.68) -ER-positive invasive breast cancer: 0.26 (0.11-0.59) -ER-negative invasive breast cancer: 0.80 (0.21-2.96) -DCIS: 0.64 (0.28-1.48) -Skeletal fracture: 1.05 (0.84-1.31) -All-cause mortality: 1.00 (0.53-1.88)</td>
</tr>
<tr>
<td>Article ID, Author, year</td>
<td>Trial</td>
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<td>Vogel, 2010a\textsuperscript{7} Vogel, 2010b\textsuperscript{4}</td>
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<td>Invasive Breast Cancer</td>
<td>Subject took medication for 5 years with median 81 month follow-up reported</td>
<td>Good/Good</td>
<td>RR Raloxifene:Tamoxifen -All cause mortality: 0.84 (0.70-1.02) -Thromboembolic events: 0.75 (0.60-0.93) -Invasive uterine cancer: 0.55 (0.36-0.83) -Uterine hyperplasia: 0.19 (0.12-0.29) -Hysterectomies: 0.45 (0.37-0.54) -Cataracts: 0.80 (0.72-0.89) -Cataract surgeries: 0.79 (0.70-0.90)</td>
</tr>
<tr>
<td>Goss, 2011\textsuperscript{5}</td>
<td>NCIC Clinical Trials Group Mammary Prevention Trial P-3</td>
<td>4560</td>
<td>Postmenopausal women age ≥ 35 with one of the following factors: a 5-year predicted breast cancer risk of 1.66% based on the modified Gail model; age ≥ 60; prior atypical ductal or lobular hyperplasia or lobular carcinoma in situ; ductal carcinoma in situ with mastectomy. Mean age 62.5 years; 93% white; 58% using</td>
<td>Invasive Breast Cancer</td>
<td>Subject took exemestane for median time of 10.2 months with a median follow-up of 35 months</td>
<td>Good/Good</td>
<td>RR Examestane:Placebo -Cardiovascular events: 0.96 (0.74-1.24) -Hot flashes: 1.26 (1.16-1.36) -Fatigue: 1.13 (1.01-1.27) -Sweating: 1.13 (1.00-1.26) -Insomnia: 1.22 (1.02-1.47) -Diarrhea: 1.58 (1.19-2.10) -Nausea: 1.28 (1.01-1.60) -Arthritis: 1.26 (1.06-1.51)</td>
</tr>
</tbody>
</table>

**Key Question 2.** What is the evidence for harms of tamoxifen citrate, raloxifene, and tibolone when used to reduce risk for primary breast cancer?
<table>
<thead>
<tr>
<th>Article ID, Author, year</th>
<th>Trial</th>
<th>n</th>
<th>Subjects</th>
<th>Primary Outcome</th>
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<td>Postmenopausal women with a 5-year predicted breast cancer risk of 1.66% based on the modified Gail model. Age ≥35 years, mean age 58.5 years; 94% white; 52% post hysterectomy; none using estrogen.</td>
<td>Invasive Breast Cancer</td>
<td>Subject took medication for 5 years with median 81 month follow-up reported</td>
<td>Good/Good</td>
<td></td>
</tr>
</tbody>
</table>

**Key Question 3**: How do outcomes for tamoxifen citrate, raloxifene, and tibolone when used for primary prevention of breast cancer vary by heterogeneity in subpopulations?

The point estimate for invasive breast cancer was higher in the raloxifene arm than in the tamoxifen arm for all categories of participant characteristics. RR Raloxifene:Tamoxifen was statistical significant for:
- no history of lobular carcinoma in situ: 1.27 (1.05-1.54)
- positive history of atypical hyperplasia: 1.48 (1.06-2.09)
- 5-year predicted breast cancer risk of >5.01: 1.33 (1.02-1.74)

| Goss, 2011<sup>5</sup> | NCIC Clinical Trials Group Mammary Prevention Trial P-3 | 4,560 -examestane (25 mg): 2,285 -placebo: 2,275 | Postmenopausal women age ≥ 35 with one of the following factors: a 5-year predicted breast cancer risk of 1.66% based on the modified Gail model: age ≥ 60; prior atypical ductal or lobular hyperplasia or lobular carcinoma in situ; ductal carcinoma in situ with mastectomy. Mean age 62.5 | Invasive Breast Cancer | Subject took examestane for median time of 10.2 months with a median follow-up of 35 months | Good/Good |

**Key Question 4**: What is the evidence that harms or secondary potential benefits listed above affect treatment choice, concordance, adherence, and persistence to treatment with tamoxifen citrate, raloxifene, and tibolone when used for primary prevention of breast cancer?

Discontinuation rate for examestane was 32.8% compared to 28.7% for placebo.
<table>
<thead>
<tr>
<th>Article ID, Author, year</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>years; 93% white; 58% using hormone-replacement therapy; 4.8% using SERMs</td>
<td></td>
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</tr>
</tbody>
</table>

Key Question 5. What methods, such as clinical risk-assessment models, have been used to identify women who could benefit from medications to reduce risk of breast cancer?

No new data.

Legend: SCEPC=Southern California Evidence-based Practice Center; NSABP=National Surgical Adjuvant Breast and Bowel Project; STAR=Study of Tamoxifen and Raloxifene; RR=risk ratio; BCPT=Breast Cancer Prevention Trial; WHI=Women’s Health Initiative; NCIC=National Cancer Institute of Canada; ER-positive=estrogen receptor positive; ER-negative=estrogen receptor negative; SERMs=selective estrogen receptor modulators; DCIS=ductal carcinoma in situ
Appendix C. Questionnaire Matrix

Surveillance and Identification of Triggers for Updating Systematic Reviews for the EHC Program

Title: Comparative Effectiveness of Medications to Reduce Risk of Primary Breast Cancer in Women

<table>
<thead>
<tr>
<th>Conclusions From CER Executive Summary</th>
<th>Is this conclusion almost certainly still supported by the evidence?</th>
<th>Has there been new evidence that may change this conclusion?</th>
<th>Do Not Know</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eight large randomized controlled trials provide data on breast cancer risk reduction in women without pre-existing breast cancer. These include one good-quality head-to-head trial of tamoxifen and raloxifene and seven fair- and good-quality placebo-controlled trials (four tamoxifen, two raloxifene, and one tibolone). Results on placebo controlled trials cannot be directly compared between types of medications because of important differences between study subjects.</td>
<td>❌</td>
<td>New Evidence:</td>
<td></td>
</tr>
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<td></td>
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</tbody>
</table>

Key Question 1: In adult women without preexisting breast cancer, what is the comparative effectiveness of selective estrogen receptor modulator (SERMs) tamoxifen citrate, and the selective tissue estrogenic activity regulator (STEAR) tibolone, when used to reduce risk for primary breast cancer on improving short-term and long-term outcomes including invasive breast cancer, noninvasive breast cancer, including ductal carcinoma in situ (DCIS), breast cancer mortality, all-cause mortality, and osteoporotic fractures?
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<th>Has there been new evidence that may change this conclusion?</th>
<th>Do Not Know</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tamoxifen (risk ratio [RR] 0.70; 0.59, 0.82; four trials), raloxifene (RR 0.44; 0.27, 0.71; two trials), and tibolone (RR 0.44; 0.27, 0.71; two trials), and tibolone (RR 0.32; 0.13, 0.80; one trial) reduce the incidence of invasive breast cancer in midlife and older women by approximately 30 percent to 68 percent. Tamoxifen and raloxifene had similar effects in the STAR (Study of Raloxifene and Tamoxifen) head-to-head trial.</strong></td>
<td>❌</td>
<td>New Evidence:</td>
<td>❌</td>
</tr>
<tr>
<td><strong>Reduction of invasive breast cancer continued at least 3 to 5 years after discontinuation of tamoxifen in the two trials providing post-treatment followup data.</strong></td>
<td>❌</td>
<td>New Evidence:</td>
<td>❌</td>
</tr>
<tr>
<td><strong>Tamoxifen (RR 0.58; 0.42, 0.79; four trials) and raloxifene (RR 0.33; 0.18, 0.61; two trials) reduced estrogen receptor positive invasive breast cancer, but not estrogen receptor negative</strong></td>
<td>❌</td>
<td>New Evidence:</td>
<td>❌</td>
</tr>
<tr>
<td>Conclusions From CER Executive Summary</td>
<td>Is this conclusion almost certainly still supported by the evidence?</td>
<td>Has there been new evidence that may change this conclusion?</td>
<td>Do Not Know</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>---------------------------------------------------------------</td>
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</tr>
<tr>
<td>invasive breast cancer, in placebo-controlled trials. They had similar effects in the STAR head-to-head trial.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tamoxifen and raloxifene did not significantly reduce noninvasive breast cancer, including DCIS, in meta-analysis of four placebo-controlled trials, although noninvasive breast cancer was significantly reduced in the NSABP P-1 (National Surgical Adjuvant Breast and Bowel Project) tamoxifen trial (RR 0.63; 0.45, 0.89). The STAR head-to-head trial indicated non statistically significant differences between raloxifene and tamoxifen (RR 1.40; 0.98, 2.00).</td>
<td>☐</td>
<td>New Evidence:</td>
<td>☐</td>
</tr>
<tr>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>All-cause mortality is similar for women using raloxifene and those using tamoxifen, and also similar for tamoxifen, raloxifene, or tibolone compared with placebo, although followup times in most trials were short. Tamoxifen does not reduce breast cancer mortality compared to placebo.</td>
<td>☐</td>
<td>New Evidence:</td>
<td>☐</td>
</tr>
<tr>
<td>☐</td>
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</tr>
<tr>
<td>Tamoxifen and raloxifene had similar effects on fractures at multiple sites in the STAR head-to-head trial. In</td>
<td>☐</td>
<td>New Evidence:</td>
<td>☐</td>
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<td>Do Not Know</td>
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<tr>
<td>placebo-controlled trials, raloxifene (RR 0.61; 0.54, 0.69; two trials) and tibolone (RR 0.55; 0.41. 0.74; one trial) reduced vertebral fractures; tamoxifen (RR 0.66; 0.45, 0.98; one trial) and tibolone (RR 0.74; 0.58, 0.93; one trial reduced nonvertebral fractures; and tibolone reduced wrist (RR 0.54; 0.35, 0.82; one trial) but not hip fractures</td>
<td></td>
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</tr>
</tbody>
</table>

**Key Question 2.** What is the evidence for harms of tamoxifen citrate, raloxifene, and tibolone when used to reduce risk for primary breast cancer?

<p>| Raloxifene caused fewer thromboembolic events (RR 0.70; 0.54, 0.91) than tamoxifen in the STAR head-to-head trial. Tamoxifen (RR 1.93; 1.41, 2.64; four trials) and raloxifene (RR 1.60; 1.15, 2.23; two trials) cause more thromboembolic events than placebo. Risk returned to normal after discontinuation of tamoxifen in the two trials providing post-treatment data. Tibolone does not increase risk for thromboembolic events, although data are limited. | New Evidence: | | |
| Tamoxifen, raloxifene, and tibolone do not increase risk for coronary heart disease events, although data for | New Evidence: | | |</p>
<table>
<thead>
<tr>
<th>Conclusions From CER Executive Summary</th>
<th>Is this conclusion almost certainly still supported by the evidence?</th>
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<tr>
<td>Tibolone are limited.</td>
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<tr>
<td>Tibolone causes more strokes than placebo (RR 2.19; 1.14, 4.23); tamoxifen and raloxifene do not increase risk for stroke.</td>
<td>☐</td>
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<tr>
<td>In the STAR head-to-head trial, raloxifene caused fewer cases of endometrial hyperplasia (RR 0.16; 0.09, 0.29) and was associated with fewer hysterectomies (RR 0.44; 0.35, 0.56) than tamoxifen, but differences for endometrial cancer were not statistically significant (RR 0.62; 0.35, 1.08).</td>
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<tr>
<td>Tamoxifen causes more cases of endometrial cancer than placebo (RR 2.13; 1.36, 3.32; three trials); raloxifene does not increase risk for endometrial cancer or uterine bleeding, and tibolone</td>
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New Evidence:
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<tr>
<td>Does not increase risk for endometrial cancer in clinical trials but was associated with more cases of endometrial cancer in a large cohort study (RR 1.79; 1.43, 2.25).</td>
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<td>Raloxifene caused fewer cataracts (RR 0.79; 0.68, 0.92) and cataract surgeries (RR 0.82; 0.68, 0.99) than tamoxifen in the STAR head-to-head trial. Tamoxifen was associated with more cataract surgeries than placebo in the NSABP P-1 trial (RR 1.57; 1.16, 2.14). Raloxifene does not increase risk for cataracts or cataract surgery.</td>
<td>☐</td>
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<td>In head-to-head comparisons, women using raloxifene reported more musculoskeletal problems, dyspareunia, and weight gain, while those using tamoxifen had more gynecological problems, vasomotor symptoms, leg cramps, and bladder control symptoms.</td>
<td>☐</td>
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<td>Most common side effects for tamoxifen are hot flashes and other vasomotor symptoms, vaginal discharge, and other vaginal symptoms such as itching or</td>
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<td>dryness; for raloxifene, vasomotor symptoms and leg cramps; and for tibolone, vaginal bleeding and reduced number and severity of hot flashes.</td>
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**Key Question 3: How do outcomes for tamoxifen citrate, raloxifene, and tibolone when used for primary prevention of breast cancer vary by heterogeneity in subpopulations?**

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<thead>
<tr>
<th>Tamoxifen and raloxifene had similar effects on breast cancer outcomes regardless of age and family history of breast cancer in the head-to-head STAR trial.</th>
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<tr>
<th>Tamoxifen reduces breast cancer outcomes in subgroups evaluated in prevention trials based on age, menopausal status, estrogen use, family history of breast cancer, and history of lobular carcinoma in situ or atypical hyperplasia. In the NSABP P-I trial, cancer rates were highest and risk reduction greatest among women in the highest modified Gail model risk category and among women with prior atypical hyperplasia.</th>
<th>New Evidence:</th>
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<tr>
<td>Raloxifene reduces breast cancer outcomes in subgroups evaluated in prevention trials based on age, age at menarche, parity, age at first live birth, and body mass index. Estimates from subgroups based on prior estrogen use, family history of breast cancer, and prior hysterectomy or oophorectomy are limited by smaller numbers of subjects.</td>
<td>❏</td>
<td>New Evidence:</td>
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<td>Thromboembolic events and endometrial cancer were more common in older (&gt;50) than younger women in the NSABP P-1 trial.</td>
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<td>New Evidence:</td>
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<td>Tibolone causes more strokes in older (&gt;70 years) than younger women.</td>
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<td>New Evidence:</td>
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<td><strong>Key Question 4.</strong> What is the evidence that harms or secondary potential benefits listed above affect treatment choice, concordance, adherence, and persistence to treatment with tamoxifen citrate, raloxifene, and tibolone when used for primary prevention of breast cancer?</td>
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<td>Comparisons of adherence and persistence rates across medications in prevention trials are limited because few trials report treatment duration, completion rates, or other measures of adherence and persistence, and trials were designed for different treatment purposes.</td>
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<td>Discontinuation rates for tamoxifen or raloxifene are generally higher than placebo. In the few trials reporting discontinuation rates, the difference between treatment and placebo groups was &lt;2 percent for adverse events and &lt;4 percent for nonprotocol-specified events.</td>
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<td>Women make decisions to use tamoxifen for risk reduction based on their concern for adverse effects as well as their risk for breast cancer, according to small descriptive studies.</td>
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<td>Women weigh their physicians’ recommendations highly when deciding whether to take tamoxifen for risk reduction, according to descriptive studies of concordance.</td>
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<td>Studies of treatment choice and concordance for raloxifene and tibolone for breast cancer risk reduction are lacking.</td>
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<td><strong>Key Question 5. What methods, such as clinical risk-assessment models, have been used to identify women who could benefit from medications to reduce risk of breast cancer?</strong></td>
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<td>Nine risk stratification models that predict an individual’s risk for developing breast cancer have been evaluated for use in clinical settings. Models consider multiple risk factors for breast cancer.</td>
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<td>Risk stratification models demonstrate good calibration, with the expected number of breast cancer cases in a study population closely matching the number of breast cancer cases observed.</td>
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<td>All models have low discriminatory accuracy in predicting the probability of breast cancer in an individual. Most models perform only slightly better than age alone as a risk predictor.</td>
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<td>A Gail score of $\geq 1.66$ percent has been used as a risk threshold in prevention trials and in Food and Drug Administration approval of tamoxifen and raloxifene for breast cancer prevention. However, this threshold has low discriminatory accuracy in predicting breast cancer in an individual.</td>
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Are there new data that could inform the key questions that might not be addressed in the conclusions?
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