AHRQ Comparative Effectiveness Review Surveillance Program

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

Original release date:
September 14, 2009

Surveillance Report 1st Assessment: November, 2011
Surveillance Report 2nd Assessment: July, 2012

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for Key Question 1, 1 of 7 conclusions for Key Question 2, and 1 of 5 conclusions for Key Question 3 are probably out of date due to longer term followup of a major trial and the availability of new drugs for this indication.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.

These findings were unchanged from the 1st assessment

Summary Decision

This CER's priority for updating is **Medium** (This is unchanged from the last assessment)

Authors:
Jennifer Schneider Chafen, MS, MD
Sydne Newberry, PhD
Margaret Maglione, MPP
Aneesa Motala, BA
Roberta Shanman, MLS
Paul Shekelle, MD, PhD

None of the investigators has any affiliations or financial involvement that conflicts with the material presented in this report.

Acknowledgments

The authors gratefully acknowledge the following individuals for their contributions to this project:

Subject Matter Experts

Claudine Isaacs, MD
Georgetown University
Chevy Chase, Maryland

Diana Petitti, MD
Arizona State University
Phoenix, Arizona

Larry Wickerham, MD
National Surgical Adjuvant Breast and Bowel Project
Pittsburgh, Pennsylvania

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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.[1] It was therefore due for a surveillance assessment in March, 2010. The Surveillance Program commenced in late summer 2010, and the first assessment of CER #17 was submitted in November, 2011. This second assessment was due to start the re-assessment in May, 2012 and was completed in July, 2012.

2. Methods

2.1 Literature Searches

The 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. The first assessment search covered 2008-July, 2011. The second assessment covered July, 2011-May, 2012. Appendix A includes the search methodology.

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. The study selection remained unchanged for the second assessment.

2.3 Expert Opinion

For the first assessment 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. For the second assessment, we reached out to the four experts with a modified matrix that included the experts prior responses. Three experts responded back.

2.4 Check for qualitative and quantitative signals

After abstracting the study conditions and findings for each new included study into an evidence table (Appendix B), we assessed whether the new findings provided a signal according to the Ottawa Method and/or the RAND Method, suggesting the need for an update. The criteria are listed in the table below.[2, 3]

	Ottawa Method
	Ottawa Qualitative Criteria for Signals of Potentially Invalidating Changes in Evidence
A1	Opposing findings: A pivotal trial or systematic review (or guidelines) including at least one new trial that characterized the treatment in terms opposite to those used earlier.
A2	Substantial harm: A pivotal trial or systematic review (or guidelines) whose results called into question the use of the treatment based on evidence of harm or that did not proscribe use entirely but did potentially affect clinical decision making.
A3	A superior new treatment: A pivotal trial or systematic review (or guidelines) whose results identified another treatment as significantly superior to the one evaluated in the original review, based on efficacy or harm.
	Criteria for Signals of Major Changes in Evidence
A4	Important changes in effectiveness short of "opposing findings"
A5	Clinically important expansion of treatment
A6	Clinically important caveat
A7	Opposing findings from discordant meta-analysis or nonpivotal trial
	Quantitative Criteria for Signals of Potentially Invalidating Changes in Evidence
B1	A change in statistical significance (from nonsignificant to significant)
B2	A change in relative effect size of at least 50 percent
	RAND Method Indications for the Need for an Update
1	Original conclusion is still valid and this portion of the original report does not need updating
2	Original conclusion is possibly out of date and this portion of the original report may need updating
3	Original conclusion is probably out of date and this portion of the original report may need updating
4	Original conclusion is out of date

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

1st assessment: 102 titles were identified from the literature searches covering 2008-July 2011. After title and abstract review, we further reviewed the full text of 19 journal articles. The remaining 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. Thirty articles were rejected because either they had already been included in the earlier report or did not include a comparison of interest. Three articles were abstracted into an evidence table.

2nd assessment: 88 titles were identified from the literature searches covering July 2011-May 2012. We followed the same inclusion/exclusion criteria from the 1st assessment. Seven articles were accepted for full text review of which two were included for the re-assessment.

Appendix B includes the cumulative data for the 5 included studies.[4-8] The two new studies are bolded.

3.2 Expert Opinion

2nd assessment: Two out of the three experts thought there was no new evidence for KQ's 1-5. One expert cited literature that was included in the previous update.

3.3 Identifying qualitative and quantitative signals

2nd assessment: In this CER we only checked for qualitative signals.[2]

Table 1: Summary Table

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC	Conclusions of validity of CER conclusion(s)	
					Prior Assessment	Cumulative Assessment
Key Question 1: In adult women without preexisting breast caner, 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?						
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	**November 2011:** 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. **July 2012:** No new data	**November 2011:** No new data **July 2012:** No new data	**November 2011:** 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. **July 2012:** Two experts thought there was no new evidence and one expert cited the literature included in the last update.	**November 2011:** 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, arzofoxifene was shown to decrease the incidence of invasive breast cancer. Further development of this drug by Lilly as been dropped. **July 2012:** Conclusion	**Up-to-date**	**Up-to-date**

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC	Conclusions of validity of CER conclusion(s)	
					Prior Assessment	Cumulative Assessment
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).				unchanged from previous update.		
Reduction of invasive breast cancer continued at least 3 to 5 years after discontinuation of tamoxifen in the two trials	**November 2011:** The STAR head-to-head follow-up (median of 81 months) showed continued reduction of invasive breast cancer at least 1 to	**November 2011:** No new data	**November 2011:** Three experts thought this conclusion was still valid. One expert thought this conclusion was out of date.	**November 2011:** Conclusion is still valid and this portion of the CER does not need updating.	**Up-to-date**	**Up-to-date**

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC	Conclusions of validity of CER conclusion(s)	
					Prior Assessment	Cumulative Assessment
providing post-treatment follow-up data.	2 years after discontinuation of both tamoxifen and raloxifene, with superiority of tamoxifen over raloxifene. **July 2012:** No new data	**July 2012** assessment: No new data	**July 2012**: Three experts thought there was no new data.	**July 2012:** Conclusion unchanged from previous update.		
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.	**November 2011:** 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. **July 2012:** Examestane, an aromatase inhibitor, was found to worsen age-related bone loss in postmenopausal women despite	**November 2011:** No new data **July 2012:** No new data	**November 2011:** Three experts thought this conclusion was still valid. One expert thought this conclusion was out of date. **July 2012:** Three experts thought there was no new data.	**November 2011:** Conclusion is probably out of date because there is a new drug available and this portion of the CER may need updating. **July 2012:** Conclusion unchanged from previous update.	**Up-to-date**	**Up-to-date**

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC	Conclusions of validity of CER conclusion(s)	
					Prior Assessment	Cumulative Assessment
	calcium and vitamin D supplementation.					
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).	**November 2011:** 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. **July 2012:** No new data	**November 2011:** No new data **July 2012*:*** No new data	**November 2011:** Three experts thought this conclusion was still valid. One expert did not know. **July 2012:** Two experts thought there was no new evidence and one expert cited the literature included in the last update.	**November 2011:** Conclusion is still valid and this portion of the CER does not need updating. **July 2012:** Conclusion unchanged from previous update.	**Up-to-date**	**Up-to-date**

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC	Conclusions of validity of CER conclusion(s)	
					Prior Assessment	Cumulative Assessment
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.	**November 2011:** 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. All cause mortality was similar for women using examestane compared with placebo. **July 2012:** No new data	**November 2011:** No new data **July 2012:** No new data	**November 2011:** All experts agreed this conclusion was still valid. **July 2012:** Two experts thought there was no new evidence and one expert cited the literature included in the last update.	**November 2011:** Conclusion is still valid and this portion of the CER does not need updating. **July 2012:** Conclusion unchanged from previous update.	**Up-to-date**	**Up-to-date**
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	**November 2011:** Examestane, an aromatase inhibitor, did not significantly reduce skeletal fracture compared to placebo. **July 2012:** Examestane, an aromatase inhibitor, was found to worsen age-related bone loss in postmenopausal	**November 2011:** No new data **July 2012:** No new data	**November 2011:** All experts agreed this conclusion was still valid. **July 2012:** Three experts thought there was no new data.	**November 2011:** Conclusion is still valid and this portion of the CER does not need updating. **July 2012:** Conclusion unchanged from previous update.	**Up-to-date**	**Up-to-date**

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC	Conclusions of validity of CER conclusion(s)	
					Prior Assessment	Cumulative Assessment
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.	women despite calcium and vitamin D supplementation.					
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	**November 2011:** The STAR head-to-head follow-up (median of 81 months) showed raloxifene caused fewer thromboembolic events than tamoxifen. **July 2012:** No new data	**November 2011:** No new data **July 2012:** No new data	**November 2011:** Three experts agreed this conclusion was still valid. One expert thought this was not true for tibolone but did not reference a study. **July 2012:** Three experts thought there was no new data.	**November 2011:** Conclusion is still valid and this portion of the CER does not need updating. **July 2012:** Conclusion unchanged from previous update.	**Up-to-date**	**Up-to-date**

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC	Conclusions of validity of CER conclusion(s)	
					Prior Assessment	Cumulative Assessment
providing post-treatment data. Tibolone does not increase risk for thromboembolic events, although data are limited.						
Tamoxifen, raloxifene, and tibolone do not increase risk for coronary heart disease events, although data for tibolone are limited.	**November 2011:** Examestane, an aromatase inhibitor, did not significantly increase risk for coronary heart disease compared to placebo. **July 2012:** No new data	**November 2011:** No new data **July 2012:** No new data	**November 2011:** Three experts agreed this conclusion was still valid. One expert thought this was not true for tibolone but did not reference a study. **July 2012:** Three experts thought there was no new data.	**November 2011:** Conclusion is still valid and this portion of the CER does not need updating. **July 2012:** Conclusion unchanged from previous update**.**	**Up-to-date**	**Up-to-date**
Tibolone causes more strokes than placebo (RR 2.19; 1.14, 4.23); tamoxifen and raloxifene do not increase risk for stroke.	**November 2011:** No new data **July 2012:** No new data	**November 2011:** No new data **July 2012:** No new data	**November 2011:** All experts agreed this conclusion was still valid. One expert noted that tibolone has a black box warning for stroke. **July 2012:** Three experts thought there was no new data.	**November 2011:** Conclusion is still valid and this portion of the CER does not need updating. **July 2012:** Conclusion unchanged from previous update.	**Up-to-date**	**Up-to-date**
In the STAR head-to-head trial, raloxifene	**November 2011:** The STAR head-to-head follow-up	**November 2011:** No new data	**November 2011:** Two experts thought this conclusion was out of	**November 2011:** Conclusion is probably out of date and this portion of	**Up-to-date**	**Up-to-date**

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC	Conclusions of validity of CER conclusion(s)	
					Prior Assessment	Cumulative Assessment
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).	(median of 81 months) showed raloxifene caused fewer cases of invasive uterine cancer, fewer cases of endometrial hyperplasia, and fewer hysterectomies than tamoxifen. **July 2012:** No new data	**July 2012:** No new data	date. Two experts thought this was still valid. **July 2012:** Two experts thought there was no new evidence and one expert cited the literature included in the last update.	the CER may need updating. **July 2012:** Conclusion unchanged from previous update.		
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	**November 2011:** No new data **July 2012:** Compared with women who received tamoxifen therapy, women who received raloxifene therapy had lower incidences of uterine cancer/endometrial hyperplasia, leiomyomas, ovarian cysts, and endometrial polyps.	**November 2011:** No new data **July 2012:** No new data	**November 2011:** All experts agreed this conclusion was still valid. **July 2012:** Three experts thought there was no new data.	**November 2011:** Conclusion is still valid and this portion of the CER does not need updating. **July 2012:** Conclusion unchanged from previous update**.**	**Up-to-date**	**Up-to-date**

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC	Conclusions of validity of CER conclusion(s)	
					Prior Assessment	Cumulative Assessment
endometrial cancer in a large cohort study (RR 1.79; 1.43, 2.25).	Women receiving tamoxifen therapy had more hot flashes, vaginal discharge, and vaginal bleeding.					
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.	**November 2011:** The STAR head-to-head follow-up (median of 81 months) showed raloxifene caused fewer cataracts and cataract surgeries than tamoxifen. **July 2012:** No new data	**November 2011:** No new data **July 2012:** No new data	**November 2011:** All experts agreed this conclusion was still valid. **July 2012:** Two experts thought there was no new evidence and one expert cited the literature included in the last update.	**November 2011:** Conclusion is still valid and this portion of the CER does not need updating. **July 2012:** Conclusion unchanged from previous update.	**Up-to-date**	**Up-to-date**
In head-to-head comparisons, women using raloxifene reported more musculoskeletal problems, dyspareunia, and weight gain, while those using	**November 2011:** Women using examestane, an aromatase inhibitor, reported more hot flashes, fatigue, sweating, insomnia, diarrhea, nausea, arthritis, joint pain, and muscle pain	**November 2011:** No new data **July 2012:** No new data	**November 2011:** All experts agreed this conclusion was still valid. **July 2012:** Three experts thought there was no new data.	**November 2011:** Conclusion is still valid and this portion of the CER does not need updating. **July 2012:** Conclusion unchanged from previous update.	**Up-to-date**	**Up-to-date**

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC	Conclusions of validity of CER conclusion(s)	
					Prior Assessment	Cumulative Assessment
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.	compared to placebo. **July 2012:** No new data					
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?						
Tamoxifen and raloxifene had similar effects on breast cancer outcomes	**November 2011:** The STAR head-to-head follow-up (median of 81 months) showed	**November 2011:** No new data	**November 2011:** Two experts thought this conclusion was out of date.	**November 2011:** Conclusion is probably out of date and this portion of the CER may need updating.	**Up-to-date**	**Up-to-date**

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC	Conclusions of validity of CER conclusion(s)	
					Prior Assessment	Cumulative Assessment
regardless of age and family history of breast cancer in the head-to-head STAR trial.	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 $\geq$ 5.01 **July 2012:** No new data	**July 2012:** No new data	Two experts thought this conclusion was still valid. **July 2012:** Three experts thought there was no new data.	**July 2012:** Conclusion unchanged from previous update.		
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-1	**November 2011:** No new data **July 2012:** No new data	**November 2011:** No new data **July 2012:** No new data	**November 2011:** All experts agreed this conclusion was still valid. **July 2012:** Three experts thought there was no new data.	**November 2011:** Conclusion is still valid and this portion of the CER does not need updating. **July 2012:** Conclusion unchanged from previous update.	**Up-to-date**	**Up-to-date**

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC	Conclusions of validity of CER conclusion(s)	
					Prior Assessment	Cumulative Assessment
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.						
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.	**November 2011:** No new data **July 2012:** No new data	**November 2011:** No new data **July 2012:** No new data	**November 2011:** All experts agreed this conclusion was still valid. **July 2012:** Three experts thought there was no new data.	**November 2011:** Conclusion is still valid and this portion of the CER does not need updating. **July 2012:** Conclusion unchanged from previous update.	**Up-to-date**	**Up-to-date**
Thromboembolic events and	**November 2011:** No new data	**November 2011:** No new	**November 2011:** All experts agreed this	**November 2011:** Conclusion is still valid and	**Up-to-date**	**Up-to-date**

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC	Conclusions of validity of CER conclusion(s)	
					Prior Assessment	Cumulative Assessment
endometrial cancer were more common in older (>50) than younger women in the NSABP P-1 trial.	**July 2012:** No new data	data **July 2012:** No new data	conclusion was still valid. **July 2012:** Three experts thought there was no new data.	this portion of the CER does not need updating. **July 2012:** Conclusion unchanged from previous update.		
Tibolone causes more strokes in older (>70 years) than younger women.	**November 2011:** No new data **July 2012:** No new data	**November 2011:** No new data **July 2012:** No new data	**November 2011:** Two experts thought this conclusion was still valid. Two experts did not know. **July 2012:** Three experts thought there was no new data.	**November 2011:** Conclusion is still valid and this portion of the CER does not need updating. **July 2012:** Conclusion unchanged from previous update.	**Up-to-date**	**Up-to-date**
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	**November 2011:** No new data **July 2012:** No new data	**November 2011:** No new data **July 2012:** No new data	**November 2011:** Three experts agreed this conclusion was still valid. One expert commented that there was no good information on adherence. **July 2012:** Two experts did not know. One expert thought there was no new data.	**November 2011:** Conclusion is still valid and this portion of the CER does not need updating. **July 2012:** Conclusion unchanged from previous update.	**Up-to-date**	**Up-to-date**

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC	Conclusions of validity of CER conclusion(s)	
					Prior Assessment	Cumulative Assessment
different treatment purposes.						
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.	**November 2011:** Discontinuation rates for examestane were 4.1% higher than for placebo **July 2012:** No new data	**November 2011:** No new data **July 2012:** No new data	**November 2011:** All experts agreed this conclusion was still valid. **July 2012:** Two experts did not know. One expert thought there was no new data.	**November 2011:** Conclusion is still valid and this portion of the CER does not need updating. **July 2012:** Conclusion unchanged from previous update.	**Up-to-date**	**Up-to-date**
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.	**November 2011:** No new data **July 2012:** No new data	**November 2011:** No new data **July 2012:** No new data	**November 2011:** Three experts agreed this conclusion was still valid. One expert did not know. **July 2012:** Two experts did not know. One expert thought there was no new data.	**November 2011:** Conclusion is still valid and this portion of the CER does not need updating. **July 2012:** Conclusion unchanged from previous update.	**Up-to-date**	**Up-to-date**

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC	Conclusions of validity of CER conclusion(s)	
					Prior Assessment	Cumulative Assessment
Women weigh their physicians' recommendations highly when deciding whether to take tamoxifen for risk reduction, according to descriptive studies of concordance.	**November 2011:** No new data **July 2012:** No new data	**November 2011:** No new data **July 2012:** No new data	**November 2011:** Three experts agreed this conclusion was still valid. One expert did not know. **July 2012:** Two experts did not know. One expert thought there was no new data.	**November 2011:** Conclusion is still valid and this portion of the CER does not need updating. **July 2012:** Conclusion unchanged from previous update.	**Up-to-date**	**Up-to-date**
Studies of treatment choice and concordance for raloxifene and tibolone for breast cancer risk reduction are lacking.	**November 2011:** No new data **July 2012:** No new data	**November 2011:** No new data **July 2012:** No new data	**November 2011:** Two experts agreed this conclusion was still valid. Two experts did not know. **July 2012:** Two experts did not know. One expert thought there was no new data.	**November 2011:** Conclusion is still valid and this portion of the CER does not need updating. **July 2012:** Conclusion unchanged from previous update.	**Up-to-date**	**Up-to-date**
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	**November 2011:** 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	**November 2011:** No new data **July 2012:** No new data	**November 2011:** 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	**November 2011:** 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.	**Up-to-date**	**Up-to-date**

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC	Conclusions of validity of CER conclusion(s)	
					Prior Assessment	Cumulative Assessment
consider multiple risk factors for breast cancer.	retained good calibration and slightly improved discriminatory accuracy. **July 2012:** No new data		project showed using breast density may have better prediction **July 2012:** Two experts thought there was no new evidence and one expert cited the literature included in the last update.	**July 2012:** Conclusion unchanged from previous update.		
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.	**November 2011:** No new data **July 2012:** No new data	**November 2011:** No new data **July 2012**: No new data	**November 2011:** Three experts agreed this conclusion was still valid. One expert did not know. **July 2012:** Three experts thought there was no new data.	**November 2011:** Conclusion is still valid and this portion of the CER does not need updating. **July 2012:** Conclusion unchanged from previous update.	**Up-to-date**	**Up-to-date**
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.	**November 2011:** No new data **July 2012:** No new data	**November 2011:** No new data **July 2012:** No new data	**November 2011:** Two experts agreed this conclusion was still valid. One expert did not know. **July 2012:** Three experts thought there was no new data.	**November 2011:** Conclusion is still valid and this portion of the CER does not need updating. **July 2012:** Conclusion unchanged from previous update.	**Up-to-date**	**Up-to-date**
A Gail score of	**November 2011:**	**November**	**November 2011:** All	**November 2011:**	**Up-to-date**	**Up-to-date**

Conclusions From CER Executive Summary	RAND Literature Search	FDA/ Health Canada/MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC	Conclusions of validity of CER conclusion(s)	
					Prior Assessment	Cumulative Assessment
>/=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.	No new data **July 2012:** No new data	**2011:** No new data **July 2012:** No new data	experts agreed this conclusion was still valid. **July 2012:** Three experts thought there was no new data.	Conclusion is still valid and this portion of the CER does not need updating. **July 2012:** Conclusion unchanged from previous update.		

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; MHRA=Medicines and Healthcare products Regulatory Agency; NSABP=National Surgical Adjuvant Breast and Bowel Project; SCEPC=Southern California Evidence-based Practice Center; STAR=Study of Tamoxifen and Raloxifene; RR=risk ratio

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Appendixes

Appendix A: Search Methodology

Appendix B: Evidence Table

Appendix C: Questionnaire Matrix

Appendix A. Search Methodology

DATABASE SEARCHED & TIME PERIOD COVERED:
Medline on OVID – 2011-5/9/2012 & 5/10/2012

LANGUAGE:
English

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 1:
1 selective estrogen receptor modulators/ or raloxifene/ or tamoxifen.mp.
2 limit 1 to (english language and yr="2011 - 2012")
3 exp Breast Neoplasms/pc
4 limit 3 to english language
6 exp Primary Prevention/
7 limit 6 to (english language and yr="2011 -Current")
8 (primar$ adj2 prevent$).mp.
9 limit 8 to (english language and yr="2011 - 2012")
10 exp Breast Neoplasms/
11 limit 10 to (english language and yr="2011 - 2012")
12 2 and 7 and 11
0
13 exp chemoprevention/
14 limit 13 to (english language and yr="2011 - 2012")
15 chemoprevent$.mp.
16 limit 15 to (english language and yr="2011 - 2012")
17 2 and 11 and 16
18 2 and 9 and 11
19 17 or 18
20 (prevent$ adj3 (breast$ adj2 (neoplas$ or tumor$ or cancer$ or malignan$))).mp.
21 limit 20 to (english language and yr="2011 - 2012")
22 2 and 21
23 4 and 22
24 19 or 23
25 (chemoprevent$ adj3 (breast$ adj2 (neoplas$ or tumor$ or cancer$ or malignan$))).mp.

26 limit 5 to (english language and yr="2011 - 2012")
27 (prevent$ adj3 (mammar$ adj2 (neoplas$ or tumor$ or cancer$ or malignan$))).mp.
28 limit 27 to (english language and yr="2011 - 2012")
29 (chemoprevent$ adj3 (mammar$ adj2 (neoplas$ or tumor$ or cancer$ or malignan$))).mp.
30 limit 29 to (english language and yr="2011 - 2012")
31 21 or 26 or 28 or 30
32 2 and 31
33 11 and 32
34 19 or 33

NUMBER OF RESULTS: 63
NUMBER WHEN LIMITED TO SPECIFIED JOURNALS: 8

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Medline on OVID – Search 2a – Variant of original search
1-exp tamoxifen/ or tamoxifen.mp. or exp raloxifene/ or raloxifene.mp. or exp placebos/ or placebo$.mp.
2-limit 1 to (english language and yr="2011 - 2012")
3-random$.mp. or exp randomized controlled trials/ or randomized controlled trial.pt. or rct$.mp.
4-limit 3 to (english language and yr="2011 - 2012")
5-exp cardiovascular diseases/ep, et or exp endometrial neoplasms/ep, et
6-limit 5 to (english language and yr="2011 - 2012")
7-2 and 4 and 6
8-exp breast neoplasms/ or (breast$ adj2 (neoplas$ or tumor$ or cancer$ or malignan$)).mp.-
9-limit 8 to (english language and yr="2011 - 2012")
10-7 and 9

NUMBER OF RESULTS: 7
NUMBER WHEN LIMITED TO SPECIFIED JOURNALS: 2

==========

Medline – Search 2b – Exact search as original
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
32-limit 31 to (english language and yr="2011 - 2012")

NUMBER OF RESULTS: 2

==========

Medline on OVID – 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/
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 (english language and yr="2011 - 2012")

NUMBER OF RESULTS: 7
NUMBER WHEN LIMITED TO SPECIFIED JOURNALS: 0

==========

Medline on OVID –Search 4
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 (english language and yr="2011 - 2012")

NUMBER OF RESULTS: 23
NUMBER WHEN LIMITED TO SPECIFIED JOURNALS: 4

==========

PubMed– Search 4 comparison:
#14- #11 NOT #12 Limits: English, Publication Date from 2011 to 2012
#13- #11 NOT #12
#12- animal* NOT (human OR humans)
#11- #9 AND #10
#10- gynecologic*[tiab] OR genital[tiab] OR adnexal[tiab] OR uterine[tiab] OR endometriosis[tiab] OR infertil*[tiab] OR ovarian[tiab] OR vulva*[tiab] OR vagina*[tiab]
#9- #1 OR #2
#8- #5 OR #6
#7- #3 OR #4
#6- genital diseases, female/
#5- genital diseases, female/ci,ep,et
#4- raloxifene/ae,po,to
#3- tamoxifen/ae,po,to
#2- raloxifene
#1- tamoxifen

NUMBER OF ADDITIONAL REFERENCES WHEN LIMITED TO SPECIFIED JOURNALS: 4

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Medline on OVID – 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 yr="2011 - 2012")
12-((tamoxifen or raloxifene) and (uterine or uterus or hysterectom$)).mp.
13-limit 12 to (english language and yr="2011 - 2012")
14-11 or 13

NUMBER OF RESULTS: 53
NUMBER WHEN LIMITED TO SPECIFIED JOURNALS: 1

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Medline on OVID –Search 6
1-(ovar$ adj5 (cancer$ or tumor$ or malignan$ or carcino$ or neoplas$)).mp.
2-exp tamoxifen/
3-exp raloxifene/
4-(tamoxifen or raloxifene).mp.
5-2 or 3 or 4
6-1 and 5
7-limit 6 to (english language and yr="2011 - 2012")

NUMBER OF RESULTS: 15
NUMBER WHEN LIMITED TO SPECIFIED JOURNALS: 0

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Medline on OVID – Search 7
1-exp cardiovascular system/
2-exp cardiovascular diseases/
3-(cardiovascular or heart or cardiac).mp.
4-exp tamoxifen/
5-exp raloxifene/
6-(tamoxifen or raloxifene).mp.
7-selective estrogen receptor modulators/
8-(selective estrogen receptor modulator$ or serm$).mp.
9-1 or 2 or 3
10-4 or 5 or 6 or 7 or 8
11-9 and 10
12-limit 11 to (english language and yr="2011 - 2012")-130

NUMBER OF RESULTS: 130
NUMBER WHEN LIMITED TO SPECIFIED JOURNALS: 3

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Medline on OVID –Search 8
1-exp cardiovascular system/
2-exp cardiovascular diseases/
3-(cardiovascular or heart or cardiac).mp.
4-exp tamoxifen/
5-exp raloxifene/
6-(tamoxifen or raloxifene).mp.
7-selective estrogen receptor modulators/
8-(selective estrogen receptor modulator$ or serm$).mp.
9-1 or 2 or 3
10-4 or 5 or 6 or 7 or 8
11-9 and 10
12 limit 11 to (english language and yr="2011 - 2012")
13-((heart$ or myocardi$ or cardi$ or atria$ or ventric$) adj5 (fibril$ or arrhythm$ or (abnormal$ adj2 rhythm$))).mp.
14-10 and 13

15-limit 14 to (english language and yr="2011 - 2012")

NUMBER OF RESULTS: 8
NUMBER WHEN LIMITED TO SPECIFIED JOURNALS: 0

==========

Medline on OVID – 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-(tamoxifen or raloxifene).mp.
8-(selective estrogen receptor modulator$ or serm$).mp.
9-(gallstone$ or gall stone$ or gallbladder$ or gall bladder$ or bile duct$ or biliary tract$ or cholelith$ or cholecyst$ or choledocholith$).mp.
10-1 or 2 or 9
11-4 or 5 or 6 or 7 or 8
12-10 and 11
13-limit 12 to (english language and yr="2011 - 2012")

NUMBER OF RESULTS: 5
NUMBER WHEN LIMITED TO SPECIFIED JOURNALS: 0

==========

Medline on OVID – Search 10 (5/10/12)
1-exp breast neoplasms/ or (breast$ adj2 (neoplas$ or tumor$ or cancer$ or malignan$)).mp.
2-tibolone.mp.
3-exp breast/
4-1 or 3
5-2 and 4
6-limit 5 to (english language and yr="2011 - 2012")

NUMBER OF RESULTS: 11
NUMBER WHEN LIMITED TO SPECIFIED JOURNALS: 0

==========

Medline on OVID – Search 11 (5/10/12)
1-exp breast neoplasms/ or (breast$ adj2 (neoplas$ or tumor$ or cancer$ or malignan$)).mp.
2-exp risk assessment/ or risk assess$.mp.
3-exp disease susceptibility/ or (disease adj5 susceptib$).mp.
4-2 or 3
5-1 and 4
6-(model$ or valid$).mp.
7-5 and 6
8-limit 7 to (english language and yr="2011 - 2012")

NUMBER OF RESULTS: 348
NUMBER WHEN LIMITED TO SPECIFIED JOURNALS: 22

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Medline on OVID – New drugs
1-(lasofoxifene$ or arzoxifene$ or anastrozole$ or exemestane$ or fenretinide$ or bisphosphonate$ or metformin$ or statin$ or nsaid$ or aspirin$ or ibuprofen$).mp.
2-limit 1 to (english language and yr="2011 - 2012")
3-exp breast neoplasms/ or (breast adj2 (cancer$ or tumor$ or malignan$ or carcino$ or neoplas$)).mp.
4-limit 3 to (english language and yr="2011 - 2012")
5-2 and 4

NUMBER OF RESULTS: 413
NUMBER WHEN LIMITED TO SPECIFIED JOURNALS: 25

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DATABASE SEARCHED & TIME PERIOD COVERED:
Cochrane – 2011-5/10/2012

LANGUAGE:
English

SEARCH 1:
breast* OR mammar*
AND
(cancer* OR tumor* OR carcino* OR adenocarcin* OR neoplas* OR malignan*) in Title, Abstract or Keywords
AND
tamoxifen OR raloxifene OR placebo* in Title, Abstract or Keywords

NUMBER OF RESULTS:
Cochrane Reviews [13] Other Reviews [2] Trials [75]

==========

SEARCH 2:
endometri* OR uterine OR uterus OR hysterect* in Title, Abstract or Keywords
AND
tamoxifen OR raloxifene in Title, Abstract or Keywords

NUMBER OF RESULTS:
Cochrane – Search 2 (5/10/12)
Cochrane Reviews [0] Other Reviews [1] Trials [6]

==========

SEARCH 3:
tibolone in Title, Abstract or Keywords

NUMBER OF RESULTS:
Cochrane Reviews [2] Other Reviews [0] Trials [4]

==========

Cochrane –New drugs (5/11/2012)
("lasofoxifene* or arzoxifene* or anastrozole* or exemestane* or fenretinide* or bisphosphonate* or metformin*or statin* or nsaid* or aspirin* or ibuprofen*) in Title, Abstract or Keywords
AND
Breast
AND
(cancer* or tumor* or tumour* OR malignan* or carcino* or neoplas*) in Title, Abstract or Keywords

NUMBER OF RESULTS:
Cochrane Reviews [1] Other Reviews [0] Trials [28]

Appendix B. Evidence Table

Article ID, Author, year	Trial	n	Subjects	Primary Outcome	Duration	Study Quality/ Applicability	Findings
Key Question 1: In adult women without preexisting breast caner, 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 *in situ* (DCIS), breast cancer mortality, all-cause mortality, and osteoporotic fractures?							
Tamoxifen vs Raloxifene							
Vogel, 2010a[3] Vogel, 2010b[4]	STAR Update	19,490 -tamoxifen (20 mg/day): 9,736 -raloxifene (60 mg/day): 9.754	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.	Invasive Breast Cancer	Subject took medication for 5 years with median follow-up of 81 months	Good/Good	RR Raloxifene:Tamoxifen -Invasive breast cancer: 1.24 (1.05-1.47) -Non-invasive breast cancer: 1.22 (0.95-1.59)
Examestane vs Placebo							
Goss, 2011[5]	NCIC Clinical Trials Group Mammary Prevention Trial P-3	4560 -examestane (25 mg) alone or with celecoxib: 2285 -placebo: 2275	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 hormone-	Invasive Breast Cancer	Subject took examestane for median time of 10.2 months with a median follow-up of 35 months	Good/Good	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)

Article ID, Author, year	Trial	n	Subjects	Primary Outcome	Duration	Study Quality/ Applicability	Findings
			replacement therapy; 4.8% using SERMs				
Cheung, 2012[7]	**NCIC Clinical Trials Group Mammary Prevention Trial P-3**	**242 -examestane (25 mg) alone or with celecoxib: 124 -placebo: 118**	**Eligible for MAP-3, not osteoporotic and not receiving drugs for bone related disease. Mean age 61.3 years;**	**Percent change from baseline to 2 years in bone mineral density at the distal radius by CT.**	**2 year follow-up**	**Good/Good**	**--Mean percent change in the total volumetric BMD at the distal radius in the examestane group was -6.1% (-7.0 to -5.2) and -1.8% (-2.4 to -1.2) in the placebo group. This difference was -4.3% (-5.3 to -3.2) p<0.0001**
Key Question 2. What is the evidence for harms of tamoxifen citrate, raloxifene, and tibolone when used to reduce risk for primary breast cancer?							
Vogel, 2010a[3] Vogel, 2010b[4]	STAR Update	19,490 -tamoxifen (20 mg/day): 9,736 -raloxifene (60 mg/day): 9.754	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.	Invasive Breast Cancer	Subject took medication for 5 years with median 81 month follow-up reported	Good/Good	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)
Goss, 2011[5]	NCIC Clinical Trials Group Mammary Prevention Trial P-3	4560 -examestane (25 mg): 2285 -placebo: 2275	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.	Invasive Breast Cancer	Subject took examestane for median time of 10.2 months with a median follow-up of 35 months	Good/Good	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)

Article ID, Author, year	Trial	n	Subjects	Primary Outcome	Duration	Study Quality/ Applicability	Findings
			Mean age 62.5 years; 93% white; 58% using hormone-replacement therapy; 4.8% using SERMs				
Runowicz, 2011[8]	**STAR Update**	**-tamoxifen (20 mg/day): 4739 -raloxifene (60 mg/day): 4717**	**Postmenopausal women with a 5-year predicted breast cancer risk of 1.66% based on the modified Gail model.**	**Incidence rates/risks of gynecologic conditions**	**Median 81 month follow-up reported**	**Good/Good**	**RR Raloxifene:Tamoxifen -Invasive uterine cancer: 0.55 (0.36-0.83) -Uterine hyperplasia: 0.19 (0.12-0.29) -Ovarian cysts: 0.60 (0.49-0.74) -Endometrial polyps: 0.30 (0.25-0.35) Tamoxifen:Raloxifene -Hot flashes (p<0.001) -Vaginal discharge (p<0.001) -Vaginal bleeding (p<0.001)**
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?							
Vogel, 2010a[3] Vogel, 2010b[4]	STAR Update	19,490 -tamoxifen (20 mg/day): 9,736 -raloxifene (60 mg/day): 9.754	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.	Invasive Breast Cancer	Subject took medication for 5 years with median 81 month follow-up reported	Good/Good	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)
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?							
Goss, 2011[5]	NCIC Clinical Trials Group Mammary	4,560 -examestane (25 mg): 2,285 -placebo: 2,275	Postmenopausal women age ≥ 35 with one of the following factors: a	Invasive Breast Cancer	Subject took examestane for median time of 10.2 months	Good/Good	Discontinuation rate for examestane was 32.8% compared to 28.7% for placebo.

Article ID, Author, year	Trial	n	Subjects	Primary Outcome	Duration	Study Quality/ Applicability	Findings
	Prevention Trial P-3		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 hormone-replacement therapy; 4.8% using SERMs		with a median follow-up of 35 months		
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							

Bold=New Studies from the July 2012 re-assessment

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

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
Key Question 1: In adult women without preexisting breast caner, 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?			
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.	☐	New Evidence: _____ _____ _____	☐
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		New Evidence:	

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
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).	☐	_____ _____ _____	☐
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.	☐	New Evidence: _____ _____ _____	☐
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.	☐	New Evidence: _____ _____ _____	☐
Tamoxifen and raloxofine did not significantly reduce noninvasive breast cancer, including DCIS, in meta-analysis of four placebo-controlled trials, although noninvasive breast	☐	New Evidence: _____	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
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).		_____ _____	
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.	☐	New Evidence: _____ _____ _____	☐
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	☐	New Evidence: _____ _____ _____	☐
Key Question 2. What is the evidence for harms of tamoxifen citrate, raloxifene, and tibolone when used to reduce risk for primary breast cancer?			

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
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 tibolone are limited.	☐	New Evidence: _____ _____ _____	☐
Tibolone causes more strokes than placebo (RR 2.19; 1.14, 4.23); tamoxifen and raloxifene do not increase risk for stroke.	☐	New Evidence: _____ _____ _____	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
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).	☐	New Evidence: _____ _____	☐
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).	☐	New Evidence: _____ _____ _____	☐
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.	☐	New Evidence: _____ _____ _____	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
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.	☐	New Evidence: _____ _____ _____	☐
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.	☐	New Evidence: _____ _____ _____	☐
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?			
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.	☐	New Evidence: _____ _____ _____	☐
Tamoxifen reduces breast cancer outcomes in subgroups evaluated in	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
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-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.		_____ _____ _____	
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.	☐	New Evidence: _____ _____ _____	☐
Thromboembolic events and endometrial cancer were more common in older (>50) than younger women in the NSABP P-1 trial.	☐	New Evidence: _____ _____ _____	☐
Tibolone causes more strokes in older (>70 years) than younger women.	☐	New Evidence: _____	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
		_____ _____	
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 purposes.	☐	New Evidence: _____ _____ _____	☐
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.	☐	New Evidence: _____ _____ _____	☐
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.	☐	New Evidence: _____ _____	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
		_____	
Women weigh their physicians' recommendations highly when deciding whether to take tamoxifen for risk reduction, according to descriptive studies of concordance.	☐	New Evidence: _____ _____	☐
Studies of treatment choice and concordance for raloxifene and tibolone for breast cancer risk reduction are lacking.	☐	New Evidence: _____ _____ _____	☐
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.	☐	New Evidence: _____ _____ _____	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
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.	☐	New Evidence: _____ _____ _____	☐
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.	☐	New Evidence: _____ _____ _____	☐
A Gail score of >/=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.	☐	New Evidence: _____ _____ _____	☐
Are there new data that could inform the key questions that might not be addressed in the conclusions?			

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know