Comparative Effectiveness of Medications To Reduce Risk of Primary Breast Cancer in Women

Appendixes

Appendix A.
Searches

Appendix A-1. Search Strategies

MEDLINE Searches

Ovid MEDLINE(R) <1950 to January Week 3 2009>
KEY QUESTIONS 2, 3, 4, 5
Search Strategy:

---

1 selective estrogen receptor modulators/ or raloxifene/ or tamoxifen
2 exp Breast Neoplasms/pc [Prevention & Control]
3 1 and 2
4 Primary Prevention
5 (primar$ adj2 prevent$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
6 exp Breast Neoplasms
7 1 and 4 and 6
8 Chemoprevention
9 chemoprevent$.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. [mp=title, original title, abstract, name of substance word, subject heading word]
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 17 to abstracts
20 18 or 19

Database: Ovid MEDLINE(R) <1996 to January Week 3 2009>
KEY QUESTIONS 1, 2, 3
Search Strategy:

---

1 exp Tamoxifen/ae, po, to
2 exp Raloxifene/ae, to, po
3 exp Placebos/ or placebo$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
4 exp Breast Neoplasms/
5 1 and 2
6 1 and 3
7 2 and 3
8 4 and 5
9 4 and 6
10 4 and 7
11 random$.mp.

12 exp Randomized Controlled Trials/
13 randomized controlled trial.pt.
14 rct$.mp.
15 11 or 12 or 13 or 14
16 8 and 15
17 9 and 15
18 10 and 15
19 16 or 17 or 18
20 exp Cardiovascular Diseases/ep, et [Epidemiology, Etiology]
21 exp Endometrial Neoplasms/ep, et [Epidemiology, Etiology]
22 exp tamoxifen/
23 exp raloxifene/
24 20 or 21
25 22 and 23
26 3 and 22
27 3 and 23
28 25 or 26 or 27
29 24 and 28
30 15 and 29
31 19 or 30
32 (200705$ or 200706$ or 200707$ or 200708$ or 200709$ or 20071$ or 2008$).ed. (634348)
33 31 and 32

Database: Ovid MEDLINE(R) <1996 to January Week 3 2009>
KEY QUESTIONS 1, 2, 3
Search Strategy:
---
1 exp Breast Neoplasms/pc [Prevention & Control]
2 exp Ovarian Neoplasms/pc [Prevention & Control]
3 1 or 2
4 (family adj5 histor$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
5 exp Genetic Predisposition to Disease/
6 brca.mp.
7 (brca1 or brca2).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
8 4 or 5 or 6 or 7
9 exp Selective Estrogen Receptor Modulators/
10 (serm or serms or tamoxifen or raloxifene).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
11 9 or 10
12 3 and 8 and 11
13 exp Contraceptives, Oral/
14 3 and 8 and 13

Database: Ovid MEDLINE(R) <1950 to January Week 3 2009>
KEY QUESTIONS 2, 3
Search Strategy:
---

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 [Chemically Induced, Epidemiology, Etiology]
8 exp Genital Diseases, Female/
9 8 and 6
10 3 and 7
11 10 or 9

Database: Ovid MEDLINE(R) <1950 to January Week 3 2009>
KEY QUESTIONS 2, 3
Search Strategy:
---

1 exp Tamoxifen/ae, po, to
2 exp raloxifene/ae, po, to
3 1 or 2
4 exp Uterine Diseases/
5 exp uterus/
6 4 or 5
7 3 and 6
8 exp Hysterectomy/
9 3 and 8
10 7 or 9
11 limit 10 to (english language and humans)

Database: Ovid MEDLINE(R) <1950 to January Week 3 2009>
KEY QUESTIONS 2, 3
Search Strategy:
---

1 (ovar$ adj5 (cancer$ or tumor$ or malignan$ or carcino$ or neoplas$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
2 exp tamoxifen/
3 exp raloxifene/
4 2 or 3
5 4 and 1
6 limit 5 to humans

Database: Ovid MEDLINE(R) <1950 to January Week 3 2009>
KEY QUESTIONS 2, 3
Search Strategy:
---
1 exp Tamoxifen/ae, po, ct, to [Adverse Effects, Poisoning, Contraindications, Toxicity]
2 exp Raloxifene/ae, ct, to [Adverse Effects, Contraindications, Toxicity]
3 Selective Estrogen Receptor Modulators/ae, co, to, po
4 1 or 2 or 3
5 exp Cardiovascular Diseases/mo, ci, co, ep, et [Mortality, Chemically Induced, Complications, Epidemiology, Etiology]
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 9 to humans
21 limit 19 to humans
22 21 not 20
23 12 and 16
24 limit 23 to humans
25 24 not 21

Database: Ovid MEDLINE(R) <1950 to January Week 3 2009>
KEY QUESTIONS 2, 3
Search Strategy:
---
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. [mp=title, original title, abstract, name of substance word, subject heading word]
6 5 and 4
7 (tamoxifen or raloxifene).mp. [mp=title, original title, abstract, name of substance word, subject heading word]

8 5 and 7
9 8 or 6

Database: Ovid MEDLINE(R) <1950 to January Week 3 2009>
KEY QUESTIONS 2, 3
Search Strategy:
---
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 limit 8 to humans
10 (gallstone$ or gall stone$ or gallbladder$ or gall bladder$ or bile duct$ or biliary tract$ or cholelith$ or CHOLECYST$ or CHOLEDOCHOLITH$).mp.
11 7 and 10
12 limit 11 to humans
13 9 or 12

Database: Ovid MEDLINE(R) <1950 to January Week 3 2009>
KEY QUESTIONS 2, 3, 4
Search Strategy:
---
1 tibolone.mp.
2 exp Breast Neoplasms/
3 exp Breast/
4 or 2
5 4 and 1

Database: Ovid MEDLINE(R) <1950 to January Week 3 2009>
KEY QUESTION 5
Search Strategy:
---
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
16 8 or 11 or 14 or 15
17 limit 16 to (english language and humans)
18 (model$ or valid$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
19 17 and 18
20 seer.mp.
21 17 and 20
22 19 or 21
23 17 not 22

Other Database Searches
Database: EBM Reviews - Cochrane Central Register of Controlled Trials <4th Quarter 2008>
KEY QUESTIONS 1, 2, 3
Search Strategy:
---
1 tamoxifen.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
2 raloxifene.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
3 placebo$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
4 1 and 2
5 1 and 3
6 2 and 3
7 4 or 5 or 6
8 ((breast$ or mammar$) adj5 (cancer$ or tumor$ or carcino$ or adenocarcin$ or neoplas$ or malignan$)).mp.
9 7 and 8

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <4th Quarter 2008>
KEY QUESTIONS 2, 3
Search Strategy:
---
1 ((tamoxifen or raloxifene) adj5 (endometri$ or uterine or uterus or hysterect$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]

Database: EBM Reviews - Cochrane Database of Systematic Reviews <4th Quarter 2008>
KEY QUESTIONS 2, 3
Search Strategy:
---
1 ((tamoxifen or raloxifene) adj5 (endometri$ or uterine or uterus or hysterect$)).mp. [mp=title, abstract, full text, keywords, caption text]

Database: EBM Reviews - Database of Abstracts of Reviews of Effects <4th Quarter 2008>
KEY QUESTIONS 2, 3
Search Strategy:
---
1 ((tamoxifen or raloxifene) adj5 (endometri$ or uterine or uterus or hysterect$)).mp. [mp=title, full text, keywords]

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <4th Quarter 2008>
KEY QUESTIONS 2, 3
Search Strategy:
---
1 tibolone.mp.

Database: EBM Reviews - Cochrane Database of Systematic Reviews <4th Quarter 2008>
KEY QUESTIONS 2, 3
Search Strategy:
---
1 tibolone.mp.

Database: EBM Reviews - Database of Abstracts of Reviews of Effects <4th Quarter 2008>
KEY QUESTIONS 2, 3
Search Strategy:
---
1 tibolone.mp.

Appendix A-2. Inclusion and Exclusion Criteria By Key Question

Key Questions	Include	Exclude	Duration and size of study	Outcomes
1. Benefits* 3. Benefits among population subgroups†	• Randomized, double-blind, placebo controlled trials of tamoxifen, raloxifene, or tibolone for breast cancer prevention. • Head-to-head trials that include direct comparisons between tamoxifen, raloxifene, or tibolone. • Trials report breast cancer results as primary or secondary outcomes.‡ • Trials enroll women without pre-existing breast cancer and can include women of all ages, pre or postmenopausal status, hysterectomy or nonhysterectomy status, US and non US. • English language publications.	• Non RCT study designs. • Non breast cancer prevention studies. • Women with pre-existing breast cancer, known precursor conditions, or known carriers of breast cancer susceptibility mutations (*BRCA1, BRCA2,* or others). • Drugs other than tamoxifen, raloxifene, or tibolone. • No breast cancer results as primary or secondary outcomes. • Laboratory or animal studies. • Non-English language publications.	≥3 months ≥100 participants	Primary or secondary breast cancer outcomes; other benefits defined by key question 1.
2. Harms§ 3. Harms among population subgroups†	• Randomized, double-blind, placebo controlled trials of tamoxifen, raloxifene, or tibolone. • Head-to-head trials that include direct comparisons between tamoxifen, raloxifene, or tibolone. • Observational studies that report results for women using tamoxifen, raloxifene, or tibolone and compares results to a nonuser group or compares results between these drug use groups. • Studies enroll women without pre-existing breast cancer and can include women of all ages, pre or postmenopausal status, hysterectomy or nonhysterectomy status, US and non US. • Health outcomes.‡ • English language publications.	• Women with pre-existing breast cancer, known precursor conditions, or known carriers of breast cancer susceptibility mutations (*BRCA1, BRCA2,* or others). • Drugs other than tamoxifen, raloxifene, or tibolone. • No harms results. • Intermediate outcomes rather than health outcomes.‡ • Laboratory or animal studies. • Non-English language publications.	≥3 months ≥100 participants	Any health outcome defined by key question 2.

Key Questions	Include	Exclude	Duration and size of study	Outcomes
4. Treatment adherence, persistence, concordance, or treatment choice†	• Randomized, double-blind, placebo controlled trials of tamoxifen, raloxifene, or tibolone for breast cancer prevention. • Head-to-head trials that include direct comparisons between tamoxifen, raloxifene, or tibolone. • Observational and descriptive studies that report results for women using tamoxifen, raloxifene, or tibolone and compares results to a nonuser group or compares results between these drug use groups. • Trials enroll women without pre-existing breast cancer and can include women of all ages, pre or postmenopausal status, hysterectomy or nonhysterectomy status, US and non US. • Observational and descriptive studies of treatment choice. • Studies include data for treatment adherence, persistence, concordance, or treatment choice. • English language publications.	• Women with pre-existing breast cancer, known precursor conditions, or known carriers of breast cancer susceptibility mutations (*BRCA1, BRCA2,* or others). • Drugs other than tamoxifen, raloxifene, or tibolone. • No adherence, persistence, concordance, or treatment choice data. • Laboratory or animal studies. • Non-English language publications.	RCTS: >3 months and >100 participants	Any measure of treatment adherence, persistence, or concordance; data on treatment choice.
5. Clinical risk assessment models	• Studies of risk stratification models for women of any age. • Models used to identify women at higher than average risk for breast cancer. • Derivation or validation studies. • Study must include discriminatory accuracy of the model. • Models must be applicable to the primary care setting. • English language publications.	• Family history/genetics models designed to determine risk for *BRCA* mutations. • Studies of individual risk factors. • Laboratory tests. • Non-English language publications.	Not specified.	Evaluation of risk models for breast cancer that include more than 1 risk factor.

*Benefit outcomes are defined by key question 1 and include:

- Invasive breast cancer
- Noninvasive breast cancer including ductal carcinoma *in situ* (DCIS)
- Breast cancer mortality
- All-cause mortality
- Osteoporotic fractures

†Population subgroups are defined by key question 3 and include but are not limited to those based on:

Age, menopausal status (pre-, peri-, postmenopausal), hysterectomy status, use of exogenous estrogen, level of risk of breast cancer (based on family history, body mass index, parity [number of pregnancies], age at first live birth, age at menarche, personal history of breast abnormalities, prior breast biopsy, estradiol levels, breast density), ethnicity and race, metabolism status (CYP 2D6 mutation), and risk for thromboembolic events (obesity, and other risk factors).

‡Definitions of types of outcomes:

- A primary outcome is the main outcome of a study that the study was designed and powered to demonstrate.
- A secondary outcome is a major outcome of a study that the study was designed and powered to demonstrate, but is not the primary outcome of the study.
- Health outcomes are signs, symptoms, conditions, or events that individuals experience, such as myocardial infarction, death, or hot flahes.
- Intermediate outcomes are health measures that individuals do not personally experience, such as a laboratory test results or bone mineral density.

§Harms outcomes are defined by key question 2 and may include but are not limited to:

- Thromboembolic events (deep vein thrombosis, pulmonary embolism)
- Cardiovascular events (coronary heart disease, stroke and transient ischemic attack, arrhythmias)
- Metabolic disorders (diabetes)
- Musculoskeletal symptoms (myalgia, leg cramps)
- Mental health (depression, mood changes)
- Genitourinary outcomes (vaginal dryness, uterine bleeding, hysterectomy, endometrial cancer, urinary symptoms)
- Adverse breast outcomes (biopsies)
- Other malignancies (incidence, death)
- Ophthalmologic disorders (cataracts)
- Gastrointestinal/hepatobiliary disorders (abdominal pain, nausea)
- Other adverse events impacting quality of life (vasomotor symptoms, sexual function, sleep disturbances, headaches, cognitive changes, peripheral edema)

Appendix B. List of Excluded Studies

1. Raloxifene and prevention of vertebral fracture (cont'd): mainly when oestrogen is contraindicated. Prescrire Int 2000;9(50):190-191. **Review/No data**

2. Summaries for patients. Using medication to prevent breast cancer: recommendations from the United States Preventive Services Task Force. Ann Intern Med 2002;137(1):I62. **Review/No data**

3. Tibolone: cancers of the breast and endometrium. Prescrire Int 2006;15(83):107. **No relevant data**

4. Abramson N, Aster RH. Retrospective assessment of hypercoagulability in breast cancer prevention trial. J Clin Oncol 2002;20(19):4133-4134. **Review/No data**

5. Abramson N, Costantino JP, Garber JE, et al. Effect of Factor V Leiden and prothrombin G20210-->A mutations on thromboembolic risk in the national surgical adjuvant breast and bowel project breast cancer prevention trial. J Natl Cancer Inst 2006;98(13):904-910. **No relevant outcomes**

6. Adomaityte J, Farooq M, Qayyum R. Effect of raloxifene therapy on venous thromboembolism in postmenopausal women. A meta-analysis. Thromb Haemost 2008;99(2):338-342. **Review/No data**

7. Al-Delaimy WK, Cho E, Chen WY, et al. A prospective study of smoking and risk of breast cancer in young adult women. Cancer Epidemiol Biomarkers Prev 2004;13(3):398-404. **Single risk factor only**

8. Aldrighi JM, Quail DC, Levy-Frebault J, et al. Predictors of hot flushes in postmenopausal women who receive raloxifene therapy. Am J Obstet Gynecol. 2004;191(6):1979-1988. **No relevant data**

9. American College of Obstetrics, Gynecologists Committee on Gynecologic Practice. ACOG committee opinion. No. 336: Tamoxifen and uterine cancer. Obstet Gynecol 2006;107(6):1475-1478. **Review/No data**

10. Andersson M, Storm HH, Mouridsen HT. Incidence of new primary cancers after adjuvant tamoxifen therapy and radiotherapy for early breast cancer. J Natl Cancer Inst 1991;83(14):1013-1017. **Wrong type of study**

11. Andrieu N, Clavel F, Auquier A, et al. Variations in the risk of breast cancer associated with a family history of breast cancer according to age at onset and reproductive factors. J Clin Epidemiol 1993;46(9):973-980. **Single risk factor only**

12. Andrieu N, Goldgar DE, Easton DF, et al. Pregnancies, breast-feeding, and breast cancer risk in the International BRCA1/2 Carrier Cohort Study (IBCCS). J Natl Cancer Inst 2006;98(8):535-544. **Family history only model**

13. Andrieu N, Prevost T, Rohan TE, et al. Variation in the interaction between familial and reproductive factors on the risk of breast cancer according to age, menopausal status, and degree of familiality. Int J Epidemiol 2000;29(2):214-223. **No relevant data**

14. Antoniou AC, Durocher F, Smith P, et al. BRCA1 and BRCA2 mutation predictions using the BOADICEA and BRCAPRO models and penetrance estimation in high-risk French-Canadian families. Breast Cancer Res 2006;8(1):R3. **Family history only model**

15. Antoniou AC, Pharoah PD, McMullan G, et al. Evidence for further breast cancer susceptibility genes in addition to BRCA1 and BRCA2 in a population-based study. Genet Epidemiol 2001;21(1):1-18. **Family history only model**

16. Antoniou AC, Pharoah PPD, Smith P, et al. The BOADICEA model of genetic susceptibility to breast and ovarian cancer [see comment]. Br J Cancer 2004;91(8):1580-1590. **Family history only model**

17. Archer DF, Hendrix S, Gallagher JC, et al. Endometrial effects of tibolone. J Clin Endocrinol Metab 2007;92(3):911-918. **Wrong type of study**

18. Arun B, Hortobagyi GN. Progress in breast cancer chemoprevention. Endocr Relat Cancer 2002;9(1):15-32. **No relevant data**

19. Ascher SM, Imaoka I, Lage JM. Tamoxifen-induced uterine abnormalities: the role of imaging. Radiology 2000;214(1):29-38. **Review/No data**

20. Ashing-Giwa KT, Padilla GV, Tejero JS, et al. Breast cancer survivorship in a multiethnic sample: challenges in recruitment and measurement. Cancer 2004;101(3):450-465. **Does not address key questions**

21. Atkins JN. The breast cancer prevention trial: a correction. JAMA 1994;272(17):1328. **Review/No data**

22. Bakour SH, Gupta JK, Khan KS. Risk factors associated with endometrial polyps in abnormal uterine bleeding. Int J Gynaecol Obstet 2002;76(2):165-168. **Review/No data**

23. Baptista MZ, Prieto VG, Chon S, et al. Tamoxifen-related vasculitis. J Clin Oncol 2006;24(21):3504-3505. **Wrong population**

24. Barakat RR. The effect of tamoxifen on the endometrium. Oncology 9(2):129-134;discussion 139-140. **Review/No data**

25. Barcenas CH, Hosain GMM, Arun B, et al. Assessing BRCA carrier probabilities in extended families. J Clin Oncol 2006;24(3):354-360. **Family history only model**

26. Barrett-Connor E, Wenger NK, Grady D, et al. Coronary heart disease in women, randomized clinical trials, HERS and RUTH. Maturitas 1998;31(1):1-7. **Review/No data**

27. Barron TI, Connolly R, Bennett K, et al. Early discontinuation of tamoxifen: a lesson for oncologists. Cancer. 2007;109(5):832-839. **Wrong population**

28. Baum M, Houghton J, Riley D. Tamoxifen to prevent breast cancer. Lancet 1991;338(8759):114. **Review/No data**

29. Becher H, Schmidt S, Chang-Claude J. Reproductive factors and familial predisposition for breast cancer by age 50 years. A case-control-family study for assessing main effects and possible gene-environment interaction [see comment]. Int J Epidemiol 2003;32(1):38-48. **Family history only model**

30. Beckmann MW, Bani MR, Fasching PA, et al. Risk and risk assessment for breast cancer: molecular and clinical aspects. Maturitas 2007;57(1):56-60. **Family history only model**

31. Beiner ME, Finch A, Rosen B, et al. The risk of endometrial cancer in women with BRCA1 and BRCA2 mutations. A prospective study. Gynecol Oncol 2007;104(1):7-10. **Wrong population**

32. Beitler JJ. Tamoxifen and sexuality: Let's listen to the data speak. J Clin Oncol 1999;17(11):3689-3690. **Wrong population**

33. Benichou J, Gail MH, Mulvihill JJ. Graphs to estimate an individualized risk of breast cancer. J Clin Oncol 1996;14(1):103-110. **No relevant data**

34. Berg AO, United States Preventive Services Task Force. Chemoprevention of breast cancer: recommendations and rationale. Am J Nurs 2003;103(5):107. **No relevant data**

35. Bergh J. Breast-cancer prevention: is the risk-benefit ratio in favour of tamoxifen? Lancet 2003;362(9379):183-184. **Review/No data**

36. Bernatsky S, Ramsey-Goldman R, Boivin J-F, et al. Do traditional Gail model risk factors account for increased breast cancer in women with lupus? J Rheumatol 2003;30(7):1505-1507. **Population not applicable**

37. Bernstein L, Patel AV, Ursin G, et al. Lifetime recreational exercise activity and breast cancer risk among black women and white women. J Natl Cancer Inst 2005;97(22):1671-1679. **Single risk factor only**

38. Bernstein L, Ross RK, Henderson BE. Prospects for the primary prevention of breast cancer. Am J Epidemiol 1992;135(2):142-152. **Review/No data**

39. Bevers TB. Raloxifene and the prevention of breast cancer. Expert Opin Pharmacother 2006;7(16):2301-2307. **Review/No data**

40. Blumenthal RS, Baranowski B, Dowsett SA. Cardiovascular effects of raloxifene: the arterial and venous systems. Am Heart J 2004;147(5):783-789. **Review/No data**

41. Boardman LA, Thibodeau SN, Schaid DJ, et al. Increased risk for cancer in patients with the Peutz-Jeghers syndrome. Ann Intern Med 1998;128(11):896-899. **Population not applicable**

42. Bober SL, Hoke LA, Duda RB, et al. Recommendation recall and satisfaction after attending breast/ovarian cancer risk counseling. J Genet Couns 2007;16(6):755-762. **No relevant outcomes**

43. Bondy ML, Newman LA. Assessing breast cancer risk: evolution of the Gail Model [comment]. J Natl Cancer Inst 2006;98(17):1172-1173. **No relevant data**

44. Bordeleau LJ, Lipa JE, Neligan PC. Management of the BRCA mutation carrier or high-risk patient. Clin Plast Surg 2007;34(1):15-27. **Family history only model**

45. Boss SM, Huster WJ, Neild JA, et al. Effects of raloxifene hydrochloride on the endometrium of postmenopausal women. Am J Obstet Gynecol 1997;177(6):1458-1464. **Review/No data**

46. Boyapati SM, Shu XO, Jin F, et al. Dietary calcium intake and breast cancer risk among Chinese women in Shanghai. Nutr Cancer 2003;46(1):38-43. **Single risk factor only**

47. Bradbury BD, Lash TL, Kaye JA, et al. Tamoxifen-treated breast carcinoma patients and the risk of acute myocardial infarction and newly-diagnosed angina. Cancer 2005;103(6):1114-1121. **Wrong population**

48. Bradbury J. CORE breast-cancer prevention trial. Lancet Oncol 2005;6(1):8. **Review/No data**

49. Bremnes Y, Ursin G, Bjurstam N, et al. Different measures of smoking exposure and mammographic density in postmenopausal Norwegian women: a cross-sectional study. Breast Cancer Res 2007;9(5):R73. **Single risk factor only**

50. Brenner DE. Cancer chemoprevention. Crit Rev Oncol Hematol 2000;33(3):155-156. **Review/No data**

51. Brewster AM, Christo DK, Lai H, et al. Breast carcinoma chemoprevention in the community setting. Estimating risks and benefits. Cancer 2005;103(6):1147-1153. **No relevant outcomes**

52. Brinker A, Beitz J. Spontaneous reports of pulmonary embolism in association with raloxifene. Obstet Gynecol 2001;98(6):1151. **Review/No data**

53. Brown K. Breast cancer chemoprevention: risk-benefit effects of the antioestrogen tamoxifen. Expert Opin Drug Saf 2002;1(3):253-267. **Review/No data**

54. Brown P. Risk assessment: controversies and management of moderate- to high-risk individuals. Breast J 2005;11 Suppl 1:S11-19. **No relevant data**

55. Bush TL, Blumenthal R, Lobo R, et al. SERMs and cardiovascular disease in women. How do these agents affect risk? Postgrad Med 2001;Spec No: 17-24. **Review/No data**

56. Bushnell C. The cerebrovascular risks associated with tamoxifen use. Expert Opin Drug Saf 2005;4(3):501-507. **Review/No data**

57. Bushnell CD, Goldstein LB. Risk of ischemic stroke with tamoxifen treatment for breast cancer: a meta-analysis. Neurology 2004;63(7):1230-1233. **Review/No data**

58. Byrne C, Rockett H, Holmes MD. Dietary fat, fat subtypes, and breast cancer risk: lack of an association among postmenopausal women with no history of benign breast disease. Cancer Epidemiol Biomarkers Prev 2002;11(3):261-265. **Single risk factor only**

59. Byrne C, Schairer C, Brinton LA, et al. Effects of mammographic density and benign breast disease on breast cancer risk (United States). Cancer Causes Control 2001;12(2):103-110. **Single risk factor only**

60. Calle EE, Rodriguez C, Walker KA, et al. Tubal sterilization and risk of breast cancer mortality in US women. Cancer Causes Control 2001;12(2):127-135. **Single risk factor only**

61. Cattaneo M, Baglietto L, Zighetti ML, et al. Tamoxifen reduces plasma homocysteine levels in healthy women. Br J Cancer 1998;77(12):2264-2266. **Wrong type of study**

62. Cersosimo RJ. Tamoxifen for prevention of breast cancer. Ann Pharmacother 2003;37(2):268-273. **Review/No data**

63. Chan K, Morris GJ. Chemoprevention of breast cancer for women at high risk. Semin Oncol 2006;33(6):642-646. **Review/No data**

64. Chang J, Powles TJ, Ashley SE, et al. The effect of tamoxifen and hormone replacement therapy on serum cholesterol, bone mineral density and coagulation factors in healthy postmenopausal women participating in a randomised, controlled tamoxifen prevention study. Ann Oncol 1996;7(7):671-675. **Wrong drugs**

65. Chen WY, Colditz GA. Risk factors and hormone-receptor status: epidemiology, risk-prediction models and treatment implications for breast cancer. Nat Clin Pract Oncol 2007;4(7):415-423. **No relevant data**

66. Chiechi LM, Secreto G. Breast cancer and replacement therapy: which women are at risk? Clin Exp Obstet Gynecol 1999;26(2):105-108. **Single risk factor only**

67. Chittacharoen A, Theppisai U, Manonai J. Transvaginal color Doppler sonographic evaluation of the uterus in postmenopausal women on daily raloxifene therapy. Climacteric 2002;5(2):156-159. **Wrong type of study**

68. Chlebowski RT, Col N, Winer EP, et al. American Society of Clinical Oncology technology assessment of pharmacologic interventions for breast cancer risk reduction including tamoxifen, raloxifene, and aromatase inhibition. J Clin Oncol. 2002;20(15):3328-3343. **Review/No data**

69. Chlebowski RT, Collyar DE, Somerfield MR, et al. American Society of Clinical Oncology technology assessment on breast cancer risk reduction strategies: tamoxifen and raloxifene. J Clin Oncol 1999;17(6):1939-1955. **Review/No data**

70. Chlebowski RT, Geller ML. Adherence to endocrine therapy for breast cancer. Oncology 2006;71(1-2):1-9. **Wrong population**

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Appendix C.
Quality and Strength of Evidence Criteria and Rating

Appendix C-1. Quality Rating Criteria* and Applicability Assessment with PICOTS

Quality Rating Criteria

Randomized Controlled Trials (RCTs) and Cohort Studies

Criteria:

- Initial assembly of comparable groups**:** RCTs—adequate randomization, including concealment and whether potential confounders were distributed equally among groups; cohort studies—consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts
- Maintenance of comparable groups (includes attrition, cross-overs, adherence, contamination)
- Important differential loss to follow-up or overall high loss to follow-up
- Measurements: equal, reliable, and valid (includes masking of outcome assessment)
- Clear definition of interventions
- Important outcomes considered
- Analysis: adjustment for potential confounders for cohort studies, or intention-to-treat analysis for RCTs; for cluster RCTs, correction for correlation coefficient

Definition of ratings based on above criteria:

Good: Meets all criteria: Comparable groups are assembled initially and maintained throughout the study (follow-up at least 80 percent); reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; important outcomes are considered; and appropriate attention to confounders in analysis.

Fair: Studies will be graded "fair" if any or all of the following problems occur, without the important limitations noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred in follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for.

Poor: Studies will be graded "poor" if any of the following major limitations exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied at all equally among groups (including not masking outcome assessment); and key confounders are given little or no attention.

Studies of Risk Assessment Tools

Adapted from the United States Preventive Services Task Force Quality Rating Criteria for Diagnostic Accuracy Studies

Criteria:

- Risk assessment tool appropriate for a primary care screening tool
- Tool evaluates diagnostic test performance in a population other than the one used to derive the instrument
- Study evaluates a consecutive clinical series of patients or a random subset
- Study adequately describes the population in which the risk instrument was tested
- Study adequately describes the instrument evaluated
- Study includes appropriate criteria in the instrument (must include age, family history and/or some other measure of risk)
- Study adequately describes the method used to calculate the risk index
- Study uses appropriate criterion to assess the risk factors (uses either a validated questionnaire or other corroborated method)
- Study evaluates outcomes or the reference standard in all patients enrolled (up to 20% loss considered acceptable)
- Follow up with standard diagnostic testing (mammogram/biopsy/pathology) performed consistently without regard for the results of the risk assessment
- Study evaluates outcomes blinded to results of the screening instrument

Definition of ratings based on above criteria:

Good: Evaluates relevant screening test appropriate for primary care setting; risk instrument is validated in a population other than the one used to derive the instrument; risk instrument adequately described; uses an appropriate reference standard (eg. SEER data); handles indeterminate results in a reasonable manner; broad spectrum of patients and adequate number of incident cases; use of primary data; appropriate duration of follow up and standardized diagnostic screening in follow up (mammogram).

Fair: Evaluates relevant available screening test; moderate sample size; medium spectrum of patients; risk instrument not validated in a population other than the one used to derive the instrument; handling of indeterminate results not reported or inadequate; inadequate follow up - either inadequate duration or inconsistent use of standardized diagnostic screening (mammogram); instrument not derived from primary data.

Poor: Has important limitations such as inappropriate reference standard, very small sample size, very narrow spectrum of patients; not appropriate for primary care.

*__Reference:__ Harris RP, Helfand M, Woolf SH, et al. Current methods of the US Preventive Services Task Force: a review of the process. *Am J Prev Med.* 2001:20(3S); 21-35.

Applicability Assessment with PICOTS: Limitations that Reduce Applicability

Population:

- Narrow eligibility criteria and/or high exclusion rate.
- Large differences between demographics of study population and that of patients in the community.
- Narrow or unrepresentative severity or stage of illness.
- Run in period with high-exclusion rate for non-adherence or side effects.
- Event rates much higher or lower than observed in population-based studies.
- Study size too small to represent the population of interest.

Intervention:

- Doses or schedules not reflected in current practice.
- Intensity of behavioral interventions that is not likely to be feasible for routine use.
- Co-interventions that are likely to modify effectiveness of therapy.
- Monitoring practices or visit frequency not used in typical practice.
- Highly selected intervention team or level of training/proficiency not widely available.

Comparator:

- Inadequate dose of comparison therapy.
- Use of sub-standard alternative therapy.

Outcomes:

- Surrogate rather than clinical outcomes.
- Failure to measure most important outcomes.
- Failure to distinguish minor from serious adverse effects.

Timing of Outcomes Measurement:

- Follow-up too short to detect important benefits or harms.
- Lack of long-term follow-up for interventions requiring long-term interventions.

Setting:

- Settings where standards of care differ markedly from setting of interest.
- Specialty population or level of care that differs importantly from that seen in primary care.

Appendix C-2. EPC GRADE Domains and Definitions for Assessing the Strength of Evidence*

Domain	Definition and Elements	Score and Application
Risk of Bias	Risk of bias is the degree to which the included studies for a given outcome or comparison have a high likelihood of adequate protection against bias (i.e., good internal validity), assessed through two main elements: • Study design (e.g., RCTs or observational studies) • Aggregate quality of the studies under consideration. Information for this determination comes from the rating of quality (good/fair/poor) done for individual studies	Use one of three levels of aggregate risk of bias: • **Low** risk of bias • **Medium** risk of bias • **High** risk of bias
Consistency	The principal definition of consistency is the degree to which reported effect sizes from included studies appear to have the same direction of effect. This can be assessed through two main elements: • Effect sizes have the same sign (that is, are on the same side of "no effect") • The range of effect sizes is narrow.	Use one of three levels of consistency: • **Consistent** (i.e., no inconsistency) • **Inconsistent** • **Unknown or not applicable** (e.g., single study) As noted in the text, single-study evidence bases (even mega-trials) cannot be judged with respect to consistency. In that instance, use "Consistency unknown (single study)."
Directness	The rating of directness relates to whether the evidence links the interventions directly to health outcomes. For a comparison of two treatments, directness implies that head-to-head trials measure the most important health or ultimate outcomes. Two types of directness, which can coexist , may be of concern: Evidence is indirect if: • It uses intermediate or surrogate outcomes instead of health outcomes. In this case, one body of evidence links the intervention to intermediate outcomes and another body of evidence links the intermediate to most important (health or ultimate) outcomes. • It uses two or more bodies of evidence to compare interventions A and B -- e.g., studies of A vs. placebo and B vs. placebo, or studies of A vs. C and B vs. C but not A vs. B. Indirectness always implies that more than one body of evidence is required to link interventions to the most important health outcomes. Directness may be contingent on the outcomes of interest. EPC authors are expected to make clear the outcomes involved when assessing this domain.	Score dichotomously as one of two levels directness • **Direct** • **Indirect** If indirect, specify which of the two types of indirectness account for the rating (or both, if that is the case) -- namely, use of intermediate/ surrogate outcomes rather than health outcomes, and use of indirect comparisons. Comment on the potential weaknesses caused by, or inherent in, the indirect analysis. The EPC should note if both direct and indirect evidence was available, particularly when indirect evidence supports a small body of direct evidence.

Precision	Precision is the degree of certainty surrounding an effect estimate with respect to a given outcome (i.e., for each outcome separately) If a meta-analysis was performed, this will be the confidence interval around the summary effect size.	Score dichotomously as one of two levels of precision: • **Precise** • **Imprecise** A precise estimate is an estimate that would allow a clinically useful conclusion.. An imprecise estimate is one for which the confidence interval is wide enough to include clinically distinct conclusions. For example, results may be statistically compatible with both clinically important superiority and inferiority (i.e., the direction of effect is unknown), a circumstance that will preclude a valid conclusion.

*Printed from: Lohr K, Helfand M, Owens D, et al. Grading the strength of a body of evidence. *J Clin Epidemiol* in press.

Appendix C-3. EPC GRADE Criteria for Assigning Strength of Evidence*

Grade	Definition
High	**High confidence that the evidence reflects the true effect.** Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	**Moderate confidence that the evidence reflects the true effect.** Further research may change our confidence in the estimate of effect and may change the estimate.
Low	**Low confidence that the evidence reflects the true effect.** Further research is likely to change the confidence in the estimate of effect and is likely to change the estimate.
Insufficient	Evidence either is unavailable or does not permit estimation of an effect.

*Printed from: Lohr K, Helfand M, Owens D, et al. Grading the strength of a body of evidence. *J Clin Epidemiol* in press.

Appendix C-4. Optional EPC GRADE Domains and Definitions for Assessing the Strength of Evidence*

Domain	Definition and Elements	Score and Application	Explanation of Non-use in Report
Coherence	Coherence is the degree of plausibility of results in relation to epidemiology or, in some cases, biology and pathophysiology.	This additional domain does not need to be described or noted unless something "implausible" has emerged, in which case EPC authors should comment on it. Use one of two levels: • **Coherent:** the results are plausible given other epidemiologic or biologic data. • **Not coherent:** the results are not plausible given the weight of epidemiologic or biologic data.:	No "implausible" findings emerged in this report.
Dose-response association	This association, either across or within studies, refers to a pattern of a larger effect with greater exposure (dose, duration, adherence)	This additional domain should be rated if studies in the evidence base have noted levels of exposure. Use one of three levels: • **Present:** Dose-response pattern observed • **Not present:** No dose-response pattern observed (dose-response relationship *not* present) • **NA (not applicable or not tested**)	No multiple dose effects were tested in the trials included in this report.
Impact of plausible residual confounders	Occasionally, in an observational study, residual confounders would work in the direction *opposite* that of the observed effect. A case in point is when a study is biased *against* finding an effect and yet it finds an effect. Thus, had these confounders not been present, the observed effect would have been even larger than the one observed.	This additional domain should be considered if a plausible impact of residual confounding exists. Use one of three levels: • **Unlikely:** Confounding unlikely to explain observed effect: Plausible residual confounders are more likely to have decreased the observed effect than to have increased the observed effect • **Possible:** Confounding may explain observed effect: Plausible residual confounders are unlikely to have decreased the observed effect and could be responsible for observed effect • **Cannot assess**	Few observational studies were included and had little impact in the GRADE table.

Domain	Definition and Elements	Score and Application	Explanation of Non-use in Report
Strength of association (magnitude of effect)	Strength of association refers to the likelihood that the observed effect is large enough that it cannot have occurred solely as a result of bias from potential confounding factors.	This additional domain should be considered if the effect size is particularly large. Use one of two levels: • **Strong:** large effect size that is unlikely to have occurred in the absence of a true effect of the intervention • **Weak:** small enough effect size that it could have occurred solely as a result of bias from confounding factors	Effect sizes were not particularly large and came from well-designed RCTs.
Publication bias	Publication bias indicates that studies may have been published selectively with the result that the estimated effect of an intervention based on published studies does not reflect the true effect. The finding that only a small proportion of relevant trials (or other studies) has been published or reported in a results database may indicate a higher risk of publication bias, which in turn may undermine the overall robustness of a body of evidence.	Publication bias need not be formally scored. However, it can influence ratings of consistency, precision, magnitude of effect (and, to a lesser degree, risk of bias and directness). If EPCs identify unpublished trials, and if those results differ from those of published studies, they can take these factors into account in their rating for consistency and in calculating a summary confidence interval for an effect. We encourage authors to comment on publication bias when circumstances suggest that relevant empirical findings, particularly negative or no-difference findings, have not been published or are not otherwise available.	No unpublished trials identified. Only very large, well known trials could provide the breast cancer outcomes needed for this report.

*Printed from: Lohr K, Helfand M, Owens D, et al. Grading the strength of a body of evidence. *J Clin Epidemiol* in press.

Appendix C-5. Quality and Applicability Ratings of Included Trials

Trials author, year	Criteria for Quality									Criteria for Applicability						
	Adequate randomization?	Blinding?	Maintenance of comparable groups?	Loss to follow-up?	Measures equal, reliable, valid?	Clear definition of interventions	Important outcomes considered?	Intention-to-treat analysis?	Rating/ limitations	Population	Intervention	Comparator	Outcomes	Timing of outcomes measures	Setting	Quality rating for applicability
Primary Prevention Trials																
STAR Vogel, 2006[12]	Method not described	Yes	68% tamoxifen, 72% raloxifene completed study	1.5% loss tamoxifen; 1.3% raloxifene	Yes	Yes	Yes	Yes	Good	Increased risk for breast cancer; broad inclusion criteria	Appropriate	Appropriate	Appropriate	Appropriate	Multi-center, relevant to primary care	Good
IBIS Cuzick, 2002[19]	Yes	Yes	64% tamoxifen, 74% placebo completed study p<0.001 ; 25% completed 5 yrs	NR; assume all included in analysis	Yes	Yes	Yes	Yes	Fair; 40% estrogen use may confound	Increased risk for breast cancer; broad inclusion criteria	Appropriate	Appropriate	Appropriate	Appropriate	Multi-center, relevant to primary care	Good
NSABP P-1 Fisher, 1998[24]	Yes	Yes	76% tamoxifen, 80% placebo completed study	1.6% loss in both groups	Yes	Yes	Yes	Yes	Good	Increased risk for breast cancer; broad inclusion criteria	Appropriate	Appropriate	Appropriate	Appropriate	Multi-center, relevant to primary care	Good
Royal Marsden Powles, 1998[25]	Yes	Yes	53% tamoxifen, 63% placebo completed study p<0.0005	11% loss in both groups	Yes	Yes	Yes	Yes	Fair; unequal use of estrogen in groups	Increased risk for breast cancer; broad inclusion criteria	Appropriate	Appropriate	Appropriate	Appropriate	Multi-center, relevant to primary care	Good
Italian Veronesi, 1998[28]	Method not described	Yes	69% tamoxifen 73% placebo completed study	<1% loss overall	Yes	Yes	Yes	Yes	Fair; hysterectomy, estrogen use may confound	Increased risk for breast cancer; prior hysterctomy	Appropriate	Appropriate	Appropriate	Appropriate	Multi-center, relevant to primary care	Fair; women in study have hysterectomy modifying risk

Trials author, year	Criteria for Quality									Criteria for Applicability						Quality rating for applicability
	Adequate randomization?	Blinding?	Maintenance of comparable groups?	Loss to follow-up?	Measures equal, reliable, valid?	Clear definition of interventions	Important outcomes considered?	Intention-to-treat analysis?	Rating/ limitations	Population	Intervention	Comparator	Outcomes	Timing of outcomes measures	Setting	
RUTH Barret-Connor, 2006[46]	Yes	Yes	80% raloxifene, 79% placebo completed study	NR; assume all included in analysis	Yes	Yes	Yes	Yes	Good	Heart disease or increased heart risk	Appropriate	Appropriate	Appropriate	Appropriate	Multi-center, relevant to primary care	Good
MORE Cummings, 1999[34]	Yes	Yes	78% raloxifene, 75% placebo completed study	NR; assume all included in analysis	Yes	Yes	Yes	Yes	Good	Osteoporosis	Appropriate	Appropriate	Appropriate	Appropriate	Multi-center, relevant to primary care	Good
LIFT Cummings, 2008[10] Ettinger, 2008[87]	Yes	Yes	91% overall received 80% of doses	NR; assume all included in analysis	Yes	Yes	Yes	Yes	Good	Osteoporosis	Appropriate	Appropriate	Appropriate	Appropriate	Multi-center, relevant to primary care	Good
Raloxifene Trials																
Cohen, 2000*[73]	Yes	Yes	Yes	35% discontinued therapy	Yes	Yes	Yes but not all harms are reported	NR	Fair	Healthy women average risk	Appropriate	Appropriate	Appropriate	Appropriate	2 Multi-center trials	Fair
Delmas, 1997[74]	Yes	NR	Yes	NR	Yes	Yes	Yes but not all harms are reported	Yes	Fair	Healthy women	Appropriate	Appropriate	Appropriate	Appropriate	Multi-center; no US sites	Poor
Goldstein, 2005[76]	Yes	Yes	Yes	40% discontinued therapy	Yes	Yes	Yes but not all harms are reported	Yes	Fair	Healthy women with prior hysterectomy	Appropriate	Appropriate	Appropriate	Appropriate	Multi-center trial; includes US sites	Fair
Johnston, 2000*[77]	Yes	Yes	Yes	23-42%	Yes	Yes	Yes but not all harms are reported	Yes	Fair	Healthy women	Appropriate	Appropriate	Appropriate	Appropriate	Multi-center trial; includes US sites	Fair
Jolly, 2003*[78]	Yes	No	Yes	NR	Yes	Yes	Yes but not all harms are reported	No	Poor; only includes those continuing therapy	Healthy women	Appropriate	Appropriate	Appropriate	Appropriate	Multi-center; includes US sites	Fair
Lufkin, 1998†[79]	Yes	Yes	NR	~10%	Yes	Yes	Yes but not all harms are reported	Yes	Fair	Osteoporosis	Appropriate	Appropriate	Appropriate	Appropriate	Multi-center	Fair

Trials author, year	Criteria for Quality								Rating/ limitations	Criteria for Applicability						Quality rating for applicability
	Adequate randomization?	Blinding?	Maintenance of comparable groups?	Loss to follow-up?	Measures equal, reliable, valid?	Clear definition of interventions	Important outcomes considered?	Intention-to-treat analysis?		Population	Intervention	Comparator	Outcomes	Timing of outcomes measures	Setting	
McClung, 2006[80]	Yes	Yes	NR	~30%	Yes	Yes	Yes but not all harms are reported	NR	Fair	Healthy	Appropriate	Appropriate	Appropriate	Appropriate	Multi-center; includes US sites	Fair
Meunier, 1999[81]	Yes	Yes	Yes	~16%	Yes	Yes	Yes but not all harms are reported	Yes	Fair	Osteoporosis	Appropriate	Appropriate	Appropriate	Appropriate	Multi-center; France	Poor
Morii, 2003[82]	Yes	Yes	Yes	~15%	Yes	Yes	Yes but not all harms are reported	NR	Fair	Japan; osteoporosis narrow inclusion criteria	Appropriate	Appropriate	Appropriate	Appropriate	Multi-center; Japan	Poor
Nickelson, 1999†[83]	NR	Yes	Yes	9.1% discontinued	Yes	Yes	Yes but not all harms are reported	Yes	Fair	Osteoporosis	Appropriate	Appropriate	Appropriate	Appropriate	2 centers; US	Fair
Palacios, 2004[84]	Yes	Yes	Yes	11-13%	Yes	Yes	Yes but not all harms are reported	Yes	Fair	Healthy women	Appropriate	Appropriate	Appropriate	Appropriate	Multi-center; no US sites	Poor
Walsh, 1998[85]	Yes	Yes	Yes	16%	Yes	Yes	Yes but not all harms are reported	Yes	Fair	Health women	Appropriate	Appropriate	Appropriate	Appropriate	Multi-center; includes US sites	Fair
Tibolone Trials																
OPAL; Bots, 2001[89]; Langer, 2006[90]	Yes	Yes for treatment group; NR for other outcomes	Yes	No; 31% tx, 30% placebo	Yes	Yes	Yes	Yes	Fair	Healthy	Appropriate	Appropriate	Appropriate	Appropriate	Multi-center; includes US sites	Fair
Landgren, 2002[91]	Yes	NR	Yes	No; 11% tx, 20% placebo	Yes	Yes	Yes	NR	Fair	Healthy; vasomotor symtoms	Appropriate	Appropriate	Appropriate	Appropriate	Multi-center; no US sites	Poor
Gallagher, 2001[92]	Yes	Yes for treatment group; NR for other outcomes	Yes	No; 34% tx, 29% placebo	Yes	Yes	Yes	Yes	Fair	Healthy	Appropriate	Appropriate	Appropriate	Appropriate	Multi-center; US	Fair
Swanson, 2006[93]	Yes	NR	Yes	No	Yes	Yes	Yes	Yes	Fair	Healthy; vasomotor symtoms	Appropriate	Appropriate	Appropriate	Appropriate	Multi-center; US	Poor
Hudita, 2003[94]	NR	NR	Yes	No	Yes	Yes	Yes	No	Poor	Healthy; symptoms	Appropriate	Appropriate	Appropriate	Appropriate	1 Center; Romania	Poor

Trials author, year	Criteria for Quality: Adequate randomization?	Blinding?	Maintenance of comparable groups?	Loss to follow-up?	Measures equal, reliable, valid?	Clear definition of interventions	Important outcomes considered?	Intention-to-treat analysis?	Rating/ limitations	Criteria for Applicability: Population	Intervention	Comparator	Outcomes	Timing of outcomes measures	Setting	Quality rating for applicability
Onalan, 2005[96]	Yes	NR	NR	No; 18% tx, 9% placebo	Yes	Yes	Yes	No	Poor	Healthy	Appropriate	Appropriate	Appropriate	Appropriate	1 Center; Turkey	Poor
Lundstrom, 2002[95]	Yes	NR	Yes	No	Yes	Yes	Only breast density	No	Fair	Healthy	Appropriate	Appropriate	Appropriate	Appropriate	1 Center; Sweden	Poor
Million Women Study Beral, 2003[96]; Beral, 2005[97]	NA	NA	NA	No	Yes	Yes	Yes	NA	Fair	Healthy; symptoms	Appropriate	Appropriate	Appropriate	Appropriate	Multi-center	Poor

Appendix C-6. Quality of Risk Assessment Tools

	Quality Criteria										
Study	Primary care tool?	Tested in secondary population?	Population adequately described?	Instrument adeqauately described?	Appropriate criteria?	Risk calculation adequately described?	Results appropriately handled?	Reference standard?	Adequate sample size?	Adequate duration of follow up?	Quality Criteria
Gail, 1989[49]	Yes	No*	Yes	Yes	Yes	Yes	Yes	No*	Yes	Yes	Good
Costantino, 1999[124]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Rockhill, 2001[122]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Chlebowski, 2007[125]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Gail M, 2007[126]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Adams-Campbell, 2007[127]	Yes	Yes	Yes	Yes	Yes	Yes	NR	Yes	Yes	Yes	Good
DeCarli, 2006[121]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Boyle, 2004[118]	Difficult†	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Fair
Chen, 2006[128]	Yes	No*	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Barlow, 2006[129]	Yes	No*	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Fair
Tice, 2008[130]	Yes	No*	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Rockhill, 2003[131]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NR	Yes	Yes	Good
Colditz, 2000[119]	Yes	No*	Yes	Yes	Yes	Yes	Yes	NR	Yes	Yes	Good

Colditz, 2004[120]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NR	Yes	Yes	Good
Tyrer, 2004[123]	Yes	No*	No*	Yes	No‡	Yes	Yes	Yes	Yes	NR	Fair
Amir, 2003[132]	Yes	Yes	No§	Yes	Yes	Yes	Yes	Yes	No	Yes	Fair

* Appropriate due to study purpose.

† Logistically difficult due to an extensive dietary questionnaire.

‡ Tyrer, 2004 did not use primary data.

§ Amir, 2003 did not use a primary care population.

Appendix D.
Evidence Tables

Appendix D-1. Evidence Table for Studies of Harms

Study*	Study Design	N (drug/ placebo or nonuser)	Participants	Dose (mg); Duration	Harms Outcomes
Tamoxifen vs Raloxifene					
Study of Tamoxifen and Raloxifene (STAR)[12,18]	RCT	9872 tamoxifen/ 9875 raloxifene	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. United States based with nearly 200 clinical sites in North America.	Tamoxifen: 20 mg/day raloxifene: 60 mg/day Mean follow-up 3.9 years with mean exposure 3.1 to 3.2 years.	Thromboembolic events combined, pulmonary embolism, deep vein thrombosis, ischemic coronary heart disease, myocardial infarction, severe angina, acute ischemic syndrome, stroke, transient ischemic attack, endometrial cancer, hysterectomy, genitourinary cancers, cataracts, cataract surgery, quality of life indicators, sexual function, musculoskeletal problems, dyspareunia, weight gain, gynecological problems, vasomotor symptoms, leg cramps, bladder control symptoms.
Tamoxifen Studies					
National Surgical Adjuvant Breast and Bowel Project P-1 Study (NSABP-1)[21-24]	RCT	6576/6599	Women age ≥60 years or age 35 to 59 years with a 5-year predicted risk of breast cancer ≥1.66% based on the modified Gail model,† or a history of lobular carcinoma *in situ.* 39% of women were <50 years old; 97% white; 38% post hysterectomy; none using estrogen. United States based with multiple clinical sites in North America.	20 mg/day Median follow-up 4.6 years, median exposure 4.0 years for initial results. Median follow-up 7.0 years for long-term results.	Pulmonary embolism, deep vein thrombosis, composite measures of coronary heart disease, myocardial infarction, acute coronary syndrome, severe angina, stroke, transient ischemic attack, endometrial cancer, gynecologic conditions, hysterectomy, vaginal symptoms (dryness, discharge), breast density, cataracts, cataract surgery, vasomotor symptoms, hot flashes, depression, quality of life indicators, sexual side effects.

Study*	Study Design	N (drug/ placebo or nonuser)	Participants	Dose (mg); Duration	Harms Outcomes
International Breast Cancer Intervention Study (IBIS-I)[19, 20]	RCT	3573/3566	Women with increased breast cancer risk based on family history and other factors.‡ Age 35 to 70 years, mean age 50.8 years; 35% post hysterectomy; 40% using estrogen. United Kingdom, Australia, New Zealand, Europe.	20 mg/day Median follow-up 4.2 years for initial results. 8.0 years follow-up for long-term results.	Pulmonary embolus, deep vein thrombosis, superficial thrombophlebitis, retinal vein thrombosis, composite cardiac outcomes, myocardial infarction, angina, stroke, transient ischemic attack, endometrial cancer, gynecologic conditions, gynecologic procedures, vaginal symptoms, breast density, breast symptoms, cataracts, vasomotor symptoms, headaches.
Royal Marsden Hospital Trial[25, 26]	RCT	1238/1233	Women with family history of breast cancer.§ Age 30 to 70 years; median age 47 years; 15% of tamoxifen and 27% of placebo group using estrogen at the beginning of trial. United Kingdom.	20 mg/day Median follow-up 5.8 years for initial results. 13.2 years follow-up for long-term results.	Composite thromboembolic events, pulmonary embolism, deep venous thrombosis, cardiovascular outcomes, stroke, endometrial thickness, cystitis, incontinence, breast symptoms, cataracts, gastrointestinal symptoms, hot flashes, weight gain, headaches.
Italian Tamoxifen Prevention Study[29, 30, 50]	RCT	2700/2708	Women with hysterectomy for reasons other than cancer. Age 35 to 70 years; median age 51 years; 14% using estrogen. Italy based with 55 clinical centers in Europe and South America.	20 mg/day Median follow-up 3.8 years for initial results. 11.2 years follow-up and 4.0 years exposure for long-term results.	Pulmonary embolism, deep venous thrombosis, visceral, retinal and superficial thrombophlebitis, myocardial infarction, atrial fibrillation, stroke, cystitis, incontinence, gastrointestinal symptoms, vasomotor symptoms, hot flashes, weight gain.

Study*	Study Design	N (drug/ placebo or nonuser)	Participants	Dose (mg); Duration	Harms Outcomes
Raloxifene Studies					
Multiple Outcomes of Raloxifene Evaluation (MORE) and Continuing Outcomes Relevant to Evista (CORE) [31-37, 39-45, 87]	RCT	MORE: 5129/2576 CORE: 2725/1286	Postmenopausal women with osteoporosis.‖ Age 31 to 80 years; median age 66.9 years; 96% white; 23% post hysterectomy; none using systemic estrogen. United States based with 180 clinical centers in 25 countries. CORE is comprised of a subset of MORE participants to further examine raloxifene's effect on breast cancer incidence.	MORE: 60 or 120 mg/day CORE: 60 mg/day Follow-up time varies; MORE results reported at 3 and 4 years and CORE at 4 and 8 years (combines the MORE and CORE data).	Thromboembolic events, pulmonary embolism, deep vein thrombosis, composite coronary heart disease measures, myocardial infarction, coronary death, silent myocardial infarction, sudden death, unstable angina, acute coronary syndrome, coronary ischemia, stroke, uterine pathology, endometrial cancer, uterine bleeding, urinary symptoms, breast density, cataracts, gastrointestinal symptoms, vasomotor symptoms, peripheral edema, leg cramps.
Raloxifene Use for the Heart (RUTH) [46, 47]	RCT	5044/5057	Postmenopausal women with coronary heart disease or multiple risk factors for heart disease.¶ Age ≥55 years; median age 67.5 years; 84% white; 23% post hysterectomy; none on estrogen. United States based with 177 clinical sites in 26 countries.	60 mg/day Median duration 5.6 years; median exposure 5.1 years.	Pulmonary embolism, deep venous thrombosis, stroke, coronary events (death from coronary causes, nonfatal myocardial infarction, acute coronary syndrome), endometrial cancer, ovarian cancer, cataracts, cholelithiasis, dyspepsia, cholecystectomy, vasomotor symptoms, peripheral edema.

Study*	Study Design	N (drug/ placebo or nonuser)	Participants	Dose (mg); Duration	Harms Outcomes
Cohen, 2000**[73]	RCT	234 (30 mg); 245 (60 mg); 243 (150 mg)/247 (placebo)	Healthy women, 2-8 years postmenopausal; none with hysterectomy. Age 45-60 years. Multi-center with US sites.	30, 60, or 150 mg/day; 3 years.	Uterine bleeding.
Delmas, 1997[74]	RCT	152 (30 mg); 152 (60 mg); 147 (150 mg)/150 (placebo)	Postmenopausal women with osteoporosis; none with hysterectomy. Mean age 55 years; 99% white. Multi-center no US sites.	30, 60, or 150 mg/day; 2 years.	Uterine bleeding, vasomotor effects including hot flashes, other gynecologic symptoms, breast symptoms.
Goldstein, 2005[76]	RCT	152 (60 mg); 157 (150 mg)/152 (placebo)	Postmenopausal women; all with hysterectomy. Mean age 53 years; 96% white. Multi-center with US sites.	60 or 150 mg/day; 3 years.	Urinary outcomes, breast symptoms.
Johnston, 2000**[77]	RCT	288 (30 mg); 286 (60 mg); 285 (150 mg)/286 (placebo)	Healthy, postmenopausal women. Mean age 54.5 years. Multi-center with US sites.	30, 60, or 150 mg/day 3 years.	Thromboembolic events, uterine bleeding, other gynecologic symptoms, breast symptoms, gastrointestinal symptoms, hot flashes, leg cramps, peripheral edema.
Jolly, 2003**[78]	RCT	163/125	Healthy, postmenopausal women remaining on therapy from Johnston, 2000 study. Mean age 55 years; 96% white. Multi-center with US sites.	60 mg/day; 5 years.	Thromboembolic events, uterine bleeding, hot flashes, leg cramps.

Study*	Study Design	N (drug/ placebo or nonuser)	Participants	Dose (mg); Duration	Harms Outcomes
Lufkin, 1998††[79]	RCT	48 (60 mg); 47 (120 mg)/ 48 (placebo)	Healthy postmenopausal women with osteoporosis; 15% with hysterectomy. Mean age 68.4 years. United States.	60 or 120 mg/day; 1 year.	Thromboembolic events, uterine bleeding, other gynecologic symptoms, breast symptoms, joint pain, dizziness, hot flashes.
McClung, 2006[80]	RCT	163/83	Postmenopausal women with osteoporosis; up to 30% with hysterectomy. Mean age 58 years. Multi-center with US sites.	60 mg/day; 2 years.	Uterine bleeding, hot flashes, leg cramps, breast symptoms, thromboembolic events.
Meuneir, 1999[81]	RCT	45 (60 mg); 42 (150 mg)/ 42 (placebo)	Postmenopausal women with osteoporosis; approximately 10% with hysterectomy. Mean age 60 years. France.	60 or 150 mg/day; 2 years.	Thromboembolic events, vasomotor effects.
Morii, 2003[82]	RCT	92 (60 mg); 95 (120 mg)/ 97 (placebo)	Postmenopausal women with osteoporosis; hysterectomy status not reported. Mean age 65 years. Japan.	60 or 120 mg/day; 1 year.	Thromboembolic events, uterine bleeding, vasomotor effects, leg cramps, breast symptoms, gastrointestinal symptoms, malaise/lethargy.
Nickelson, 1999††[83]	RCT	48 (60 mg); 47 (120 mg)/ 48 (placebo)	Postmenopausal women with osteoporosis; 15% with hysterectomy. Mean age 69 years. United States.	60 or 120 mg/day; 1 year.	Vasomotor effects, mood, depression, cognition, anxiety symptoms.

Study*	Study Design	N (drug/ placebo or nonuser)	Participants	Dose (mg); Duration	Harms Outcomes
Palacios, 2004[84]	RCT	167/159	Postmenopausal women; 25% with hysterectomy; Mean age 58 years. Multi-center with no US sites.	60 mg/day; 8 months.	Thromboembolic events, uterine bleeding, vasomotor effects, breast symptoms, influenza syndrome, joint pain, mood, depression, anxiety symptoms, weight gain, malaise/lethargy.
Walsh, 1998[85]	RCT	95 (60 mg); 101 (120 mg)/98 (placebo)	Healthy postmenopausal women; 19-31% post hysterectomy. Mean age 59 years; 90% white. Multi-center with US sites.	60 or 120 mg/day; 6 months.	Vaginal bleeding, breast symptoms, weight gain, hot flashes.
Christodoulakos, 2006[86]	Prospe ctive cohort	137 raloxifene/ 204 tibolone/ 189 nonuser	Postmenopausal women with menopausal symptoms or osteoporosis; none with hysterectomy. Age 42-66. Menopause clinic in Greece.	60 mg/day	Uterine bleeding.
Tibolone Studies					
Long-Term Intervention on Fractures with Tibolone (LIFT)[10, 87]	RCT	2267/2267	Women with bone mineral density T-score ≤-2.5 at the hip or spine or T-score ≤-2.0 and radiologic evidence of a vertebral fracture. Age 60 to 85 years; mean 68 years. 22% post hysterectomy; none on estrogen. United States based with 80 clinical sites in 22 countries.	1.25 mg/day; median exposure 2.8 years.	Death, coronary heart disease, bradycardia, stroke, transient ischemic attack, venous thromboembolism, cervical cancer, colon cancer, endometrial cancer, pelvic pain, vaginal infection, vaginal discharge, vaginal bleeding, breast discomfort, weight gain, gastroenteritis.

Study*	Study Design	N (drug/ placebo or nonuser)	Participants	Dose (mg); Duration	Harms Outcomes
Osteoporosis Prevention and Arterial effects of tiboLone (OPAL)[88-90]	RCT	290/288	Healthy postmenopausal women; 18% post hysterectomy (0% in US, 30% in Europe). Mean age 58.7 years (range 45-79 years); 96% Caucasian; 1% Black; 2% Asian; 1% Other. United States and Europe.	2.5 mg/ day; 36 months.	Endometrial cancer, uterine cancer, vaginal bleeding/ spotting, musculoskeletal disorders.
Landgren, 2002[91]	RCT	149 (0.625 mg); 143 (1.25 mg); 154 (2.5 mg); 151 (5 mg)/143 (placebo)	Healthy postmenopausal women with vasomotor symptoms; none with hysterectomy. Mean age 52 years (range 40-60). Sweden, Netherlands, Norway, and Finland.	0.625, 1.25, 2.5, or 5 mg/day; 36 months.	Deep venous thrombosis, pulmonary embolism, concussion, headache, vertigo, abdominal pain, vaginal bleeding and spotting, retinal detachment, cholecystitis, hot flashes, sweating.
Gallagher, 2001[92]	RCT	153 (0.3 mg); 158 (0.625 mg); 154 (1.25 mg); 155 (2.5 mg)/ 150 (placebo)	Healthy postmenopausal women; 3% post hysterectomy. Mean age 52.4 years. United States.	0.3, 0.635, 1.25, or 2.5 mg/day; 24 months.	Deep venous thrombosis, pulmonary embolism, vaginal bleeding, moniliasis, allergy, anxiety, nervousness, herpes simplex infection, back pain, rhinitis, headache, weight gain, respiratory tract infection, hot flashes, arthralgia, accidental injury, influenza-like symptoms, sinusitis, pain, abdominal pain.
Swanson, 2006[93]	RCT	136 (1.25 mg); 126 (2.5 mg)/ 134 (placebo)	Postmenopausal women with vasomotor symptoms; none with hysterectomy. Mean age 51-53 years; 90-93% Caucasian, 5-7% Black, 2-3% Other. United States.	1.25 or 2.5 mg/day; 3 months.	Coronary heart failure, hot flashes, genital atrophy, nocturia, urinary urgency, kidney stone, headache, upper respiratory symptoms, nausea, breast pain, uterine spasm, enlarged abdomen, genital pruritus, weight gain, vaginal bleeding.

Study*	Study Design	N (drug/ placebo or nonuser)	Participants	Dose (mg); Duration	Harms Outcomes
Hudita, 2003[94]	RCT	45 (1.25 mg); 41 (2.5 mg)/34 (placebo)	Healthy postmenopausal women with vasomotor symptoms; none with hysterectomy. Mean age 54-56 years. Romania.	1.25 or 2.5 mg/day; 6 months.	Hot flashes, sweating, vaginal dryness, sexual function, breast density, breast discomfort, vaginal bleeding/spotting, headache, nausea, fluid retention.
Onalan, 2005[96]	RCT	76/54	Postmenopausal women; none with hysterectomy. Mean age 52.4 years. Menopause clinic in Turkey.	2.5 mg/day; 12 months.	Depression.
Lundstrom, 2002[95]	RCT	51/55	Healthy postmenopausal women; hysterectomy status not reported. Age range 50-70 years. Sweden.	2.5 mg/day; 6 months.	Breast density, breast pain.
Million Women's Study Beral, 2003[98]	Prospective cohort	18,186/ 392,757	Women invited for breast cancer screening who were using tibolone for menopausal symptoms; hysterectomy status not reported. Mean age 55.9 years (range 50-64 years). United Kingdom.	Dose varied; 2.6 years.	Vaginal bleeding.
Million Women's Study Beral, 2005[97]	Prospective cohort	28,028/ 395,785	Postmenopausal women with no previous cancer or hysterectomy using tibolone for menopausal symptoms. Mean age 58 years. United Kingdom.	Dose varied; 3.1 years.	Endometrial cancer.

*Quality and applicability ratings described in Appendix C-5.

†STAR & NSABP-1: The Gail model includes age, number of first-degree relatives with breast cancer, nulliparity or age at first live birth, number of benign breast biopsies, pathologic diagnosis of atypical hyperplasia, and age at menarche. The original model was further modified to predict expected rates of invasive breast cancer only (not invasive and noninvasive as originally designed) and to allow for race-specific determinations of risk.

‡IBIS: 2-fold relative risk for ages 45 to 70, 4-fold relative risk for ages 40 to 44, 10-fold relative risk for ages 35 to 39 based on family history criteria. All criteria permit entry to trial at age 45 years.
1. First-degree relative who developed breast cancer at or before age 50.
2. First-degree relative with bilateral breast cancer (permits entry from age 40; if relative diagnosed before age 40, permits entry at age 35).
3. Two or more first-degree or second-degree relatives with breast cancer (permits entry from age 40 if both developed breast cancer before age 50, permits entry at age 35 if both relatives are first-degree and both developed breast cancer before age 50).
4. Benign breast biopsy and first-degree relative with breast cancer.
5. Lobular carcinoma in situ (permits entry from age 35).
6. Atypical hyperplasia (permits entry from age 40).
7. Nulliparous and a first-degree relative who developed breast cancer.
8. Risk equivalent (strong family history, not fitting specific categories, but judged to be at higher risk than eligibility category by the study chairman).
§Family history criteria for Royal Marsden Hospital Trial:
1. One first-degree relative under 50 years old with breast cancer, or
2. One first-degree relative with bilateral breast cancer, or
3. One affected first-degree of any age plus another affected first-degree or second-degree relative
4. Benign breast biopsy and a first-degree relative with breast cancer
‖MORE:
Study Group 1: Femoral neck or lumbar spine bone mineral density T-score <-2.5.
Study Group 2: Low bone mineral density and one or more moderate or severe vertebral fractures or 2 or more milder vertebral fractures (20% to 25% reduction in height); or at least 2 moderate fractures (25% to 40% reduction from expected vertebral height), regardless of bone mineral density.
¶Participants were required to have a cardiovascular risk score of 4 or more according to a point system: established coronary heart disease (4 points), arterial disease of the leg (4 points), at least 70 years old (2 points), diabetes mellitus (3 points), cigarette smoking (1 point), hypertension (1 point), and hyperlipidemia (1 point).
**Cohen, 2000, Johnston, 2000, and Jolly, 2003 include some of the same study participants.
††Lufkin, 1998 and Nickelson, 1999 include some of the same study participants.

Appendix D-2. Harms Outcomes from Trials

Thromboembolic Events

All Thromboembolic Events-STAR

Trial Name	N		Length of Treatment (years)	Length of FU (years)	Tamoxifen		Raloxifene			
	Tamoxifen	Raloxifene			No.	Rate	No.	Rate	RR	95% CI
STAR										
Vogel, 2006[12]	9726	9745	5	6	141	3.71	100	2.61	0.7	0.54-0.91

All Thromboembolic Events- Tamoxifen Trials

Trial Name	N		Length of Treatment (years)	Length of FU (years)	Placebo		Tamoxifen				
	Placebo	Tamoxifen			No.	Rate	No.	Rate	RR	95% CI	Notes
Royal Marsden											
Powles, 2007[26]	1233	1238	7.8	13.2	3	0.31	8	0.82	2.62	0.69-9.87	Active treatment
Powles, 2007[26]	1233	1238	8	13.2	6		5				Post treatment P = 1.0
Powles, 1998[25]	1233	1238		5.8		0.8	5	0.68	0.85	0.26-2.79	
Italian											
Dicensi, 2005[27]	2708	2700	5	11	9	0.94	10	1.02	1.09	0.44-2.68	on treatment
IBIS											
Cuzick, 2007[20]	3375	3579	5	8	36	2.02	68	3.8			Active treatment
Cuzick, 2007[20]	3575	3579			24	2.24	26	2.42			Post treatment
NSABP											
Fisher, 1998[24]	6707	6681	4	4	2.8	1.07	53	2.03	1.9	1.20-3.00	

All Thromboembolic Events- Raloxifene trials

Trial Name	N			Length of Treatment (years)	Length of FU (years)	Placebo		R 60		R 120			
	Placebo	R60	R120			No.	Rate	No.	Rate	No.	Rate	RR	95% CI
MORE													
Grady, 2004[39]					3.3	14	1.7	59	3.5			2.1	1.2-3.8
RUTH													
Barrett-Connor, 2006[46]	5057	5044			5.6	71	2.53	103	3.67			1.44	1.06-1.95

All Thromboembolic Events- LIFT Trial

	N		Length of	Placebo		Tibolone				
	Placebo	Tibolone	Treatment	No.	Rate	No.	Rate	RR	95% CI	Notes
Venous thromboembolism	2257	2249	34 months	9	1.3	5	0.8	0.57	0.19-1.69	p=0.31

Deep Vein Thrombosis- STAR

Trial Name	N		Length of Treatment (years)	Length of FU (years)	Tamoxifen		Raloxifene			
	Tamoxifen	Raloxifene			No.	Rate	No.	Rate	RR	95% CI
STAR Vogel, 2006[12]	9726	9745	5	6	87	2.29	65	1.69	0.74	0.53-1.03

Deep Vein Thrombosis- Tamoxifen trials

Trial Name	N		Length of Treatment (years)	Length of FU (years)	Placebo		Tamoxifen		RR	95% CI
	Placebo	Tamoxifen			No.	Rate	No.	Rate		
Royal Marsden										
NR										
Italian										
Decensi, 2005[27]	2708	2700			8	0.83	9	0.92	1.1	0.43-2.86
IBIS										
NR										
NSABP										
Fisher, 2005[23]	6707	6681	5 years	7 years	34	0.84	49	1.21	1.44	0.91-2.30
Age ≤ 49					12	0.76	16	1.01	1.34	0.59-3.10
Age ≥ 50					22	0.89	33	1.33	1.49	0.84-2.68
Fisher, 1998[24]	6707	6681	5 years	69 months	22	0.84	35	1.34	1.60	0.91-2.86
Age ≤ 49					8	0.78	11	1.08	1.39	0.51-3.99
Age ≥ 50					14	0.88	24	1.51	1.71	0.85-3.58

Deep Vein Thrombosis- Raloxifene trials

Trial Name	N			Length of Treatment (years)	Length of FU (years)	Placebo		R 60		R 120		RR	95% CI	Notes
	Placebo	R60	R120			No.	Rate	No.	Rate	No.	Rate			
MORE														
Grady, 2004[39]						7	0.8		combined 2.5			3.13	1.41-6.95	
RUTH														
Barrett-Connor, 2006**[46]	5057	5044			5.6	47	1.67	65	2.32			1.37	0.94-1.99	Annualized rates

Cardiovascular Events

Cardiovascular Outcomes- STAR

Trial Name	N		Length of Treatment (years)	Length of FU (years)	Tamoxifen		Raloxifene			
	Tamoxifen	Raloxifene			No.	Rate	No.	Rate	RR	95% CI
STAR										
Vogel, 2006[12]										
All ischemic coronary heart disease			5	3.9	114	3	126	3.29	1.1	0.85-1.43
Myocardial Infarction					48	1.26	37	0.96	0.77	0.48-1.20
Severe angina (requiring PCI or CABG)					51	1.34	63	1.64	1.23	0.84-1.81
Acute ischemic syndrome (new Q waves or angina requiring hospitalization)					15	0.39	26	0.68	1.72	0.88-3.50

Cardiovascular Outcomes- Tamoxifen trials

Trial Name	N		Length of Treatment (years)	Length of FU (years)	Placebo		Tamoxifen					Outcome assessment
	Placebo	Tamoxifen			No.	Rate	No.	Rate	RR	95% CI	Notes	
Royal Marsden												
Powles 2007[26]: Active	1233	1238	8	13.2	10	1.25	12	1.02	0.82	0.35-1.89	p= 0.7	"Cardiovasc-ular problems" not further defined.
Post					11		14				p= 0.7	
Italian												
Veronesi, 2007[29]: Myocardial Infarction	2708	2700	5	4	5	0.48	5	0.49	1.04	0.3-3.58		

Trial Name	N		Length of Treatment (years)	Length of FU (years)	Placebo		Tamoxifen		RR	95% CI	Outcome assessment
	Placebo	Tamoxifen			No.	Rate	No.	Rate			
Veronesi, 2007[29]:					21	2.01	35	3.48	1.73	1.01-2.98	Cardiac Arrhythmias, Atrial Fibrillation
IBIS											
Cuzick, 2007[20] CHD events	3575	3579	5	96 months	71	2.73	64	2.37	1.15	0.81-1.64	Checklist of predefined side effects asked directly during main trial
All cardiac Active					71	3.98	64	3.59	0.9	0.63-1.28	Mailed questionaires during follow-up
Post					52	4.85	58	5.42	1.12	0.75-1.66	Illnesses confirmed with record review
MI; Active					7	0.39	2	0.11	0.29	0.03-1.5	
Post					8	0.75	7	0.65	0.88	0.27-2.76	
NSABP											
Fisher, 2005[23] Total CHD	6707	6681	5	7	109	2.7	113	2.79	1.03	0.79-1.36	Total CHD includes: MI, acute coronary syndrome, severe angina
Fisher, 1998[24] Total CHD			5	69 months	62	2.37	71	2.73	1.15	0.81-1.64	
Fisher, 2005[23] MI					44	1.09	43	1.06	0.97	0.62-1.52	
Fisher, 2005[23] ACS					32	0.79	36	0.89	1.12	0.68-1.86	
Fisher, 2005[23] Severe angina					33	0.82	34	0.84	1.03	0.62-1.71	
Fisher, 1998[24] MI	6707	6681	4	4	28	1.07	31	1.19	1.11	0.65-1.92	

Cardiovascular Outcomes- Raloxifene Trials

Trial Name	N Placebo	N R60	N R120	Length of Treatment (years)	Length of FU (years)	Placebo No.	Placebo Rate	R 60 No.	R 60 Rate	R 120 No.	R 120 Rate	RR	95% CI	Notes
MORE														
Keech, 2005[41] Cumulative CVD events (MI, CVA, CABG, PCA)	2576	2557		4	1	23		25						P time trend 0.575
					2	47		40						
					3	71		76						
					4	96		82						
Barret-Connor, 2002[32]: CHD	2576	5129		3.4	3.4	55		45				0.88	0.53-1.40	60 mg
										56		1.02	0.71-1.47	120 mg
RUTH														
Barrett-Connor, 2006[46] Coronary events (death from coronary causes, non-fatal MI, ACS)	5057	5044			5	553		533				0.95	0.84-1.07	
Death CVD (CVD causes, MI, stroke, ACS)						1041		1067				1.01	0.93-1.10	
Fatal CHD						273		253				0.92	0.77-1.09	
Non-fatal MI						208		183				0.87	0.71-1.06	

Cardiovascular Outcomes- LIFT trial

	N Placebo	N Tibolone	Length of Treatment	Placebo No.	Placebo Rate	Tibolone No.	Tibolone Rate	RR	95% CI	Notes
CHD	2257	2249	34 m	20	3	27	4.1	1.37	0.77-2.45	p=0.28
Sinus bradycardia	2257	2249	34m	52	NR	33	NR	NR	NR	p=0.008

Stroke- STAR

Trial Name	N		Length of Treatment (years)	Length of FU (years)	Tamoxifen		Raloxifene		RR	95% CI	Notes
	Tamoxifen	Raloxifene			No.	Rate	No.	Rate			
STAR											
	9726	9745	5	6	53	1.39	51	1.33	0.96	0.92-1.32	R/T

Stroke- Tamoxifen trials

Trial Name	N		Length of Treatment (years)	Length of FU (years)	Placebo		Tamoxifen		RR	95% CI	Notes
	Placebo	Tamoxifen			No.	Rate	No.	Rate			
Royal Marsden											
Powles, 2007[26]: Active	1233	1238	7.8	13	9	0.94	7	0.72	0.76*	0.28-2.05*	P = 0.6; Stroke not defined
Powles 2007[26]: Post					7	0.93	3	0.41	0.44*	0.11-1.69*	P = 0.3
Italian											
Veronesi, 2007[29] All cerebro-vascular	2708	2700	4	11	7	0.67	12	1.19	1.78	0.70-4.52	only includes AEs during active treatment
Veronesi, 2007[29] Stroke only			4	11	2	0.19	6	0.59	3.11	0.63-15.4	Stroke not further defined
IBIS											
Cuzick, 2007[20]: Active	3575	3579	5	5	8.5	0.45	8	0.45	1	0.33-3.06	Stroke not further defined
Cuzick, 2007[20]: Post			5	3	3	0.37	7	0.65	1.75	0.45-8.16	
NSABP											
Fisher, 1998[24]	6707	6681	4	4	24	0.91	38	1.45	1.59	0.93-2.77	

Trial Name	N		Length of Treatment (years)	Length of FU (years)	Placebo		Tamoxifen		RR	95% CI	Notes
	Placebo	Tamoxifen			No.	Rate	No.	Rate			
Fisher, 2005[23]	6707	6681	5	7	50	1.23	71	1.75	1.42	0.97-2.08	Stroke not further defined
Age ≤ 49					8	0.5	9	0.57	1.13	0.39-3.36	
Age ≥ 50					42	1.7	62	2.5	1.47	0.97-2.22	

Stroke- Raloxifene trials

Trial Name	N			Length of Treatment (years)	Length of FU (years)	Placebo		R 60		R 120		RR	95% CI	Notes
	Placebo	R60	R120			No.	Rate	No.	Rate	No.	Rate			
MORE														
Barrett-Connor, 2002[32]	2576	2557	2572	3.4	4	32		22		26		0.69	0.40-1.18	Raloxifene 60mg
												0.81	0.49-1.36	Raloxifene 120mg
CORE														
NR														
RUTH														
Barrett- Connor, 2006[46]	5057	5044		5.6	5.6	224	7.97	249	8.88			1.10	0.92-1.32	

Stroke- LIFT Trial

N		Length of Treatment	Placebo		Tibolone		RR	95% CI	Notes
Placebo	Tibolone		No.	Rate	No.	Rate			
2257	2249	34 months	13	1.9	28	4.3	2.19	1.14-4.23	> 70 yrs 6.6; 60-69 yrs 3.4. includes ischemic and hemorrhagic stroke

Transient Ischemic Attack- STAR

Trial Name	N Tamoxifen	N Raloxifene	Length of Treatment (years)	Length of FU (years)	Tamoxifen No.	Tamoxifen Rate	Raloxifene No.	Raloxifene Rate	RR	95% CI	Notes
STAR											
	9726	9745	5	6	41	1.08	50	1.3	1.21	0.79-1.88	R/T

Transient Ischemic Attack- Tamoxifen trials

Trial Name	N Placebo	N Tamoxifen	Length of Treatment (years)	Length of FU (years)	Placebo No.	Placebo Rat e	Tamoxifen No.	Tamoxifen Rate	RR	95% CI
Royal Marsden										
Powles, 2007[26]: Active	NR									
Post	NR									
Italian										
Veronesi, 2007[29]	2708	2700	4	5	5	0.48	6	0.59	1.24	0.38-4.08
IBIS										
Cuzick, 2007[20]: Active	3575	3579	5	5	9	0.5	4	0.22	0.44	0.11-1.57
Post			5	3	13	1.21	13	1.21	1	0.43-2.34
NSABP										
Fisher, 2005[23]	6707	6681	7		34	0.84	31	0.76	0.91	0.54-1.52
Age ≤ 49					7	0.44	4	0.25	0.57	0.12-2.25
Age ≥ 50					27	1.1	27	1.09	0.99	0.56-1.76
Fisher, 1998	6707	6681	4	4	25	0.95	19	0.73	0.76	0.40-1.44

Transient Ischemic Attack- LIFT trial

	N Placebo	N Tibolone	Length of Treatment	Placebo No.	Placebo Rate	Treatment No.	Treatment Rate	RR	95% CI	notes
TIA	2257	2249	34 months	0.20%	NR	0.30%	NR	NR	NR	Reported as rare

Genitourinary Outcomes

Uterine Outcomes- STAR

Trial Name	N Tamoxifen	N Raloxifene	Length of Treatment (years)	Length of FU (years)	Tamoxifen No.	Tamoxifen Rate	Raloxifene No.	Raloxifene Rate	RR	95% CI	Notes
STAR											
Hyperplasia	9726	9745	5	6	84	4.69	14	0.76	0.16	0.09-0.29	
Hysterectomy					244	13.57	111	6.04	0.44	0.35- 0.56	
Uterine bleeding						NR		NR			
Uterine cancer						2		1.25	0.62	0.35-1.08	

Uterine Outcomes- Tamoxifen trials

Trial Name	N Placebo	N Tamoxifen	Length of Treatment (years)	Length of FU (years)	Placebo No.	Placebo Rate	Tamoxifen No.	Tamoxifen Rate	RR	95% CI	Notes
Royal Marsden											
Powles, 2007[26]	1233	1238	_	13.2	5	0.29	13	0.76	2.59	0.93-7.24	Entire trial period
Hysterectomy					96		177				
Period abnormality					439		496				Active Treatment
Period abnormality					87		119				Post Treatment
IBIS											
Total Uterine cancer	2292	2347		8	11	0.60	17	0.91	1.51	0.71-3.23	Active and post
Vasomotor/Gyn					1983		2389		1.2	1.16-1.25	Active Treatment
Vasomotor/Gyn					1438		1508		1.06	0.99-1.12	Post Treatment
NSABP											
Fisher, 2005[23]	4194	4097	5 Y	7	17	0.68	53	2.24	3.28	1.87-6.03	
Uterine cancer cumulative											
Uterine <49					9	0.82	12	1.16	1.42	0.55-3.81	
Uterine cancer ≥ 50					8	0.58	48	3.08	5.33	2.47-13.17	
Fisher, 1998[24]	4194	4097		4	15	0.91	36	2.3	2.53	1.35-4.97	

Uterine Outcomes- Raloxifene trials

Trial Name	N Placebo	N R60	N R120	Length of Treatment (years)	Length of FU (years)	Placebo No.	Placebo Rate	R 60 No.	R 60 Rate	R 120 No.	R 120 Rate	RR	95% CI	Notes
MORE														
Grady, 2004[39] Endometrial cancer	1999	3960		3.3	3.3	5	NR	9	NR			0.9	0.3	
Uterine bleeding						72		79		65				P 0.946
Endometrial cavity fluid						76		99		111				P 0.009
CORE														
Martino, 2004[51] Endometrial hyperplasia					4	2	0.2	1	0.05					P 0.24
Endometrial hyperplasia					8	3	0.29	8	0.37					P > 0.99
RUTH														
Barrett-Connor, 2006[46] Endometrial Cancer	3882	3900		5.6	5.6	17	0.79	21	0.97			1.23	0.65-2.33	P>0.53
Benign uterine/ uterine bleeding						107		102						P > 0.74
Uterine sarcoma						0		1						
Ovarian cancer						10		17						P 0.17

Vaginal Outcomes- Tamoxifen trials	N		Length of Treatment (years)	Length of FU (years)	Placebo		Tamoxifen				
Trial Name	**Placebo**	**Tamoxifen**			**No.**	**Rate**	**No.**	**Rate**	**RR**	**95% CI**	**Notes**
Royal Marsden											
Powles, 2007[26]	1233	1238	8	13.2							
vaginal discharge					167		321				Active Treatment P < 0.001
Vaginal discharge					17		41				Post Treatment P < 0.001
Vaginal symptoms					17		37				Active Treatment P = 0.008
Vaginal symptoms					0		1				Post Treatment P = 0.5
Italian											
Veronesi, 2007[29]: Vaginal dryness	1697	1638	5	11.2		29.9		34.1	1.14	0.97-1.34	
Vaginal discharge						17.6		66.6	3.44	2.9-4.09	
IBIS											
Cuzick, 2002[19] "gynecologic or vasomotor"	3566	3573	5	50 months	2414		2922				P < 0.0001
NSABP											
Fisher, 1998[24]: Vaginal discharge moderately to more bothersome	6707	6681	5	5	13%		29%				

Vaginal Outcomes- Raloxifene trials

Trial Name	N Placebo	N R60	N R120	Length of Treatment (years)	Length of FU (years)	Placebo No.	Placebo Rate	R 60 No.	R 60 Rate	R 120 No.	R 120 Rate	RR	95% CI	Notes
MORE														
Cauley, 2001[33]	2576	2557	2572	3	4									Other than bleeding; not different than placebo (P>0.7) P 3.6%, R60 4.1%, R120 3.2%
RUTH														
NR														

Vaginal Outcomes – LIFT Trial

	N Placebo	N Tibolone	Length of Treatment	Placebo No.	Placebo Rate	Tibolone No.	Tibolone Rate	RR	95% CI	Notes
vaginal infection	2257	2249	34 months	56	NR	186	NR	NR	NR	p=0.007
vaginal discharge	2257	2249	34 months	40	NR	221	NR	NR	NR	p<0.001
vaginal bleeding	1773	1746	34 months	45	NR	165	NR	NR	NR	Those with uterus; p <0.001

Urinary Outcomes- STAR

Trial Name	N Tamoxifen	N Raloxifene	Length of Treatment (years)	Length of FU (years)	Tamoxifen No.	Tamoxifen Rate	Raloxifene No.	Raloxifene Rate	RR	95% CI
STAR										
Bladder Cancer	9726	9745	5	6		0.18		0.16	0.85	0.24-2.96

Urinary Outcomes- Tamoxifen trials

Trial Name	N Placebo	N Tamoxifen	Length of Treatment (years)	Length of FU (years)	Placebo No.	Placebo Rate	Tamoxifen No.	Tamoxifen Rate	RR	95% CI	Notes
Royal Marsden											
Bladder symptoms	1233	1238	8	13.2	25		27				Active Treatment P=0.9
Post					1		3				P = 0.4
Italian											
Active	2708	2700	5	11	140	14.4	202	21.9	1.52	1.23-1.89	
IBIS											
NR											
NSABP											
NR											

Breast Outcomes

Breast Density Outcomes- Tamoxifen trials

Trial Name	N Placebo	N Tamoxifen	Length of Treatment (years)	Length of FU (years)	Placebo No.	Placebo Rate	Tamoxifen No.	Tamoxifen Rate	RR	95% CI	Notes
Royal Marsden											
NR											
Italian											
NR											
IBIS											
Cuzick, 2004[58]	430	388	18	18	3.50%		7.90%				Decreased density
				54 months	7.30%		13.70%				Decreased density
NSABP											
Brisson, 2000[55]	33	36	3.3-3.5	1.0 - 3.4							Women with lower breast density: 38.5% (T) vs 6.7% (P); P = 0.069
				3.5 - 5							47.8% vs 22%, P=0.114

ER Negative Breast Cancer- STAR

Trial Name	N Tamoxifen	N Raloxifene	Length of Treatment (years)	Length of FU (years)	Tamoxifen No.	Tamoxifen Rate	Raloxifene No.	Raloxifene Rate	RR	95% CI	Notes
STAR											
Vogel, 2006[12]	9726	9745	5	6	44	1.16	51	1.34			R/T 1.15 (0.75-1.77)

ER Negative Breast Cancer- Tamoxifen trials

Trial Name	N Placebo	N Tamoxifen	Length of Treatment (years)	Length of FU (years)	Placebo No.	Placebo Rate	Tamoxifen No.	Tamoxifen Rate	RR	95% CI
Royal Marsden										
Powles, 2007[26]	1233	1238		13.24	17	1	24	1.4	1.4	0.7-2.6
Italian										
Veronesi, 2007[29]	2708	2700		11	19	0.64	21	0.7	1.1	0.59-2.05
IBIS										
Cuzick, 2007[20]	3375	3579	5	8	35	1.23	35	1.23	1	0.61-1.65
NSABP										
Fisher,1998[24]	6599	6576	5	47.7 months	1	1.2		1.46	1.22	0.74-2.03
Fisher, 2005[23]			5	7	42	1.06	56	1.39	1.31	0.86-2.01

ER negative Breast Cancer- raloxifene trials

Trial Name	N Placebo	N R60	N R120	Length of Treatment (years)	Length of FU (years)	Placebo No.	Placebo Rate	R 60 No.	R 60 Rate	R 120 No.	R 120 Rate	RR	95% CI
MORE	2576	2557	2572		4	4		9				1.13	0.35-3.66
CORE													
Martino, 2004[51]	1286	2725			4	3	0.55	7	0.61			1.13	0.29 - 4.35
RUTH													
Barrett-Connor, 2006[46]	5057	5044			5.6	9		13				1.44	0.61 - 3.36

Breast Outcomes – LIFT Trial

	N		Length of	Placebo		Tibolone				
	Placebo	Tibolone	Treatment	No.	Rate	No.	Rate	RR	95% CI	Notes
Breast Discomfort	2257	2249	34 months	65	NR	203	NR	NR	NR	P<0.001

Opthalmalogic Disorders

Opthalmologic Outcomes- STAR

	N		Length of	Length	Tamoxifen		Raloxifene				
Trial Name	Tamoxifen	Raloxifene	Treatment (years)	of FU (years)	No.	Rate	No.	Rate	RR	95% CI	Notes
STAR											
Cataracts	9726	9745	5	6	394	12.3	313	9.7	0.79	0.68-0.92	Self report
Cataracts surgery					260	8	215	6.6	0.82	0.68-0.99	

Opthalmologic Outcomes- Tamoxifen trials

	N		Length of Treatment	Length of	Placebo		Tamoxifen				
Trial Name	Placebo	Tamoxifen	(years)	FU (years)	No.	Rate	No.	Rate	RR	95% CI	Notes
Royal Marsden											
Powell, 2007[26] Cataracts	1233	1238	8	13.2	3	0.18	12	0.70	3.99	1.13-14.14	Active Treatment
Italian											
Veronesi, 2007[29] "Opthamologic diseases"	2708	2700	5	11	118	11.65	112	11.39	0.98	0.75- 1.27	Active Treatment
IBIS											
Cuzick, 2007[20]: Cataracts	3575	3579	60 months	96 months	34	1.90	29	1.63	0.85	0.52-1.40	Active
Cataracts : Post					20		38		1.92	1.12 - 3.29	Active
Eye complaints : Active					896		901		1	0.93 - 1.09	Self report
Eye complaints: Post					597		622		1.05	0.95 - 1.17	
NASABP											
Fisher, 2005[23]: Cataracts	6131	6101	5	7		22.9		27.8	1.21	1.10-1.34	
Cataracts surgery						7.58		10.54	1.39	1.19-1.63	
Fisher, 1998[24]: Cataracts	6131	6101	5	69 months	507	21.72	574	24.82	1.14	1.01-1.29	
Cataracts surgery					73	3	114	4.72	1.57	1.16-2.14	

Opthalmologic Outcomes- Raloxifene trials

Trial Name	N Placebo	N R60	N R120	Length of Treatment (years)	Length of FU (years)	Placebo No.	Placebo Rate	R 60 No.	R 60 Rate	R 120 No.	R 120 Rate	RR	95% CI	Notes
MORE														
Grady, 2004[39]: Cataracts	2576	5129			3.3	160		291				0.9	0.8-1.1	Self report
Cataracts surgery					3.3	86		163				1	0.7-1.2	
CORE														
RUTH														
Barrett-Connor, 2006[46] Cataracts	5057	5044			5.6	391	13.91	374	13.34			0.96	0.83-1.11	P = 0.56 Unsolicited Self report

Gastrointestinal Disorders

Gastrointestinal Outcomes – LIFT Trial

	N Placebo	N Tibolone	Length of Treatment	Placebo No.	Placebo Rate	Tibolone No.	Tibolone Rate	RR	95% CI	Notes
Gastroenteritis	2257	2249	34 months	87	NR	57	NR	NR	NR	P<0.01

Other Adverse Events That Impact Quality of Life

Vasomotor Outcomes- tamoxifen trials

Trial Name	N		Length of Treatment (years)	Length of FU (years)	Placebo		Tamoxifen		RR	95% CI	Notes
	Placebo	Tamoxifen			No.	Rate	No.	Rate			
Royal Marsden											
Powles, 2007[26] Hot flashes	1233	1238	8	13.2	394		598				Active P<0.001
Post					47		73				P < 0.001
Vasomotor: Active					96		162				P < 0.001
Post					10		19				P = 0.1
Italian											
Veronesi, 2007[29] Hot flashes	1697	1638	5	11.2	446	67.2	635	119.3	1.78	1.57-2.0	
IBIS											
Cuzick, 2007[20] Gynecologic & vasomotor	3566	3573	5	50	1983		2389		1.2	1.16-1.25	Predefined categories, can't separate gyn/vm
Gynecologic : Post					1438		1508		1.06	0.99 - 1.12	
NSABP											
Fisher, 1998[24]	6707	6681	5	69 months	28.70 %		45.70%				Hot flashes moderately or more bothersome

Weight Outcomes – LIFT Trial

	N		Length of	Placebo		Tibolone				
	Placebo	Tibolone	Treatment	No.	Rate	No.	Rate	RR	95% CI	Notes
Weight Gain	2121	2050	34 months	81	NR	109	NR	NR	NR	NR

Mortality

Total Death- STAR

	N		Length of Treatment	Length of	Tamoxifen		Raloxifene			
Trial Name	Tamoxifen	Raloxifene	(years)	FU (years)	No.	Rate	No.	Rate	RR	95% CI
STAR					101	2.64	96	2.49	0.94	0.71-1.26

Total Death- Tamoxifen

	N		Length of Treatment	Length of	Placebo		Tamoxifen				
Trial Name	Placebo	Tamoxifen	(years)	FU (years)	No.	Rate	No.	Rate	RR	95% CI	Notes
Royal Marsden											
Powles, 1998[25]: Total deaths					9		6				
Powles, 1998[25]: Deaths-Breast Cancer					5		5				
Powles, 2007[26]	1233	1238	8	13.2	54		54		0.99	0.68-1.44	P = 0.99
Italian											
Veronesi, 2007[29]	1697	1638	5	11.2	38		36		0.95	0.6-1.49	
IBIS											
Cuzick, 2002[19]	3566	3573	5	50 months	11		25		1.55	0.68-3.65	P=0.028
Cuzick, 2007[20]			5	96 months	55		65		1.18	0.81-1.73	
NSABP											
Fisher, 2005[23]	6707	6681	5	7	114	2.8	126	3.08	1.1	0.85-1.43	
Fisher, 1998[24]			5	69 months	71		57		0.81	0.56-1.16	

Total Death- Raloxifene trials

Trial Name	N			Length of Treatment (years)	Length of FU (years)	Placebo		R 60		R 120				
	Placebo	R60	R120			No.	Rate	No.	Rate	No.	Rate	RR	95% CI	Notes
MORE														
Barrett-Connor, 2004[31]	2576	2557	2572		4	36		62				0..85	0.56-1.28	Raloxifene 60 + 120mg
CORE														
Martino, 2005[43]					4	29		47						P=0.27
RUTH														
Barrett-Connor, 2006[46]	5057	5044		5.6	5.6	595		554				0.92	0.82-1.03	

Total Death

Total Death- LIFT trial

N		Length of Treatment	Placebo		Tibolone				
Placebo	Tibolone		No.	Rate	No.	Rate	RR	95% CI	Notes
2257	2249	34 m	28	1.2	26	1.2	NR	NR	p=0.89

Raloxifene Trials

Outcome	Morii, 2003[82]	Delmas, 1997[74]	Cohen, 2000[73]	McClung, 2006[80]	Lufkin, 1998[79]	Nickelsen, 1999[83]	Meunier, 1999[81]	Jolly, 2003[78]
Leg cramps	o			+				o
Anxiety								
Depression / mood change						o		
Ovarian cancer								
Vaginal bleeding	o	o	o	o	o			o
Urinary symptoms								
Sexual symptoms								
Gynecologic		o			o			
Breast symptoms	o	o		o	o			
GI symptoms	+							
Headaches								
Peripheral edema								
Weight gain								
Influenza syndrome								
Flushing	o	o		+		o	o	+
Malaise /lethargy	+ **							
Pain/ joint pain					+			

Outcome	Raloxifene Trials				Tibolone Trials		
	Goldstein, 2005[76]	Palacios, 2004[84]	Walsh, 1998[85]	Johnston, 2000[77]	Bots, 2001[89] Langer, 2006[90]	Landgren, 2002[91]	Gallagher, 2001[92]
Leg cramps				o			
Anxiety							o
Depression / mood change		o					
Ovarian cancer							
Vaginal bleeding		o	o	o	+		o
Urinary symptoms	o						
Sexual symptoms							
Gynecologic				o	o		
Breast symptoms	o	o	o	o			
GI symptoms				o		o	
Headaches						o	o
Peripheral edema				o			
Weight gain		o	+				o
Influenza syndrome		o					o
Flushing		o	+	+		–	– , o#
Malaise /lethargy		o					
Pain/ joint pain		o				o	o

Tibolone Trials

Outcome	Swanson, 2006[93]	Hudita, 2003[94]	Onalan, 2005[96]	Lundstrom, 2002[95]	Beral, 2003[98], 2005[97]
Leg cramps					
Anxiety					
Depression / mood change			–		
Ovarian cancer					
Vaginal bleeding	o	+, o‡			
Urinary symptoms	–				
Sexual symptoms	–	–			
Gynecologic	o§	-‖			+
Breast symptoms	o	o		o¶	
GI symptoms					
Headaches	o				
Peripheral edema					
Weight gain	o				
Influenza syndrome	o				
Flushing	–	–			
Malaise /lethargy	o				
Pain/ joint pain					

*Statistically significant differences between treatment and placebo groups are indicated by: + outcome increased in treatment groups; - outcome decreased in treatment groups; O no differences between treatment and placebo groups for the outcome; blank cells, outcome not reported.

‡ + at 3 months; O at 6 months

§Uterine spasm, enlarged abdomen, genital pruritus.

‖Vaginal dryness, sexual function.

¶Breast density, breast pain.

- for 2.5 mg/daily; O for 0.3, 0.625, and 1.25 mg/day.

**Comparing 120 mg to placebo or 60 mg.