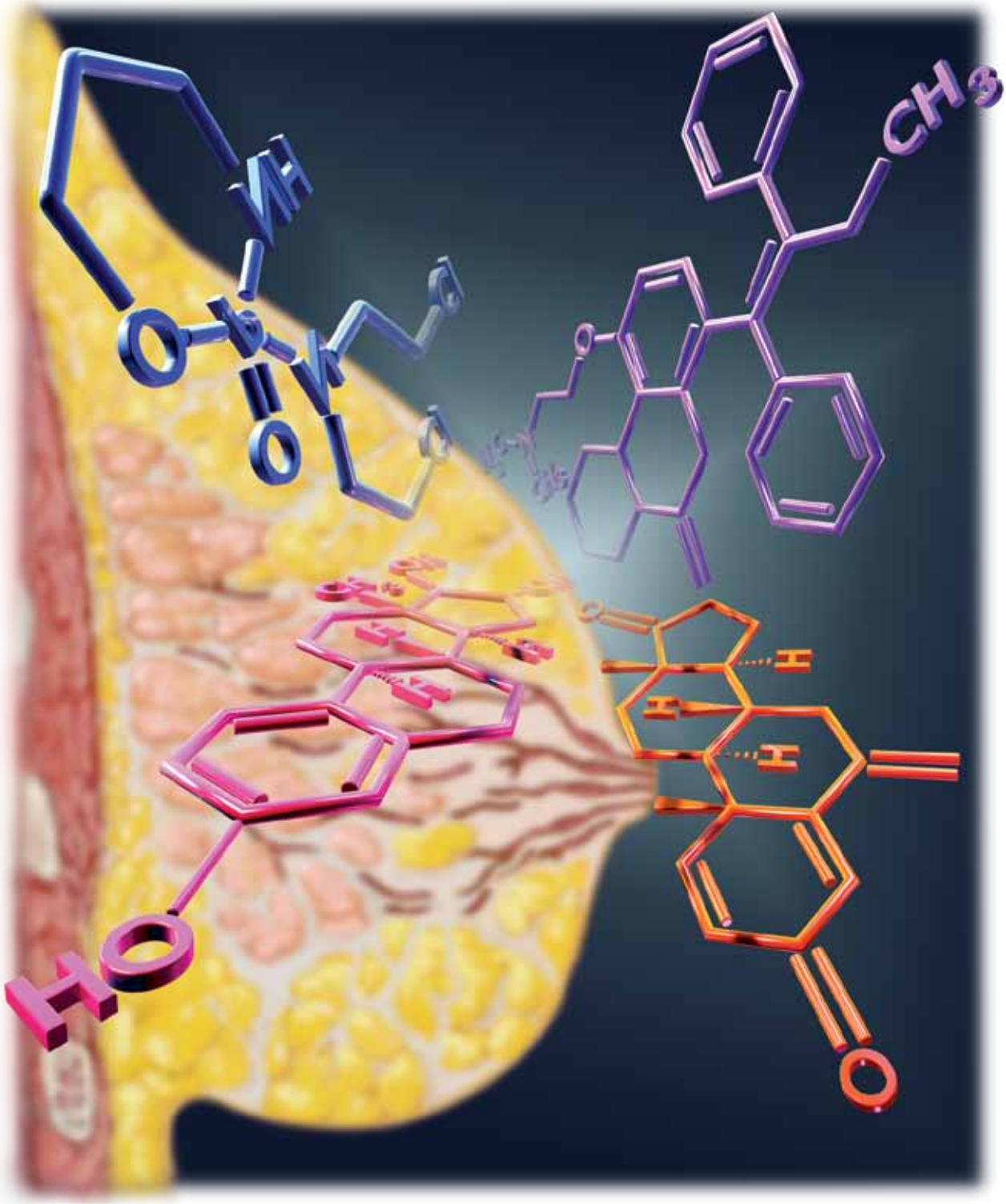

In women at normal risk for breast cancer, unopposed estrogen lowers the rate of the malignancy and the likelihood of mortality if the cancer occurs—but is not recommended as a prophylactic agent. Tamoxifen and other chemoprophylactic drugs can halve the rate of breast cancer in high-risk women but are not without drawbacks.

ILLUSTRATION: CRAIG ZUCKERMAN FOR OBG MANAGEMENT

BREAST HEALTH

A look at findings from the estrogen-alone arm of the WHI, chemoprophylaxis for high-risk women, and fertility preservation for young breast cancer survivors

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The effects of breast cancer on obstetric and gynecologic practices are pervasive. In this article, we touch on three aspects of breast cancer that are particularly relevant to the practicing ObGyn:

- the need to identify women at high risk for breast cancer and select those who would benefit from a discussion of the advantages and risks of chemoprophylaxis, which can reduce the likelihood of breast cancer by 50% or more
- the need for strategies to manage menopausal symptoms in the general population without increasing the risk of breast cancer. The traditional approach to this problem changed dramatically with the Women's Health Initiative (WHI), which demonstrated an increased risk of breast cancer in women taking conjugated equine estrogen and progestin. The widely publicized initial findings of the estrogen-progestin arm of the WHI sharply contrast the equally relevant, somewhat unexpected, and less publicized results of the estrogen-alone arm, which demonstrated a substantial and statistically significant decrease in the incidence of breast cancer, even after estrogen was discontinued.
- the potential effects of breast cancer treatment on ovarian function in young women. This year, of the approximately 250,000 women who will be diagnosed with invasive breast cancer, more than 50,000 women will be of reproductive age. Most of these young women will require adjuvant chemotherapy; as a result, many will experience the premature onset of menopause. Along with the attendant loss of fertility these women will face, many will also develop distressing and life-altering menopausal symptoms. Management of these women before and after initiation of chemotherapy requires an understanding of both the expected effects of the chemotherapy and knowledge of how to actively manage these women with strategies to either prevent these events or to manage menopausal symptoms.

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A look at the lower rate of breast cancer in the estrogen-alone arm of the WHI

Anderson GL, Chlebowski RT, Aragaki AK, et al. Conjugated equine oestrogen and breast cancer incidence and mortality in postmenopausal women with hysterectomy: extended follow-up of the Women's Health Initiative randomised placebo-controlled trial. Lancet Oncol. 2012;13(5):476–486.

FAST TRACK

Women in the estrogen-alone arm of the WHI were 63% less likely to die of breast cancer, compared with women taking placebo

From 1993 through 1998, the WHI enrolled 10,739 postmenopausal women in the largest prospective trial evaluating the effect of hormone therapy (HT) on various clinical outcomes. The women were randomly allocated to three groups:

- conjugated estrogen with medroxyprogesterone acetate
- conjugated estrogen alone (in women with a prior hysterectomy)
- placebo.

The negative effects of estrogen plus progestin on the risk of breast cancer were the most widely discussed oucomes.[1] Shortly after the findings from this arm of the study were published, the use of HT in the United States declined dramatically and unequivocally.[2]

In 2012, WHI published the results of the estrogen-alone arm in the British cancer specialty journal *Lancet Oncology*. As shown in the **TABLE** below, the incidence of breast cancer was statistically significantly lower (23%) in the estrogen group than in the placebo group. Women who were treated with estrogen alone were also 63% less likely to die of breast cancer, and all-cause mortality was 38% lower; both of these findings were statistically significant. Not only was there a significant reduction in the incidence of invasive breast cancer while the subjects were taking estrogen, but that reduction continued for a

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Estrogen alone reduced both breast cancer incidence and breast cancer mortality while women were on therapy and for 5 years after discontinuing therapy. This finding should reassure women who have undergone hysterectomy, as well as their clinicians, that estrogen alone reduces the future likelihood of breast cancer. It should be noted that the effect of estrogen alone in women in higher-risk categories did not show a reduction in breast cancer, and for this reason, the authors cautioned against considering the use of estrogen alone in menopausal women as a breast cancer chemoprophylaxis agent.

Breast cancer incidence and mortality in the estrogen-only arm of the WHI, compared with placebo*

Event	Estrogen only (n = 5,310)	Placebo (n = 5,429)	Hazard ratio (95% confidence interval)
Invasive breast cancer	151 (0.27%)	199 (0.35%)	0.77 (0.62–0.95)
Node-negative breast cancer	88 (0.16%)	134 (0.24%)	0.67 (0.51–0.88)
Breast cancer mortality	6 (0.009%)	16 (0.024%)	0.37 (0.13–0.91)
All-cause mortality	30 (0.046%)	50 (0.076%)	0.62 (0.39–0.97)

* Median follow-up of 11.8 years

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UPDATE
breast health

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median of 4.7 years of follow-up after discontinuation of estrogen.

The incidence figure is somewhat remarkable (199 in the placebo group versus 151 in the estrogen-alone group) in that it was nearly the exact reverse of the estrogen-progestin arm of the WHI trial (199 in the estrogen/progestin group vs 150 in the placebo group).[3]

FAST TRACK

Tamoxifen reduced the risk of invasive breast cancer among women at high risk for the malignancy by 49% in the NSABP P-1 trial

All breast cancer chemoprophylactic agents carry risks as well as benefits

Goss P, Ingle J, Ales-Martinez J, et al. Exemestane for breast-cancer prevention in postmenopausal women. N Engl J Med. 2011;364(25):2381–2391.

Cheung A, Tile L, Cardew S, et al. Bone density and structure in healthy postmenopausal women treated with exemestane for the primary prevention of breast cancer: a nested substudy of the MAP.3 randomized controlled trial. Lancet Oncol. 2012;13(3):275–284.

Vogel V, Costantino J, Wickerham L, et al. Update of the National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene (STAR) P-2 Trial: preventing breast cancer. Cancer Prev Res. 2010;3(6):696–706.

The number of new cases of breast cancer in the United States last year reached nearly a quarter-million. Clearly, reducing this number remains an important goal.[4] Chemoprevention—the use of medication to reduce cancer risk—may be offered to women who are at high risk of developing breast cancer.

In the National Surgical Adjuvant Breast and Bowel Project (NSABP) P-1 trial, tamoxifen (a selective estrogen-receptor modulator) was shown to reduce the risk of invasive breast cancer by 49% in a high-risk population, resulting in the FDA approving tamoxifen as the first drug for breast cancer prevention.[5] The P-1 trial was followed by the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial, which demonstrated relative equivalence between the two medications as cancer prevention agents in menopausal women.[6] Serious side effects of these medications limit their use among eligible women, although raloxifene seems to be associated with fewer adverse events. In the update of the STAR trial with an average of 81 months of follow-up, the risk ratio for adverse events (raloxifene:tamoxifen)

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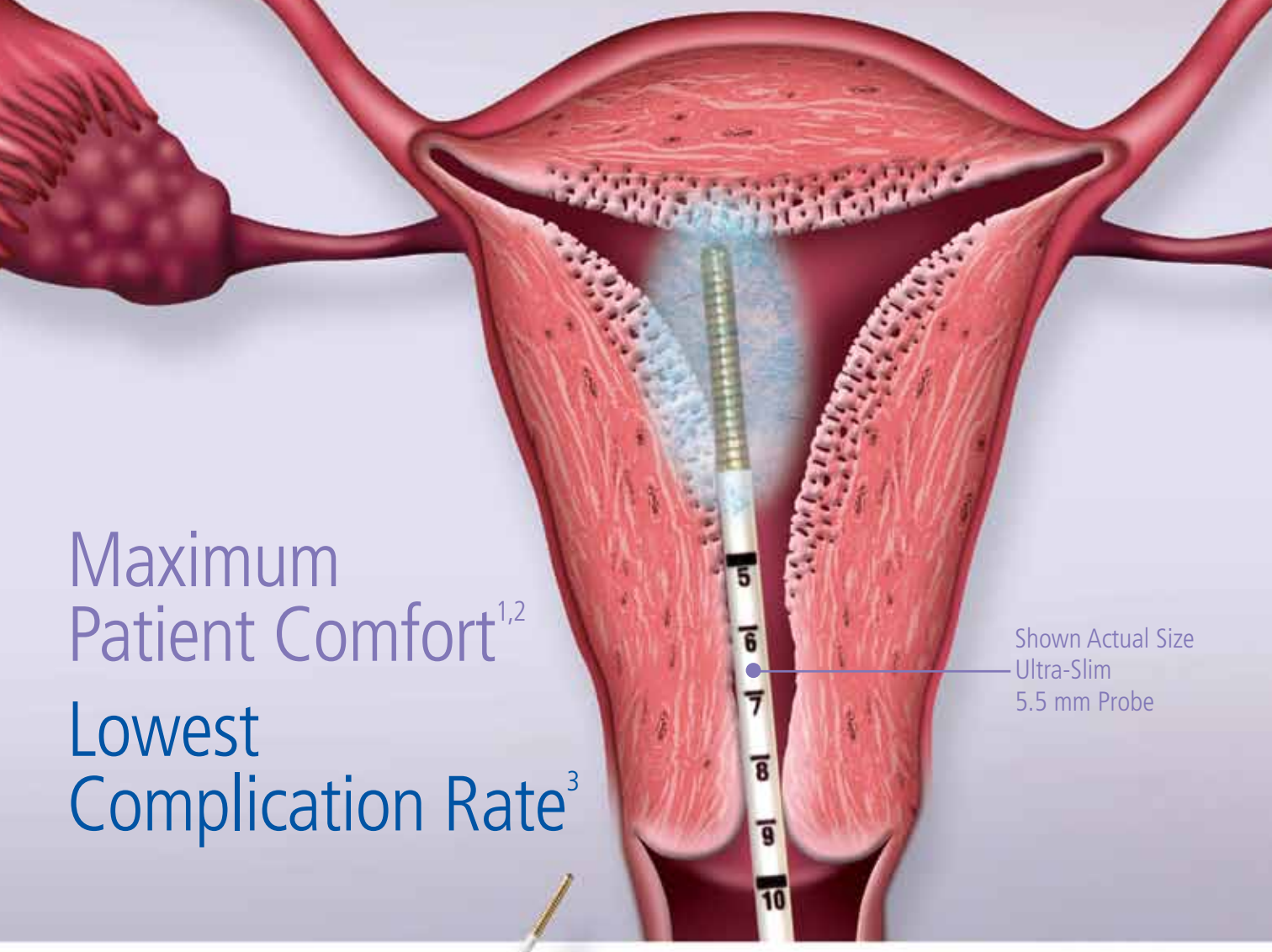

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6 Clark et al; Bipolar Radiofrequency Compaired with Thermal Balloon Endometrial Ablation in the Office; Obstetrics & Gynecology; Jan 2011

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WHAT THIS EVIDENCE MEANS FOR PRACTICE

Chemoprophylaxis reduces the risk of breast cancer in high-risk women by about 50%. Who are good candidates for these medications? Based on these trials, menopausal women considered at high risk might include those with a Gail risk score of at least 1.66% (ie, risk of developing breast cancer in 5 years), age 60 years or older, and women with biopsy results demonstrating atypical hyperplasia or lobular carcinoma in situ (LCIS). (The Gail model is available at www.cancer.gov/bcrisktool.) Tamoxifen is the only option for premenopausal women age 35 and older. Those who have histologic markers of risk (atypical hyperplasia, LCIS) likely stand to derive the greatest benefit.[4]

was 0.75 for thromboembolic events, 0.55 for endometrial cancer, and 0.19 for uterine hyperplasia.

Another drug used for cancer treatment has now entered the prevention scene. In 2011, the NCIC Clinical Trials Group Mammary Prevention.3 trial (NCIC CTG MAP.3) compared exemestane (an aromatase inhibitor) with placebo for menopausal women at high risk for breast cancer, demonstrating a 65% relative reduction in the incidence of invasive breast cancer. This study validated another option for cancer prevention in high-risk women, although its adoption is likely also to be limited by side effects, including vasomotor symptoms, a high rate of arthralgias, and vaginal dryness/dyspareunia. The greatest concern may be the potential effect on bone density. Though the rates of serious adverse events including fracture did not differ in the MAP.3 trial at 35 months of follow-up, women on exemestane had significantly larger losses of bone mineral density, compared with controls.

FAST TRACK

About 1 in every 3,000 breast cancers is diagnosed during pregnancy, lactation, or 12 months postpartum

Managing the reproductive health concerns of young women with breast cancer

Azim H, Kroman N, Paesmans M, et al. Prognostic impact of pregnancy after breast cancer according to estrogen receptor status: a multicenter retrospective study. J Clin Oncol. 2013;31(1):73–79.

Howard-Anderson J, Ganz P, Bower J, Stanton A. Quality of life, fertility concerns, and behavioral health outcomes in younger breast cancer survivors: a systematic review. J Natl Cancer Inst. 2012;104(5):1386–1405.

Of the approximately 230,000 new cases of invasive breast cancer identified in 2011, 50,430 cases involved women less than 50 years of age.[4] For these women, the diagnosis of cancer raises multifaceted concerns, including the physical changes that accompany breast cancer treatment, concerns about recurrence and mortality, and significant sexual and reproductive consequences of treatment that alters ovarian function. Pregnancy-associated breast cancers (breast cancers diagnosed during pregnancy, lactation, and for 12 months postpartum) represent a small subset of these cancers and occur in about 1 in 3,000 pregnancies. One might anticipate that this rate will increase as women continue to delay childbearing, because pregnancy-associated breast cancers are more common in older women.

In the review article by Howard-Anderson and colleagues, the importance of these reproductive health consequences in young women diagnosed with breast cancer is highlighted. The women who transition to menopause as a result of chemotherapy (reported to range from 33%–73%) experience more symptoms, including hot flashes, night sweats, breast pain, vaginal dryness, and lack of sexual desire. Sixty-one percent of women younger than 40 years at diagnosis

reported that they were concerned about menopause, and 30% reported that this concern influenced their treatment decisions. Thirty-nine percent of women in this group had major concerns about treatment-associated infertility, and only half of the women studied felt that their fertility concerns were adequately addressed.

On a positive note, for women who successfully achieve pregnancy after breast cancer, pregnancy outcomes appear to be similar to those of their nonpregnant peers. In the study by Azim and colleagues, women who became pregnant after a breast cancer diagnosis had disease-free survival that was statistically similar to that of matched women who did not have subsequent pregnancies. In addition, this outcome did not differ based on estrogen/progesterone receptor status (ER/PR positive or negative).

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Both alkylating chemotherapeutic agents (eg, cyclophosphamide) and selective estrogen receptor modulating agents (for women with estrogen-receptor–positive tumors) are routine parts of adjuvant treatment for premenopausal women with invasive breast cancers.

These agents can have profound effects on both ovarian hormonal function and fertility. ObGyns and reproductive endocrinology/infertility specialists have a great opportunity to partner with our oncology colleagues to enhance the counseling that young women receive before, during, and after breast cancer treatment.

Women who are considering future childbearing should receive information about the impact of breast cancer treatment on fertility and options for fertility preservation prior to initiating treatment. For women who have completed childbearing, information on what to expect if menopause occurs and available options for symptom relief can be empowering as they make treatment decisions.

References

1. Grady D. Study finds new risks in hormone therapy. New York Times. http://www.nytimes.com/2003/06/25/us/study-finds-new-risks-in-hormone-therapy.html?pagewanted=all&src=pm. Published June 25, 2003. Accessed February 11, 2013.
2. Hersh AL, Stefanick ML, Stafford RS. National use of menopausal hormone therapy: annual trends and response to recent evidence. JAMA. 2004;291(1):47–53.
3. Chlebowski RT, Kuller LH, Prentice RL, et al; Women's Health Initiative Investigators. Breast cancer after use of estrogen plus progestin in postmenopausal women. N Engl J Med. 2009;360(6):573–587.
4. American Cancer Society. Breast Cancer Facts and Figures, 2011–2012. Atlanta, GA: American Cancer Society. http://www.cancer.org/research/cancerfactsfigures/breastcancerfactsfigures/breast-cancer-facts-and-figures-2011-2012. Accessed February 11, 2013.
5. Fisher B, Constantino J, Wickerham L, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Natl Cancer Inst. 1998;90(18):1371–1388.
6. Vogel V, Costantino J, Wickerham DL, et al. Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes. The NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 Trial. JAMA. 2006;295(23):2727–2741.