We are IntechOpen,
the world's leading publisher of
Open Access books
Built by scientists, for scientists

6,900
Open access books available

185,000
International authors and editors

200M
Downloads

154
Countries delivered to

Our authors are among the

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

CLARIVATE ANALYTICS
BOOK CITATION INDEX
INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Reducing the Risk of Endometrial Cancer in Patients Receiving Selective Estrogen Receptor Modulator (SERM) Therapy

Victor G. Vogel
Geisinger Health System
USA

1. Introduction

Selective Estrogen Receptor Modulators (SERMs) are synthetic compounds originally designed as oral contraceptives in the 1960s. During the ensuing decades, they have been shown to be effective for the prevention of both invasive and *in situ* breast cancer, for the treatment and prevention of osteoporosis, and for the primary prevention of breast cancer. This chapter will review the most important agents focusing on their uterine effect derived from dozens of clinical trials that have explored their efficacy for the listed indications. We will compare and contrast the agents and highlight recent development of newer, more efficacious SERMs that have an improved safety profile.

2. Tamoxifen

The finding of a decrease in contralateral breast cancer incidence following tamoxifen administration for adjuvant therapy led to the concept that the drug might play a role in breast cancer prevention. To test this hypothesis, the National Surgical Adjuvant Breast and Bowel Project initiated the Breast Cancer Prevention Trial (P-1) in 1992. Women at increased risk for breast cancer were randomly assigned to receive placebo or 20 mg/day tamoxifen for 5 years (Fisher et al. 1998). Gail's algorithm, based on a multivariate logistic regression model using combinations of risk factors, was used to estimate the risk of occurrence of breast cancer over time.

Tamoxifen reduced the risk of invasive breast cancer by 49%, with cumulative incidence through 69 months of follow-up of 43.4 versus 22.0 per 1000 women in the placebo and tamoxifen groups, respectively. The decreased risk occurred in women aged 49 years or younger (44%), 50–59 years (51%), and 60 years or older (55%); risk was also reduced in women with a history of lobular carcinoma in situ (56%) or atypical hyperplasia (86%) and in those with any category of predicted 5-year risk. Tamoxifen reduced the risk of noninvasive breast cancer by 50% (two-sided P<.002). Tamoxifen reduced the occurrence of estrogen receptor-positive tumors by 69%, but no difference in the occurrence of estrogen receptor-negative tumors was seen. Tamoxifen administration did not alter the average annual rate of ischemic heart disease; however, a reduction in hip, radius (Colles'), and spine fractures was observed.

2.1 Endometrial cancer

The rate of endometrial cancer was increased in the tamoxifen group by more than 2.5-fold (risk ratio = 2.53; 95% confidence interval = 1.35–4.97); this increased risk occurred predominantly in women aged 50 years or older. All endometrial cancers in the tamoxifen group were stage I (localized disease); no endometrial cancer deaths have occurred in this group. No liver cancers or increase in colon, rectal, ovarian, or other tumors was observed in the tamoxifen group. The rates of stroke, pulmonary embolism, and deep-vein thrombosis were elevated in the tamoxifen group; these events occurred more frequently in women aged 50 years or older.

	No. of events		Rate per 1000 women				
Type of cancer	Placebo	Tam	Placebo	Tam	Diff	RR‡	95% CI
Invasive	17	53	0.68	2.24	−1.56	3.28	1.87 to 6.03
≤49 y at entry	9	12	0.82	1.16	−0.34	1.42	0.55 to 3.81
≥50 y at entry	8	41	0.58	3.08	−2.50	5.33	2.47 to 13.17
In situ cancer	3	1	0.12	0.04	0.08	0.35	0.01 to 4.36

Table 1. Events and incidence rates of invasive and *in situ* endometrial cancer in the placebo and tamoxifen groups by age at study entry in the BCPT.

The average annual rate of invasive endometrial cancer per 1000 participants was 2.30 in the tamoxifen group and 0.91 in the placebo group. The increased risk was predominantly in women 50 years of age or older. The relative risk of endometrial cancer was 4.01 (95% CI 4 1.70–10.90) in women aged 50 years or older, and increase in incidence after tamoxifen administration was observed early in the follow-up period. Through 66 months of follow-up, the cumulative incidence was 5.4 per 1000 women and 13.0 per 1000 women in the placebo and tamoxifen groups, respectively. Fourteen (93%) of the 15 invasive endometrial cancers that occurred in the placebo group were International Federation of Gynecology and Obstetrics (FIGO) stage I, and one (7%) was FIGO stage IV. All 36 invasive endometrial cancers that occurred in the group receiving tamoxifen were FIGO stage I. Four *in situ* endometrial cancers were reported; three of these occurred in the placebo group and one in the tamoxifen group. The cumulative incidence of invasive endometrial carcinoma along with other side effects in the trial through seven years of follow-up is shown in Figure 1.

Through 66 months of follow-up, the cumulative incidence was 5.4 per 1000 women and 13.0 per 1000 women in the placebo and tamoxifen groups, respectively. These rates are shown in Figure 2. Fourteen (93%) of the 15 invasive endometrial cancers that occurred in the placebo group were International Federation of Gynecology and Obstetrics (FIGO) stage I, and one (7%) was FIGO stage IV. All 36 invasive endometrial cancers that occurred in the group receiving tamoxifen were FIGO stage I. Four in situ endometrial cancers were reported; three of these occurred in the placebo group and one in the tamoxifen group.
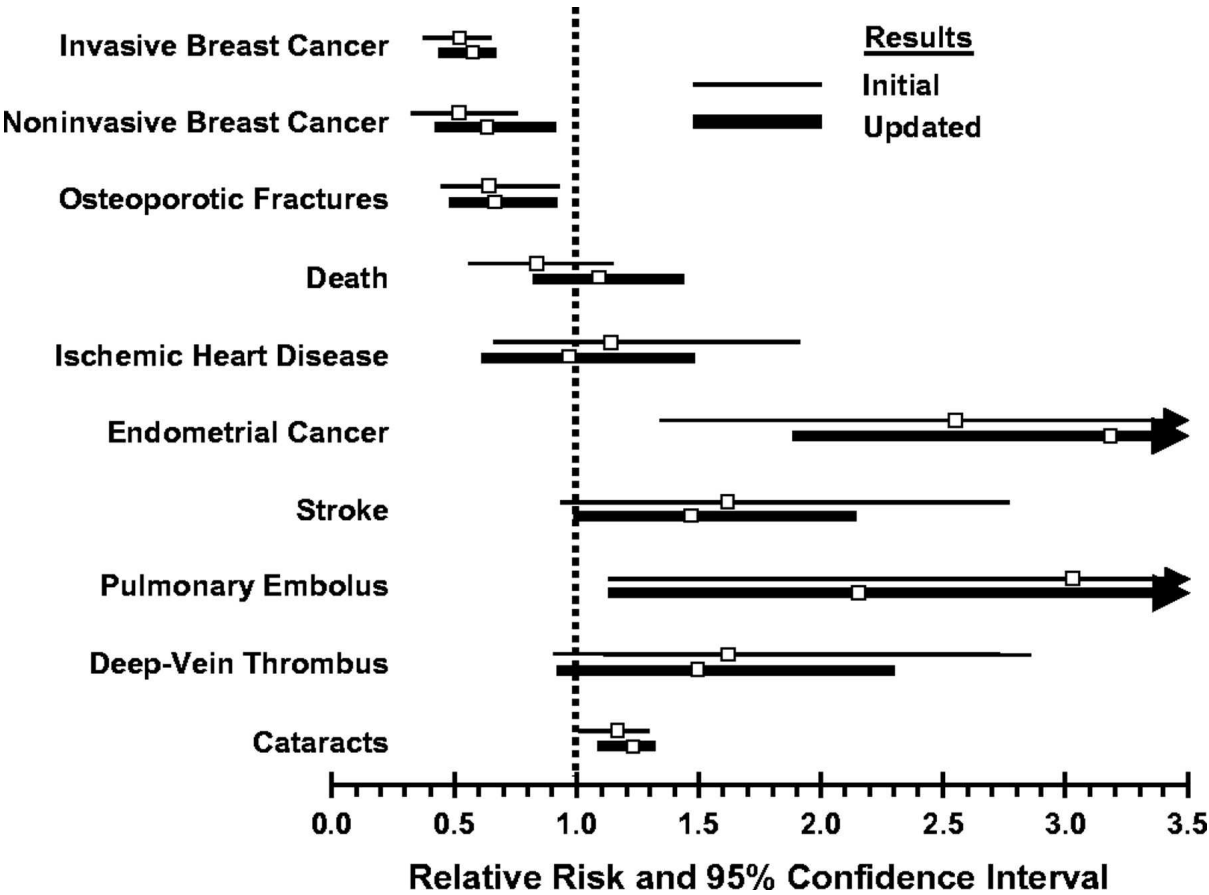
Fig. 1. Comparison of relative risks (with 95% confidence intervals) of benefits and undesirable effects of tamoxifen from the initial and updated results of NSABP P-1. (Fisher 2005).
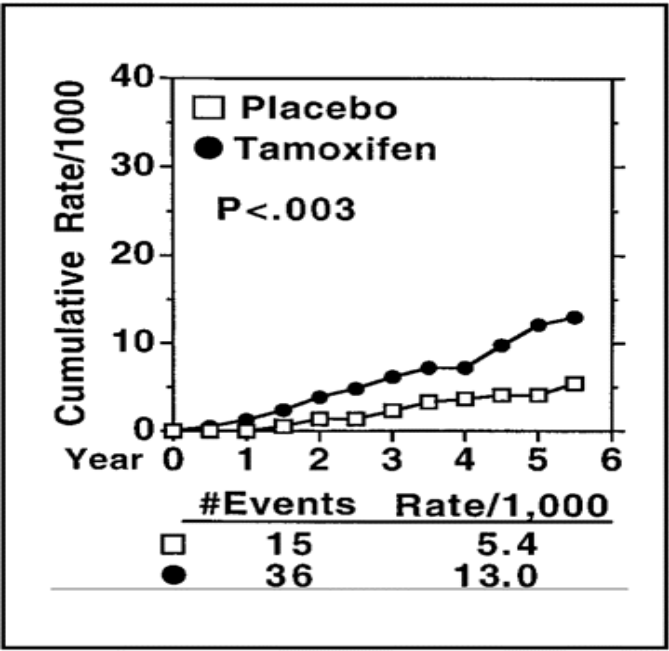

Fig. 2. Cumulative incidence of invasive endometrial carcinoma through seven years of follow-up.

After 7 years of follow-up, women who received tamoxifen still had a statistically significantly increased risk of invasive endometrial cancer (RR = 3.28, 95% CI = 1.87 to 6.03) (Fisher et al. 2005). Again, the risk was not increased in women aged 49 years or younger (RR = 1.42, 95% CI = 0.55 to 3.81), but there was a statistically significant increase in risk in women aged 50 years or older (RR = 5.33, 95% CI = 2.47 to 13.17). The cumulative rate of invasive endometrial cancer through 7 years of follow-up was 4.68 per 1000 women in the placebo group and 15.64 per 1000 women in the tamoxifen group, respectively (*P*<.001). Of the 70 cases of endometrial cancer (17 in the placebo group and 53 in the tamoxifen group), 67 cases (15 in the placebo group and 52 in the tamoxifen group) were International Federation of Gynecology and Obstetrics (FIGO) stage I. Of the remaining two cases in the placebo group, one was stage III and one was stage IV. The remaining case in the tamoxifen group was stage III. Four cases of endometrial cancer *in situ* were observed: three in the placebo group and one in the tamoxifen group. In addition to these cases of endometrial cancer, there were four cases of uterine sarcoma, one in the placebo group and three in the tamoxifen group.

2.2 Gynecologic and vasomotor symptoms

Vaginal discharge was reported in almost 55% of women on tamoxifen in the NSABP-P1 trial, and 78% of women on tamoxifen reported bothersome hot flashes during treatment. Results from the Italian trial, which included only women who had a hysterectomy, also showed a statistically significant increase in vaginal discharge for women taking tamoxifen (RR = 3.44; 95% CI, 2.90 to 4.09).17

3. Raloxifene

Raloxifene was the first of a benzothiophene series of antiestrogens to be labeled a SERM. Raloxifene has the ability to bind to and activate the estrogen receptor while exhibiting tissue-specific effects distinct from estradiol (Vogel 2007). As a result, raloxifene was specifically developed to maintain beneficial estrogenic activity on bone and lipids and antiestrogenic activity on endometrial and breast tissue. In December 1997, the U.S. Food and Drug Administration (FDA) labeled raloxifene for the prevention of osteoporosis. These agents work by inducing conformational changes in the estrogen receptor resulting in differential expression of specific estrogen-regulated genes in different tissues. Activation of the estrogen receptor by raloxifene may involve multiple molecular pathways that may result in gene expression of ligand-, tissue- and/or gene-specific receptors

Raloxifene undergoes extensive systemic biotransformation, but it does not appear to be metabolized by the cytochrome P450 pathway. Clinically significant interactions are unlikely to occur with drugs typically eliminated by this route. Raloxifene has a plasma elimination half-life of approximately 27 hours. This prolonged elimination half-life has been attributed to the drug's reversible systemic metabolism and significant enterohepatic cycling.

Raloxifene appears to lack proliferative effects on endometrial tissue. Data from both animal and human studies demonstrate that raloxifene has minimal effects on the uterus and causes no significant changes in the histologic appearance of the endometrium (Boss et al. 1997). Two six-month studies involving a total of 969 postmenopausal women showed that endometrial thickness did not differ between women receiving raloxifene (30 to 150 mg per day) and those receiving placebo (Delmas et al. 1997).

In healthy, postmenopausal women raloxifene (200 to 600 mg per day given over eight weeks) does not induce endometrial proliferation as measured by endometrial biopsies. By

comparison, 77 percent of the women who receive unopposed estrogen (0.625 mg per day of conjugated estrogen) have moderate to marked estrogenic proliferation of endometrial tissue. Women who received conjugated estrogen were also noted to have a much higher incidence of vaginitis than those who received raloxifene or placebo.

A trial in 136 healthy postmenopausal women compared the stimulatory effects on the uterus of raloxifene (150 mg per day) and continuous hormone replacement therapy (0.625 mg per day of conjugated estrogen with 2.5 mg per day of medroxyprogesterone). After a period of 12 months, the women who received estrogen replacement therapy experienced significant changes in endometrial thickness and uterine volume. In contrast, the women who were treated with raloxifene exhibited no changes in either parameter. Additional short-term trials appear to support the view that raloxifene does not produce endometrial stimulation.

3.1 MORE/CORE trials uterine events

The MORE trial randomized 7,705 postmenopausal women younger than 81 years (mean age= 66.5 years) with osteoporosis to raloxifene or placebo (Cummings et al. 1999). The primary aim of the MORE study was to test whether 3 years of raloxifene reduced the risk of fracture in postmenopausal women with osteoporosis, and the occurrence of breast cancer was a secondary end point. Women were excluded if they took estrogens within 6 months of randomization and were not permitted to take concomitant estrogen replacement therapy with the study drug. With a median follow-up of 40 months, raloxifene reduced the risk of invasive breast cancer by 76% in postmenopausal women with osteoporosis, largely accounted for by a 90% reduction in ER-positive breast cancer. Raloxifene did not reduce the risk of ER-negative breast cancer. There was no apparent decrease in ER-negative cancers. In addition, raloxifene decreased the risk of vertebral fractures and decreased low-density lipoprotein cholesterol levels. Raloxifene did not increase the risk of endometrial cancer, endometrial hyperplasia or vaginal bleeding (Table 2) but was associated with a threefold increase in thromboembolic events. More women in the raloxifene group reported increased rates of hot flashes, leg cramps, and peripheral edema.

The Continuing Outcomes Relevant to Evista (CORE) trial was designed to evaluate the efficacy of an additional 4 years of raloxifene therapy in preventing invasive breast cancer in women who participated in the MORE trial (Martino et al. 2004). CORE was a multicenter, double-blind, placebo-controlled clinical trial. The CORE trial was conducted in the subset of the MORE women who agreed to participate in what was an extension of the MORE trial, with a change in the primary endpoint from vertebral fracture incidence to invasive breast cancer. A secondary objective of the CORE trial was to examine the effect of raloxifene (at 60 mg/day) on the incidence of invasive ER-positive breast cancer. Women who had been randomly assigned to receive raloxifene (either 60 or 120 mg/day) in MORE were assigned to receive raloxifene (60 mg/day) in CORE (n= 3510), and women who had been assigned to receive placebo in MORE continued on placebo in CORE (n=1703). Women in the raloxifene group had a 59% reduction in the incidence of all invasive breast cancer compared with women in the placebo group and a 66% reduction in the incidence of invasive ER-positive breast cancers compared with women in the placebo group. By contrast, the incidence of invasive ER-negative breast cancer in women who received raloxifene was not statistically significantly different from that in women who received placebo. The overall incidence of breast cancer, regardless of invasiveness, was reduced by 50% in the raloxifene group

compared with the placebo group. Again, there was no observed increase in the risk of endometrial cancer attributable to raloxifene.

	CORE enrollees, % (No.)					
	4 years beginning at visit 1 of the CORE trial			8 years beginning at randomization in the MORE trial		
	Placebo group	Raloxifene group†		Placebo group	Raloxifene group§	
Adverse event	(N = 1286)	(N = 2725)	P ‡	(N = 1286)	(N = 2725)	P ‡
Vaginal bleeding[l]	0.20 (2)	0.19 (4)	>.99	1.36 (14)	1.25 (27)	.87
Endometrial hyperplasia[l]	0.20 (2)	0.05 (1)	.24	0.29 (3)	0.37 (8)	>.99
Endometrial cancer[l]	0.30 (3)	0.19 (4)	.69	0.39 (4)	0.32 (7)	.75

[*] CORE = Continuing Outcomes of Relevant to Evista; MORE = Multiple Outcomes of Raloxifene Evaluation.
[†] Dose of 60 mg of raloxifene per day during the CORE trial.
[‡] Based on two-sided Fisher's exact test.
[§] Doses of 60 mg or 120 mg of raloxifene per day during the MORE trial and 60 mg of raloxifene per day during the CORE trial.
[l] Includes only women who had an intact uterus at baseline of the MORE trial. For 4 years beginning at visit 1 of CORE, n = 1008 and n = 2138 for the placebo and raloxifene groups, respectively. For 8 years beginning at randomization in MORE, n = 1026 and n = 2167 for the placebo and raloxifene groups, respectively.

Table 2. Rates of adverse events among the CORE enrollees*.

3.2 RUTH Trial

The Raloxifene Use and the Heart (RUTH) trial randomly assigned 10,101 postmenopausal women (mean age, 67.5 years) with CHD or multiple risk factors for coronary heart disease (CHD) to 60 mg of raloxifene daily or placebo and followed them for a median of 5.6 years (Barrett-Connor et al. 2006). The two primary outcomes were coronary events (i.e., death from coronary causes, myocardial infarction, or hospitalization for an acute coronary syndrome) and invasive breast cancer.

As compared with placebo, raloxifene had no significant effect on the risk of primary coronary events, and it reduced the risk of invasive breast cancer (40 vs. 70 events; hazard ratio, 0.56; 95 percent confidence interval, 0.38 to 0.83; absolute risk reduction, 1.2 invasive breast cancers per 1000 women treated for one year); the benefit was primarily due to a reduced risk of estrogen-receptor–positive invasive breast cancers. There was no significant difference in the rates of death from any cause or total stroke according to group assignment, but raloxifene was associated with an increased risk of fatal stroke. Raloxifene reduced the risk of clinical vertebral fractures. Raloxifene did not significantly affect the risk of CHD. There was no significant difference between the treatment groups in the number of women with one or more reported adverse events. More women in the raloxifene group than in the placebo group permanently discontinued use of the study drug because of an adverse event.

Four common adverse events (an acute coronary syndrome, anxiety, constipation, and osteoporosis) were reported more frequently in the placebo group than in the raloxifene group, and seven (arthritis, cholelithiasis, dyspepsia, hot flush, intermittent claudication, muscle spasm, and peripheral edema) were reported more frequently in the raloxifene group than in the placebo group (P≤0.05). Hot flushes, leg cramps, peripheral edema, and gallbladder disease, all special search categories, were more common in women assigned to raloxifene than to placebo. The rates of cholecystectomy did not differ significantly between the treatment groups (P=0.25). The incidences of endometrial cancer and all cancers other than breast cancer did not differ significantly between treatment groups. Few details were provided about the endometrial cancers that were observed.

3.3 STAR Trial

The Study of Tamoxifen and Raloxifene (STAR Trial) was conducted to compare the relative effects and safety of raloxifene and tamoxifen on the risk of developing invasive breast cancer and other disease outcomes (Vogel et al. 2006). It was carried out by The National Surgical Adjuvant Breast and Bowel Project Study and was a prospective, double-blind, randomized clinical trial conducted in nearly 200 clinical centers throughout North America. Patients were 19,747 postmenopausal women of mean age 58.5 years who had increased 5-year breast cancer risk. Women received either oral tamoxifen (20 mg/d) or raloxifene (60 mg/d) daily over 5 years. Outcome measures included the incidence of invasive breast cancer, uterine cancer, noninvasive breast cancer, bone fractures, and thromboembolic events.

At the time of the planned, initial analysis, there were 163 cases of invasive breast cancer in women assigned to tamoxifen and 168 in those assigned to raloxifene (incidence, 4.30 per 1000 vs. 4.41 per 1000; RR = 1.02; 95% confidence interval [CI], 0.82-1.28). There were 36 cases of uterine cancer with tamoxifen and 23 with raloxifene (RR = 0.62; 95% CI, 0.35-1.08).
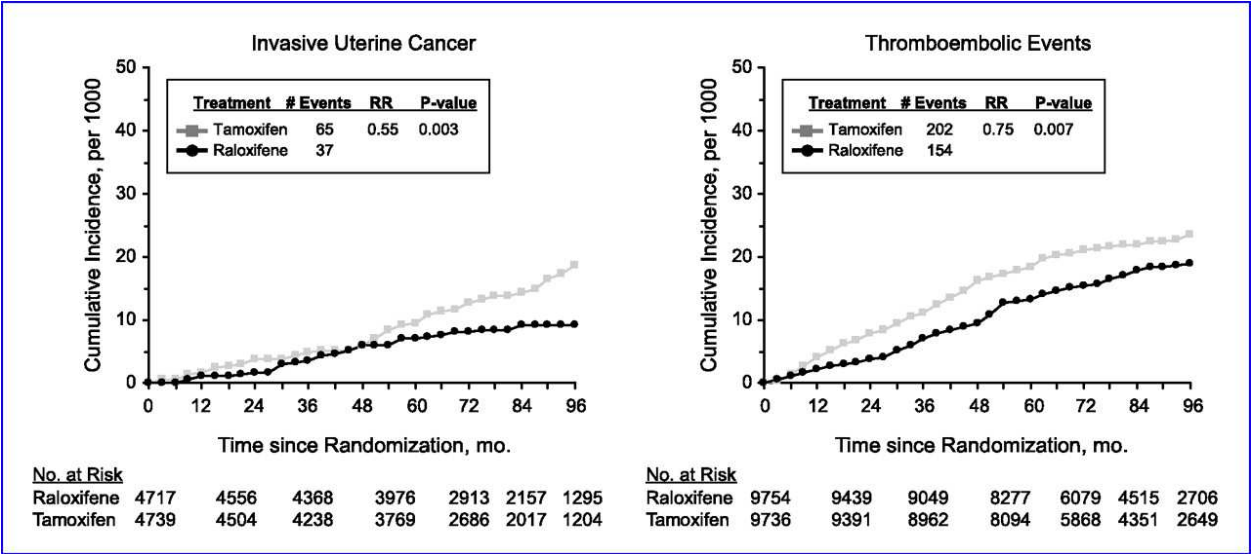

Fig. 3. Invasive uterine cancer and thromboembolic events in the STAR Trial.

After a median of 47 months of follow-up, there was a trend toward a decreased incidence of uterine cancer in the raloxifene group, but the difference was not statistically significant—36 cases (tamoxifen) vs. 23 (raloxifene). Annual incidence rates were 2.00 per 1000

(tamoxifen) and 1.25 per 1000 women (raloxifene) (RR = 0.62; 95% CI, 0.35-1.08). Cumulative incidence rates through 7 years were 14.7 per 1000 (tamoxifen) and 8.1 per 1000 (raloxifene) (P = .07,). These events are shown in Figure 3. Only 1 case of uterine cancer occurred among women younger than 50 years, in a participant in the tamoxifen group. The majority of women who developed uterine cancer (56 [91%]) were diagnosed with stage I disease. Of the remaining cases, there was 1 case of stage II disease in each of the treatment groups, 2 with stage III disease in the raloxifene group, and 1 with stage IV disease in the raloxifene group. Two of these cases were mixed Mullerian cell type; both were in the tamoxifen group.

Table 3 shows that while there were no statistically significant differences with respect to risk of uterine cancer, there were differences between the treatment groups indicating that the effect of raloxifene on the uterus is less than that of tamoxifen. Among those who did not have a diagnosis of uterine cancer, there was a statistically significant difference between the groups in the incidence of uterine hyperplasia. The rates were 84% less in the raloxifene-treated group (14 cases) than in the tamoxifen-treated group (84 cases) (RR, 0.16; 95% CI, 0.09-0.29). This magnitude of difference between treatment groups was evident for hyperplasia both with and without atypia. For the tamoxifen and raloxifene groups, respectively, there were 12 cases and 1 case with atypia (RR, 0.08; 95% CI, 0.00-0.55) and 72 and 13 cases without atypia (RR, 0.18; 95% CI, 0.09-0.32). There also was a statistically significant difference between the treatment groups in the number of hysterectomies performed during the course of follow-up. Among women who were not diagnosed with endometrial cancer, there were 244 hysterectomies performed in those assigned to tamoxifen compared with 111 in those assigned to raloxifene (RR, 0.44; 95% CI, 0.35-0.56).

After 81 months of follow-up, the incidence of invasive uterine cancer was significantly lower in the raloxifene group (Vogel et al. 2010). The annual average rate per 1,000 was 2.25 in the tamoxifen group compared with 1.23 in the raloxifene group (RR = 0.55; 95% CI, 0.36–0.83). In the original report, the difference between treatment groups for the rate of invasive uterine cancer was not statistically significant. The average annual incidence rate of uterine hyperplasia, the majority of which was hyperplasia without atypia, was 5 times higher in the tamoxifen group (4.40 per 1,000) than in the raloxifene group (0.84 per 1,000; RR = 0.19; 95% CI, 0.12–0.29). The number of hysterectomies performed in the tamoxifen group, including those done for benign disease, was more than double that performed in the raloxifene group (RR = 0.45; 95% CI, 0.37–0.54).

Disease/uterine event	Events, *n*		Rate per 1,000			RR*	RR (95% CI)
	Tam	Ralox	Tam	Ralox	Diff		
Uterine disease and hysterectomy							
Invasive Cancer	65	37	2.25	1.23	1.02	0.55	0.36–0.83
Hyperplasia	126	25	4.40	0.84	3.56	0.19	0.12–0.29
Without atypia	104	21	3.63	0.70	2.93	0.19	0.11–0.31
With atypia	22	4	0.77	0.13	0.64	0.17	0.04–0.51
Hysterectomy during follow-up	349	162	12.08	5.41	6.67	0.45	0.37–0.54

Table 3. Uterine Events in the Study of Tamoxifen and Raloxifene (STAR Trial).

Previous studies had shown that raloxifene does not increase the risk of uterine malignancy when compared with placebo. In the STAR trial, only 59 invasive uterine cancers were diagnosed in both study groups during more than 76,000 woman-years of follow-up. As noted above, approximately 25% fewer cases of uterine cancer were diagnosed in the raloxifene than in the tamoxifen group. Although uterine cancer of the mixed Mullerian type occurred in only 2 cases in the tamoxifen group of the STAR trial, there have been isolated case reports of this tumor associated with raloxifene. The rates of uterine cancer were 2.00 per 1000 (tamoxifen) and 1.25 per 1000 (raloxifene), but this difference did not reach statistical significance. Endometrial hyperplasia, however, a risk factor for endometrial cancer, was far more common in the tamoxifen-treated group than in the raloxifene group (RR, 0.16; 95% CI, 0.09-0.29). The number of participants undergoing a hysterectomy for non–cancer-related reasons was significantly reduced 56% in the raloxifene group. It is important to note that the difference between the treatment groups in non–cancer-related hysterectomies has likely caused an underestimate of the true magnitude of endometrial cancer risk associated with tamoxifen and an underestimate of the true magnitude of difference between the two treatment groups for this end point.

These data demonstrate that raloxifene is nearly as effective as tamoxifen in reducing the risk of invasive breast cancer and has a lower risk of thromboembolic events and cataracts but a non-statistically significant higher risk of noninvasive breast cancer.

3.3.1 Summary for uterine cancer, uterine hyperplasia, and hysterectomy for raloxifene and tamoxifen in the STAR Trial

In the STAR Trial, there was a trend toward a decreased incidence of uterine cancer in the raloxifene group, but the difference was not statistically significant—36 cases (tamoxifen) vs. 23 (raloxifene). Annual incidence rates were 2.00 per 1000 (tamoxifen) and 1.25 per 1000 women (raloxifene) (RR, 0.62; 95% CI, 0.35-1.08). Cumulative incidence rates through 7 years were 14.7 per 1000 (tamoxifen) and 8.1 per 1000 (raloxifene) (P = 0.07,). Only 1 case of uterine cancer occurred among women younger than 50 years, in a participant in the tamoxifen group. At the time of analysis, clinicopathological stage was unknown for 3 cases (1 in the tamoxifen group, 2 in the raloxifene group). The majority of the others who developed uterine cancer (56 [91%]) were diagnosed with stage I disease. Of the remaining cases, there was 1 case of stage II disease in each of the treatment groups, 2 with stage III disease in the raloxifene group, and 1 with stage IV disease in the raloxifene group. As noted, two of these cases were mixed Mullerian cell type; both were in the tamoxifen group.

While there were no significant differences with respect to risk of uterine cancer in the STAR trial, there were differences between the treatment groups indicating that the effect of raloxifene on the uterus is less than that of tamoxifen. Among those who did not have a diagnosis of uterine cancer, there was a statistically significant difference between the groups in the incidence of uterine hyperplasia. The rates were 84% less in the raloxifene-treated group (14 cases) than in the tamoxifen-treated group (84 cases). This magnitude of difference between treatment groups was evident for hyperplasia both with and without atypia. For the tamoxifen and raloxifene groups, respectively, there were 12 cases and 1 case with atypia (RR, 0.08; 95% CI, 0.00-0.55) and 72 and 13 cases without atypia (RR, 0.18; 95% CI, 0.09-0.32). There also was a statistically significant difference between the treatment

groups in the number of hysterectomies performed during the course of follow-up. Among women who were not diagnosed with endometrial cancer, there were 244 hysterectomies performed in those assigned to tamoxifen compared with 111 in those assigned to raloxifene (RR, 0.44; 95% CI, 0.35-0.56).

3.3.2 STAR quality of life

No significant differences existed between the tamoxifen and raloxifene groups in patient-reported outcomes for physical health, mental health, and depression, although the tamoxifen group reported better sexual function (Land et al. 2006). Although mean symptom severity was low among these postmenopausal women, those in the tamoxifen group reported more gynecological problems, vasomotor symptoms, leg cramps, and bladder control problems, whereas women in the raloxifene group reported more musculoskeletal problems, dyspareunia, and weight gain.

3.4 Raloxifene summary

The selective estrogen-receptor modulator (SERM) tamoxifen became the first U.S. Food and Drug Administration (FDA)–approved agent for reducing breast cancer risk but did not gain wide acceptance for prevention, largely because it increased the risk of endometrial cancer and thromboembolic events. The FDA approved the SERM raloxifene for breast cancer risk reduction following its demonstrated effectiveness in preventing invasive breast cancer in the Study of Tamoxifen and Raloxifene (STAR). Raloxifene caused less toxicity (versus tamoxifen), including reduced thromboembolic events and endometrial cancer. The risk ratio (RR; raloxifene:tamoxifen) for invasive breast cancer was 1.24 (95% confidence interval [CI], 1.05–1.47) and for noninvasive disease, 1.22 (95% CI, 0.95–1.59). Compared with initial results, the RRs widened for invasive and narrowed for noninvasive breast cancer.

With follow-up extended to 81 months in the STAR Trial, toxicity relative risks (raloxifene:tamoxifen) were 0.55 (95% CI, 0.36–0.83; $P = 0.003$) for endometrial cancer (this difference was not significant in the initial results), 0.19 (95% CI, 0.12–0.29) for uterine hyperplasia, and 0.75 (95% CI, 0.60–0.93) for thromboembolic events. There were no significant mortality differences. Long-term raloxifene retained 76% of the effectiveness of tamoxifen in preventing invasive disease and grew closer over time to tamoxifen in preventing noninvasive disease, with far less toxicity (e.g., highly significantly less endometrial cancer). These results have important public health implications and clarify that both raloxifene and tamoxifen are good preventive choices for postmenopausal women with elevated risk for breast cancer.

Invasive uterine cancer and uterine hyperplasia are well-established toxicities associated with tamoxifen treatment. When compared with tamoxifen, raloxifene does not have such a profile. The incidence of invasive uterine cancer is significantly lower in the raloxifene group ($P = 0.003$). The annual average rate per 1,000 was 2.25 in the tamoxifen group compared with 1.23 in the raloxifene group (RR = 0.55; 95% CI, 0.36–0.83). In the original report of the STAR trial (Vogel et al. 2006), the difference between treatment groups for the rate of invasive uterine cancer was not statistically significant. The average annual incidence rate of uterine hyperplasia, the majority of which was hyperplasia without atypia, was 5 times higher in the tamoxifen group (4.40 per 1,000) than in the raloxifene group (0.84 per

1,000; RR = 0.19; 95% CI, 0.12–0.29). The number of hysterectomies performed in the tamoxifen group (349), including those done for benign disease, was more than double that performed in the raloxifene group (162; RR = 0.45; 95% CI, 0.37–0.54).

4. Lasofoxifene

Lasofoxifene is a nonsteroidal selective estrogen-receptor modulator that decreases bone resorption, bone loss, and low-density- lipoprotein (LDL) cholesterol in postmenopausal women. It is a potent third-generation SERM that was developed because of its potentially attractive pharmacological profile as an agent for risk reduction of fractures, breast cancer, and heart disease in postmenopausal women at increased risk of osteoporotic fractures. Preclinical laboratory evidence showed that lasofoxifene reduced bone loss and cholesterol, prevented experimental breast cancers, and did not cause endometrial hyperplasia (Cummings et al. 2010). Early clinical studies confirmed its potency relative to raloxifene in reducing bone loss and serum cholesterol, whereas neither agent increased the risk for endometrial hyperplasia.

As we have seen, currently available selective estrogen receptor modulators reduce the risk of breast cancer, but they are not widely used. In the Postmenopausal Evaluation and Risk-Reduction with Lasofoxifene (PEARL) trial, lasofoxifene reduced the risk of estrogen receptor–positive breast cancer, non-vertebral and vertebral fractures, coronary artery disease, and stroke.

The effects on total breast cancer (invasive and ductal carcinoma in situ, ER- positive and estrogen receptor–negative) and ER- positive invasive breast cancer were also assessed. Postmenopausal women (n = 8556) aged 59–80 years with low bone density and normal mammograms were randomly assigned to two doses of lasofoxifene (0.25 and 0.5 mg) or placebo. The primary endpoints of the PEARL trial were incidence of ER+ breast cancer and non-vertebral fractures at 5 years (LaCroix et al. 2010). A nested case–control study of 49 incident breast cancer case patients and 156 unaffected control subjects from the PEARL trial was performed to evaluate treatment effects on risk of total and ER- positive invasive breast cancer by baseline serum estradiol and sex hormone–binding globulin levels. Breast cancer was confirmed in 49 women. Compared with placebo, 0.5 mg of lasofoxifene significantly reduced the risk of total breast cancer by 79% (hazard ratio = 0.21; 95% confidence interval [CI] = 0.08 to 0.55) and ER+ invasive breast cancer by 83% (hazard ratio = 0.17; 95% CI = 0.05 to 0.57). The effects of 0.5 mg of lasofoxifene on total breast cancer were similar regardless of Gail breast cancer risk score, whereas the effects were markedly stronger for women with baseline estradiol levels greater than the median (odds ratio = 0.11; 95% CI = 0.02 to 0.51) vs. those with levels less than the median (odds ratio = 0.78; 95% CI = 0.16 to 3.79).

These data confirm that a 0.5-mg dose of lasofoxifene appears to reduce the risks of both total and ER-positive invasive breast cancer in postmenopausal women with osteoporosis.

Lasofoxifene at a dose of 0.5 mg per day, as compared with placebo, is associated with reduced risks of vertebral fracture, non-vertebral fracture, ER-positive breast cancer, coronary heart disease events, and stroke. Lasofoxifene at a dose of 0.25 mg per day, as compared with placebo, is associated with reduced risks of vertebral fracture and stroke. Both the lower and higher doses, as compared with placebo, were associated with an increase in venous thromboembolic events, respectively. Endometrial cancer occurred in

three women in the placebo group, two women in the lower-dose lasofoxifene group, and two women in the higher-dose lasofoxifene group. Endometrial cancers were diagnosed in two women in each lasofoxifene group and three women in the placebo group. Endometrial hyperplasia was confirmed in two women in the higher-dose lasofoxifene group, three women in the lower-dose lasofoxifene group, and no women in the placebo group. This SERM may represent a much safer option than either tamoxifen or raloxifene for the prevention of both osteoporosis and invasive breast cancer.

A prospective study established the gynecological effects of 5 years of treatment with lasofoxifene versus placebo in postmenopausal osteoporotic women (Goldstein et al. 2011). The results are shown in Table 4. A total of 8,556 women aged 59 to 80 years with femoral neck or spine bone mineral density T scores of -2.5 or lower were randomly assigned to receive either lasofoxifene 0.25 mg/day, or lasofoxifene 0.5 mg/day, or placebo, for 5 years.

	Lasofoxifene 0.25 mg/day	Lasofoxifene 0.50 mg/day	Placebo
Endometrial cancer (number of cases)	2	2	3
Uterine hyperplasia (number of cases)	3	2	0
Vaginal bleeding (percent)	2.2%*	2.6%*	1.3%
Surgery for prolapsed or incontinence (percent)	1.9%*	1.6%	1.2%
Endometrial polyps (percent)	8.8%*	5.5*	3.3%

*Statistically significant difference from placebo.

Table 4. Rates of gynecological events among postmenopausal women taking lasofoxifene.

Endometrial cancer was confirmed for two women in each lasofoxifene group and for three women in the placebo group. Endometrial hyperplasia and vaginal bleeding occurred in more women treated with either 0.25 mg/day or 0.5 mg/day lasofoxifene than in women treated with placebo. Lasofoxifene treatment resulted in a small increase in endometrial thickness versus placebo. Similar numbers of women required surgery for pelvic organ prolapse or urinary incontinence in the placebo and 0.5 mg/day lasofoxifene groups. These findings indicate that 5 years of lasofoxifene treatment result in benign endometrial changes that do not increase the risk for endometrial cancer or hyperplasia in postmenopausal women.

5. Population risks and benefits of SERM therapy

The risks associated with tamoxifen therapy are shown in Table 5. Using the rates shown in the table, we can calculate that among the more than 65 million women aged 35–79 years without reported breast cancer in the United States in 2000, 10 million women (Freedman et

al. 2003) would have been eligible for tamoxifen chemoprevention. The percentage of U.S. women who would be eligible varied dramatically by race, with 18.7% (95% CI = 17.8% to 19.7%) of white women, 5.7% (95% CI = 4.3% to 7.5%) of black women, and 2.9% (95% CI = 2.1% to 3.9%) of Hispanic women being eligible. Of the 50 million white U.S. women aged 35–79 years, more than 2.4 million (would have a positive benefit/risk index for tamoxifen chemoprevention. Of the 7 million black U.S. women aged 35–79 years, only 42,000 would have a positive benefit/risk index. Among white women, more than 28,000 breast cancers would be prevented or deferred if those women who have a positive net benefit index took tamoxifen over the next 5 years.: A substantial percentage of U.S. women are eligible for chemoprevention according to FDA criteria, and a percentage of them would have an estimated net benefit. Nevertheless, this latter percentage corresponds to more than two million women.

Revised estimates show that of the more than 9 million white U.S. women in 2010 who would be eligible for tamoxifen chemoprevention, about one-third would derive a net benefit from taking the drug on the basis of their age and breast cancer risk factors (Freedman et al. 2011). Among the white women who would benefit from tamoxifen, approximately more than 58,000 invasive breast cancers will develop over the next 5 years. If all 2 431 911 women in the US with an estimated net benefit/risk index took tamoxifen over the next 5 years, and if the risk reduction of 49% applies, then 28 492 of these breast cancers would be prevented, or deferred, which would be a substantial achievement.

Type of event	Age groups for white women (years)					Age groups for black women (years)				
	35-39	40-49	50-59	60-69	70-79	35-39	40-49	50-59	60-69	70-79
Life-threatening events										
Hip fracture	1	1	22	52	151	1	1	12	20	57
Endometrial cancer	−2	−16	−120	−206	−223	−1	−6	−52	−126	−119
(without uterus)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
Stroke	−2	−13	−32	−91	−196	−8	−36	−90	−200	−228
Pulmonary embolism	−7	−15	−49	−85	−177	−20	−46	−145	−189	−273
Severe events										
Deep vein thrombosis	−13	−15	−16	−28	−44	−37	−45	−48	−63	−69
Other events										
Colles' fracture	11	11	19	25	25	9	9	10	10	9
Spine fracture	2	2	23	46	90	1	1	13	17	62
Cataracts	−35	−35	−101	−269	−384	−35	−35	−100	−264	−377

Table 5. Numbers of non-breast cancer events prevented (positive number) or caused (negative number) in 5 years among 10,000 women treated with tamoxifen (Gail et al. 1999).

For non-Hispanic white women age 50 years or older with a uterus, raloxifene displays a better benefit/risk profile than tamoxifen overall (Freedman et al. 2011). For tamoxifen, women age 50 to 59 years with a 5-year risk of invasive breast cancer of 4.5% to 6.5% showed moderate evidence of net positive benefit, and women with risk of 7.0% or higher showed strong evidence. For women age 50 to 59 years with a 5-year risk of invasive breast cancer less than 4.0%, the risks outweighed the benefits. The risks outweighed the benefits for women age 60 years or older, regardless of IBC risk. In contrast, for raloxifene, there was strong evidence that benefits outweighed risks, compared with placebo, for women age 50 to 59 years with a 5-year breast cancer risk of 3.5% or higher and for women age 60 to 69 years with an risk of 6.5% risk or higher. There was moderate evidence of a net benefit for women age 50 to 59 years with a 5-year risk of 2.0% to 3.0%, women age 60 to 69 years with a 5-year risk of 3.0% to 6.0%, and women age 70 to 79 years with a 5-year IBC risk of 4.0% or higher. For postmenopausal black and Hispanic women with a uterus, raloxifene also displayed a better benefit/risk profile than tamoxifen and in a similar pattern to that for whites. Net benefit indices tended to be larger in Hispanic women and smaller in black women than in white women, however.

6. American Society of Clinical Oncology (ASCO) recommendations for breast cancer risk reduction

In premenopausal women, tamoxifen for 5 years reduces the risk of breast cancer for at least 10 years, particularly estrogen receptor (ER) –positive invasive tumors. Women ≤ 50 years of age experience fewer serious side effects. Vascular and vasomotor events do not persist post-treatment across all ages. In postmenopausal women, raloxifene and tamoxifen reduce the risk of ER-positive invasive BC with equal efficacy. Raloxifene is associated with a lower risk of thromboembolic disease, benign and malignant uterine conditions, and cataracts than tamoxifen in postmenopausal women. No evidence exists establishing whether a reduction in risk of breast cancer from either agent translates into reduced BC mortality.

6.1 2009 Recommendation for the Use of tamoxifen to reduce the risk of developing breast cancer

Five years of tamoxifen (20 mg/d) may be offered to women at increased risk of breast cancer to reduce their risk of estrogen receptor (ER) –positive invasive breast cancers for up to 10 years (Visvanathan et al. 2009). Eligible women include those with a 5-year projected breast cancer risk ≥ 1.66% (according to the National Cancer Institute [NCI] Breast Cancer Risk Assessment Tool based on the Gail model23 —available at http://www.cancer.gov/bcrisktool) or women with LCIS. The benefit of taking tamoxifen for more than 5 years is unknown. The greatest clinical benefit and the fewest side effects were derived from the use of tamoxifen in younger (premenopausal) women 35 to 50 years of age who are unlikely to experience thromboembolic sequelae or uterine cancer, women without a uterus, and women at high risk of breast cancer (Newman and Vogel 2007). Vascular and vasomotor side effects were observed to decline post-treatment across all ages. Tamoxifen is not recommended in women with a prior history of deep vein thrombosis (DVT), pulmonary embolus (PE), stroke, or transient ischemic attack. Combined use of tamoxifen for breast cancer prevention and hormone therapy (HT) is currently not

recommended. Follow-up should include a baseline gynecologic examination before initiation of treatment and annually thereafter, with a timely work-up for abnormal vaginal bleeding. The risks and benefits of tamoxifen should be given careful consideration during the decision-making process. There has been no mortality differences observed in the tamoxifen prevention trials so far, most likely because these trials were not powered to detect such outcomes. Nevertheless, a reduction in breast cancer incidence is considered to be an important health outcome in and of itself.

6.2 ASCO 2009 recommendation for the use of raloxifene to reduce the risk of developing breast cancer

For postmenopausal women at increased risk for breast cancer, raloxifene (60 mg/d) for 5 years may be offered as another option to reduce the risk of ER-positive invasive breast cancer. Raloxifene has been shown to be equally efficacious to tamoxifen in reducing breast cancer risk in postmenopausal women. However, raloxifene was not as effective in reducing the incidence of noninvasive breast cancer compared with tamoxifen, although the association was not statistically significant. In the STAR trial, raloxifene was associated with a more favorable side-effect profile compared with tamoxifen, including a statistically significant lower risk of thromboembolic disease, benign uterine complaints, and cataracts as compared with tamoxifen. Raloxifene, like tamoxifen, is not known to have an effect on overall or breast cancer–specific mortality in women at increased risk of breast cancer. However, the risk reduction trials were not powered to detect a reduction in breast cancer incidence rather than mortality, as it was felt to be an important end point in and of itself. Raloxifene may be used for longer than 5 years in women with osteoporosis in whom breast cancer risk reduction is an additional potential benefit. Raloxifene is not recommended in premenopausal women or in women with a prior history of DVT, PE, stroke, or transient ischemic attack. In postmenopausal women, the risks and benefits of both tamoxifen and raloxifene, including risks of noninvasive breast cancer, adverse events, and impact on quality of life, should be discussed in detail with women before coming to a decision about risk reduction strategies.

7. References

Barrett-Connor, E; Mosca, L; Collins, P; Geiger, MJ; Grady, D; Kornitzer, M; McNabb, MA; Wenger, NK & Raloxifene Use for The Heart (RUTH) Trial Investigators. (2006). Effects of raloxifene on cardiovascular events and breast cancer in postmenopausal women. *The New England Journal of Medicine* Vol.355, No.2, (Jul 13), pp. 125-37, ISSN 1533-4406; 0028-4793.

Boss, SM; Huster, WJ; Neild, JA; Glant, MD; Eisenhut, CC & Draper, MW. (1997). Effects of raloxifene hydrochloride on the endometrium of postmenopausal women. *American Journal of Obstetrics and Gynecology* Vol.177, No.6, (Dec), pp. 1458-64, ISSN 0002-9378; 0002-9378.

Cummings, SR; Eckert, S; Krueger, KA; Grady, D; Powles, TJ; Cauley, JA; Norton, L; Nickelsen, T; Bjarnason, NH; Morrow, M; Lippman, ME; Black, D; Glusman, JE; Costa, A & Jordan, VC. (1999). The effect of raloxifene on risk of breast cancer in postmenopausal women: Results from the MORE randomized trial. multiple

outcomes of raloxifene evaluation. *JAMA : The Journal of the American Medical Association* Vol.281, No.23, (Jun 16), pp. 2189-97, ISSN 0098-7484; 0098-7484.

Cummings, SR; Ensrud, K; Delmas, PD; LaCroix, AZ; Vukicevic, S; Reid, DM; Goldstein, S; Sriram, U; Lee, A; Thompson, J; Armstrong, RA; Thompson, DD; Powles, T; Zanchetta, J; Kendler, D; Neven, P; Eastell, R & PEARL Study Investigators. (2010). Lasofoxifene in postmenopausal women with osteoporosis. *The New England Journal of Medicine* Vol.362, No.8, (Feb 25), pp. 686-96, ISSN 1533-4406; 0028-4793.

Delmas, PD; Bjarnason, NH; Mitlak, BH; Ravoux, AC; Shah, AS; Huster, WJ; Draper, M & Christiansen, C. (1997). Effects of raloxifene on bone mineral density, serum cholesterol concentrations, and uterine endometrium in postmenopausal women. *The New England Journal of Medicine* Vol.337, No.23, (Dec 4), pp. 1641-7, ISSN 0028-4793; 0028-4793.

Fisher, B; Costantino, JP; Wickerham, DL; Cecchini, RS; Cronin, WM; Robidoux, A; Bevers, TB; Kavanah, MT; Atkins, JN; Margolese, RG; Runowicz, CD; James, JM; Ford, LG & Wolmark, N. (2005). Tamoxifen for the prevention of breast cancer: Current status of the national surgical adjuvant breast and bowel project P-1 study. *Journal of the National Cancer Institute* Vol.97, No.22, (Nov 16), pp. 1652-62, ISSN 1460-2105; 0027-8874.

Fisher, B; Costantino, JP; Wickerham, DL; Redmond, CK; Kavanah, M; Cronin, WM; Vogel, V; Robidoux, A; Dimitrov, N; Atkins, J; Daly, M; Wieand, S; Tan-Chiu, E; Ford, L & Wolmark, N. (1998). Tamoxifen for prevention of breast cancer: Report of the national surgical adjuvant breast and bowel project P-1 study. *Journal of the National Cancer Institute* Vol.90, No.18, (Sep 16), pp. 1371-88, ISSN 0027-8874; 0027-8874.

Freedman, AN; Graubard, BI; Rao, SR; McCaskill-Stevens, W; Ballard-Barbash, R & Gail, MH. (2003). Estimates of the number of US women who could benefit from tamoxifen for breast cancer chemoprevention. *Journal of the National Cancer Institute* Vol.95, No.7, (Apr 2), pp. 526-32, ISSN 0027-8874; 0027-8874.

Freedman, AN; Yu, B; Gail, MH; Costantino, JP; Graubard, BI; Vogel, VG; Anderson, GL & McCaskill-Stevens, W. (2011). Benefit/Risk assessment for breast cancer chemoprevention with raloxifene or tamoxifen for women age 50 years or older. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology* Vol.29, No.17, (Jun 10), pp. 2327-33, ISSN 1527-7755; 0732-183X.

Gail, MH; Costantino, JP; Bryant, J; Croyle, R; Freedman, L; Helzlsouer, K & Vogel, V. (1999). Weighing the risks and benefits of tamoxifen treatment for preventing breast cancer. *Journal of the National Cancer Institute* Vol.91, No.21, (Nov 3), pp. 1829-46, ISSN 0027-8874; 0027-8874.

Goldstein, SR; Neven, P; Cummings, S; Colgan, T; Runowicz, CD; Krpan, D; Proulx, J; Johnson, M; Thompson, D; Thompson, J & Sriram, U. (2011). Postmenopausal evaluation and risk reduction with lasofoxifene (PEARL) trial: 5-year gynecological outcomes. *Menopause (New York, N.Y.)* Vol.18, No.1, (Jan), pp. 17-22, ISSN 1530-0374; 1072-3714.

LaCroix, AZ; Powles, T; Osborne, CK; Wolter, K; Thompson, JR; Thompson, DD; Allred, DC; Armstrong, R; Cummings, SR; Eastell, R; Ensrud, KE; Goss, P; Lee, A; Neven, P; Reid, DM; Curto, M; Vukicevic, S & PEARL Investigators. (2010). Breast cancer incidence in the randomized PEARL trial of lasofoxifene in postmenopausal osteoporotic women. *Journal of the National Cancer Institute* Vol.102, No.22, (Nov 17), pp. 1706-15, ISSN 1460-2105; 0027-8874.

Land, SR; Wickerham, DL; Costantino, JP; Ritter, MW; Vogel, VG; Lee, M; Pajon, ER; Wade, JL,3rd; Dakhil, S; Lockhart, JB,Jr; Wolmark, N & Ganz, PA. (2006). Patient-reported symptoms and quality of life during treatment with tamoxifen or raloxifene for breast cancer prevention: The NSABP study of tamoxifen and raloxifene (STAR) P-2 trial. *JAMA : The Journal of the American Medical Association* Vol.295, No.23, (Jun 21), pp. 2742-51, ISSN 1538-3598; 0098-7484.

Martino, S; Cauley, JA; Barrett-Connor, E; Powles, TJ; Mershon, J; Disch, D; Secrest, RJ; Cummings, SR & CORE Investigators. (2004). Continuing outcomes relevant to evista: Breast cancer incidence in postmenopausal osteoporotic women in a randomized trial of raloxifene. *Journal of the National Cancer Institute* Vol.96, No.23, (Dec 1), pp. 1751-61, ISSN 1460-2105; 0027-8874.

Newman, LA & Vogel, VG. (2007). Breast cancer risk assessment and risk reduction. *The Surgical Clinics of North America* Vol.87, No.2, (Apr), pp. 307,16, vii-viii, ISSN 0039-6109; 0039-6109.

Visvanathan, K; Chlebowski, RT; Hurley, P; Col, NF; Ropka, M; Collyar, D; Morrow, M; Runowicz, C; Pritchard, KI; Hagerty, K; Arun, B; Garber, J; Vogel, VG; Wade, JL; Brown, P; Cuzick, J; Kramer, BS; Lippman, SM & American Society of Clinical Oncology. (2009). American society of clinical oncology clinical practice guideline update on the use of pharmacologic interventions including tamoxifen, raloxifene, and aromatase inhibition for breast cancer risk reduction. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology* Vol.27, No.19, (Jul 1), pp. 3235-58, ISSN 1527-7755; 0732-183X.

Vogel, VG. (2007). Raloxifene: A selective estrogen receptor modulator for reducing the risk of invasive breast cancer in postmenopausal women. *Women's Health (London, England)* Vol.3, No.2, (Mar), pp. 139-53, ISSN 1745-5065; 1745-5057.

Vogel, VG; Costantino, JP; Wickerham, DL; Cronin, WM; Cecchini, RS; Atkins, JN; Bevers, TB; Fehrenbacher, L; Pajon, ER; Wade, JL,3rd; Robidoux, A; Margolese, RG; James, J; Runowicz, CD; Ganz, PA; Reis, SE; McCaskill-Stevens, W; Ford, LG; Jordan, VC; Wolmark, N & National Surgical Adjuvant Breast and Bowel Project. (2010). Update of the national surgical adjuvant breast and bowel project study of tamoxifen and raloxifene (STAR) P-2 trial: Preventing breast cancer. *Cancer Prevention Research (Philadelphia, Pa.)* Vol.3, No.6, (Jun), pp. 696-706, ISSN 1940-6215; 1940-6215.

Vogel, VG; Costantino, JP; Wickerham, DL; Cronin, WM; Cecchini, RS; Atkins, JN; Bevers, TB; Fehrenbacher, L; Pajon, ER,Jr; Wade, JL,3rd; Robidoux, A; Margolese, RG; James, J; Lippman, SM; Runowicz, CD; Ganz, PA; Reis, SE; McCaskill-Stevens, W; Ford, LG; Jordan, VC; Wolmark, N & National Surgical Adjuvant Breast and Bowel Project (NSABP). (2006). 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 : The Journal of the American Medical Association* Vol.295, No.23, (Jun 21), pp. 2727-41, ISSN 1538-3598; 0098-7484.
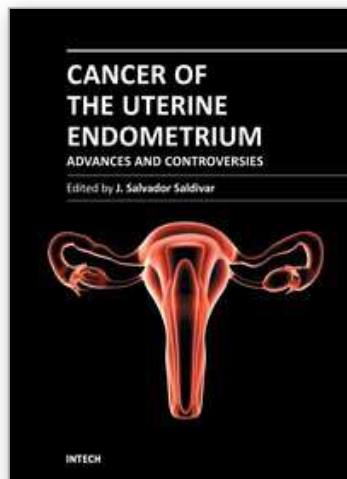
Cancer of the Uterine Endometrium - Advances and Controversies

Edited by Dr J.S. Saldivar

The book Cancer of the Uterine Endometrium - Advances and Controversies brings together an international collaboration of authors who share their contributions for the management of endometrial carcinoma. The scope of the text is not basic, but rather aims to provide a comprehensive and updated source of advances in the diagnosis and therapeutic strategies in this field of gynecologic cancer. Each section in the book attempts to provide the most relevant evidence-based information in the biology and genetics, modern imaging, surgery and staging, and therapies for endometrial cancer. It is hoped that future editions will bring additional authors to contribute to this endeavor. To this end, it is our patients who will benefit from this work.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Victor G. Vogel (2012). Reducing the Risk of Endometrial Cancer in Patients Receiving Selective Estrogen Receptor Modulator (SERM) Therapy, Cancer of the Uterine Endometrium - Advances and Controversies, Dr J.S. Saldivar (Ed.), ISBN: 978-953-51-0142-0, InTech, Available from:
http://www.intechopen.com/books/cancer-of-the-uterine-endometrium-advances-and-controversies/reducing-the-risk-of-endometrial-cancer-in-patients-receiving-serm-therapy

INTECH

open science | open minds