VOLUME 23 · NUMBER 8 · MARCH 10 2005

JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

Selective Estrogen-Receptor Modulators for Primary Prevention of Breast Cancer

Carol J. Fabian and Bruce F. Kimler

J Clin Oncol 23:1644-1655. © 2005 by American Society of Clinical Oncology

From the Departments of Internal Medicine and Radiation Oncology, University of Kansas Medical Center, Kansas City, KS.

Submitted October 29, 2004; accepted November 29, 2004.

Authors' disclosures of potential conflicts of interest are found at the end of this article.

Address reprint requests to Carol J. Fabian, MD, University of Kansas Medical Center, 3901 Rainbow Blvd, Kansas City, KS 66160; e-mail: cfabian@kumc.edu.

0732-183X/05/2308-1644/$20.00

DOI: 10.1200/JCO.2005.11.005

INTRODUCTION

Selective estrogen receptor modulators (SERMs) impact a variety of biologic processes regulated by activated estrogen receptor (ER). Depending on the target tissue, physiologic conditions, and their structure, SERMs may exhibit either estrogen antagonist or estrogen agonist effects. SERMs have a long history in the treatment of breast cancer, based on estrogen antagonist activity in ER-positive breast cancer cells. Beginning with tamoxifen, SERMs have moved to the prevention arena, where their partial estrogen effects may provide other organ benefits, particularly for postmenopausal women. It is because of these partial estrogen agonist effects on organs such as the bone, vagina, CNS, and cardiovascular system that SERMs are likely to remain preferable to pure antiestrogens as primary breast cancer prevention agents in the context of total women's health.[1] The ideal SERM should function as an antiestrogen in the breast and uterus and a partial estrogen agonist in skeletal, cardiovascular, CNS, gastrointestinal tract, and vagina. Further, this ideal SERM should be devoid of procoagulant effects and should not be associated with an increase in perimenopausal symptoms. Although several generations of SERMs have been developed, the ideal SERM for prevention remains elusive. We will review progress to date for SERMs as single agents and potential for combination therapy in the future.

BIOLOGY BEHIND THE MULTIFACETED ACTION OF SERMs

Depending on their structure and context, SERMs differentially modify expression of multiple genes whose transcription is regulated by activated ER.[2,3] A SERM's gene- and tissue-specific estrogen agonist or antagonist activity is determined primarily by whether coactivators or corepressors are preferentially bound to the SERM/ER nuclear receptor transcription complex.[4-7]

The ability of a SERM to block coactivator recruitment into the ER-ligand binding pocket is dependent on its three-dimensional structure.[8] When estrogen binds to ER, a conformational change occurs such that helix 12 is repositioned, exposing multiple coactivator sites. Subsequent to coactivator binding, full estrogen agonist transcription is initiated at both ER-activating function domains (AF-1 and -2).[9,10] SERMs block full closure of helix 12, reducing the number of coactivation binding sites so that one or both activation domains are inhibited.[9,10] SERMs such as tamoxifen, which block activation of AF-2 but not AF-1, might be expected to have partial estrogen agonist activity for a wider spectrum of target genes/tissue than SERMs such as raloxifene, arzoxifene, or acolbifene, which also block AF-1 activation.[9,11] Frasor et al,[3] using DNA microarrays, have recently shown that tamoxifen indeed appears to have estrogen agonist effects on more genes than does raloxifene.

Estrogen agonist or antagonist effects are also dependent on the organ-specific type and amount of ER (Table 1) available for ligand binding as well as the type of target gene promoter, estrogen response element (ERE), or AP-1 (Table 2).[15-36] For example, estrogen, when combined with ERβ and acting at genes with an AP-1 type promoter, inhibits rather than facilitates gene transcription.[16,17] Tamoxifen, when combined with ERβ and a target gene promoter that uses an ERE, will function as an estrogen antagonist similar to the situation for ERα.[13,15,18] However, when tamoxifen is combined with ERβ and the target gene has an AP-1 type promoter, tamoxifen becomes a partial estrogen agonist.[15,18,19] Generally, the amount of ERα increases and ERβ decreases during the promotion and progression phases of breast cancer[20,21]; however, breast cancers which have a substantial amount of ERβ may exhibit tamoxifen resistance.[22,23] Whether the same principles apply in the prevention setting is unclear.

The relative level of coactivators and corepressors in the nucleus may determine the agonist/antagonist profile of a SERM.[23,24] Coactivator levels are increased by activation of the MAP kinase pathway.[24] Mitogenic signaling is rapidly upregulated when estrogen is bound to membrane ER. Under these circumstances (nongenomic pathway), estrogen in the presence of ligands (insulin-like growth factor [IGF] -1, transforming growth factor alpha) for tyrosine kinase receptors (IGF receptor [IGFR], HER-2, epidermal growth factor receptor [EGFR]) serves as a co-factor for activation of the tyrosine kinase receptors.[6,25-29] The rapid cell cycle effects observed via activated membrane ER are distinct from the slower genomic pathway in which activated nuclear ER serves as a transcription factor for synthesis of a number of proteins, including several growth factors and their receptors.[2,6] A SERM's relative potency depends on many factors including its bioavailability, serum and tissue half-life, affinity for the estrogen receptor, and rate of ubiquination of the ligand-ER complex.[9,30,31]

In summary, the organ-specific response to an individual SERM depends not only on the drug's structure and pharmacologic properties, but also upon the target tissue's ERα:ERβ ratio, whether target genes are activated by ERE or an AP-1 transcription complex, and the level of MAP kinase pathway activation.[32-36]

Table 1. Tissue Type and Predominant Estrogen Receptors

Tissue	Estrogen-Receptor Type
Breast	α, β (α elevated in cancer)
Uterus	α, β (mostly α)
Ovary	α, β
Blood Vessels	β
Heart	α, β
Bone	α, cortical β, cancellous
Brain	α, hypothalmus β, whole brain
Gut	β
Immune	β
Liver	α, β (mostly α)

NOTE. Adapted from Bord et al,[12] Kuiper et al,[13] and Gustafsson.[14]

Table 2. Determinants of Whether a SERM Displays Estrogen Agonist or Antagonist Effects

SERM structure
(1) Inhibitors AF2
(2) Inhibitors AF2 + AF1
Tissue factors
(1) Level of ERα
(2) Level of ERβ
(3) Level of activated EGFR, HER-2, IGFR
(4) Amount of co-activators co-repressors
Target gene
(1) Promoter activated by ERE
(2) Promoter activated by AP-1
E2 + ERα + ERE or AP-1 agonist
Tam + ERα + ERE or AP-1 antagonist
E2 + ERβ + ERE agonist
Tam + ERβ + ERE antagonist
E2 + ERβ + AP-1 antagonist
Tam + ERβ + AP-1 agonist

Abbreviations: SERM, selective estrogen-receptor modulator; AF, activating function domain; ER, estrogen receptor; EGFR, epidermal growth factor receptor; IGFR, insulin-like growth factor receptor; ERE. estrogen response element; AP, activating protein; E2, estradiol; Tam, tamoxifen.

TAMOXIFEN

Tamoxifen is a SERM with predominate estrogen antagonist effects in the breast, partial estrogen agonist activity in the bone, cardiovascular system and CNS, and predominant estrogen agonist effects in the uterus, liver, and vagina.[37-45] The estrogen agonist effects of tamoxifen on the uterus and liver, which result in an increased incidence of uterine cancer and thromboembolic phenomena, keep it from being considered an ideal SERM. Nonetheless, tamoxifen is the only US Food and Drug Administration–approved drug in the United States for breast cancer risk reduction.[46]

In an overview of four completed primary prevention trials in which tamoxifen was to be given for 5 or more years (National Surgical Adjuvant Breast and Bowel Project [NSABP] P-1,[47] International Breast Cancer Intervention Study-1,[48] Royal Marsden,[49] and Italian[50]), women randomly assigned to tamoxifen had a 36% reduction in the incidence of ductal carcinoma-in-situ (DCIS) and a 46% reduction in invasive breast cancer.[51] ER-positive tumors were reduced by 48% in the overview, but no significant reduction was observed in the incidence of ER-negative tumors.[51] The excess of serious side effects in women taking tamoxifen (116 events) almost offset the reduction in cancer incidence (176 cases).[51] The incidence of endometrial cancer was increased 2.4-fold, deep venous thrombosis 1.9-fold, and cerebral vascular accident 1.5-fold.[51] The increase in uterine epithelial hyperplasia, as well as uterine cancer, may be the result of

tamoxifen-induced increases in the steroid receptor coactivator (SRC) and increases in uterine IGF-1 and IGFR activation.[52] In the overview analysis, a nonsignificant increase in death from any cause was observed in women randomly assigned to tamoxifen.[51] Despite the favorable effect of tamoxifen on several risk biomarkers for coronary artery disease, there was no significant reduction in coronary artery disease–related events.[51] However, another meta-analysis, which included 25 breast cancer treatment trials in addition to the four prevention trials, indicated that tamoxifen significantly decreased myocardial infarction deaths.[53] Because of major side effects and incomplete efficacy, it has been estimated that only one in four women meeting the National Surgical Adjuvant Breast and Bowel Project P-1 minimum eligibility requirement (5-year Gail risk $\geq$1.67%) for tamoxifen would have a favorable benefit:risk ratio. Fear of both major and minor side effects and uncertainty over who will benefit often make tamoxifen unattractive to healthy women.[47,48]

Despite endorsement by the American Society of Clinical Oncology and the US Food and Drug Administration, only 5% to 30% of eligible high-risk women agree to take tamoxifen for primary prevention following a recommendation by their health care provider.[54-56] By selecting women with high short-term risk, and those most likely to respond to SERMs, the benefit:risk ratio can be maximized.[57,58] Women with a deleterious mutation in *BRCA1* or *BRCA2*, or with a prior diagnosis of DCIS, lobular carcinoma-in-situ (LCIS), and/or atypical hyperplasia, have $\geq$ 5% 5-year risk of breast cancer.[59-62] This level of risk is generally associated with clinical benefit from prevention tamoxifen regardless of a woman's age or whether or not her uterus is intact.[57] A limited number of studies in *BRCA1/2* mutation carriers appear to indicate benefit for tamoxifen despite the observation that the majority of *BRCA1*-associated cancers are ER-negative.[63-65] Study results have been mixed, however. Randomization to tamoxifen was correlated with a reduction in breast cancers in *BRCA2*-, but not *BRCA1*-associated cancers in the National Surgival Adjuvant Breast and Bowel Project (NSABP) P-1 trial.[66] Atypical hyperplasia, LCIS, and the majority of non–high-grade DCIS lesions are characterized by a high proportion of ER positive cells,[20] which in turn predict favorable outcome to tamoxifen in adjuvant trials.[67-69] The finding of any of these precancerous lesions would then most likely result in a benefit:risk ratio which would favor tamoxifen use.[47] Hershman et al[70] have determined that 5 years of tamoxifen is likely to be cost effective for women with prior atypical ductal hyperplasia, LCIS, and/or 5-year Gail risk >5%, particularly if the drug is started before the age of 60 years. However, the majority of women at increased risk on the basis of family history have never had a diagnostic biopsy.

The high incidence and multicentric distribution of atypical ductal and lobular hyperplasia in prophylactic mastectomy specimens from women of hereditary breast cancer families suggests that atypical hyperplasia should be amenable to discovery by random tissue sampling in high-risk women.[71] Approximately 20% of women with a median age of 44 years at increased risk by virtue of a first-degree relative or multiple second-degree relatives with breast cancer, prior precancerous biopsy, or contralateral breast cancer can be expected to exhibit atypia in their cytology specimens when cells are harvested by random periareolar fine needle aspiration.[72] Similar figures are reported for ductal lavage[73]. Detection of atypia by nipple aspirate fluid harvest or random periareolar fine needle aspiration has been associated in prospective studies with a substantial increase in relative risk in average- and high-risk populations, respectively.[72,74] In addition to breast tissue morphology, other biomarkers have also been associated with increase in risk for breast cancer including serum IGF-1 and its binding protein 3 (IGFBP-3) in premenopausal women; serum bioavailable estradiol, free testosterone and sex hormone binding globulin (SHBG) in postmenopausal women; and mammographic breast density in both pre- and postmenopausal women.[59,75-77] It is unknown at present whether detection of atypia or any other risk biomarker will increase the likelihood that eligible women will take prevention tamoxifen following a recommendation for its use. However, Vogel et al[56] reported that eligible women with a prior diagnostic biopsy exhibiting atypical hyperplasia were more likely than women without atypical hyperplasia to enter the NSABP P-1 or the Study of Tamoxifen and Raloxifene (STAR) trials.

Tamoxifen use has been observed to have a favorable effect on many risk markers including serum IGF-1, IGFBP-3, SHBG, mammographic breast density, and subsequent prevalence of breast biopsies with benign breast disease with and without atypical hyperplasia.[78-80] Consequently, modulation of many of these risk biomarkers is used in early clinical trials to evaluate promising new prevention strategies.[81,82] It is not yet clear that favorable risk biomarker modulation accurately predicts prevention of breast cancer for an individual woman.

In summary, the most serious adverse events attributable to tamoxifen are the increased risk of uterine cancer and thromboembolic phenomena. Furthermore, up to one half of ER-positive breast cancers and the majority of ER-negative cancers are not prevented with tamoxifen.[47,48,51,83] Despite these drawbacks, the use of tamoxifen has been judged to be cost effective as a primary breast cancer prevention agent in women with prior atypical hyperplasia carcinoma-in-situ, and/or 5-year Gail risk >5%.

Current SERM prevention research aims to enhance the benefit:risk ratio observed with tamoxifen through: (1) use of low-dose tamoxifen to reduce side effects; (2) development of new SERMs with a more favorable

estrogen antagonist/agonist profile; (3) development of combination therapy including SERMs for prevention of ER-positive tamoxifen resistant and ER-negative breast cancer.

Low-Dose Tamoxifen

Reduction in the proliferation marker Ki67 after several weeks of tamoxifen has been associated with subsequent clinical response in cancer treatment trials.[84] Consequently, reduction in proliferation between baseline core biopsy and re-excision 4 to 6 weeks later in women with DCIS or a small invasive cancer is often used to define a potentially effective dose range for a prevention agent in the so-called presurgical clinical model.[81,82] Using this model, Decensi et al[85] recently reported the results of a trial in which women were randomly assigned to one of two low doses (1 or 5 mg) or a standard dose (20 mg) of tamoxifen administered daily for 4 weeks between biopsy and definitive surgical resection of their breast cancer. Women with ER-negative and ER-positive tumors not undergoing preoperative treatment served as nonrandomized controls. Despite a >10-fold difference in tamoxifen serum concentration, there were no significant differences in change in breast tissue Ki-67 (Fig 1)[85] in the two low-dose (1 or 5 mg/d) versus standard dose (20 mg/d) arms.[85,86] However, there was a significant difference in change in Ki-67 between the tamoxifen treatment groups (relative median decrease of 15%) and controls (relative median increase of 13%). A dose response relationship was observed for levels of several blood protein biomarkers reflecting tamoxifen's estrogen agonist effects on the liver. These include increased levels of SHBG and decreased levels of C-reactive protein, fibrogen, antithrombin III, and low-density lipoprotein (LDL) cholesterol. These observations added further support to the authors' hypothesis that low-dose tamoxifen might be an effective estrogen antagonist in the breast, but the reduced dosage would result in a less potent estrogen agonist effect on the liver and uterus and fewer serious side effects. In support of this hypothesis, de Lima et al[87] observed that tamoxifen in doses of 5, 10, or 20 mg was able to significantly suppress proliferation in fibroadenomas in premenopausal women.

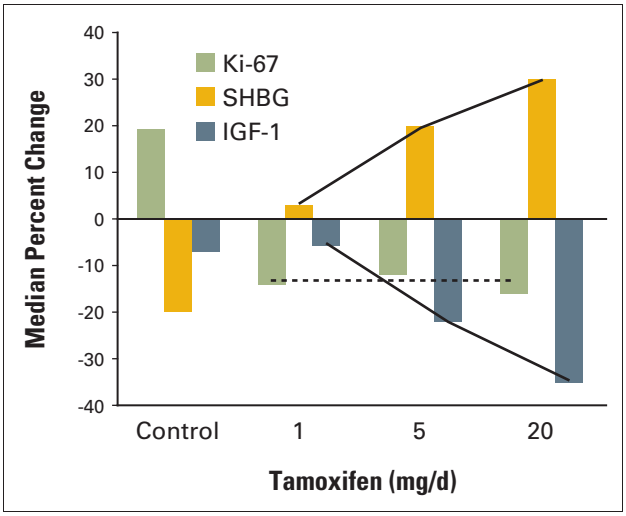

Fig 1. Dose-dependent changes in serum levels of sex hormone binding globulin (SHBG) and insulin-like growth factor-1 (IGF-1) versus dose-independent changes in Ki-67 expression observed in breast cancer patients treated with low doses of tamoxifen.[85]

Raloxifene

Raloxifene belongs to the benzothiophene class of SERMs. Its structural differences (Fig 2) from the triphenylethylene tamoxifen lead to a slightly different tissue-specific estrogen agonist/antagonist profile,[88] which includes greater estrogen agonist activity in bone but reduced estrogen agonist activity in the uterus.[89] Preclinical studies predicted less efficacy than tamoxifen in inhibiting estradiol stimulated tumors.[90,91] Clinical studies have shown little activity in the usual dose of 60 mg/d in women with metastatic breast cancer previously exposed to tamoxifen,[92] but modest activity with higher doses of the drug.[93]

Because of its estrogen agonist activity in bone, raloxifene was explored as an agent for osteoporosis prevention in the Multiple Outcomes of Raloxifene (MORE) trial. In this trial, postmenopausal women with osteopenia or osteoporosis and a mean age of 66.5 years were randomized to 4 years of raloxifene 60 mg/m^2 or 120 mg/m^2 versus placebo. Raloxifene at both dose levels significantly reduced the rate of vertebral fractures at 3 years compared to placebo.[94,95]

A secondary analysis of the MORE trial also indicated a significant reduction in breast cancer incidence for women randomly assigned to raloxifene.[96,97] Raloxifene reduced the incidence of all breast cancers by 62%, invasive breast cancer by 72%, and invasive ER-positive breast cancer by 84%. Similar to findings for tamoxifen in the NSABP P-1 trial, there was no reduction of ER-negative tumors.[97] Unlike tamoxifen in the NSABP P-1 trial, no reduction in DCIS was observed for women randomly assigned to raloxifene. Importantly, randomization to raloxifene was not associated with an excess of uterine cancers or episodes of postmenopausal uterine bleeding.[97]

Raloxifene, like tamoxifen, is associated with an increase in procoagulant activity, probably as a result of its estrogen agonist–like effects on the liver.[98] Women randomly assigned to raloxifene in the MORE trial had a three-fold excess of thromboembolic events compared with the placebo group, similar to that observed for women randomly assigned to tamoxifen in the NSABP P-1 trial.[96] Raloxifene's effects on the neuorendocrine system are also similar to tamoxifen,[99] leading to elevations in follicle stimulating hormone (FSH) and estradiol in

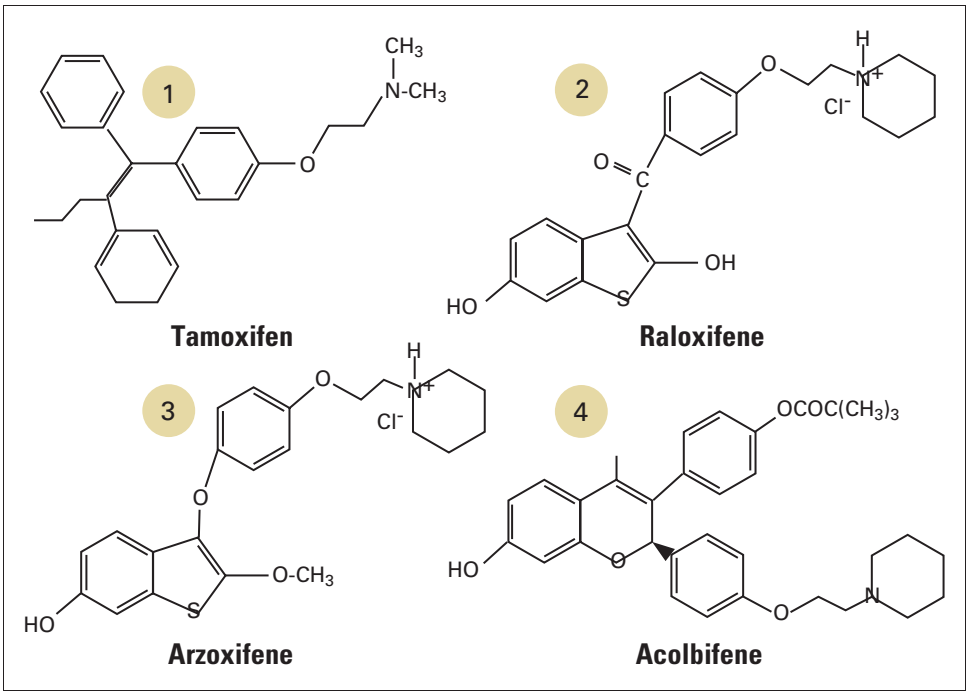

Fig 2. Chemical structure of four generations of selective estrogen receptor modulators (SERMs) representative of the four generations of SERM development.

premenopausal women[100] and reductions in FSH and lutenizing hormone (LH) in postmenopausal women[101] and an increase in hot flashes.[102,103] In an integrated analysis of several trials, hot flashes were reported in 28% of women randomly assigned to raloxifene versus 21% of those randomly assigned to placebo.[104] Similar to tamoxifen,[105,106] prolonged administration of raloxifene in elderly women does not appear to impair cognition.[107]

Raloxifene's partial estrogen agonist effects on the liver results in reduction of total and LDL cholesterol, C-reactive protein, and homocysteine.[102,108,109] However, little change in triglycerides or high-density lipoproteins has been observed.[108] With the exception of triglycerides, the effects on lipids are similar to those observed for tamoxifen.[39,110-114] Raloxifene administration is associated with an increase in leptin in pre- and postmenopausal women,[115,116] similar to that observed for tamoxifen.[117,118] Increases in leptin may be associated with increased risk of breast and colorectal cancer.[119-122] In the MORE trial, women at increased risk for coronary disease who were randomly assigned to raloxifene had a 40% reduction in cardiovascular related events ($P = .03$) but there was no reduction in cardiovascular events for the group as a whole.[123]

Similar to tamoxifen, raloxifene use has been observed to have a favorable effect on serum hormones and growth factors that have been identified as risk markers. Specifically, raloxifene causes an increase in SHBG[124,125] and IGFBP-3[115,126] in pre- and postmenopausal women, and a decrease in IGF-1 in postmenopausal women.[126,127]

The same effects on bone mineral density were observed with raloxifene as had been reported for tamoxifen; density was reduced in premenopausal women and increased in postmenopausal women.[37,108,124]

Investigators and study participants in the MORE trial were given the option of further participation in a 4-year extension trial of raloxifene versus placebo. The extension was entitled the "Continuing Outcomes Relevant to Evista (CORE)" trial. Breast cancer incidence was a primary end point in CORE. Since there were no obvious differences between the 60-mg and the 120-mg dose levels in MORE, those women randomly assigned to either dose in MORE were given 60 mg of raloxifene per day, and those originally randomly assigned to placebo were continued on placebo. Approximately two thirds of the women who participated in MORE contributed data to CORE. For women participating in the 4 years of CORE, total breast cancers were reduced by 50%, invasive breast cancer was reduced by 59%, and ER-positive invasive breast cancer was reduced by 66%. Similar to MORE, there was no reduction in DCIS or ER-negative invasive breast cancer for women randomly assigned to raloxifene.[128] There was no significant difference in overall or breast cancer–specific survival. The CORE study is important, as reduction in breast cancers in the raloxifene group continued over the entire 8-year period (an overall relative reduction of 58% in MORE plus CORE). Whether this is a direct result of continuing raloxifene for another 4 years or a carry-over effect from the initial 4 years is difficult to determine. Participants in the MORE and CORE study were of relatively average risk for their age group. Approximately half the subjects had a 5-year Gail risk $\leq$ 1.67%. Thus, prolonged raloxifene administration appears safe and

beneficial for average-risk, postmenopausal, osteopenic women for both osteoporosis and breast cancer prevention.

It is important to note that in the MORE trial women with detectable estradiol levels (≥ 2.7 pg/mL) had a higher cancer incidence rate than the group at large and were the only ones who appeared to derive significant benefit from raloxifene. Women with undetectable estradiol levels had a similar low risk with or without raloxifene administration.[129]

Is raloxifene equivalent to tamoxifen for breast cancer prevention in high-risk, postmenopausal women, with perhaps fewer side effects? This question is being addressed in the National Cancer Institute–sponsored STAR trial in which postmenopausal women with a 5-year Gail risk of ≥ 1.67% and/or LCIS were randomly assigned to 5 years of tamoxifen or raloxifene.[56] If equivalence in breast cancer risk reduction with fewer serious adverse events is observed with raloxifene, it would likely become the new standard of care for primary breast cancer prevention in postmenopausal women. However, tamoxifen would remain the standard of care for premenopausal women.

The potential cardioprotective effects of raloxifene for postmenopausal women are being examined in the Raloxifene Use for the Heart (RUTH) trial in which 10,000 women were randomly assigned to 60 mg of raloxifene or placebo. The primary end point is the incidence of myocardial infarction, but the incidence of breast cancer and osteoporotic fractures will also be examined as secondary outcomes.[130]

Raloxifene After Tamoxifen

Raloxifene does not appear effective for tamoxifen-resistant tumor cells, thus there would seem to be little rationale at present for treating women who have received 5 years of therapeutic or prevention tamoxifen with raloxifene for the purpose of breast cancer risk reduction.[91,92] Preclinical studies indicate that raloxifene may stimulate endometrial cancer cells previously exposed to tamoxifen, and it has been suggested that administration of raloxifene to women with an intact uterus previously exposed to 5 years of tamoxifen may further increase the risk of endometrial cancer over that observed with tamoxifen alone.[91]

Third- and Fourth-Generation SERMs

Arzoxifene is a third-generation SERM of the benzothiophene class (Fig 2), similar in structure to raloxifene, but modified to improve bioavailability and potency.[131] Acolbifene is a fourth-generation SERM of the benzopyrans class. In preclinical models, both drugs are more potent than tamoxifen or raloxifene for inhibiting growth of tamoxifen sensitive tumors.[131-135] Both agents are able to suppress growth of tumor cells in some tamoxifen-resistant xenograft models. Arzoxifene is able to inhibit growth of tamoxifen resistant MCF-7 cells but not tamoxifen resistant T47-D cells; acolbifene suppresses growth in the tamoxifen resistant ZR75-1 cell line.[136-138] Unlike tamoxifen, acolbifene blocks the stimulatory effect of growth factors on the AF-1 activation site of ER; like tamoxifen, acolbifene also blocks activation of the AF-2 site.[139,140]

Both arzoxifene and acolbifene have demonstrated activity in metastatic breast cancer. Arzoxifene in doses ranging from 10 to 200 mg/d produced a 19% clinical benefit rate in subjects previously treated with tamoxifen and chemotherapy in a phase I trial.[141] Significant reductions in bone turnover markers, LDL and total cholesterol, FSH, and LH were seen beginning at the 10 mg/d dose.[141]

Response rates of 26% to 43% in women with tamoxifen-sensitive metastatic breast cancer have been reported for arzoxifene at 20 mg/d,[142,143] with a 10% objective response rate in tamoxifen-resistant patients.[142] Acolbifene in doses of 20 to 40 mg has also undergone phase II testing in 43 women who had previously been exposed to tamoxifen, of whom 22 could be classified as tamoxifen sensitive and 21 as resistant. The overall objective response rate was 18% in tamoxifen-sensitive and 5% in tamoxifen-resistant patients.[144] Both drugs were well tolerated in phase I and II trials with no evidence of uterine hypertrophy. Hot flashes, muscle and bone pain, fatigue, asthenia, and nausea were the most frequent complaints.[141,142,144]

Preclinical studies of both drugs in ovarectomized rats indicate favorable effects on cholesterol, bone mineral density, and uterine weight, supporting their use as potential prevention agents.[131,134,145,146] Similar to the situation for raloxifene, preclinical models indicate that arzoxifene may stimulate growth of endometrial cancers arising after prolonged tamoxifen treatment.[147] An increase in uterine thickness was observed in five of 25 previously tamoxifen-exposed women at the 50-mg dose level.[142] Both drugs may be more effective than raloxifene in preventing bone loss.[146,148] In preclinical models, acolbifene prevented diet and oopherectomy-induced insulin resistance,[149,150] which has been implicated as a risk factor for postmenopausal breast cancer.[151]

In the nitrosomethylurea model for breast cancer prevention, arzoxifene was a highly potent chemoprevention agent. It was superior to raloxifene and at least equal to tamoxifen.[132] Acolbifene has been shown to be effective in preventing breast cancer in the dimethylbenz(a)anthracene rat model.[134]

Arzoxifene has undergone preliminary clinical evaluation as a potential breast cancer chemoprevention drug utilizing the presurgical model.[152] In both phase IA and phase IB trials, decreases in the molar ratio of serum IGF-1:IGFBP-3 and increases in serum SHBG were observed, consistent with favorable modulation of these two risk biomarkers.[75,76] Reduction in proliferation was noted in the phase IA dose-finding trial at 20 mg/d; however, a significant difference in reduction in proliferation

between placebo versus arzoxifene was not observed in the IB study, perhaps due to the confounding effects of the profound reduction in proliferation associated with stopping hormone replacement therapy between biopsy and re-excision for a sizable proportion of both the arzoxifene and placebo groups.[152] A phase II, placebo-controlled, biomarker modulation study has recently been completed in women at high risk for development of breast cancer. The primary end point is change in breast tissue morphology as assessed by random periareolar fine needle aspiration. A randomized phase III trial of arzoxifene versus placebo has been initiated in postmenopausal women ≥ 60 years of age with prevention of vertebral fractures and breast cancer as two primary end points. Acolbifene has not yet entered clinical prevention trial testing, but reduction in the amount of ERα in rat mammary gland and uterus, as well as in human ZR-75-1 and MCF cells, has been observed in preclinical studies.[153-155]

In summary, both arzoxifene and acolbifene are promising new SERMS for prevention in that they both have some activity in tamoxifen-resistant metastatic breast cancer. Moreover, preclinical studies predict greater preservation of bone mineral density but fewer unfavorable effects on the uterus than with tamoxifen or raloxifene in tamoxifen-naïve women.

Circumventing Resistance to SERMs With Combination Therapy

The partial estrogen agonist profile of tamoxifen and other SERMs may promote the health of other several estrogen responsive organs, but it also may enable the development of resistance via upregulation of the MAP kinase and AKT pathways. Upregulation of these pathways in turn results in an increase in transcriptional activity of coactivators and ER.[23,136,156-159] Lack of ERα expression, as well as reduction in the level of corepressors, are other potential mechanisms of tamoxifen resistance.[35] Combination therapy employing a SERM plus another agent which might reduce MAP kinase and PI-3 kinase signaling would be predicted to reduce the development of tamoxifen-resistant breast cancer.[160,161]

Approximately 30% of breast cancers are ERα-negative, although ≥ 40% of ERα-negative tumors are ERβ-positive.[9] ER expression may be lost through hypermethylation of the ER promoter, which could theoretically be overcome by combining a histone deacetylase inhibitor with a demethylating agent.[162-164] Preclinical work has indicated that ER can be re-expressed,[165,166] but currently available demethylating agents or histone deacetylase inhibitors may have too many side effects for use in the prevention setting.[167-169] Phytoestrogens such as soy may have histone deacetylase inhibitory properties.[170] Furthermore, soy products contain genestein, which has been observed to inhibit HER-2/*neu* activation and promote apoptosis in breast cancer cell lines.[171] An in vitro study by Tanos et al[172] indicated synergistic effects of genestein and tamoxifen on human dysplastic and malignant epithelial cells. On the other hand, genestein blocked the inhibitory effects of tamoxifen on growth in an ovarectomized xenograft model.[173] The different results of studies involving genestein and other phytoestrogens may in some part be due to differences in dose as well as hormonal environment and timing of exposure.[174-176] The estrogen antagonist effects of phytoestrogens may be mediated via their preferential binding of ERβ, which blunts the full agonist effects of ERα.[177-179] The lignan component of flaxseed, another phytoestrogen, may inhibit the PI-3 kinase pathway via inhibition of activation of vascular endothelial growth factor receptor and IGFR.[180-182] Reduced proliferation has been observed with flaxseed in an MDA-MB-435 mouse mammary tumor model.[180] Clinical prevention trials with various phytoestrogens are underway. Pilot trials of combination therapy with phytoestrogens and SERMs should be considered in the future.

Gefitinib is an EGFR tyrosine kinase inhibitor that exhibited only minimal activity in treatment of refractory metastatic breast cancer as a single agent.[183] However, it has shown activity in the ER-negative HER-2/*neu* transgenic mouse model[184] and was able to restore tamoxifen sensitivity in the MCF-7/HER-2 overexpressing mouse xenograft model.[185] In a placebo-controlled trial using the presurgical model, 14 days of gefitinib significantly reduced proliferation in progesterone receptor–positive DCIS, as well as normal adjacent breast tissue.[186] Although gefitinib will undoubtedly be tested in combination with SERMs and other endocrine agents in women with established breast cancer, concerns regarding the side effect profile (rash, diarrhea, nausea, and lung toxicity) may limit enthusiasm for evaluation in the prevention setting.[187]

Breast cancer development is often associated with loss of expression of the tumor suppressor gene retinoic acid receptor beta 2 (*RARβ2*).[188] Retinoic acid derivatives can induce reexpression of RARβ and inhibit signaling mediated through the MAP kinase pathway.[188] A variety of retinoic acid analogues have been found to prevent both ER-positive and ER-negative breast cancer.[189,190] The retinoic acid analogue fenretinide appeared to have modest activity in preventing contralateral breast cancer in premenopausal women in an Italian adjuvant trial.[191] A variety of preclinical studies have suggested enhancement of apoptosis when SERMs are combined with various retinoic acid derivatives.[192-197] Decensi et al[198] recently reported that fenretinide did not appear to improve risk biomarker modulation over that observed with low-dose tamoxifen alone. The type of SERM and retinoic acid analog may be critical to the success of combination treatment. Suh et al[192] have found that the combination of arzoxifene and a retinoic acid X receptor agonist

LG100268 (a targretin analog) was the most powerful inducer of apoptosis of all SERMs and retinoids tested by that laboratory to date. The mechanism appeared to be a profound induction of TGFβ-3.[194] Synergism may also allow lower doses of retinoic acid analogs to be used, which would reduce side effects.[160,199] Low doses of these two agents were also effective in preventing breast cancer in both ER-positive and ER-negative preclinical models.[192,194] The increase in apoptosis suggests the combination might be effective in restoring tissue homeostasis following short-term use rather than requiring long-term chronic exposure over years.[161]

The Future

Another direction in SERM prevention research includes development of highly specific ERβ agonists in the hope of avoiding estrogen agonist effects on breast and uterus mediated via ERα, but providing estrogen agonist effects on other organs. Unfortunately, one of the early compounds, ERβ-041, was not effective in preventing bone loss or vasomotor instability in ovarectomized animal models, although it did not manifest any estrogenic response in the breast or uterus.[200] Development of compounds that do not cross the blood brain barrier might, to some degree, avoid the hot flashes encountered to date with all SERMs. Development of transdermal formulations would avoid a first-pass effect through the liver and theoretically might reduce procoagulant effects observed with SERMs. The development of predictive biomarkers such as those for tamoxifen in the adjuvant setting[201] might be possible from benign precancerous tissue in the prevention setting as well.

With the continuing development of a strong biologic rationale for selective modulation of specific estrogen receptors, it would appear that there is much promise in the use of SERMs for primary prevention of breast cancer and for women's health.

Authors' Disclosures of Potential Conflicts of Interest

The following authors or their immediate family members have indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. Consultant: Carol J. Fabian, Pfizer, Amgen, AstraZeneca, Sankyo. Honoraria: Carol J. Fabian, Pfizer, Amgen, AstraZeneca, Sankyo. Research Funding: Carol J. Fabian, Pfizer, Novartis; Bruce F. Kimler, Pfizer, Novartis. For a detailed description of these categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section of Information for Contributors found in the front of every issue.

REFERENCES

1. Goldstein SR: Selective estrogen receptor modulators: A new category of therapeutic agents for extending the health of postmenopausal women. Am J Obstet Gynecol 179:1479-1484, 1998

2. Levin ER: Cell localization, physiology, and nongenomic actions of estrogen receptors. J Appl Physiol 91:1860-1867, 2001

3. Frasor J, Stossi F, Danes JM, et al: Selective estrogen receptor modulators: Discrimination of agonistic versus antagonistic activities by gene expression profiling in breast cancer cells. Cancer Res 64:1522-1533, 2004

4. Horwitz KB, Jackson TA, Bain DL, et al: Nuclear receptor coactivators and corepressors. Mol Endocrinol 10:1167-1177, 1996

5. MacGregor JI, Jordan VC: Basic guide to the mechanisms of antiestrogen action. Pharmacol Rev 50:151-196, 1998

6. Fuqua SA, Russo J, Shackney SE, et al: Estrogen, estrogen receptors and selective estrogen receptor modulators in human breast cancer. J Womens Cancer 2:21-32, 2000

7. Brzozowski AM, Pike AC, Dauter Z, et al: Molecular basis of agonism and antagonism in the oestrogen receptor. Nature 389:753-758, 1997

8. Jensen EV, Jordan VC: The estrogen receptor: A model for molecular medicine. Clin Cancer Res 9:1980-1989, 2003

9. Howell A, Howell SJ, Clarke R, et al: Where do selective estrogen receptor modulators (SERMs) and aromatase inhibitors (AIs) now fit into breast cancer treatment algorithms? J Steroid Biochem Mol Biol 79:227-237, 2001

10. Bentrem D, Fox JE, Pearce ST, et al: Distinct molecular conformations of the estrogen receptor alpha complex exploited by environmental estrogens. Cancer Res 63:7490-7496, 2003

11. Katzenellenbogen JA, O'Malley BW, Katzenellenbogen BS: Tripartite steroid hormone receptor pharmacology: Interaction with multiple effector sites as a basis for the cell- and promoter-specific action of these hormones. Mol Endocrinol 10:119-131, 1996

12. Bord S, Horner A, Beavan S, et al: Estrogen receptors alpha and beta are differentially expressed in developing human bone. J Clin Endocrinol Metab 86:2309-2314, 2001

13. Kuiper GG, Carlsson B, Grandien K, et al: Comparison of the ligand binding specificity and transcript tissue distribution of estrogen receptors alpha and beta. Endocrinology 138:863-870, 1997

14. Gustafsson JA: Estrogen receptor beta–A new dimension in estrogen mechanism of action. J Endocrinol 163:379-383, 1999

15. Paech K, Webb P, Kuiper GG, et al: Differential ligand activation of estrogen receptors ERalpha and ERbeta at AP1 sites. Science 277:1508-1510, 1997

16. Pettersson K, Delaunay F, Gustafsson JA: Estrogen receptor beta acts as a dominant regulator of estrogen signaling. Oncogene 19:4970-4978, 2000

17. Hall JM, McDonnell DP: The estrogen receptor beta-isoform (ERbeta) of the human estrogen receptor modulates ERalpha transcriptional activity and is a key regulator of the cellular response to estrogens and antiestrogens. Endocrinology 140:5566-5578, 1999

18. Shiau AK, Barstad D, Loria PM, et al: The structural basis of estrogen receptor/coactivator recognition and the antagonism of this interaction by tamoxifen. Cell 95:927-937, 1998

19. Montano MM, Muller V, Trobaugh A, et al: The carboxy-terminal F domain of the human estrogen receptor: Role in the transcriptional activity of the receptor and the effectiveness of antiestrogens as estrogen antagonists. Mol Endocrinol 9:814-825, 1995

20. Allred DC, Mohsin SK, Fuqua SA: Histological and biological evolution of human premalignant breast disease. Endocr Relat Cancer 8:47-61, 2001

21. Shaaban AM, O'Neill PA, Davies MPA, et al: Declining estrogen receptor-β expression defines malignant progression of human breast neoplasia. Am J Surg Pathol 27:1502-1512, 2003

22. Speirs V, Malone C, Walton DS, et al: Increased expression of estrogen receptor beta mRNA in tamoxifen-resistant breast cancer patients. Cancer Res 59:5421-5424, 1999

23. Clarke R, Liu MC, Bouker KB, et al: Antiestrogen resistance in breast cancer and the role of estrogen receptor signaling. Oncogene 22:7316-7339, 2003

24. Smith CL, Nawaz Z, O'Malley BW: Coactivator and corepressor regulation of the agonist/antagonist activity of the mixed antiestrogen, 4-hydroxytamoxifen. Mol Endocrinol 11:657-666, 1997

25. Migliaccio A, Pagano M, Auricchio F: Immediate and transient stimulation of protein tyrosine phosphorylation by estradiol in MCF-7 cells. Oncogene 8:2183-2191, 1993

26. Migliaccio A, Di Domenico M, Castoria G, et al: Tyrosine kinase/p21ras/MAP-kinase pathway activation by estradiol-receptor complex in MCF-7 cells. EMBO J 15:1292-1300, 1996

27. Lee SK, Choi HS, Song MR, et al: Estrogen receptor, a common interaction partner for a subset of nuclear receptors. Mol Endocrinol 12: 1184-1192, 1998

28. Endoh H, Sasaki H, Maruyama K, et al: Rapid activation of MAP kinase by estrogen in the bone cell line. Biochem Biophys Res Commun 235:99-102, 1997

29. Razandi M, Pedram A, Park ST, et al: Proximal events in signaling by plasma membrane estrogen receptors. J Biol Chem 278: 2701-2712, 2003

30. Goldstein SR, Siddhanti S, Ciaccia AV, et al: A pharmacological review of selective oestrogen receptor modulators. Hum Reprod Update 6:212-224, 2000

31. Wijayaratne AL, McDonnell DP: The human estrogen receptor-alpha is a ubiquitinated protein whose stability is affected differentially by agonists, antagonists, and selective estrogen receptor modulators. J Biol Chem 276:35684-35692, 2001

32. Osborne CK, Zhao H, Fuqua SA: Selective estrogen receptor modulators: Structure, function, and clinical use. J Clin Oncol 18:3172-3186, 2000

33. Hong SH, Privalsky ML: The SMRT corepressor is regulated by a MEK-1 kinase pathway: Inhibition of corepressor function is associated with SMRT phosphorylation and nuclear export. Mol Cell Biol 20:6612-6625, 2000

34. Osborne CK, Bardou V, Hopp TA, et al: Role of the estrogen receptor coactivator AIB1 (SRC-3) and HER-2/neu in tamoxifen resistance in breast cancer. J Natl Cancer Inst 95:353-361, 2003

35. Lavinsky RM, Jepsen K, Heinzel T, et al: Diverse signaling pathways modulate nuclear receptor recruitment of N-CoR and SMRT complexes. Proc Natl Acad Sci USA 95:2920-2925, 1998

36. Carroll JS, Lynch DK, Swarbrick A, et al: p27(Kip1) induces quiescence and growth factor insensitivity in tamoxifen-treated breast cancer cells. Cancer Res 63:4322-4326, 2003

37. Powles TJ, Hickish T, Kanis JA, et al: Effect of tamoxifen on bone mineral density measured by dual energy x-ray absorptionmetry in health premenopausal and postmenopausal women. J Clin Oncol 14:78-84, 1996

38. Jordan VC: Estrogen, selective estrogen receptor modulation, and coronary heart disease: Something or nothing. J Natl Cancer Inst 93:2-4, 2001

39. Grey AB, Stapleton JP, Evans MC, et al: The effect of the anti-estrogen tamoxifen on cardiovascular risk factors in normal postmenopausal women. J Clin Endocrinol Metab 80: 3191-3195, 1995

40. Love RR, Surawicz TS, Williams EC: Antithrombin III level, fibrinogen level and platelet count change with adjuvant tamoxifen therapy. Arch Intern Med 152:317-320, 1992

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

42. Shewmon DA, Stock JL, Abusamra LC, et al: Tamoxifen decreases lipoprotein (a) in patients with breast cancer. Metabolism 43:531-532, 1994

43. Anker G, Lonning PE, Ueland PM, et al: Plasma levels of the atherogenic amino acid homocysteine in post-menopausal women with breast cancer treated with tamoxifen. Int J Cancer 60:365-368, 1995

44. Bergman L, Beelen ML, Gallee MP, et al: Risk and prognosis of endometrial cancer after tamoxifen for breast cancer. Comprehensive Cancer Centres' ALERT Group. Assessment of liver and endometrial cancer risk following tamoxifen. Lancet 356:881-887, 2000

45. Ellmen J, Hakulinen P, Partanen A, et al: Estrogenic effects of toremifene and tamoxifen in postmenopausal breast cancer patients. Breast Cancer Res Treat 82:103-111, 2003

46. Chlebowski RT, Collyar DE, Somerfield MR, et al: American Society of Clinical Oncology technology assessment of breast cancer risk reduction strategies: Tamoxifen and raloxifene. J Clin Oncol 17:1939-1955, 1999

47. Fisher B, Costantino JP, Wickerham DL, 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 90:1371-1388, 1998

48. Cuzick J, Forbes J, Edwards R, et al: First results from the International Breast Cancer Intervention Study (IBIS-I): A randomised prevention trial. Lancet 360:817-824, 2002

49. Powles T, Eeles R, Ashley S, et al: Interim analysis of the incidence of breast cancer in the Royal Marsden Hospital tamoxifen randomised chemoprevention trial. Lancet 352:98-101, 1998

50. Veronesi U, Maisonneuve P, Costa A, et al: Prevention of breast cancer with tamoxifen: Preliminary findings from the Italian randomised trial among hysterectomised women. Lancet 352:93-97, 1998

51. Cuzick J, Powles T, Veronesi U, et al: Overview of the main outcomes in breast-cancer prevention trials. Lancet 361:296-300, 2003

52. Klotz DM, Hewitt SC, Korach KS, et al: Activation of a uterine insulin-like growth factor I signaling pathway by clinical and environmental estrogens: requirement of estrogen receptor-alpha. Endocrinology 141:3430-3439, 2000

53. Braithwaite RS, Chlebowsk RT, Lau J, et al: Tamoxifen and breast cancer meta-analysis of vascular and neoplastic events associated with tamoxifen. J Gen Intern Med 18:937-947, 2003

54. Port ER, Montgomery LL, Heerdt AS, et al: Patient reluctance toward tamoxifen use for breast cancer primary prevention. Ann Surg Oncol 8:580-585, 2001

55. Morrow M, Hou N, Tchou J, et al: Acceptance of tamoxifen (TAM) chemoprevention varies with the cause of breast cancer risk. Proc Am Soc Clin Oncol 22:538, 2003 (abstr 2165)

56. Vogel VG, Costantino JP, Wickerham DL, et al: Re: tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Natl Cancer Inst 94:1504,2002

57. Gail MH, Costantino JP, Bryant J, et al: Weighing the risks and benefits of tamoxifen treatment for preventing breast cancer. J Natl Cancer Inst 91:1829-1846, 1999

58. Freedman AN, Graubard BI, Rao SR, et al: Estimates of the number of US women who could benefit from tamoxifen for breast cancer chemoprevention. J Natl Cancer Inst 95:526-532, 2003

59. Page DL, Dupont WD: Anatomic markers of human premalignancy and risk of breast cancer. Cancer 66:1326-1335, 1990

60. Cancer risks in BRCA2 mutation carriers. The Breast Cancer Linkage Consortium. J Natl Cancer Inst 91:1310-1316, 1999

61. Brose MS, Rebbeck TR, Calzone KA, et al: Cancer risk estimates for BRCA1 mutation carriers identified in a risk evaluation program. J Natl Cancer Inst 94:1365-1372, 2002

62. Fisher B, Dignam J, Wolmark N, et al: Tamoxifen in treatment of intraductal breast cancer: National Surgical Adjuvant Breast and Bowel Project B-24 randomised controlled trial. Lancet 353:1993-2000, 1999

63. Narod SA, Brunet JS, Ghadirian P, et al: Tamoxifen and risk of contralateral breast cancer in BRCA1 and BRCA2 mutation carriers: A case-control study. Hereditary Breast Cancer Clinical Study Group. Lancet 356:1876-1881, 2000

64. Foulkes WD, Goffin J, Brunet JS, et al: Tamoxifen may be an effective adjuvant treatment for BRCA1-related breast cancer irrespective of estrogen receptor status. J Natl Cancer Inst 94:1504-1506, 2002

65. Cappelletti V, Veneroni S, Coradini D, et al: Re: Tamoxifen may be an effective treatment for BRCA1-related breast cancer irrespective of estrogen receptor status. J Natl Cancer Inst 95: 629-630, 2003

66. King MC, Wieand S, Hale K, et al: Tamoxifen and breast cancer incidence among women with inherited mutations in BRCA1 and BRCA2: National Surgical Adjuvant Breast and Bowel Project (NSABP-P1) Breast Cancer Prevention Trial. JAMA 286:2251-2256, 2001

67. Early Breast Cancer Trialists' Collaborative Group: Tamoxifen for early breast cancer: An overview of the randomized trials. Lancet 351: 1451-1467, 1998

68. Bardou VJ, Arpino G, Elledge RM, et al: Progesterone receptor status significantly improves outcome prediction over estrogen receptor status alone for adjuvant endocrine therapy in two large breast cancer databases. J Clin Oncol 21:1973-1979, 2003

69. Allred D, Bryant J, Land S, et al: Estrogen receptor expression as a predictive marker of the effectiveness of tamoxifen in the treatment of

DCIS: Findings from NSABP rotocol B-24. Breast Cancer Res Treat 76:S36, 2002 (abstr 30; suppl 1)

70. Hershman D, Sundararajan V, Jacobson JS, et al: Outcomes of tamoxifen chemoprevention for breast cancer in very high-risk women: A cost-effectiveness analysis. J Clin Oncol 20: 9-16, 2002

71. Hoogerbrugge N, Bult P, deWidt-Levert LM, et al: High prevalence of premalignant lesions in prophylactically removed breasts from women at hereditary risk for breast cancer. J Clin Oncol 21:41-45, 2003

72. Fabian CJ, Kimler BF, Zalles CM, et al: Short-term breast cancer prediction by random periareolar fine-needle aspiration cytology and the Gail risk model. J Natl Cancer Inst 92:1217-1227, 2000

73. Dooley WC, Ljung BM, Veronesi U, et al: Ductal lavage for detection of cellular atypia in women at high risk for breast cancer. J Natl Cancer Inst 93:1624-1632, 2001

74. Wrensch MR, Petrakis NL, Miike R, et al: Breast cancer risk in women with abnormal cytology in nipple aspirates of breast fluid. J Natl Cancer Inst 93:1791-1798, 2001

75. Endogenous Hormones and Breast Cancer Collaborative Group: Endogenous sex hormones and breast cancer in postmenopausal women: reanalysis of nine prospective studies. J Natl Cancer Inst 94:606-616, 2002

76. Hankinson SE, Willett WC, Colditz GA, et al: Circulating concentrations of insulin-like growth factor-I and risk of breast cancer. Lancet 351:1393-1396, 1998

77. Boyd NF, Lockwood GA, Bying JW, et al: Mammographic densities and breast cancer risk. Cancer Epidemiol Biomarkers Prev 7:1133-1144, 1998

78. Bonanni B, Johansson H, Gandini S, et al: Effect of low dose tamoxifen on the insulin-like growth factor system in healthy women. Breast Cancer Res Treat 69:21-27, 2001

79. Cuzick J, Warwick J, Pinney E, et al: Tamoxifen and breast density in women at increased risk of breast cancer. J Natl Cancer Inst 96:621-628, 2004

80. Tan-Chiu E, Wang J, Costantino JP, et al: Effects of tamoxifen on benign breast disease in women at high risk for breast cancer. J Natl Cancer Inst 95:302-307, 2003

81. Fabian CJ, Kimler BF, Elledge RM, et al: Models for early chemoprevention trials in breast cancer. Hematol Oncol Clin North Am 12:993-1017, 1998

82. Fabian CJ, Kimler BF, Mayo MS, et al: Clinical approaches to the discovery and testing of new breast cancer prevention drugs, in Kelloff GJ, Hawk ET, Sigman CC (eds): Cancer Chemoprevention Volume 2: Strategies for chemoprevention. Humana Press, Totowa, NJ, pp 13-238, 2004

83. Swain SM, Wilson JW, Mamounas EP, et al: Estrogen receptor status of primary breast cancer is predictive of estrogen receptor status of contralateral breast cancer. J Natl Cancer Inst 96:516-523, 2004

84. Chang J, Powles TJ, Allred DC, et al: Prediction of clinical outcome from primary tamoxifen by expression of biologic markers in breast cancer patients. Clin Cancer Res 6:616-621, 2000

85. Decensi A, Robertson C, Viale G, et al: A randomized trial of low-dose tamoxifen on breast cancer proliferation and blood estrogenic biomarkers. J Natl Cancer Inst 95:779-790, 2003

86. Kisanga ER, Gjerde J, Guerrieri-Gonzaga A, et al: Tamoxifen and metabolite concentrations in serum and breast cancer tissue during three dose regimens in a randomized preoperative trial. Clin Cancer Res 10:2336-2343, 2004

87. de Lima GR, Facina G, Shida JY, et al: Effects of low dose tamoxifen on normal breast tissue from premenopausal women. Eur J Cancer 39:891-898, 2003

88. Grese TA, Sluka JP, Bryant HU, et al: Molecular determinants of tissue selectivity in estrogen receptor modulators. Proc Natl Acad Sci U S A 94:14105-14110, 1997

89. Black LJ, Sato M, Rowley ER, et al: Raloxifene (LY139481 HCl) prevents bone loss and reduces serum cholesterol without causing uterine hypertrophy in ovariectomized rats. J Clin Invest 93:63-69, 1994

90. Lee ES, Schafer JM, Yao K, et al: Cross-resistance of triphenylethylene-type antiestrogens but not ICI 182,780 in tamoxifen-stimulated breast tumors grown in athymic mice. Clin Cancer Res 6:4893-4899, 2000

91. O'Regan RM, Gajdos C, Dardes RC, et al: Effects of raloxifene after tamoxifen on breast and endometrial tumor growth in athymic mice. J Natl Cancer Inst 94:274-283, 2002

92. Buzdar AU, Marcus C, Holmes F, et al: Phase II evaluation of LY156758 in metastatic breast cancer. Oncology 45:344-345, 1988

93. Gradishar W, Glusman J, Lu Y, et al: Effects of high dose raloxifene in selected patients with advanced breast carcinoma. Cancer 88:2047-2053, 2000

94. Ettinger B, Black DM, Mitlak BH, et al: Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: Results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. JAMA 282:637-645, 1999

95. Kanis JA, Johnell O, Black DM, et al: Effect of raloxifene on the risk of new vertebral fracture in postmenopausal women with osteopenia or osteoporosis: A reanalysis of the Multiple Outcomes of Raloxifene Evaluation trial. Bone 33: 293-300, 2003

96. Cummings SR, Eckert S, Krueger KA, et al: The effect of raloxifene on risk of breast cancer in postmenopausal women: Results from the MORE Randomized Trial. Multiple outcomes of raloxifene evaluation. JAMA 281:2189-2197, 1999

97. Cauley JA, Norton L, Lippman ME, et al: Continued breast cancer risk reduction in postmenopausal women treated with raloxifene: 4-year results from the MORE trial. Multiple outcomes of raloxifene evaluation. Breast Cancer Res Treat 65:125-134, 2001

98. Walsh BW, Kuller LH, Wild RA, et al: Effects of raloxifene on serum lipids and coagulation factors in healthy postmenopausal women. JAMA 279:1445-1451, 1998

99. Jordan VC, Fritz NF, Tormey DC: Endocrine effects of adjuvant chemotherapy and long-term tamoxifen administration on node-positive patients with breast cancer. Cancer Res 47:624-630, 1987

100. Baker VL, Draper M, Paul S, et al: Reproductive endocrine and endometrial effects of raloxifene hydrochloride, a selective estrogen receptor modulator, in women with regular menstrual cycles. J Clin Endocrinol Metab 83:6-13, 1998

101. Cheng WC, Yen ML, Hsu SH, et al: Effects of raloxifene, one of the selective estrogen receptor modulators, on pituitary-ovary axis and prolactin in postmenopausal women. Endocrine 23:215-218, 2004

102. Draper MW, Flowers DE, Huster WJ, et al: A controlled trial of raloxifene Hcl: Impact on bone turnover and serum lipid profile in healthy postmenopausal women. J Bone Miner Res 11: 835-842, 1996

103. Davies GC, Huster WJ, Lu Y, et al: Adverse events reported by postmenopausal women in controlled trials with raloxifene. Obstet Gynecol 93:558-565, 1999

104. Cohen FJ, Lu Y: Characterization of hot flashes reported by healthy postmenopausal women receiving raloxifene or placebo during osteoporosis prevention trials. Maturitas 34:65-73, 2000

105. Ganz PA, Castellon SA, Silverman DH: Estrogen, tamoxifen, and the brain. J Natl Cancer Inst 94:547-549, 2002

106. Day R, Ganz PA, Costantino JP: Tamoxifen and depression: More evidence from the National Surgical Adjuvant Breast and Bowel Project's Breast Cancer Prevention (P-1) Randomized Study. J Natl Cancer Inst 93:1615-1623, 2001

107. Yaffe K, Krueger K, Sarkar S, et al: Cognitive function in postmenopausal women treated with raloxifene. N Engl J Med 344:1207-1213, 2001

108. Delmas PD, Bjarnasan NH, Mitlak BH, et al: Effects of raloxifene on bone mineral density, serum cholesterol concentrations, and uterine endometrium in postmenopausal women. N Engl J Med 337:1641-1647, 1997

109. Walsh BW, Paul S, Wild RA, et al: The effects of hormone replacement therapy and raloxifene on C-reactive protein and homocysteine in healthy postmenopausal women: A randomized, controlled trial. J Clin Endocrinol Metab 85:214-218, 2000

110. Brun LD, Gagne C, Rousseau C, et al: Severe lipemia induced by tamoxifen. Cancer 57:2123-2126, 1986

111. Love RR, Newcomb PA, Wiebe DA, et al: Effects of tamoxifen therapy on lipid and lipoprotein levels in postmenopausal patients with node-negative breast cancer. J Natl Cancer Inst 82:1327-1332, 1990

112. Guetta V, Lush RM, Figg WD, et al: Effects of the antiestrogen tamoxifen on low-density lipoprotein concentrations and oxidation in postmenopausal women. Am J Cardiol 76:1072-1073, 1995

113. Hozumi Y, Kawano M, Saito T, et al: Effect of tamoxifen on serum lipid metabolism. J Clin Endocrinol Metab 83:1633-1635, 1998

114. Decensi A, Bonanni B, Guerrieri-Gonzaga A, et al: Biologic activity of tamoxifen at low doses in healthy women. J Natl Cancer Inst 90:1461-1467, 1998

115. Eng-Wong J, Hursting SD, Venzon D, et al: Effect of raloxifene on insulin-like growth factor-I, insulin-like growth factor binding protein-3, and leptin in premenopausal women at high risk for developing breast cancer. Cancer Epidemiol Biomarkers Prev 12:1468-1473, 2003

116. Tommaselli GA, Di Carlo C, Nasti A, et al: Effects of bilateral ovariectomy and postoperative hormonal replacement therapy with 17beta-estradiol or raloxifene on serum leptin levels. Menopause 10:160-164, 2003

117. Ozet A, Arpaci F, Yilmaz MI, et al: Effects of tamoxifen on the serum leptin level in patients with breast cancer. Jpn J Clin Oncol 31:424-427, 2001

118. Marttunen MB, Andersson S, Hietanen P, et al: Antiestrogenic tamoxifen and toremifene increase serum leptin levels in postmenopausal breast cancer patients. Maturitas 35:175-179, 2000

119. Hu X, Juneja SC, Maihle NJ, et al: Leptin–A growth factor in normal and malignant breast cells and for normal mammary gland development. J Natl Cancer Inst 94:1704-1711, 2002

120. Petridou E, Papadiamantis Y, Markopoulos C, et al: Leptin and insulin growth factor I in relation to breast cancer. Cancer Causes Control 11:383-388, 2000

121. Mantzoros CS, Bolhke K, Moschos S, et al: Leptin in relation to carcinoma in situ of the breast: A study of pre-menopausal cases and controls. Int J Cancer 80:523-526, 1999

122. Tessitore L, Vizio B, Jenkins O, et al: Leptin expression in colorectal and breast cancer patients. Int J Mol Med 5:421-426, 2000

123. Barrett-Connor E, Grady D, Sashegyi A, et al: Raloxifene and cardiovascular events in osteoporotic postmenopausal women: Four-year results from the MORE (Multiple Outcomes of Raloxifene Evaluation) randomized trial. JAMA 287:847-857, 2002

124. Zujewski J, Eng-Wong J, Reynolds J, et al: A phase 2 trial of raloxifene in premenopausal women at high risk for developing invasive breast cancer. Breast Cancer Res Treat 76: S108, 2002 (abstr 417; suppl 1)

125. Reindollar R, Koltun W, Parsons A, et al: Effects of oral raloxifene on serum estradiol levels and other markers of estrogenicity. Fertil Steril 78:469-472, 2002

126. Duschek EJ, de Valk-de Roo GW, Gooren LJ, et al: Effects of conjugated equine estrogen vs. raloxifene on serum insulin-like growth factor-i and insulin-like growth factor binding protein-3: A 2-year, double-blind, placebo-controlled study. Fertil Steril 82:384-390, 2004

127. Torrisi R, Baglietto L, Johansson H, et al: Effect of raloxifene on IGF-I and IGFBP-3 in postmenopausal women with breast cancer. Br J Cancer 85:1838-1841, 2001

128. Martino S, Cauley JA, Barrett-Connor E, et al: Continuing Outcomes Relevant to Evista: Breast cancer incidence in postmenopausal osteoporotic women in a randomized trial of raloxifene. J Natl Cancer Inst 96:1751-1761, 2004

129. Cummings SR, Duong T, Kenyon E, et al: Serum estradiol level and risk of breast cancer during treatment with raloxifene. JAMA 287: 216-220, 2002

130. Blumenthal RS, Baranowski B, Dowsett SA: Cardiovascular effects of raloxifene: The arterial and venous systems. Am Heart J 147: 783-789, 2004

131. Sato M, Turner CH, Wang T, et al: LY353381.HCl: A novel raloxifene analog with improved SERM potency and efficacy in vivo. J Pharmacol Exp Ther 287:1-7, 1998

132. Suh N, Glasebrook AL, Palkowitz AD, et al: Arzoxifene, a new selective estrogen receptor modulator for chemoprevention of experimental breast cancer. Cancer Res 61:8412-8415, 2001

133. Gutman M, Couillard S, Roy J, et al: Comparison of the effects of EM-652 (SCH57068), tamoxifen, toremifene, droloxifene, idoxifene, GW-5638 and raloxifene on the growth of human ZR-75-1 breast tumors in nude mice. Int J Cancer 99:273-278, 2002

134. Luo S, Labrie C, Bélanger A, et al: Prevention of development of dimenthylbenz(a)anthracene (DMBA)-induced mammary tumors in the rat by the new nonsteroidal antiestrogen EM-800 (SCH 57050). Breast Cancer Res Treat 49:1-11, 1998

135. Roy J, Couillard S, Gutman M, et al: A novel pure SERM achieves complete regression of the majority of human breast cancer tumors in nude mice. Breast Cancer Res Treat 81:223-229, 2003

136. Schafer JM, Lee ES, Dardes RC, et al: Analysis of cross-resistance of the selective estrogen receptor modulators arzoxifene (LY353381) and LY117018 in tamoxifen-stimulated breast cancer xenografts. Clin Cancer Res 7:2505-2512, 2001

137. Couillard S, Gutman M, Labrie C, et al: Comparison of the effects of the antiestrogens EM-800 and tamoxifen on the growth of human breast ZR-75-1 cancer xenografts in nude mice. Cancer Res 58:60-64, 1998

138. Simard J, Labrie C, Bélanger A, et al: Characterization of the effects of the novel nonsteroidal antiestrogen EM-800 on basal and estrogen-induced proliferation of T-47D, ZR-75-1 and MCF-7 human breast cancer cells in vitro. Int J Cancer 73:104-112, 1997

139. Tremblay A, Tremblay GB, Labrie C, et al: EM-800, a novel antiestrogen, acts as a pure antagonist of the transcriptional functions of estrogen receptors alpha and beta. Endocrinology 139:111-118, 1998

140. Tremblay A, Tremblay GB, Labrie F, et al: Ligand-independent recruitment of SRC-1 to estrogen receptor beta through phosphorylation of activation function AF-1. Mol Cell 3:513-519, 1999

141. Munster PN, Buzdar A, Dhingra K, et al: Phase I study of a third-generation selective estrogen receptor modulator, LY353381.HCL, in metastatic breast cancer. J Clin Oncol 19:2002-2009, 2001

142. Buzdar A, O'Shaughnessy JA, Booser DJ, et al: Phase II, randomized, double-blind study of two dose levels of arzoxifene in patients with locally advanced or metastatic breast cancer. J Clin Oncol 21:1007-1014, 2003

143. Baselga J, Llombart-Cussac A, Bellet M, et al: Randomized, double-blind, multicenter trial comparing two doses of arzoxifene (LY353381) in hormone-sensitive advanced or metastatic breast cancer patients. Ann Oncol 14:1383-1390, 2003

144. Labrie F, Champagne P, Labrie C, et al: Activity and safety of the antiestrogen EM-800, the orally active precursor of acolbifene, in tamoxifen-resistant breast cancer. J Clin Oncol 22:864-871, 2004

145. Ma YL, Bryant HU, Zeng Q, et al: Long-term dosing of arzoxifene lowers cholesterol, reduces bone turnover, and preserves bone quality in ovariectomized rats. J Bone Miner Res 17:2256-2264, 2002

146. Martel C, Picard S, Richard V, et al: Prevention of bone loss by EM-800 and raloxifene in the ovariectomized rat. J Steroid Biochem Mol Biol 74:45-56, 2000

147. Dardes RC, Bentrem D, O'Regan RM, et al: Effects of the new selective estrogen receptor modulator LY353381.HCl (Arzoxifene) on human endometrial cancer growth in athymic mice. Clin Cancer Res 7:4149-4155, 2001

148. Fabian CF, Lukert B, Chamberlain C, et al: Effects of arzoxifene, a third generation SERM, on serum osteocalcin levels and bone mineral density in pre- and post-menopausal women at increased risk for breast cancer. Proc Am Assoc Cancer Res 43:822, 2002 (abstr 4081)

149. Picard F, Deshaies Y, Lalonde J, et al: Effects of the estrogen antagonist EM-652.HCl on energy balance and lipid metabolism in ovariectomized rats. Int J Obes Relat Metab Disord 24:830-840, 2000

150. Lemieux C, Picard F, Labrie F, et al: The estrogen antagonist EM-652 and dehydroepiandrosterone prevent the metabolic disturbances induced by an obesity-promoting diet and ovariectomy. Obes Res 11:477-490, 2003

151. Furberg AS, Veierod MB, Wilsgaard T, et al: Serum high-density lipoprotein cholesterol, metabolic profile, and breast cancer risk. J Natl Cancer Inst 96:1152-1160, 2004

152. Fabian CJ, Kimler BF, Anderson J, et al: Breast cancer chemoprevention phase I evaluation of biomarker modulation by arzoxifene, a third generation selective estrogen receptor modulator. Clin Cancer Res 10:5403-5417, 2004

153. Luo S, Martel C, Gauthier S, et al: Long term inhibitory effects of a novel antiestrogen on the growth of ZR-75-1 and MCF-7 human breast cancer tumors in nude mice. Int J Cancer 73: 735-739, 1997

154. Luo S, Martel C, Sourla A, et al: Comparative effects of 28-day treatment with the new antiestrogen EM-800 and tamoxifen on estrogen-sensitive parameters in the intact mouse. Int J Cancer 73:381-391, 1997

155. Luo S, Sourla A, Labrie C, et al: Combined effects of dehydroepiandrosterone and EM-800 on bone mass, serum lipids, and the development of dimethylbenz(a)anthracene (DMBA)-induced mammary carcinoma in the rat. Endocrinology 138:4435-4444, 1997

156. Schiff R, Massarweh S, Shou J, et al: Breast cancer endocrine resistance: How growth factor signaling and estrogen receptor coregulators modulate response. Clin Cancer Res 9:447S-454S, 2003

157. Nicholson RI, Hutcheson IR, Harper ME, et al: Modulation of epidermal growth factor receptor in endocrine-resistant, oestrogen

receptor-positive breast cancer. Endocr Relat Cancer 8:175-182, 2001

158. Martin MB, Franke TF, Stoica GE, et al: A role for Akt in mediating the estrogenic functions of epidermal growth factor and insulin-like growth factor I. Endocrinology 141:4503-4511, 2000

159. Lee AV, Cui X, Oesterreich S: Cross-talk among estrogen receptor, epidermal growth factor, and insulin-like growth factor signaling in breast cancer. Clin Cancer Res 7:4429s-4435s, 2001 (suppl 12)

160. Sporn MB: Hobson's choice and the need for combinations of new agents for the prevention and treatment of breast cancer. J Natl Cancer Inst 94:242-243, 2002

161. Sun SY, Hail N, Jr., Lotan R: Apoptosis as a novel target for cancer chemoprevention. J Natl Cancer Inst 96:662-672, 2004

162. Cameron EE, Bachman KE, Myohanen S, et al: Synergy of demethylation of histone deacetylase inhibition in the re-expression of genes silenced in cancer. Nat Genet 21:103-107, 1999

163. Nan X, Ng HH, Johnson CA, et al: Transcriptional repression by the methyl-CpG-binding protein MeCP2 involves a histone deacetylase complex. Nature 393:386-389, 1998

164. Gilbert J, Gore SD, Herman JG, et al: The clinical application of targeting cancer through histone acetylation and hypomethylation. Clin Cancer Res 10:4589-4596, 2004

165. Cheng JC, Matsen CB, Gonzales FA, et al: Inhibition of DNA methylation and reactivation of silenced genes by zebularine. J Natl Cancer Inst 95:399-409, 2003

166. Yan L, Nass SJ, Smith D, et al: Specific inhibition of DNMT1 by antisense oligonucleotides induces re-expression of estrogen receptor-alpha (ER) in ER-negative human breast cancer cell lines. Cancer Biol Ther 2:552-556, 2003

167. Marks PA, Richon VM, Breslow R, et al: Histone deacetylase inhibitors as new cancer drugs. Curr Opin Oncol 13:477-483, 2001

168. Richon VM, O'Brien JP: Histone deacetylase inhibitors: A new class of potential therapeutic agents for cancer treatment. Clin Cancer Res 8:662-664, 2002

169. Sandor V, Bakke S, Robey RW, et al: Phase I trial of the histone deacetylase inhibitor, depsipeptide (FR901228, NSC 630176), in patients with refractory neoplasms. Clin Cancer Res 8:718-728, 2002

170. Galvez AF, Chen N, Macasieb J, et al: Chemopreventive property of a soybean peptide (lunasin) that binds to deacetylated histones and inhibits acetylation. Cancer Res 61:7473-7478, 2001

171. Li Y, Bhuiyan M, Sarkar FH: Induction of apoptosis and inhibition of c-erbB-2 in MDA-MB-435 cells by genistein. Int J Oncol 15:525-533, 1999

172. Tanos V, Brzezinski A, Drize O, et al: Synergistic inhibitory effects of genistein and tamoxifen on human dysplastic and malignant epithelial breast cells in vitro. Eur J Obstet Gynecol Reprod Biol 102:188-194, 2002

173. Ju YH, Doerge DR, Allred KF, et al: Dietary genistein negates the inhibitory effect of tamoxifen on growth of estrogen-dependent human breast cancer (MCF-7) cells implanted in athymic mice. Cancer Res 62:2474-2477, 2002

174. Allred CD, Ju YH, Allred KF, et al: Dietary genistin stimulates growth of estrogen-dependent breast cancer tumors similar to that observed with genistein. Carcinogenesis 22:1667-1673, 2001

175. Mueller SO, Simon S, Chae K, et al: Phytoestrogens and their human metabolites show distinct agonistic and antagonistic properties on estrogen receptor alpha (ERalpha) and ERbeta in human cells. Toxicol Sci 80:14-25, 2004

176. Cotroneo MS, Wang J, Fritz WA, et al: Genistein action in the prepubertal mammary gland in a chemoprevention model. Carcinogenesis 23:1467-1474, 2002

177. Kuiper GG, Lemmen JG, Carlsson B, et al: Interaction of estrogenic chemicals and phytoestrogens with estrogen receptor beta. Endocrinology 139:4252-4263, 1998

178. Kim H, Peterson TG, Barnes S: Mechanisms of action of the soy isoflavone genistein: Emerging role for its effects via transforming growth factor beta signaling pathways. Am J Clin Nutr 68:1418S-1425S, 1998 (suppl 6)

179. An J, Tzagarakis-Foster C, Scharschmidt TC, et al: Estrogen receptor beta-selective transcriptional activity and recruitment of coregulators by phytoestrogens. J Biol Chem 276:17808-17814, 2001

180. Chen J, Stavro PM, Thompson LU: Dietary flaxseed inhibits human breast cancer growth and metastasis and downregulates expression of insulin-like growth factor and epidermal growth factor receptor. Nutr Cancer 43:187-192, 2002

181. Dabrosin C, Chen J, Wang L, et al: Flaxseed inhibits metastasis and decreases extracellular vascular endothelial growth factor in human breast cancer xenografts. Cancer Lett 185:31-37, 2002

182. Chen J, Thompson LU: Lignans and tamoxifen, alone or in combination, reduce human breast cancer cell adhesion, invasion and migration in vitro. Breast Cancer Res Treat 80:163-170, 2003

183. Baselga J, Albanell J, Ruiz A, et al: Phase II and tumor pharmacodynamic study of gefinitib (ZD1839) in patients with advanced breast cancer. Proc Am Soc Clin Oncol 22:7, 2003 (abstr 24)

184. Moulder SL, Yakes FM, Muthuswamy SK, et al: Epidermal growth factor receptor (HER1) tyrosine kinase inhibitor ZD1839 (Iressa) inhibits HER2/neu (erbB2)-overexpressing breast cancer cells in vitro and in vivo. Cancer Res 61:8887-8895, 2001

185. Bharwani L, Schiff R, Mohsin SK, et al: Inhibiting the EGFR/HER2 pathway with gefitinib and/or trastuzumab restores tamoxifen sensitivity in HER2-overexpressing tumors. Breast Cancer Res Treat 82:S13, 2003 (suppl 1)

186. Bundred NJ, Anderson EA, Gee J, et al: Randomised, double-blind, placebo-controlled trial of short-term effects of gefitinib ('Iressa', ZD1839) on ductal carcinoma in situ. Breast Cancer Res Treat 82:S10, 2003 (suppl 1)

187. Wolf M, Swaisland H, Averbuch S: Development of the novel biologically targeted anticancer agent gefitinib: Determining the optimum dose for clinical efficacy. Clin Cancer Res 10:4607-4613, 2004

188. Widschwendter M, Berger J, Muller HM, et al: Epigenetic downregulation of the retinoic acid receptor-beta2 gene in breast cancer. J Mammary Gland Biol Neoplasia 6:193-201, 2001

189. Rubin M, Fenig E, Rosenauer A, et al: 9-Cis retinoic acid inhibits growth of breast cancer cells and down-regulates estrogen receptor RNA and protein. Cancer Res 54:6549-6556, 1994

190. Wu K, Zhang Y, Xu XC, et al: The retinoid X receptor-selective retinoid, LGD1069, prevents the development of estrogen receptor-negative mammary tumors in transgenic mice. Cancer Res 62:6376-6380, 2002

191. Veronesi U, DePalo G, Marubini E, et al: Randomized trial of fenretinide to prevent second breast malignancy in women with early breast cancer. J Natl Cancer Inst 91:1847-1856, 1999

192. Suh N, Lamph WW, Glasebrook AL, et al: Prevention and treatment of experimental breast cancer with the combination of a new selective estrogen receptor modulator, arzoxifene, and a new rexinoid, LG 100268. Clin Cancer Res 8: 3270-3275, 2002

193. Rendi MH, Suh N, Lamph WW, et al: The selective estrogen receptor modulator arzoxifene and the rexinoid LG100268 cooperate to promote transforming growth factor beta-dependent apoptosis in breast cancer. Cancer Res 64:3566-3571, 2004

194. Farris MR, Risingsong R, Williams C, et al: The SERM, arzoxifene, and the rexinoid LG100268, synergize to promote apoptosis in estrogen receptor positive and negative breast cancer cells as well as in a rat breast cancer model. Proc Am Assoc Cancer Res 44:519-520, 2003 (abstr R2642)

195. Grubbs CJ, Reddy VR, Brouillette WJ, et al: Efficacy of two new RXR selective retinoids, RA-II-40 A and RA-IV-10A, on mammary cancers induced by methylnitrosourea (MNU) in Sprague-Dawley rats. American Association for Cancer Research Frontiers in Cancer Prevention Research: 36, 2003 (abstr A139)

196. Anzano MA, Byers SW, Smith JM, et al: Prevention of breast cancer in the rat with 9-cis-retinoic acid as a single agent and in combination with tamoxifen. Cancer Res 54:4614-4617, 1994

197. Anzano MA, Peer CW, Smith JM, et al: Chemoprevention of mammary carcinogenesis in the rat: Combined use of raloxifene and 9-cis-retinoic acid. J Natl Cancer Inst 88:123-125, 1996

198. Decensi A, Bonanni B, Guerrieri-Gonzaga A, et al: A randomized 2×2 biomarker trial of low-dose tamoxifen and fenretinide in premenopausal women at-high risk for breast cancer. Proc Am Soc Clin Oncol 22:14S, 2004 (abstr 1001)

199. Mohsin SK, Elledge RM, Arun B, et al: Breast cancer prevention using RXR-selective retinoid (Targretin) in high risk women – initial report of a phase II randomized clinical trial. Breast Cancer Res Treat 82: S176, 2003 (abstr 1029; suppl 1)

200. Harris HA, Albert LM, Leathurby Y, et al: Evaluation of an estrogen receptor-beta agonist in animal models of human disease. Endocrinology 144:4241-4249, 2003

201. Paik S, Shak S, Tang G, et al: Multi-gene RT-PCR assay for predicting recurrence in node negative breast cancer patients -NSABP studies B-20 and B-14. Breast Cancer Res Treat 82:S10-S11, 2003 (suppl 1)