Breast Cancer Prevention
Myths versus Facts

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Internal Medicine Grand Rounds
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This is to acknowledge that Dawn Klemow, M.D. has disclosed financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Dawn Klemow will not be discussing off-label uses in her presentation.

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GOAL:

Provide a comprehensive and thorough review of the current understanding of breast cancer prevention.

OVERVIEW OF CONTENT AND OBJECTIVES:

1. Discuss the role of common supplements and medications in reducing breast cancer risk.
2. Discuss the impact of diet and exercise in risk reduction.
3. Review the data regarding SERM's and aromatase inhibitors in risk reduction strategies.
4. Future directions and how to counsel our patients.

Introduction

For women in the United States, breast cancer is the most common non-dermatologic cancer and the second leading cause of cancer death. Although breast cancer incidence rates dropped by close to 7% between 2002 and 2007 after a dramatic decline in the use of hormone replacement therapy, breast cancer incidence rates have now stabilized and it estimated that 1 in 8 (12%) of women in the US will develop an invasive breast cancer in their lifetime. It is therefore of paramount importance that prevention strategies continue to be an area of active interest and research. A variety of interventions have been proposed and evaluated to alter breast cancer risk and at this time I would like to review the salient data pertinent to breast cancer risk reduction.

The Role of Soy in Breast Cancer Reduction

There has been much interest in the potentially protective role of soy. Not expectantly, recent attention has been focused on factors that affect estrogen regulation and exposure due to the convincing data that estrogen is involved in certain subtypes of breast cancer. Isoflavones, the predominant phytoestrogen in soy products, are diphenolic compounds with a chemical structure similar to I7*b* estradiol, which have an affinity for both ER*b* and Er*a* receptors, with preferential binding to ERb. This preferential binding provides one ER dependent mechanism for the proposed chemopreventive action of isoflavones as there is evidence that ER*b* transactivation inhibits the stimulatory effects of Er*a* transactivation on breast cell proliferation. In addition to modulating estrogenic function, isoflavones have been shown to have anticancer effects through inhibition of DNA topoisomerase I and II, antiangiogenesis, aromatase inhibition, antioxidant and anti-inflammatory effects, and inhibition of tyrosine kinases whose actions are crucial to the control of cellular growth and apoptosis. The most common isoflavone, genistein, has been shown to influence multiple regulatory pathways involved in cellular growth and survival. The PI3kinase/Akt pathway is a central gatekeeper for crucial cellular functions including glucose metabolism, cellular proliferation, apoptosis, transcription, and cell migration. PTEN, a tumor suppressor gene, down-regulates the AKT pathway, thus inhibiting tumor cell growth. Genistein, in in-vitro mammary cell studies, has been shown to promote PTEN expression. Similar effects of genistein on E-cadherin, another potent tumor suppressor gene involved in breast carcinogenesis, have been reported.

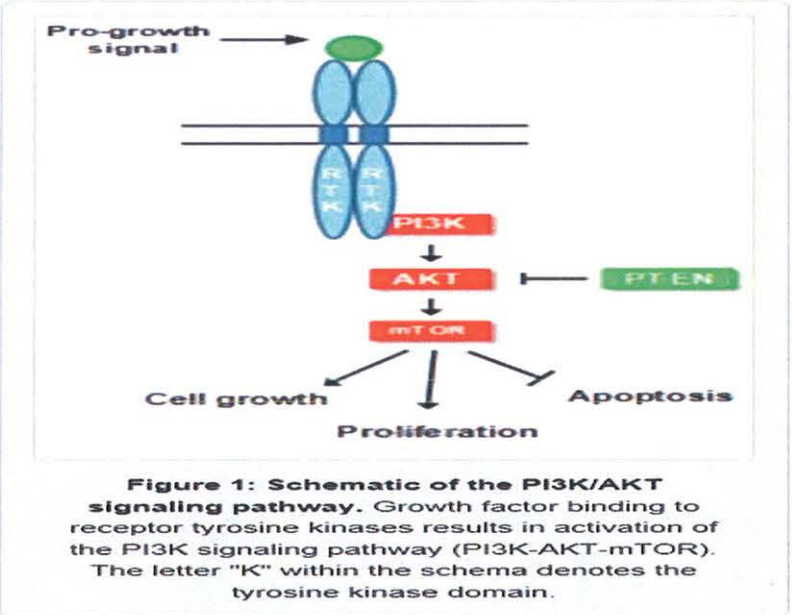

Figure 1: Schematic of the PI3K/AKT signaling pathway. Growth factor binding to receptor tyrosine kinases results in activation of the PI3K signaling pathway (PI3K-AKT-mTOR). The letter "K" within the schema denotes the tyrosine kinase domain.

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There is much conflicting data in the literature regarding soy in regards to its role in breast cancer prevention. In part, the conflict arises due to the heterogeneity of the population studies, the types and quantities of soy ingested, and the age at which soy ingestion begins. Migration studies have suggested childhood environmental exposure has a profound impact on breast cancer risk. Breast cancer rates are consistently higher in Western countries than in Asia; yet among Asian migrants to the U.S., breast cancer risk increases over several generations and eventually approaches that of the U.S. in a population-based case control study of breast cancer among Asians born in the U.S., initiating soy intake in childhood or adolescence was associated with a relative risk of breast cancer of 0.4 and 0.8 respectively, with the greatest benefit being in those who were high consumers. In addition, Asian women who consumed soy both during childhood and adult life derived the most benefit.[1] It has been reported that childhood soy intake was about twice as protective against breast cancer as was consumption during teenage years.[2] In contrast, multiple studies examining initiating soy intake in adulthood have shown less consistent benefit. [3]

One proposed mechanism for the benefits of soy exposure in childhood is early promotion of mammary tissue differentiation, as the undifferentiated epithelial cells are the structures most susceptible to chemical carcinogens. Another postulated mechanism is the downregulation of the Wnt signaling pathway which drives the proliferation of mammary progenitor cells and prevents their differentiation, suggesting that early life exposure protects the breast by affecting mammary stem cell behavior. Although much is still unknown in regards to the effects of soy on breast cancer risk, there is sufficient data to support its benefits, especially when consumed from early childhood.[3]

Large differences in study results exist between Asian and Western populations in regards to benefit, possibly due to the low amount of soy consumption that is typical of the Western diet. Studies have also varied in regards to how much soy needs to be ingested to obtain beneficial effects. There does appears however to be a significant dose response relationship with those ingesting greater than 20mg/day (equivalent to a serving of tofu) of isoflavones reaping the greatest benefit.[1]

What about Soy after a diagnosis of breast cancer?

In contrast to the correlations of soy consumption and breast cancer development, exposure of pre-existing estrogen dependent tumors to the estrogenic effects of dietary genestein may have a negative outcome by stimulating growth. In vitro and in vivo studies have shown that genistein stimulates growth of MCF-7 human breast cancer cells.[4] A number of epidemiological and animal models have shown that consumption of highly enriched soy products such as the supplements and soy enriched foods consumed in Westernized countries is potentially more deleterious than consumption of isoflavones in less processed forms.[5] Only prospective intervention studies would definitely answer the question of safety of soy products in breast cancer survivors and it is doubtful for ethical reasons that these studies would ever be done. Therefore, for the time being, the current recommendation for breast cancer survivors of avoiding highly enriched soy products seems the safer choice.

Exercise and breast cancer risk reduction

Many prospective studies have investigated the association between physical activity and breast cancer risk with most finding a 10% to 30% reduction in risk in physically active women.[6] Studies have shown that exercise can reduce chronic inflammation by inducing anti-inflammatory effects. On a molecular level, during exercise IL-6 is produced by contracting muscle fibers, which in turn acts as a myokine that can inhibit pro-inflammatory cytokine expression. Exercise can also reduce adiposity by IL6 mediated lipolysis and by diminishing levels of adipose derived cytokines TNFα and IL1B. In addition, significant decreases in fasting insulin, IGF-1, and IGFBP-3 have been consistently reported. Studies have varied by frequency and intensity of exercise. As of 2010, 73 separate studies have addressed the issue of exercise and breast cancer risk reduction, with the majority revealing a reduction in risk with 40% of these studies reaching statistical significance. The magnitude of risk reduction was on average 25% when comparing the most to the least active study participants. The types and durations of activity varied with greater benefits seen with higher intensity and longer durations of exercise. A number of studies also examined physical activities at various times of life. The greatest average risk reduction (27%) was observed for sustained activity over the adult lifetime particularly if initiated in adolescence, but a 17% risk reduction was seen as well in participants who initiated exercise after age 50. In subgroup analysis, both pre- and postmenopausal women experienced a benefit from exercise, with a slightly stronger risk reduction observed for postmenopausal women (31%) vs. premenopausal women (27%).[7]

In regards to BMI, the greatest benefit of physical activity was observed among lean women with a BMI<22 who experienced an average risk reduction of 27% vs. women with normal BMI's (22-24.9) at 24% and overweight women (BMI 25.0-30) at 18% risk reduction. No benefit was observed for obese women (BMI>30) but the number of studies including this subset was small (n=5 studies). In regards to ethnicity, the greatest impact of physical activity was observed in Asian and African American women who experienced an average decrease of 41%. Lesser impacts were observed in Indian (37%), Hispanic (28%), and Caucasian (20%) women. Four studies have examined the influence of a family history of breast cancer on the association between physical activity and breast cancer risk. Of those reported, a positive family history essentially negated the effects of exercise (21% vs. 1%), but given the small sample size, caution should be taken in interpreting this data. In regards to the effects of exercise on hormonal status of subsequent breast cancer development, the data was inconsistent, but in general, the impact was greater for women with ER-/PR- cancer (on average 27%) vs. ER+/PR+ cancers (14%).[7]

Breast Cancer, Adiposity, and Exercise

Physical activity may influence cancer risk by means of weight control, in addition to altering several interrelated biologic pathways relevant to cancer, including hyperinsulinemia, chronic inflammation, concentrations of adipocytokines, and sex steroid hormones, as well as effects on immune function.

The Alberta trial, a randomized controlled trial of 320 sedentary postmenopausal women aged 50-74, examined the effects of 45 minutes of aerobic exercise five times per week for one year. This intervention program resulted in reductions in estradiol concentrations and increases in sex hormone binding globulin (SHBG) that were consistent with a reduced risk of breast cancer.[8] Physical activity may influence circulating estrogens by reducing adiposity, which decreases the conversion of androgens to estrogen by aromatase. In this particular study, additional adjustments for weight change attenuated the effect of exercise intervention on SHBG but not on free estradiol levels. Therefore, physical activity appears to have a beneficial effect independent of changes in weight. In this trial, the main analysis showed an inverse effect of exercise on insulin levels, HOMA-IR (a method used to quantify insulin resistance and beta cell function), and leptin levels ($p<0.001$), and a positive effect on the adiponectin/leptin (A/L) ratio, an emerging novel marker of insulin resistance ($P< 0.0001$). Secondary analysis suggests that a loss of total and central adiposity may be required to effect these changes.[8]

Another large study, the Nurse's Health Initiative revealed similar results. Analyzing data of postmenopausal women, significantly lower breast cancer risks were associated with higher activity. In this study, weight change since 18 years of age, BMI, HRT, and family history of breast cancer did not modify the association between total activity and breast cancer risk. In addition, the association did not differ by ER/PR status or by ductal or lobular subtypes.[6]

McTiernan examined estrogen levels in 170 postmenopausal sedentary women over a 12 month period of moderate-intensity exercise, to include at least 45 minutes five days per week vs. controls. The decrease in estradiol levels exhibited a positive correlation with loss of body fat mass. The author postulated that the association between increased physical activity and reduced risk for postmenopausal breast cancer may be partly explained by effects on serum estrogen levels.[9]

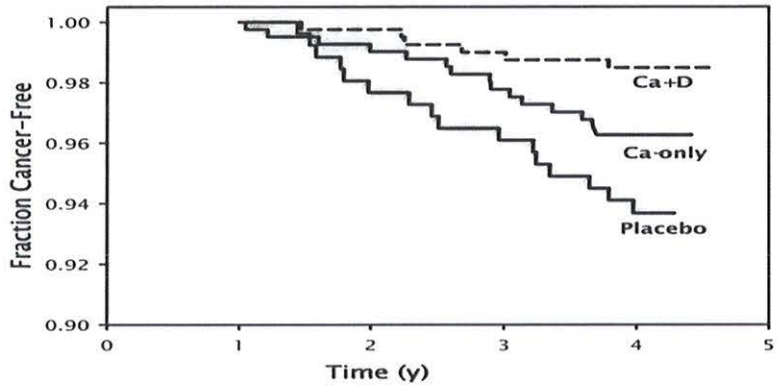
It would appear that exercise is one modifiable lifestyle change that women can adopt that may substantially reduce their lifetime risk of breast cancer. Therefore implementation of a regular physical activity regimen should be part of a healthy lifestyle adopted by women starting in adolescence and continued throughout their lifetime.

Calcium, Vitamin D and breast cancer risk

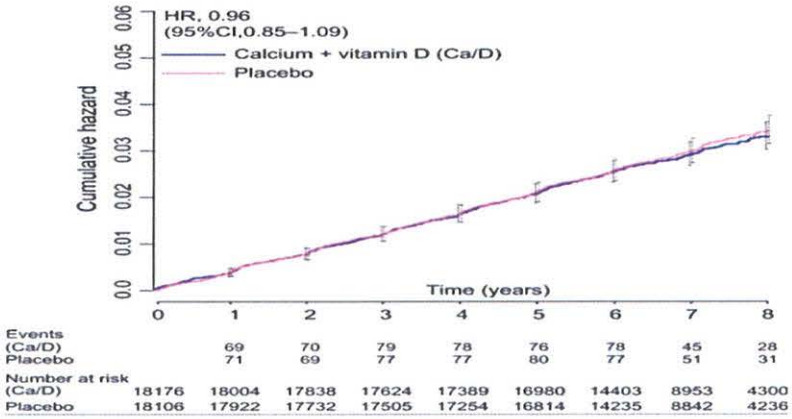
Vitamin D has been reported to have anticancer activity against many cancer types, including breast, colorectal and prostate cancers. Much controversy exists regarding the benefit relating in part to many confounding variables. The overall relationship between vitamin D and calcium intake, levels of circulating vitamin D and calcium intake, levels of circulating vitamin D metabolites, and cancer risk are not clear. Vitamin D has been found to participate in regulating apoptosis, cell proliferation and differentiation, immune function, as well as having anti-angiogenic effects.

A four year double blind placebo controlled trial of 1179 postmenopausal women randomized to receive 1400-1500mg supplemental calcium alone, supplemental calcium plus 1100 IU vitamin D3, or placebo and evaluated the incident cancer risk of all types. Vitamin D intervention was sufficient to raise 25(OH)

vitamin D levels > 80nmol/L. In comparison to the placebo group, the RR of developing cancer at study end was 0.402 for the calcium + vitamin D (p=0.013) and 0.532 for the calcium only group (p= 0.063).[10]



In contrast, the Women's Health Initiative (WHI), a trial of 36, 282 postmenopausal women randomized to l000 mg of elemental calcium with 400 IU of vitamin D3 vs. placebo for a mean of 7 years found no benefit in reduction of breast cancer risk with calcium and vitamin D3 supplementation. [11]



A meta-analysis revealed a significant 9% decrease in breast cancer risk for women with 25(OH) vitamin D levels in the highest quartile (>30ng/ml) vs. those in the lowest (<20ng/ml) (RR=.91).[12]

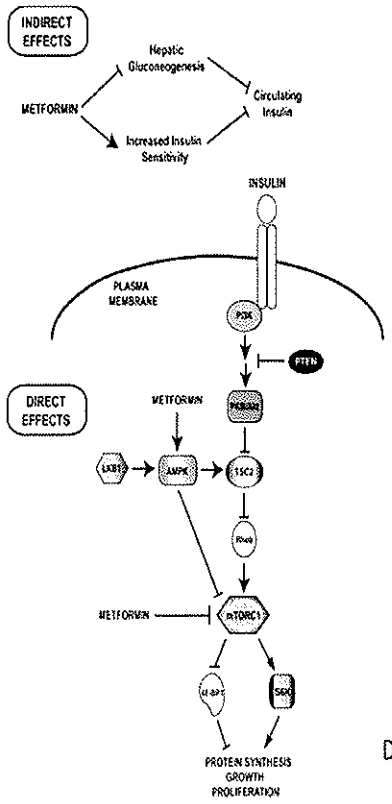
Mammographic density, a known variable associated with increased breast cancer risk was evaluated in the Nurse's Health Study (NHS). This case controlled study of 960 postmenopausal women found no relationship between plasma 25(OH) vitamin D levels and mammographic density.[13]

In conclusion, there is insufficient evidence to support a significant association between oral intake and/or circulating plasma levels of vitamin D and risk of breast cancer. Studies in the literature are heterogeneous, revealing conflicting results with confounding variables not always accounted for. Further research is needed, directed at looking at perhaps the safety and efficacy of higher doses of

vitamin D before women should be advised to increase their vitamin D intake in order to lower breast cancer risk.

Metformin and Breast Cancer Risk

In the WHI, 9277 medication treated cases of women with DM were identified in the cohort and followed for an average of 11.1 years. 2,963 of these women were being treated with metformin. 422 women developed invasive breast cancer during this time period. After adjusting for confounding variables, including BMI, Gail score risk, HRT, and physical activity, women on metformin compared to other diabetic medications had a 38% lower risk of ER+PR+ breast cancers (p=0.2).[14] Given these findings, pursuits were undertaken to evaluate how metformin might impact cancer risk. Studies have shown that metformin exerts its cell growth inhibitory effects by activating AMPK, a cellular energy sensor. Activation of AMPK inhibits the MTOR signaling pathway, thus inhibiting signaling pathways that promote cell growth and proliferation. This mechanism may contribute to the antineoplastic effects of metformin. In addition, metformin has been shown to inhibit aromatase activity, providing a mechanism to reduce local production of estrogen within breast tissue as well as circulating estrogen levels. Although results look promising, the number of patients in the WHI study on metformin was small, and further research is needed to substantiate these findings.



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Anti-Inflammatories and Breast Cancer

Numerous epidemiologic studies have examined the association between NSAIDs, aspirin, and breast cancer risk reduction with equivocal results. Several cohort studies have found a reduced risk of breast cancer associated with aspirin use. Others have failed to find any association or have even suggested an

increased risk. Few meta-analysis of an association have been performed, and most have had methodological limitations. A protective role of NSAIDs in breast carcinogenesis is biologically plausible. In vitro and animal studies have consistently shown that NSAIDs inhibit cyclooxygenases and inactivating COX-2 may interrupt the carcinogenic process in the breast via multiple pathways-including inhibition of angiogenesis, promotion of apoptosis, and suppression of estrogen synthesis via decreased aromatase activity. Studies have demonstrated that the level of prostaglandins is higher in breast cancer cells than in normal tissue, making the inhibition of prostaglandin synthesis a potentially promising intervention to decrease breast cancer risk.[15]

In the Nurse's Health II study, one of the few trials looking at the potential benefit of aspirin and NSAID's in premenopausal women, a total of 112, 292 premenopausal women were followed from l989-2003. Overall, 1,345 cases of invasive breast cancer were documented. Multivariate analysis controlled for the most common known risk factors including age at first birth, alcohol consumption, BMI, BCP use, history of benign breast disease, and positive family history. Compared with non-users, current regular users of aspirin (≥2x/wk.) were not at a decreased risk of breast cancer (RR-1.07). Duration of use among current users (<5 years vs. >5 years) was not associated with risk (RR=1.03). No association with hormone status of breast cancer was seen. (RR=0.97) for ER+/PR+ and (RR=1.21) for ER-/PR-.[16]

In contrast, the Institutes of Health-AARP Diet and Health Study examined 127,383 women aged 51-72 with no prior history of breast cancer. This prospective cohort study examined reported use over the prior 12 month period. No statistically significant association with the exception of a reduction in ER+ breast cancer was found with daily aspirin use (RR=0.84).[15]

In 2010, a prospective observational study using data of 4,164 women from the NHS II diagnosed with Stages I-III breast cancer reported a significant decrease in distant relapse and mortality with the use of aspirin. For those women using aspirin 2 to 5 times per week, a 71% reduction in risk of breast cancer death and a 60% reduction in distant reoccurrence were seen. This association did not differ appreciably by stage, menopausal status, BMI or ER status. Although very encouraging, this study must be interpreted with caution. This was an observational study, with information on dose and frequency of aspirin use, treatment, and distant reoccurrence being self-reported.[17]

In conclusion, more research is needed, including prospective, randomized clinical trials to evaluate the role of aspirin and NSAIDs in breast cancer prevention and in decreasing risk of breast cancer reoccurrence and mortality.

Statins

Statins are a therapeutic class of drugs that reduce plasma cholesterol levels and are used to manage and prevent coronary artery disease. There is a growing body of evidence, however, that statins appear to induce apoptosis and reduce cell invasiveness in various cell lines, including mammary carcinomas. It appears that only the lipophilic statins (lovastatin, simvastatin) are able to permeate the cell membrane and affect cell proliferation, survival, and motility. In vitro studies have shown inhibition of the Ras-Raf-Mek/Erk cascade upon exposure to lipophilic statins.[18] Despite encouraging in vitro data, studies to date have not shown convincing evidence that statin use decreases breast cancer risk and further research is needed.

Alcohol Use and Risk of Breast Cancer

Alcohol consumption is a known risk factor for breast cancer. This association is thought to be largely hormonally driven and may vary by subtype of breast cancer. The WHI study reported, via a prospective

cohort study of 87,724 postmenopausal women, that drinking 7 or more alcoholic beverages/week was more strongly associated with lobular carcinomas than ductal carcinomas. (HR=1.82 vs. HR=1.14 respectively), and that higher quantities of alcohol intake were associated with an increased risk of invasive breast cancer overall. This and other studies as well have shown a correlation between alcohol consumption and ER+/PR+ breast cancers, suggesting the association is likely hormonally driven, with an average increase in risk of 7-12% per each l0gm/day of alcohol consumed.[19]

There are several potential mechanisms by which alcohol consumption may increase breast cancer risk. Higher levels of circulating estrogen have been associated with alcohol consumption, and in vitro, ethanol increases cellular responsiveness to estrogen, stimulates the transcriptional activity of the estrogen receptor alpha (Erα), and downregulates the mRNA and protein levels of the BRCA1 tumor suppressor gene. These findings lend credence to the possibility that alcohol consumption may have multiple mechanisms in which if affects breast cancer risk.

Alcohol Use and Breast Cancer Reoccurrence

The LACE Study (Life after Cancer Epidemiology), a prospective cohort study of 1,897 early stage breast cancer survivors, after accounting for other known risk factors, revealed a 1.3 to1.5 fold increased risk of breast cancer reoccurrence and breast cancer death respectively with consumption of 6gms of alcohol or more per day (3-4 drinks per week). The associations appeared stronger among postmenopausal and overweight women, suggesting the effects of alcohol might be specific for certain subgroups of women.[20]

The mechanism by which alcohol promotes breast cancer metastasis is not known, but one possibility is through the suppression of the Nm23 metastatic suppressor gene which encodes proteins known to inhibit multiple metastatic-related processes.[21]

In conclusion, from both the standpoint of breast cancer prevention and reoccurrence, moderation is the key.

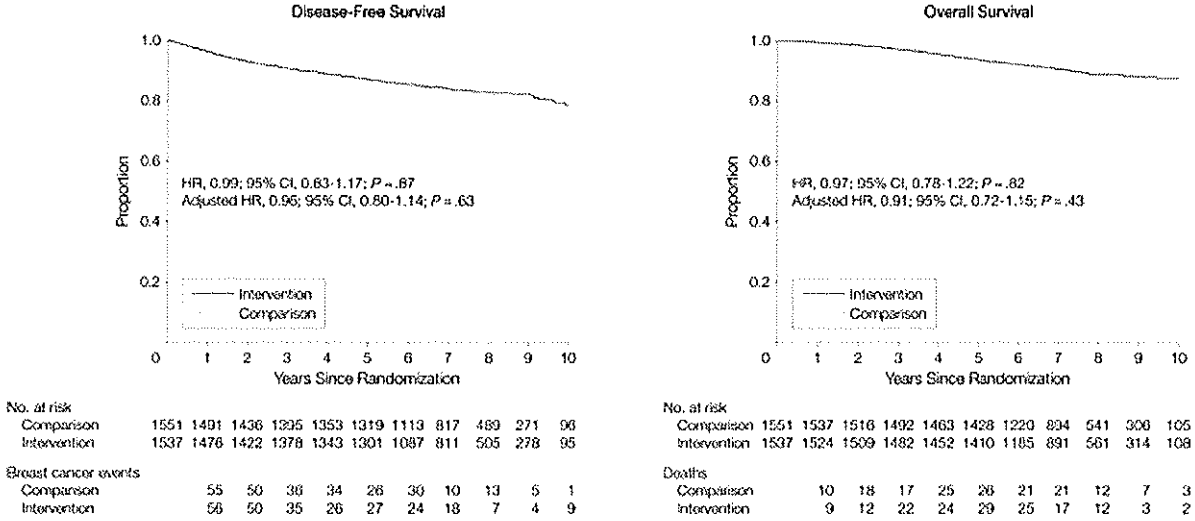
Diet and Breast Cancer Prevention

Numerous studies have addressed the issue of diet and breast cancer risk. Conflicting results have been shown in regards to whether or not dietary interventions can impact the risk of initial breast cancer diagnosis or reoccurrence. Only the two largest trials will be addressed.

The WHEL study was a prospective, randomized controlled trial of 3088 women with a prior history of Stages I-III invasive breast cancer ages 18-70. The intervention group was given a dietary regimen to include 30gms of fiber, 8 servings of fruits and vegetables, and 15-20% of energy intake from fat daily. With a mean follow-up of 7.3 years, no difference in breast cancer events or mortality was observed.[22]

Table 3. Study Events

Study Outcomes	No. of Events	
	Intervention	Comparison
Confirmed breast cancer event	256	262
Local	35	28
Regional	10	10
Distal	168	189
New primary	43	35
Confirmed deaths	155	160
Breast cancer	127	135
Other cancer	12	15
Heart disease	2	5
Other	14	5



The WINS study was a randomized, multicenter, phase III prospective clinical trial to test the effects of a dietary intervention designed to reduce fat intake in postmenopausal women with resected early-stage breast cancer receiving conventional cancer management. 2,437 women were randomly assigned in a ratio of 40:60 to dietary intervention (975) or control (1,462). The intervention group was placed on a reduced fat diet targeting 15 % of daily calories to be from fat intake. The primary endpoint was DFS. The results revealed women in the intervention group to have a 24% lower risk of relapse (HR=0.76) compared to the control group. On subset analysis the impact was greater for ER-/PR- tumors than ER+ (HR=0.58), but was not statistically significant.[23]

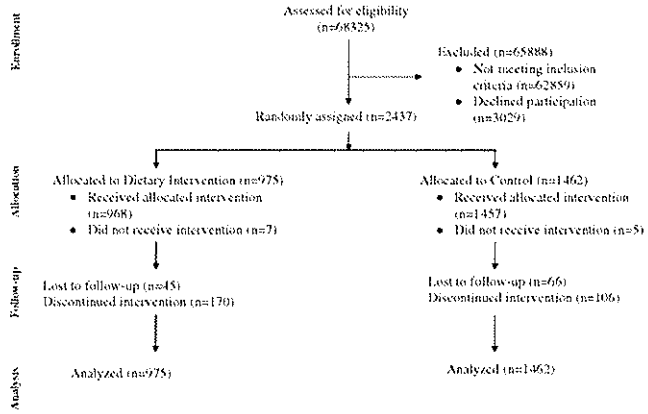
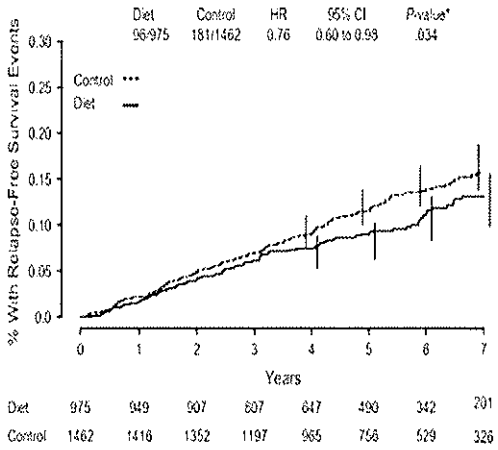


Table 5.
Relapse-free survival, by baseline characteristics and intervention g

Variable	Relapse events/total N: Dietary Intervention	Control	HR (95% CI)
BMI†			
<25	33/371	95/563	0.83 (0.54 to 1.27)
25–30	33/325	62/484	0.77 (0.51 to 1.18)
>30	29/261	61/377	0.66 (0.42 to 1.04)
Axillary lymph nodes‡			
Positive	40/258	72/392	0.83 (0.57 to 1.21)
Negative	56/710	109/1062	0.77 (0.56 to 1.07)
ER§			
Positive	68/770	122/1189	0.85 (0.63 to 1.14)
Negative	28/205	59/273	0.58 (0.37 to 0.91)
PgR‖			
Positive	55/641	97/960	0.83 (0.59 to 1.15)
Negative	28/268	75/414	0.54 (0.35 to 0.83)
Receptor subgroups‡			
ER+, PgR+	49/598	90/921	0.83 (0.58 to 1.17)
ER+, PgR−	12/121	27/199	0.73 (0.37 to 1.46)
ER−, PgR+	6/43	7/39	0.57 (0.17 to 1.87)
ER−, PgR−	16/147	48/215	0.44 (0.25 to 0.77)



In comparing the two studies, there were important differences that could have potentially affected the, outcome. In the WINS study, women in the intervention group lost on average approximately 2.5kg compared to the control group, which may have lowered their risk of reoccurrence, independent of a reduced fat intake. There was no significant weight loss in the WHEL study participants. Women in the WINS group were post-menopausal only, whereas pre- and post-menopausal women were included in the WHEL trial. In the WINS study, there was considerable drop off in self-reporting (40% by 5 years) vs. 85% for the WHEL trial.

Although more research is needed, these two large trials would suggest that dietary patterns do not exert a major influence in regards to risk of breast cancer reoccurrence. In regards to primary prevention, studies are conflicting and inconsistent in regards to the benefits of a low fat, high fruits and vegetables diet (the Mediterranean diet), but given that weight control is enhanced by this approach, there may be some benefit indirectly. The data on restricting red meats and regular consumption of fish high in Omega 3 fatty acids is not convincing, but again, for general health reasons, is a reasonable approach to take.

Obesity and Breast Cancer Risk

Obesity is associated with increased risk and worsened prognosis for postmenopausal breast cancer, but the underlying mechanisms remain unclear. Given that the prevalence of obesity in U.S. women remains very high and that childhood obesity rates are rising, it is imperative that the mechanisms underlying the connection between obesity and breast cancer risk are elucidated and that new targets and strategies are discovered to impact obesity rate and to inhibit the obesity-breast cancer link. In vitro animal studies have revealed multiple potential mechanisms by which obesity may impact breast cancer risk to include 1) increased insulin/insulin-like growth factor (IGF-1) levels and increased signaling through the rapamycin (MTOR) pathway; 2) altered estrogen metabolism particularly involving increased aromatase activity and thus the conversion of androgens to estradiol; 3) adipokine signaling, particularly involving increased leptin and decreased adiponectin; and 4) a variety of possible , although poorly characterized, inflammatory signals.[24, 25] Evidence for cross-talk between these pathways is increasing, but the critical interactions are as yet not well understood. To examine each mechanism further:

1. The role of the IGFR receptor

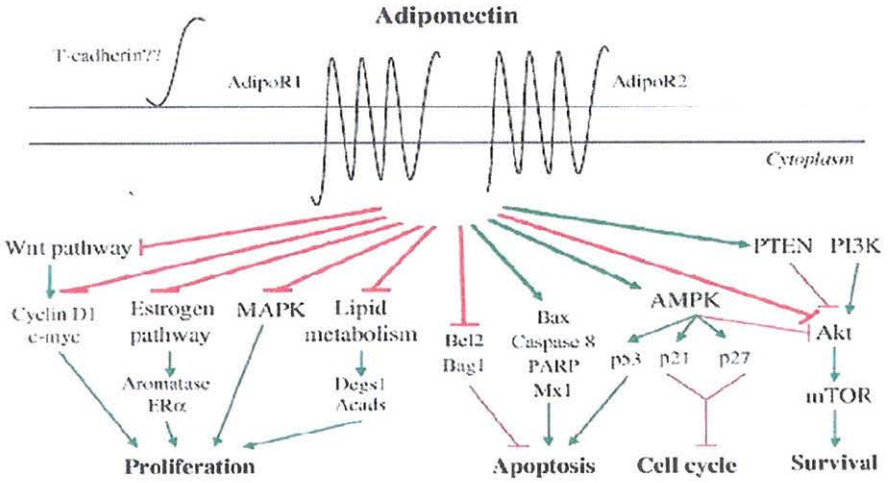
   In obese women, an excess of adipose tissue associated with elevated levels of insulin and IGF have been documented, which have mitogenic activities likely involved in breast tumor development and progression. Activation of the IGFR signaling pathway sets into motion a cascade of tyrosine kinase phosphorylation that leads to cellular proliferation and inhibition of cellular apoptosis.

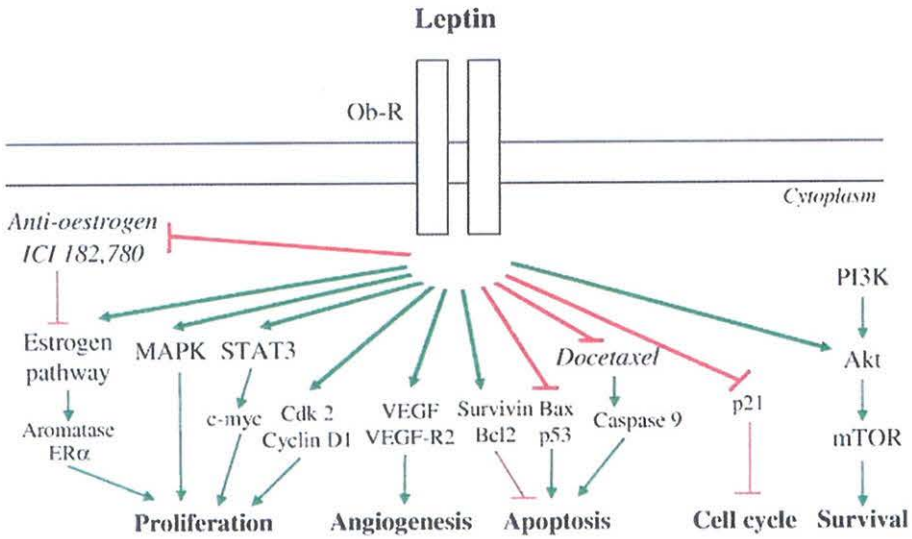
2. Action of Aromatase

   Adipose tissue is the main source of estrogen production in postmenopausal women. An enhanced number of adipocytes amplify androgen aromatization to estrogen. Obese women therefore have higher circulating estrogen levels, a known risk factor for the development of breast cancer.

3. The Adipokines

   Adiponectin and leptin are both secreted by adipose tissue and oppose each other's actions. In obese women, circulating levels of adiponectin are decreased, and conversely, leptin levels are increased. In vitro experiments have shown that the proliferative activity of leptin is mediated via different signaling pathways. Leptin induces the PI3K/Akt survival pathway and the MAPK pathway by inducing ERK1 and ERK2 phosphorylation. Leptin promotes expression of the c-myc oncogene, Cyclin D1 and VEGF thus promoting cellular proliferation and reduces Bax expression, resulting in down-regulation of apoptosis. Adiponectin, on the other hand, exerts antiproliferative effects on mammary tissue through a decrease in AKT phosphorylation and downregulation of c-myc and cyclin D protein expression. In addition, it has been shown to induce cellular apoptosis. Although the effects of both adiponectin and leptin are not completely understood, they have been found to be co-expressed in breast carcinomas and the adjacent normal tissue, suggesting they play a role in tumorigenesis. Through caloric restriction, the adiponectin/leptin ratio can be favorably altered one mechanism by which diet and resultant weight loss can potentially decrease breast cancer risk.





4. Adipocytes and Inflammation

The role of adipocyte-promoted inflammation leading to carcinogenesis is still not clear, but local release by adipocytes of pro-inflammatory cytokines, including VEGF, IL6, COX-2, TNF-a, and bFGF have been documented and may be involved in breast cancer development and tumor progression. The crosstalk between adipocytes and stromal macrophages promote release of NFkB, a transcriptional regulator that induces aromatase activity and is a potent promoter of cell survival.

In conclusion, there is convincing evidence that obesity is a potent risk factor for both breast cancer development and prognosis. Studies would suggest that breast cancers that do develop in obese patients present at later stages, carry a worse prognosis, and can increase breast cancer mortality by up to 30%.[26]

Biphosphonates and Breast Cancer Prevention

Evidence from several sources has suggested that the use of bisphosphonates may reduce the risk of breast cancer incidence and relapse. One of the largest cohort studies, the WHI, enrolled 154,768 women, of which 2,816 were bisphosphonate users at baseline. After adjusting for BMD differences between users and nonusers, after a mean follow-up of 7.8 years, bisphosphonate users had a 32% lower incidence of invasive breast cancer compared with nonusers ($p<0.01$). The incidence of ER+ breast cancer was reduced by 30% ($p=0.02$) in bisphosphonate users and ER- tumors by 34% ($p=0.27$).[27] A second trial, the Northern Israel study involved 4,039 postmenopausal patients and showed similar results.[28] Biologic plausibility for these findings includes angiogenesis inhibition and increased cancer surveillance via activation of gamma delta T cells. Two adjuvant trials in early stage breast cancer revealed conflicting results. The ABCSG-12 trial evaluating premenopausal women treated with ovarian suppression and hormonal therapy plus zoledronic acid or placebo showed a relative reduction of 36% in the risk of disease progression.[29] In contrast, the recently reported AZURE trial showed no benefit in DFS with the addition of zoledronic acid to adjuvant therapy. On subset analysis however, women greater than five years postmenopausal exhibited a 29% improvement in OS.[30] Although these various trials are thought provoking, standard of care does not support the use of bisphosphonates to prevent breast cancer incidence or progression at this time.

Chemoprevention

In 2009, an estimated 192,000 new cases of breast cancer and 40,000 deaths occurred in the United States alone. It has been estimated that more than 2,000,000 women could benefit from chemoprevention but <1% have been offered it or elected not to take it due to concerns regarding the risk: benefit ratio. It is often difficult to accept the prospect of immediate potential adverse effects of a medication to accrue benefits at some unknown time in the future. Bias on the part of the physician informing the patient can also affect the decision a woman makes, depending on the description of the treatment and strength of the recommendation. With the results of the first trials that showed a benefit in risk reduction with the use of Tamoxifen, a first generation SERM, these issues became of prime importance for healthy women at risk.

In 1992, the NSABP implemented a randomized trial, the P-1 study to evaluate the role of Tamoxifen for the prevention of breast cancer in women considered to be at increased risk for the disease. 13,388 women were randomized. Women were included if they were $\geq$60 years of age, 35-59 with a 5-yr predicted risk based on the Gail model of 1.66%, or had a history of LCIS. At its first reporting in 1998, women who took Tamoxifen for five years had a 49% reduction in risk of developing invasive and non-invasive breast cancer compared to placebo. The reduction seen was in hormone receptor positive tumors only. Risk was reduced by 56% for patients with LCIS and 86% for those with ADH. In regards to side effects there was a 2.5 fold higher incidence of endometrial cancer primarily in postmenopausal women in the Tamoxifen treated group, a 19% reduction in bone fracture incidence, no difference in myocardial ischemic events, but a higher incidence of venous thrombotic events and CVAs in the Tamoxifen treated group (RR=1.60 for DVT, 3.01for PE and 1.59 for CVA). The risk for cataract surgery was also increased in the treated group (RR=1.5). This was the first trial to support the hypothesis that

breast cancer could be prevented in a population of women at increased risk for the disease. The results were updated in 2005, showing a persistent risk reduction with Tamoxifen use of 43% for invasive breast cancer and 37% for noninvasive breast cancer.[31]

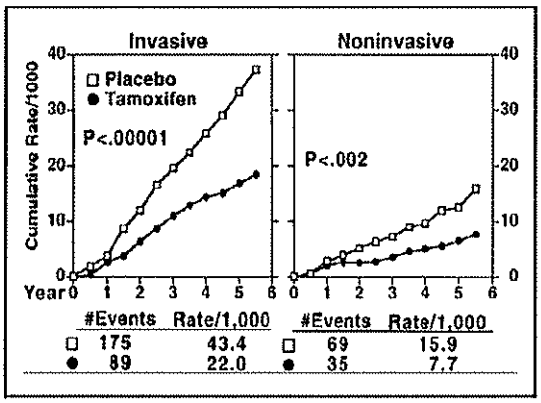


Fig. 2. Cumulative rates of invasive and noninvasive breast cancers occurring in participants receiving placebo or tamoxifen. The *P* values are two-sided.

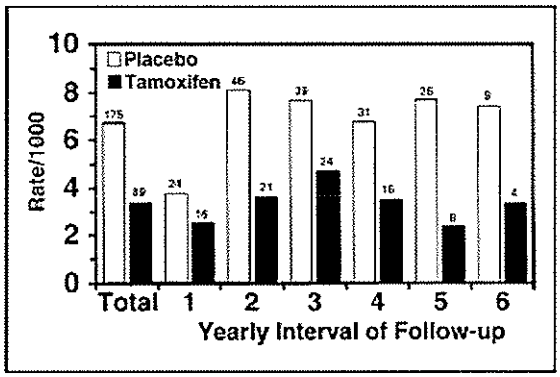


Fig. 3. Rates of invasive breast cancer occurring in participants receiving placebo or tamoxifen, by yearly interval of follow-up. Numbers above the bars indicate numbers of events.

Fig. 5. Cumulative rates of invasive endometrial cancer occurring in participants receiving placebo or tamoxifen. The *P* value is two-sided.

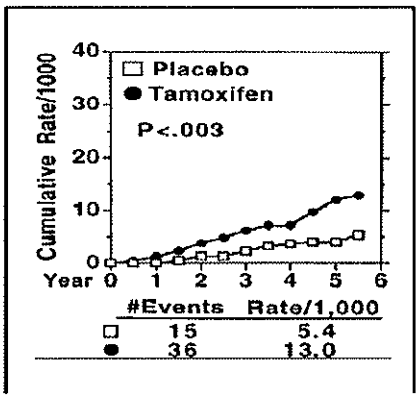
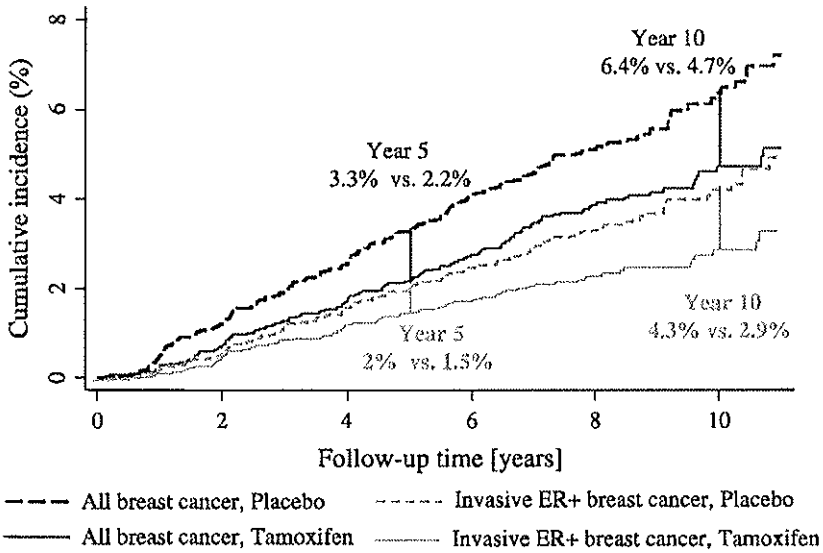


Table 8. Average annual rates of vascular-related events by age at study entry

Type of event by age at entry	No. of events		Rate per 1000 women		Risk ratio	95% confidence interval
	Placebo	Tamoxifen	Placebo	Tamoxifen		
Stroke*	24	38	0.92	1.45	1.59	0.93–2.77
<50 y old	4	3	0.39	0.30	0.76	0.11–4.49
≥50 y old	20	35	1.26	2.20	1.75	0.98–3.20
Transient ischemic attack	25	19	0.96	0.73	0.76	0.40–1.44
<50 y old	4	3	0.39	0.30	0.76	0.11–4.49
≥50 y old	21	16	1.32	1.01	0.76	0.37–1.53
Pulmonary embolism†	6	18	0.23	0.69	3.01	1.15–9.27
<50 y old	1	2	0.10	0.20	2.03	0.11–119.62
≥50 y old	5	16	0.31	1.00	3.19	1.12–11.15
Deep vein thrombosis‡	22	35	0.84	1.34	1.60	0.91–2.86
<50 y old	8	11	0.78	1.08	1.39	0.51–3.99
≥50 y old	14	24	0.88	1.51	1.71	0.85–3.58

The International Breast Cancer Intervention Study (IBIS I) trial also evaluated the role of Tamoxifen by randomizing 7,152 women at risk to Tamoxifen vs. placebo for five years of therapy. Results showed a reduction rate of 32% for invasive and noninvasive breast cancers with treatment. Adverse events were similar to those seen in the P1 trial. An 8 year follow up published in 2007 confirmed a persistent benefit of Tamoxifen (RR=0.73) even after the intervention period of five years of therapy had been completed.[32]



The Royal Marsden trial started in 1986 with randomization of 2,494 at risk women to 5 years of Tamoxifen vs. placebo. At the initial 8 year follow up evaluation, no benefit to Tamoxifen was seen so this was initially considered a negative trial. At the 20 year follow up however, a 52% reduction in risk was seen in the Tamoxifen treated patients.[33]

With the success of the P1 trial, the NSABP embarked on a second trial, the P2 Prevention trial, also named the STAR trial. In this multicenter, prospective, double-blinded, randomized trial beginning in 1999, 19,747 women at increased breast cancer risk were randomized to Tamoxifen vs. Raloxifene, a second generation SERM that had already shown impressive reductions in breast cancer incidence in the MORE and CORE trials.[34] These trials were undertaken to evaluate the benefit of Raloxifene in decreasing the risk of fracture in postmenopausal women with osteoporosis. In these trials, a secondary endpoint was incidence of invasive breast cancer where reductions of up to 66% were seen. Unlike the P1 trial, all women in this trial were postmenopausal but otherwise the entry criteria were basically the same. The results revealed no difference in the rates of invasive breast cancer with five years of treatment (RR=1.02) with fewer cases of noninvasive breast cancer in the Tamoxifen arm (RR=1.4). Fewer cases of uterine cancer were seen in the Raloxifene arm (RR=0.62) and fewer thrombotic events (RR=0.70). The risk of osteoporosis, stoke, and cardiac events were similar. The differences between arms were not statistically significant.[35] The STAR trial results were updated in 2010. The salient facts included a 24% higher rate of invasive breast cancer in the raloxifene arm and a 22% higher rate of noninvasive cancers compared to the Tamoxifen arm. In favor of Raloxifene was the lesser incidence of side effects including 45% less uterine cancers and 25% less thromboembolic events. The rate of cataract development and the subsequent need for cataract surgery was 20% less. There was no

statistically significant difference in mortality between the two groups. Both Tamoxifen and Raloxifene are now approved for breast cancer prevention.[34]

Table 5
Rates of thromboembolic events, cataracts and cataracts surgery—NSABP STAR Trial (P-2)

Type of Event	Events, *n*		Rate per 1,000				
	Tamoxifen	Raloxifene	Tamoxifen	Raloxifene	Difference*	RR†	RR (95% CI)
Thromboembolic events							
Thromboembolic events	202	154	3.30	2.47	0.83	0.75	0.60–0.93
Pulmonary embolism	84	68	1.36	1.09	0.27	0.80	0.57–1.11
Deep-vein thrombosis	118	86	1.93	1.38	0.55	0.72	0.54–0.95
Cataracts and Cataract Surgery							
Developed cataracts during follow-up‡	739	603	14.58	11.69	2.89	0.80	0.72–0.89
Developed cataracts and had cataract surgery‡	575	462	11.18	8.85	2.33	0.79	0.70–0.90

Abbreviations: CI, confidence interval; NSABP STAR, National Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene; RR, risk ratio
*Rate in the tamoxifen group minus rate in the raloxifene group.
†Risk ratio for women in the raloxifene group compared to women in the tamoxifen group.
‡Women at risk were those with no prior history of cataracts at entry (8,341 and 8,256 tamoxifen and raloxifene participants, respectively)

Table 3
Annual rates of noninvasive breast cancer and uterine disease/hysterectomy—NSABP STAR Trial (P-2)

	Events, *n*		Rate per 1,000				
Disease/uterine event type	Tamoxifen	Raloxifene	Tamoxifen	Raloxifene	Difference*	RR†	RR (95% CI)
Noninvasive breast cancer							
DCIS	70	86	1.15	1.40	−0.25	1.22	0.88–1.69
LCIS	33	34	0.54	0.55	−0.01	1.02	0.61–1.70
Mixed	8	17	0.13	0.28	−0.15	2.11	0.86–5.64
Total	111	137	1.83	2.23	−0.40	1.22	0.95–1.59
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

The Next Generation

Although SERM's have been the mainstay of chemoprevention, the use of antiestrogens, previously approved as adjuvant therapy and treatment of advanced disease, moved into the prevention arena. In 2004 the MAP.3 trial was initiated. In this randomized, placebo-controlled trial 4,560 postmenopausal women with either a Gail risk score of 1.66%, prior atypical ductal or lobular hyperplasia, LCIS, or DCIS treated with mastectomy were randomized to exemestane vs. placebo for 5 years of therapy. BRCA1 & BRCA2 mutation carriers were excluded. The results revealed a 65% relative reduction in the annual incidence of breast cancer, reported this year at a median 35 month follow up (HR=0.35). Differences in toxicity between the two groups were small, consisting primarily of hot flashes, insomnia, arthralgias, fatigue, and sexual dysfunction. Although no approval from the FDA for the indication of primary risk reduction is expected to be filed, given the impressive results of this trial, it is expected that aromatase inhibitors will be embraced by the oncology community as chemoprevention agents.[36]

Future Directions

Although significant progress has been made in the field of breast cancer prevention, more work is needed. Future studies are needed in the development of effective preventive agents with less toxicity, better tools for accurate risk assessment, and therapy to impact the risk of ER- disease. In the era of new targeted therapies, proteomics, and gene expression signatures of various cancers, we need to continue to focus research on the role prevention can play in the complex and multifaceted steps that lead to the cancerization of a cell. In addition, we need better tools to assess risks in the minority populations as the prevention studies to date were comprised primarily of Caucasian women. We need to implement effective educational programs to make women aware of modifiable risk factors and the role they can play in reducing their own risk. In addition, we need better tools to educate the population of primary care physicians who are on the frontline in caring for women so that appropriate referrals of women at increased risk of breast cancer can be made to oncologists and breast surgeons. With such a low percentage of high risk women taking advantage of the most effective therapy available to them, that being SERM's, and now with the results of the MAP.3 trial, anti-estrogens, it is even more crucial that we encourage our patients to make the healthy lifestyle changes that can make a positive impact in lowering their risk of breast cancer.

To quote Nancy Davidson MD:
"Breast cancer is the second most common cause of death from cancer and one of the most feared diagnoses for women in the United States. We have the knowledge and tools to reduce its incidence today. We have run out of excuses. What are we waiting for?"

REFERENCES

1. Wu AH, Yu MC, Tseng CC, Pike MC. Epidemiology of soy exposures and breast cancer risk. British journal of cancer 2008;98(1): 9-14.
2. Korde LA, Wu AH, Fears T, et al. Childhood soy intake and breast cancer risk in Asian American women. Cancer Epidemiol Biomarkers Prev 2009;18(4): 1050-9.
3. Messina M, Hilakivi-Clarke L. Early intake appears to be the key to the proposed protective effects of soy intake against breast cancer. Nutr Cancer 2009;61(6): 792-8.
4. Hsieh CY, Santell RC, Haslam SZ, Helferich WG. Estrogenic effects of genistein on the growth of estrogen receptor-positive human breast cancer (MCF-7) cells in vitro and in vivo. Cancer Res 1998;58(17): 3833-8.
5. Allred CD, Allred KF, Ju YH, Goeppinger TS, Doerge DR, Helferich WG. Soy processing influences growth of estrogen-dependent breast cancer tumors. Carcinogenesis 2004;25(9): 1649-57.
6. Eliassen AH, Hankinson SE, Rosner B, Holmes MD, Willett WC. Physical activity and risk of breast cancer among postmenopausal women. Archives of internal medicine 2010;170(19): 1758-64.
7. Friedenreich CM. The role of physical activity in breast cancer etiology. Semin Oncol 2010;37(3): 297-302.
8. Friedenreich CM, Neilson HK, Woolcott CG, et al. Changes in insulin resistance indicators, IGFs, and adipokines in a year-long trial of aerobic exercise in postmenopausal women. Endocrine-related cancer 2011;18(3): 357-69.
9. McTiernan A, Tworoger SS, Ulrich CM, et al. Effect of exercise on serum estrogens in postmenopausal women: a 12-month randomized clinical trial. Cancer Res 2004;64(8): 2923-8.
10. Lappe JM, Travers-Gustafson D, Davies KM, Recker RR, Heaney RP. Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial. The American journal of clinical nutrition 2007;85(6): 1586-91.
11. Chlebowski RT, Johnson KC, Kooperberg C, et al. Calcium plus vitamin D supplementation and the risk of breast cancer. Journal of the National Cancer Institute 2008;100(22): 1581-91.
12. Chen P, Hu P, Xie D, Qin Y, Wang F, Wang H. Meta-analysis of vitamin D, calcium and the prevention of breast cancer. Breast cancer research and treatment 2010;121(2): 469-77.
13. Green AK, Hankinson SE, Bertone-Johnson ER, Tamimi RM. Mammographic density, plasma vitamin D levels and risk of breast cancer in postmenopausal women. International journal of cancer. Journal international du cancer 2010;127(3): 667-74.
14. Chlebowski RT. Metformin and breast cancer incidence in postmenopausal diabetic women in the Women's Health Initiative (WHI). J Clin Oncol 2011;29.
15. Gierach GL, Lacey JV, Jr., Schatzkin A, et al. Nonsteroidal anti-inflammatory drugs and breast cancer risk in the National Institutes of Health-AARP Diet and Health Study. Breast cancer research : BCR 2008;10(2): R38.
16. Eliassen AH, Chen WY, Spiegelman D, Willett WC, Hunter DJ, Hankinson SE. Use of aspirin, other nonsteroidal anti-inflammatory drugs, and acetaminophen and risk of breast cancer among premenopausal women in the Nurses' Health Study II. Archives of internal medicine 2009;169(2): 115-21; discussion 21.
17. Holmes MD, Chen WY, Li L, Hertzmark E, Spiegelman D, Hankinson SE. Aspirin intake and survival after breast cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2010;28(9): 1467-72.
18. Campbell MJ, Esserman LJ, Zhou Y, et al. Breast cancer growth prevention by statins. Cancer research 2006;66(17): 8707-14.

19. Li CI, Chlebowski RT, Freiberg M, et al. Alcohol consumption and risk of postmenopausal breast cancer by subtype: the women's health initiative observational study. Journal of the National Cancer Institute 2010;102(18): 1422-31.
20. Kwan ML, Kushi LH, Weltzien E, et al. Alcohol consumption and breast cancer recurrence and survival among women with early-stage breast cancer: the life after cancer epidemiology study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2010;28(29): 4410-6.
21. Wong AW, Paulson QX, Hong J, et al. Alcohol promotes breast cancer cell invasion by regulating the Nm23-ITGA5 pathway. Journal of experimental & clinical cancer research : CR 2011;30: 75.
22. Pierce JP, Natarajan L, Caan BJ, et al. Influence of a diet very high in vegetables, fruit, and fiber and low in fat on prognosis following treatment for breast cancer: the Women's Healthy Eating and Living (WHEL) randomized trial. JAMA : the journal of the American Medical Association 2007;298(3): 289-98.
23. Chlebowski RT, Blackburn GL, Thomson CA, et al. Dietary fat reduction and breast cancer outcome: interim efficacy results from the Women's Intervention Nutrition Study. Journal of the National Cancer Institute 2006;98(24): 1767-76.
24. Hursting SD. Inflammatory talk: linking obesity, NF-kappaB, and Aromatase. Cancer prevention research 2011;4(3): 285-7.
25. Saxena NK, Taliaferro-Smith L, Knight BB, et al. Bidirectional crosstalk between leptin and insulin-like growth factor-I signaling promotes invasion and migration of breast cancer cells via transactivation of epidermal growth factor receptor. Cancer research 2008;68(23): 9712-22.
26. Patterson RE, Cadmus LA, Emond JA, Pierce JP. Physical activity, diet, adiposity and female breast cancer prognosis: a review of the epidemiologic literature. Maturitas 2010;66(1): 5-15.
27. Chlebowski RT, Chen Z, Cauley JA, et al. Oral bisphosphonate use and breast cancer incidence in postmenopausal women. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2010;28(22): 3582-90.
28. Rennert G, Pinchev M, Rennert HS. Use of bisphosphonates and risk of postmenopausal breast cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2010;28(22): 3577-81.
29. Gnant M, Mlineritsch B, Stoeger H, et al. Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 62-month follow-up from the ABCSG-12 randomised trial. The lancet oncology 2011;12(7): 631-41.
30. Coleman RE, Marshall H, Cameron D, et al. Breast-cancer adjuvant therapy with zoledronic acid. The New England journal of medicine 2011;365(15): 1396-405.
31. 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. Journal of the National Cancer Institute 1998;90(18): 1371-88.
32. Cuzick J, Forbes JF, Sestak I, et al. Long-term results of tamoxifen prophylaxis for breast cancer--96-month follow-up of the randomized IBIS-I trial. Journal of the National Cancer Institute 2007;99(4): 272-82.
33. Powles TJ, Ashley S, Tidy A, Smith IE, Dowsett M. Twenty-year follow-up of the Royal Marsden randomized, double-blinded tamoxifen breast cancer prevention trial. Journal of the National Cancer Institute 2007;99(4): 283-90.
34. 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. Journal of the National Cancer Institute 2004;96(23): 1751-61.
35. Vogel VG, Costantino JP, Wickerham DL, et al. Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. JAMA : the journal of the American Medical Association 2006;295(23): 2727-41.

36. Goss PE, Ingle JN, Ales-Martinez JE, et al. Exemestane for breast-cancer prevention in postmenopausal women. The New England journal of medicine 2011;364(25): 2381-91.

Additional Reading:

1. Hodgson et al. Metaanalysis of studies of alcohol and breast cancer with consideration of the methodological issues. Cancer Causes Control 2006;17(6):759-770.
2. Obesity and breast cancer: status of leptin and adiponectin in pathological processes. Michael E. Grossman, et al. in Cancer Metastasis Rev (2010) 29:641-653