Can Breast Cancer Be Prevented?

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"He is a better physician that keeps diseases off us, than he that cures them being on us; prevention is so much better than healing because it saves the labour of being sick."

Thomas Adams, 1618

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Biographical Information

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Interests: My focused interests are in the prevention and treatment of breast cancer. Research interests include screening evaluation of dense breasts in high risk women, breast conservation issues in locally advanced breast cancer patients, and chemopreventive interventions for women at increased risk for breast cancer.

Breast Cancer Statistics

Breast cancer is one of the major cancer burdens worldwide. The incidence has been increasing for several decades; in the year 2000, close to one million women worldwide will be diagnosed with breast cancer representing 21% of all new female cancers. In that same year, nearly 400,000 women will lose their life to this disease, representing 10% of all female cancer deaths worldwide.[1] In the United States this year alone, the American Cancer Society estimates 175,000 new cases of female breast cancer and that 43,300 lives will be lost to fighting this disease.[2] For Texans, this will represent 11,300 new cases in 1999 and 2,800 deaths.

Percentage of US Population Developing Invasive Cancer

		Birth to 39 Yr	40 to 59 Yr	60 to 79 Yr	Birth to Death
All sites*	Male	1.65 (1 in 61)	8.25 (1 in 12)	34.94 (1in 3)	44.66 (1 in 2)
	Female	1.95 (1 in 51)	9.14 (1 in 11)	22.33 (1 in 5)	38.03 (1 in 3)
Breast		0.43 (1 in 231)	4.00 (1in 25)	6.88 (1 in 15)	12.5 (1in 8)

*excludes basal and squamous cell skin cancers
Data Source: NCI SEER Program results 1998

Breast Cancer Incidence

Female breast cancer incidence rates significantly increased during 1973-1990 with a 25% increase in the incidence rate noted between 1979 and 1987 in both premenopausal and postmenopausal women. Rates subsequently leveled from 1990-1995 and are decreasing in younger women. Despite stabilization of rates during the latter period, the estimates of new breast cancer cases increased between 1988 and 1996[2] while, for all sites combined, cancer incidence rates declined an average of –0.7% per year from 1990 to 1995.[3] On the basis of current incidence rates, it is estimated that the chance a woman will develop breast cancer at some time during her lifetime is now one in eight.[4] The noted increased incidence is best understood in light of two factors: women are living longer and dying less of competing causes and secondly, screening has led to increased breast cancer detection. A first look at underlying risk factors must start with the population at large and birth cohort data. This data parallels underlying political, social, and economic forces at given intervals in the population and links socioeconomic risk factors to the evolving risks of breast cancer.

The Birth Cohort Phenomenon: Trends in Time

Analyses by birth cohort show largely similar patterns in Britain, Canada and the United States: increasing risk for breast cancer death for women born from the end of the 19th century to the mid 1920's, then declining risk for women born successively later. Evaluation of trends in breast cancer mortality however is not as straightforward and existing birth cohort trends may partially explain decreases in mortality for certain age groups. Examination of women whose prime childbearing years coincided with the Great Depression in the 1930's and the Second World War in the 1940s indicate they were more likely to be childless and or to have fewer children. The post war baby boom has turned that around with the women, now in the age cohort that gets the most breast cancer, also representing the cohort that started having children early, the parents of the baby boomers and hence may partially explain emerging declines in breast cancer mortality. The women of the next generation themselves, that is the baby boomers themselves, are beginning to reach the age of breast cancer risk. These women are more likely to delay childbearing, reversing the pattern, so their breast cancer rates are expected to be higher but that is not yet evident and in fact appears to be declining. The baby boomers depart from what had previously been a close relationship between childbearing trends and breast cancer risk. Coming up with an explanation attributable to any risk factor that would indicate breast cancer risk should be going down is difficult. In fact, if you examine the baby boomers, they are taller and more obese than their parents, and they were the first generation to have oral contraceptives available all their lives. Changes in mortality occurring across several age groups is most likely best explained by a change in coding, ascertainment, or the introduction of improvements in medical interventions. Thus, early detection and successful treatment are the most probable sources for the declines in breast cancer mortality and not alterations in risk factors.[5]

Declining Breast Cancer Mortality in the United States

Reductions in breast cancer mortality appears to be consistent (about 1% to 2% annually) in countries with a higher incidence of breast cancer such as Canada, the United Kingdom, and the United States, whereas in countries where the incidence is lower, such as Italy, no such trend has been observed yet.[6] In the United States, this translates to a decrease on an average of 1.7% per year during 1990-1995.[3] The decline is evident for every decade of age under age 80 and there is no indication this decrease in breast cancer mortality will abate.[5] Trends related to lifestyle, early diagnosis, or quality of treatment may underlie this finding. Evaluation of risk factors themselves does not appear to be responsible for this trend.

The Role of Epidemiology: World Wide Patterns Offer Etiologic Clues

Epidemiology is the study of the occurrence of illness and the relation between disease and characteristics of people and their environment.[7] This discipline plays a key role in cancer prevention and control. Epidemiologic methods have allowed cancer researchers to identify risk factors specific to certain cancers as well as estimate the proportion of cancer deaths attributable to established risk factors. This link between lifestyle and cancer has been based on ecologic studies showing differences in cancer rates between and within countries as well as over time. International trends demonstrate breast cancer incidence and mortality rates are the highest in North America and northern Europe, intermediate in southern Europe and Latin America, and lowest in Asia and Africa.[8] These geographically different areas also exhibit different age incidence curves. Overall patterns of breast cancer mortality suggests differences in risk are attributable to factors thought important in the etiology of the disease. While the role of dietary differences has been closely scrutinized, the issue remains far from being settled.

Migrant Studies[8-10]

- illustrate *environmental* rather than genetic factors responsible for international variation
- first generation Japanese migrants to Hawaii have breast cancer rates similar to Japan
- 2nd and 3rd generation descendants develop cancer at the rate of the host country
- risk is affected by time interval since migration

With such an epidemic on the horizon, is it reasonable to assume that breast cancer can be prevented? What is known about modifiable risk factors and those that aren't? If the greatest risk factor is age, what interventions are currently available to reduce other known risks? Elucidation of the determinants underlying recognized factors in addition to studies of other factors conferring risk or protection are needed in effort to advance the understanding of breast cancer risks as well as to aid in devising strategies for prevention.

Nature versus Nurture: What do Studies of Twins Reveal?

Clarifying the relative importance of contributions from "nature" versus those from "nurture" and their interactions has been the theme of many studies. Concordance for disease in twin pairs provides some insight into the relative contributions of environmental and genetic factors to disease occurrence. A look at the low concordance rates among monozygotic (MZ) twins also suggests a greater influence of environment. Cancer incidence in identical twins indicates that having "identical" genes is not a very good predicator of cancer incidence and mortality, implicating environmental factors as significant influences on cancer risk. A cohort study of white male US veterans from 1946-1990 assessed the effect of inherited predisposition to cancer in 5,690 MZ twin pairs and 7,248 dizygotic (DZ) twin

pairs. A 40 % greater concordance for death from cancer among MZ twins than among DZ twin pairs was noted, however, 1/3 died from smoking associated cancers further supporting the influence of environment on cancer Other studies confirm these findings[11, 12] with results generally indicating that inherited predisposition does not explain a large proportion of either all cancer incidence or all cancer mortality. In the Danish study, no significant genetic predisposition could be demonstrated for cancers of the breast, colon, rectum, or leukemia between MZ or DZ twin pairs. Cotwins of MZ breast cancer patients exhibited a significantly higher number of breast cancer cases than expected, however the same was also true for cotwins of DZ breast cancer cases, once again suggesting that environmental similarities may have contributed to the increased risk of breast cancer in these twin pairs. Thus environmental modulation of gene expression is evident, even with known gene mutations, suggesting that interventional strategies have the potential to reduce risk for both environmentally and genetically determined cancers.[13]

Risk Factors

Parity

Nulliparity, a well established risk factor dating back to a 18th century, has been associated with increased risk since the earliest mortality studies of nuns. It carries with it an increased relative risk of about 1.4 times the risk of women who have born children.[14] The number of pregnancies affects risk independently of age at first birth although only a small protective effect is noted.[15] This protective effect of parity has been noted mainly for breast cancer diagnosed in women age 50 or older. Some studies suggest that lactation[16, 17] does not have an independent effect on the parity [18-20] and early age at first birth, recent studies have found that as the months of breast feeding increases, the risk of breast cancer decreases, particularly for premenopausal women.[21-23] Since the evidence is compounded by parity; i.e., nulliparous women do not lactate, the greater risk of nonlactating women may be attributable to the nulliparous state rather than absence of lactation history. The mechanism of action of this effect is not completely defined but may be a result of interrupting ovulation or by modifying pituitary and ovarian hormone function. Finally, the older the age at which a woman gives birth to her first child, the greater her risk of breast cancer. The reason for this association is vague and stems largely from data supporting a protective role for early pregnancy related changes in breast tissue such that it is rendered less susceptible to carcinogenic agents.

Age of Menarche and Menopause

The earlier age of menarche, with its associated earlier onset of "regular" menstrual cycles, the higher the risk of breast cancer.[15, 24] A review of case control studies suggests that a 20% decrease in breast cancer risk is seen for each year after age 12 that menarche is delayed.[25] Likewise the later the age of menopause, the higher a woman's risk. It has been estimated that women who experience natural menopause before the age of 45, have only

half the breast cancer risk of those whose menopause occurs after the age of 55.[26] Perhaps the best piece of supporting data, confirming the role of total hormonal exposure, is the data with regards to bilateral oophorectomy before age 40 which confers a lifelong reduction in risk estimated at the level of almost 50 %.[26, 27] So while the number of years of menstrual activity is of etiologic importance, it may be possible that these events, in of themselves, represent independent risk factors for breast cancer.

Exogenous Hormones

Oral Contraceptives

Intensive studies have been performed evaluating the safety and risks of oral contraceptives (OC) and estrogen replacement therapy (ERT) as they relate to breast cancer. The results for both remain controversial but it should be acknowledged that at least a low level risk is present in certain subsets of women. Many studies have found that oral contraceptive use does not affect risk of breast cancer in the majority of women regardless of brand, dose, or type of estrogen and progesterone.[34, 35] A large overview analysis of 54 epidemiologic studies indicates a slight increase in the risk of breast cancer with hormonal contraceptives.[36] The relative risk does vary with time from last use; current users have a relative risk of 1.24. For women who have not taken contraceptives for 1 to 4 years, the risk is 1.16 and for women who have not taken contraceptives for 5 to 9 years, the risk falls to 1.07. For women who have not taken contraceptives for 10 years, there appears to be no increased risk of breast cancer. Three separate metaanalysis have been performed and most would agree that long term use of OCs is associated with a statistically significant positive trend towards an increased risk of premenopausal breast cancer but no association with breast cancer development after the age of 45 years.[37-39]The risk remains the highest in recent and current users, younger women, and prolonged use prior to first full term pregnancy, with the risk declining with time since last use.

Risk Factors for Breast Cancer and Their Related Hormonal Changes

Risk Factor	Hormonal Change/Association	Impact on Risk
Western vs Oriental lifestyle	↑ Estradiol	↑↑↑
Early age at menarche	↑ Duration of exposure to estradiol and progesterone	↑↑
Late age at menopause	↑ Duration of exposure to estradiol and progesterone	↑↑ (see age-incidence curves; Figure 3)
Obesity, postmenopausal (fat distribution, abdominal)	↑ Estradiol	↑
First pregnancy	↑↑ Estradiol and progesterone	↑ in 10 years after delivery then ↓ (see Figure 2)
Estrogen replacement therapy Oral contraceptives (long-term use) (?)	↑ Estradiol Mixed	↑
↑ 16 alpha-hydroxylation of estrogens	↑ 16 alpha-hydroxyestone	?

↑ = Slight increase in risk; ↑↑ = Moderate increase in risk; ↑↑↑ = Large increase in risk; ↓ = Decrease in risk; ? = Unknown.

Hormone Replacement Therapy

In a metaanalysis of 16 studies, Steinberg found that the relative risk for ERT in women with a family history was 3.4 compared to 1.5 for women who had never have used ERT.[40] In addition a RR of 1.3 was found for women who used ERT for more than 15 years. A prospective evaluation of hormone use from the Nurses' Health Study, with a 12 year followup, revealed that women currently using unopposed estrogen had a RR of 1.4 compared to 1.54 for use of estrogen and progesterone.[41] Colditz demonstrated in a metaanalysis, that the RR for women with 10 or more years of estrogen use was 1.23 and supported the previous conclusion that the addition of progesterone did not reduce the risk of ERT for breast cancer. On the other hand, Dupont and Page have reported a metaanalysis of studies of replacement estrogens and breast cancer risk, concluding that the combined results showed menopausal therapy with conjugated estrogens at doses 0.625 mg/day or less did not increase risk.[42] Finally, results of the Iowa Women's Health Study[43] suggest that exposure to HRT was associated with an increased risk of invasive breast cancer but with favorable histology and prognosis and that the overall risks and benefits of hormone use should be re-examined in the context of these findings. After more than 5 decades of ERT use in the United States and scores of epidemiologic studies, this question still can not be answered definitively.

Increasingly, hormone replacement therapy (HRT) is prescribed for many postmenopausal women in the United States both to decrease acute menopausal symptoms and to promote long term health benefits. More precise quantitation of those latter benefits with current HRT regimens is presently under study (Women's Health Initiative Trial), but the benefits are potentially important. A study involving 121,000 nurses has shown that HRT taken for 5 years is associated with a reduced risk of coronary artery disease deaths as well as death from cancer. After 10 years of HRT however, the magnitude of the reduction in risk of death is partially attenuated due to an increased risk of death in women taking HRT for more than 10 years.[44]

Body Build

For postmenopausal women, body weight and various indicators of weight for height are positively associated with breast cancer risk.[28-30] Adult weight gain increases the risk of postmenopausal breast cancer while weight loss, as an adult, may be protective.[28] For postmenopausal women, the major source of estrogen is from extraglandular conversion of adrenal androgens. Peripheral fat tissue is increased in obesity with resultant increased conversion of adrenal androgens (e.g. androstenedione) to estrone by an aromatase enzyme present in peripheral fat tissue. In addition the quantity of circulating serum she hormone binding globulin (SHBG) in postmenopausal women is inversely related to weight, with lean women having higher levels of SHBG and thus lower circulating levels of free estrogens. Regional distribution of adipose tissue may be related to breast cancer risk independently of total weight; two studies[31] have reported an increase risk among women with a higher ratio of central to peripheral fat deposition although another study refutes this.[32] Increased overall and central adiposity is associated with increased levels of bioavailable estrogen and in the case of postmenopausal women, with increased breast cancer risk. Whether height increases breast cancer risk independently of weight is uncertain.[28, 30, 33]

Dietary Fat

Dietary fat is thought to play a role in at least 35% of cancers including a role in breast cancer. Most of this data stems from animal data; marked variation in international correlations between per capita fat "disappearance" data and breast cancer incidence and mortality rates; migrant studies;[8] and temporal increases in breast cancer incidence paralleling higher rates of fat intake.[45] Most epidemiologic case-control and cohort studies, on the other hand, have found weak association (either positive or negative) or no association between total fat, saturated fat, or animal fat intake in adulthood or childhood and subsequent breast cancer risk. In fact, the most recent published study examining the association of dietary fat intake, fatty acids, and the risk of breast cancer failed to demonstrate any evidence of its role in decreasing breast cancer risk[46] and echo the results of Hunter's findings from a combined analysis of seven cohort fat studies.[47] Some of the difficulties in respect to this issue is that reductions in dietary fat to no more than 20% - 25 % can be accompanied by changes in other dietary components including total calories, fiber, carbohydrates, fruits and vegetables, carotenoids and other micronutrients that may also alter sex steriod metabolism and serum estradiol levels.[48]

A recent metaanalysis of dietary fat intake, serum estrogen levels, and the risk of breast cancer demonstrated that a lowering of dietary fat can result in a lowering of serum estradiol level and such dietary modifications may still offer an approach to breast cancer prevention.[49] One of the mechanisms by which low dietary fat is presumed to reduce estrogen levels is by lowering overall energy intake and consequently reducing adipose tissue storage and production of hormones.[50] This effect of diet, on endogenous hormones that may be involved in breast cancer etiology, has been considered in other studies, again with inconsistent or inconclusive results.[51-54] Studies of dietary fiber suggest that increases in fiber are inversely associated with levels of serum estradiol and other estrogens.[48] And finally, dietary carotenoids and vitamins C and E can neutralize reactive oxygen species, may reduce oxidative DNA damage, genetic mutations, and also may enhance host immunologic functions due to their antioxidant properties. A modestly lower risk of premenopausal breast cancer was associated with long term consumption of these nutrients in women participating in the Nurses' Health Study.[55]

Alcohol Consumption

A modest positive association between alcohol consumption and the risk of breast cancer has been observed by many epidemiologic studies although not all. This potentially modifiable behavior has been the subject of over 50 studies. Results have been inconsistent with regards to whether the risk varies with the type of alcoholic beverage consumed or whether the risk is associated with quantity consumed.[56] A metaanalysis concluded that a positive relationship between alcohol intake and breast cancer risk however, there was statistically significant heterogeneity, raising doubts about whether regarding the association.[57] Factors that may modify the relationship between alcohol and breast cancer are also not possible from the published data. A recent pooled analysis of cohort studies demonstrated a 41% higher risk of

invasive breast cancer was seen in women consuming 30 to 60 g/d however, women consuming 60g/d or more of alcohol consumption had a 31% higher risk of invasive breast cancer.[58] Beverage specific estimates were not statistically different from one another. Menopausal status also did not significantly modify the relationship.

Biological mechanisms to account for these findings have been posed. Several studies have found women with alcoholism have higher estrogen levels than moderate consumers.[59] Several intervention studies have found that estradiol levels increased significantly when alcohol was administered to premenopausal women and postmenopausal women on estrogen replacement therapy. Either increased secretion or decreases in metabolic clearance has been postulated to explain the finding of increased estrogen levels in these women. In addition alcohol may affect the permeability of membranes to carcinogens, inhibit the detoxification of carcinogens, activate procarcinogens, or act as a cocarcinogen and thus affect breast cancer risk.[60] A prospective study of folate intake (since alcohol is a known folate antagonist) suggests that the excess risk of breast cancer associated with alcohol consumption may be reduced by folate.[61]

Relative Risk for Breast Cancer According to Level of Daily Alcohol Intake[58]

Alcohol intake	Relative Risk	95 % Confidence Limits
30 to 60 g/day	1.41	1.18 - 1.69
>60 g/day	1.31	0.86 – 1.98

Practically Speaking, Are Risk Factors Really Modifiable?

All women are at risk for the development of breast cancer. Most of the aforementioned risk factors represent low relative risks and thus demonstrate only a slight increase in breast cancer risk. Identifying certain women at higher risk than others, must be done with extreme caution, as women tend to over estimate their risk. Also several of the risk factors for breast cancer are not manipulable or present limited opportunity for change. Other risk factors are theoretically subject to change but they are so embedded in the social and cultural matrix that it is impractical to intervene. Nulliparity or age at first birth represent major life choices that women are unlikely to alter on the basis of the effect on breast cancer risk. In the case of breast cancer, the risk factors neither present as great a potential for control, nor are as clear cut as those for lung or cervical cancer.

Limitations in the Application of Risk Factors to Breast Cancer Prevention

- nonmanipulable nature of most risk factors
- 70% to 80% of women with breast cancer have no significant risk factors[62]
- most important risk factor remains advancing age
- no primary risk factor, unlike lung cancer, has emerged after decades of studies
- established risk factors do not account for a large proportion of breast cancer incidence
- all risk factors, combined, explain less than 30 % of breast cancer incidence[63]
- long latency between intervention and effect
- absence of controlled studies

The great advantage of risk factor intervention, as a cancer control strategy, is that it reduces incidence, therefore avoiding all morbidity and mortality that would have occurred in the persons otherwise destined to experience the disease.

Are Breast Cancer Risks Related to *In Utero* Events?

A second problem in risk factor intervention is that several risk factors for breast cancer are related to relatively early life events, if known at all. The inability to alter these risk factors, however, has thus far limited their relevance for prevention. This is perhaps best evident in the *in utero* exposure to diethylstilbestrol (DES) resulting in a cumulative excess risk of 1/1000 of clear cell adenocarcinoma of the vagina. But more importantly, these DES women face a 20% to 30% increased risk for breast cancer. The rationale supporting the role of early life risks rest on the *in utero* development of the mammary gland, when it is in a partly undifferentiated state and may be susceptible to intrauterine influences that confer increases in risks for breast cancer.[64] Accumulating evidence also implicates the importance of *in utero* dietary exposures with increased risks of breast cancer in adulthood.

Further implications of early life risk exposure, with a great latency for breast cancer development, is evident from radiation exposure data. Individuals exposed during their early teens, a time during ongoing breast development, to the atomic bomb in Japan, experienced the greatest increase in breast cancer incidence than survivors at either ends of the age spectrum. However, the breast cancer development did not occur at an earlier age.[65] Likewise, data from survivors of childhood Hodgkin's disease treated with mantle radiation, also reinforce the emerging role of early carcinogenic insults resulting in the later development of breast cancer.[66] In these Hodgkin's survivors, developing breast tissue exposure to radiation therapy during their early teens, resulted in an increased risk for breast cancer 2 decades later. The importance of these findings underscore the role of early risk factor exposures, both identified and unidentified, to later life risks for breast cancer. It appears that the hormonal milieu the breast tissue is exposed to, functions as a promoter.

Given the long natural history of breast cancer, *events that likely occur before age 20 or even in utero,* set the stage for disease that appears 1 to 3 decades later.[67]

Intervention is difficult as the time between intervention and expected modification on cancer risk is unknown. Mounting large-scale preventive interventions has been limited by effectiveness of the intervention.[63] To date, most of breast cancer risk factors have been used to optimize the effectiveness of early detection. Caution must be exercised in recommending early onset breast cancer screening on the presence of risk factors. A risk factor should only lead to early onset screening if it is indicative of early onset of disease. Most risk factors are not predicative of early onset. The majority of evidence points to only a family history of early onset breast cancer (such as carriers of BRCA1 and 2) as representing a substantial risk factor for early onset breast cancer.

Have We Been Able to Identify the High Risk Cohorts?

Risk is a relative term derived by comparing the incidence of a disease in a group having a particular risk factor or trait with the incidence of the same disease in a comparison group of individuals who do not carry the risk factor but who otherwise the same.[68]The major problem with all prevention strategies is the precise identification of the target population. Quantification of risk using multivariate regression models is possible but the available models may not accurately reflect the degree of risk. Regardless of how risk is quantified, it is also important to place an individual's risk in qualitative terms (average, slightly elevated, moderately elevated) and to provide a specific plan to monitor the risk.

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The Gail model is based on data collected from the Breast Cancer Detection Demonstration Project (BCDDP), a large observational study of 280,000 Caucasian women willing to undergo annual mammographic examinations between 1973 and 1980. Using logistic regression techniques, this model allows one to estimate the likelihood that a woman of a given age with certain risk factors will develop breast cancer over a specified time interval by computation of individualized absolute risk. The model has now been assessed and validated by two other populations: the Texas Breast Screening Project and the Nurses' Health Study.

Gail Model Significant Predictors of Lifetime Risk

- age
- age of menarche
- age at first birth
- number of breast biopsies
- family history in first degree relatives

Critics of the Gail model raised ethical concerns regarding the value of individual breast cancer risk prediction in the absence of safe and effective preventive regimens. The NSABP P1 trial used a modified version of the Gail model to select women, at increased risk of breast cancer, for participation in the tamoxifen trial. The findings from the NSABP P1 trial led the FDA to their first approval of a drug for chemoprevention.

Cancer Prevention – Perspectives and Implications

Cancer prevention is commonly divided into three categories:

- **primary:** avoidance of cancer causing exposures and behaviors
- **secondary:** screening individuals at an earlier stage.
- **tertiary:** chemoprevention

The development of a cancer chemoprevention agent should be a logical sequence of studies, starting with preclinical epidemiological studies that suggest a compound may have efficacy. Laboratory studies must show *in vivo* and *in vitro* activity and its effect on cancer incidence must then follow.[69] Cancer prevention methodologies rely on the ability to intervene in tumorigenesis at some point to prevent the progression from normal tissue to a premalignant lesion or from a premalignant lesion to a fully evolved primary cancer. Aiming at a high risk population selects subjects that are likely to have target lesions that have progressed from normal stage to a more advanced stage of tumoriogenesis, perhaps even only on a molecular level. The validity of the intervention as an effective measure depends on a finite rate of spontaneous regressions of the precursor lesion. The purpose of doing a prevention trial is to provide the most reliable answer to the question of whether a given intervention can prevent cancer.

Chemoprevention: Pharmacology or Biology?

Do we really know enough about cancer to undertake chemoprevention in pharmacological terms? This is a reminder that our models of cancer have been evolving rapidly and there have been many surprises along the way. At the very least, the list of new mechanisms in this disease, implicates a consideration of agents beyond those that suppress proliferation or prevent mutagenesis. Such undiscovered processes may even explain the failure of agents that, until recently, we felt secure enough to test in large scale trials such as trials of beta carotene. A null answer can mean good hypothesis, good science, wrong agent. An increase in risk, as evident by an increase in lung cancer following beta carotene, suggests that the model, not the agent, is wrong. For breast cancer, tamoxifen is not the end of the cancer prevention effort anymore than penicillin was the end of the development of antibiotics.

Lessons in the Developmental Biology of Breast Cancer

A broad understanding of the major physiologic factors in breast cancer provides a basis for prevention strategies. The initiation, promotion, progression model from skin carcinogenesis does not appear to be as useful for breast cancer but does emphasize the multistep nature of malignancy development and the prolonged multiyear nature of the process.[67] Two key physiologic variables in breast cancer, lobular maturation and hormonal exposure, provide a rational model that can account for the epidemiologic observations. As in the majority of

breast cancer cases, the unidentified exposure-cause that acts as an initiator, may not be as critical to the initiation of malignant transformation of breast epithelia as previously thought.

Russo and Russo[64, 70, 71] recognized lobular maturation and permanent differentiation of breast terminal end-bud cells as critical events in susceptibility to breast malignancy in animals. Their human tissue studies reveal 4 types of human breast lobules. Their maturation and differentiation, under the influence of significant hormonal perturbations, provide a basis for defining events. Lobule 1 is an undifferentiated structure dominant in women before pregnancy. Cells in these lobules appear to exhibit increased sensitivity to malignant transformation, and appear to be the cells of origin of the most common breast cancer, ductal carcinoma. Pregnancy results in differentiation of the cells in most breast lobules to semidifferentiated (lobule 2) or fully differentiated (lobule 3) states resulting in a protective effect for breast cancer risk decades later.

Hormonal exposure is the second critical event in breast cancer development. Menstrual cycling significantly affects the incidence of breast cancer. Given the long natural history of breast cancer, 10 + years, the rapid increase in incidence by the third decade of life suggests that events in women's lives before age 20 set the stage for disease appearance 1 to 3 decades later. In fact, lower endogenous estradiol levels of Asian women and the subsequent impact of lower estradiol early in life, may explain their lower incidence of breast cancer. Therefore the major hormonal increases during pregnancy are associated with increased risk in the years immediately following pregnancy; the lobular differentiating effects of pregnancy are associated with decreased overall risks beginning about a decade later.

Breast Lobule Maturation and Differentiation

Lobule Type[a]	Characteristics	Altering Factors	Role in Breast Pathology
Type 1	Undifferentiated structure with 6-11 ductules Increased susceptibility to carcinogenesis		Origin of atypical ductal hyperplasia, ductal carcinoma in situ, and invasive cancers
	↓	← Menarche, hormonal stimulation, pregnancy	
Type 2	Semi differentiated		Origin of lobular atypia, lobular carcinoma in situ, and lobular carcinomas
	↓	← Pregnancy	
Type 3	Fully differentiated with 80 ductules		Origin of adenomas, fibroadenomas, sclerosing adenosis
	↓	← Lactation	
Type 4	Differentiated for lactation		

[a]Involution of types 1, 2, and 3 to terminally differentiated structures appears to occur in postmenopausal years. Adapted from Russo and Russo.

Can We Draw Parallels Between Chemotherapy and Chemoprevention?

Combination chemotherapy is so deeply embedded by extensive clinical trials proving the efficacy of multiple agents, in combination or sequentially. From our chemotherapy experience, single agents select out for clones of cancer cells capable of surviving; polypharmacy reduces the likelihood of such clones emerging. Selection occurs because specific cells are capable, by a variety of means, of resisting the cytotoxic, apoptosis-inducing, and other actions of the therapeutic agents. By the same token, chemopreventive agents, by inducing differentiation, reducing proliferation or mutation, are equally capable of acting as agents of selection. Cells that survive chemopreventive agents may be just as capable of acting as agents of clonal expansion as any survivor of a cytotoxic agent. This kind of selection that may explain why agents as apparently benign and beneficial as beta carotene can actually increase the risk of lung cancer in individuals known to have large numbers of initiated cells.

What is a Chemoprevention Trial?[72]

- definitive primary endpoint is cancer incidence
- two sided hypothesis testing
- randomization with placebo control versus intervention
- large scale ($n > 1000$)

Definitive chemoprevention represents not only suppression or reversal of human carcinogenesis but also an advancement of our understanding of carcinogenesis and cancer prevention.

Animal Models of Breast Cancer

Breast cancer is based on the model of endocrine promotion where a transformed cell may be activated to form a tumor under the stimulus of estrogen.[73] Experimental data demonstrate breast cancer promotion by estrogens in animal models that may be blocked by antiestrogen maneuvers such as ovarian ablation or anti-estrogen therapy.[74] Female mice infected with mouse mammary tumor virus develop breast tumors during the 2nd year of life. Early, long term tamoxifen therapy prevents the appearance of mammary tumors associated with mouse mammary tumor virus infection. Early pregnancy or administration of progesterone results in earlier appearance of the tumors, while early oophorectomy (before 6 months of age) prevents mammary tumor development. The earlier oophorectomy is performed after the carcinogenic insult, the more effective it is. Hence, in animal models, timely implementation of tamoxifen or oophorectomy, both antiestrogen strategies, yields the best results in terms of tumor prevention. Unfortunately, we are unaware of the nature and timing of the carcinogenic insult in women.

Tamoxifen, administered at different intervals at the time of a chemical carcinogen, also significantly impacts on the ability of the carcinogen to result in a carcinogenic process.[74] Hormone dependent breast cancer cell lines transplanted into immune deficient mice that are then challenged with the mouse mammary tumor virus, 7,12-dimethylbenzanthracene (DMBA), or *N*-nitrosmethlyurea (NMU) result in the development of mammary tumors.[75] Tamoxifen inhibits the growth of estradiol-stimulated hormone dependent MCF-7 cells inoculated into the mammary of oophorectimized athymic mice. Long term administration of tamoxifen suppresses tumor growth; however, tumor cell proliferation occurs in all animals when tamoxifen is withdrawn and estrogens are administered.[76] Chemical initiation by DMBA followed by a period of promotion with estrogen, prolactin, and progesterone will result in the appearance of tumors 3-4 months later. Treatment of tamoxifen at the time of DMBA administration reduces the number of tumors found at 4 months to less than 10% of those in control groups.[74]

Overall, the animal model systems demonstrate that intervention soon after initiation is the most effective form of breast cancer prevention. In addition, changes in the hormonal milieu affects the process of carcinogenesis, either by altering the receptivity of the epithelial tissue to carcinogens or by preventing the process of promotion to produce an invasive carcinoma.

Rationale Behind the Selection of Tamoxifen

- animal studies support tamoxifen's role in decreasing breast cancer risks
- interfered with the initiation and promotion of tumors in experimental systems
- inhibited growth of malignant cells by a variety of mechanisms
- proven value in treating metastatic breast cancer
- reduced tumor recurrences
- prolonged survival when administered as postoperative adjuvant therapy
- reduced incidence of contralateral breast cancer

Tamoxifen's History:

- 1966 tamoxifen synthesized by Imperial Chemical Industries in Great Britain
- originally designed as an oral contraceptive but was found to increase fertility
- 1969 first evaluations in advanced breast cancer patients (replaced DES)
- 1974 began use in early breast cancer to prevent recurrences
- 1978 FDA approved for the treatment of metastatic breast cancer
- 1986 FDA approval for adjuvant therapy for LN + postmenopausal breast cancer
- 1986 a tamoxifen chemoprevention trial initiated in UK
- 1989 FDA approval for advanced breast cancer in the premenopausal setting
- 1990 approved for the adjuvant setting for node negative patients
- 1992 U.S. multicenter chemoprevention trial initiated
- 1993 FDA approval for advanced breast cancer in males
- July 1998 FDA approval for use in reducing contralateral breast cancers
- Oct. 29,1999 tamoxifen FDA approved for "reducing incidence of breast cancer in women at high risk"

Tamoxifen for Early Breast Cancer: an Overview of the Randomized Trials[77]

Based on 30,000 women in 55 trials comprising 87% of world wide evidence

- 10.9% absolute improvements in 10 yr survival in LN +
- 5.6 % absolute improvements in 10 yr survival in LN –
- these benefits occurred irrespective of age, menopausal status, whether chemotherapy was given, or dose of tamoxifen
- for 1, 2, and 5 years of adjuvant tamoxifen, proportional recurrence reductions were 21%, 29%, 47% respectively during about ten years of followup
- proportional mortality reductions were 21%, 17%, 26% respectively
- proportional reductions in incidence of contralateral breast cancer were 13%, 26%, and 47% respectively

Tamoxifen's Potential to Prevent Breast Cancer

The most compelling data for chemopreventive-chemosuppressive actions of tamoxifen in breast cancer derives from observations on the occurrence of second primary breast tumors in women participating in adjuvant trials. In the adjuvant setting, the goal of tamoxifen is to eradicate disease or control the growth of occult metastatic disease that would otherwise be fatal. The Stockholm trial of adjuvant tamoxifen for 2 or 5 years in postmenopausal patients found a significant reduction in the incidence of contralateral breast cancer in tamoxifen treated patients (47 v 29 events) after a median followup of 7 years.[78] Benefit was greatest during the first two years but there was a continued reduction in the followup period more than 10 years after treatment ceased. There was no evidence that contralateral cancers had any worse outcome occurring during or after tamoxifen.[79] In the United States, the National Surgical Breast and Bowel Project (NSABP) B-14 observation of a nearly 50 % reduction in contralateral breast cancers served as the basis for the current National Cancer Institute-sponsored Breast Cancer Prevention Trial (BCPT). The 5 year planned duration of tamoxifen for the NSABP P1 trial was derived from data from multiple studies of which the the B14 trial is most notable one. This demonstrated that 5 years of tamoxifen significantly reduced the incidence of new primary breast cancers in the contralateral breast (52 v 29 events), but no additional benefit was found for 10 years of tamoxifen over that found with 5 years of treatment.[80]

Launching of the NSABP P1 Breast Cancer Prevention Trial (BCPT)

Tamoxifen had already been shown to prevent breast cancer in one specific setting. The recent overview of randomized tamoxifen trials demonstrated with 1, 2, or 5 years of tamoxifen, the proportional reductions in the incidence of contralateral breast cancer was 13%, 26%, and 47% and they were independent of age.[77] Not only confirming these results,[75, 77, 81, 82] a tamoxifen associated reduction in mortality due to contralateral breast cancer was demonstrated.[83] In addition the proportional reduction in contralateral breast cancer appeared to be the same in women whose initial tumor was ER negative. Interestingly the results of these two recent tamoxifen metaanalyses were not even available when the NSABP P1 trial was launched. They, however, retrospectively support the rationale on which the BCPT was based. Compliance monitoring by measurement of tamoxifen's active metabolite, *N*-desmethyl tamoxifen, also made tamoxifen an ideal choice for a prevention trial. Finally the non-life threatening nature of the toxicities reported, at the time the BCPT was conceived, also lent support to its evaluation in a major prospective prevention trial.

The NSABP P1 Trial: Putting Results into Perspective

Eligibility:

- ages of 35 to 59 years with a 5 year predicted risk for breast cancer of at least 1.66%
- 60 years of age or older
- life expectancy of 10 years
- history of LCIS
- mammogram and breast exam that demonstrated no risk of breast cancer

Randomization: Double Blind Placebo Control

- placebo for 5 years: 6, 599 women
- tamoxifen for 5 years: 6,576 women

Followup: 47.7 months

NSABP P1 Results[84]

Characteristic	Placebo	Tamoxifen	Relative Risks
Invasive breast Ca	175	89	49 % reduction
Noninvasive breast Ca	69	35	0.50
Breast Cancer Deaths	6	3	
Endometrial Ca	15	36	2.53
Deaths	1	0	
Other Ca Deaths	36	20	
Stroke	24	38	1.59
Deaths	3	4	
DVT	22	35	1.6
Pulm Embolus	6	18	3.01
Deaths	0	3	
Heart Disease	62	71	1.15
Deaths	12	13	
Fractures	137	111	0.81
Cataracts	507	574	1.14

How Do We Interpret the Results?

- results are only applicable to the populations that resemble trial participants
- women with significantly elevated risks can benefit
- toxic effects observed were exactly as previously experienced
- risk of uterine cancer was low
- it is possible to slow or preempt breast cancer carcinogenesis with tamoxifen

Other Chemoprevention Trials: Negative Results?

Italian Tamoxifen Prevention Trial

Eligibility:

- women ages 35 to 70 years
- must have undergone a total hysterectomy
- annual mammography
- could continue on HRT

Randomization: Double Blind Placebo Control

- placebo: 2,708 ➡➡➡ 1966 on intervention
- tamoxifen: 2,700 ➡➡➡ 1871 on intervention
- only 149 completed 5 years of treatment
- 1,422 withdrew, one half in the first year

Followup: 46 months

Italian Randomized Tamoxifen Trial[85]

Characteristic	Placebo	Tamoxifen
Breast Ca	22	19
Breast Ca & on HRT	8	1
CVA	5	9
DVT	3	6
Pulm Embolism	1	1
Vascular Events	18	38

Since accrual was limited to to hysterectomized women, their risk of breast cancer may be less than a cohort of women with the same age distribution since only 26.3% had conservation of the ovaries. Subgroup analysis demonstrated a protective effect of tamoxifen in the women who took hormone replacement therapy throughout the study however a high incidence of vasccular events was noted. Another subgroup analysis demonstrated a nonsignificant advantage of tamoxifen over placebo in women with at least one first degree relative with breast cancer. In conclusion tamoxifen was not significantly protective against women at normal or slightly reduced risk of the disease, at least in the duration of the followup. No deaths from breast cancer have been reported.

Royal Marsden Hospital Tamoxifen Chemoprevention Study

Eligibility:

- ages 30 to 70 years
- must have increased risk due to family history
- all had at least one first degree affected relative
- annual mammography
- HRT allowed

Randomization: Double Blind Placebo Control

- placebo: 1,244 women
- tamoxifen: 1,250 women

Followup: 70 months

Royal Marsden Hospital Tamoxifen Study[86]

Characteristic	Placebo	Tamoxifen
Breast Ca	30	32
Deaths	1	4
Noninvasive Ca	4	4
Endometrial Ca	1	4
Breast Ca & HRT	13	12
DVT	2	4
Pulmonary Embolism	2	3

Why Do the Results Differ?

- British and Italian study populations are too small to detect differences
- they were a younger study populations, hence at lower risk
- British study population had a stronger family histories
- poor compliance
- concurrent HRT permitted
- British trial tamoxifen administered more than 5 years
- preventive effect in NSABP P1 trial due to treatment of occult cancers

Where Does Raloxifene (Evista) Fit In?

Raloxifene (LY139481) or its hydrochloride salt, previously known as keoxifene, was discovered two decades ago.[87] It is a benzothiopene derivative synthesized in an effort to find antiestrogens that had greater estrogen antagonism and less intrinsic estrogen-agonist activity than tamoxifen for the treatment of breast cancer. The estrogen-antagonistic region of raloxifene is characterized by a piperdine side chain and the orthogonal orientation of this basic side chain is thought to contribute to the lack of raloxifene's uterotrophic effects. Classified as a selective estrogen receptor modulator (SERM), a term that describes compounds that interact with the estrogen receptor but have tissue specific activities, it competes with endogenous estrogens for estrogen receptor binding and either activates or blocks estrogen action. Although raloxifene has a higher affinity for the estrogen receptor than tamoxifen, it is less efficacious than tamoxifen in the rat mammary tumor model.[88] Reports of raloxifene in patients with established breast cancer are quite limited and consists of two clinical reports that include 32 postmenopausal patients treated for advanced disease. In one study, a dose of 200 mg/d resulted in no objective tumor response in 14 patients with tamoxifen resistant disease. In a more recent trial, raloxifene in a dose of 300 mg/d resulted in 3 objective responses in 18 patients with ER + disease.[89] However, at present, only the most preliminary information regarding raloxifene's influence on clinical breast cancer is available.[90] Thus, it may be able to achieve a better overall preventive profile than with tamoxifen when the risks of endometrial cancer and fracture, in addition to the risk of breast cancer, are taken into account.

The MORE (Multiple Outcomes of Raloxifene Evaluation) trial was initially designed to test the hypothesis that raloxifene would reduce the risk of fractures in postmenopausal women. Breast cancer was not specifically addressed at entry, nor was breast cancer development a primary outcome measure.[90]

On December 9, 1997 Raloxifene was approved for the prevention of osteoporesis.

The MORE Trial

Eligibility:

- age younger than 81 years
- must have osteoporesis defined by T-score of at least 2.5 SDs below mean
- breast mammography or sonography, optional after first year but mandatory after two and three years

Randomization: Double Blinded to 60 mg or 120 mg Raloxifene or Placebo

- placebo: 2,576 women
- raloxifene: 5,129 women
  - 60 mg raloxifene: 2,557 women
  - 120 mg raloxifene: 2,572 women

Followup: 40 months

Multiple Outcomes of Raloxifene Evaluation (MORE) Trial[91]

Characteristic	Placebo	Raloxifene 60 mg	Raloxifene 120 mg
Breast Ca	27	13	
Noninvasive Breast Ca	5	3	4
Endometrial Ca	4	4	2
Thromboembolic Disease	8	25	24
DVT	5	18	20
Pulm Embolus	3	10	7

Other Ongoing TamoxifenTrials

- **ISIB:** International Breast Cancer Intervention Study
- **ATTom**: Adjuvant Tamoxifen Treatment offer more?
- **ATLAS**: Adjuvant Tamoxifen Longer Against Shorter

These last two trials are designed pragmatically, with randomization at the point when "substantial uncertainty" arises, as to whether to stop or continue adjuvant tamoxifen for at least five more years.

NSABP P2: Is the Answer in the STARS?

The Study of Tamoxifen and Raloxifene (STAR) trial is designed to compare tamoxifen with raloxifene, a drug shown to be useful in preventing osteoporesis and which seems to lack the stimulatory effect on the endometrium, with breast cancer incidence as a primary endpoint.

Women who are good candidates for tamoxifen cancer prevention should be encouraged to enroll in this NSABP P2 STAR prevention trial which is open here at UTSWMC (contact person: Karen Smith, RN 214 648-5442). This trial opened July 1, 1999 and will attempt to confirm preliminary data that raloxifene diminishes breast cancer incidence and will show whether it is as efficacious in doing so as tamoxifen. Because there is no placebo group, all women enrolled in this trial will receive an active agent for a period of 5 years. Thus the STAR trial will compare tamoxifen, known to reduce the occurrence of breast cancer with another drug, raloxifene, which may be safer with regards to endometrial stimulation but whose *total effectiveness in breast cancer risk reduction is not yet measured.*

BRCA1 and BRCA2: What is the Data With Regards to Tamoxifen?

When the NSABP P1 trial opened in 1992, the genes for BRCA1 and BRCA2 were not yet cloned. Plans to analyze collected and stored blood from a subgroup of patients from the prevention trial are underway.[92] Among women diagnosed with breast cancer before the age of 36 years in the UK, a recent study found that only 5.9 % carried an identifiable BRCA1 or BRCA 2 mutation. The rate was even lower for women diagnosed between ages 36 and 45 years. In these high risk families, the risk of breast cancer in female mutation carriers was only a third of the incidence seen in the initial cancer prone families. Perhaps then, in families where the gene is highly penetrant, adverse modifiers may be present that enhance the effect of the mutation on cancer risk. This study closely estimates data derived from other less selected populations, suggesting a lifetime risk of breast cancer in the range of 36 – 56 % for BRCA1 and BRAC2 mutation carriers. It remains very unclear if tamoxifen can modify the carcinogenic effect of the underlying mutation for either BRCA1 and BRCA2 carriers or women with strong family histories. Extreme caution should be undertaken before offering tamoxifen to these women with any amount of assurance since BRCA1 and BRCA2 associated noninvasive[93] and invasive tumors[94] are largely ER negative. Data from the NSABP P1 trial demonstrates a lack of benefit of tamoxifen in the reducing the incidence of ER negative tumors and thus, there may be reason to doubt its efficacy in this group of high risk patients for whom prophylactic mastectomy remains an option. Furthermore, data from the Royal Marsden tamoxifen chemoprevention trial did not confirm a decrease in incidence of breast cancer. Participant's eligible for their study had to demonstrate the presence of a strong family history as an entry criteria. This fosters a whole new avenue of research as to other chemoprevention strategies for this group of high risk patients.

Conclusions:

- For women with a ≥ 1.66% defined 5 year projected risk of breast cancer, tamoxifen may be offered to reduce the risk of breast cancer
- Tamoxifen is appropriate if the primary goal of therapy is to lower the risk of breast cancer
- There is insufficient information regarding whether tamoxifen reduces mortality from breast cancer in high risk women
- Currently there is insufficient evidence to determine if tamoxifen provides overall health benefits
- It is premature to recommend raloxifene to lower the risk of breast cancer outside a clinical setting
- Raloxifene should be reserved for its use to prevent bone loss
- There are no current published data on raloxifene in premenopausal women

Questions That Remain Unanswered

- What is the optimal dose and duration of tamoxifen for prevention?
- What is the most optimal age should tamoxifen be administered?
- What level of risk warrants intervention with tamoxifen?
- What is tamoxifen's role for women with a strong family history?
- What should the high risk patient do after tamoxifen?
- Will a reduction in incidence translate into a reduction in mortality?

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