

International Breast Cancer Research Foundation

The epidemiology, causes and
prevention of breast cancer

Richard R. Love, MD

A Scientific Review Report

September, 1999

Contents

REPORT SUMMARY 1

Incidence and Mortality 1

Causes and Prevention 1

INCIDENCE 2

ETIOLOGY 3

BIOLOGY 4

EPIDEMIOLOGY 5

Descriptive Epidemiology 5

Breast Lobule Maturation and Differentiation 6

Genetic or DNA Damaging Causes of Breast Cancer 7

Hormonal Exposures and Modifiers [Table 2] 8

PREVENTION 11

TABLES 14

- 1 Chances of Being Diagnosed with Breast Cancer at Different Age Intervals 14
- 2 Risk Factors for Breast Cancer According to Hypothesized Mechanisms of Action and Direction of Impact on Risk 15
- 3 Breast Lobule Maturation and Differentiation 16
- 4 Family History and Relative Risk of Breast Cancer 17
- 5 Prevention Counseling by Age 18
- 6 Considerations in Assessing Benefits and Risks for Hormonal Therapies in Healthy Women 19

FIGURES 20

- 1 US Breast Cancer Incidence Rates over Time 20
- 2 Mortality from Breast Cancer in Younger and Older Women in the US 21
- 3 Breast Cancer Incidence in US and Japan 22
- 4 Estrogen Receptor Protein Levels over 20 Years 23
- 5 Impact of Hormonal Exposure 24
- 6 Cumulative Incidence of Breast Cancer in 1373 Postmenopausal Women according to Age-Specific Quartile of Metacarpal Bone Mass at Baseline 25
- 7 Age at First Full-Term Pregnancy 26
- 8 Risk after First Pregnancy 27
- 9 Breast Cancer Risk according to Number of Completed Pregnancies 28

REFERENCES 29

REPORT SUMMARY

Incidence and Mortality

In the United States over the last 50 years the incidence of breast cancer has steadily increased at about 1% per year, with an accelerated period of greater annual increases in the 1980s and early 1990s because of increased early detection measures. In the United States, the age-specific incidence of breast cancer increases throughout life. At age 40, approximately one woman per 1000, while at 60, one per 400, is diagnosed annually with breast cancer. In the United States, overall mortality from breast cancer has been stable over many years until recently when annual decreases have been seen. Mortality rate decreases appear to be greater in younger women.

Causes and Prevention

Breast cancer develops over many years following multiple causal events. Initial breast epithelial DNA damage occurs with radiation, spontaneously, and perhaps with tobacco exposure, and these effects are perpetuated in the presence of other inherited DNA mutations which prevent usual DNA damage repair. These processes are particularly important in the window of time when breast epithelium is undifferentiated - from the time of menarche until a first full-term pregnancy.

Cumulative estrogen exposure, modified by a number of factors (age at menarche, pregnancy, weight gain, alcohol, hormone replacement therapy), influences later preclinical phases of breast cancer development.

Feasible and likely effective prevention strategies include: avoidance of radiation, alcohol, and tobacco; increased fruit and vegetable intake and regular exercise and avoidance of weight gain, particularly early in life; and lactation for long periods. The role of antiestrogen chemopreventive treatment is incompletely defined at present, although one large trial has shown a 50% reduction in incidence of breast cancer in high risk women.

INCIDENCE

In the United States, breast cancer is the most frequently diagnosed major cancer in women (approximately 180,000 cases in 1998 and over 44,000 deaths).² Breast cancer accounts for approximately one-third of all cancers diagnosed in American women and approximately 18 percent of all cancer deaths in women.² Worldwide, breast cancer is a major public health problem; there are approximately 1 million new cases annually, the majority of which occur in premenopausal women.¹

In the United States, a woman's risk of developing breast cancer is estimated at 1 in 8 if she lives to be 110.³ This risk estimate is modified according to estimates of the probability of surviving through each decade of life.³ Thus women over age 90 should contribute very little to an easily understandable overall risk statistic, since numbers of such older women are small compared to the numbers of younger women. Several additional points should be made about this 1 in 8 estimate. More than half the risk is incurred after age 60, and one-third of the risk occurs after age 75. This risk estimate is not very useful in counseling women about their risks of breast cancer and it is subject to misinterpretation often⁴. The estimate does not suggest that if there are 8 women together in a room, on average one will develop breast cancer. Further, women suggested to be at greater than usual risk of breast cancer do not have risks which are multiples of this 1 in 8 estimate. It is more useful for physicians to consider risk estimates over time spans of 10 or 20 years. Recently, epidemiologists have developed more understandable ways of presenting breast cancer risk data. Feuer and colleagues³ have employed (detailed in Table 1) life table methods that use age-specific incidence rates for only the first primary breast cancer and adjust for other causes of death. Their data show the likelihood of being diagnosed with breast cancer over different age intervals. The table shows that the chance of developing cancer by age 50 is 1 in 50 and these chances decrease over time as an individual woman ages without being diagnosed with breast cancer. For example, a 40-year-old woman has a 1 in 14 chance of developing breast cancer by age 70, while a 60-year-old woman has only a 1 in 28 chance of developing breast cancer by age 70.

Another widely used risk estimate model has been developed by Gail and colleagues⁵ who studied a population of women who participated in a demonstration mammography screening project. These researchers reported the experience that these women had in being diagnosed with breast cancer over various time intervals. In addition, the researchers studied the impact of specific risk factors, such as a family history of breast cancer or a previous breast biopsy which showed benign disease, had on the rates of breast cancer occurrence. Gail found that a 40-year-old woman had a 1 in 35 chance of developing breast cancer by the time she was 60 if her relative risk was 1. This is lower than the 1 in 26 figure reported by Feuer, whose reported data for an "average" population was made up of both low-risk and high-risk women. However, this hypothetical 40-year-old woman had a 1 in 25 chance of breast cancer by age 60 if she had a relative risk of 2 and a 1 in 13 chance if she had a relative risk of 5. The Gail model was used in selecting women participants for the recently completed National Surgical Adjuvant Breast and Bowel Project breast cancer prevention trial with tamoxifen, and the data from that trial will provide further practical tools for estimating breast cancer risk in individual women.⁶

The incidence of breast cancer has been increasing in the United States, as illustrated in Figure 1. There have been two distinct periods of increases. During the first period from 1940 through approximately 1982 incidence increased at a little over 1%/year. During a second period, an increase of about 4 percent per year has characterized a 15 year span until recently⁷. The increases over time seen in this figure are suggested to be due to three factors.⁷ Approximately 30 percent of the total increase over time is due to changes in "causative" dietary, lifestyle, hormonal, and reproductive factors reviewed below⁸ and about 60 percent of the total increase, particularly the recent increases, is attributable to the detection of (subclinical) breast cancers as a result of more widespread mammographic screening.^{7,9} Approximately 10 percent of increased incidence is attributable to women living longer and decreased mortality from other causes⁷. One would expect that if mammographic screening is responsible for a majority of the increase in breast cancer incidence, once the prevalent cases in the population are discovered, incidence rates should decline to a baseline "true" incidence rate. The recent stabilization of incidence supports this analysis⁷.

While the incidence of breast cancer has been increasing in the United States (Figure 1), overall mortality from the disease has been stable⁷ (Figure 2). This unchanged mortality rate suggests that breast

cancer cases identified in the fifteen years following 1980 have not been followed long enough to have an impact on the death rate, were diagnosed at earlier, more curable stages, were treated successfully, or were somehow less lethal. Evidence to support an hypothesis about increased curability comes from data showing that most of the excess cancers were tumors measuring less than 2 cm in diameter or *in situ* cancers¹⁰. These are the types of lesions that mammography would be expected to identify. If this explanation is the most true one, then further reduction in mortality from breast cancer can be expected. The possibility that the biology of breast cancer is changing so that on balance the disease is less lethal, is suggested by data showing a decrease in mortality of almost 25% in women under 50 in the period 1970-82, while in recent years mortality in women over 50 has increased¹¹ (Figure 2).

The evidence of breast cancer increases with age in all populations with some variations in the rate until menopause, after which time different patterns are seen according to geographic region (Figure 3). In western populations, the increases in incidence are most rapid in the premenopausal years, become slightly less rapid at menopause, and then continue to rise throughout life. In contrast, in Asian populations in the 1970s and 1980s, the increases in the premenopausal years were less rapid (than in Western populations) and gradual decreases in incidence have been observed after menopause. These patterns are important in two ways, In combination with the age compositions of populations, they influence the overall incidence figures. Thus increased longevity in Western women will be associated with an overall breast cancer incidence increase without any meaningful real increase. Secondly, true age specific incidence patterns provide insights into the causal biology of breast cancer.

ETIOLOGY

While a complete, comprehensive picture of the causal biology of breast cancer is not yet available, many major components of the picture are known. Breast cancer incidence rates vary nearly 10-fold among populations; the highest rates are in Western countries (over 100 cases/100,000 women) and the lowest are in Asian countries (10 to 15/100,000 women)¹². When a low-risk population migrates to an area of high incidence, the low-risk population gradually assumes the breast cancer incidence of the high-risk population.^{13,14} Incidence rates have increased rapidly in some countries such as Japan where major lifestyle changes have also occurred.¹⁴ These observations strongly suggest that environmental and lifestyle factors are important in the etiology of breast cancer. At the same time, it has long been observed that breast cancer is more prevalent in some families, which account for approximately 5 percent of all cases¹⁵.

BIOLOGY

An enhanced understanding of the biology of breast cancer is critical if we are to make progress in prevention and in improving outcomes for patients with this disease. While the specific cause for the transformation of a normal breast ductal epithelial cell into a malignant one is unknown, several important alterations can occur within that cell that make breast cancer a potentially lethal disease. Breast tissue and breast malignancies are dependent on estrogen for their growth. Most breast cancers have measurable levels of estrogen receptor protein and cells that stain positive for this protein and these tumors are more responsive to hormonal therapies. Over time, practically all breast cancers become hormone independent and capable of sustained growth in the absence of estrogen.¹⁶ The mechanisms involved in this conversion from hormone dependence to hormone independence are becoming clearer. Estrogen works to stimulate cell growth by binding to the estrogen receptor. Then this receptor-ligand complex binds to specific DNA sites and activates genes responsible for synthesizing important growth factors.¹⁷ In the acquisition of hormone independence, it appears that some cells mutate their estrogen receptor,¹⁸ while others acquire the ability to secrete these growth factors without the need for estrogen stimulation.¹⁹ These cells lose the estrogen receptor protein and can produce such growth-inducing compounds as transforming growth factor alpha (TGF- α)²⁰ and epidermal growth factor (EGF)²¹ without an estrogenic stimulus. It is unknown whether this acquisition of hormone independence results from a mutation that takes place spontaneously during the course of the disease, or whether tumors contain a great deal of

heterogeneity early on and the overgrowth of hormone-independent cells is a function of natural selection. This biologic information is also important in prognosis. Cells that express the EGF receptor²² and overexpress the *HER-2/neu* gene,²³ which codes for a protein structurally similar to the EGF receptor, have both been associated with poor prognosis in breast cancer patients. In addition to the definition of additional prognostic markers for breast cancer outcome, research into growth factor secretion and growth factor effects offer the potential for new therapies in breast cancer. For example, antibodies that bind and occupy growth factor receptors could be potential targets for antineoplastic therapy in breast, as well as other cancers. To date, the most useful such therapy developed has been a humanized antibody to HER-2-neu, therapy with which causes regression of metastatic tumors in approximately 15% of patients whose tumors overexpress the HER-2-neu gene²⁴.

Breast cancer involves many genetic alterations. Karyotypic analyses suggest that a truly diploid breast cancer may not exist.²⁵ The DNA content and the percent of cells in active cell cycle (S-phase fraction) of cancer cells can now be measured from fixed sections. It appears that S-phase fraction may be a prognostic indicator of outcome in node-negative breast cancer.²⁶ In large clinical trial populations primary tumor ploidy and S-phase fraction are being studied to see if these can aid in identifying specific subsets of patients in need or not in need of additional therapies. The retinoblastoma gene, *RB-1*, a tumor suppressor gene, is reported to be altered in 15 to 20 percent of breast cancer patients.²⁷ The gene for p-53, a cell cycle regulating protein, is found to be altered in a substantial number of the breast cancer specimens studied.²⁸ A gene on the long arm of chromosome 17 associated with a hereditary form of breast cancer has recently been identified and will be discussed later in this chapter. The oncogene *C-myc* is amplified in approximately one-third of breast cancers²⁹ and point mutations in the *H-ras* proto-oncogene have also been detected.³⁰ Understanding the genetic instability that accompanies breast cancer as well as amplification or mutation of specific genes will give further insights into the causation and progression of breast cancer.

In common with other solid tumors, breast cancer exhibits two other biologic properties that contribute to its potential lethality. The first is the presence or acquisition of chemotherapy drug resistance and the second is the ability to metastasize.

EPIDEMIOLOGY

The descriptive and analytic epidemiology of breast cancer is complex because the disease is clearly multicausal and significant interactions among multiple causes (which are themselves changing in frequency) confound interpretations of our available information³¹. Only limited numbers of causes (or risk factors) can be evaluated in single studies; thus the results from single studies provide relative but not absolute pictures of the spectrum of causes and their strengths. At present no comprehensive, all-cause inclusive model for breast cancer development has been proposed, although obvious components are well recognized³¹. One clinically important conclusion from these broad statements is that the relative risk figures from many epidemiologic studies are of very limited use in quantifying risk for individual women, and indeed the absence of accepted comprehensive models makes current risk estimates for individuals very uncertain (Tables 1 and 2).

A discussion of breast cancer epidemiology is important not only as a basis for understanding disease development but also in understanding disease biology. And it is in understanding disease biology and characteristics that the foundations of successful treatment lie.

This section is structured on a physiologic framework, considering the identified or hypothesized risk factors or causes of breast cancer according to their biologic mechanisms of action (Table 2).

Descriptive Epidemiology

The earlier sections of this chapter have summarized some of the major descriptive epidemiology: in the U.S. incidence has been steadily increasing over a long period, there has been an accelerated increase in incidence since the mid 1980s attributed to screening (Figure 1), and overall mortality has been stable in the U.S., with perhaps a recent decrease (Figure 2). Mortality trends have not been the

same for older and younger women however (Figure 2), for reasons which are poorly understood. Old women appear to have suffered greater mortality from breast cancer in the U.S. until recently while younger women have benefitted from a significant decline which began about 1970¹¹. The increase in mortality in older women appears not to be artefactual (that is it is not because of a change in the age structure of the population) and is perplexing because increased screening efforts and the clear benefits of widely-used adjuvant hormonal therapy (see below) which began in the early-mid 1980s might have been expected to affect sooner the overall trend favorably. Similarly, in younger women, decreased mortality is seen in the 1970-mid 80s period, for which there is no obvious explanation; this period antedated widespread use of adjuvant chemotherapy which might produce such a trend. One clue to a broad understanding of these mortality data may lie in data suggesting that the average level of estrogen receptor protein in primary breast tumors has been increasing significantly³² (Figure 4). Such data imply that the biology of breast cancers themselves may be changing. To date research relating known risk factor changes to these mortality trends has not clarified the picture. On the whole these incidence and mortality trends however, reinforce an impression that the control of breast cancer involves a moving target. When the age specific incidence of breast cancer in the U.S. is graphed on logarithmic scales, a figure with two apparently distant slopes is seen (Figure 5). For many solid tumors similar graphs show single straight lines. This figure for breast cancer allows several interpretations, the most important of which are that multiple, perhaps 4-6 events are responsible for the expression of clinical disease, the earliest of these occurs in the first two decades of life, and menopause has a profound influence on the rate of disease development. A simple model that concludes that the 4-6 events are mutations seems unrealistic because of the large numbers of cells which continued dividing after initial mutation, and because of the necessity for a high frequency of mutation³³. The profoundly different slopes of age specific incidence figures in western and eastern populations (Figure 3) when combined with the observation that migrants from east to west take on the incidence of this disease of this adopted culture¹⁴, strongly imply that broad lifestyle factors over many years influence the rate of disease occurrence and that inherited factors play only a minor role in the overall breast cancer incidence differences among populations.

Breast Lobule Maturation and Differentiation

While the specific impacts of hormonal changes throughout the menstrual cycle have been difficult to elucidate, the broad impacts of major reproductive events on hormonal alterations or breast development have been described³⁴⁻³⁷. As outlined in Table 3, initially undifferentiated lobules with cells which are significantly sensitive to carcinogenic insult, become semi- and fully-differentiated under the influence successively of menarche, pregnancy and lactation. In individual women therefore, the timing of these factors may have a profound influence in determining whether other factors are important. For example, radiation exposure to undifferentiated breast tissue (as with treatment for Hodgkin's Disease in young girls or women) is associated with markedly increased risk of later breast cancer while shorter exposures given to women in their 30s and 40s are associated with minimal increased risk^{38,39}.

Genetic or DNA Damaging Causes of Breast Cancer (Table 1)

While increased risk for breast cancer has long been associated with occurrence of the disease among close family members⁴⁰, it has only been in the last decade that a greater understanding has developed of the likely mechanisms which explain the wide range of increased risk observed. Broadly, approximately 5% of women with breast cancer have a family history which suggests that an inherited factor may have been important in these cases⁴¹. The occurrence of breast cancer in close or first degree relatives [mother, sister(s), daughter(s)] at younger ages, and bilaterally, each and together suggest that inherited factors may be important in particular individuals, and when all are present, risk for breast cancer is markedly increased [Table 4]. For example, if both the mother and sister of a healthy woman

have had premenopausal breast cancer, the likelihood of breast cancer approaches 50%⁴². While occurrence of breast cancer among more than single individuals in a family may reflect common exposures to environmental carcinogens, it appears that in most of these families specific genetic changes confer increased susceptibility⁴¹. Genetic linkage studies have established that mutations on a large gene or chromosome 17 (17q21) called BCRA 1, are likely to be associated with slightly less than half of breast cancer cases occurring in families¹⁵. Mutations in a second gene, BCRA2 (13q12-13) account for most of the other half of familial cases, and mutations in the p53 gene (17p12-13) account for a small fraction also. Approximately 3.3% of American patients with breast cancer have BCRA 1 or 2 mutations¹⁵. These genes are thought to be tumor suppressor genes, mutations in which facilitate the development of malignancies. Recent data suggest that the BCRA gene mutations may be expressed as DNA repair deficiency and may influence genetic stability^{43,44}. BCRA 1 and 2 appear to work through the same pathways⁴⁴. Environmental factors appear to modify expression (or penetrance) of these genetic mutations^{45,46}. While commercial tests are now available for some BCRA mutations, the general consensus among experts is that currently these tests should only be used in research studies.

Irradiation, presumably because of resultant DNA damage and mutations, is a cause of breast cancer. Breast irradiation to doses which are carcinogenic has occurred as a result of exposure to atomic bomb blasts, fluoroscopic examinations for tuberculosis, and radiation treatments for mastitis, enlargement of the thymus, acne, asthma, and Hodgkin's disease^{39,40}. The ages of women at the time of irradiation profoundly influence the risk; the younger the age of exposure, the greater the risk. By age 40, usual diagnostic radiation exposures as from mammography, confer minimal to negligible risk, with the possible exception that women heterozygous for the ataxia telangiectasia gene may have increased risk throughout life⁴⁷. There is a long latency period after exposure to irradiation before the appearance of more frequent breast cancers - 10-20 years.

Tobacco smoking is a probable DNA-damaging cause of breast cancer⁴⁸. Interpretation of studies of smoking and breast cancer has been compounded by several factors. Tobacco smoking may alter menstrual cycle hormonal patterns and age at menopause in ways which decrease risk of breast cancer⁴⁹. Age at exposure to tobacco smoke appears to be important; smoking in the teenage years is associated with increased risk presumably because the pool of undifferentiated breast cells which are more sensitive to such carcinogenic damage is greater during these years prior to a full term pregnancy^{37,49}. Finally, menopausal status and N-acetyl transferase 2 genotype appear to interact in modifying risk of breast cancer⁵⁰. In sum, it appears that for some women, tobacco smoking is a risk factor for breast cancer and that this influence is important in the initial phases of the disease process.

Inherited, radiation or carcinogen (tobacco smoke)-induced, or random DNA damage - genetic mutations may be more or less likely to be expressed ultimately in clinical breast cancers depending on a number of factors. One new category of exposures that may be important in this regard is intrauterine hormonal changes. Studies have suggested that circumstances which decrease (toxemia) or increase (neonatal jaundice or prematurity) exposure of the fetus (and fetal breast tissue) to estrogen are associated with subsequent risk of breast cancer⁵¹. Since hormonal changes are not usually considered genotoxic, if this hypothesis is further supported, it is more likely that such estrogen exposures change the numbers or susceptibility of breast cells to later DNA damaging exposures. A less complicated hypothesis concerns the possible protective effects of micronutrients, particularly during the years prior to a full term pregnancy. Two recent studies have suggested that carotenoid and perhaps folic acid intake may be protective against breast cancer^{52,53}. Exposure to adequate quantities of these nutrients may be particularly important in facilitating DNA repair in susceptible adolescent breast epithelia⁵⁴.

Hormonal Exposures and Modifiers [Table 2]

The occurrence of breast cancer is strongly influenced by hormonal factors. Perhaps the three strongest illustrations of this relationship are the change in age specific incidence of breast cancer which occurs at menopause [Figure 5], the relationship between metacarpal bone mass and breast cancer risk⁵⁵, and the recent data showing a 50% reduction in breast cancer incidence with tamoxifen - a breast antiestrogen⁶. As Figure 5 shows, age specific incidence of breast cancer in US women increases linearly

[when graphed as here on a log-log scale] until the late forties, at which time the rate of increase changes abruptly, becoming less rapid. If women undergo bilateral ovariectomy at earlier ages, similarly the rate of incidence increase abruptly changes³⁴. These observations make it clear that the appearance of clinically recognized breast cancer is dependent on hormonal exposure. The observation that metacarpal bone mass is associated with breast cancer risk emphasizes the point that it is cumulative hormonal exposure which appears to be important⁵⁵. Greater metacarpal bone mass is a surrogate for greater cumulative estrogen exposure [Figure 6]. Treatment in healthy women for 3-4 years with tamoxifen, a breast cancer-cell estrogen antagonist, has been reported in one recent large study, to be associated with a halving of breast cancer incidence⁶. Since the development of preclinical breast cancer is believed to occur over many years [as the data showing increased occurrence of cancer 10-20 years after excess radiation exposure suggest³⁹], such evidence for effects of long term hormonal differences is consistent.

The relationship of hormonal exposures, primarily estrogen, and breast cancer risk is supported by data of different types: those of hormone physiology and reproductive events, and those of apparent hormone modifiers [Table 2]. Earlier ages at menarche are associated progressively with greater risk of breast cancer later in life^{34,56}. Presumably this occurrence has such adverse effects by increasing the total number of menstrual cycles and thus cumulative estrogen exposure to the breast in a woman's life, or also by increasing the time during which undifferentiated susceptible breast epithelia can be affected by DNA damage prior to a full term pregnancy³⁷. The determinants of age at menarche are not well understood; nutritional, exercise, and inherited factors are likely the most influential, but their relative strengths and specifics of timing and factors are not defined³¹. Age at menarche differs markedly in populations, and is generally decreasing over recent years. Girls in Asian societies are reported to reach menarche at 15-16, while currently American girls are beginning to have menstrual periods at 10-11³¹. Characteristics of menstrual cycles which are also independently associated with subsequent risk of breast cancer are also influenced by age at menarche. Shorter lengths of cycles, and earlier age at establishing regular cycles are associated with increased risk and with early age at menarche⁵⁷.

The relationship of age at first full term pregnancy and breast cancer risk is well established and strong⁵⁸ [Figure 7]. The mechanism underlying this relationship has been referred to earlier in this chapter^{36,37} [Table 3]. A full term pregnancy and its associated hormonal events stimulate the differentiation of breast ductules. After this, breast tissues are less susceptible to DNA damage and less likely to divide and preserve and perpetuate cells with genetic changes which might lead to cancers. The risk of breast cancer following a full term pregnancy is, however, a function of time from the pregnancy⁵⁹ [Figure 8]. In the 5-10 years immediately following a pregnancy risk for breast cancer is increased, presumably consequent to the tumor promotional effects of estrogenic and lactational hormones which are markedly increased during pregnancy⁵⁹. Preclinical cancers, already partially established are thus pushed along in their development by the hormonal changes of pregnancy. After the passage of a decade however, the epithelial-differentiating effects of pregnancy on the risk of breast cancer became dominant and risk of breast cancer falls for women who have had a pregnancy compared to those without [Nulliparous in Figure 8].

Increased parity also decreases risk of breast cancer in a remarkably linear fashion⁶⁰ [Figure 9], and this observation is further evidence that the differentiating effect of pregnancies is critical in modulating breast cancer risk.

In more recent years, a relationship between cumulative time of lactation and breast cancer risk has been demonstrated in several studies, particularly with respect to risk for breast cancer in premenopausal women. Periods of lactation (over 1 or more pregnancies) beyond 6-12 months are associated with decreased risk^{61,62}. The mechanisms through which this risk reduction are mediated are incompletely understood, but breast duct epithelial differentiation, omission of menstrual cycles during lactation with associated decreased estrogenic hormone exposure to the breast, and permanent down-regulation of prolactin levels after lactation is finished have been hypothesized to be important.

Given the clear evidence that hormonal changes modulate breast cancer risk, the use of oral contraceptive hormonal preparations and postmenopausal hormonal replacement therapies is also of concern. A multiplicity of studies on oral contraceptives and postmenopausal hormonal therapy has not provided a clear picture of the relationship. Recently the Collaborative Group on Hormonal Factors in

Breast Cancer gathered data from over 50 studies^{63,64}. A small increase in risk [relative risk 1.23] was found in current users of oral contraceptives; this excess risk disappeared by 10 years after cessation of these drugs⁶³. Hormone replacement therapy is associated with increased risk of breast cancer by 2% for each year of use⁶⁴. This increased risk rapidly disappears with cessation of use. Data on particular hormone replacement preparations (estrogen alone versus combined estrogen- progesterone therapies) are sparse and do not permit any firm conclusions about safer or riskier preparations.

A variety of exposures are suggested to influence breast cancer risk through modification of hormonal levels or metabolism. In recent years regular alcohol consumption has been consistently demonstrated to be associated with increased risk of breast cancer in a dose dependent manner^{65,66}. While alcohol may increase endogenous hormone levels⁶⁷, it may also have direct effects on breast epithelia⁶⁵. Most, but not all, studies have suggested that increased levels of physical activity are associated with decreased risk of breast cancer⁶⁸⁻⁷². The details of this relationship are difficult to study and quantify; recreational and occupational physical activity levels have been more studied while nonspecific occupational activities, more common in women, have received little attention. The mechanisms whereby levels of physical activity influence risk are unclear. Physical exertion may modify hormone levels and/or reduce numbers of menstrual cycles. Physical activity levels may also influence body mass, or immune system function.

Body mass is associated with breast cancer risk, but the relationship is complex. In premenopausal women increased body mass is associated with decreased risk of breast cancer; menstrual cycle irregularities reflecting disrupted hormonal regulation and levels are believed to be mediators of this association^{73,74}. In contrast, increased body mass in postmenopausal women is associated with increased risk for breast cancer⁷³. The explanation for this has been that obese women have increased levels of estrogenic hormones⁷⁵. The distribution of body fat, and the timing of weight gain appear to influence whether this relationship is observed in studies. In general, weight gain throughout life and abdominal adiposity appear to be important variables associated with increased risk^{73,74,76}.

Laboratory animal studies and large population data relationships in people suggest an association between excess caloric or fat intake and increased risk of breast cancer⁷⁷⁻⁷⁹. Epidemiologic case control studies have directly supported this association while usually more powerful cohort studies have not⁸⁰⁻⁸². An ongoing trial of a low fat diet in Canada and a larger trial - The Women's Health Initiative - in the United States may provide more direct evidence on this complicated relationship. Other than the possible protective effect of micro-nutrients - carotenoids discussed earlier, the other most compelling hypothesis concerns the protective effects of phytoestrogens particularly from soy foods, a risk of breast cancer⁸³. A recent study suggested a specific mechanism for such a protective effect: lowering of serum estrogens⁸⁴. Other factors possibly associated with risk of breast cancer include height. Greater height (and suggested greater breast cancer risk) may reflect nutritional differences early in life and associated growth hormone and insulin-like growth factor changes⁸⁵. Increased DDT levels and exposure have been suggested to be associated with increased risk of breast cancer^{86,87}. More data are needed before a firm association can be asserted.

Tissue Changes in Individual Women

Numerous studies have shown relationships between breast tissue characteristics in individual women and increased risk of breast cancer^{88,89}. Such characteristics are assumed to reflect the impact of risk factors previously discussed. They may or may not represent changes in breast tissue on direct pathways to the development of breast cancer.

Increased glandular tissue density seen on mammograms is associated with increased risk of breast cancer, and as suggested, is likely to be reflective of the presence of other risk factors for cancer^{90,91}. Interventions considered to possibly decrease risk of breast cancer are associated with decreases in glandular tissue density^{92,93}. Women with breast symptoms or signs that reflect overstimulation of glandular tissue or physiologic or biologic changes associated with increased risk of breast cancer, are themselves at increased risk^{88,89}. When breast tissue biopsies show evidence of proliferative changes in ductal tissues (hyperplasia), abnormal cells [atypical hyperplasia] and finally

lobular or ductal carcinoma *in situ*, risk for the development of invasive breast cancer is substantially increased in those individual women⁹⁴.

PREVENTION

Breast cancers appear to develop over several years during which multiple "causes" contribute to their initiation, promotion and progression. Several "causes" have favorable effects on health otherwise or are unavoidable. In this context the goals of interventions to prevent breast cancer occurrence and to decrease mortality must also be to promote better health overall.

The goals of interventions broadly fall into two categories. A first goal is the prevention of critical DNA damage and the enhancing of DNA repair; interventions here are directed at the earliest - initiation stages of breast cancer development. A second goal is the reduction of breast epithelial exposure to estrogen or to the effects of estrogen. The favorable impacts of interventions appear to vary according to when they occur in a woman's life.

In the preadolescent and adolescent years, interventions directed at the first goal - limiting epithelial DNA damage - appear most important⁵⁴ [Table 5]. Limited data suggest that some inherited mutations associated with increased risk for breast cancer exert their deleterious effects by preventing DNA repair⁴³. Specific factors which cause DNA damage include radiation⁴⁷ and perhaps tobacco smoking⁴⁸⁻⁵⁰, and thus limiting these as much as possible in the susceptible undifferentiated breast epithelium of young girls is one preventive strategy³⁷. The balance of energy or caloric intake and energy expenditure in exercise and physical activity influence the age of menarche and characteristics of menstrual cycles in girls^{95,96}. Educating and counseling girls to achieve an optimal balance of these which avoids excessive weight gain is likely to lead to later age at menarche and later establishment of regular menstrual cycles, which in turn will decrease the length of time from menarche to first full-term pregnancy, a time of heightened susceptibility to DNA damage of undifferentiated breast epithelium^{37,54}. Finally, adequate intake of critical dietary constituents, particularly carotenoids and perhaps folic acid, may be especially important during these developmental years by enhancing DNA repair^{52,54}.

During childbearing years, early first full-term pregnancy is clearly likely to reduce risk of breast cancer by causing terminal differentiation of breast epithelium^{37,58}. Similarly, long duration of lactation is likely to be beneficial through similar mechanisms, while also causing some favorable hormonal changes^{61,62}. Again, during these years avoidance of excessive weight gain and regular exercise are likely to be beneficial, and finally limited alcohol consumption should be encouraged^{65,68,85}. As discussed earlier, lactation, weight gain, exercise and alcohol are factors which appear to modify breast cancer risk through hormonal mechanisms.

During the fifth decade of life - the 40s - and beyond, again regular exercise, avoidance of weight gain, and weight loss are desirable. Surgical oophorectomy with hormonal replacement therapy (perhaps optimally with estrogen alone) should be considered particularly when there are other medical indications for gynecologic surgery⁹⁷. The physiologic change from the rapidly rising and falling monthly pattern of estrogenic hormones in cycling women, to a steady state lower level of estrogen is reflected by marked decreased long-term risk of breast cancer.

Finally, the use of hormonal therapies in pre, peri, and particularly postmenopausal women is associated with changes in risk of breast cancer⁹⁸. Estrogen alone is associated with a risk increase of 2% for each year of use⁶⁴; this risk falls rapidly with cessation of use. Combination hormone therapies, for which there are fewer data, appear associated with significantly greater risk of breast cancer⁹⁹. Breast antiestrogen hormones, tamoxifen and raloxifen, are associated with decreased risk of breast cancer in some but not all studies. In a meta-analysis of adjuvant studies, 5 years of tamoxifen was associated with a 47% reduction in contralateral breast cancer¹⁰⁰. In a large American trial, shorter-term tamoxifen was associated with a similar 45% reduction in incidence of breast cancer in healthy women at increased risk⁶. In contrast, two smaller European studies in healthy women have reported no evidence of decreased incidence of breast cancer with tamoxifen^{101,102}. An American study of raloxifen, in healthy postmenopausal women with osteoporosis, has shown a marked reduction in breast cancer occurrence¹⁰³. Conclusions regarding benefits to particular groups of women - by menopausal status or specific risk

factors are not currently evident.

Each of these hormonal therapies has other short- and long-term health benefits and risks, which are less well defined for combination estrogen and progesterone therapies, tamoxifen and raloxifen. Overall mortality rates appear lower with estrogen therapy, which is also associated with decreased rates of cardiovascular disease, bone fractures, mood disturbance and vasomotor (hot flash) symptoms⁹⁸. While beneficial effects on bone mineral density in postmenopausal women are seen with tamoxifen and raloxifen^{104,105}, effects on fracture rates are less studied. Cardiovascular risk factor changes are seen with tamoxifen and raloxifen, in favorable lipid and lipoprotein reductions, but the long-term effects of these remain uncertain^{105,106}. Tamoxifen is clearly associated with increased risk for pulmonary embolism, thrombophlebitis, uterine endometrial cancer, and cataract⁶. Vasomotor symptoms are increased with both tamoxifen and raloxifen^{105,107}. The impacts of tamoxifen and raloxifen treatment on overall mortality rates, and rates of second cancers, mood disturbances, and other central nervous system processes, are incompletely defined, as are the optimal duration of treatment and the consequences of stopping treatment. These data about benefits and risks need to be considered in light of the specific circumstances of individual women⁹⁸ [Table 6].

TABLES

Table 1. Chances of Being Diagnosed with Breast Cancer at Different Age Intervals

		To Age:						
From Age:	30	40	50	60	70	80	90	Ever
0	1:2, 525	1:217	1:50	1:24	1:14	1:10	1:8	1:8
30		1:233	1:50	1:23	1:13	1:9	1:8	1:8
40			1:63	1:26	1:14	1:10	1:8	1:8
50				1:41	1:17	1:11	1:9	1:9
60					1:28	1:14	1:11	1:10
70						1:24	1:16	1:14

(Adapted from Feuer³, with permission.)

Table 2 . Risk Factors for Breast Cancer According to Hypothesized Mechanisms of Action and Direction of Impact on Risk (increase; decrease)

Gene or DNA-damaging or repair risk factors

Inherited genetic mutations BCRA1, BCRA2, P53

Irradiation

Cigarette smoking [particularly in young and individuals with specific genotypes]

or Intrauterine/birth hormonal changes: neonatal jaundice, prematurity() or toxemia ()

Vitamins and micro-nutrient consumption [particularly in younger women]

Hormonal exposures

Younger age at menarche

Older age at menopause

Older age at first full term pregnancy

Increased parity

Lactation history

Exogenous hormones: oral contraceptives, postmenopausal hormonal therapies

Modifiers of hormonal exposure

Increased body mass; in postmenopausal women; in premenopausal women

Alcohol

Physical activity

Diet Calories Fat Soy

Notes:

In this table only the direction in which risk is influenced is indicated (or) because the strength of each

of these risk factors in individual women is difficult to quantify. Usual practice is to quantify risk in groups with or without a particular characteristic [without, relative risk = 1] but whether a particular factor is important in an individual woman varies greatly according to other factors present.

Table 3. Breast Lobule Maturation and Differentiation

Lobule Type ^a	Characteristics	Altering Factors	Role in Breast Pathology
Type 1	Menarche, hormonal stimulation, pregnancy	Undifferentiated with 6-11 ductiles	Origin of atypical ductal hyperplasia, ductal carcinoma <i>in situ</i> , and invasive cancers
Type 2	Semi-differentiated	Pregnancy	Origin of lobular atypia, lobular carcinoma <i>in situ</i> , and lobular carcinomas
Type 3	Fully differentiated with 80 ductules	Lactation	Origin of adenomas, fibroadenomas, sclerosing adenosis
Type 4	Differentiated for lactation		

^aInvolvement of types 1, 2, and 3 to terminally differentiated structures appears to occur in postmenopausal years.

Breast Lobule Maturation and Differentiation. Adapted from *Russo J, Russo IH. Toward a physiological approach to breast cancer prevention. Cancer Epidemiol Biomarkers Prev 1994; 3:353-364*³⁷.

Table 4. Family History and Relative Risk of Breast Cancer⁴²

	Approximate relative risk
No close (first degree) relatives [mother, sister, daughter] with breast cancer	1.0
One close relative with breast cancer	1.5-2.0
Two close relatives with breast cancer	5.0
Close relative with bilateral postmenopausal breast cancer	10
Close relative with bilateral premenopausal breast cancer	20

Table 5. Prevention Counseling by Age

Preadolescence, adolescence

Limit chest and breast radiation
 Tobacco
 Regular exercise
 Avoid excessive calories and weight gain
 Increase fruits and vegetables: carotenoids and folic acid

Childbearing years

Early first full-term pregnancy
 Lactation, for long duration(s)
 Avoid weight gain
 Regular exercise
 No or limited alcohol

In the 40s

Avoid weight gain
 Weight loss
 Regular exercise
 Surgical oophorectomy [when gynecologic surgery is otherwise indicated]

Menopausal years

Weight loss
 Hormonal therapies: estrogen, estrogen plus progesterone, tamoxifen, raloxifen

Table 6. Considerations in Assessing Benefits and Risks for Hormonal Therapies in Healthy Women

Menopausal symptoms: vasomotor or
 mood disturbance

Personal and family history of

Vascular disease [pulmonary embolism, heart disease, thrombophlebitis]
 Lipid disorders
 Osteoporosis
 Diabetes
 Obesity
 Mood disturbance [postpartum depression, bipolar disease]

FIGURES

Figure 1 US Breast Cancer Incidence Rates over Time

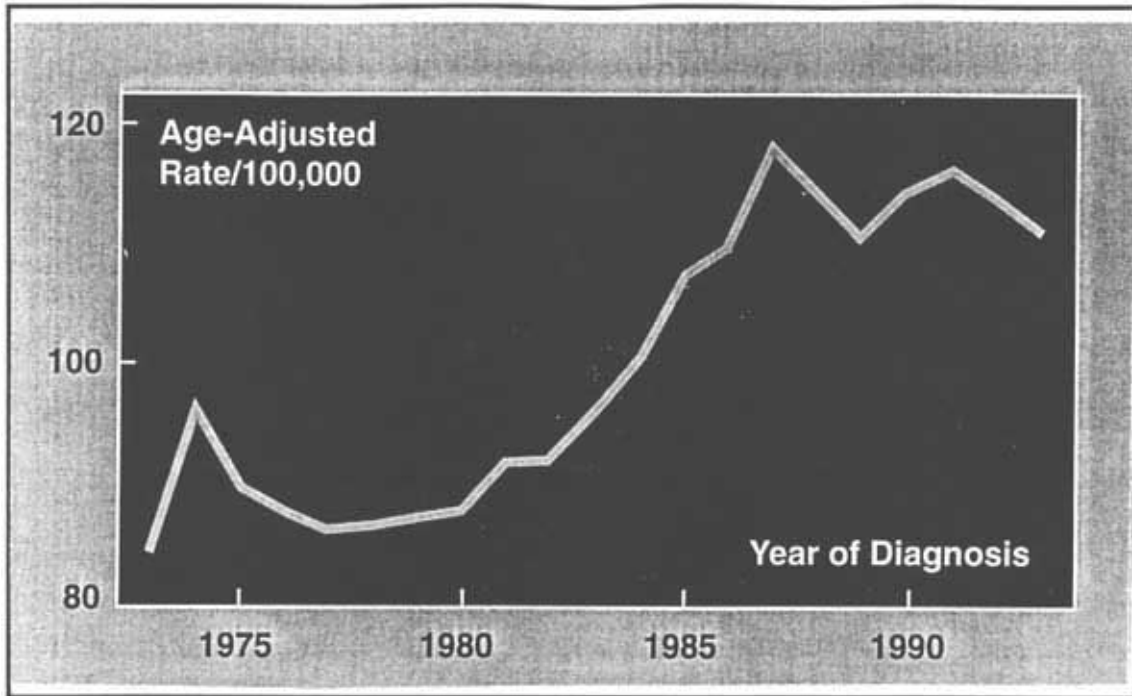


Figure 1: US Breast Cancer Incidence Rates over Time. Adapted from *Chu KC, Tarone RE, Kessler LG, Ries LAG, Hankey BF, Miller BA, et al. Recent trends in U.S. breast cancer incidence, survival, and mortality rates. J Natl Cancer Inst 1996;88(21):1571-1579.*

Figure 2 Mortality from Breast Cancer in Younger and Older Women in the US

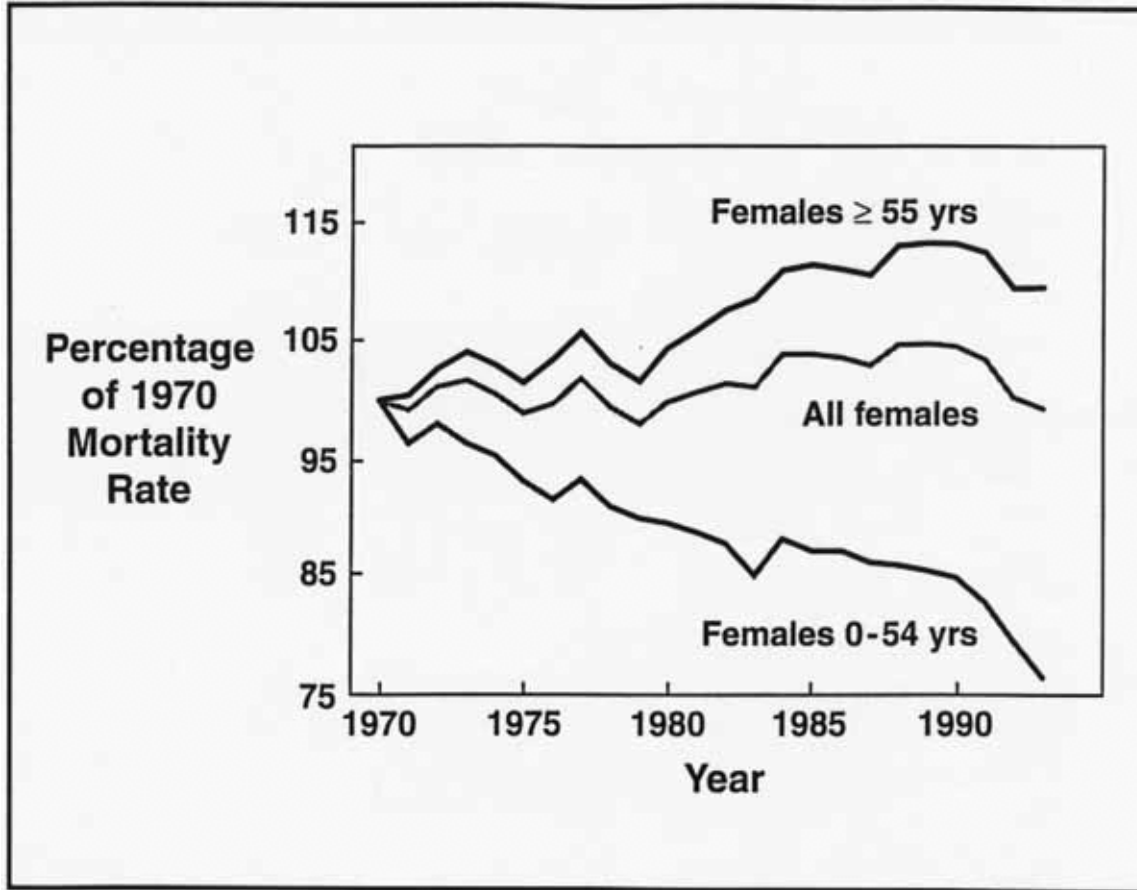


Figure 2: Mortality from Breast Cancer in Younger and Older Women in the US. From Bailar 3rd JC, Gornik HL. *Cancer undefeated*. *N Engl J Med* 1997;336(22):1569-1574.

Figure 3 Breast Cancer Incidence in US and Japan

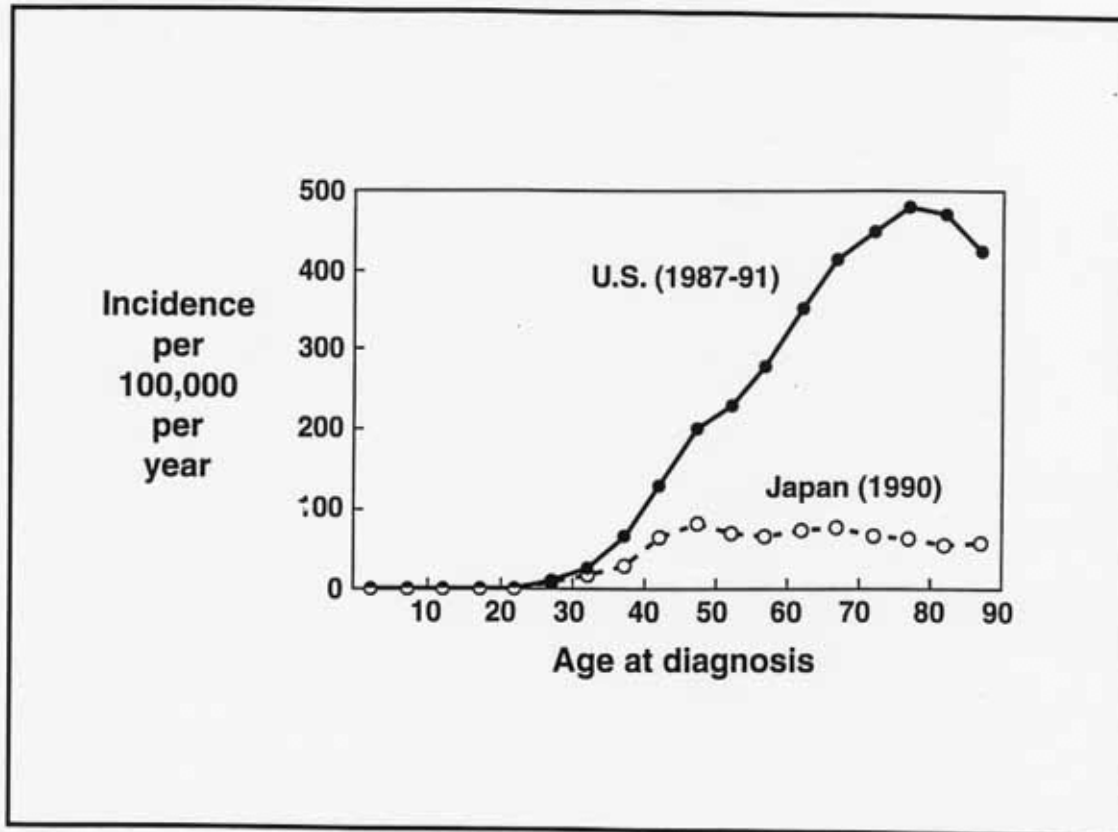


Figure 3: Breast Cancer Incidence in US and Japan. Adapted from Petrakis NL, Ernster VL, King M-C. Breast. In: Schottenfeld D, Fraumeni Jr JF, editors. *Cancer Epidemiology and Prevention*. Philadelphia: W. B. Saunders Company; 1982. p. 855-870.

Figure 4 Estrogen Receptor Protein Levels over 20 Years

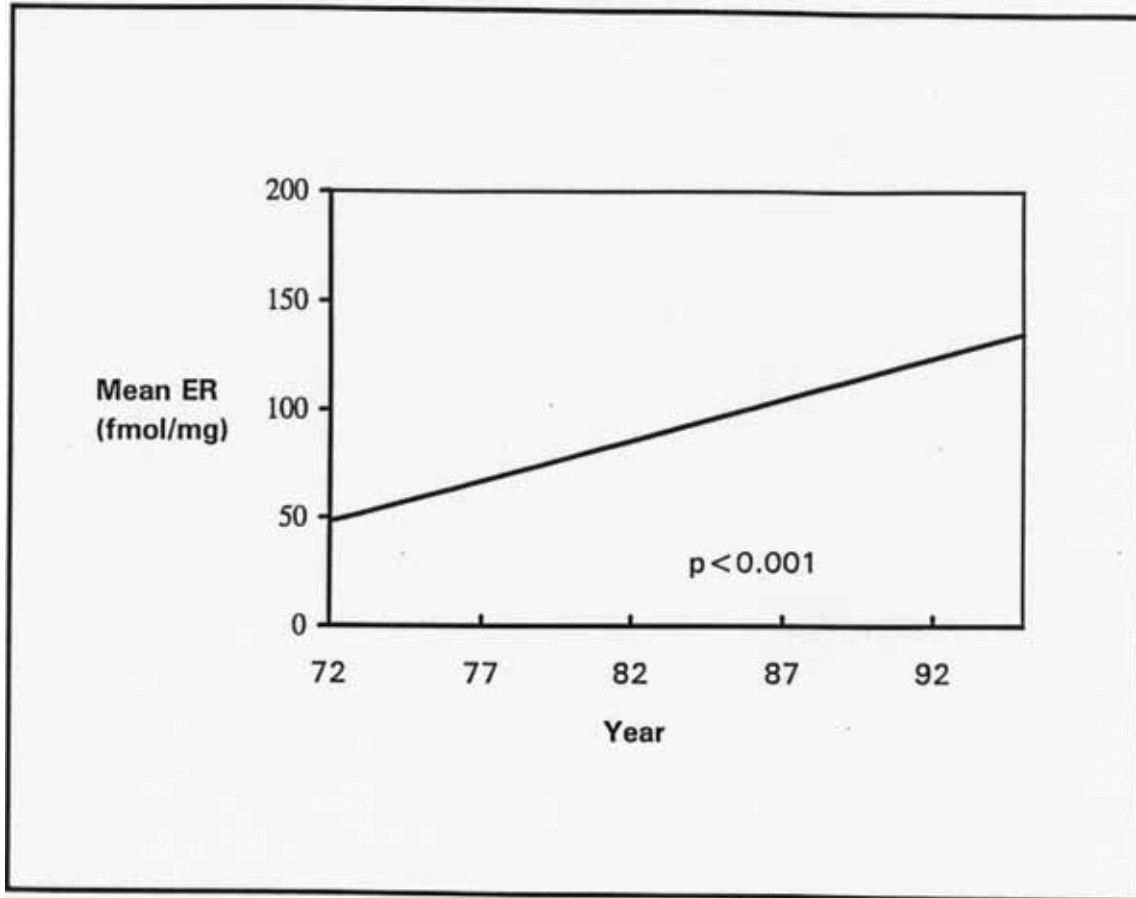


Figure 4: Estrogen Receptor Protein Levels over 20 years. Adapted from Pujol P, Hilsenbeck SG, Chamness GC, Elledge RM. Rising levels of estrogen receptor in breast cancer over 2 decades. *Cancer* 1994;74(5):1601-1606.

Figure 5 Impact of Hormonal Exposure



Figure 5: Impact of Hormonal Exposure—Age-incidence curves of breast cancer among three groups of US women: those with natural menopause at age 50, those with natural menopause at age 45, and those undergoing a bilateral ovariectomy at age 35. None of the groups received hormone replacement therapy. Adapted, with permission, from Pike MC, Ross RK, Lobo RA, Key TJA, Potts M, Henderson BE. LHRH agonists and the prevention of breast and ovarian cancer. *Br J Cancer* 1989;60(1):142-148.

Figure 6 Cumulative Incidence of Breast Cancer in 1373 Postmenopausal Women according to Age-Specific Quartile of Metacarpal Bone Mass at Baseline

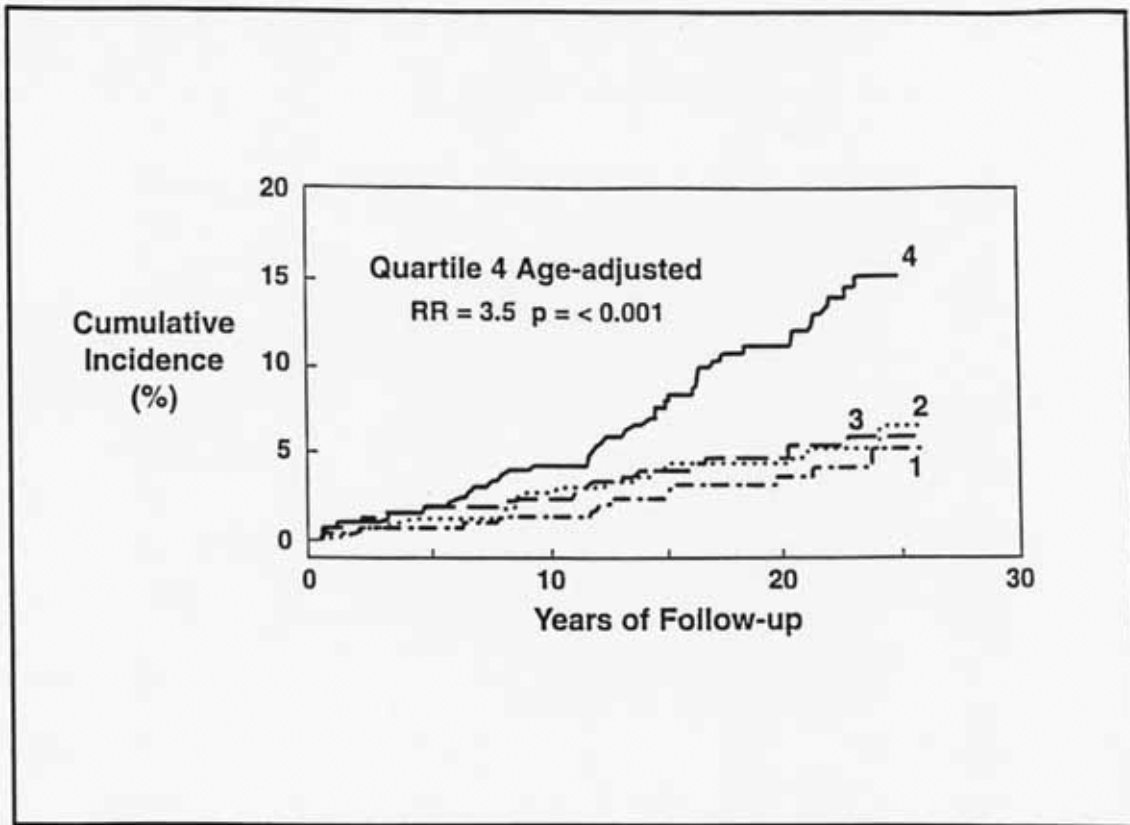


Figure 6: Cumulative Incidence of Breast Cancer in 1373 Postmenopausal Women according to Age-Specific Quartile of Metacarpal Bone Mass at Baseline. From Zhang YQ, Kiel DP, Kreger BE, Cupples LA, Ellison RC, Dorgan JF, et al. Bone mass and the risk of breast cancer among postmenopausal women. *N Engl J Med* 1997;336(9):611-617.

Figure 7 Age at First Full-Term Pregnancy

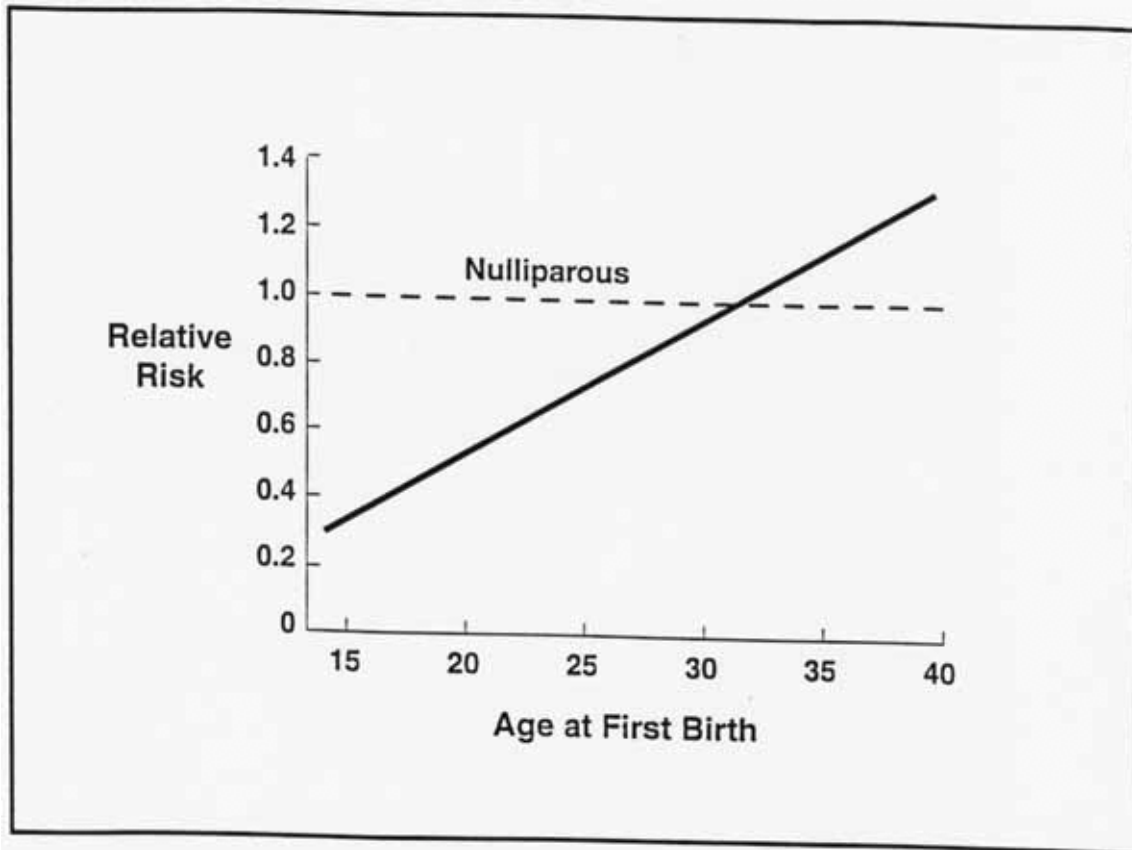


Figure 7: Age at First Full-Term Pregnancy—Age at first birth and relative risk of breast cancer in 4,323 cases and 12,699 controls. Adapted, with permission, from MacMahon B, Cole P, Lin TM, Lowe CR, Mirra AP, Ravnihar B, et al. Age at first birth and breast cancer risk. *Bull World Health Organ* 1970;43(2):209-221.

Figure 8 Risk after First Pregnancy

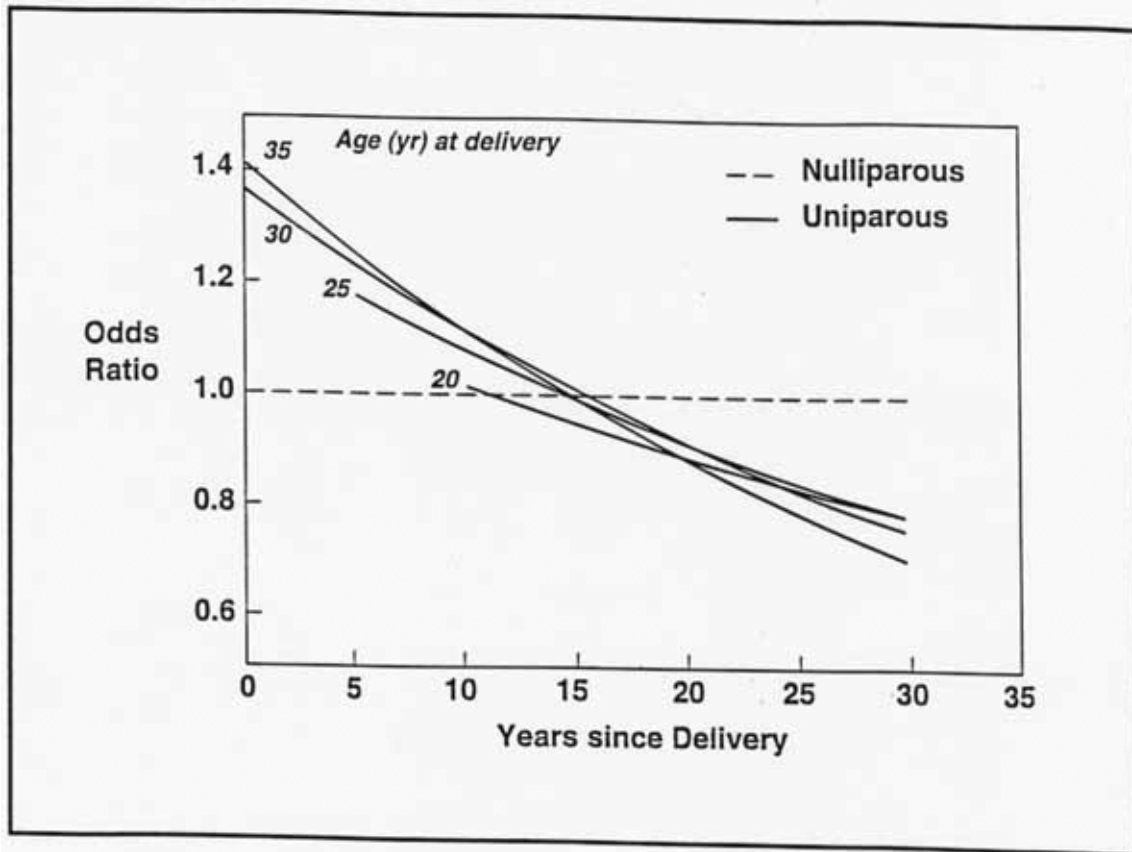


Figure 8: Risk After First Pregnancy—Risk of breast cancer in uniparous women relative to years since delivery. Adapted, with permission, from *Lambe M, Hsieh C, Trichopoulos D, Ekblom A, Pavia M, Adami HO. Transient increase in the risk of breast cancer after giving birth. N Engl J Med 1994;331(1):5-9.*

Figure 9 Breast Cancer Risk according to Number of Completed Pregnancies

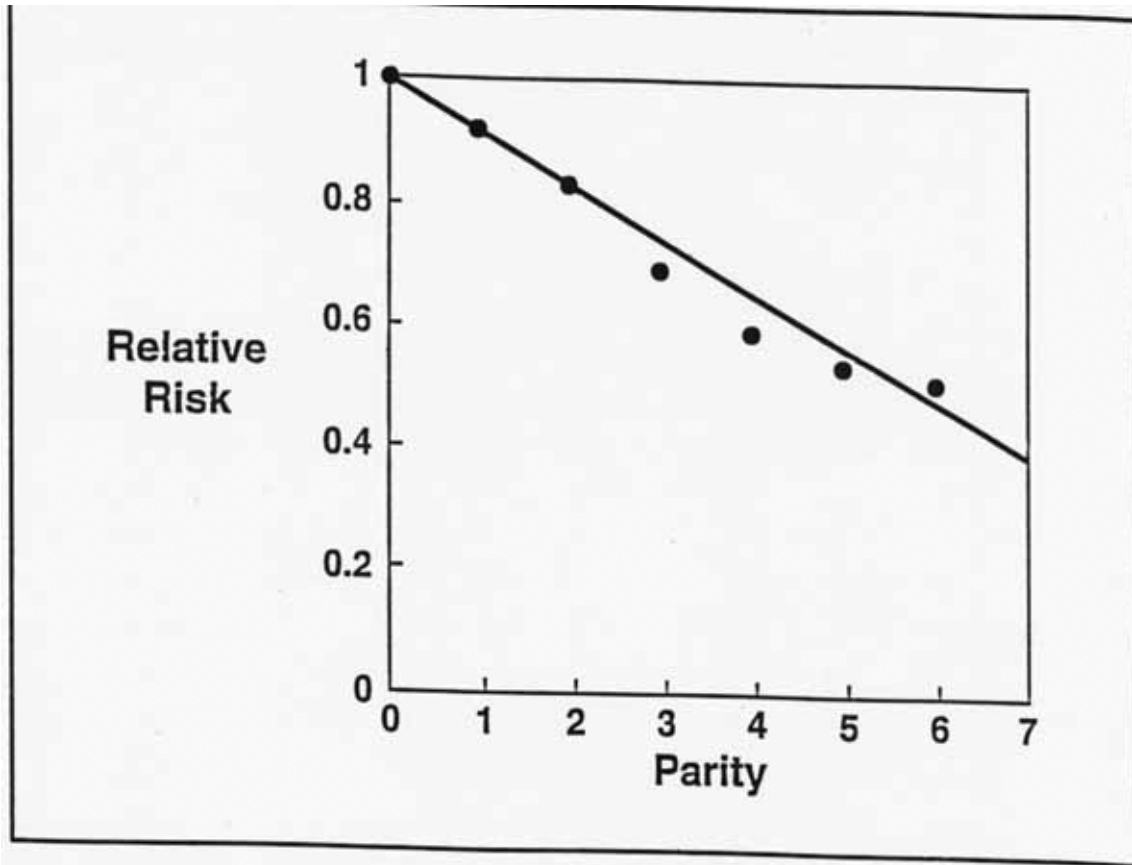


Figure 9: Breast Cancer Risk According to Number of Completed Pregnancies. From Layde PM, Webster LA, Baughman AL, Wingo PA, Rubin GL, Ory HW. The independent associations of parity, age at first full term pregnancy, and duration of breastfeeding with the risk of breast cancer. *J Clin Epid* 1989;42(10):963-973.

REFERENCES

1. Parkin DM, Pisani P, Ferlay J. Estimates of the worldwide incidence of eighteen major cancers in 1985. *International Journal of Cancer*. 54(4):594-606, 1993.
2. American Cancer Society Cancer Facts and Figures-1998. American Cancer Society, Atlanta, GA, 1998.
3. Feuer EJ, Wun LM, Boring CC, Flanders WD, Timmel MJ, Tong T. The lifetime risk of developing breast cancer. *Journal of the National Cancer Institute*. 85(11):892-7, 1993.
4. Swanson GM. Breast cancer risk estimation: a translational statistic for communication to the public. *Journal of the National Cancer Institute*. 85(11):848-9, 1993.
5. Gail MH, Brinton LA, Byar DP, Corle DK, Green SB, Schairer C, Mulvihill JJ. Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. *Journal of the National Cancer Institute*. 81(24):1879-86, 1989.
6. Fisher B, Costantino JP, Wickerham DL, Redmond CK, Kavanah M, Cronin WM, Vogel V, Robidoux A, Dimitrov N, Atkins J, Daly M, Wieand S, Tan-Chiu E, Ford L, Wolmark N. 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*. 90(18):1371-88, 1998.
7. Chu KC, Tarone RE, Kessler LG, Ries LA, Hankey BF, Miller BA, Edwards BK. Recent trends in U.S. breast cancer incidence, survival, and mortality rates. *Journal of the National Cancer Institute*. 88(21):1571-9, 1996.
8. White E. Projected changes in breast cancer incidence due to the trend toward delayed childbearing. *American Journal of Public Health*. 77(4):495-7, 1987.
9. Lantz PM, Remington PL, Newcomb PA. Mammography screening and increased incidence of breast cancer in Wisconsin. *Journal of the National Cancer Institute*. 83(21):1540-6, 1991.
10. Kerlikowske K, Grady D, Rubin SM, Sandrock C, Ernster VL. Efficacy of screening mammography. A meta-analysis. *JAMA*. 273(2):149-54, 1995.
11. Bailar JC 3rd, Gornik HL. Cancer undefeated. *New England Journal of Medicine*. 336(22):1569-74, 1997.
1. Muir CS, Nectoux J. International patterns of cancer. In: Schottenfeld D, Fraumeni JF, eds. *Cancer epidemiology and prevention*. 2nd Edition. New York: Oxford University Press, pp. 141-167, 1996.
12. Kelsey JL, Horn-Ross PL. Breast cancer: magnitude of the problem and descriptive epidemiology. *Epidemiologic Reviews*. 15(1):7-16, 1993.
13. Ziegler RG, Hoover RN, Pike MC, Hildesheim A, Nomura AM, West DW, Wu-Williams AH, Kolonel LN, Horn-Ross PL, Rosenthal JF, et al. Migration patterns and breast cancer risk in Asian-American women. *Journal of the National Cancer Institute*. 85(22):1819-27, 1993.
14. Newman B, Mu H, Butler LM, Millikan RC, Moorman PG, King MC. Frequency of breast cancer attributable to BRCA1 in a population-based series of American women. *JAMA*. 279(12):915-21, 1998.

15. Clarke R, Dickson RB, Brunner N: The process of malignant progression in human breast cancer. *Ann Oncol* 1:401-407, 1990.
16. McCarty KJ, McCarty KS: Steroid modulation of the expression of growth factors and oncogenes in breast cancer. *Cancer Treat Res* 53:197-220, 1991.
17. Fuqua SAW, Chamness GC, McGuire WL: Estrogen receptor mutations in breast cancer. *J Cell Biochem* 51:135-139, 1993.
18. Lippman ME, Dickson RB, Bates S et al: 8th San Antonio Breast Cancer Symposium—plenary lecture. Autocrine and paracrine growth regulation of human breast cancer. *Breast Cancer Res Treat* 7:59-70, 1986.
19. Bates SE, Davidson NE, Valverius EM et al: Expression of transforming growth factor alpha and its messenger ribonucleic acid in human breast cancer: its regulation by estrogen and its possible functional significance. *Mol Endocrinol* 2:543-555, 1988.
20. Dickson RB, Huff KK, Spencer EM, Lippman ME: Induction of epidermal growth factor-related polypeptides by 17 beta-estradiol in MCF-7 human breast cancer cells. *Endocrinology* 118:138-142, 1986
21. Nicholson S, Richard J, Sainsbury C et al: Epidermal growth factor receptor (EGFr); results of a 6 year follow-up study in operable breast cancer with emphasis on the node negative subgroup. *Br J Cancer* 63:146-150, 1991.
22. Slamon DJ, Godolphin W, Jones LA et al: Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer. *Science* 244:707-712, 1989.
23. Hortobagay GN and Hung M-C. The role of the HER-2 gene and its product in the management of primary and metastatic breast cancer. *ASCO Educational Book*, pp. 146-154, Fall, 1998.
24. Ponten J, Holmberg L, Trichopoulos D et al: Biology and natural history of breast cancer. *Int J Cancer Suppl* 5:5-21, 1990.
25. Clark GM, Mathieu MC, Owens MA et al: Prognostic significance of S-phase fraction in good-risk, node-negative breast cancer patients. *J Clin Oncol* 10:428-432, 1992.
26. Varley JM, Armour J, Swallow JE et al: The retinoblastoma gene is frequently altered leading to loss of expression in primary breast tumours. *Oncogene* 4:725-729, 1989.
27. Thor AD, Moore DI, Edgerton SM et al: Accumulation of p53 tumor suppressor gene protein: an independent marker of prognosis in breast cancers. *J Natl Cancer Inst* 84:845-855, 1992.
28. Escot C, Theillet C, Lidereau R et al: Genetic alteration of the *c-myc* protooncogene (MYC) in human primary breast carcinomas. *Proc Natl Acad Sci USA* 83:4834-4838, 1986.
29. Thor A, Ohuchi N, Hand PH et al: ras gene alterations and enhanced levels of ras p21 expression in a spectrum of benign and malignant human mammary tissues. *Lab Invest* 55:603-615, 1986.
30. Trentham-Dietz A, Love RR, Newcomb PA. Population-based prevention strategies. In:

Clinical Management of Breast Cancer Risk, Vogel, VG. Ed., Blackwell Science, Malden, MA, 1999.

31. Pujol P, Hilsenbeck SG, Chamness GC, Elledge RM. Rising levels of estrogen receptor in breast cancer over 2 decades. *Cancer*. 74(5):1601-6, 1994.

32. Squire JA, Whitmore GF, Phillips RA. Genetic basis of cancer. Inc: The Basic Science of Oncology, 3rd Edition, Tannock, IF and Mills RP eds. McGraw-Hill, New York, 1998.

33. Pike MC, Krailo MD, Henderson BE, Casagrande JT, Hoel DG. 'Hormonal' risk factors, 'breast tissue age' and the age-incidence of breast cancer. *Nature*. 303(5920):767-70, 1983.

34. Pike MC, Spicer DV, Dahmouh L, Press MF. Estrogens, progestogens, normal breast cell proliferation, and breast cancer risk. *Epidemiologic Reviews*. 15(1):17-35, 1993.

35. Russo J, Russo IH. Influence of differentiation and cell kinetics on the susceptibility of the rat mammary gland to carcinogenesis. *Cancer Research*. 40(8 Pt 1):2677-87, 1980.

36. Russo J, Russo IH. Toward a physiological approach to breast cancer prevention. *Cancer Epidemiology, Biomarkers & Prevention*. 3(4):353-64, 1994.

37. Hancock SL, Tucker MA, Hoppe RT. Breast cancer after treatment of Hodgkin's disease. *J Natl Cancer Inst* 85:25-31, 1993.

38. Tokunaga M, Land CE, Yamamoto T, Asano M, Tokuoka S, Ezaki H, Nishimori I. Incidence of female breast cancer among atomic bomb survivors, Hiroshima and Nagasaki, 1950-1980. *Radiation Research*. 112(2):243-72, 1987.

39. Anderson DE, Badzioch MD. Risk of familial breast cancer. *Cancer* 56:383-387, 1985.

40. Newman B, Millikan RC, King MC. Genetic epidemiology of breast and ovarian cancers. *Epidemiologic Reviews*. 19(1):69-79, 1997.

41. Ottman R, Pike MC, King MC, Henderson BE. Practical guide for estimating risk for familial breast cancer. *Lancet* 2:556-558, 1983.

42. Abbott DW, Freeman ML, Holt JT. Double-strand break repair deficiency and radiation sensitivity in BRCA2 mutant cancer cells [see comments]. [Journal Article] *Journal of the National Cancer Institute*. 90(13):978-85, 1998.

43. Chen JJ, Silver DP, Walpita D, Cantor SB, Gazdar AF, Tomlinson G, et al. Stable interactions between the products of the BRCA1 and BRCA2 tumor suppressor genes in mitotic and meiotic cells. *Mol Cell* 2(3):317-328, 1998.

44. Egan KM, Stempler MJ, Rosner BA, et al. Risk factors for breast cancer in women with a breast cancer family history. *Cancer Epidemiology, Biomarkers & Prevention*. 7:359-364, 1998.

45. Brunet JS, Chadirian P, Rebbeck TR, et al. Effect of smoking on breast cancer in carriers of mutant BRCA1 or BRCA2 genes. *J Natl Cancer Inst*. 90(10):761-766, 1998.

46. Swift M, Morrell D, Massey RB, Chase CL. Incidence of cancer in 161 families affected by ataxia-telangiectasia. *New England Journal of Medicine*. 325(26):1831-6, 1991.

47. Hirayama T. Health effects of active and passive smoking. *In*: Smoking and Health, edited by M. Aoki, S. Hisamian and S. Taminoga. Amsterdam: Elsevier, 1988.
48. Palmer JR. Rosenberg L. Clarke EA. Stolley PD. Warshauer ME. Zauber AG. Shapiro S. Breast cancer and cigarette smoking: a hypothesis. *American Journal of Epidemiology*. 134(1):1-13, 1991.
49. Ambrosone CB. Freudenheim JL. Graham S. Marshall JR. Vena JE. Brasure JR. Michalek AM. Laughlin R. Nemoto T. Gillenwater KA. Shields PG. Cigarette smoking, N-acetyltransferase 2 genetic polymorphisms, and breast cancer risk. *JAMA*. 276(18):1494-501, 1996.
50. Ekblom A. Hsieh CC. Lipworth L. Adami HQ. Trichopoulos D. Intrauterine environment and breast cancer risk in women: a population-based study. *Journal of the National Cancer Institute*. 89(1):71-6, 1997.
51. Freudenheim JL. Marshall JR. Vena JE. Laughlin R. Brasure JR. Swanson MK. Nemoto T. Graham S. Premenopausal breast cancer risk and intake of vegetables, fruits, and related nutrients. *Journal of the National Cancer Institute*. 88(6):340-8, 1996.
52. Longnecker MP, Newcomb PA, Mittendorf R, Greenberg ER, Willett WC. Intake of carrots, spinach, and supplements containing vitamin A in relation to risk of breast cancer. *Cancer Epidemiol, Biomarkers Prev* 6:887-892, 1997.
53. Colditz GA. Frazier AL. Models of breast cancer show that risk is set by events of early life: prevention efforts must shift focus. *Cancer Epidemiology, Biomarkers & Prevention*. 4(5):567-71, 1995.
54. Zhang Y. Kiel DP. Kreger BE. Cupples LA. Ellison RC. Dorgan JF. Schatzkin A. Levy D. Felson DT. Bone mass and the risk of breast cancer among postmenopausal women. *New England Journal of Medicine*. 336(9):611-7, 1997.
55. Hsieh CC. Trichopoulos D. Katsouyanni K. Yuasa S. Age at menarche, age at menopause, height and obesity as risk factors for breast cancer: associations and interactions in an international case-control study. *International Journal of Cancer*. 46(5):796-800, 1990.
56. Apter D. Reinila M. Vihko R. Some endocrine characteristics of early menarche, a risk factor for breast cancer, are preserved into adulthood. *International Journal of Cancer*. 44(5):783-7, 1989.
57. MacMahon B. Lin TM. Lowe CR. Mirra AP. Ravnihar B. Salber EJ. Trichopoulos D. Valaoras VG. Yuasa S. Lactation and cancer of the breast. A summary of an international study. *Bulletin of the World Health Organization*. 42(2):185-94, 1970.
58. Lambe M. Hsieh C. Trichopoulos D. Ekblom A. Pavia M. Adami HO. Transient increase in the risk of breast cancer after giving birth. *New England Journal of Medicine*. 331(1):5-9, 1994.
59. Layde PM, Webster LA, Baughman AL et al: The independent associations of parity, age at first full term pregnancy, and duration of breastfeeding with the risk of breast cancer. *J Clin Epidemiol* 42:963-973, 1989.
60. Newcomb PA, Storer BE, Longnecker MP, Mittendorf R, Greenberg ER, Clapp RW, Burke

KP, Willett WC, MacMahon B. Lactation and a reduced risk of premenopausal breast cancer. *N Engl J Med* 330:81-87, 1994.

61. Michels KB, Willett WC, Rosner BA, Manson JE, Hunter DJ, Colditz GA, Hankinson SE, Speizer FE. Prospective assessment of breastfeeding and breast cancer incidence among 89,887 women. *Lancet*. 347(8999):431-6, 1996.

62. Calle EE, Heath CW, Mirallemcmahill HL, et al. Breast cancer and hormonal contraceptives--Collaborative reanalysis of individual data on 53,297 women with breast cancer and 100,239 women without breast cancer from 54 epidemiological studies. *Lancet* 347:1713-1727, 1996.

63. Collaborative Group on Hormone Factors in Breast Cancer. Breast cancer and hormone replacement therapy: -Collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. *Lancet* 350:1047-1059, 1997.

64. Longnecker MP. Alcoholic beverage consumption in relation to risk of breast cancer: meta-analysis and review. *Cancer Causes & Control*. 5(1):73-82, 1994.

65. Smith-Warner SA, Spiegelman D, Yaun SS, van den Brandt PA, Folsom AR, Goldbohm RA, Graham S, Holmberg L, Howe GR, Marshall JR, Miller AB, Potter JD, Speizer FE, Willett WC, Wolk A, Hunter DJ. Alcohol and breast cancer in women: a pooled analysis of cohort studies. *JAMA*. 279(7):535-40, 1998.

66. Reichman ME, Judd JT, Longcope C, Schatzkin A, Clevidence BA, Nair PP, Campbell WS, Taylor PR. Effects of alcohol consumption on plasma and urinary hormone concentrations in premenopausal women. *Journal of the National Cancer Institute*. 85(9):722-7, 1993

67. Bernstein L, Henderson BE, Hanisch R, Sullivan-Halley J, Ross RK. Physical exercise and reduced risk of breast cancer in young women. *Journal of the National Cancer Institute*. 86(18):1403-8, 1994.

68. Thune I, Brenn T, Lund E, Gaard M. Physical activity and the risk of breast cancer. *New England Journal of Medicine*. 336(18):1269-75, 1997.

69. Coogan PF, Newcomb PA, Clapp RW, Trentham-Dietz A, Baron, JA., Longnecker MP. Physical activity in unusual occupation and risk of breast cancer (United States). *Cancer Causes Control* 8:626-631, 1997.

70. Friedenreich CM, Rohan TE. A review of physical activity and breast cancer. *Epidemiology*. 6(3):311-7, 1995.

71. Rockhill B, Willett WC, Hunter DJ, Manson JE, Hankinson SE, Spiegelman D, Colditz GA. Physical activity and breast cancer risk in a cohort of young women. *Journal of the National Cancer Institute*. 90(15):1155-60, 1998.

72. Le Marchand L, Kolonel LN, Earle ME, Mi M-P. Body size at different periods of life and breast cancer risk. *Am J Epidemiol*; 128:-137-152, 1998.

73. Barnes-Josiah D, Potter JD, Sellers TA, et al. Early body size and subsequent weight gain as predictors of breast cancer incidence (Iowa, United States). *Cancer Causes Control* 6:112-118,

1995.

74. Cauley JA, Gutai FP, Kuller LH, et al. The epidemiology of serum sex hormones in postmenopausal women. *Am J Epidemiol*; 129:1120-1131, 1989.
75. Folsom AR, Kaye SA, Prineas RJ, Potter JD, Gapstur SM, Wallace RB. Increased incidence of carcinoma of the breast associated with abdominal adiposity in postmenopausal women. *Am J Epidemiol*; 131:794-803, 1990.
76. Freedman LS, Clifford C, Messina M. Analysis of dietary fat, calories, body weight, and the development of mammary tumors in rats and mice: a review. *Cancer Res*, 50:5710-5719, 1990.
77. Prentice RL, Kakar F, Hursting S, Sheppard L, Klein R, Kushi LH. Aspects of the rationale for the Women's Health Trial. *J Natl Cancer Inst*; 80:802-814, 1988.
78. Wynder EL, Cohen LA, Muscat JE, Winters B, Dwyer JT, Blackburn G. Breast cancer: weighing the evidence for a promoting role of dietary fat. *J Natl Cancer Inst*, 89:766-775, 1997.
79. Willett WC, Hunter DJ, Stampfer MJ, et al. Dietary fat and fiber in relation to risk of breast cancer. *JAMA*, 268:2037-2044, 1992.
80. Hunter DJ, Spiegelman D, Adami H-O, et al. Cohort studies of fat intake and the risk of breast cancer—a pooled analysis. *N Engl J Med*, 334:356-361, 1996.
81. Howe GR, Hirohata T, Hislop TG, et al. Dietary factors and risk of breast cancer: combined analysis of 12 case-control studies. *J Natl Cancer Inst*, 82 :561-569, 1990.
82. Tham DM, Gardner CD, Haskell WL. Clinical review 97: Potential health benefits of dietary phytoestrogens: a review of the clinical, epidemiological, and mechanistic evidence. *Journal of Clinical Endocrinology & Metabolism*. 83(7):2223-35, 1998.
83. Nagata C, Takatsuka N, Inaba S, Kawakami N, Shimizu H. Effect of soymilk consumption on serum estrogen concentrations in premenopausal Japanese women. *J Natl Cancer Inst*, 90(23):1830-1835, 1998.
84. Trentham-Dietz A, Newcomb PA, Storer BE, et al. Body size and risk of breast cancer. *Am J Epidemiol*, 145:1011-1019, 1997.
85. Wolff MS, Toniolo PG, Lee EW, Rivera M, Dubin N. Blood levels of organochloride residues and risk of breast cancer. *J Natl Cancer Inst*, 85(8):648-652, 1993.
86. Krieger N, Wolff MS, Hiatt RA, Rivera M, Vogelman J, Orentreich N. Breast cancer and senim organochlorines: a prospective study among white, black, and Asian women. *J Natl Cancer Inst*, 86(8):589-599, 1994.
87. Carter CL, Corle DK, Micozzi MS et al: A prospective study of the development of breast cancer in 16,692 women with benign breast disease. *Am J Epidemiol* 128:467-477, 1988.
88. London SJ, Connolly JL, Schnitt SJ, Colditz GA: A prospective study of benign breast disease and the risk of breast cancer. *JAMA* 267:941-944, 1992.
89. Boyd NF, Byng JW, Jong RA, Fishell EK, Little LE, Miller AB, Lockwood GA, Tritchler DL, Yaffe MJ. Quantitative classification of mammographic densities and breast cancer risk: results

from the Canadian National Breast Screening Study. *Journal of the National Cancer Institute*. 87(9):670-5, 1995.

90.Byrne C. Schairer C. Wolfe J. Parekh N. Salane M. Brinton LA. Hoover R. Haile R. Mammographic features and breast cancer risk: effects with time, age, and menopause status. *Journal of the National Cancer Institute*. 87(21):1622-9, 1995.

91.Spicer DV. Ursin G. Parisky YR. Pearce JG. Shoupe D. Pike A. Pike MC. Changes in mammographic densities induced by a hormonal contraceptive designed to reduce breast cancer risk. *Journal of the National Cancer Institute*. 86(6):431-6, 1994.

92.Prentice RL. Breast mammographic changes among women adopting a low-fat eating pattern. *Journal of the National Cancer Institute*. 89(7):466-7, 1997.

93.Dupont WD, Page DL: Risk factors for breast cancer in women with proliferative breast disease. *N Engl J Med* 312:146ñ151, 1985.

94.Merzenich, H., H. Boeing, and J. Wahrendorf. Dietary fat and sports activity as determinants for age at menarche. *Am J Epid* 138(4):217-224, 1993.

95.Petridou, E., E. Syrigou, N. Toupadaki, X. Zavitsano, W. Willett, and D. Tfichopoulos. Determinants of age at menarche as early life predictors of breast cancer risk. *Intl J Cancer*, 68 (2):193-198, 1997.

96.Pike MC, RK. Ross, RA. Lobo, TJA. Key, M Potts, and BE Henderson. LHRH agonists and the prevention of breast and ovarian cancer. *Br J Cancer* 60 (1):142-148, 1989.

97.Colditz, GA. Relationship between estrogen levels, use of hormone replacement therapy and breast cancer. *J Natl Cancer Inst*, 90:14-23, 1998.

98.Colditz G, and Rosner B. Use of estrogen plus progestin is associated with greater increase in breast cancer risk than estrogen alone. *Am J Epid* 147 (11):S64 (Abstr 254), 1998.

99.Early Breast Cancer Trialists' Collaborative Group. Tamoxifen for early breast cancer: an overview of the randomised trials. *Lancet* 351 (9114):1451-1467, 1998.

100.Powles T, Eeles R, Ashley S, Easton D, Chang J, Dowsett M, Tidy A, Viggers J, and Davey J. Interim analysis of the incidence of breast cancer in the Royal Marsden Hospital tamoxifen randomized chemoprevention trial. *Lancet* 352:98-101, 1998.

101.Veronesi U, Maisonneuve P, Costa A, Sacchini V, Maltoni C, Robertson C, Rotmensz N, and Boyle P. Prevention of breast cancer with tamoxifen: preliminary findings from the Italian randomised trial among hysterectomised women. *Lancet* 352:93-97, 1998.

102.Cummings SR, Norton L, Eckert S, Grady D, Cauley D, Knickerbocker R, Blac DM, Nickelsen T, Glusman J, and Krueger K. Raloxifene reduces the risk of breast cancer and may decrease the risk of endometrial cancer in postmenopausal women. Two-year findings from the multiple outcomes of raloxifene evaluation (MORE) trial. *Proc ASCO* 17:2a (Abstr *3), 1998.

103.Love RR, Mazess RB, Barden HS, Epstein S, Newcomb PA, Jordan VC, Carbone PP, and DeMets DL. Effects of tamoxifen on bone mineral density in postmenopausal women with breast cancer. *N Engl J Med*, 326 (13):852-6, 1992.

104. Delmas PD, Bjarnason NH, Mitlak BH, Ravoux AC, Shah AS, Huster WJ, and et al. Effects of raloxifene on bone mineral density, serum cholesterol concentrations, and uterine endometrium in postmenopausal women. *N Engl J Med*, 337:1641-1647, 1997.

105. Love RR, Wiebe DA, Newcomb PA, Cameron L, Leventhal H, Jordan VC, Feyzi J, and DeMets DL. Effects of tamoxifen on cardiovascular risk factors in postmenopausal women. *Ann Intern Med*, 115(11):860-864, 1991b.

106. Love RR, Cameron L, Connell BL, and Leventhal H. Symptoms associated with tamoxifen treatment in postmenopausal women. *Arch Intern Med* 151(9):1842-7, 1991b.