Breast cancer

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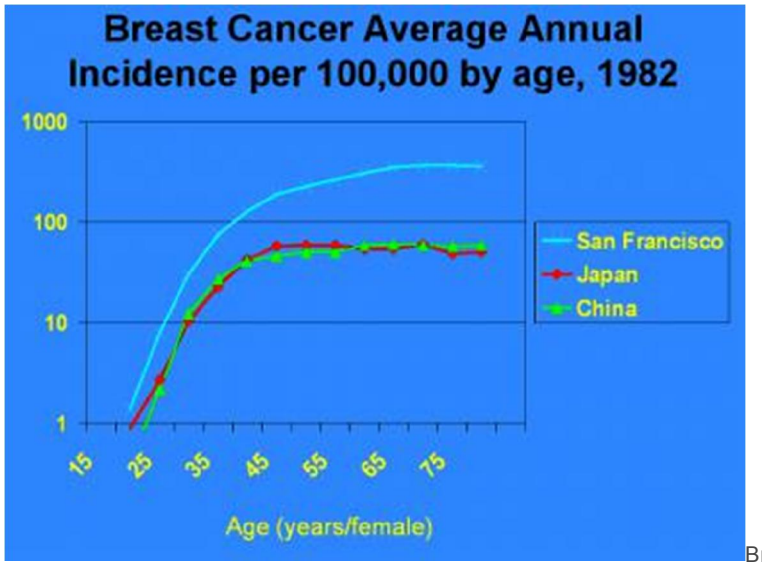
Breast cancer is the most commonly diagnosed cancer among women, with approximately 182,000 women diagnosed with breast cancer annually in the United States, accounting for approximately 26% of all incident cancers among women.Each year, 40,000 women die of breast cancer, making it the second-leading cause of cancer deaths among American women after lung cancer. The lifetime risk of dying of breast cancer is approximately 3.4%.

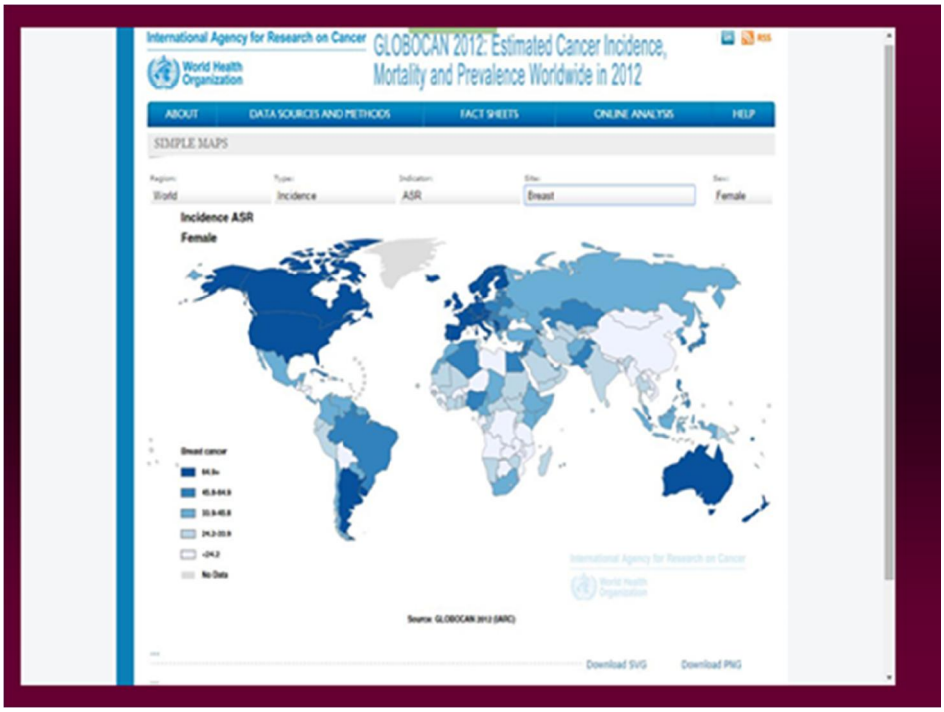
Variation among populations

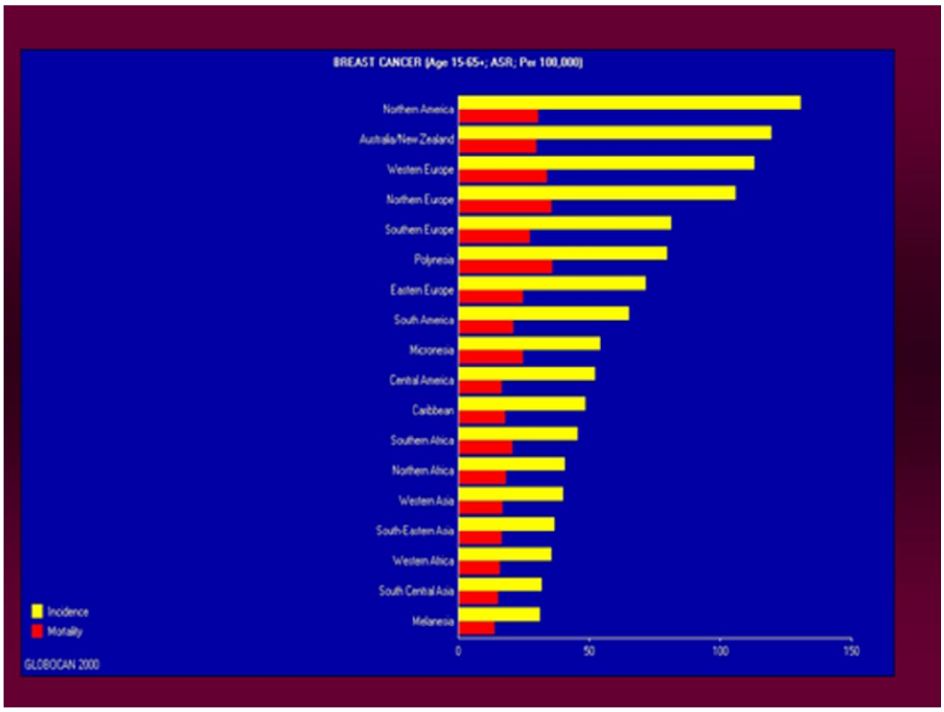
The international incidence of female breast cancer varies markedly, being highest in the United States and Northern Europe, intermediate in Southern and Eastern Europe and South America, and lowest in Asia. From 1983 to 1987, the age-adjusted incidence rate of breast cancer varied by factor of about 5 between countries (see image below). However, incidence rates have been rising in traditionally low-incidence Asian countries, particularly in Japan, Singapore, and urban areas of China, as these regions make the transition toward a Western-style economy and pattern of reproductive behavior.



Breast cancer incidence.

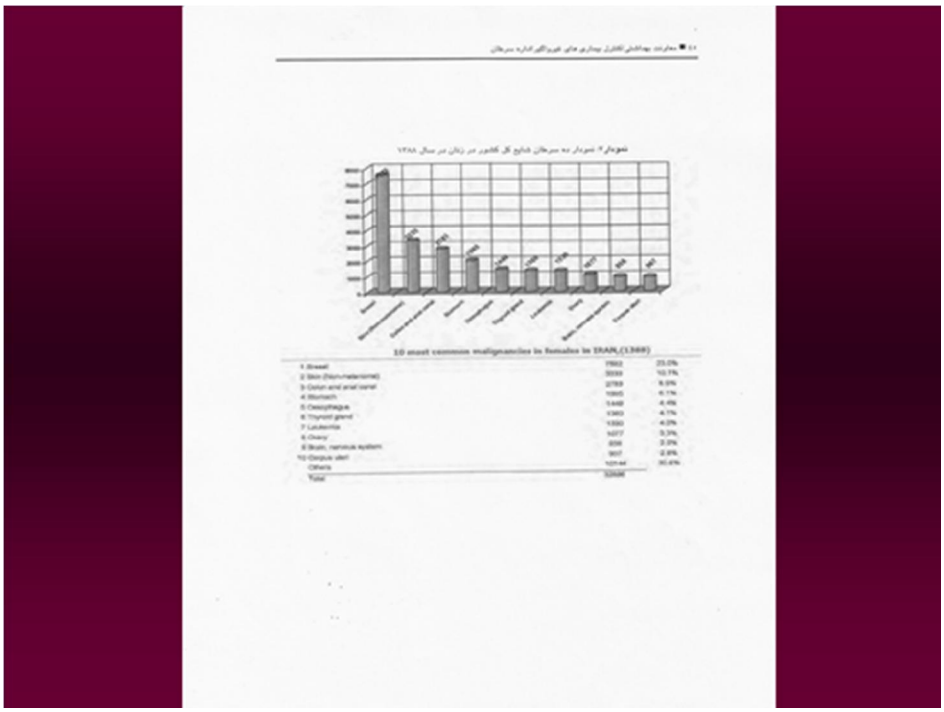
Breast cancer incidence in the world according to WHO in 2012
And the age standard rate of breast cancer are in the the figure number 1 and 2




BREAST CANCER (Age 15-65+; ASR; Per 100,000)
Northern America
Australia/New Zealand
Western Europe
Northern Europe
Southern Europe
Polynesia
Eastern Europe
South America
Micronesia
Central America
Caribbean
Southern Africa
Northern Africa
Western Asia
South-Eastern Asia
Western Africa
South Central Asia
Melanesia
0
50
100
150
Incidence
Mortality
GLOBOCAN 2000

The incidence of breast cancer in Iran is 24 per 100000 and it seems that it accrue one decade earlier than USA and Europe and is shown in figure number 3

The incidence rate of breast cancer in iran is like fig 4



Age-incidence curve of breast cancer risk

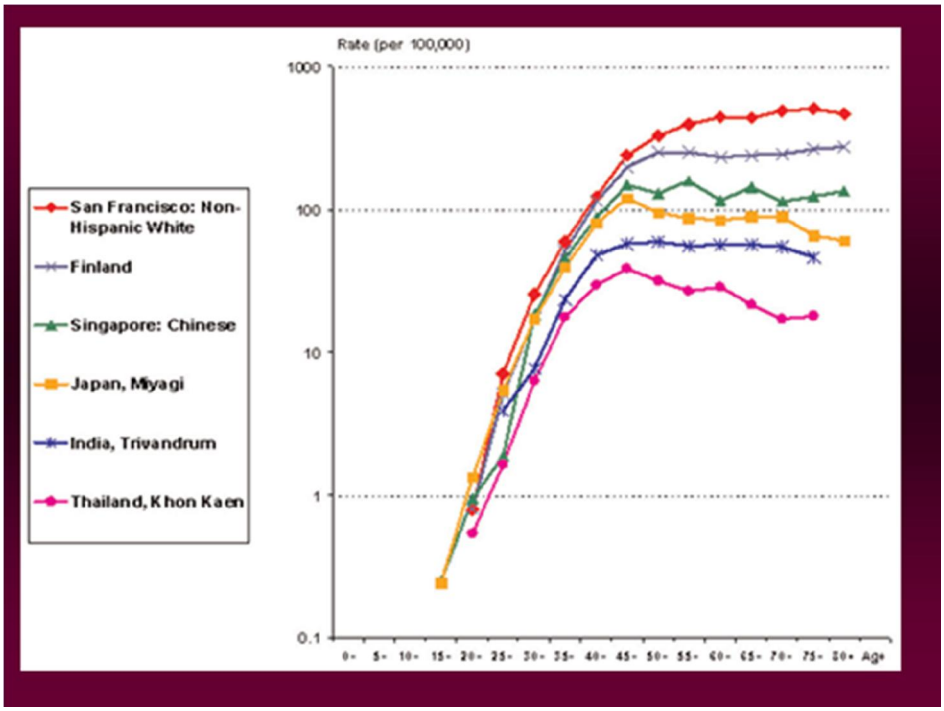
Breast cancer incidence rates increase sharply with age, becoming substantial before age 50 years. During the premenopausal years, the rate of increase in incidence is common around the world, approximately 8%-9% per year. The rate of increase in breast cancer incidence continues throughout life but slows substantially after menopause, to approximately 2%-3% per year. Reproductive hormones account for this dependence of incidence on menopausal status.(fig 5)

Trends in incidence and mortality around the world

Since the 1950s, breast cancer incidence has been increasing in many of the lower-risk countries, as well as in high-risk Western countries. Some of the recent increases in incidence in high-risk populations may be due in part to greater use of mammography, as in the United States. This appears to be the case in Sweden and in England and Wales. However, in Norway, a substantial increase in breast cancer incidence occurred between 1983 and 1993 despite low use of mammographic screening.

Breast cancer incidence rates have nearly doubled in recent decades in traditionally low-risk countries such as Japan and Singaporeand in the urban areas of China. Dramatic changes in lifestyle in such regions brought about by growing economies, increasing affluence, and increases in the proportion of women in the industrial workforce have affected the population distribution of established breast cancer risk factors, including age at menarche and fertility and nutritional status, including height and weight. These changes have resulted in a convergence toward the risk-factor profile of Western countries.

Ovarian hormones initiate breast development, and monthly menstrual cycles induce regular breast cell proliferation until menopause.



Risk Factor of breast cancer

Age at menarche

Earlier age at menarche has been consistently associated with increased risk of both premenopausal and postmenopausal breast cancer. Early menarche may be associated with more rapid onset of regular ovulatory menstrual cycles and hence greater lifetime exposure to endogenous hormones. Evidence also suggests that early menarche may relate to higher postmenopausal estrogen levels.

Pregnancy and age at first full-term pregnancy

Nulliparous women are at more of a risk of breast cancer than parous women. This risk is evident after age 40-45 years, in part owing to the adverse effect of first pregnancy raising incidence among parous women for a number of years when compared to nulliparous women of the same age. In fact, the risk of breast cancer is increased for the first decade following the first pregnancy. The proliferation of breast cells during the first pregnancy results in differentiation into mature breast cells prepared for lactation, but this proliferation may also lead to growth of mutated cells and excess risk over the next decade. Evidence for a similar effect of second and subsequent pregnancies is less clear, perhaps because of the maturation of the breast during the first pregnancy.

The first pregnancy is associated with permanent changes in the glandular epithelium and changes in the biologic properties of the mammary cells. After the differentiation of pregnancy, epithelial cells have a longer cell cycle and spend more time in G1, the phase that allows for DNA repair. The longer the interval from menarche to first pregnancy, the greater the adverse effect of the first pregnancy .The later the age at first full-term pregnancy, the more likely that DNA mistakes have occurred that will be propagated with the proliferation of mammary cells during pregnancy.

The susceptibility of mammary tissue to carcinogens decreases after the first pregnancy, reflecting the differentiation of the mammary gland. This is also seen in the age-dependent susceptibility of the breast to radiation, seen most clearly with the follow-up of women exposed to atomic bomb.

Number and spacing of births

A higher number of births is consistently related to lower risk of breast cancer; each additional birth beyond the first reduces long-term risk of breast cancer. In addition to a protective effect of higher parity, more closely spaced births are associated with a lower lifetime risk of breast cancer.

Lactation

As early as 1926, it was proposed that a breast never used for lactation is more predisposed to cancer. The overall evidence from case-control and cohort studies supports a reduction in risk with longer duration of breastfeeding. The most extensive pooled analysis from almost 50 studies in 30 countries has shown an overall 4% reduction in risk per 12 months of breastfeeding for all parous women.

The authors estimate that, if women in developed countries had the number of births and lifetime duration of breastfeeding of women in developing countries, the cumulative incidence of breast cancer by age 70 years would be reduced by as much as 60%. About two-thirds of this reduction would be related to breastfeeding. Evidence from the

United States in the 1990s is consistent with the combined data from around the world showing protection against premenopausal and postmenopausal breast cancer.

Spontaneous and induced abortion

Close to one-quarter of all clinically identified pregnancies in the United States end as induced abortions. Breast cells may be most vulnerable to mutation when breast tissue consists of rapidly growing and undifferentiated cells, such as during adolescence and pregnancy. In early pregnancy, the number of undifferentiated cells increases as rapid growth of the breast epithelium is taking place. If the pregnancy continues to term, these cells differentiate by the third trimester, decreasing the number of cells susceptible to malignancy. The interruption of the differentiation of breast cells that results from spontaneous and induced abortions has been hypothesized to increase a woman's risk of developing breast cancer.

By far the strongest study to date on the association between breast cancer and abortion was a population-based cohort study made up of 1.5 million Danish women born April 1, 1935, through March 31, 1978. Of these women, 280,965 (18.4%) had had one or more induced abortions. After adjusting for potential confounders of age, parity, age at delivery of first child, and calendar period, the risk of breast cancer for women with a history of induced abortion was not different from women who had not had an induced abortion

(relative risk [RR] = 1.0; 95% CI, 0.94-1.06). The number of induced abortions in a woman's history also had no significant relation to risk of breast cancer.

A statistically significant increase in risk was found among the very small number of women with a history of second-trimester abortion. Results from this population-based prospective cohort provide strong evidence against an increase in risk of breast cancer among women with a history of induced abortion during the first trimester. Comparable results have been observed in a large cohort of women in China and the California Teachers Study. Taken as a whole and accounting for the limitations of the case-control study design, the available evidence does not support any important relation between induced abortion and risk of breast cancer.

Age at menopause

Age at menopause and risk of breast cancer has been well described for many years. Women who have undergone bilateral oophorectomy at a young age have a greatly reduced risk of breast cancer. Women with bilateral oophorectomy before age 45 years have approximately half the risk of breast cancer compared to those with a natural menopause at age 55 years or older. On average, the risk of breast cancer increases by some 3% per year of delay in age at menopause.

The reduction in risk of breast cancer with early menopause is likely due to the reduction of breast cell division with the termination of menstrual cycles and the decline in endogenous hormone levels, which become substantially lower than during the premenopausal years.

Several lines of evidence have long suggested that sex hormones play a central role in the etiology of breast cancer. As noted above, rates of breast cancer increase rapidly in the premenopausal years, but the rate of increase slows sharply at menopause, when endogenous hormone levels decline. In addition, several reproductive variables that alter estrogen status affect risk of breast cancer; for example, early age at menarche and late age at menopause increase risk of breast cancer. After menopause, adipose tissue is the major source of estrogen, and obese postmenopausal women have both higher levels of endogenous estrogen and a higher risk of breast cancer. In addition, hormonal manipulations such as antiestrogens evaluated in randomized controlled trials (eg, tamoxifen, raloxifene) prevent breast cancer.

Epidemiologic study of endogenous hormones and breast cancer risk

In contrast to clinical needs, in which discerning grossly abnormal from normal hormone levels is the focus, epidemiologic studies are usually aimed at relating modest differences within the normal range of levels to risk of subsequent cancer. Considerable laboratory error has been reported in studies of assay reproducibility. Low reproducibility could result in true (and important) exposure/disease associations being missed. Varying sensitivities and specificities of different laboratory assays have also complicated the comparison of results between studies.

Estrogens

Estradiol, considered the most biologically active endogenous estrogen, circulates in blood either unbound ("free") or bound to sex hormone binding globulin (SHBG) or albumin. Free or bioavailable (free plus albumin-bound) estradiol is thought to be readily available to breast tissue and thus may be more strongly related to risk than total estradiol. Postmenopausally, estrone is the source of most circulating estradiol, and estrone sulfate is the most abundant circulating estrogen. Both normal and malignant breast cells have sulfatase and aromatase activity, such that estrone and estrone sulfate could serve as a ready source of intracellular estradiol.

A pooled analysis of all prospective studies of endogenous estrogens and androgens in postmenopausal women combined data from 9 prospective studies that included 663 breast cancer cases and 1765 healthy controls.[30] Mean age of the participants ranged from 58-72 years, and the median time from blood collection to diagnosis ranged from 2-12 years. The risk of breast cancer increased with increasing estrogen levels. For example, the RRs (95% CI) for increasing quintile of estradiol level, all relative to the lowest quintile, were 1.4 (1.0-2.0), 1.2 (0.9-1.7), 1.8 (1.3-2.4), and 2.0 (1.5-2.7).

Other estrogens were similarly related to risk. The RRs for the top quintile, relative to the bottom quintile, were 2 or more for free estradiol, estrone, and estrone sulfate. The variation in RRs between studies was not statistically significant. These data and subsequent prospective studies provide strong evidence for a direct link between plasma estrogens and breast cancer risk in postmenopausal women. Furthermore, consistent with the hormonal origins of breast cancer, plasma levels of estradiol are directly related to risk of ER-positive breast tumors but not ER-negative tumors. Data on premenopausal estrogen levels and breast cancer risk are more limited, in large part

because of the complexities related to sampling during the menstrual cycle. In a prospective analysis of samples from Nurses Health Study II, Eliassen and colleagues evaluated data on 197 cases of breast cancer diagnosed after blood collection and 394 matched controls. Women in the highest (versus the lowest) quartiles of follicular total and free estradiol levels had statistically significantly increased risks of breast cancer; the associations were stronger for invasive breast cancer and for estrogen and progesterone receptor-positive tumors. Luteal estradiol levels were not associated with breast cancer risk.

Higher levels of total and free testosterone and androstenedione in both menstrual cycle phases were associated with modest, non–statistically significant increases in overall risk of breast cancer and with stronger, statistically significant increases in risks of invasive and receptor-positive cancers.

[1]Androgens and breast cancer risk

Androgens have been hypothesized to increase breast cancer risk either directly, by increasing the growth and proliferation of breast cancer cells, or indirectly, by their conversion to estrogen. In postmenopausal women, the best summary of evidence on circulating androgens and breast cancer risk is from the pooled analysis of 9 prospective studies described above. Testosterone was positively associated with breast cancer risk: the RRs (95% CI) for increasing quintile category (all relative to the lowest quintile of levels) were 1.3 (1.0-1.9), 1.6 (1.2-2.2), 1.6 (1.1-2.2), and 2.2 (1.6-3.1).

Findings were generally similar for other androgens with RRs of 2 or more comparing top versus bottom quintiles for androstenedione, dehydroepiandrosterone, and for dehydroepiandrosterone sulfate. When estradiol was added to the statistical models, RRs for the androgens were only modestly attenuated, suggesting an independent effect of circulating androgens on cancer risk.

Among premenopausal women, data on circulating androgens are more limited. No association was found between testosterone and breast cancer risk in two prospective studies, but a positive association for receptor-positive tumors was found in Nurses Health Study II. Again, the data are too limited to draw any firm conclusions relating androgen levels to breast cancer risk in premenopausal women.

Prolactin

Substantial laboratory evidence suggests that prolactin could play a role in breast carcinogenesis. Prolactin receptors have been found on more than 50% of breast tumors, and prolactin increases the growth of both normal and malignant breast cells in vitro, although these findings have not been entirely consistent. Prolactin administration is well documented to increase mammary tumor rates in mice.

A number of small case-control studies of prolactin levels and breast cancer risk have been conducted; the largest of these included 66 cases. To date, only two prospective studies have been conducted. In the first, of 40 postmenopausal breast cancer cases,

women in the top quintile of prolactin levels had a nonsignificant 63% higher risk of breast cancer compared to those in the bottom quintile. In a prospective analysis of prolactin and breast cancer risk from the Nurses' Health Study, a significant doubling of risk was seen comparing top to bottom quintile.

Insulin-like growth factor

Insulin-like growth factor I (IGF-I) is a polypeptide hormone with structural homology to insulin, and it is regulated primarily by growth hormone. There is increasing evidence that the growth hormone-IGF-I axis stimulates proliferation of both breast cancer and normal breast epithelial cells.

Since oral contraceptives were first introduced in the 1960s, they have been used by many millions of women. In 1988, over 10.7 million US women were oral contraceptive users. Most combined oral contraceptives contain ethinyl estradiol (or mestranol, which is metabolized to ethinyl estradiol) and a progestin.

The estrogen dose in oral contraceptives has ranged from 100 µg or more in 1960 to 20-30 µg in the more recent past, although formulations continue to change. Patterns of use have also changed considerably over time, with both increasing durations of use and a trend toward earlier ages at first use. Over 50 epidemiologic studies have evaluated the relationship between oral contraceptive use and breast cancer risk and have been combined in a reanalysis that provides a rigorous summary of evidence.

Any use of oral contraceptives

In several meta-analyses and a large pooled analysis, “ever” use of oral contraceptives was not associated with breast cancer risk. Although this finding is reassuring, defining oral contraceptive use this way is misleading because women in the "ever" use category is a mix of women with long- and short-term use, so that any true relationship with one particular aspect of oral contraceptive use may be missed.

Duration of use and time since last use

Most studies have observed no significant increase in breast cancer risk with long durations of use. Individual data from 54 epidemiologic studies were collected and analyzed centrally. In this large pooled analysis, data from 53,297 women with breast cancer and 100,239 women without breast cancer were evaluated, and no overall relationship was observed between duration of use and risk of breast cancer. Current and recent users of oral contraceptives had a significantly increased risk of breast cancer (RR for current vs never users = 1.24; 95% CI, 1.15-1.33). This increased risk subsided within 10 years of stopping oral contraceptive use (RR by years since stopping use vs never use: 1-4 years, 1.16; 5-9 years, 1.07; 10-14 years, 0.98; >15 years, 1.03).

A modestly increased risk of breast cancer was observed among current and recent oral contraceptive users, and no independent effect of long duration of use on risk of breast cancer was observed, even among very young women. Thus, the increased risk of breast cancer observed among young long-term oral contraceptive users in past individual studies appear primarily due to recent use of oral contraceptive rather than to duration of use. These data suggest that oral contraceptives may act as late-stage

promoters. Table 1 summarizes the excess cases of breast cancer that would be generated in a population of 10,000 women using oral contraceptives at different ages.(table 1)

Table 1. Excess Cases of Breast Cancer Due to Use of Oral Contraceptives for 5 Years

Age at Starting Use, y	Cases Among Users	Cases Among Nonusers	Cumulative Excess Cases per 10,000
16-19	4.5	4	0.5
20-24	17.5	16	1.5
25-29	48.7	44	4.7
30-34	110	100	11.1
35-39	180	160	21
40-44	260	230	32

Use before a first full-term pregnancy or at an early age

Because any influence of oral contraceptives on the breast has been hypothesized to be greatest prior to the cellular differentiation that occurs with a full-term pregnancy, a number of investigators have evaluated the effect of oral contraceptive use prior to a first full-term pregnancy. In several more recent studies not included in these meta-analyses, no increase in risk was observed. In the pooled analysis, a significant trend of increasing risk with first use before age 20 years was observed. Among women diagnosed at age 30-34 years, the RR associated with recent oral contraceptive use was 1.54 if use began before age 20 years and 1.13 if use began at age 20 years or older.

Type and dosage of oral contraceptives

The specific oral contraceptive formulation might be important in determining cancer risk, but studies of this issue are difficult because study participants may not be able to remember specific formulations and may use a number of formulations over time; very large studies are needed for enough statistical power to examine individual brands, and no satisfactory classification system exists to categorize specific oral contraceptive formulations by their effect on breast tissue. Although few studies have evaluated this issue, overall, there is no consistent evidence of a differential effect according to type or dose of either estrogen or progestin. Data on specific formulations remain inconclusive.

Interactions with other breast cancer risk factors

Interactions of oral contraceptive use with other breast cancer risk factors have been evaluated in many studies. However, limited statistical power in these analyses have resulted in wide confidence limits and, thus, a limited ability to detect true differences. Also, in many studies, the categorization of oral contraceptives was generally "ever versus never" use, a crude and uninformative definition. Possible interactions with other breast cancer risk factors were evaluated in detail for the first time in the collaborative pooling project, with oral contraceptive use defined in terms of recency and age at first use. The relationship between oral contraceptive use and breast cancer did not vary appreciably by family history of breast cancer, weight, alcohol intake, or other breast cancer risk factors.

Progestin-only contraceptives

These contraceptives include progestin-only pills ("mini-pill"), depot-medroxyprogesterone (DMPA), and implantable levonorgestrel (Norplant). Although the progestin-only pill has been evaluated in a few studies, no increase in breast cancer risk has been observed to date for ever users. In the studies in which duration of use was evaluated, longer-term users were observed to have either a similar or lower risk of breast cancer compared to never users, although an increase in risk similar to that observed for combined oral contraceptives was reported in a prospective study.

DMPA, an injectable contraceptive, has also had limited study in relation to breast cancer risk. In the most extensive study of this relationship, no significant increase in risk was observed with increasing duration of use (RR for more than 3 years of use vs never use = 0.9; 95% CI, 0.6-1.4). Norplant, a long-acting contraceptive that is implanted subdermally, was introduced in the United States in 1990. No epidemiologic data have been published on Norplant's effect, if any, on breast cancer risk.

Summary of oral contraceptives and breast cancer risk

Results of more than 50 studies have provided considerable reassurance that there is little, if any, increase in risk with past oral contraceptive use in general, even among women who have used oral contraceptives for 10 or more years. In the pooled analysis, long-term use among young women was not independently associated with an increase in breast cancer risk, but current users and recent users (< 10 years since last use) had a modest elevation in risk compared to never users.

Current and recent users, the group that appears to have a modest increase in risk, are generally young (< 45 years) and thus have a low absolute risk for breast cancer. Hence, a modest increase in their risk will result in few additional cases of breast cancer. Nevertheless, this increased risk among current and recent users should be considered and balanced against benefits, including reduced ovarian cancer risk, in the overall decision of whether to use oral contraceptives. Recent findings suggest that long-term use of triphasic preparations containing levonorgestrel may account for most of this excess risk

Postmenopausal estrogens have been used for over half a century. By the mid-1970s, almost 30 million prescriptions were being filled annually in the United States. A challenge in studying the relationship between postmenopausal hormones and breast cancer is the substantial variation in formulations and patterns of use that has occurred over time. By the time sufficient use of one type of hormone has occurred to allow a detailed epidemiologic evaluation, new formulations are already being introduced.

The possible relation between postmenopausal estrogen use and risk of breast cancer has been investigated in over 60 epidemiologic studies over the past 30 years. Most of these studies have been summarized in previous meta-analyses and a large pooled analysis. Subsequently data from randomized controlled trials have confirmed the epidemiologic relations of hormone therapy to increased risk of breast cancer, and the International Agency for Research on Cancer (IARC) has now classified estrogen plus progestin therapy as a human carcinogen. A summary of these findings, plus a more

detailed discussion of several of the most important and most recent studies, is provided below. Particular attention is focused on use of estrogen along versus estrogen plus progestin therapy.

Any use

Ever users of postmenopausal estrogens have little or no increase in risk of breast cancer compared with women who have never used this therapy. As for oral contraceptives, ever use is a poor measure of exposure because it fails to distinguish between short and long duration and recent and past users, nor does it distinguish type of hormone therapy used. Hence, it does not provide meaningful evidence on the overall safety of hormone therapy.

Duration of use

In the meta-analyses, significant increases in risk of approximately 30%-45% with more than 5 years of use have been observed. In updated results from the Nurses' Health Study, with 1935 breast cancer cases, an excess risk of breast cancer was limited to women with current or very recent use of postmenopausal hormones. Within this group, the risk increased with longer duration of use and was statistically significant among current users of 5 or more years' duration (eg, compared to never users of postmenopausal hormones, RR for 10 or more years of use = 1.47; 95% CI, 1.22-1.76). Risk is greater for users of estrogen plus progestin compared to users of estrogen alone.

These epidemiologic results were corroborated by the Women's Health Initiative (WHI), a randomized controlled trial of estrogen plus progestin use that showed a significant increase in risk of breast cancer with duration of use of this hormone combination. Given the high dropout and noncompliance with therapy during the trial, analysis of compliers showed a substantially greater increase in risk with duration of therapy closer to that observed in epidemiologic studies, which, by their nature, evaluate risk among compliers or users of hormone therapy.

Recency of use

Data on recency of use have been sparse because many studies have not distinguished current from past users. One meta-analysis calculated a RR for current use of 1.63 for women with natural menopause and 1.48 for women with surgical menopause. In a second one, the summary RR was 1.40 (95% CI, 1.20-1.63) comparing current to never users. In the report from the Nurses' Health Study cohort, an excess risk of breast cancer was limited to women with current or very recent use of postmenopausal hormones. In the Breast Cancer Detection Demonstration Project (BCDDP) cohort, a positive association with invasive breast cancer was noted among current users of 5-15 or more years' duration.

These relationships were evaluated in considerable detail in the pooled analysis that combined results of 51 epidemiologic studies. Importantly, in these analyses, women with an uncertain age at menopause were excluded (eg, women with simple hysterectomies), as inadequate accounting for age at menopause in the analysis can lead to substantial attenuation of the observed relationships between postmenopausal hormone use and breast cancer risk. The investigators observed a statistically significant association between current or recent use of postmenopausal hormones and risk of breast cancer; the positive association was strongest among those with the longest duration of use. No significant increase in breast cancer risk was noted for women who had quit using postmenopausal hormones 5 or more years in the past, regardless of their duration of use.

Type, dosage, and mode of delivery of estrogen

Growing epidemiologic data now address the effects of dose and type of estrogen on breast cancer risk. Data from the pooled analysis show no significant differences in the magnitude of risk were observed according to either the type of estrogen used (conjugated estrogen vs other) or the estrogen dose (< 0.625 vs ≥1.25 mg). Although the effect of estrogen use on breast cancer risk could be reasonably hypothesized to vary by mode of estrogen delivery (eg, patch estrogen, by avoiding the first pass effect in the liver, does not increase SHBG to the extent that oral preparations do), no important differences were observed in the largest study to date. The Million Women Study included over 40,000 users of transdermal estrogen and observed no significant difference in RR of breast cancer (1.24) compared to that among the 60,000 users of oral therapy (1.32).

Risk according to breast cancer risk factor profile

The risk associated with postmenopausal hormone use was assessed in a number of specific subgroups in the pooled analysis.Risk did not appear to vary according to reproductive history, alcohol intake, smoking history, or family history of breast cancer.

However, the RRs associated with 5 or more years of postmenopausal hormone use were highest among the leanest women (*P* for heterogeneity=0.001); this interaction has been consistently observed. Risk of unopposed estrogen therapy is also more clearly observed to increase with duration of use among women with bilateral oophorectomy than those without, again consistent with precise statistical control for underlying risk of breast cancer, as age at menopause is more accurately assessed in women undergoing bilateral oophorectomy than in those who have hysterectomy without oophorectomy. This consistent finding that risk of unopposed estrogen is attenuated among overweight and obese women may account for the apparent lower risk of breast cancer among women in the WHI trial of unopposed estrogen, given the overweight and obese population included in the trial.

Use of estrogen plus progestin

The addition of a progestin to estrogen regimens has become increasingly common, as it minimizes or eliminates the increased risk of endometrial hyperplasia and cancer associated with using unopposed estrogens. In the United States, by the mid-1980s, almost 30% of postmenopausal hormone prescriptions included a prescription for progestin. The impact of an added progestin to the risk of breast cancer has been evaluated only in the last 20 years.

Two of the first studies to assess this relationship suggested that the addition of a progestin could decrease breast cancer risk. However, these studies were small, and potentially important confounders (eg, age, parity) were not accounted for in the analyses. Since this time, additional studies have assessed this relationship and together indicate that there is no protective effect of typical doses used in postmenopausal hormone therapy.More recent studies also support this increase in risk with combination estrogen plus progestin.

In addition to their effect on breast cancer, postmenopausal hormones also have a major impact on other aspects of women's health. Results from the WHI (a large randomized clinical trial) definitively show that, after 5 years of use, estrogen plus progestin does more overall harm to women than good. Although the WHI studied only one specific type and dose of estrogen plus progestin (Prempro), because widespread use of estrogen plus progestin is relatively recent, few data are available to evaluate the effect of different formulations, doses, or schedules of use of progestin on risk of breast cancer.

The British Million Women Study, with over 9,000 cases of breast cancer during follow-up, again confirms the excess risk of breast cancer among women currently using combination estrogen plus progestin and notes this is a significantly greater RR than using estrogen alone. Risk increased with duration of use but did not vary significantly according to the progestogen content or whether use was sequential or continuous.The possibility remains that dose of progestogen is important, but variation in studies to date has not allowed rigorous and valid comparisons.

Receptor status and histologic subtypes of breast cancer

Consistent evidence from larger epidemiologic studies shows combination estrogen plus progestin and unopposed estrogen therapy are associated with increased risk of estrogen receptor–positive breast cancer. While the WHI did not observe any significant difference in the distribution of invasive cancer by receptor status, the trial had limited power to detect an association with fewer than 500 cases of breast cancer. While it has been suggested that risk is limited to lobular subtypes of breast cancer, most evidence does not support this claim, and, given the higher proportion of receptor-positive tumors in lobular rather than ductal cancers, a stronger RR observed for lobular cancer would be expected for this subset of breast cancers.

Decline in breast cancer incidence

Numerous studies in the United States and internationally have reported on the decline in breast cancer incidence after 2002.Based on data from the San Francisco mammography registry, prescribing of estrogen and progestin peaked in 1999. Before

publication of the Heart and Estrogen/Progestin Replacement Study (HERS), the use of hormone therapy was increasing at 1% per quarter but declined by 1% per quarter after the publication. This decline in prescribing continued until the publication of the WHI in 2002, at which point a more substantial decline of 18% per quarter was observed. The peak and decline through 1999 to 2002 is concordant with the HERS report in 1998 showing a significant increase in coronary heart disease (CHD) in the first year of therapy among women with prevalent coronary disease, as well as no long-term benefit in reducing CHD.

The growing epidemiologic evidence published since 2000 on the adverse effects of combination therapy on breast cancer added further evidence against the use of this therapy. Based on the prevalence of use of estrogen and progestin in California, Clarke et al estimate a population attributable risk (PAR, or the proportion of cases caused by estrogen and progestin) of up to 11% based on a prevalence of use of 30% and a RR of 1.4. Given that substantially higher RRs of 2 or more have been reported, this estimate of the PAR is conservative. Assuming a prevalence of use of 17.5%, the average reported for California in 2001, a RR of 1.49 gives a PAR of 7.9%, and a RR of 2.0 gives a PAR of 14.9%.

Evidence for breast cancer incidence rates now clearly shows a parallel drop in breast cancer consistent with the pattern of decreased prescribing. The rigorous, state-of-the-art analysis using joint point analysis and drawing on SEER incidence data from 1975-2003 shows a significant decrease in the incidence of invasive breast cancer from 1999-2003 in all 5-year age groups from 45 years and older and a sharp decrease largely limited to ER-positive tumors in those aged 50-69 years between 2002 and 2003. If screening were to account for a drop in incidence, rates of in situ disease would also need to drop, as they are detected almost only with mammography.

Follow-up of women in routine screening shows a similar drop in incidence, further ruling out changes in screening patters as the explanation. Data from the WHI add further support to this decrease in risk after cessation and the late promoter effect of combination therapy.

Others have analyzed SEER data over a shorter period or draw on the unique resources of the California tumor registry and the HMO datasets[1] to show similar relationships between change in hormone therapy and a decrease in breast cancer incidence. Most recently, Robbins and Clarke evaluated the change in prescribing as estimated from the California Health Interview Survey (CHIS) for almost 3 million non-Hispanic white women aged 45-74 years against the change in breast cancer incidence across 58 counties in California. This thoughtful analysis shows that, from 2001-2004, incidence declined by 8.8% in the counties with the smallest estrogen and progestin reductions, by 13.9% in those with intermediate reductions, and by 22.6% in counties with the largest reductions in combination postmenopausal hormone therapy.

Between 2001 and 2003, CHIS data did not show any significant change in the proportion of women who reported having a mammogram in the previous 2 years, adding further evidence against this as a plausible major explanatory factor in the observed declines in incidence. Even more evidence in support of this relationship

between decrease in estrogen and progestin and breast cancer comes from declines in incidence that parallel those in the United States as reported in New Zealand and Germany. Based on these data and the IARC classification of estrogen plus progestin as a carcinogen, it can be concluded that removal of estrogen plus progestin acting as a promoter accounts for this rapid drop in incidence.

Summary of postmenopausal hormone use and breast cancer risk

Although some aspects of the relationship between postmenopausal hormones and breast cancer risk remain unresolved, several areas of clear agreement have emerged. Combination estrogen plus progestin therapy is carcinogenic in women and causes breast cancer. The adverse effect of combination therapy is greater than that observed for estrogen alone. Whether some forms of progestin are safer remains under study.

Overall, the findings indicate an increased risk in two important subgroups of users: users of long duration and current users. In general, users of long duration are more likely to be current users, so, in many studies, these two groups overlap substantially. From a biological perspective, these are the groups one would most expect to demonstrate a relationship with breast cancer risk, as exogenous estrogens appear to act as a promoter at a late stage.

Nutritional factors have been prominent among the hypothesized environmental determinants of breast cancer that account for the large variation in breast cancer incidence around the world and the large increases in rates among the offspring of migrants from countries with low incidence to countries with high incidence. The dominant hypothesis has been that high fat intake increases risk, although evidence from randomized interventions and combined analysis of prospective epidemiologic cohort studies

] fails to show a significant relation.

Milk consumption through premenopausal years (a highly consistent behavior over time) increases risk of premenopausal breast cancer and in more recent studies is associated with greater weight gain in adolescence and with the development of acne among girls. High-fat dairy foods have also been related to risk of premenopausal breast cancer.

The World Cancer Research Fund has conducted extensive systematic literature reviews and meta-analysis of published studies relating diet to risk of premenopausal and postmenopausal breast cancer and concluded that there is limited evidence supporting a role for components of diet such as fiber, fat, soy, and vitamins (A, C, D, E) in relation to breast cancer risk.[54] Alcohol, on the other hand, shows a convincing causal relation.

Alcohol

Substantial evidence now supports a positive association between alcohol consumption and breast cancer risk. In a pooled analysis of case-control and cohort studies (58,515 cases of breast cancer), women consuming 35-44 g/day of alcohol (about 3 drinks per day) had a RR of 1.32 (1.19-1.45) compared to nondrinkers. The risk increased by 7.1% (95% CI, 5.5%-8.7%) for each 10 g/day. Similar results were observed in a pooled

analysis of the 6 largest cohort studies that allowed for additional control for other dietary factors. The risk of breast cancer increased monotonically with increasing intake of alcohol, with no statistical evidence of heterogeneity among studies. For a 10-g/day increase in alcohol, breast cancer risk increased by 9% (4%-13%). Adjustment for known breast cancer risk factors and dietary variables hypothesized to be related to breast cancer had little impact on the association with alcohol. In the collective literature, beer, wine, and liquor all contribute to the positive association, strongly suggesting that alcohol per se is responsible for the increased risk.

In intervention studies, consumption of approximately two alcoholic drinks per day increased total and bioavailable estrogen levels in premenopausal women, and single doses of alcohol acutely increased plasma estradiol levels in postmenopausal women, suggesting a mechanism by which alcohol may increase breast cancer risk.

In several large prospective studies, high intake of folic acid appeared to completely mitigate the excess risk of breast cancer due to alcohol, although folic acid intake was not associated with breast cancer risk among nondrinkers. This relationship was confirmed using plasma folic acid levels. Because alcohol inactivates folic acid metabolites and low folate levels are associated with increased misincorporation of uracil into DNA, this finding suggests another possible mechanism for the adverse effects of alcohol.

Caffeine

Considerable speculation that caffeine may be a risk factor for breast cancer followed a report that women with benign breast disease experienced relief from symptoms after eliminating caffeine from their diet. Most case-control studies, however, have not observed evidence of a positive association with breast cancer. In prospective studies, no increase in breast cancer risk has been seen. Similarly, no evidence for an association between tea consumption and risk of breast cancer has been seen in epidemiologic studies. Thus, the epidemiologic evidence is not compatible with any substantial increase in breast cancer risk associated with drinking coffee or tea.

Physical activity

Among postmenopausal women, physical activity may lower breast cancer risk by reducing fat stores, which convert androstenedione to estrone. Physical activity may also increase levels of sex hormone-binding globulin (SHBG), which would reduce bioavailable estrogens. Increased physical activity also reduces insulin resistance and hyperinsulinemia, which has been hypothesized to be related to breast cancer. The relation of physical activity to breast cancer risk has been addressed in over 100 case-control and cohort studies, which were summarized by an IARC working group, which concluded that the evidence was sufficient to establish that physical activity is protective against breast cancer.

The most compelling evidence for a relationship between long-term physical activity and breast cancer risk comes from studies among premenopausal women. Bernstein noted that higher levels of physical activity related to later onset of regular menses and showed that sustained higher activity levels through premenopausal years produced a

substantial reduction in risk of breast cancer.[1] Risk was reduced by approximately 40% among those who were consistently most active.

Such findings have been replicated in the prospective Nurses Health Study II cohort, in which lifetime activity was assessed in 1997 and women were followed for 6 years. Sustained activity from ages 12-22 years showed a 25% reduction in premenopausal breast cancer.These levels of activity may not be sufficient to modify hormone levels in premenopausal women but are sufficient to impact insulin metabolism and risk of type 2 diabetes in women.

Other studies show a significant increase in estrogen among premenopausal women with low leisure time physical activity and positive associations between insulin levels and postmenopausal breast cancer.The insulin receptor is a significant major predictor of reduced disease-free survival in women with node-negative breast cancer. This finding supports the potential importance of the insulin pathway in breast cancer biology.

Obesity

Postmenopausal adiposity is an established risk for postmenopausal breast cancer. Components of energy balance have been evaluated in numerous studies indicting that highest energy intake, highest body mass index (BMI), and lowest energy expenditure may combine to more than double the risk of breast cancer. In the combined analysis of prospective studies of endogenous hormone levels, evaluation of BMI showed that a substantial component of this relation with postmenopausal breast cancer is mediated through hormone levels. Results from a study by Seo et al suggested that obesity may modify the structure of adipose tissue in the breast which promotes breast tumorigenesis by altering mammary extracellular matrix (ECM) mechanics.

Height

Energy restriction powerfully reduces mammary tumor incidence in rodents. Because children who experience energy deprivation during growth do not attain their full potential height, attained height may be used as a proxy for childhood energy intake. Study of height in a longitudinal cohort of adolescents shows milk intake directly related to increased peak height velocity, supporting the role of diet in modifying height.

Most of the case-control and cohort studies of attained height and risk of breast cancer suggest a modest positive association. In a pooled analysis of large cohort studies (4385 cases among 337,819 women), the RRs for an increment of 5 cm of height were 1.02 (95% CI, 0.96-1.10) for premenopausal women and 1.07 (95% CI, 1.03-1.12) for postmenopausal women.

Several large cohort studies have been conducted in Scandinavia, and, in all of them, positive associations have been observed. In the studies of Vatten and Kvinnsland, the positive trend between height and risk of breast cancer was most nearly linear in the birth cohort of women (1929-1932) who lived through their peripubertal period during the Second World War, a time when food was scarce and average attained greater

height reduced. Collectively, these data provide convincing evidence that attained greater height is associated with a modest increase in risk of breast cancer.

Weight and weight change during adulthood

Attained weight and weight change in adults provides the most sensitive measures of the balance between long-term energy intake and expenditure. The inverse relation between body weight (typically used as BMI) and incidence of premenopausal breast cancer has been consistently seen as summarized in a systematic review and meta-analysis of both case-control and cohort studies. Heavier premenopausal women, even at the upper limits of what are considered to be healthy weights, have more irregular menstrual cycles and increased rates of anovulatory infertility, suggesting that their lower risk may be due to fewer ovulatory cycles and less exposure to ovarian hormones. Increased rates of menstrual irregularity and anovulatory infertility are also seen among very lean women, but such women are uncommon in Western populations.

In both case-control and prospective studies conducted in Western countries, the association between BMI and risk of breast cancer among postmenopausal breast cancer has been weakly positive. The reduction in breast cancer risk associated with being overweight in early adult life is strongly inverse during premenopausal years and appears to persist throughout later life, thus attenuating the effect of postmenopausal adiposity. Thus, an elevated BMI in a postmenopausal woman represents two opposing risks: a protective effect due to the correlation between early weight and postmenopausal weight and an adverse effect due to elevated estrogens after menopause.

For this reason, weight gain from early adult life to after menopause should be more strongly related to postmenopausal breast cancer risk than attained weight. Weight gain and risk of postmenopausal breast cancer has been consistently supported by both case-control and prospective studies. The adverse effect of excessive weight or weight gain on risk of postmenopausal breast cancer is also obscured by the use of postmenopausal hormones. Thus, to quantify the impact of weight or weight gain on postmenopausal breast cancer risk, an analysis should be limited to women who have never used postmenopausal hormones.

Among women who never used postmenopausal hormones in the Nurses' Health Study, those who gained 25 or more kg after age 18 years had double the risk of breast cancer compared with women who maintained their weight within 2 kg.

Updated data from the Nurses’ Health Study shows that weight loss that is sustained is directly related to reduced risk of breast cancer, particularly when focusing on the interval after menopause. These results highlight the temporal relation between adiposity and risk, and the benefits of weight reduction among postmenopausal women.

Genetic Factors

Family history of breast cancer in a first-degree relative is a consistent risk factor; risk increases with earlier age at diagnosis in the relatives and the number of relatives affected. In the Nurses' Health Study, for instance, the RR associated with a maternal diagnosis before age 40 years was 2.1 and was 1.5 for maternal diagnosis after age 70 years. For women with both an affected mother and at least one affected sister, the RR was 2.5.

However, most women with breast cancer do not have a family history of the disease in a first-degree relative, and only 2%-5% of breast cancers are estimated to be attributable to the inheritance of rare, highly penetrant, germline mutations in genes, although this proportion is higher at younger ages of diagnosis. Mutations in*BRCA1* and *BRCA2* are responsible for most of these inherited breast cancers; mutations in *p53* (causing Li-Fraumeni syndrome) and *PTEN* (causing Cowden syndrome) account for a small proportion of inherited breast cancers. Mutations in each of these genes occur in much less than 1% of the population.

Polymorphisms are usually defined as a sequence variant in a gene that occurs in more than 1% of alleles. Polymorphisms in genes that code for enzymes, receptors, or other proteins that act in metabolic pathways of potential relevance to breast cancer may influence the function of these proteins and thus create between-person differences in metabolic activity that may alter risk of breast cancer. Candidates include genes for carcinogen-metabolizing enzymes, steroid hormone-metabolizing enzymes, DNA repair genes, and receptors such as the estrogen and progesterone receptors. If these polymorphisms cause only modest increases in risk or confer risk only in conjunction with exposure to carcinogens, they would not cause noticeable familial aggregation. As these polymorphisms may be very common, their population-attributable risks may be large even if the RRs are modest.

The genome wide association studies have identified 6 breast cancer susceptibility alleles that are common in the population, but the clinical utility of such genetic risk is not yet clear.

Precursor neoplastic lesions

Benign breast disease (BBD) includes a number of breast abnormalities. These benign conditions vary in their cellular and pathologic features and, most importantly, in their impact on subsequent breast cancer risk. The 3 most clinically relevant groups are defined by changes in breast cells and include (1) nonproliferative, (2) proliferative without atypia, and (3) proliferative with atypia.

Nonproliferative lesions include cysts, apocrine metaplasia, and mild hyperplasia of usual type. Women with these lesions are at the same risk of breast cancer as women without a breast biopsy.

Proliferative lesions without atypia (eg, intraductal papilloma, sclerosingadenosis, moderate hyperplasia of usual type) are associated with a 1.5- to 2-fold increased risk of breast cancer compared to nonproliferative lesions.

Atypical ductal (ADH) and lobular (ALH) hyperplasias make up the group of proliferative lesions with atypia. Atypical hyperplasias are similar to in situ carcinomas in that they are both characterized by proliferation of epithelial cells, but they do not share all of the morphologic and pathologic features. These lesions are associated with a 3.5- to 6-fold increased risk of subsequent breast cancer. A large follow-up of 9087 women for a median of 15 years by investigators at Mayo Clinic showed that risk was greater among women diagnosed prior to menopause and that there was no interaction between histologic findings and family history of breast cancer.

Other risk factors such as alcohol and hormone use do not appear to act differently according to types of benign breast disease, indicating that prevention strategies apply across women with and without a history of benign lesions.

Mammograms and breast density

After extensive family history of breast cancer, mammographic density is the strongest risk factor for the development of breast cancer. Women with dense breasts have 4 times the likelihood of developing breast cancer compared to women without dense breasts. It is also well known that breast tissue density increases in about 25%-30% of women who begin hormone replacement therapy and that, conversely, breast density decreases in some women who are placed on tamoxifen or raloxifene.

The authors have shown that single-nucleotide polymorphisms (SNPs) in the IGF pathway are related to risk of mammographically dense breasts and that the relation of mammographic density to increased breast cancer risk is independent of circulating hormone levels. These findings suggest long-term energy balance may operate to modify breast density and requires further evaluation of energy balance and the microbiome to refine our understanding.

Other medical conditions

Various diseases and medications are known or suspected to cause or to be associated with modifications of hormones and/or growth factors and thus may influence breast cancer risk.

Women with osteoporosis and low bone density are at significantly lower risk for beast cancer, a reflection of their lower hormone levels.

Type 2 diabetes has been suggested to increase risk of breast cancer. Studies have often lacked information about the type and severity of diabetes, making the interpretation of the various findings difficult. Prospective plasma-based studies now provide more direct evidence supporting a positive relation between insulin levels and risk for beast cancer. Further studies of the relationship between breast cancer and

insulin resistance are warranted because insulin resistance is increasing sharply in many populations and is modifiable through increases in physical activity, dietary changes, and maintenance of a lean body weight.

Strong evidence suggests that nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, inhibit colon carcinogenesis in humans, thus providing a rationale to investigate an inhibitory role of NSAIDs in breast carcinogenesis. Some epidemiologic studies have shown modest reductions in risk of breast cancer associated with NSAID use, while others have found none. Evidence for risk reduction appears stronger for aspirin than for nonaspirin NSAIDs. Because most NSAID use is sporadic, it may be difficult to capture patterns of use on a questionnaire. Unanswered questions remain regarding the effect of regular NSAID use for long durations, the effect of different doses, and the effects of different nonaspirin NSAIDs.

Antibiotic use and breast cancer risk

Several large database studies including Group Health Cooperative and the Saskatchewan prescription database show an increased risk with long-term use that rises to a twofold increase with over a total of 1,000 days of use. Other comparable pharmacy record systems (such as Denmark) have not shown as strong a relation. No clear drug class effect has been observed. This evidence, though still evolving, nevertheless points to the possibility that modification in the gut microbiome through extended use of antibiotics may significantly modify risk of breast cancer.

Silicone breast implants

Most studies examining the relation of silicone breast implants with breast cancer risk have actually reported lower rates of breast cancer among women with implants. Reported reductions in risk in some of these studies have been large (on the order of 50% or 60%).

A large retrospective cohort study was conducted to clarify the relation between breast implants and subsequent breast cancer.In this study, over 12,000 women who had breast implants prior to 1989 and over 3000 comparison women who had had plastic surgery not involving silicone during the same time period, responded to a medical questionnaire. In analyses based on external and internal comparisons, the women who had had breast implants were not at elevated risk of breast cancer. There was no statistically significant heterogeneity in risk according to age or calendar year in which implants were received (in part, this calendar year variable was a surrogate for type of implant), nor was there variation in risk of breast cancer by preimplantation chest or cup size.

Overall, there is strong epidemiologic evidence that breast implants do not lead to increased risk of breast cancer.

Ionizing Radiation

The knowledge that ionizing radiation to the chest in cumulative moderate-to-high doses (eg, 1-3 Gy) at young ages substantially increases breast cancer risk comes from

several lines of evidence, including atomic bomb survivor studies, studies of diagnostic-therapeutic uses of radiation, and occupational studies. Among survivors of the atomic bombing of Hiroshima and Nagasaki, breast cancer risk was strongly associated with estimated breast tissue dose of radiation.[19] Further, the excess risk of breast cancer associated with each radiation dose depended heavily upon the age at the time of the bombing, being highest for women exposed before age ten years. For women exposed after age 40 years, there was no significant elevation in subsequent breast cancer risk.

Studies of diagnostic radiation have revealed a similar pattern of excess risk of breast cancer associated both with higher doses and with younger ages at exposure. Studies of therapeutic radiation for nonmalignant and malignant disease have revealed the same pattern. In a study of women exposed to radiation therapy to the chest as treatment for Hodgkin disease, the excess risk of breast cancer was dependent on dose and age at irradiation.

Other Environmental Factors

Organochlorines are among the potential environmental factors of greatest concern as causes of breast cancer. Epidemiologic studies of breast cancer and environmental exposures to synthetic chemicals have concentrated on biologically persistent organochlorines. This class of compounds includes pesticides, eg, 2,2-bis(*p* -chlorophenyl)-1,1,1-trichloromethane (DDT), chlordane, hexachlorocyclohexane (HCH, lindane), hexachlorobenzene (HCB), kepone, and mirex; industrial chemicals, eg, polychlorinated biphenyls (PCBs) and polybrominated biphenyls (PBBs); and dioxins (polychlorinated dibenzofurans [PCDFs] and polychlorinated dibenzodioxin [PCDDs]), produced as combustion byproducts of PCBs or contaminants of pesticides.

Many of these chemicals are weak estrogens and may act as estrogenic agents in breast tissue, thereby hypothesized to increase breast cancer risk by mimicking endogenous estradiol. Other compounds, specifically the dioxins and some PCB congeners, exhibit antiestrogenic activity and may be protective against breast cancer.

Studies of occupational exposure to organochlorines have not supported an association with increased breast cancer risk. Fewer cases were observed than expected in studies of women occupationally exposed to phenoxyl herbicides and PCBs. However, these studies are limited by few workers exposed and difficulties of exposure assessment.

The results of small case-control studies of organochlorine levels and breast cancer risk have been mixed. However, the large case-control study conducted on Long Island, New York, observed no association with breast cancer risk for blood levels of dichlorodiphenyldichloroethane (DDE), chlordane, dieldrin, or common PCB congeners.

Several prospective studies have also used stored blood samples collected prior to diagnosis to evaluate the relationship between DDE and total PCBs with breast cancer. A pooled study reanalyzing data from the 5 large studies in the northeast found no association between PCBs and DDE levels and breast cancer risk when comparing the highest and lowest quintiles.Based on this body of evidence, organochlorines appear

unlikely to be an important breast cancer risk factors or an explanation for breast cancer trends over time.

Electromagnetic fields

Electromagnetic fields (EMF) have been proposed to alter breast cancer risk, perhaps by altering melatonin secretion by the pineal gland. In case-control studies designed specifically to study occupational exposure to EMF and breast cancer in women, small increases in risk have been inconsistently observed. However, in those studies, misclassification of exposure remains a concern. Because classifications are based on "usual" occupation, often obtained from death certificates, duration of exposure and personal work tasks could not be accounted for in most of the studies, and adjustment for known breast cancer risk factors was limited or entirely absent.

Active and passive smoking

The relationship between active cigarette smoking and risk of breast cancer has been extensively evaluated in both case-control and cohort studies; collectively, the data provide strong evidence against any major overall relationship, as the 2004 Report of the US Surgeon General concluded the data suggest no causal relationship between active smoking and breast cancer. The question of passive or secondhand smoke exposure and risk of breast cancer was extensively reviewed in the 2006 report of the Surgeon General. After thorough evaluation of the many epidemiologic studies, the report concluded that the overall evidence is mixed and does not strongly or consistently support a causal relationship between secondhand smoke and breast cancer.

Prevention

For prevention and control of breast cancer in primary level we should do intervention on correctable risk factors in strong relation (RR.4) there is no factor but in moderate level (RR =2-4)factors such as never marriage – no children – obesity after menopause –alcohol usage in the low level (RR<2) we should control factors such as high fat usage – low physical activity –use of Di ethyl acetyl bestrol –contraceptive pills –HRT

In primary prevention attributable risk of risk factors is an important issue that we have to suggest and attributable risk of correctable factors (table N.2)

Correctable attributable risk in breast cancer

Risk factor	Best estimation (%)	Range estimation (%)
Obesity after menopause	12	8-16
First delivery after 30 years	7	1-13
Without child	5	1-9
Large amount of X-Ray to chest	5	1-3

For prevention in secondary level we should do screening program first of all self examination of breast for every month and timed by physician.

For years, the American Cancer Society (ACS) urged women to start mammograms at age 40, but they recently changed their guidelines. They now recommend beginning them at age 45, or at 40 if the patient chooses.

the American College of Obstetricians and Gynecologists (ACOG), say that starting at 40 is best. Meanwhile, the U.S. Preventive Services Task Force Services (USPSTF) says that women can wait until 50.

There's also the related issue of how often to get tested. ACOG says go annually. USPSTF says every 2 years. The most recent ACS guidelines suggest getting annual mammograms between ages 45 and 54; after that, they say it's OK to wait 2 years between screenings.

For tertiary level of prevention , rehabilitation and mental health consulting is recommended.