Breast Cancer:
Epidemiology and Risk Factors

by Miguel R. Kamat, M.D., M.P.H.
Medical Officer
U.S. Public Health Service,
Adjunct Assistant Professor
USUHS Department of Radiology & Nuclear Medicine

Breast cancer poses a public health challenge because of

- the immense burden of disease it imposes on women today, and
- the demonstrated potential to reduce mortality through population-based screening with mammography

PART I

DESCRIPTIVE EPIDEMIOLOGY

STATISTICS

Incidence

- most frequently diagnosed malignancy among US women (excluding cancers of the skin)
- accounts for nearly one-third of all cancers detected
- 175,000 cases in 1999, by American Cancer Society (ACS) estimates

Mortality

- second leading cause of death from cancer among women
- accounts for nearly one-sixth of cancer deaths
- 43,300 deaths in 1999, by ACS estimates

Lifetime probability

- 1 in 9 women

Incidence and mortality in men

- less than 1% of the annual incidence and mortality for both sexes
- 1300 new cases and 400 deaths in 1999

TRENDS – UNITED STATES

Incidence

- Age adjusted incidence rate demonstrated an annual increase of less than 1% per year during 1973-80, according to data from the Surveillance Epidemiology and End-Results Program (SEER) of the National Cancer Institute
- Between 1980 and 1987, the rate jumped from 85 to 112.3 per 100,000 women, an increase of 32% or 4% per year
- From 1987 to 1989, the rate declined to 106
- In 1990, the rate rose to 109.5
- It further rose to 111.4 in 1991
- It declined to 109.7 in 1992

<u>Interpretation</u>

The above figures indicate that there has been no consistent trend since the 1987 peak. These increases and decreases in incidence rates reflect a screening effect i.e. the observed short term increase is not due to a change in the underlying epidemiology of the disease but to a change in the rate of case detection, due to higher participation rates in screening.

For instance, in 1974, when Mrs. Betty Ford and Mrs. Happy Rockefeller were diagnosed with breast cancer, many women underwent breast examinations that year either for screening or symptomatic purposes. The increase was short lived, as incidence rates declined after 1975 to the earlier 1973 levels, and patterns of gradual increase.

Mortality

- During 1989-92, African American women experienced a higher overall age adjusted mortality rate than white women

	African American women	White women
Mortality	31.3 per 100,000	27.2 per 100,000

- The order of magnitude was reversed depending on the age group considered:

	African American women	White women
$\leq$ 64 years	21.1 per 100,000	15.9 per 100,000
> 64 years	124.8 per 100,000	127.9 per 100,000

- For the broader period 1973-92, whites showed an overall decline of 2.6%, whereas African Americans an overall increase of 18.6%
- Stratification by age group:

	African American women	White women
< 50 years	increase of 2.4%	decline of 17.6%
$\geq$ 50 years	increase of 25.1%	increase of 1.7%

TRENDS – INTERNATIONAL

Incidence

- Most common cancer in women (21% of all new cases0
- Third most frequent cancer in the world
- 796,000 new cases in 1990
- Highest incidence in the US and Northern/Central Europe; intermediate in Southern Europe/Latin America; lowest in Asia and Africa
- The differential between western rates and those in India, China and Japan may be as much as 3 to 4
- Migration phenomenon: Japanese American women in Hawaii, after one or two generations of residence in the US, demonstrate an incidence rate closer to the US SEER average than to Japanese women in Japan, an observation that supports a role for environmental factors in the genesis of breast cancer

Mortality

- Breast cancer is the leader cause of global cancer mortality among women
- 14.1% of cancer deaths in women

- Fifth leading cause of cancer mortality in the world

SOURCES OF DATA

- ACS estimates incidence by applying 1979-91 SEER incidence data to the Census population projection for the current year
- Mortality data (1979-91) are obtained from the Division of Vital Statistics of the National Center for Health Statistics
- No nationwide disease registry exists, but nine cancer registries contribute to the SEER database in the United States
- Of these five are statewide, and four urban:
  Statewide: Connecticut, Hawaii, Iowa, New Mexico and Utah
  Urban: Detroit, Atlanta, San Francisco-Oakland and Seattle-Puget Sound
- The crude rate (# of newly diagnosed cases per 100,000 women) is age-standardized to counter the influence of underlying population shifts
- Thus, an age-standardized rate neutralizes the effect of a growing number of women in an aging population entering the screening age group, and instead reflects the underlying trends in the epidemiology of the disease and/or breast cancer detection

AGE AND INCIDENCE

The incidence of breast cancer increases with age, as follows:

- Rare before age 25
- Increases rapidly up to menopause
- Curve is slightly flatter at this age
- Peaks at 76-79 years

Different breast cancer age-specific rates (data compiled in 1996)

- 4.8% in ages 30-39
- 17.8% among ages 40-49
- 23.8% among ages 50-59
- 26.3% among ages 60-70
- 26.6% among women older than 70 years
- 77% of new diagnoses are made in women over 50 years old

Trends in age-specific incidence rates 1973-92

- under 40 age group: incidence declined somewhat
- 40-59 year age group: incidence increased 9-15%

- 60-79 year age group: incidence increased greater than 40%
- over 85 year age group: smaller increase

Although the incidence of breast cancer has decreased somewhat in younger women, the public perception of this trend is just the opposite. This may reflect the fact that growing numbers of women who were born since 1945 ("baby boomers") have entered the screening age group (30s,40s), increasing the numbers of new cases in this group and thus giving rise to this perception. For example:

- in the 30-39 year age group, there were 11,550,000 women in 1970, but 21,060,000 women in 1990
- among the 40-49 year age group, there were 25% more women in 1985-90 than in 1975-80

BLACK VS. WHITE

Overall, age-adjusted incidence rates are higher among white women (112.4 vs. 100.2).

- higher among blacks in the 44 year and under age group
- higher among whites in the 45 year and older age group

1973-92 trend

- similar in both groups for the 50 year and older group (37.6% blacks vs. 33.1% whites)
- four times as high for blacks in the under 50 year group (25.1% blacks vs. 6.3% whites)

STAGE AT DIAGNOSIS

With increasing use of screening mammography in asymptomatic women:

- percentage of in situ cases has doubled
  - rate of detection of carcinoma in situ increased from 4 per 100,000 in 1973 to slightly less than 15 per 100,000 in 1989
- percentage of Stage I cases diagnosed has increased by greater than 50% since 1980
  - rate of detection of cancers smaller than 1 cm increased from 9 per 100,000 in 1982 to 35 per 100,000 in 1989

Cases with regional or distant metastasis decreased 9% and 10% respectively between 1982 and 1989.

Overall Five Year Survival

Overall 5 year survival is favorable: 83.1% (1986) for all stages of invasive disease. Improved from 74.3% in 1974-76 mainly due to greater improvements in average survival for white women (74.9% to 84.4%). For African American women, it only increased from 62.7% to 68.9% in the same period. Further, 5 year survival is lower and poorer at each stage (68.9% for African American women versus 84.4% for whites). Reasons for this discrepancy are socioeconomic, less access to mammography, and diagnosis at a later stage.

USE OF SCREENING MAMMOGRAPHY

Dramatic increase in the number of women availing of screening mammography.

- In 1978-83, only 15-20% of American women had ever had a mammogram.
- By 1987, this number had increased to 39% [NCI sponsored Cancer Control Supplement to the National Health Interview Survey]
- In 1992, 74% of American women had had a mammogram [Mammography Attitudes and Usage Survey, put together by the Jacobs Institute of Women's Health]
- Reasons for this increased utilization of screening mammography:
    - Growth of scientific support for the modality
    - Increasing acceptance by providers and women
    - Improved access
    - Adherence to recommended guidelines

LIFETIME RISK

Lifetime risk is estimated by the NCI to have increased as follows:

- 1:20 in 1940
- 1:9 in 1989
- 1:8 in 1996
- 1:9 in 1998

Reasons for this increasing trend include increasing longevity and the increased incidence of breast cancer.

Please note that risk varies over different decades, and thus the average risk over particular intervals (i.e. over periods of 10 and 20 years) is considerably less and therefore less intimidating than the estimated lifetime risk.

Thus, a 40 year old woman has a

- 1:63 chance of developing breast cancer by age 50
- 1:26 chance of developing breast cancer by age 60
- 1:14 chance of developing breast cancer by age 70

RISK ASSESSMENT MODELS

Risk models attempt to quantitate an individual's actual risk of developing breast cancer.

Gail Model

- proposed by Gail and Benichou in 1994
- based on the experience of women from the Breast Cancer Detection Demonstration Project (BCDDP)
- model incorporates five risk factors:
  - age at menarche
  - age at first live birth
  - family history
  - number of previous breast biopsies
  - presence of atypical hyperplasia in a breast biopsy specimen
- it then computes an individualized absolute risk of developing breast cancer in a specified time frame
- good predictor of risk among white women screened in accordance with ACS guidelines, but may overestimate risk for women who are not routinely screened
- model is also available in the form of an interactive computer program

Claus Model

- developed in 1991
- uses data from the Cancer and Steroid Hormone Study
- more relevant to the population not undergoing routine screening

Risk assessment models are useful because they estimate the direct underlying probability of an event over time in contrast to relative risk

which compares the risk of an individual with a known risk profile to one without. Relative risk may result in an inflated perception of risk.

Unfortunately, risk perceptions are often made on the basis of relative risks quoted in the literature.

PART II

ANALYTIC EPIDEMIOLOGY – RISK FACTORS

Risk factors explain only about 21-29% of breast cancer cases.

Strong Risk Factors

- *Age*: the incidence of breast cancer increases with age, as discussed earlier
- *Sex*: as obvious as it may seem, female sex is a major risk factor
- *Family History* (discussed below)
- *Personal History* (discussed below)
- *B*enign *Breast Disease* (discussed below)
- *Reproductive History* (discussed below)

Family History

- A first-degree relative (mother, sister, daughter) with breast cancer before the age of 50 confers a relative risk of 2.5
- History of disease in mother and sister together increases relative risk to 13.6
- A relative with bilateral breast cancer may put a woman at particularly high risk
- Breast cancer in males may be related to breast cancer in female relatives in much the same way:

- A male relative with breast cancer may place female family members at high risk
- Conversely, a mother with breast cancer may increase the risk of male breast cancer 2.33-fold; an affected sister may increase the risk 2.23-fold
- Male breast cancer may also be particularly strongly related to early onset female breast carcinoma in first degree relatives

Hoskins in 1995 grouped women with a family history of breast cancer into moderate-risk and high-risk families:

Moderate-risk families have a history of postmenopausal breast cancer in one or two family members in the absence of ovarian cancer.

High-risk families are characterized by:

- Early onset of breast cancer
- Bilateral or multifocal disease
- Two or more first-degree relatives with breast and/or ovarian cancer.
- They account for 5% of breast cancer cases and 25% of women diagnosed before age 30
- They have a high probability of mutation in a dominantly-inherited breast cancer susceptibility gene BRCA-1, or linkage to BRCA-2
- In 30% of high-risk families, no association with either of the above genes has been documented

Genetic Basis of Breast Cancer

Genetic susceptibility results in highly risk, but is rare (only 5% of cases). Genes can be transmitted through either sex.

BRCA-1

- About one-third of familial cases
- Present on the long arm of chromosome 17
- Families have an elevated risk of breast and ovarian cancer

- They also have significant excesses of colon and prostate cancers
- There may be a familial relationship with endometrial cancer as well
- Multiple primary cancers: incidence of breast cancer was increased by 10-40% after a first primary cancer of the ovary, according to studies; conversely, incidence of ovarian cancer increased 30-70% after a first primary breast cancer.
- For breast and endometrial cancers, the corresponding figures are 20-30% and 40%

BRCA-2

- Localized to long arm of chromosome 13
- Families are at higher risk for male breast cancer
- Lower risk for ovarian cancer than BRCA-1 families
- High risk for female breast cancer

A few cases of genetic breast cancer arise from mutations in the p53 gene on the short arm of chromosome 17.

Patients with bilateral breast cancer, those who develop a combination of breast cancer and another epithelial cancer, and those who develop the disease at an early age are most likely to have genetically predisposed breast cancer. Using molecular-based testing, high-risk families can be separated into those family members carrying the susceptibility factor who have a near 100% chance of developing breast cancer over their lifetime from others in the family with a breast cancer risk comparable to the general population. For such people at high risk, knowledge of genetic status could help them make informed decisions regarding potential options – intensified screening, chemoprevention or even prophylactic mastectomy.

Genetic Syndromes

A small number of breast cancer patients are involved in other familial syndromes.

Li-Fraumeni syndrome

- Family members develop multiple primary cancer at an early age
- Characterized by a range of childhood and adult cancers, such as breast cancer, brain tumors, soft tissue sarcoma, osteosarcoma, leukemia and adrenocortical carcinoma.

Cowden's disease

- Autosomal dominant
- Hamartomas
- Tumors: fibrocystic breast disease, breast carcinoma, thyroid tumors, GI polyps, lipomas
- Multiple mucocutaneous lesions

Peutz-Jeghers syndrome

- Autosomal dominant
- Mucocutaneous pigmentation
- GI hamartomas
- Increased risk of non-GI tumors including bilateral breast cancer

Ataxia-telangiectasia

- Autosomal recessive
- Female carriers may have a five-fold increased risk of breast cancer, even following diagnostic or occupational doses of ionizing radiation (no consensus though on this theory)

Personal History

- History of cancer in one breast places contralateral breast at increased risk
- Personal history of endometrial or ovarian cancer increases risk for breast cancer
- Ovarian cancer predisposes to a younger age of onset of breast cancer than does endometrial cancer

Benign Breast Disease

- Significant increased risk (five-fold) associated with severe atypical hyperplasia
- Slightly increased risk (1.5-2 times) associated with proliferative lesions such as moderates epithelial hyperplasia, sclerosing adenosis and duct papillomas
- No increased risk with fibroadenoma or inflammation

Reproductive History

A longer duration of cyclic ovarian activity is associated with greater risk. For example,

- Early age at menarche
- Late menopause
- Nulliparity
- Late age at first birth

Women who have their first child after age 30 have about twice the risk of those with a first child born at age 20.

The highest risk group are those whose first child is born after age 35; these women are actually at higher risk than nulliparous women.

At the other extreme, each year of delay initiating childbearing increases risk by 3.5%.
Earlier menopause (before 45 years of age) has been observed to convey a 30% reduction of risk compared with menopause after 50 years. Surgical menopause (bilateral oophorectomy) before the age of 35 reduces the risk of

breast cancer to only 40% of those undergoing natural menopause.

Weak Risk Factors or Risk Factors without a firm association with Breast Cancer risk

- Hormonal Replacement Therapy
- Oral Contraceptives
- Lactation
- Exercise
- Ionizing Radiation
- Dietary fat/Body Weight
- Body Height
- Micronutrients
- Alcohol intake
- Smoking

Hormonal Replacement Therapy

Estrogen replacement therapy has been inconsistently linked to breast cancer. Only after 20 or more years of use was an increase in risk observed in women in the BCDDP. Lesser periods of use showed no meaningful increase in risk.

The Nurses Health Study revealed a small increase in risk after more than 5 years of use. Studies have revealed that combined estrogen and progesterone treatment showed a greater risk than unopposed estrogen therapy.

Oral Contraceptives

Prolonged use (for four year or more) initiated at a young age and before a first term pregnancy has been linked in some studies to greater risk of premenopausal breast cancer.

Lactation

Lactation may exert a protective effect for premenopausal breast cancer, but the effect of this factor may be confounded by a second, inextricably tied variable, parity.

Exercise

A protective association between exercise and breast cancer risk has been observed in some studies, with risk decreasing with increases in hours of physical activity per week. Women who spent 3.8 or more hours per week on physical exercise have been shown to demonstrate a risk of 0.42. Young women performing exercise may protect themselves against the development of early onset breast cancer.

Ionizing Radiation

For low-dose exposure, such as occurs in screening and diagnostic mammography, the known reduction in mortality from early screening far outweighs the potential life threat.

High-dose radiation exposure of course is known to cause breast cancer. Some examples include the experiences of Japanese atomic survivors, women with postpartum mastitis treated with radiation and tuberculosis patients receiving multiple fluoroscopies.

However, early exposure to radiation during rapid breast formation increases risk later in life.

Dietary Fat/Body Weight

Obesity is associated with increase in risk in postmenopausal women, but no relationship with or slightly inverse relationship with risk in premenopausal women.

The distribution of body fat may have an independent effect on risk apart from body weight per se: upper body (central or abdominal) adiposity increases risk..

Mechanisms:

- Excess levels of free circulating estrogens

- Suppressed levels of circulating sex hormone-binding globulin

Attempts to study the effects of different fatty acids (polyunsaturates vs. saturates) on breast cancer risk have revealed no particular or consistent association of either with increased risk.

- In Spain, a study suggested that consumption of olive oil (rich in monounsaturated fat) was associated with a reduced risk of breast cancer.
- In Greece, no such effect was duplicated.
- One study showed no differences in fatty acid contents of adipose tissue samples from breast cancer and control subjects.

Body Height

Adult height is associated positively with breast cancer risk. Nutritional factors early in life before maximum height is attained may play a role.

Micronutrients

A report from the Nurses Health Study described a modest protective effect of Vitamin A against risk. Other studies suggest some benefit for Vitamin C and dietary fiber. These reports have not been widely confirmed.

Alcohol Intake

Breast cancer risk may be increased by as much as 70% by intake of two drinks daily. It is estimated that as much as 13% of breast cancer incidence in the U.S. may be related to alcohol consumption. Alcohol may act via effects on the endocrine system, such as by alteration of estrogen metabolism in the liver, or by effects on pituitary function.
Modest levels of alcohol intake have beneficial effects on health, such as a decreased risk of cardiovascular disease. A judicious balance between these two opposing considerations is recommended when advising on the possible health effects of alcohol intake. Perhaps abstinence may be recommended for those

women with unusually high risk of breast cancer but lower than average risk for heart disease.

Smoking

Smoking is not significant in the etiology of breast cancer.

Preventive Strategies

The majority of risk factors are beyond a woman's control to alter, Such as age, heredity, race, family history and onset of menarche and menopause.

Other factors, such as increased parity and a decision to have a full-term pregnancy before age 20 years, are lifestyle choices that are not easily modifiable based on breast cancer risk.

Still others, like diet modification, exercise and reduced alcohol intake, although advisable for good general health, are not interventions that will definitely reduce breast cancer risk.

Therefore, women at average risk are advised to adhere to routine screening in accordance with recommended guidelines. These consist of annual screening after age 50. Between 40 and 50 years of age, the professional societies and the American Cancer Society recommend annual screening, while the NIH/NCI recommends a mammogram within every 2 years.

Women at exceptionally high risk can avail of the options of intensified screening, chemoprevention and prophylactic mastectomy. Intensified (early onset) screening is recommended if a risk factor is indicative of earlier onset of disease. For example, screening could be initiated 5 years before the age at which the patient's first-degree relative was diagnosed with breast cancer.

References

1. American Cancer Society, CA A Cancer Journal for Clinicians 2000
2. American Cancer Society, CA A Cancer Journal for Clinicians, January/February 1999, Vol. 49, No. 1

3. Parker S.L., Tong T., Bolden S., Wingo P.A., Cancer Statistics, 1996, CA Cancer J CLIN 1996; 65:5-27
4. Smith R.A., The Epidemiology of Breast Cancer, RSNA Categorical Course in Breast Imaging 1995; pp. 7-20
5. Smith R.A., Giusti R.M., Pathogenesis and Epidemiology of Breast Cancer, Gynecologic Oncology: Current Diagnosis and Treatment, pp. 272-286
6. Moormeier J., Breast Cancer in Black Women, Ann Intern Med. 1996; 124:897-905
7. Benichou J., Mitchell H.G., Mulvihill J.J., Graphs to Estimate an Individualized Risk of Breast Cancer, Journal of Clinical Oncology, Vol. 14, No. 1 (January), 1996: pp. 103-110
8. Helzlsouer K.J., Epidemiology, prevention, and early detection of breast cancer, Current Opinion in Oncology 1995, 7: 489-494
9. McPherson K. Steel C.M., Dixon J.M., Breast Cancer – Epidemiology, Risk Factors, and Genetics, BMJ, Vol. 309, 15 October 1994, pp. 1003-1006
10. Garfinkel L. Boring C.C., Heath C.W., Changing Trends. An Overview of Breast Cancer Incidence and Mortality, Proceedings of the National Conference on Breast Cancer, American Cancer Society, Cancer 1994; 74:222-7
11. Mettlin C., The Relationship of Breast Cancer Epidemiology to Screening Recommendations, Cancer 1994; 74:228-30
12. Thompson W.D., Genetic Epidemiology of Breast Cancer, Cancer 1994; 74:279-87
13. Byers T., Nutritional Risk Factors for Breast Cancer, Cancer 1994; 74:288-95
14. Kelsey J.L., Horn-Ross P.L., Breast Cancer: Magnitude of the Problem and Descriptive Epidemiology, Epidemiologic Reviews, 1993, Vol. 15, No. 1, pp. 7-16
15. Mettlin C., Breast Cancer Risk Factors. Contributions to Planning Breast Cancer Control, Cancer 1992; 69:1904-1910
16. Kelsey J.L., Breast Cancer Epidemiology: Summary and Future Directions, Epidemiologic Reviews, 1993, Vol. 15, No. 1, pp. 256-263