BREAST CANCER—EPIDEMIOLOGY, RISK FACTORS, AND GENETICS

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Worldwide incidence of cancers in women (1980)

Site of cancer	No of cases (1000s)	% Of total
Breast	572	18
Cervix	466	15
Colon and rectum	286	9
Stomach	261	8
Endometrium	149	5
Lung	147	5
Ovary	138	4
Mouth and pharynx	121	4
Oesophagus	108	4
Lymphoma	98	3

Computer enhanced mammogram of a breast cancer.

Percentage of all deaths in women attributable to breast cancer.

With 570 000 new cases in the world each year, breast cancer remains the commonest malignancy in women and comprises 18% of all female cancers. The incidence among women aged 50 approaches two per 1000 women per year, and the disease is the single commonest cause of death among women aged 40-50, accounting for about a fifth of all deaths in this age group. In the United Kingdom, where the age standardised incidence and mortality is the highest in the world, there are more than 15 000 deaths each year, and the incidence is increasing slowly, particularly among elderly women, by about 1-2% a year.

Of every 1000 women aged 50, two will recently have had breast cancer diagnosed and about 15 will have had a diagnosis made before the age of 50, giving a prevalence of breast cancer of nearly 2%.

Standardised mortality for breast cancer in different countries.

Risk factors for breast cancer

Age specific incidence and mortality for breast cancer in United Kingdom.

Annual incidence of breast cancer in Japanese women in Japan, Hawaii, and San Francisco and in white women from San Francisco.

Age

The incidence of breast cancer increases with age, doubling about every 10 years until the menopause, when the rate of increase slows dramatically. Compared with lung cancer, the incidence of breast cancer is higher at younger ages. In some countries there is a flattening of the age-incidence curve after the menopause.

Geographical variation

Age adjusted incidence and mortality for breast cancer varies by at least a factor of seven between countries. The difference between Far Eastern and Western countries is diminishing but is still about fivefold. Studies of migrants from Japan to Hawaii show that the rates of breast cancer in migrants assume the rate in the host country within one or two generations, indicating that environmental factors are of greater importance than genetic factors.

Age at menarche and menopause

Women who start menstruating early in life or who have a late menopause have an increased risk of developing breast cancer. Women who have a natural menopause after the age of 55 are twice as likely to develop breast cancer as women who experience the menopause before the age of 45. At one extreme, women who undergo bilateral oophorectomy before the age of 35 have only 40% of the risk of breast cancer of women who have a natural menopause.

Age at first pregnancy

Nulliparity and late age at first birth both increase the lifetime incidence of breast cancer. The risk of breast cancer in women who have their first child after the age of 30 is about twice that of women who have their first child before the age of 20. The highest risk group are those who have a first child after the age of 35; these women appear to be at even higher risk than nulliparous women. An early age at birth of a second child further reduces the risk of breast cancer.

Family history

Up to 10% of breast cancer in Western countries is due to genetic predisposition. Breast cancer susceptibility is generally inherited as an autosomal dominant with limited penetrance. This means that it can be transmitted through either sex and that some family members may transmit the abnormal gene without developing cancer themselves. It is not yet known how many breast cancer genes there may be. About a third of the familial cases are thought to be due to a mutation in the BRCA1 gene on the long arm of chromosome 17. This gene has just been cloned, and preliminary reports suggest that it is a large gene and that mutations are not confined to particular regions. Some inherited BRCA1 mutations seem to be associated with only a modestly increased risk of breast cancer. A second hereditary breast cancer locus, BRCA2, has been identified on the long arm of chromosome 13. In addition, a few cases arise from mutations in the p53 gene on the short arm of chromosome 17.

Established and probable risk factors for breast cancer

Factor	Relative risk	High risk group
Age	>10	Elderly
Geographical location	5	Developed country
Age at menarche	3	Menarche before age 11
Age at menopause	2	Menopause after age 54
Age at first full pregnancy	3	First child in early 40s
Family history	≥2	Breast cancer in first degree relative when young
Previous benign disease	4-5	Atypical hyperplasia
Cancer in other breast	>4	
Socioeconomic group	2	Groups I and II
Diet	1.5	High intake of saturated fat
Body weight:		
Premenopausal	0.7	Body mass index >35
Postmenopausal	2	Body mass index >35
Alcohol consumption	1.3	Excessive intake
Exposure to ionising radiation	3	Abnormal exposure in young females after age 10
Taking exogenous hormones:		
Oral contraceptives	2	Use for ≥4 years when young
Hormone replacement therapy	1.5	Use for ≥10 years
Diethylstilbestrol	2	Use during pregnancy

Family tree of family with genetically inherited breast cancer.

Many families affected by breast cancer show an excess of ovarian, colon, prostatic, and other cancers attributable to the same inherited mutation. Patients with bilateral breast cancer, those who develop a combination of breast cancer and another epithelial cancer, and women who get the disease at an early age are most likely to be carrying a genetic mutation that has predisposed them to developing breast cancer. Most breast cancers that are due to a genetic mutation occur before the age of 65, and a woman with a strong family history of breast cancer who is still unaffected at 65 probably has not inherited the genetic mutation.

Severe atypical lobular hyperplasia.

A woman's risk of breast cancer is doubled if she has a first degree relative (mother, sister, or daughter) who developed the disease before the age of 50, and the younger the relative when she developed breast cancer the greater the risk. For example, a woman whose sister developed breast cancer aged 30-39 has a cumulative risk of 10% of developing the disease herself by age 65, but that risk is only 5% (close to the population risk) if the sister was aged 50-54 at diagnosis. The risk increases by between four and six times if two first degree relatives develop the disease. For example, a woman with two affected relatives, one who was aged under 50 at diagnosis, has a 25% chance of developing breast cancer by the age of 65.

Cumulative risk of breast cancer in women who were aged 10-19 years when exposed to radiation from atomic bombs during second world war.

Previous benign breast disease

Women with severe atypical epithelial hyperplasia have a four to five times higher risk of developing breast cancer than women who do not have any proliferative changes in their breast. Women with this change and a family history of breast cancer (first degree relative) have a ninefold increase in risk. Women with palpable cysts, duct papillomas, sclerosis adenosis, and moderate or florid epithelial hyperplasia have a slightly higher risk of breast cancer (1.5-2 times) than women without these changes, but this increase is not clinically important.

Radiation

A doubling of risk of breast cancer was observed among teenage girls exposed to radiation during the second world war. Ionising radiation also increases risk later in life, particularly when exposure is during rapid breast formation. Mammographic screening is associated with a net decrease in mortality from breast cancer among women aged over 50; the effect of such exposure on younger women remains unclear.

Relation between breast cancer mortality in various countries and fat consumption.

Lifestyle

Diet—Although there is a close correlation between the incidence of breast cancer and dietary fat intake in populations, the true relation between fat intake and breast cancer does not appear to be particularly strong or consistent.

Weight—Obesity is associated with a twofold increase in the risk of breast cancer in postmenopausal women whereas among premenopausal women it is associated with a reduced incidence.

Alcohol intake—Some studies have shown a link between alcohol consumption and incidence of breast cancer, but the relation is inconsistent and the association may be with other dietary factors rather than alcohol.

Smoking is of no importance in the aetiology of breast cancer.

Relative risk of breast cancer before menopause in relation to use of oral contraceptives before first term pregnancy

Length of use (months)	Relative risk (95% confidence interval)
0	1
1-24	1.04 (0.9 to 1.2)
25-48	1.21 (1.0 to 1.5)
49-96	1.34 (1.1 to 1.6)
>96	1.61 (1.2 to 2.2)

Oral contraceptive

There is no increase in risk in women who have used oral contraceptives in their late 20s for spacing pregnancies. However, use of oral contraceptives for four years or more by younger women before their first term pregnancy almost certainly increases the risk of premenopausal breast cancer. Whether such women also have an increased risk of postmenopausal breast cancer will not be known until exposed women achieve that age. Studies of nulliparous users of oral contraceptives indicate that there may be an effect on early stage carcinogenesis, which would not be evident for a considerable period. This was the situation for women exposed to diethylstilbestrol while pregnant during the 1940s and '50s, with the increased risk of breast cancer not becoming apparent until 20 to 40 years after exposure. Since use of oral contraceptives by young women was not common until the 1970s, data on any association with risk of breast cancer remain immature.

Hormone replacement therapy

Studies of unopposed oestrogen for hormone replacement therapy show that the risk of breast cancer is increased by up to 50% after 10 to 15 years' use. This effect is less than an equivalent natural delay in the menopause. Fewer data are available on the use of combined oestrogen and progestogen preparations, but the only large study published to date shows a greater risk for the combined treatment than for unopposed therapy. The benefits of hormone replacement therapy in reducing ischaemic heart disease and osteoporosis and improving menopausal symptoms suggest that for the first 10 years of use the overall effects of therapy on morbidity and mortality are likely to be beneficial.

Prevention of breast cancer

Cumulative incidence of contralateral breast cancer in randomised trial of adjuvant tamoxifen treatment.

Screening as it is currently practised can reduce mortality but not incidence, and then only in a particular age group, and advances in treatment have produced only modest survival benefits. A better appreciation of factors important in the aetiology of breast cancer would raise the possibility of disease prevention.

Hormonal control—One promising avenue for primary prevention is influencing the hormonal milieu of women at risk. During trials of tamoxifen as an adjuvant treatment for breast cancer, the number of contralateral breast cancers was less than expected, suggesting that this drug might have a role in preventing breast cancer. Studies comparing tamoxifen with placebo in women at high risk of breast cancer are currently under way, but results from such prevention trials will need to be interpreted cautiously. It is clear that tamoxifen will probably reduce the initial incidence of breast cancer, but only if there is a consequent reduction in mortality will we know that tamoxifen is effective in reducing the number of breast cancers developing rather than just delaying their presentation.

Dietary intervention—If specific dietary factors are found to be associated with an increased risk of breast cancer dietary intervention will be possible. However, reduction of dietary intake of such a factor in whole communities may well be difficult to achieve without major social and cultural changes.

Other preventive agents—Retinoids affect the growth and differentiation of epithelial cells, and experiments suggest that they may have a role in preventing breast cancer. A clinical trial of a retinoid is currently under way. Selenium is another possible cancer preventing agent.

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