

Breast cancer is the most common cancer affecting women worldwide. Prediction models stratify a woman's risk for developing cancer and can guide screening recommendations based on the presence of known and quantifiable hormonal, environmental, personal, or genetic risk factors. Mammography remains the mainstay breast cancer screening and detection but magnetic resonance imaging and ultrasound have become useful diagnostic adjuncts in select patient populations.

The management of breast cancer has seen much refinement with increased specialization and collaboration with multidisciplinary teams that include surgeons, oncologists, radiation oncologists, nurses, geneticist, reconstructive surgeons and patients. Evidence supports a less invasive surgical approach to the staging and management of the axilla in select patients. In the era of patient/tumor specific management, the advent of molecular and genomic profiling is a paradigm shift in the treatment of a biologically heterogenous disease.

Breast cancer is the most common cancer and also the leading cause of cancer mortality in women worldwide. Approximately 1.38 million new breast cancer cases were diagnosed in 2008 with almost half of all breast cancer cases and nearly 60% of deaths occurring in lower income countries. There is a large variation in breast cancer survival rates around the world, with an estimated 5-year survival of 80% in high income countries to below 40% for low income countries.

Low and middle income countries face resource and infrastructure constraints that challenge the goal of improving breast cancer outcomes by early detection, diagnosis and treatment. In high income countries like the United States, approximately 232,340 women will be diagnosed and 39,620 will die of breast cancer in 2013. For an American woman, the lifetime risk of developing breast cancer is 12.38% or 1 in 8. The significant decrease in breast cancer-related mortality in the United States from 1975 to 2000 is attributed to continued improvement in both screening mammography and treatment. According to the World Health Organization, improving breast cancer outcome and survival by early detection remains the cornerstone of breast cancer control.

**Age, reproductive factors, personal or family history of breast disease, genetic pre-disposition and environmental factors have been associated with an increased risk for the development of female breast cancer.**

### **Age**

The risk of developing breast cancer increases with age. By using the Surveillance, Epidemiology, and End Results (SEER) database, the probability of a woman in the United states developing breast cancer is a lifetime risk of 1 in 8; 1 in 202 from birth to age 39 years of age, 1 in 26 from 40-59 years, and 1 in 28 from 60-69 years.

### **Personal history**

A personal history of breast cancer is also a significant risk factor for the development of a second ipsilateral or contralateral breast cancer. In fact, the most common cancer amongst breast cancer survivors is a metachronous contralateral breast cancer. Factors associated with an increased risk of a second breast cancer include an initial diagnosis of DCIS, stage IIB, hormone receptor negative cancers, and young age.

### **Breast pathology**

Proliferative breast disease is associated with an increased risk of breast cancer. Proliferative breast lesions without atypia, including usual ductal hyperplasia, intraductal papillomas, sclerosing adenosis and fibroadenomas confer only a small increased risk of breast cancer development, approximately 1.5 – 2 times that of the general population. Atypical hyperplasia including both ductal and lobular, usually incidentally found on screening mammography, confers a substantial increased risk of breast cancer. Women with atypia have an approximately 4.3 times greater risk of developing cancer compared to the general population.

### **Family history**

A woman's risk of breast cancer is increased if she has a family history of the disease. In the Nurses' Health Study follow-up, women with a mother diagnosed before age 50 had an adjusted relative risk of 1.69 and women with a mother diagnosed at 50 or older had a relative risk of 1.37 compared to women without a family history of breast cancer. A history of a sister with breast cancer also demonstrated an increased relative risk of 1.66 if the diagnosis was made prior to age 50 and a relative risk of 1.52 if diagnosed after age 50 compared to patients without a family history. The highest risk is associated with increasing number of first degree relatives diagnosed with breast cancer at a young age (under age 50). Compared with women who had no affected relative, women who had one, two or three or more affected first degree relatives had risk ratios of 1.80, 2.93 and 3.90, respectively.

### **Genetic predisposition**

Approximately 20%-25% of breast cancer patients have a positive family history but only 5%-10% of breast cancer cases demonstrate an autosomal dominant inheritance. Genetic predisposition alleles have been described in terms of clinical significance. High-risk predisposition alleles conferring a 40%-85% lifetime risk of developing breast cancer include BRCA1 and BRCA2 mutations, mutations in TP53 gene resulting in Li-Fraumeni syndrome, PTEN resulting in Cowden syndrome, STK11 causing Peutz-Jegher's syndrome, Neurofibromatosis (NF1) and (CDH-1) E-Cadherin. Half of the breast cancer predisposition syndromes are associated with mutations in BRCA1 and BRCA2. Women with BRCA1 or BRCA2 deleterious mutations have a significantly higher risk of developing breast cancer. Lifetime breast cancer risk ranges from 65% to 81% for BRCA1 mutation carriers and 45% to 85% for BRCA2 carriers. Moderate risk genes including homozygous ataxia-telangiectasia (ATM) mutations, somatic mutations in tumor suppressor gene CHEK2, and BRCA1 and BRCA2 modifier genes BRIP1 and PALB2 confer a 20%-40% lifetime risk of breast cancer. Numerous low-risk common alleles have been identified largely through genome-wide association studies and the clinical application in the presence of these mutations is yet to be determined.

**The cycles of endogenous estrogen levels throughout a woman's lifetime have implications for the development of or the protection against breast cancer.**

### **Early menarche**

Early age at menarche is a risk factor among both pre- and postmenopausal women for developing breast cancer. Delay in menarche by two years is associated with corresponding risk reduction of 10%. Within the European Prospective Investigation into Cancer and Nutrition cohort, women who had early menarche ( $\leq 13$  years) demonstrated a nearly twofold increase in risk of hormone receptor positive tumors.

### **Parity and age at first full term pregnancy**

Nulliparous women are at an increased risk for the development of breast cancer compared to parous women. Young age at first birth has an overall protective effect, whereas relatively advanced age at first birth confers a relative risk of breast cancer greater than that of a nulliparous woman. Compared to nulliparous women the cumulative incidence of breast cancer in women experiencing their first birth at age 20, 25, and 35 years was 20% lower, 10% lower and 5% higher, respectively.

### **Breast feeding**

Evidence suggests that breast feeding has a protective effect against the development of breast cancer. Breast feeding may delay return of regular ovulatory cycles and decrease endogenous sex hormone levels. It has been estimated that there is a 4.3% reduction for every one-year of breast feeding.

### **Testosterone**

High endogenous sex hormone levels increase the risk of breast cancer in both premenopausal and postmenopausal women. High levels of circulating testosterone in postmenopausal women have been linked to increased risk of developing breast cancer

[relative risk (RR), 2.86-3.28].

### **Age at menopause**

Later onset of menopause has also been associated with increased breast cancer risk. Every year delay in the onset of menopause confers a 3% increase in risk and every five year delay in the onset of menopause confers a 17% increase in risk of breast cancer.

### **Exogenous Hormone Exposure**

Evidence suggests a relationship between the use of hormone replacement therapy (HRT) and breast cancer risk. Breast cancers related to HRT use are usually hormone receptor positive. When compared with patients who do not use HRT, breast cancer risk is higher in HRT users. An international meta-analysis examining the risk of breast cancer with HRT found that in women who did not use HRT, RR increased by a factor of 1.028 for each year older at menopause, comparable to the relative risk of 1.023 per year in women who use HRT or for those who ceased to use HRT up to four years previously.

In the Woman's Health Initiative randomized control trial, combined estrogen plus progestin in postmenopausal women with an intact uterus significantly increased the risk of breast cancer, delayed breast cancer detection and diagnosis, and significantly increased breast cancer mortality. The study was terminated early because of increased mortality in the combined estrogen plus progestin group. By contrast, the use of estrogen alone by postmenopausal women without a uterus did not interfere with breast cancer detection and statistically significantly decreased the risk of breast cancer. Data from the Nurses' Health Study, however, suggest that women who use unopposed postmenopausal estrogen increase their risk of breast cancer by 23% at age 70.

Timing and duration of HRT seem to be important factors associated with breast cancer risk as well. Breast cancer risk from exogenous hormone exposure is inversely associated with time from menopause. Women initiating hormone therapy closer to menopause have a higher breast cancer risk. Long term (> 5 years) combined HRT use has been associated with

the highest risk whereas short-term use of combined estrogen-progestin therapy does not appear to confer a significantly increased risk (RR = 1.023 per year).

Modifiable risk factors including the excessive use of alcohol, obesity and physical inactivity account for 21% of all breast cancer deaths worldwide.

### **Alcohol consumption**

Alcohol consumption has been associated with increased breast cancer risk that is statistically significant at levels as low as 5.0 to 9.9 g per day, equivalent to 3 to 6 drinks per week (RR = 1.15; 95%CI: 1.06-1.24; 333 cases/100000 person-years). Binge drinking, but not frequency of drinking, was associated with breast cancer risk after controlling for cumulative alcohol intake. Alcohol intake both earlier and later in adult life was independently associated with risk.

### **Physical activity**

Consistent physical activity has been shown to reduce the risk of breast cancer in a dose dependent manner, with modest activity conferring a 2% decrease in risk and vigorous activity a 5% decrease in risk.

### **Obesity**

Obesity, specifically in postmenopausal women, has also been shown to increase a woman's risk of breast cancer. In the EPIC multicenter prospective cohort study, postmenopausal women who did not use HRT had elevated breast cancer risk with increasing weight, body mass index (BMI) and hip circumference. In this cohort, multivariate relative risk was 1.28 for overweight women (BMI 25.0-29.9) and obese women (BMI > 30.0) compared to women in the normal weight range. Lean women on HRT are incongruously at an increased risk of breast cancer (RR = 2.04) compared to their overweight (1.93) and obese (1.39) counterparts.

Insulin resistance and hyperinsulinemia have been studied as a risk factor for the comorbidities associated with obesity including cardiovascular disease and diabetes. Insulin has anabolic effects on cellular metabolism and insulin receptor overexpression has been demonstrated in human cancer cells. Hyperinsulinemia has been shown to be an independent risk factor for breast cancer in non-diabetic postmenopausal women and may help to explain the relationship between obesity and breast cancer.

## **Radiation**

Radiation exposure from various sources including medical treatment and nuclear explosion increases the risk of breast cancer. Radiation to the chest wall for treatment of childhood cancer increases the risk of breast cancer linearly with chest radiation dose. Survivors of childhood cancers who received therapeutic radiation are at a dose dependent risk for the development of breast cancer, and those treated for Hodgkin's disease are at highest risk (RR = 7). Radiation effects on the development of female breast cancer have also been demonstrated in Japan post nuclear attack on Hiroshima and Nagasaki and positively correlate with age younger than 35 years at time of exposure. The incidence of breast cancer has also increased in areas of Belarus and Ukraine. A significant two fold increase was seen in the most contaminated areas around Chernobyl following the nuclear accident and manifest in women who were younger at the time of the exposure.

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