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RESEARCH ARTICLE

RISK FACTORS AND TREATMENT OF BREAST CANCER

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ABSTRACT

Breast cancer is the second commonest cancer worldwide in 2008 (1.4 million new cases: 11% of all global cancers and 360,000 deaths) and the commonest potentially fatal cancer of women (Stuckey 2011). Breast cancer incidence has been increasing worldwide for decades, and there is currently a greater than 4-fold variation in age-standardized incidence rates between countries with the lowest (East and Southern Africa) and highest (Western Europe, North America and Australia/New Zealand) incidence (Stuckey 2011). Less than 10% of breast cancers can be attributed to an inherited genetic mutation (Stuckey 2011). Breast cancer is more commonly associated with environmental, reproductive, and lifestyle factors, some of which are potentially modifiable. There are several ways to treat breast cancer, depending on its type and stage. Some treatments are local, meaning they treat the tumor without affecting the rest of the body (Maughan, Lutterbie, and Ham 2010). Types of local therapy used for breast cancer include Surgery and Radiation therapy. Systemic treatments: Drugs used to treat breast cancer are considered systemic therapies because they can reach cancer cells almost anywhere in the body. Breast cancer, is one of the most common cancers in the world and although its incidence is more in some developed countries, death is higher in countries with low level of development. Therefore, better plans for screening and early detection programs in these countries are suggested. Both modifiable and non-modifiable risk factors have been identified that increase a woman's risk of breast cancer. The incidence of breast cancer, both in the United States and worldwide, is increasing. However, with the advent of regular screening, more women are being diagnosed with early-stage disease.

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INTRODUCTION

Breast cancer is the second commonest cancer worldwide in 2008 (1.4 million new cases: 11% of all global cancers and 360,000 deaths) and the commonest potentially fatal cancer of women(Stuckey 2011).Breast cancer incidence has been increasing worldwide for decades, and there is currently a greater than 4-fold variation in age-standardized incidence rates between countries with the lowest (East and Southern Africa) and highest (Western Europe, North America and Australia/New Zealand) incidence (Stuckey 2011). It is potentially one of the most curable of cancers; however, 5-year relative survival rates currently cover a 7-fold range based on analysis of data from cancer registries worldwide: 13% in Gambia, 31%-54% in India, 40% and 55% in the Philippines, 46% in Uganda, 57%-66% in Thailand, 57%-81% in South Korea, 58% in Zimbabwe, 58%-90% in China, 70% in Cuba and Costa Rica, 77% in Turkey, 60%-80% in Europe and 92% in the USA (Kreiter *et al*. 2014).

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In 2015, cancer caused over 8.357 million deaths globally and was the second leading cause of death behind cardiovascular diseases(Fitzmaurice *et al*. 2017). Even though these impressive numbers are testimony that the "war on cancer" has not been won, recent developments in personalized medicine and novel treatment approaches like immunotherapy have raised hope of significantly improving cancer survival(Fitzmaurice *et al*. 2017). Survival rates between and within high-income countries differ for reasons such as variation in education, access to specialized care, effective treatment, and insurance status(Kreiter *et al*. 2014). The full potential of cancer prevention for reducing incidence and mortality is far from being realized, and efforts are especially lagging in low-income countries.

Epidemiology of Women Breast Cancerin United States: Breast cancer incidence and death rates increase with age; about 95 % of new cases occur in women 40 years of age and older (Ban and Godellas 2014). Breast cancer incidence rates in the United States continue to rise after menopause and are highest in the older age categories. Age-standardized incidence rates are higher among white women than black women,

although black women in the United States have a higher mortality rate than white women. Incidence rates for Asian/Pacific Islander, American Indian/Alaska Native, and Hispanic women in the United States are generally lower than those for white or black women(Stuckey 2011). The incidence of breast cancer in the United States increased until about 2000 then decreased from 2002 to 2003(Coughlin and Ekwueme 2009). A woman's lifetime risk of breast cancer, regardless of race, has increased steadily from the 1930s through the end of the 20th century(Ban and Godellas 2014). According to the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute, female breast cancer represents 14% of all new cancer cases in the United States. According to the 2008 to 2012 data, the number of new cases of female breast cancer was 124.8 per 100,000 women per year(Ban and Godellas 2014). Between the years 2010 to 2012, the lifetime probability of developing female breast cancer was 12.3%, or approximately 1 in 8. The American Cancer Society estimates that 249,260 cases of breast cancer in both sexes will be diagnosed in the year 2016(Ban and Godellas 2014).

Age-Related Incidence in United States: Female breast cancer is most frequently diagnosed in women aged 55 to 64 (Fig. 1), and the median age at diagnosis is 61 years (Stuckey 2011). Fewer than 5% of breast cancers occur in women under the age of 40, and as with most malignancies, the risk increases with age. However, the rate at which it increases decreases after menopause(Stuckey 2011).

Breast Cancer Survival in United States: In the United States, survival from breast cancer has increased steadily over the second half of the 20th century as the proportion of non-metastatic diagnoses has increased(Howell *et al*. 2014). Ten-year survival rates among all women in the United States were 61% for women diagnosed in 1973, and 83% for those diagnosed in 1992. More recently, in 2015, 40,290 deaths were estimated to be due to female breast cancer (SEER) and between 2010 and 2012; the probability of dying from female breast cancer was estimated to be 2.7%(Stuckey 2011). Among those diagnosed between 2005 and 2011, the 5-year relative survival was found to be 89%. This is thought to be due to both the increase in utilization of population-wide screening and advances in treatment(Stuckey 2011).

Breast Cancer Incidence and Mortality: Between 1988 and 1992, the overall incidence of breast cancer in the United States was highest among white women, followed by African Americans, Asians, Hispanics, and American Indian women. This trend persists across all age groups except before age 40, where African American women have the highest incidence rate (Tao *et al*. 2015). In both whites and African Americans, breast cancer mortality increases with age, with the rate of increase decreasing after menopause. Interestingly, African Americans have higher age-specific mortality until approximately age 57, when mortality for whites surpasses that of African Americans (Ban and Godellas 2014). African American women are significantly less likely to be diagnosed with stage I disease when compared with non-Hispanic white women (37.0% vs. 50.8%). This group was also found to have a higher probability of presenting with nodal metastases with a small-sized (r2.0 cm) breast cancer compared with non-Hispanic white women (24.1% vs. 18.4%), suggesting that African Americans may be predisposed to more aggressive tumors (Ban and Godellas 2014). African Americans have a high risk of breast cancer recurrence, and this trend persists when controlling for both age and tumor size (Ban and Godellas 2014). Not surprisingly, a multivariate analysis found that the 7-year actuarial risk of death from stage I cancer was highest for black women (6.2%) when compared with white women (3.0%). The difference in mortality has been noted to be increasing. These trends are thought to be due in part to health care quality and access disparities(Stuckey 2011). However, different responses to treatment and adherence to treatment, as well as alterations in risk factors such as nutrition, obesity, and reproductive practices may also play a role.

Risk Factors of Breast Cancer: Less than 10% of breast cancers can be attributed to an inherited genetic mutation(Stuckey 2011). Breast cancer is more commonly associated with environmental, reproductive, and lifestyle factors, some of which are potentially modifiable.

Hormonally Mediated Risk Factors of Breast Cancer: Estrogen's carcinogenic effects have been proposed as 2 pathways. The first involves active signaling through the estrogen receptor (ER) that alters gene expression, increasing proliferation and therefore the likelihood of mutations (Kamińska *et al*. 2015). The second pathway involves the oxidative metabolism of estrogen into quinone metabolites. These quinone metabolites can then form depurinating DNA adducts or alternatively be oxidized and reduced into catechols to create reactive oxygen species, causing oxidative damage to DNA (Stuckey 2011). Prolonging exposure to estrogen in a woman's life would therefore theoretically increase her risk of developing breast cancer.

Parity: A pooled analysis of 20 studies by ClavelChapelon and colleagues estimated that each term pregnancy led to a 3% decrease in risk of premenopausal breast cancer(Kamińska *et al*. 2015). This protective effect was noted to be even stronger in postmenopausal breast cancers, with a 12% decrease in risk with each term pregnancy. From the numerous studies of reproductive risk factors and breast cancer, the historical teaching is that an early first birth and increasing number of full-term births are associated with a long-term reduction in risk. However, this long-term protective effect is thought to be preceded by a short-term adverse effect during the first 0 to 5 years after delivery(Stuckey 2011). The proposed biological mechanism linking parity and this transient risk increase includes hormonal stimulation and pro-inflammatory stimuli during wound healing(Stuckey 2011).

Pregnancy-related Breast Cancer: Breast cancer is the most common cancer in pregnant and postpartum women. About 1:3000 pregnancy-related cases of breast cancer are diagnosed per year (Stuckey 2011). For some women, particularly in those of lower socioeconomic status, pregnancy is a period of time when a significant proportion of lifetime health care and associated screening is obtained. This increase in the receipt of health care likely leads to a relative increase in pregnancy related breast cancer incidence. However, with the inherent difficulty of interpreting abnormal breast exam and radiographic changes in pregnant and breastfeeding women, there are likely breast cancers that go undiagnosed during this period, as well (Stuckey 2011). It has been widely accepted that the increased risk of breast cancer following pregnancy is thought to be due to the ability of pregnancy-related hormonal fluctuations to promote the proliferation of small cancers (Kamińska *et al*. 2015).

Number of Live Births: In a 2006 meta-analysis of results from epidemiological studies investigating parity in relation to hormone receptor– positive (ER+ /PR+) and hormone receptor–negative (ER – /PR –) cancer risk, each birth was found to reduce the risk of hormone receptor–positive cancer by 11%(Stuckey 2011). However, parity was not found to be associated with hormone receptor– negative cancer. From a cohort of 2897 women with breast cancer in the Nurses' Health Study, there was a trend for those with a parity of at least 3 children to be inversely associated with the risk for luminal A breast cancer when compared to nulliparous women, but this association was not observed in the other subtypes (Washbrook 2006).Similarly, in a population-based case-control study of women with breast cancer age 20 to 44, increasing number of live births was associated with decreased breast cancer risk in all 3 tumor types, but this was only statistically significant in ER-positive breast cancer.

Breastfeeding: Breastfeeding has traditionally been thought to be associated with an overall decrease in risk of breast cancer, given the hypoestrogenic state it confers. In one study in 2002, for each additional 12 months of breastfeeding, the risk of premenopausal breast cancer was reduced by 4% (Stuckey 2011). More recent studies have sought to clarify this association with respect to breast cancer subtype. Several other studies have found a statistically significant reduction in the risk of triple-negative breast cancer, but have failed to demonstrate a persistent association with ER positive breast cancer (Stuckey 2011). Similarly, in a more recent population-based case-controlled study, breastfeeding was not associated with a reduction in risk of either ER-positive or Her2- over expressing breast cancer, but was associated with a reduced risk of triple-negative disease. Adding to the potential validity of this newer research is that these studies were performed in different regions of the United States and have included different age ranges (Washbrook 2006).

Menopause: In the United States, the average age of menopause is 51. Women who undergo menopause earlier are at a relatively lower risk of breast cancer than women who undergo menopause at a later time (Kamińska 2015). One study found a relative risk of 2 for menopause after the age of 55, when compared with menopause before 45 years of age. A worldwide collaboration analysis of data from 117 epidemiological studies from 35 countries including 118,964 women with breast cancer, none of whom had used postmenopausal HRT, demonstrated a consistent finding of a greater risk of breast cancer among premenopausal women when compared with postmenopausal women of the same age(Stuckey 2011). In analyses of postmenopausal women in this same pooled analysis, the relative risk of breast cancer increased by a factor of 1.029 for every delayed year of menopause. Adjustment by ethnicity, age of menarche, family history of breast cancer, and hormonal contraceptive use altered the excess relative risk estimate by <1%(Kamińska 2015).

Smoking: In the past, conclusive evidence linking smoking to breast cancer has been difficult to demonstrate. Indeed, the 2004 Surgeon General's report on cigarette smoking concluded that there was no consistent evidence for an association between cigarette smoking and breast cancer (Stuckey 2011). However, more recent evidence has emerged that suggests that cigarette smoking and exposure to secondhand smoke may in fact increase risk for breast cancer and worsen survival outcomes (Stuckey 2011). On the basis of 22 cohort reports published before 2012 and 27 case control reports published from 2000 to 2011, the Surgeon General's 2014 report concludes that ever-smoking is associated with a significant increase in RR of about 10%. This effect seems to be stronger for current smokers than for former smokers, and seems to have a dose-response relationship with an increase in that risk with 20 pack-years. Smoking has also been found to affect breast cancer mortality. Patients who smoke have been shown to undergo less mammographic screening, which may contribute to a higher stage disease at diagnosis. In addition, significant data have shown that continuing to smoke after diagnosis worsens prognosis(Washbrook 2006).

Breast Density: Mammographic density is associated with an increased risk of breast cancer, both at screening and at certain intervals after a negative screening mammogram (Washbrook 2006). Breast cancers originating in areas of mammographically dense tissue are more commonly associated with high-grade histology, lymphovascular invasion, and advanced stage when compared with those arising within more radiolucent tissue(Stuckey 2011). Despite suggesting a poorer prognosis, two large retrospective studies failed to demonstrate a significant association between mammographic density and breast cancer–specific survival(Stuckey 2011).

Prevention of Breast Cancer

Lifestyle Modification: Dietary and physical activity interventions have not consistently been shown to modify breast cancer risk(Howell *et al*. 2014). Recent epidemiological data are shifting attention away from fat consumption and placing it more on the metabolic consequences of obesity, which might be best managed by liberalizing fat to reduce carbohydrate consumption. Alcohol consumption increases breast cancer risk in a dose-dependent manner with a 10% relative increase in risk per drink per day. However, limited alcohol consumption may have some health benefits(Howell *et al*. 2014).

Chemoprevention: Chemoprevention describes pharmacologic interventions to reverse, suppress, or inhibit carcinogenic progression to invasive cancer. Numerous randomized clinical trials have evaluated selective ER modifiers (SERMs) and aromatase inhibitors (AIs) in the primary prevention setting(Narod 2015). Tamoxifen reduces breast cancer risk by 20–43%, but has not yet been shown to impact breast cancerspecific or overall survival. Tamoxifen reduces the risk for ER-positive breast cancer by 62%, but does not affect the risk for ER-negative breast cancer. Tamoxifen increases the risk for endometrial cancer, stroke, venous thromboembolism, and cataracts, but not ischemic heart disease (Narod 2015). These risks are higher for older women.

Prophylactic Surgery

Bilateral Salpingoophorectomy: Among BRCA gene mutation carriers, bilateral salpingoophorectomy (BSO) reduces breast cancer risk by 37–72% with greater effects in women predisposed to develop ER-positive breast cancer(Narod 2015). Bilateral salpingoophorectomy has also been associated with reduced breast cancer-specific and all-cause mortality, especially in BRCA1 mutation carriers.

Bilateral Prophylactic Mastectomy: Bilateral prophylactic mastectomy is reserved for the highest risk women, where the benefits are anticipated to outweigh the risks(Howell *et al*. 2014). The most common complications of prophylactic mastectomy are bleeding, infection, and skin flap necrosis. 8–64% of women will experience one or more complications and 52–71% will require reoperation. Prophylactic mastectomy also has a significant impact on body image and psychosocial function(Narod 2015).Mastectomy does not completely eliminate breast cancer risk because, short of removing all of the chest wall skin, it is impossible to eradicate all terminal duct-lobular units (TDLU) in many women(Stuckey 2011).

Treatment of Breast Cancer: There are several ways to treat breast cancer, depending on its type and stage. Some treatments arelocal, meaning they treat the tumor without affecting the rest of the body (Maughan, Lutterbie, and Ham 2010). Types of local therapy used for breast cancer include Surgery and Radiation therapy. Systemic treatments: Drugs used to treat breast cancer are considered systemic therapies because they can reach cancer cells almost anywhere in the body. They can be given by mouth or put directly into the bloodstream. Depending on the type of breast cancer, different types of drug treatment might be used, including Chemotherapy, Hormone therapy and Targeted therapy. Many women get more than one type of treatment for their cancer(Maughan, Lutterbie, and Ham 2010).

Conclusion

Breast cancer, is one of the most common cancers in the world and although its incidence is more in some developed countries, death is higher in countries with low level of development. Therefore, better plans for screening and early detection programs in these countries are suggested. Both modifiable and non-modifiable risk factors have been identified that increase a woman's risk of breast cancer. The incidence of breast cancer, both in the United States and worldwide, is increasing. However, with the advent of regular screening, more women are being diagnosed with early-stage disease.

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