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Breast Cancer Incidence, Mortality and Its Risk Factors among Women Worldwide, 2015

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Abstract
Breast cancer is the top cancer in women both in the developed and the developing world. And is increasing, particularly in developing countries where the majority of cases are diagnosed in late stages as well as by the lack of adequate diagnostic and treatment facilities.
The incidence of breast cancer is increasing in the developing world due to increase life expectancy, increase urbanization and adoption of western lifestyles. Several risk factors for breast cancer have been well documented. However, for the majority of women presenting with breast cancer, it is not possible to identify specific risk factors. Although some risk reduction might be achieved by preventing, these strategies cannot eliminate the majority of breast cancers that develop in low- and middle-income countries where breast cancer is diagnosed in very late stages. This paper reviews the current patterns of breast cancer in worldwide and examines breast cancer risk factors with the intention that knowing they could eventually have an impact in reducing the incidence of breast cancer in the long term.
Keywords: Breast Cancer; Incidence; Mortality; Risk Factors

1. Introduction

The most commonly diagnosed cancers worldwide were those of the lungs (1.8 million, 13.0% of the total), breast (1.7 million, 11.9%), and colo-rectum (1.4 million, 9.7%). The most common causes of cancer death were cancers of the lung (1.6 million, 19.4% of the total), liver (0.8 million, 9.1%), and stomach (0.7 million, 8.8%). Breast cancer in women is a major public health problem throughout the world.

It is the most common cancer among women both in developed and developing countries. One in ten of all new cancers diagnosed worldwide each year is a cancer of the female breast. It is also the principal cause of death from cancer among women globally. More than 1.1 million cases are diagnosed and more than 410,000 patients die of it worldwide.[1] In 2012, 1.7 million women were diagnosed with breast cancer and there were 6.3 million women alive who had been diagnosed with breast cancer in the previous five years. Since the 2008 estimates, breast cancer incidence has increased by more than 20%, while mortality has increased by 14%. Breast cancer is also the most common cause of cancer death among women (522 000 deaths in 2012) and the most frequently diagnosed cancer among women in 140 of 184 countries worldwide. It now represents one in four of all cancers in women**.** [2]

It is the second most common cancer now, after lung cancer, when ranked by cancer occurrence in both sexes. About 55% of the global burden is currently experiencing in developed countries, but incidence rates are rapidly rising in developing countries.

2. Geographical burden and variations worldwide

Breast cancer is the most common cancer among women with an estimated 1.15 million incident cases diagnosed in 2002, comprising of one fifth of the estimated 5.0 million cancer cases diagnosed each year in the world; it accounted for 410,000 deaths and 4.4 million 5-year prevalent cases (World 1,060,200, More developed 629,100 and Less developed 431,100). More developed countries accounted for 641, 600 cases and 190,900 deaths while less developed countries accounted for 509,700 cases and 219,600 deaths. The projections of breast cancer cases for the year 2030 for different regions of the world are shown that there will be 2.7 million new cases in the world in 2030, with more than 60% of the cases (1.72 million) occurring in the less developed regions of the world via assuming current trends in incidence rates hold constant.

This projection conservatively assumes that current rates will remain constant, which, given the recent rise in breast cancer incidence rates across many developing countries is unlikely to be the case**.**[3] Thus, in the future the worldwide burden of breast cancer, particularly in less developed countries, is likely to continue to grow.

Breast cancer incidence and mortality vary considerably by world region. The estimated age-standardized rates varied from 18.7 per 100,000 women in China to 99.4 per 100,000 women in North America. In general, the incidence is high (greater than 80 per 100,000) in developed regions of the world and low (less than 30 per 100,000) in developing regions; the range of mortality rates is much less (approximately 6–23 per 100,000) because of the more favourable survival of breast cancer in (high-incidence) developed regions**.**[1]

In general, the high rates of breast cancer in developed countries are the consequence of a higher prevalence of the known risk factors for the disease, many of which – early age at menarche, nulli parity, late age

at first birth, late age at any birth, low parity, exposure to exogenous hormones (e.g., oral contraceptives and menopausal hormone therapy), obesity, and late menopause – relate to the hormonal (largely estrogen) milieu to which the breast is exposed from menarche to the cessation of ovulation at menopause. While incidence rates are less than 40 per 100,000 women in most less developed countries, breast cancer is still the most common cancer among women in the majority of less developed countries. This is partly because a shift in lifestyles is causing an increase in incidence, and partly because clinical advances to combat the disease are not reaching women living in these regions.[4]

Incidence rates are intermediate (30–60 per 100,000) in several Asian populations such as Hong Kong, Singapore, and the Philippines as they are in Puerto Rico and Brazil, and most eastern European populations.[4] Comparatively lower rates (10–30 per 100,000) are seen in several Chinese populations, in eastern African populations in Zimbabwe and Uganda, Algeria in North Africa, several Southeast Asian countries (Thailand and Vietnam), and several registries in India.

3. Age-specific variations in incidence of breast cancer

A distinct age-specific incidence pattern is observed for breast cancer. It is characterized by a rapid increase in incidence rate before menopause (up to age 50 years) and the rate of increase in incidence rates is much lower thereafter. This pattern may be due to the diminishing levels of circulating estrogens after menopause.[5] Interestingly, in low-incidence developing countries, the age-specific incidence slope of the curve after the menopause may be flat, indicating no increase in incidence rates following menopause or may be even negative, implying lower rates after menopause. This is a consequence of increasing risks of occurrence in consecutive generations of women rather than a real decline in risk with age.[6] The comparatively younger age structure of populations and a flat age–incidence curve after menopause result in lower mean age at diagnosis of breast cancer cases in developing countries than that observed in European and American populations.

4. Trends in incidence and mortality of breast cancer

The trends in breast cancer incidence and mortality over time are complex. Over the past several decades the incidence of breast cancer has increased almost everywhere. In general terms, the largest increases in incidence have been seen in populations with historically low-incidence rates, often in developing countries, whereas relatively recent departures from the long-term trend of increasing rates have only recently been observed in several, mainly Western countries.

The changing patterns of breast cancer screening, childbearing and breastfeeding, exogenous hormonal intake, and lifestyle factors, including obesity and reduced physical activity have certainly contributed to trends in incidence. On the other hand, mortality is now decreasing in many high-risk countries due to a combination of the introduction of mammography screening, and improved awareness and intensified early clinical diagnosis resulting in the diagnosis of more small, early stage tumors; and advances in both primary and adjuvant treatments for breast cancer.

5. Explanations for reductions in breast cancer mortality rates in developed countries

Mammography screening for women aged 50–69 years is effective in reducing breast cancer mortality and the declining trend in mortality in developed countries could be partly attributed to increased mammography screening. One of the indirect beneficial effects of screening might have been a shift toward earlier diagnosis of breast cancer and better organization of breast cancer management, as a result of the publicity surrounding the disease and its prevention.[7]

Reductions in mortality before the introduction of screening, and in those countries without screening activity, indicate that several improvements in disease management, including the establishment of treatment protocols, adjuvant treatment policies, improved chemotherapy and hormonal treatment options, and better therapeutic guidelines, could have accounted for part of the observed declines in mortality. Mathematical modeling of data from the USA suggests that both screening and adjuvant therapy were near equal contributors to the significant decline in breast cancer mortality observed between 1975 and 2000.[8]

6. Trends in developing countries

Most developing countries from where incidence data are available have low to moderate rates of breast cancer occurrence compared to developed countries.[9, 10]

In Africa, breast cancer ranks as the second most frequent cancer after cervical cancer .[11, 12] Breast cancer was the most diagnosed cancer and the leading cause of cancer death among women in 2008 in Africa (92,600 cases, 50,000 Deaths) However, it is the most common malignancy in North Africa and in urban settings within the sub-Saharan region.[13] In the few data sets available for the study of time trends in Africa, increases in incidence are apparent

Southern African women have the highest breast cancer incidence rates of all African regions, in part

because of a higher prevalence of reproductive risk factors for breast cancer, including early menarche and late childbearing among the more affluent predominantly white population.[14]

7. Risk factors of breast cancer

Patterns in breast cancer incidence have been extensively studied to identify a number of reproductive, menstrual, lifestyle, and genetic risk factors.[15] This epidemiologic evidence indicates that estrogen exposure plays a primary role in breast cancer etiology.[16]

7.1. Menstrual and Reproductive Factors

In general, menstrual and reproductive risk factors are thought to influence breast cancer risk through their effects on the duration of exposure to high estrogen levels and their effects on breast tissue differentiation.

7.1.1. Age at Menarche

In contrast to invasive breast cancer, most studies have reported null associations between age at menarche and risk of (breast carcinoma in suite) BCIS. Studies examining BCIS risk concurrently with invasive breast cancer risk have found that women with earlier age at menarche had increased risk of invasive breast cancer but not BCIS. [17-19]

7.1.2. Age at Menopause

Few studies have examined BCIS risk in relation to age at menopause. Three of four studies to do so have reported a positive association, with odds ratio ranging between 1.3 and 2.9 for women at least 55 years old at menopause compared to women less than 45 years old at menopause. [19- 22]

7.1.3. Age at First Birth

Age at first birth is consistently observed to be related to BCIS risk, with odds ratios around 1.5–2.0 for women at least 30 years old at first birth compared to women less than 20 years old at first birth.[21- 23]

7.1.4. Parity

A10–20% reduction in BCIS risk per pregnancy is generally reported, such that women with four or more pregnancies are typically half as likely to develop BCIS as nulliparous women.[18-23] Each study that has evaluated both BCIS and invasive breast cancer in relation to parity has reported that the relation appears to be stronger with BCIS.[18-20, 24, 25]

7.1.5. Lactation

Despite much attention, the relation between lactation and invasive breast cancer is unclear. Overall, the evidence suggests that long-term breastfeeding appears to provide a protective effect against invasive breast cancer among premenopausal women.[26] Very few studies have examined BCIS risk in relation to lactation. BCIS risk and duration of breastfeeding reported that there is no relation.[19] Women who had breastfed for at least 24 months were at a reduced risk of BCIS compared to parous women who never breastfed.[20] In contrast, it found that duration of breastfeeding was positively associated with BCIS risk: women who breastfed for at least 24 months were twice as likely to develop BCIS as those who never breastfed (95% CI: 1.1–3.6).[27] Further research will be required to determine if lactation plays a role in BCIS initiation or the progression of BCIS to invasive breast cancer.

7.2. Lifestyle Factors

7.2.1. Body Size

The relation between body weight and invasive breast cancer risk varies Wwith menopausal status. Body mass index (BMI) is inversely associated with risk among premenopausal women and positively associated with risk among postmenopausal women.[28] Obese premenopausal women are more likely to have irregular menstrual cycles and ovulatory infertility,[29] whereas after menopause, adipose tissue becomes the primary source of estrogen synthesis.[30]

With some exceptions, most studies have reported significant inverse associations between BMI and BCIS risk in premenopausal women,[17,25] with risk reduced by approximately 50% in the highest compared to lowest BMI categories.[18, 20, 24, 27, 31]

It has been suggested that the inverse association between BMI and BCIS risk in premenopausal women may be attributable at least in part to a difficulty in detecting in situ lesions in younger women with high BMI.[20]

The relation between BMI and BCIS risk in postmenopausal women is less clear. Four of six studies have reported a null association between BMI and BCIS.[17, 19, 24, 25] whereas one found a positive association.[20] and other found an inverse association.[27] Only one study has examined postmenopausal BCIS risk in relation to weight gain. One study found that women who gained more than 50 pounds since age 18 were 50% more likely to develop BCIS than women with 0–15 pounds of weight gain. [22]

7.2.2. Physical Activity

Physical activity is now recognized as a protective factor which decreases invasive breast cancer risk through a variety of potential mechanisms.[7] Though data are limited, three studies have observed a similar inverse relation

with BCIS risk, with up to a 40% reduction in risk for women in the highest categories of activity.[19,32,33] In contrast, one population-based case control study found no association between physical activity and BCIS risk, despite finding an inverse relation with invasive breast cancer risk .[34]

7.2.3. Alcohol

Alcohol consumption is an established risk factor for invasive breast cancer.[35] Studies examining alcohol consumption in relation to BCIS risk have reported conflicting results. The majority of studies have reported a null relation, yet three found risk increases of 25–55% for more than 15 grams of alcohol intake per week compared to abstainers.[19, 36, 37]

7.2.4. Smoking

Breast cancer has not consistently been found to be associated with smoking, although risk may vary across different subgroups.[35] This may be due to a balance between the carcinogenic and antiestrogenic properties of cigarette smoke Carcinogens in cigarette smoke may initiate tumors while the antiestrogenic components may prevent progression to an invasive stage. Alternatively, the antiestrogenic effects of smoking could prevent the promotion of benign breast disease to in situ cancer. The evidence examining the relation of smoking to BCIS risk is sparse. Two studies have reported a null association whereas a recent study found a weak inverse association between smoking and BCIS risk (OR=0.8 for current vs. never smokers).[21, 38, 22]

7.3. Postmenopausal Hormones

Observational studies and clinical trials have demonstrated an increased risk of breast cancer in women who have used postmenopausal hormones.[39, 40]

Risk appears to be most increased among current users and women using combined estrogen and progesterone rather than estrogen-only regimens.[39, 41] Notably, the Women's Health Initiative reported no increase in BCIS risk with either combined or estrogen-only regimens, although there was likely insufficient power to detect a weak association.[40,41] In contrast, the majority of observational studies have found that ever use of postmenopausal hormones is associated with increased BCIS risk, with odds ratios ranging from 1.2 to 2.4. [20-22, 42-45]

7.3.1. Oral Contraceptives

A pooled analysis of 54 studies suggested a small increase in overall breast cancer risk associated with oral contraceptive use, with the relative risk declining from 1.24 in current users to 1.01 in women who discontinued use over 10 years ago.[46]

Relatively few studies have examined oral contraceptives in relation to BCIS risk specifically, with nearly all of them finding no association.[19, 21, 47-49] Only one study observed a weak positive association, with ever users having an 11% increase in risk compared to never users.[50] The two studies which examined both BCIS and invasive breast cancer risk in relation to oral contraceptive use found no relation to BCIS but a modest positive association with invasive breast cancer.[19, 47]

7.4. Diet

A variety of dietary components, notably dietary fat, fruits and vegetables, vitamin C, and beta-carotene have been investigated in relation to breast cancer, with generally inconclusive findings.[51, 52] Additionally, study done in USA have reported that women in the highest quartile of ''sweets'' intake were at a 53% increased risk of developing BCIS.[53]

7.5. Genetics, Personal, and Family History of Breast Disease Factors

7.5.1. BRCA1/2

Women with mutations in either BRCA1 or BRCA2 have a lifetime breast cancer risk of about 80%, as well as an increased ovarian cancer risk.[54] The role of BCIS in the inherited breast/ovarian cancer syndrome associated with these mutations remains unclear. An early study found that among 36 families carrying BRCA1 mutations, 202 invasive breast cancers but only 4 cases of BCIS were diagnosed.[55]

Additionally, two recent studies found that while proliferative fibrocystic changes were more common in high risk women with BRCA mutations, no differences in BCIS were observed.[56, 57] These findings have led some researchers to suggest that tumorigenesis in BRCA1/2 mutation carriers may be accelerated compared to that in non-carriers, such that tumors pass quickly through pre-invasive stages.

7.5.2. Genetic Polymorphisms

Few studies have examined single nucleotide polymorphisms (SNPs) in relation to BCIS risk separately from invasive breast cancer. Study reported a 41% reduction in BCIS risk with single nucleotide polymorphisms, but no difference in invasive breast cancer risk, for women with a VEGF (vascular endothelial growth factor) polymorphism that is thought to be associated with increased VEGF expression.[58]

7.5.3. Benign Breast Disease

Benign breast disease is generally classified into three primary categories: non proliferative breast disease, proliferative breast disease without atypia, and proliferative breast disease with atypia.[59] Risk of invasive breast

cancer increases with these successive categories of disease.

Studies examining BCIS risk in relation to benign breast disease have used previous breast biopsy or cyst aspiration as an indicator of benign disease. Risk of BCIS is approximately twice as high in women with a history of benign breast disease as in those without.[18, 20, 22]

7.5.4. Family History

Similar to invasive breast cancer, women with at least one first degree relative with breast cancer are approximately twice as likely to develop BCIS as those with no family history.[22, 27, 48] This relation appears to be slightly stronger in premenopausal than postmenopausal women.[20, 24, 25]

7.6. Biomarkers of Risk

7.6.1. Mammographic Breast Density

Mammographic breast density is emerging as one of the strongest risk factors for invasive breast cancer.[60]

An early study by Boyd et al. (1992) indicated that women with greater than 75% breast density had a 9.7-fold increase in risk of developing BCIS or atypical hyperplasia compared to those with no areas of density. Subsequent studies have found less extreme increases in risk, generally reporting odds ratios of 1.5–5.0 for the highest density categories compared to the lowest.[25, 49, 61] In the two studies that examined density in relation to BCIS and invasive breast cancer risk concurrently, a 10–25% stronger association was observed for BCIS.[25, 49]

7.7. Environmental Pollution

Few studies have evaluated BCIS risk in relation to environmental pollutants. The Long Island Breast Cancer Study Project has reported no relation between

BCIS risk and blood levels of bis (4-chlorophenyl)-1, 1-dichloroethane (DDE), polychlorinated biphenyls (PCBs), or chlordane.[62] However, a borderline significant association with polycyclic aromatic hydrocarbons (PAH) was observed, with a 50% increase in BCIS risk among women with detectable blood levels of PAH–DNA adducts.[63] This relation was similar to that reported for invasive breast cancer.

Overall, few significant differences in direction or magnitude of effect have been established in risk factors for BCIS as compared with invasive breast cancer.

Possible exceptions include age at menarche, for which most studies have reported null associations with BCIS, and parity and breast density, which appear to be more strongly related to BCIS than invasive breast cancer.

Given the moderate effect sizes associated with most breast cancer risk factors, increased precision in BCIS studies will be necessary to distinguish subtle differences from invasive breast cancer.

There is some suggestion that the association between BCIS risk and parity, alcohol, diet, and BRCA mutations may be limited to or stronger for DCIS compared to LCIS. In contrast, benign breast disease may be more strongly related to LCIS. Unfortunately, there have been too few studies to fully establish these differences by BCIS histology

8. CONCLUSION

Due to changing exposures to reproductive and lifestyle characteristics over time, women are at increasingly high risk of breast cancer, with incidence rates increasing in most countries in the past few decades, making cancer of the breast in women a major health problem worldwide. The most rapid increase in burden is observed in developing countries, where breast cancer risk has historically been low relative to western countries.

This increase is widely attributed to the ‘‘westernization’’ of lifestyles, an ill defined surrogate for changes in factors such as childbearing, anthropometric attributes, and lifestyle characteristics. With respect to mortality, the introductions of screening and substantial improvements in treatment have led to recent dramatic reductions in breast cancer mortality rates in developed countries.

However, in order to effectively curb the emerging epidemic of breast cancer in developing countries where survival rates are currently much poorer than those in developed countries, strategies to deliver screening and treatment strategies in a cost effective and culturally appropriate manner will be needed.

An urgent need in breast cancer control today is to develop effective and affordable approaches to the early detection, diagnosis, and treatment of breast cancer among women living in less developed countries. It is critical to bring morbidity and mortality in line with progress made in recent years in more developed parts of the world.

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