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EPIDEMIOLOGICAL RISK FACTORS FOR BREAST CANCER – A REVIEW

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ABSTRACT

The rising global incidence, morbidity and mortality from breast cancer has led to intensified efforts in the search for etiological factors of the disease. While international variations in the incidence of the disease may implicate a role for environmental factors, available evidence indicates that lifetime estrogen exposure may be a critical factor in breast carcinogenesis. While increasing age and the female sex are well-recognized risk factors, reproductive characteristics such as age at menarche and menopause, menstrual irregularity, age at first and last childbirth, parity and breastfeeding have also been linked to breast carcinogenesis. Early menarche and late menopause are associated with increased lifetime exposure to estrogens. In addition, a long period from Tanner stage breast-2 to onset of ovulatory cycles and a long period of luteal inadequacy and anovulatory cycles characteristic of the perimenopausal years creates long estrogen windows favorable for tumor induction. The intense differentiation of the terminal duct lobular unit associated with each full term pregnancy and release of various hormones, autocrine and paracrine growth factors during lactation may explain the protective effects of early age at first full term pregnancy, parity and lactation of breast cancer risk. A protective role for xenoestrogens has been postulated and evidence is emerging in support of an increased breast cancer risk with abortion and prolonged use of postmenopausal hormone replacement therapy. Appreciating relevant risk factors for breast cancer in the population is central to any preventive and control program aimed at reducing the burden of the disease through the design and implementation of culturally sensitive interventions.

Key Words: Breast cancer, risk factors, estrogens, parity.

INTRODUCTION

Breast cancer is currently the most common malignancy in Nigerian women and the incidence seems to be on the increase[1]. The actual cause of breast cancer is unknown but epidemiological studies have implicated some etiological factors. These factors include age, sex, heredity, reproductive risk factors, diet and previous breast disease. Most of the studies on the role of these risk factors in breast cancer susceptibility were conducted in Caucasian populations. While these factors may be at play in our population, daily observations by clinicians in our environment seem to indicate that the epidemiological characteristics of the disease in our patients differ from that in Caucasian populations. For example, most patients with breast cancer in our environment are multiparous and they practice prolonged lactation; factors that are thought to be protective against breast cancer.

Although several investigators have examined the clinico-pathological characteristics of the disease in Nigeria[2-5], there are few studies on the risk factors for breast cancer in African populations south of the Sahara[2,6]. We are currently investigating the role of these factors in 250 cases of breast cancer and 250 controls recruited from hospitals in Midwestern and Southeastern Nigeria. The aim of this review is two-fold; one is to stimulate the interest of researchers in this field on the need for research to examine the relevant risk factors for breast cancer in women in sub-Saharan Africa and secondly to sensitize policy makers and the general public on the need for better-focused health education and other preventive strategies.

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Incidence of Breast Cancer in Nigeria

The incidence of breast cancer in women has been rising in the past half century and the rise is occurring more rapidly in population groups that hitherto enjoyed a low incidence of the disease. The estimated incidence of breast cancer in Nigeria in 1976 was 15.3 per 100,000 but this rose to 33.6 per 100,000 by 1993[2]. Despite this doubling in incidence, many clinicians believe that this is an underestimate of the true incidence of the disease due to poor access to medical services, socioeconomic factors, lack of efficient population-based cancer registries and the absence of a breast cancer-screening program in Nigeria. The peak incidence of the disease in Nigeria is 10-15 years earlier than the peak age range for

Caucasians and postmenopausal breast cancer account for only 20-30 percent of cases[2-4]. Late presentation and poor survival are marked features of breast cancer in Nigeria[7]. The main histological pattern is infiltrating ductal carcinoma with marked stromal reaction; with infiltrating poorly differentiated anaplastic tumors accounting for a third of cases.

Reproductive Risk Factors

For the past two centuries, it has been suspected that sex hormones particularly estrogens may play some role in the etiology of breast cancer. It was, however, in the early 1970s that the role of these hormones in the causation of the disease was demonstrated by MacMahon et al[8]. In 1983, Pike and colleagues[9] observed that when the age-incidence curve was plotted on a log-log scale, the curve produced assumed a straight line until approximately age 50 years, when a decrease in the curve is noted, indicating that the premenopausal period probably creates a fertile period for the pathophysiological processes culminating in the manifestation of the disease. Since then, a lot of studies have been conducted in an attempt to explain the role of female hormones in the etiology and biological behavior of breast cancer. Several reproductive risk factors have been implicated in the etiology of the disease, including age at menarche and menopause, menstrual irregularity, age at first full-term pregnancy, parity, breastfeeding, and age at last childbirth. Other related hormonal factors include use of hormonal contraceptives, hormone replacement therapy and environmental exposure to hormone-related substances (xenohormones).

Age at menarche

There is strong evidence that early menarche and late menopause increases the risk of breast cancer while late menarche and early menopause tends to be protective. A possible biological explanation is that women with an early age at menarche have a longer exposure to endogenous estrogens. Furthermore, it was found that an early menarcheal age is associated with a higher estrogen production level during post-menarcheal years[10]. It is known that estrogens initiate the proliferation of breast tissue. There is a greater probability of replication errors causing pre-neoplastic lesions in proliferating tissue[11]. Other risk factors in the etiologic network that act later in life (sometimes called promoters) may alter these pre-neoplastic lesions into cancer.

Menstrual irregularity

It has also been reported that the age of onset of regular menstrual cycles may have a role to play in mammary carcinogenesis and this has been supported by findings from various studies. Irregular menstrual cycles or delay in the establishment of regular menses, independent of age at menarche was associated with decreased the risk in some studies[12].

Age at menopause

Various workers have reported the protective role of early menopause against breast cancer. Results indicate that the hormonal pattern of premenopausal women [cyclic production of relatively large amounts of estradiol (E) and progesterone (Pg)] causes a greater increase of risk of breast cancer than the hormonal pattern in postmenopausal women (constant low E and very low Pg). This evidence has been strengthened by the demonstration of the protective effect conferred by artificial menopause following surgical oophorectomy in women by several investigators[13]. This reduction in risk is most likely attributable specifically to removal of the ovaries, and the earlier age at oophorectomy, the lower the risk[13].

Age at First Full-Term Pregnancy

First full-term pregnancy before age of 18 years reduces the risk of breast cancer and the risk is significantly higher in women with first full term pregnancy after the age of 35 years[14]. Most studies have also found that for first births over the entire childbearing period, the lower a woman's age at first birth, the lower the risk[15]. While some studies have reported no protective effect for early age at first full term pregnancy others have found that age over 30 years at first child birth was associated with an increased risk of breast cancer relative to nulliparous women[16].

Parity

The effect of parity on breast cancer risk is not clearly understood. In most studies, high parity is found to be associated with low rates of breast cancer, but the extent to which this relationship can be explained by an inverse association between parity and age at first birth varies between studies[17]. Several studies have reported a protective effect of parity independent of the effect of age at first full term pregnancy. Kvale et al[18] found a consistent and highly significant inverse association between high parity and breast cancer. The apparent protective effect of high parity was found in all subgroups of the patients according to demographic variables and could not be explained by other reproductive factors. There appear to be consistency in this finding across studies conducted in both high-risk, intermediate-risk and low-risk areas. The protective effect of parity seems stronger in postmenopausal than in premenopuasal women, possibly on account of the confounding effect of time since last birth in younger

women. Some studies have reported no protective effect for early age at first full term pregnancy.

The long-term protective effects of pregnancy are contrasted with the observation that the risk of carcinogenesis is actually increased in the short term after a pregnancy[19]. It is known that hormones induce carcinogenesis by inducing cell proliferation, which is an essential component of carcinogenesis. This hypothesis is explained by the observation that increased cell proliferation results in a larger pool of cells that are susceptible to defective DNA repair. This in turn leads to mutations, which are subsequently propagated through increased mitotic activity present in proliferating cells, and can result in cancer formation. However, it has been shown that full term pregnancy induces differentiation of cells in the terminal duct lobular unit (TDLU) in the breast and this effect produces the long term effect of slowing the cell cycle in the epithelial cells of this location, which allows more time for DNA repair, which in turn will lead to decreased carcinogenesis[20].

Breastfeeding

A number of epidemiological studies have investigated the relationship between breastfeeding and breast cancer risk. Overall, studies suggest a 20-30 percent reduction in risk among women who have ever breastfed[21]. More consistently, a longer duration of breastfeeding has been associated with breast cancer risk reductions as great as 40-60 percent[22]. Recently, age at first lactation has been identified as the arbiter of risk, with an earlier age at initiation of lactation being associated with a stronger reduction in risk for premenopausal women and possibly for postmenopausal women[23]. However, because of the very strong correlation between age at first birth and age at first lactation, the independent effect of age at first lactation is difficult to isolate. It is notable that in countries with low risk of breast cancer, the protection conferred by lactation appears to be stronger and to be sustained throughout the postmenopausal period as well.

However, the association between lactation and breast cancer risk remains inconclusive. Some studies suggest that an inverse association may exist only among premenopausal women particularly among those with a longer duration of breastfeeding and with early age at first breastfeeding[24].

Use of hormonal contraceptives

The relationship between exogenous hormones, primarily hormonal contraceptives and hormone replacement therapy, to breast cancer has been researched extensively. The lack of total consistency among many studies may be attributed in part to the fact that these exposures are not static. Changes in pattern of use, reductions in hormone dose, and temporal considerations all contribute to the difficulty in comparing the many studies[25].

The Collaborative Group on Hormonal Factors in Breast Cancer was set up in 1992 to gather and reanalyze data from the many epidemiological studies that have addressed this issue in an effort to provide more definitive information on the risk associated with oral contraceptive use[26]. The results of their analyses of data pooled from 54 studies were reassuring, with ever use of oral contraceptives associated with a very small increase in risk (relative risk 1.07). The greatest risk was observed among current and recent users (within 4 years of diagnosis), with the risks declining with increasing time since last use. No increased risk was apparent for women who have discontinued use 10 or more years ago. Duration of use, age at first use, or dose of the oral contraceptive had little effect on breast cancer risk, once recency of use was taken into account. The data also indicated that tumors diagnosed among oral contraceptive users were more likely to be localized to the breast than among non-users. The only case control studies that have examined reproductive risk factors for breast cancer in Nigeria did not report any significant risk for hormonal contraceptive use. Two studies have specifically examined the relationship between oral contraceptive use and breast cancer risk among African American adolescents found an elevated breast cancer risk among users, particularly for first use below the age of 20 years[27].

Hormone replacement therapy

Available evidence suggests that menopausal estrogens are associated with a modest increase in breast cancer risk. Long-term use (5 years or more) among current users or recent users appears to be associated with a 30-50% increase in breast cancer risk. Reports from both the Collaborative Group on Hormonal Factors in Breast Cancer and the US Nurses Health Study support these risk estimates[28,29]. The results of various meta-analyses have been examined. The meta-analysis by Steinberg et al[30] focused on risk of breast cancer according to duration of use and revealed no increase in risk with less than 5 years of use. However for each year after 5 years of use, a proportional increase in relative risk of 0.015 was found. The highest risk calculated was 1.3 (95% CI, 1.2-1.6) for more than 15 years of use.

Induced abortion

Epidemiological evidence of a positive association between induced abortion and the incidence of breast cancer was first presented by Segi et. al.[31] in 1957 based on cases diagnosed between 1948 and 1952. Since then, several reports have appeared in the literature that shows either no risk or

an elevated risk for breast cancer following induced abortion.

After an extensive and detailed meta-analysis of the existing literature on the subject, Brind et al[32] noted that a significant positive association exists between induced abortion and breast cancer risk, independent of the effect an induced abortion has in delaying first full term pregnancy. Moreover, the increased risk is seen in both prospective and retrospective studies from around the world, in populations with the widest imaginable differences in ethnicity, diet, socioeconomic and lifestyle factors and which differ in many aspects of design, and whose data extend over more than half a century in time[32]. This finding is consistent with the existing knowledge on human biology, oncology and reproductive endocrinology, and supported by a coherent body of laboratory data as well as epidemiological data on other risk factors involving estrogen excess, all of which together point to a plausible and likely mechanism by which the surging estradiol of the first trimester of pregnancy, if it is aborted, may significantly add to a women's breast cancer risk.

Induced abortion is on the increase in most urban centers in Nigeria, particularly among adolescent girls who resort to induced abortion as a means of family planning. This is likely to have a profound effect on the breast cancer risk in the population in the next decades unless urgent steps are taken to encourage ways to prevent unwanted adolescent pregnancies.

Prenatal Factors

It has been speculated that prenatal factors may play some role in the etiology of breast cancer. Trichopoulos[33] proposed that intrauterine exposure to high concentrations of endogenous pregnancy estrogens might have an important complementary role in the natural history of breast cancer. Estrogens are important for breast carcinogenesis in several animal species and factors that increase the risk of cancer when they act postnatally may also increase the risk in the offspring when they act in utero[34]. Birth weight is a risk factor for breast cancer and it has been shown that birth weight increases with maternal parity, apparently due to growth-promoting effects of estrogens during the intrauterine periods. Some studies have reported a positive association between breast cancer risk and higher birth order[35] and this risk factor is likely to be more significant in populations with high parity as is seen in Nigeria. In fact, the only study on reproductive risk factors in Nigeria found that higher birth order is associated with higher risk of breast cancer[6].Other Risk Factors

Xenohormones

In the past few decades, it has been speculated that compounds or agents in the environment that function as xenoestrogens can affect the rate and type of estradiol metabolites produced in the body, alter binding with the estrogen receptor, induce breast cell proliferation, and thereby influence the development of breast cancer and other hormonally-related diseases. Dees and colleagues have recently reported that some xenoestrogens in synthetic chemicals (e.g., DDT) and food additives such as red dye number 3, markedly increase breast cancer cell proliferation[36]. It has been shown that xenoestrogens in some species, herbs, and food, can bind with the receptor and cause it to be less active, effectively blocking or dampening cell proliferation[37]. Other natural xenoestrogens, such as lignans associated with the fiber portion of seeds and grains, reduces fecal transit time and adsorbs fecal mutagens and conjugated estrogens, indirectly reducing the amount of bioavailable hormones. Soy products, such as genistein, also appear to reduce the risk of breast cancer, despite their ability to bind with the estrogen receptor[37]. Thus, genistein has been tied with inhibition of protein tyrosine kinase, an enzyme associated with oncogene products, and it also appears to inhibit angiogenesis, the growth of new red blood vessels that can foster the growth of cancerous cells.

Benign breast disease

A diagnosis of certain types of benign breast disease such as fibrocystic disease may increase the risk of breast cancer[38]. Most studies have indicated a two- to four-fold increase in risk of breast cancer in patients with fibrocystic disease.

Radiation

There is abundant evidence from follow-up studies of survivors of the atomic bombs in Japan[39], of women undergoing radiation treatment for acute post partum mastitis and of women who underwent fluoroscopy in the course of treatment by pneumothorax for tuberculosis[40] that radiation in high doses can cause breast cancer. Exposure of the breasts to radiation while a woman is 10-19 years of age is associated with an especially high risk[39,40], a trend not seen in other cancers. Two reasons for this increased sensitivity might be that (a) the breasts are rapidly developing during these ages, or (b) most women have not given birth to their first child at this time, and the breasts may be more susceptible before first birth occurs[39].

Nutrition and breast cancer risk

Changes in metabolic/endocrine risk factors could be contributing both to the rising incidence and also to a recent alteration in the biological characteristics of breast cancer. Obesity favors the development of insulin resistance in individuals known to have a genetic predisposition to the condition. A relationship between hyperinsulinemia and breast cancer risk was shown in a case-control study involving 223 Dutch women aged between 38 and 75 presenting with early breast cancer[41]. The serum levels of C peptide, a marker of hyperinsulinemia, were found significantly higher in breast cancer cases than in either the controls or the other cancer groups. Abdominal obesity is linked to hyperinsulinemia in both pre- and postmenopausal women. Insulin levels affect plasma lipid levels, and dyslipidemia is increased in the presence of abdominal obesity. The relative importance of abdominal obesity and hyperinsulinemia is uncertain in relation to a role in mammary carcinogenesis, but in a subset of women, the metabolic/endocrine concomitants of hyperinsulinemia associated with changes in the bioactivity of insulin-like growth factors (IGFs) in breast tissue, might act synergistically with increased estrogen bioactivity[42].

Body build

Several studies have shown a moderate positive association between body size and risk for breast cancer[43]. Weight, weight/height ratios, and total body mass have been considered in various studies, but there is no consistent finding as to which indicators are most strongly correlated with breast cancer risk, probably because these measures are so highly correlated with each other. Moreover, when premenopausal and postmenopausal women are considered separately, an association with body size seems to be quite consistently for postmenopausal women but not for premenopausal women[44].

Alcohol

Most studies find drinking alcohol increases the risk of breast cancer. Alcohol also appears to increase circulating levels of estradiol. Marsha Reichman[45] reported that two drinks of ethanol a day elevate serum estrogens. Studies find a 10% increase in risk for women who have one drink per day compared to nondrinkers, and a 20% increase at two drinks per day[46].

Smoking

Despite years of inconclusive studies, recently both active and passive smoking have been reported to increase the risk of breast cancer[47]. When contrasted with women who had never been exposed to smoke, passive smokers who had been exposed to 2 hours a day for 25 years had 3.2 times the risk compared to women with no such exposures, and active smokers (20 or more cigarettes per day) had 4.6 times the risk of breast cancer[47]. Perera et. al[48] have demonstrated the presence of carcinogen-DNA adducts, biomarkers characteristic of tobacco smoke and polycyclic aromatic hydrocarbons in the breast tissue of women with breast cancer.

Electromagnetic Fields/Melatonin

Exposure to 60 megaHertz electromagnetic fields and to light at night has been linked experimentally with reductions in melatonin, a natural hormone that suppresses prolactin and estrogen levels. Several recent epidemiological studies suggest that women with workplace exposures to electromagnetic fields are at increased risk of breast cancer, although the evidence remains inconsistent[49]. Findings indicate that electromagnetic fields impede cellular communication and also reduce melatonin levels[49].

A recent study by Cos et al[50] suggest that melatonin may modify DNA synthesis in MCF-7 human breast cancer cells, causing an antiproliferative effect.

Physical activity

Strenuous physical activity in adolescence and young adult life has been inversely related to subsequent breast cancer risk, possibly by delaying menarche and the onset of regular ovulatory activity. In a comprehensive review of studies published up to 1997, seven out of nine studies on occupational activity showed some reduction of risk among more active women, at least in some subgroups; 11 out of 16 studies on recreational activity showed also some reduction in risk[51]. However, no association was observed for recreational physical activity in a population-based case-control study including 1668 cases under the age of 45 years in three areas of the US[52], as well as in a report from the Nurses' Health Study II, based on 372 breast cancer cases in young women[53].

Conclusion

There is no doubt that hormones both endogenous and exogenous are central to the etiology of breast cancer but the mechanisms through which these effects are mediated are far from being completely understood. Various hypotheses, each with its own merits and demerits have been examined based on available evidence. It is important to note some differences in the reproductive characteristics of our population compared with the developed countries. Women in sub-Saharan Africa practice prolonged lactation, have low use of hormonal contraceptives and hormone replacement therapy, are extremely lean

and have low use of tobacco. These factors appear to be protective against breast cancer. However, trends towards increasing westernization in the past few decades are likely to alter the balance. Improved nutrition and lifestyle are likely to reduce the age at menarche; the quest for more education is likely to delay marriage and childbearing, reduce parity and cumulative duration of breastfeeding. Also the need to prevent unwanted pregnancies is likely to encourage use of hormonal contraceptives. In addition, the intensification of oil exploration in the Niger Delta in Nigeria with incessant oil spillage and environmental pollution may increase exposure to toxic polycyclic aromatic hydrocarbons, agents that have been implicated in the etiology of breast and other cancers. Also, the recent intensification of tobacco and alcohol production and advertisement in Nigeria are likely to increase smoking and alcohol consumption in the next few decades.

Identifying risk factors for breast cancer in any population has great potential for developing risk assessment tools for that population with the aim of identifying high-risk individuals for primary and secondary prevention. Experience with the original Gail Model[54] (developed from predominantly white populations) showed that it underestimated breast cancer risk when applied to African American women in the United States. Consequently, Newman and colleagues in collaboration with Gail validated the Gail Model in African American women using data from a multicenter case-control population of 3,283 African American women and 5,974 white American women[68]. The risk identification rate for African American women in the Gail Model is 5.6 percent while the Newman-Gail Model identifies 19 percent, a risk identification rate equivalent to that in white women by the Gail Model[55]. Importing risk assessment tools from the developed countries may not accurately identify high risk women in our population who might benefit from current preventive strategies such as tamoxifen chemoprevention; hence the need for more studies in sub-Saharan African populations. We consider this a challenge for investigators in this region.

In addition, there is a general consensus that there is gross underestimation of the incidence of malignant diseases in this region due to the absence of population-based cancer registries in most countries and lack of reliable census figures and incomplete reporting of births and deaths. There is urgent need to ascertain the true incidence of breast cancer in the region through the establishment and adequate funding of population-based cancer registries. Accurate data on the incidence of the disease will facilitate an enabling framework for improved cancer care in the population. We recommend increased culturally-sensitive, better-focused health education and breast cancer awareness campaigns. Health-policy makers, public health practitioners and other interest groups have tremendous role to play in initiating and sustaining these campaigns. Breast cancer screening programs should be integrated into the current health care delivery systems. Nurses working at the primary health care centers should be trained to conduct periodic breast examination in addition to teaching women within their locality the techniques for breast self examination (BSE). Individuals at risk should be referred to local hospitals and tertiary institutions for screening mammography. These screening programs should be funded through appropriate agencies such as the National Health Insurance Schemes.

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