

# PREDISPOSITIONS OF CARCINOMA OF THE BREAST: A REVIEW

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## ABSTRACT

**BACKGROUND:** Breast cancer is an ancient disease and the leading malignancy affecting women. The incidence is high in developed countries while it is low but increasing in developing countries. The aim of this review is to update and summarize the predisposing factors of breast cancer.

**METHODS:** Literature review was conducted using google search engine and hinari. Selected papers were taken for further reference and using books from author's collection.

**RESULTS:** The cause of breast cancer is unknown but predisposing factors have been identified to indicate increase susceptibility to developing the disease.

**CONCLUSION:** Breast is the commonest malignancy affecting women worldwide.

**KEY WORDS:** Breast, cancer, predisposing factors



## INTRODUCTION

**B**reast cancer is an abnormal growth of the glandular breast tissue and it occurs in both males and females.

It is an ancient disease and has been mentioned in almost every period of recorded history. Ancient Egyptians were the first to note the disease more than 3,500 years ago and concluded that there was no absolute cure.

Hippocrates in 450B.C described breast cancer as a humoral disease<sup>1</sup>. This theory was carried on by Galen in 200A.D who also described some pharmacological

agents to manage its symptoms such as opium, castor oil, licorice, sulphur as well as incantations to the gods. It was not until doctors achieved greater understanding of the circulatory system in the 17<sup>th</sup> century that they could establish a link between breast cancer and lymph nodes in the axilla<sup>2</sup>. The French Surgeon Jean Louis Petit and later the Scottish Surgeon Benjamin Bell were the first to remove the lymph nodes, breast tissue and underlying chest muscle for breast cancer patients. Their successful work was carried on by William Stewart Halsted who started performing mastectomies in 1882 and his procedure became known as Halsted Radical Mastectomy<sup>2</sup>. This procedure remained popular in the surgical management of breast cancer up to the 1970s, when a new understanding of metastasis led to perceiving cancer as a systemic illness as well as a localized one,

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and more sparing procedures were developed that proved equally effective.

Carcinoma of the breast is the leading malignancy affecting women and the commonest cause of cancer mortality worldwide<sup>3-5</sup>. Incidence rates are higher in developed countries while they are low but increasing in developing countries<sup>6-8</sup>. This variation may be due to demographic factors such as longer life expectancy, better reporting and awareness of the disease, and improved access to clinical care seen in developed countries<sup>9-10</sup>. Genetic factors are also considered to contribute to the differences in incidence<sup>11</sup>.

In Africans generally, carcinoma of the breast tends to present at a relatively younger age, with larger tumours, multiple nodal involvement and poorer clinical and pathological prognostic factors compared with Caucasian patients<sup>12-14</sup>. The aim of this review is to update and summarize the predisposing factors of breast cancer.

## RESULTS

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The cause of breast cancer is unknown but predisposing factors (of which various researchers reported their experiences) have been identified to indicate increase susceptibility to the disease.

## DISCUSSION

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Carcinoma of the breast is a major and important form of malignancy worldwide with an estimated annual incidence of about one million cases worldwide, with two hundred thousand in the United States and three hundred and twenty thousand cases in Europe<sup>15-17</sup>. The incidence of breast cancer is rising in population groups that hitherto enjoyed a low incidence. In Nigeria for example, the incidence rate rose from 13.8 – 15.3 per 100,000 in the 1980s to 33.6 per 100,000 in 1992, and 116 per 100,000 in 2000<sup>9</sup>. Prior to the increase in incidence, it was believed that there was under-reporting owing to low awareness, poor access to medical facilities, poverty, socio-cultural factors and absence of breast screening programmes<sup>18</sup>.

Between 1960 and 1980, the cancer registry of University College Hospital, Ibadan recorded 17,496

cases of cancer with breast cancer being the fourth commonest cancer overall and the second commonest in women. However, between 1980 and 1989, it had become the commonest malignancy<sup>19</sup>.

The cause of breast cancer is unknown, but certain risk factors have been identified to predispose to increased susceptibility to the disease. These risk factors include:

**GENDER:** It is a disease of women with less than 1% being males<sup>20</sup>. A retrospective study conducted in Pakistan and published in 2006 observed carcinoma of the breast affecting males in 5.9% of all cases and a male to female ratio of 1:16<sup>21</sup>.

Muguti in Zimbabwe observed over a 31/2 year period that only 2% of patients with carcinoma of the breast were males<sup>22</sup>. The annual incidence in Zimbabwe is 14 per 100,000 for females and 0.4 per 100,000 for males<sup>22</sup>. Anyanwu observed a male to female ratio of 1:67 in a 10 year review from Eastern Nigeria<sup>23</sup>.

**AGE:** Carcinoma of the breast is rare below the age of 20 years but thereafter the incidence steadily rises so that by the age of 90 years nearly 20% of women are affected<sup>24</sup>.

The incidence in Africa peaks between ages 35 and 45, approximately 10-15 years earlier than the peak incidence for western countries<sup>23,25-27</sup> and it is suggested to be due to the lower life expectancy (46 years for Nigerian women; World Health Statistics 2006) and the younger population age in this environment<sup>9</sup>. A study from Zimbabwe<sup>22</sup> reported a second but smaller increase in incidence occurring between the ages of 60 and 69 years. Adebamowo and Adekunle in a prospective study in 1999<sup>19</sup> observed a mean age of 43 years in breast cancer patients which is similar to previous observations from other centers in Africa<sup>22,26-27</sup>.

**PREVIOUS BREAST CANCER:** The risk of contralateral breast cancer was about five times that in the general female population. Some other studies<sup>28-29</sup> have confirmed the higher risk of women who have previously had one breast cancer. The development of a second breast cancer may be a clinical manifestation of a multifocal origin of the first cancer or may be an entirely new cancer. Robbins and Bergs in 1964

prospectively followed up 1458 women who had ipsilateral breast cancer treated by radical mastectomy. Ninety four new primary contra lateral breast cancers were found during a follow up period of 20 years.

**FAMILY HISTORY:** This is a strong risk factor<sup>30</sup>. Handerson and Pike, and Lynch and Marcus have documented the importance of hereditary and genetic predisposition to cancer of the breast<sup>31,32</sup>. In a study by Lynch and Marcus of 328 patients, 68% were sporadic, 23% were familial, and 9% were hereditary<sup>32</sup>. Definitions suggested by Lynch and Marcus are as follows:

- A) Sporadic breast cancer: a patient with cancer of the breast with no family history of cancer of the breast through 2 generations involving siblings, offspring, parents, aunts, uncles and both sets of grandparents.
- B) Familial breast cancer: A patient with cancer of the breast with a family history including one or more 1<sup>st</sup> or 2<sup>nd</sup> degree relative with breast cancer that does not fit the hereditary breast cancer definition.
- C) Hereditary breast cancer: A patient with cancer of the breast with a positive family history of breast cancer and sometimes related cancer such as ovarian or colonic cancers. There is early age at premenopausal onset, increased incidence of bilateral breast cancer and multiple primary cancers. It is inherited as an autosomal dominant trait.

Linkage to BRCA 1 gene is present in most patients with hereditary breast cancer and this gene is mapped to a region of the chromosome 17q. BRCA 2 gene was mapped to the q 12-13 region of chromosome 13 and is linked to most families with male hereditary breast cancer.

A summary of studies before 1963 on familial aggregation of breast cancer indicated that female relatives of women with breast cancer have 2 or 3 times the general populations' breast cancer rate<sup>33</sup>. This increased risk appears as great for paternal relatives as those on the maternal side<sup>33,34</sup>. It has been reported that 5 - 10% (9000-18,000 cases per year in USA) of women who develop breast cancer does so because of an inheritable predisposition<sup>35</sup>. Dumetriscu

and Cotarla found that women with one, two and three or more first degree relatives have an increased breast cancer risk when compared to women who do not have an affective relative<sup>36</sup>. Adebamowo and Adekunle in 1999 found only 2% of breast cancer patients with a positive family history in a prospective study involving 250 patients with breast cancer at Ibadan<sup>19</sup>. It was also observed that family history of breast cancer was difficult to elicit in Ibadan for several reasons such as lack of proper records, fear of stigmatization, low life expectancy and social taboos<sup>37</sup>, all of which contribute to the lack of data<sup>19</sup>. A study from Zimbabwe observed family history in 6% of patients<sup>22</sup>.

**NULLIPARITY:** This increases the risk of developing breast cancer<sup>15</sup>. With increasing age at the time of first pregnancy, the risk increases proportionately. Women who have their first full term pregnancy before the age of 18 have a lower risk, about 1/3<sup>rd</sup> that of women with first pregnancy over 35 years<sup>15</sup>. This relative increased risk in the latter group is speculated to be due to persistent exposure to endogenous oestrogens in the absence of appropriate concentration of progesterone. Rosenberg et al<sup>38</sup> evaluated breast cancer risk in relation to parity among South African women and found an association between nulliparity and breast cancer.

**AGE AT FIRST PREGNANCY:** Rosenberg et al<sup>38</sup> observed that women who had their first child at 30 years or older, had a 2-fold increase in breast cancer risk compared to women who had their first child at 18 years or younger<sup>38</sup>. In another study in South Africa, women who developed breast cancer had an older age at first birth and a higher level of education compared to control group<sup>39</sup>. Oestriol is non carcinogenic whereas oestrone and oestrodial have been shown to be carcinogenic. During pregnancy, oestriol production increases proportionately over the production of carcinogenic oestrogen<sup>40</sup>. Subsequent pregnancies are believed to have much less effect<sup>40</sup>.

**AGE AT MENARCHE AND MENOPAUSE:** Women who attained menarche before the age of 12 years have an increased risk compared to those whose menarche is after this age. Several studies have highlighted the role of prolonged exposure to endogenous oestrogen as a risk factor of breast carcinoma<sup>41-43</sup>. Early menarche, late menopause, low parity, older age at first full term pregnancy are all associated with a

higher risk of breast cancer.

Age at menarche decreases while that of menopause increases and therefore increase incidence observed as a society gets more affluent and living standard improves<sup>44</sup>.

However in the study by Adebamowo and Adekunle, the mean age at menarche in both study and control groups was about 15 years<sup>19</sup>. In another study of nearly 2000 African cancer patients reported by Ihekweba at Ibadan, he also did not identify any correlation between breast cancer risk and parity, risk and age at menarche or risk and lactation<sup>45</sup>.

**IRRADIATION:** Women exposed to irradiation especially during high mitotic activities (e.g. pregnancy, menarche) have an increased risk of developing cancer of the breast. An increased risk has also been observed in women treated by irradiation for post partum mastitis and patients receiving multiple chest radiographs during assessment of pulmonary tuberculosis<sup>46</sup>. This increased risk became apparent after a latent period of 10-15 years. Mackenzie in 1965 reported an increased risk for women undergoing repeated fluoroscopy during pneumothorax treatment for pulmonary tuberculosis. A subsequent report has confirmed this increased risk following multiple fluoroscopy<sup>47</sup> and also following radiation therapy for acute post partum mastitis<sup>47</sup>.

A report from atomic bomb casualty commission<sup>48</sup> showed that the breast is more susceptible to carcinogenic effect of ionizing radiation during periods of high mitotic activities such as pregnancy and at menarche<sup>48</sup>.

**OBESITY:** This is associated with an increased risk of breast cancer especially in post menopausal patients. In a case control study from Ibadan by Adebamowo et al involving 234 breast cancer patients, it was observed that postmenopausal obesity was associated with breast cancer risk when measured as a function of waist- hip ratio<sup>49</sup>. Another analysis of the same population also demonstrated this association when obesity was estimated by body mass index (BMI) to be greater than 30.

**DIET:** There is experimental evidence to suggest that high fat diet in rats and mice is associated with an

increase in the number of breast tumours in these animals. The exact mechanism of this risk is not known. However, no definitive evidence is available to associate high fat diet with breast cancer in humans. A popular suggestion is that fat contains some pro-carcinogens which are simply converted to carcinogens on ingestion. The increasing consumption of high fat diet in some countries with previously low incidence like Japan has been linked to rising incidence of breast cancer<sup>50</sup>. A typical diet in Africa consists mainly of grains, vegetables and fibre with little fat or protein. In studies by Djuric<sup>51</sup> and Boyd<sup>52</sup>, it was suggested that this nutritional intake pattern may be protective against breast cancer. Physiologically relevant concentrations of a potential chemo-protective agent (by means of dose dependent inhibition of DNA synthesis) have been identified in at least one vegetable, *veronia amygdalina* that is consumed heavily in West Africa<sup>53</sup>.

**ORAL CONTRACEPTIVE PILLS:** There is a slightly increased risk of developing breast cancer in women who take oestrogen based oral contraceptive pills. In the study by Adebamowo and Adekunle<sup>19</sup> at Ibadan, it was observed that 4% of patients with breast cancer had used oral contraceptive pills compared to 0.8% of control. Some researchers believe that intake of oral contraceptive pills does not predispose to the development of breast cancer. A study of about 4575 women between 35 and 64 years of age with breast cancer when compared to about 4682 control did not detect any association between breast cancer and oral contraceptive use<sup>54</sup>.

**BENIGN BREAST DISEASE:** Multiple papillomatosis may be regarded as a risk factor of carcinoma of the breast. Anyanwu studied breast cancer from 4 hospitals in Eastern Nigeria and found out that 12% of patients reported a prior history of benign breast disease<sup>23</sup>. Haagensen reported the follow-up results of his patients with gross cystic disease and multiple intraductal papillomata. He found that the ratio of observed to expected subsequent cancers in patients with gross cystic disease is 3:1 and 4:1 for multiple intraductal papilloma. He followed up his patients for about 5 – 10 years. This stresses the importance of subjecting every breast lump to biopsy, submitting any biopsy specimen for histology and a good follow-up programme for the patients<sup>55</sup>.

**BREAST FEEDING:** This decreases the life time incidence of breast cancer by decreasing the cumulative number of ovulating menstrual cycles. Coogan and colleagues<sup>39</sup> evaluated breast cancer risk related to lactation among South African women and postulated that lactation causes differentiation of ductal epithelial cells which is protective against carcinogens. However, some other earlier studies had indicated little or no difference in the lactation experience of breast cancer patients and controls<sup>56, 57</sup>. Most of these studies were in countries with high breast cancer rates.

**ALCOHOL:** This has been found to be a risk factor for breast cancer<sup>58</sup>. The primary mechanism may be attributed to increased oestrogen level<sup>58</sup>. A study of more than one million middle aged British women concluded that each daily alcoholic beverage increases the incidence of breast cancer by 11 cases per 1000 women<sup>59</sup>.

## CONCLUSION

Breast cancer is the commonest malignancy affecting women worldwide. It is commoner in developed countries but with increasing incidence in developing countries. The peak age incidence in developing countries is one to two decades lower than that in developed countries.

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