Is Breast Cancer a Deficiency Disease?

Richard A. Wiseman
PhD, LRCP, MRCS, DObstRCOG, DTM&H

Consultant in Epidemiology;
Former Senior Lecturer, Department of Epidemiology & Population Health, London School of Hygiene & Tropical Medicine.

Contact via the username "**raw**" at the domain name "**RichardAWiseman.com**";
Backup contact via the username "**jdaw1**" at the domain name "**jdawiseman.com**".

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Abstract

Numerous factors, conditions or agents have been proposed as the cause of breast cancer but together they account for only a small percentage of all cases. An overarching hypothesis to account for these disparate associations and inconsistencies is that there is a natural element present in the diet of normal food which is protective; in geographical areas or in conditions where low levels or deficiency of this element occur, protection is lost and breast cancer more readily develops. This agent is fat soluble, accounting for the increased incidence in obesity, and leaches out with age accounting for the increased post-menopausal incidence. Differences in incidence between various groups, such as those with or without breast-cancer susceptibility genes, or between men and women, may be accounted for by a gradient in threshold.

This hypothesis is testable. At the same time, many putative causes such as micro-nutrients, vitamins, or trace elements can be investigated; some, such as selenium, have been investigated but gave conflicting results; selenium deficiency perhaps in association with sub-clinical vitamin E deficiency, remains a possibility. A proposed investigation is outlined.

Keywords: Breast cancer; Epidemiology; Causation; Deficiency; Hypothesis.

Richard A. Wiseman is medically qualified and has a PhD from London University. He is the author of numerous published articles, primarily on epidemiology, which include:

— Wiseman R.A. and Woodruff A.W., "Toxocariasis in Africa and Malta", *Trans R Soc Trop Med & Hyg*. 1971; 65; 439-449.

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— Wiseman R.A., Breast cancer hypothesis: A single cause for the majority of cases, *Journal of Epidemiol. & Community Health*, 2000; 54: 851-858. [1]

1. Introduction

The cause of the majority of breast cancer cases remains unknown. Most women who develop the disease are ostensibly at low risk. Some studies have proposed that in individual cases there are specific agents—such as organochlorines, alcohol, smoking, radiation, reproductive history, etc—which are causative, so the disease is said to be 'sporadic'. However, no general overarching hypothesis has been postulated to account for the majority of cases.

This review attempts to correct that omission, and postulates a hypothesis which accounts for the epidemiological findings.

2. Background Epidemiology

For references for this section see Wiseman, 2000 [1].

2.1. Genes

Genetic inheritance is only an infrequent causative factor: BRCA1 and BRCA2 susceptibility genes are associated with 4%-8% of breast cancer cases, thus 92%-96% arise without such genes. Even with such genes, the risk of developing overt disease varies according to age, suggesting that an environmental trigger is needed. The example of three sisters with BRCA1 genetic inheritance is pertinent: one develops breast cancer at 25 years, another at 55 years, and the third dies at 75 years of an unrelated illness, presumably before the condition developed. If an environmental trigger was present (but at differing times) in these three, it may also occur in those whose condition is described as 'sporadic'.

Ethnic groups from the same gene pool (eg. Chinese of Han race, Japanese) develop dissimilar rates to their origins after migration to different locations (eg. Hawai, San Francisco) when they adopt new cultural habits, especially Western life-styles.

In most patients with breast cancer there is a low incidence of family history, although some families have a clustering of

breast cancer in association with ovarian or colon cancer affecting a number of individuals through many generations. There is a two- to three-fold increase in breast cancer risk in mothers or sisters of breast cancer patients; such familial clustering may be due to inherited susceptibility but may also be associated with other features held in common: social class, country at birth, age at first-term pregnancy, dietary habits, etc.

In percentage terms, however, genetic inheritance or familial predisposition play only a small part.

2.2. Industrialisation

Despite the multiplicity of reports suggesting that pesticides, or herbicides, or other chemicals or pollutants may be implicated, the evidence is that environmental exposure by pollution or industrialisation is not associated with breast cancer.

- Breast cancer incidence rates in England and Wales are random in respect to rural, urban or metropolitan districts.
- Rates have been shown to be random in respect to industrialised or non-industrialised countries.
- Differences between social classes all of whom live in the same areas, localities, or counties cannot be accounted for by industrialisation.
- In the small city-state of Singapore, generations of different ethnic groups have lived under the same environmental conditions but continue to record rates dissimilar to each other.
- Similarly, in Bombay (Mumbai) where the environment is the same for all women, breast cancer rates are 25% higher in Muslim women than Hindu women [2].

It can be concluded that breast cancer is not associated with industrialisation nor urbanisation but is simply random.

2.3. Infection

Although antibodies to murine mammary tumour virus (and antigens related to it) have been identified in human breast cancer cells, they have also been found respectively in healthy controls and in lactating women without breast cancer.

If an infecting agent is causative it is likely to be transmitted by close contact, especially breast feeding. However, the evidence is that breast-fed infants as compared to bottle-fed have a decreased risk in some studies, whilst others showed no association; and no increased risk was found in daughters breast-fed by mothers who subsequently developed breast cancer.

None of these findings is consistent with vertical transmission.

There is no evidence of horizontal transmission, i.e., by direct person-to-person contact.

2.4. Oestrogens

Cumulative exposure to oestrogens is associated with most risk factors—age at menarche, menopause, first pregnancy, etc—but there are numerous inconsistencies.

- There is a surge of oestrogens in pregnancy, particularly in late pregnancy, but breast cancer during pregnancy or timely thereafter is rare.
- Long-term administration of oestrogens to premenopausal women as with oral contraceptives has arguably not caused an increase in prevalence nor incidence in the target age-group.
- Oestradiol levels in postmenopausal women—when breast cancer prevalence rises and incidence is at its highest—are one third of the lowest level in premenopausal women.
- Postmenopausal women taking hormone replacement therapy (HRT) have raised oestrogen levels compared to women not taking HRT, but the excess risk, if there is any at all, is exceedingly small.
- Men develop breast cancer; the majority are normal men with normal hormone levels and proven male fertility.

Accordingly, it may be deduced that oestrogens are not directly responsible for breast cancer, as has been frequently claimed, but even if indirectly associated may be simply permissive, acting as promoters or co-agents but are not themselves causative.

2.5. Diet

It has been shown that dietary factors play a major role: animal experiments have repeatedly demonstrated that challenged mice or rats consuming a high fat diet have a higher mammary tumour incidence; in human population studies there has been a significant correlation fairly consistently for post-menopausal women between fat consumption and breast cancer incidence

and mortality, particularly for weight gain in adulthood and central obesity; and relative deprivation in wartime Norway and a rationed diet in the United Kingdom during and after WWII were associated with rapid decreases in breast cancer mortality which rose again when dietary impositions were reversed.

2.6. Conclusions from review of epidemiology

Genetic inheritance and/or familial clustering play a role in only a small cohort of the population; industrialisation, chemicals, urbanisation and infection are not causative of breast cancer and there is not even an association in the vast majority of cases; oestrogens are possibly permissive but are not directly causative; dietary fat is associated with risk but is not itself the causative agent.

3. Hypothesis

One overarching hypothesis can explain all these disparate features. The hypothesis is that there is an essential agent—or combination of agents—which is protective against the development of breast cancer; under certain conditions this agent is able to leach out, permitting breast cancer to develop.

The agent is a micro-nutrient, trace element, vitamin or proto-vitamin found in soils in varying amounts in different localities. It is taken up by plants, grains, possibly by fruits, to enter the food chain in differing quantities in different areas or by different cultures with different dietary habits.

The concentrations in soils, then in plants, determine the amount in the food chain, which therefore varies according to the geographical region or locality. Thus the levels in humans will differ according to the geographical region or locality within a country and with the food culture of the local population. The differences in soil and plant concentrations in different countries, and the different dietary habits, account for the wide variation between breast cancer incidence in, for instance, China and Japan as compared to many Western countries.

Differences in concentrations between different localities within a country also account for differences in incidence of breast cancer in different parts of, say, China where on average incidence is low, or western parts of the USA where it is high. The amount of the agent, or lack of it, in the blood or tissues and possibly breast tissue of individuals in the human population is a major determinant of breast cancer incidence.

The agent is probably fat-soluble, such that an increased amount of body fat is able to absorb a greater amount of the agent as compared to lean individuals. This depletes the levels of the agent in body tissues and thus accounts for the association of higher incidence in women who are or become obese.

Increased fat intake as in a Western diet therefore produces systemic depletion of the agent, accounting for the higher incidence in Western countries or those that have adopted a Western diet. For example, because of high concentrations of this protective factor in Japanese foodstuffs, in one study overweight Japanese women had a *lower* incidence than lighter Dutch women [3].

As foodstuffs are processed or moved from one country (or locality) to another, breast cancer incidence becomes more homogenous. Additionally, the greater incidence of breast cancer in the higher social classes in the 1950s and 1960s (e.g., in the U.K.) due to the greater consumption of fatty foods by the higher social classes has now been reversed as those in the lower classes now consume more fatty and sugar-filled foods.

Increase of breast cancer incidence with age is related to the agent leaching out as a result of age-induced changes or not being as fully absorbed.

Oestrogens are tumour promoters, stimulating oestrogen-dependent breast tissue when levels of this critical agent fall below a specific individual threshold. In areas or populations where the tissue levels of this agent are low, high oestrogen concentrations will be associated with increased incidence, but where tissue levels of the agent are high, incidence of breast cancer will be low despite high oestrogen levels from natural or artificial sources. This accounts, for instance, for the Japanese/Dutch results referred to above.

Differences in incidence between varying groups may be accounted for by a deficiency gradient in threshold: women with genetic predisposition need only a small fall in levels of the agent; women who develop overt unilateral disease have a moderate deficiency; women with bilateral cancer have a greater deficiency; men with breast cancer have severe depletion.

4. Consideration of Some Putative Factors

Since the protective agent or factor is unknown, it may be necessary to examine a wide range of vitamins and proto-vitamins, trace elements or micronutrients to determine if breast cancer is associated with deficiency of any one, or more than one acting together.

4.1. Selenium Deficiency

Selenium is present in soils and taken up by plants, vegetables and cereals to enter the food chain. Much of the variation in the selenium content of foods results from large-scale differences of uptake in the amounts and availabilities of plants [4]. Variation can occur within a particular geographic region according to specific climatic conditions during the growing season.

Several regions in the world have soils that contain low amounts, including some regions of China which have historical problems with selenium deficiency in livestock, and with Keshan disease, a selenium-responsive cardiomyopathy in humans associated with very low selenium levels. Some parts of the United States (the northern plains, parts of the south-west) have selenium-rich soils; concentrations in different countries vary widely, not always consistently with breast cancer incidence [5].

Selenium is a crucial component of a number of enzymes which protect against oxidative damage. Numerous experiments in animals have shown that high selenium intake protects against carcinogen-induced tumours [6][7] including spontaneous [8] or chemically-induced breast cancer [9]. Marginal deficiency of selenium has been reported in the populations of even affluent countries [10].

China has historically a low breast cancer prevalence but a number of large areas with low selenium in soils. Some geographical studies have suggested an inverse relationship between plasma selenium and cancer incidence but others have not. Similarly intervention trials—supplementation of soil or diet with selenium—have in a few instances shown a protective effect against total cancer, or specific sites, but not of breast [11] but other studies have shown no effect at all.

In humans most but not all observational studies have shown that selenium-high diets are associated with a lower incidence of cancer [12][13][14]. Willett *et al*. [15] reported the risk of cancer for subjects in the lowest quintile for selenium levels was twice that of subjects in the highest—an association strongest for prostatic and g.-i. cancers—whilst Salonen *et al.* [16] observed an increased relative risk of 5.8; and in another study [17] low blood selenium was associated with lung cancer mortality. However, in all these studies other factors may have been involved.

The majority of clinical investigations have found an inverse relationship between selenium (in blood, serum, nail, hair) and cancer in different sites, as well as specifically with breast cancer. However, such reports are not consistent, since a number of well-conducted case-control or cohort investigations detected no relationship between selenium levels in plasma, nails or hair and cancer incidence [18]. For example, a large Dutch case-referent study nested in a cohort [19] found no relation between nail selenium levels and breast cancer risk in premenopausal women; serum levels could not pre-diagnostically detect women at higher risk of breast cancer. Similarly, the US the Nurses' Health Study [20] reported that mean selenium nail levels were almost identical between breast cancer cases and controls for both premenopausal and postmenopausal women.

The occasional report of a positive association between alcohol and breast cancer risk might be explained by the finding of low selenium concentrations in association with alcohol intake [21].

Selenium concentrations fall with age in some [22][23], (but not all [24]) studies which, if correct, might fit with the hypothesis of a protective agent leaching out.

Some investigators have pointed out that low selenium states in association with breast or other cancers may reflect disease-mediated changes [25] although other studies were designed specifically to obviate this [16].

The majority of ecologic correlation studies, clinical case-control or cohort investigations suggest an association between low selenium and cancer incidence, including breast cancer, but the lack of consistency might suggest that selenium deficiency is unlikely to be the sole putative factor, although the totality of evidence suggests that it seems to be directly or indirectly involved in causality.

4.2. Vitamin E deficiency

Vitamin E (tocols, tocotrienols that exhibit the activity of alpha-tocopherol) is highly lipophilic and the major anti-oxidant in membranes, able to break the transfer of free electrons in cells. It is thus anti-carcinogenic.

Although clinical deficiency states cause myopathies, neuropathies, liver disturbances and increased erythrocyte fragility, nothing is known regarding long-term effects (if any, and if it exists) of chronic sub-clinical deficiency.

Experiments with chemically-induced tumours in rats, which were given selenium and vitamin E supplementation, showed that Vitamin E supplementation had no anti-tumour effect of its own but potentiated the anti-carcinogenic activity of selenium [26].

The clinical study by Willet *et al*. [15] reported that the two-fold significant risk of cancer associated with the lowest selenium tertile was increased to six-fold in the sub-group with the lowest Vitamin E concentrations.

It is thus possible that low levels of Vitamin E are necessary to express the full anti-carcinogenic activity of selenium deficiency.

4.3. Vitamin A deficiency

Even marginal states of Vitamin A deficiency lead to susceptibility to severe infections, but without other clinical signs. Vitamin A, which is fat-soluble, is required for night vision, cell differentiation, embryogenesis, growth and immune response, and protovitamin A has some anti-oxidant activity. On the last two grounds, low levels might conceivably be involved in cancer-permissiveness, but it seems unlikely because, in countries where deficiencies of Vitamin A or its precursors are common, breast cancer incidence is lower than in Western countries.

4.4. Trace Elements

For many trace elements little is known, or little has been reported, regarding deficiency states [27]. The possibility that chronic sub-clinical deficiency of one or more trace elements or minerals might lead to overt but later disease, including malignant disease, is a concept that has not been considered in medicine but is biologically quite possible.

A number of these compounds are toxic and possibly carcinogenic when given/absorbed in high doses – an early review concluded that arsenic, beryllium, cadmium, chromium and nickel were possible human carcinogens [28]. The U.S. Nurses' Health Study [29] reported no association between arsenic, copper, iron and zinc in toe-nail clippings and established breast cancer risk, but there was a marginally significant positive association with chromium in postmenopausal women. Zinc has been examined in many studies with variable results, but more often with higher levels in serum or tissue for breast cancer cases than controls. The concentrations in blood, sera or breast tissue of a number of other elements have also been investigated in breast cancer cases and controls [30][31][32][33][34], although not all elements and not systematically.

As for deficiency states, compounds which might be relevant are those which have shown anti-oxidant activity or an effect on the immune system [35][36] and therefore when deficient this activity will be diminished. Boron deficiency, as one example, affects calcium metabolism and the activity of many enzymes; low levels impair the immune system. Chronic sub-clinical deficiency affecting the immune system might fit well with a cancer-inducing agent.

Mineral or trace elements which might be examined include aluminium, antimony, boron, cadmium, manganese, molybdenum, nickel, strontium, and glutathione.

5. Testing Proposal

5.1. Type of investigation

Blood samples, or tissue samples if available or nail samples where appropriate, could be processed for levels of the above factors and elements to determine if there is any association with women with unilateral breast cancer, bilateral breast cancer, men with breast cancer and age-matched controls from each of the above cohorts.

For some putative factors, erythrocyte estimation would be preferred instead of blood or plasma, but this may not be practical, especially if the samples were taken a relatively long time ago and have deteriorated.

5.2. The Cohort

A number of large-scale clinical investigations have been undertaken and still are being progressed from which blood, plasma, tissue or other sample-sites have been collected and could be used for the above proposal: the Nurses' Health Study in the USA, the EPIC investigation in Europe, as well as a number of others, have such materials.

Because patient recruitment, history taking, follow-up, and sampling have already been conducted, and such studies have previously obtained funds for those activities, the additional cost of the proposed investigations would be modest.

The results should reveal whether or not the hypothesis is valid, and whether deficiency of one or more factors is permissive for breast cancer to develop.

6. References

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