

Background Briefing | The Biology of Breast Cancer

Background

Cancer is a complex disease involving many stages of development, often over long periods of time. The “causes” of cancer are numerous and not always known. They fall into two broad groups:

Intrinsic factors: our genetic inheritance, along with acquired biological errors that occur at random and accumulate as we age;

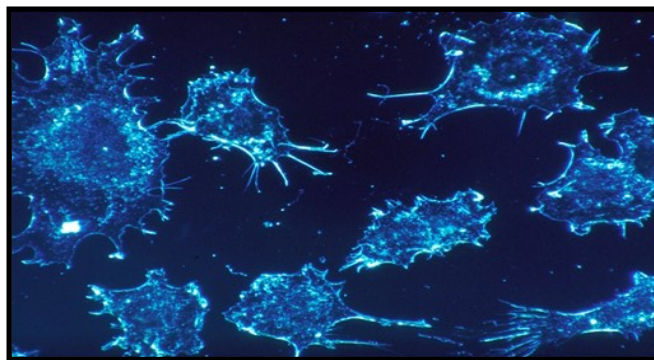
External factors: which include our exposure to known risks (such as smoking) and our exposure to environmental hazards around us, many of which we may not recognise as risks.

It is the external factors that we may be able to control or avoid, provided we know what they are. This information sheet describes the current state of our understanding of breast cancer, including its biological basis and the way in which the disease is triggered and develops. Whilst breast cancer can be treated and treatment is constantly improving, it can also be prevented and if we can better understand the causes of the breast cancer we are better equipped to help stop it from happening at all.

Breast Cancer: The statistics

Western Europe has the highest incidence of breast cancer with rates almost four times greater than in parts of Eastern Asia or Middle Africa (1). In the UK, between 2004 and 2013, the age-standardised incidence rate for breast cancer increased by 5.5% (2) a rate of increase too fast to be explained by changes in heritable, intrinsic factors, or by some remarkable increase in “bad luck”.

Evidence suggests that the risk of developing breast cancer is strongly linked to geographical location (3). Immigrants moving from a country with low breast cancer incidence to one with a higher incidence will,



Human Cancer in Culture Dr Cecil Fox, National Cancer Institute, NIH

within a single generation, acquire the higher risk profile of their adopted country (4). Migration does not alter an individual’s intrinsic risk factors, but it will bring about changes in lifestyle and external or environmental factors.

Evidence also suggests that modern day living is impacting our risk of breast cancer. One study found that within a group of women with a known genetic predisposition to breast cancer, (carrying a *BRCA1* mutation), those born prior to 1940 had a lower risk of developing the disease than those born after 1940 (5).

The Role of DNA in Cancer

DNA plays a central role in cancer development. Cell growth is regulated by DNA, which essentially sends instructions to our cells. Each time a new cell is formed by division, the instructions (or DNA) are copied. Ideally they should be copied exactly each time, but sometimes they are not. DNA contains repair genes which are able to self-correct mistakes in the structure of the DNA as they occur. However, some mistakes - known as mutations - do not get corrected; instead the error is reproduced and passed on. Over time, mutations accumulate, and their combined effects can lead to cancers.

Random gene mutation occurs infrequently. However, the more often a cell divides, the greater the risk of

Background Briefing | The Biology of Breast Cancer

mutations occurring and accumulating. Anything that accelerates the rate of cell division (DNA copying) also increases the likelihood of mutations occurring. Oestrogens (female sex hormones), for example, can stimulate cell division. Other agents such as X-rays, ultraviolet light and some chemicals can also increase mutation rates, by damaging DNA directly. Not all changes to DNA are genetic mutations. Other changes which can have damaging effects on gene function can also be caused by chemicals in the environment.

Breast Cancer: Overview

Breast Cancer occurs when abnormal cells in the breast grow in an uncontrolled manner. It occurs in both men and woman, but women are at greater risk due to their breast development and lifelong exposure to oestrogens.

“Breast cancer” is a diverse group of diseases. Sub-types have different properties in relation to hormone sensitivity, invasiveness as well as menopausal status (see box “Common types of Breast Cancer”). Characteristically there is often a long latency period between breast tissue changes and development of breast cancer (6).

Oestrogens are present in relatively high concentrations in the breast and play a central role in many breast cancers (7). Oestrogens exert their effects on cells at very low concentrations. They act by entering cells and binding to specific proteins called oestrogen receptors. These can then bind to specific DNA sequences in the cell’s nucleus resulting in rapid cell multiplication and differentiation (8). Rapid cell multiplication means there is less time for DNA repair, leading to DNA damage and mutations (9). Oestrogen break-down products also contribute to risk; they can bind to DNA and generate mutations in critical genes that initiate breast cancer (10).

Structure of the breast

Breast development begins in the womb (*in utero*), and continues during puberty and pregnancy. At puberty, female sex hormones, predominantly oestrogens, are produced in the ovaries and promote the development of breasts and female reproductive organs. During pregnancy, increased concentrations of oestrogens and progesterone (produced by the ovaries, and later, the placenta) result in further breast growth and development (11).

The breast is made up of cells, connective tissue, glands and fatty (adipose) tissue. Its primary purpose is to provide milk, produced by mammary glands which are surrounded by adipose tissue. The milk is made within small sacs called lobules and delivered to the nipple via a network of small tubes or ducts made of epithelial tissue (see Figure 1).

The breast also contains two networks of circulating fluids. Blood vessels supply breast tissues with oxygen and other nutrients and the lymphatic system drains away excess fluids. Both the blood and the lymph are important parts of the body’s overall immune system - they contain cells which can recognise and destroy invading bacteria and damaged cells such as cancer cells. In the human breast, most lymph drains into axillary lymph nodes, located in the armpit region. The breast also contains blood vessels and auxiliary cells (e.g. fibroblasts, endothelial cells & immune cells) surrounded by an extracellular matrix, which contains proteins and growth factors that stimulate cellular growth and multiplication (12).

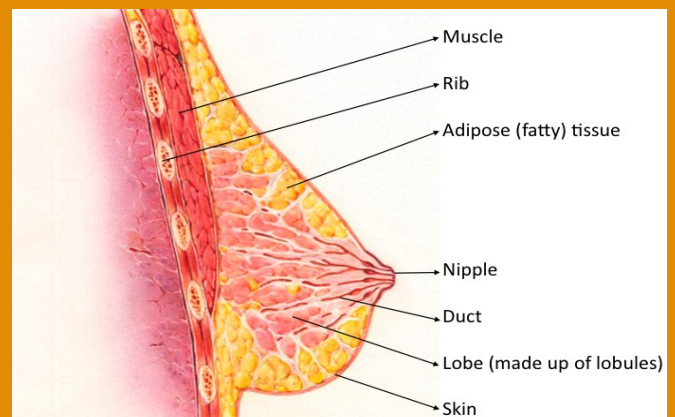


Figure 1: Lateral view of breast

Image credit: Medical art services, I. Christensen, Wellcome images

Background Briefing | The Biology of Breast Cancer

Oestrogen and Epigenetic mechanisms

Oestrogens can also induce changes which do not affect the primary DNA sequence of a gene, but which nonetheless alter its properties (13). These changes are known as “epigenetic” (in contrast to “genetic” mutations, which do change the primary DNA sequence). Epigenetic changes are of equal importance to genetic changes in their potential effects. For example, cells contain genes that suppress the formation of tumours (“tumour suppressor genes”). This function can be lost as a result of either a genetic mutation or an epigenetic change. Likewise, other genes that regulate cell growth and behaviour when functioning normally, can stimulate uncontrolled growth when they are damaged. These are known as “oncogenes”, and again, the damage may be in the form of a genetic mutation or an epigenetic change. The concept of epigenetics is of particular interest in relation to environmental causes of breast cancer.

Causes and Risk Factors

Breast cancer is one of many cancers that cannot be ascribed to a simple cause. Because of this it is preferable to think in terms of “risks” rather than “causes”. As has been described above, some risks are inherited and some are incurred throughout our lives.

New research into the “causes” of cancer (14) raises the possibility that risk factors which are beyond an individual’s control (the inherited, intrinsic factors) may contribute only modestly to the overall chance of developing breast cancer. This question is not yet settled (15) but one estimate (16) is that intrinsic factors may be dominant in less than 10-30% of all cancers. If confirmed, this would mean most “causes” of breast cancer are not intrinsic and are therefore potentially avoidable.

Common types of Breast Cancer

Breast carcinomas typically begin in the cells of the ducts or the lobules (see Figure 1).

In situ breast carcinoma (also called non-invasive breast cancer) is an early form of breast cancer, which remains localised to the breast. The most common form is ductal carcinoma in situ (DCIS); if left untreated DCIS may become invasive. Another common non-invasive breast cancer is lobular carcinoma in situ (LCIS). This type of carcinoma is not cancerous (so does not spread), although its presence is correlated with an increased chance of developing cancer, at a later stage.

Invasive breast cancer can spread outside the breast. Invasive ductal breast cancer occurs in epithelial cells that line the breast ducts and accounts for around 80% of all breast cancers. Invasive lobular breast cancer occurs in lobes and accounts for around 10% (17).

Cancers that grow in response to high concentrations of oestrogen, progesterone and/or human epithelial growth factor 2 (HER2) are known as hormone receptor positive cancers. The most common of these is oestrogen receptor positive cancer. Cells from these tumours produce additional oestrogen receptors and depend on oestrogen to grow (18). Triple negative cancers are rarer and do not have additional hormone receptors.

Breast cancer may spread to other sites in the body through the blood stream or, more often, the lymphatic system. Cancer cells that spread from a breast tumour are often detected in the axillary lymph (19).

Biological Risk Factors

Oestrogens: Naturally occurring oestrogens increase the risk of developing breast cancer, mainly because of their ability to increase rates of cell division and their ability to promote the growth of oestrogen-responsive tumours (20).

Background Briefing | The Biology of Breast Cancer

Gender: Females have a higher lifetime exposure to oestrogens. After menopause, fat tissue becomes the main source of oestrogens for women (21) and is the main source for men (22).

Pregnancy and breast feeding: Women who have children at a younger age have a reduced risk of developing breast cancer. Reasons for this are unclear, although early (and multiple) pregnancy is thought to decrease the proportion of cells that are hormone receptor-positive and reduce expression of cancer-associated genes (23). Breast feeding reduces breast cancer risk as a result of changes in hormone levels and breast tissue (24). However, pregnant women have a higher risk of breast cancer due to this increase in reproductive hormones.

Age: As time passes and our cells undergo more divisions, DNA mutations accumulate and there is a higher chance that mutations associated with cancer will occur (25). As a woman ages, the levels of androgens (male sex hormones) and progesterone that normally exert inhibitory effects on the growth of breast tumours reduce, thereby increasing breast cancer risk (26).

Family history and genetics: Our genetic makeup is associated with our breast cancer risk and is thought to account for approximately 20-30% of all breast cancer cases (27). Around 5-10% occur as a result of a single gene mutation, such as those affecting the *BRCA* gene. Although the best known form of inherited breast cancer, only 2-3% of all breast cancers are associated with inherited *BRCA* mutations. If a parent carries a *BRCA* mutation, there is a 50% chance it will be passed on to their child. *BRCA1* and *BRCA2* are tumour suppressor genes (28) and if faulty, can make cells more susceptible to further mutations, resulting in an increased likelihood

of a cell becoming cancerous. Men with mutations in these genes also have an increased breast cancer risk (29). Other genes associated with increased risk affect the cell's ability to repair DNA, again making them more vulnerable to mutations and so becoming cancerous.

Benign breast disease: Benign (non-cancerous) breast lumps are common in women. Those with certain types have an increased risk of developing breast cancer (30).

High breast density: Mammographically dense breast tissue is associated with epithelial cell proliferation which is also associated with breast cancer (31).

Environment and Lifestyle

As well as biological factors, breast cancer risk is affected by environmental factors and lifestyle choices. It is important to remember that the factors listed below represent statistical correlations; they are not "causes".

Weight: Being overweight is associated with an increased risk of breast cancer. Obesity is associated with higher levels of circulating oestrogens in the body which in turn increases breast cell division and the rate of growth of oestrogen-responsive tumours (32). Lack of physical activity (33) and a diet low in fruit and vegetables is thought to contribute to increased risk (34). It has been suggested that phytoestrogens present in certain vegetables (e.g. soybeans) may help prevent breast cancer (35); more research is needed to confirm this.

Alcohol consumption: Alcohol metabolism produces chemically reactive molecules containing oxygen which may increase cell proliferation and cause mutations that can contribute to breast cancer.

Background Briefing | The Biology of Breast Cancer

Additionally, alcohol metabolism involves conversion of alcohol to acetaldehyde. Acetaldehyde can induce DNA damage associated with cancers (36). Alcohol intake is also associated with increased concentrations of circulating oestrogens in the body (37).

Ionizing radiation exposure, especially during adolescence, is known to be associated with an increased risk of breast cancer (38). Radiation can damage DNA and generate mutations.

Other carcinogens: Dioxins, polychlorinated hydrocarbons (39) and tobacco smoke (40), have all been linked to breast cancer, mainly when exposure occurs between menarche and first pregnancy. Air pollution, especially nitrogen oxides originating from car exhaust fumes, may also increase premenopausal breast cancer risk (41).

Shift work is associated with increased breast cancer risk (42), possibly due to a decreased production of melatonin, a hormone thought to have cancer protective properties.

Endocrine disrupting Chemicals

There is growing scientific evidence that routine exposures to substances known as endocrine disrupting chemicals (EDCs) can lead to cell changes that may increase the risk of developing breast cancer (43). EDCs are chemicals that interfere with the normal hormonal regimes within the body. Some EDCs mimic and enhance the effects of the body's normal oestrogen production. Others interfere with the natural binding of hormones to cell receptors, and others may cause epigenetic changes which switch genes on or off within certain cells (44). In a healthy body there is a finely regulated control of hormonal levels and actions. EDCs present in the external



Credit: Shutterstock, Alisa Studio
Endocrine disrupting chemicals can be found in everyday products such as soaps and shampoos

environment can interfere with this balance, in potentially harmful ways. Likely sources of EDCs are presented in the following section.

EDCs and Breast Cancer

A number of synthetic oestrogens increase the risk of breast cancer.

Diethylstilboestrol (DES) was once used as a drug treatment to reduce the risk of miscarriage, but was later found to increase breast cancer risk (by 40%) in those who used it (45). It also increases breast cancer risk in daughters of women who used this drug (46).

Hormone Replacement Therapy (HRT) is used to relieve symptoms of menopause, and involves the administration of oestrogens with or without progesterone, or its synthetic derivatives. Breast cancer risk is thought to increase during the period woman undergo HRT, although increased risk is no longer evident within five to ten years of stopping treatment (47).

Oral contraceptive pill use (which often contains the synthetic oestrogen, ethinyl oestradiol) can increase breast cancer risk slightly. Again, the risk is no longer apparent 10 years after its use has stopped (48).

Background Briefing | The Biology of Breast Cancer

Other endocrine disrupting chemicals: The above are examples of a medical or voluntary exposure to a risk; matters of individual need or choice. A more contentious debate surrounds other endocrine disrupting chemicals which we are usually involuntarily exposed to, such as bisphenol A (BPA), a synthetic oestrogen used in plastics, parabens used as preservatives in food and cosmetics, and phthalates, used in plastics and fragrances. All are weakly oestrogenic in tissue culture, and some have been found to act additively with natural oestrogens and other compounds (49, 50) to adversely impact the breast, in a way which could increase its vulnerability to breast cancer. Although most EDCs do not directly cause genetic mutations, several that are associated with increased breast cancer risk, including BPA, cause epigenetic changes that may be associated with breast cancer (51). These are examples of risks that may be pervasive and unrecognised and to which we are unknowingly or involuntarily exposing ourselves. [For further information on EDCs and breast cancer see our EDC Info sheet].

Are environmental and chemical exposures relevant?

Some have argued that the amounts of harmful chemicals to which we are involuntarily exposed is too low to represent any real risk. However, we question the assumption that we should not be concerned.

Laboratory studies have shown that effects of individual EDCs may be additive, as mentioned. This means that a combination of chemicals, even at low concentrations may have a greater effect than exposure to any one of them on its own. A recent Spanish study (52) found high levels of oestrogen mimics present in blood serum are positively

correlated with increased breast cancer risk. Curiously, it has also been shown that the effects of some EDCs are greater at lower concentrations - an effect known as a non-monotonic dose response (53). We are now exposed to these chemicals on a daily basis throughout our lives. This means the human body is exposed to hundreds of chemicals, from the earliest stages of *in utero* development, through puberty, during pregnancy and into menopause. Therefore, at key developmental stages when (oestrogen-driven) growth of breast tissue occurs, sensitivity to hormone mimics increases, along with an increased risk of breast cancer. The long latency period between the exposure to a risk and the development of breast cancer is precisely the reason why it is so difficult to pinpoint a causal relationship. However, continuous lifelong exposure to hormone disrupting chemicals makes it a certainty that they will be present at precisely the stage when they are most likely to produce an undesirable outcome.

Breast Cancer UK is calling for:

- Increased research investment into all of the risk factors associated with breast cancer
- An improved cancer strategy based on better understanding of the causes of cancer & acknowledgement of the environmental causes of the disease
- Greater investment and efforts towards primary prevention
- Improved chemicals regulation of harmful chemicals including EDCs, & their phase out from products such as food & drinks packaging, cosmetics and toys

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Background Briefing | The Biology of Breast cancer

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Background Briefing | The Biology of Breast cancer

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