Factors influencing the risk of breast cancer – established and emerging

The Health & Environment Alliance (HEAL) is an international non-governmental organisation that aims to improve health through public policy that promotes a cleaner and safer environment. Our work draws on the findings of the environmental health science revolution, which is revealing the impact of environmental degradation on health in an ever widening range of diseases and conditions. We represent a diverse network of more than 50 citizens', patients', women's, health professionals' and environmental organisations across Europe and we have a strong track record in bringing environmental health science and policy to an increasing number of fora. Our vision is that of a healthy planet for healthy people.

http://www.env-health.org/

CHEM Trust is a UK charity whose aim is to protect humans and wildlife from harmful chemicals. CHEM Trust's particular concerns are related to hormone disruptors, the cocktail effect of chemicals and the role of chemical exposures in early life. Exposure to undesirable chemicals may arise from contamination of the food chain and from the use and disposal of many everyday products such as TVs, computers, cars, construction materials, toys, toiletries and cosmetics. CHEM Trust is working towards a goal where chemicals play no part in causing impaired reproduction, deformities, disease or deficits in neurological function. CHEM Trust is committed to engaging with medical, scientific and patient communities to raise the level of dialogue on the role of chemicals in chronic disease, and the wider implications this may have for disease prevention strategies.

http://www.chemtrust.org.uk/

Chemicals Health Monitor *aims to improve public health by ensuring that key scientific evidence on the links between chemicals and ill-health are translated into policy as quickly as possible. The strategy involves fostering dialogue, sharing perspectives and promoting greater collaboration between policy makers and governments on the one hand and scientific researchers, medical and health professionals, patient groups, environmental organisations and the public on the other. We work to highlight the compelling scientific basis for added controls over certain chemicals; and encourage EU policies that are precautionary and participatory, especially with regard to the implementation of REACH, and the substitution of hazardous chemicals.*

The project was launched by the Health and Environment Alliance (http://www.env-health.org/) in collaboration with other partner organisations across Europe in March 2007.

http://www.chemicalshealthmonitor.org/

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Introduction

Most of us will know of someone affected by breast cancer, be they a family member, friend or acquaintance. Faced with a diagnosis of breast cancer, many women ask, "why me"? Unfortunately, there is no easy answer to this question. There is still a lot we do not know about breast cancer. But the good news is that our understanding is increasing all the time, and this will provide new avenues for preventing the disease, which is of course the best outcome. Also, thanks to better treatment and earlier diagnosis, more women are surviving the disease than ever before.

The high incidence of the disease in developed European countries, and the sharp increase of new cases in the rapidly developing eastern European countries[1], is a cause for concern. This rate of increase is happening so quickly that it cannot be attributed mainly to hereditary factors. At least part of the reason must lie in our environment and/or how we live today.

This briefing will outline:

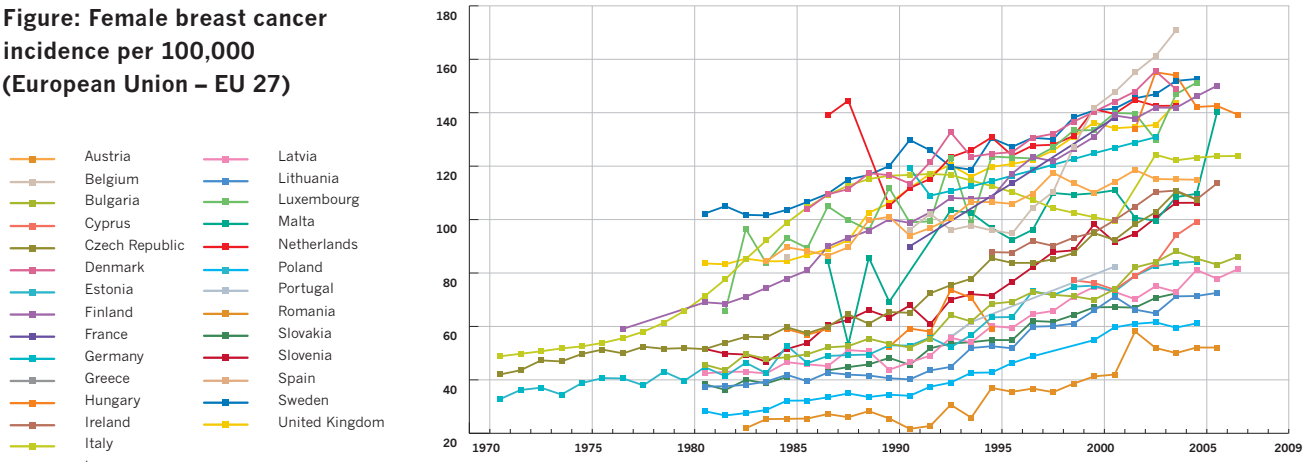
1. The established risk factors for breast cancer, and
2. The current thinking regarding the involvement of certain chemical exposures in breast cancer, and in particular, the concerns about man-made chemicals which mimic the female hormone oestrogen.

Doctors and scientists largely agree about factors that can influence a woman's chances of getting breast cancer, such as age, weight, the number of children she has and the possession of certain so-called 'breast cancer genes'[2]. These are known as 'established risk factors'.

However, all the established risk factors together can only explain about half of breast cancer cases and for the remainder, scientists and doctors are still unsure of the causes[2,3]. One of the suggested additional risk factors for breast cancer is the environment, i.e. the world around us. This may come as a surprise to some people, as it is often thought that breast cancer is largely an inherited disease. This is not the case. And the proportion of breast cancers related to specific inherited genes is in fact very low; only around 1 in every 10 to 20 cases is due to inherited "breast cancer genes"[2,4]. Indeed, there is evidence from studies on twins suggesting the environment, rather than genes, has more influence on the chance of developing breast cancer (see "Environmental Factors" on page 7). Therefore, to improve prevention of the disease there is a need to identify the factors in our environment that might be responsible and try to minimise our exposure.

One of the environmental factors that may be important in breast cancer is exposure to certain man-made chemicals. New evidence is emerging to support the theory that exposure to pollutants in our environment, food and water, and to chemicals in consumer products in our homes, offices and schools may be a risk factor for breast cancer [5,6,7,8].

Figure: Female breast cancer incidence per 100,000 (European Union – EU 27)



Source: WHO/Europe; European HFA Database, June 2007

1. Established Risk Factors

The established risk factors for breast cancer may increase a woman's chances of developing the disease. However, having one or more risk factors does not necessarily mean that a woman will get breast cancer, and no single factor can explain any given case of breast cancer as it is a complex disease with often many different contributing causes. There are some risk factors that women have control over, such as alcohol consumption, weight gain after menopause, and exercise, while others such as age, age of onset of menstruation or menopause are not within a woman's control.

The Established Risk Factors outlined in this briefing are the following:

- Genetic predisposition and family history;
- Natural oestrogen;
- Oestrogen in pharmaceutical products – the Oral Contraceptive "The Pill" and HRT (Hormone Replacement Therapy);
- Weight gain and lack of exercise;
- Alcohol consumption;
- Other risk factors.

Genetic predisposition and family history

The widely held view that breast cancer is largely a genetic disease is inaccurate. For 9 out of 10 women with breast cancer, specific inherited genes do not seem to be responsible for the development of the disease[9], and 8 out of 9 women who develop breast cancer do not have an affected mother, sister, or daughter[10].

There are a small percentage of women who have faulty versions of genes called BRCA1 and BRCA2, and having these genes does make them particularly susceptible to developing breast cancer[11,12]. These genes are very rare. Other rare variations in certain genes can also increase a woman's breast cancer risk[13]. Even if a woman has one or more of these kinds of genes, it still does not mean she will develop the disease. This is because, as with many genes, lifestyle and environmental factors influence whether these genes will make their presence felt (see "Environmental Factors" on page 7).

Natural oestrogen

One of the most established risk factors for breast cancer is a woman's total lifetime exposure to oestrogen[14]. Although oestrogen is produced in a woman's body (in the ovaries) and is essential for the development of the breast, paradoxically oestrogen is also involved in the development of breast cancer via the stimulation and proliferation of breast cancer cells[15,16]. In fact, the longer oestrogen is circulating in a woman's body, the greater the risk of developing breast cancer. For example, it is well known that the greater number of menstrual cycles a woman goes through in her life, the greater her overall risk for breast cancer. Put more simply, if a woman starts her periods earlier than average and goes through the menopause later, her body is exposed to more natural oestrogen (released from the ovaries during every menstrual cycle) over her lifetime and she therefore has an increased risk of developing breast cancer. For women who start their periods earlier than average, the risk is increased by 5% per year[17], and for late menopause the risk is increased by 3% per year[18].

Similarly, having children reduces a woman's lifetime exposure to her own oestrogen and therefore her breast cancer risk[19]. Each pregnancy is thought to decrease breast cancer risk by 7%[20]. This is because for the duration of pregnancy the ovaries are not producing oestrogen. It is thought that this is one of the reasons why breast cancer incidence is increasing in western societies, as women are now having fewer children later in life, or no children at all.

Research indicates that breastfeeding also reduces breast cancer risk and that the longer a woman breastfeeds, the greater the reduction in risk, with a 4.3% decrease in cancer for every 12 months of breast feeding[20,21]. It is not fully understood why this should be, but scientists think that breastfeeding may change the cells in the breast and may make them less prone to developing cancer.

Oestrogen in pharmaceutical products - The Pill and HRT

The contraceptive pill (which contains female hormones) has been shown to slightly increase a woman's breast cancer risk. This risk slowly disappears after coming off the pill, and is no longer an issue 10 years after cessation of use[22].

Post-menopausal use of Hormone Replacement Therapy (HRT) drugs can increase a woman's risk of breast cancer[18,23,24,25]. It is therefore very important that women discuss all options carefully with their doctor before starting HRT, and weigh up the severity of their symptoms against possible side effects. In the USA, Germany and France, figures show that breast cancer incidence has actually decreased slightly in recent years, which is thought to be due to the drop in the number of women being prescribed HRT[26,27,28].

The well documented evidence that a woman's lifetime exposure to both her own natural oestrogen and to oestrogen in pharmaceutical products (i.e. the Pill and HRT) influences her risk of breast cancer makes a very compelling case for suspecting that our constant exposure to man-made chemicals which mimic oestrogen may also play a role (see "Environmental Factors" on page 7).

Weight gain and lack of exercise

Weight gain and being overweight are risk factors for breast cancer in women who have gone through the menopause[29,30]. The advice would be to adopt a diet that avoids weight gain.

Physical activity reduces a woman's breast cancer risk[29,31] so regular exercise is advisable. The UK Government currently recommends 30 minutes of moderate activity five days per week[32].

Alcohol consumption and smoking

Drinking alcohol has consistently been shown to increase breast cancer risk, in both pre- and post-menopausal women[33,34]. In the UK, it is recommended that women limit the amount of alcohol they drink to 14 units a week (one unit is a glass of wine, half a pint of beer or a measure of spirits)[35]. A recent collaborative survey, looking at over 50 separate studies, also suggests that drinking even small amounts of alcohol can increase the risk. It was shown that 8.8% of women who abstain from alcohol develop breast cancer by the time they are 80 years old, but of those drinking between 2 units and 4 units/day 10.1% and 11.6% respectively will develop breast cancer by the time they are 80[36].

Smoking has long been thought to have no significant effect on breast cancer risk[2,35]. However, recent research has suggested exposure to tobacco smoke may increase risk. Exposure to second-hand smoke (passive smoking), has been found to slightly increase breast cancer risk[37] and research suggests that smoking whilst a teenager can also increase a woman's risk post-menopause[38,39]. However, more research is needed before the association between cigarette smoke and breast cancer is clearly defined. In the meantime, not smoking has other clear health benefits.

Other risk factors

As well as those described above, other risk factors for breast cancer include radiotherapy treatment for Hodgkins lymphoma[40,41], having dense breasts[42], being taller than average[43] and having certain kinds of non-cancerous breast disease[44].

In addition, exposure to ionizing radiation such as X-rays has been shown to increase cancer risk but this should not stop women having mammograms as the potential benefit of early detection of a breast tumour is believed to far outweigh any risk of exposure to a tiny amount of x-ray radiation during the scan[35]. Nevertheless, in future, alternative methods for early detection could be developed that would be preferable. Research also suggests women working predominantly at night are at increased risk of breast cancer[45,46,47,48]. This could be due to exposure to 'light at night', which suppresses the production of melatonin, a hormone which is thought to be able to prevent the growth of cancerous cells and which may also increase the release of oestrogen from the ovaries[45]. However, more work is needed to fully confirm a link between light at night and breast cancer.

Phytoestrogen (plant oestrogen) – an unclear role in breast cancer

Phytoestrogen is found in plants and plant derived foods such as soy beans and flaxseeds and can act like oestrogen in the body, but the research on its potential involvement in breast cancer is conflicting[50]. While some studies have found no association between phytoestrogen and breast cancer, others suggest that phytoestrogen can have a protective effect against breast cancer. Clearly more research is needed on the subject of phytoestrogen before their involvement in breast cancer, if any exists, becomes clear.

With perhaps the exception of night shift work where further research is warranted to confirm the risk, all the 'established or known risk factors' outlined above are those that scientists and doctors agree can make a difference to a woman's risk of developing breast cancer. However, it is also agreed that they only account for around half of diagnosed breast cancers. So what could be causing the other 50% of cases? And why are more women, and younger women[51], developing the disease?

Established risk factors for breast cancer - all of which increase a woman's oestrogen exposure

- Starting periods early
- Late onset of the menopause
- Not having children or having them later in life
- Not breastfeeding or breast feeding for only a short time
- Use of oral contraceptives
- Use of hormone replacement therapy
- Obesity
- Regular intake of alcohol[49]

2. Environmental factors

Breast cancer is caused by a *combination* of hormonal, genetic, lifestyle and "environmental" factors. It is factors in our environment i.e. the world around us, that are thought to be responsible for at least some of the unexplained proportion (50%) of cases.

Studies on twins and migrant women have illustrated just how important our environment can be. Research on twins in Scandinavia has shown that only 27% of the breast cancers recorded could be explained by genetic factors and therefore 73% of the risk was due to environmental factors[52]. The study's authors said that their findings "indicate that the environment has the principal role...". More evidence suggesting our environment can influence our chances of getting cancer comes from research on Japanese women (who traditionally have a much lower incidence of breast cancer than western women) who migrate to the USA. Within one or two generations the incidence of breast cancer in the descendants of migrant Japanese women increases to become similar to that of US women[53].

The environment can also strongly influence breast cancer risk even in women who have a high likelihood of getting the disease because of their 'breast cancer' genes. Women with one or more faulty BRCA genes who were born before 1940 have a 24% chance of developing breast cancer by the age of 50, but women with the genes born after 1940 have a 67% risk of being diagnosed by the same age[12]. This indicates that some other factor that is now more prevalent in our environment is involved and it is not just faulty genes that determine the risk of contracting breast cancer.

Exposure to man-made chemicals

So what in our environment could be causing these changes? Scientists are still unsure about what environmental factors are involved in breast cancer, but one compelling theory, with an increasing amount of evidence, is exposure to certain man-made chemicals that can mimic hormones. Our reliance on synthetic chemicals has increased dramatically over the last 50 years, and they are an integral part of our everyday 21st century lives, providing many lifestyle benefits. Unfortunately however, remarkably few of the man-made chemicals in use today have been adequately assessed for their safety and toxicity[54], and it is now clear that a few of these chemicals have undesirable properties. Of particular concern are chemicals which are known to cause cancer in the mammary (breast) tissue in laboratory studies ("mammary carcinogens")[8], and chemicals that can mimic oestrogen. Oestrogen mimicking chemicals are part of a group of chemicals called hormone disruptors or "endocrine disrupting" chemicals (the endocrine glands secrete hormones in the body). Concern about these chemicals amongst scientists worldwide has escalated in recent years. The remainder of this briefing focuses on hormone disrupting chemicals and explores their potential involvement in breast cancer.

Not all chemicals are bad. In fact, all of us are exposed to natural and man-made chemicals in the air we breathe, the food we eat, the water we drink and the consumer products we use in our daily lives. But it is increasingly being recognised that we need to identify those chemicals which do have harmful properties and stop using them. Laboratory tests allow scientists to identify those chemicals which can mimic oestrogen, and those which are suspected to cause cancer.

Synthetic oestrogen – e.g. The Pill and HRT

Artificial oestrogen such as the contraceptive pill and HRT, have been shown to increase a woman's risk of breast cancer (see previous section).

Another form of artificial oestrogen, a drug called diethylstilbestrol (DES) was given to women in the 1950s and 60s to prevent miscarriage. Not only was it not effective at doing this, but research has also shown that it doubled the risk of breast cancer for the daughters of the women who took it[55]. This shows how a hormone, when present at the wrong time (in this case during the development of baby girls in the womb) can lead to problems later in life. What if hormone mimicking environmental chemicals to which pregnant women are exposed today have similar effects?

Some chemicals found in our environment that have oestrogen-disrupting properties

- DDT – although banned in Europe for decades, the breakdown products of this pesticide are still found in the food chain, and therefore food is the main exposure route[56].
- Several other pesticides e.g. some pyrethroid insecticides[57,58] and methoxychlor, which is now banned, also act on the oestrogen receptor[59].
- Polychlorinated biphenyls (PCBs) – used in capacitors and transformers, and some building materials. Manufacture has long ceased in Europe but because PCBs are highly persistent, exposure still occurs, mostly via food[60,61].
- Dioxins – these are by-products which are not produced intentionally but are released during burning coal, oil or chlorinated materials. They are released from incinerators, pulp and paper mills, and factories, such as metal processing works. They are highly toxic and found in the food chain [8,62].
- Bisphenol A (BPA) - used in plastics and resins to make water and food storage containers, food and drink can linings, tableware, dental sealants and babies' bottles. Exposure occurs via leaching of BPA into the food and drink from the containers[63].
- Parabens - preservatives and antioxidants used in toiletries and cosmetics e.g. underarm deodorants. Test tube experiments suggest several parabens can disrupt oestrogen, and butyl-paraben and butyl-paraben absorbs through the skin[64,65].
- UV filters - e.g. benzophenone and 4-MBC. Several chemicals used in sun creams are able to disrupt oestrogen and cause effects in animals. Some oestrogenic UV filters can be absorbed through the skin[66,67,68,69].
- Alkylphenols – including nonyl phenol (NP) and octyl phenol (OP) – from plastics, paints, inks and detergents, and used in textile processing. Nonyl phenol is now highly regulated, but both NP and OP are oestrogenic in organisms. May be found as contaminants in food. Exposure can arise via skin absorption, inhalation and food[70,71].

Unfortunately, early studies on the link between chemicals and breast cancer did not look at multiple exposures at critical times. This may be the reason why such studies have been largely inconclusive.

The more scientists learn about the role of chemicals in human health the clearer it becomes that a different approach is needed, one which examines exposure to chemicals in a more relevant way. Research has recently highlighted two critical factors:

i) The cocktail of oestrogen mimicking chemicals to which we are all exposed (the "cocktail effect") and
ii) The vulnerable stages of development when exposure occurs ("timing").

These realizations have made the theory of oestrogen-mimicking chemicals and their involvement in breast cancer increasingly plausible. Studies have been published which investigate the timing and nature of exposure to oestrogen-mimicking chemicals and provide invaluable insight into the complicated origins of breast cancer.

I) THE COCKTAIL EFFECT

Despite the theory of the role of oestrogen mimicking chemicals in breast cancer, it will be almost impossible to prove the involvement of specific chemicals, particularly because we are never exposed to single chemicals on their own. Our modern lifestyles expose us to a cocktail of different chemicals, many of which have hormone-like properties. Recent studies show that a number of different chemicals can add to the effects of natural oestrogen, even when those man-made oestrogen mimicking chemicals are present at very low levels that would not cause an effect on their own[5,72]. There is new evidence that for some women current exposure to a mixture of oestrogen mimicking chemicals can influence the risk of breast cancer. A study among Spanish women shows, for the first time, that breast cancer risk is associated with the total amount of certain man-made oestrogen mimicking chemicals (excluding natural hormones) found in a woman's body[73]. This is the first evidence that oestrogen mimicking chemicals in our environment can play a role in the development of breast cancer.

II) TIMING OF EXPOSURES

As well as looking at the mixture of chemicals to which we are exposed, it is vital to look at the amounts during the most important times of development such as development in the womb and during puberty.

A recent study in the US has highlighted the profound impact that chemicals can have if exposure occurs during puberty. The study showed that women exposed during puberty to relatively high levels of DDT were five times more likely to develop breast cancer later in life than women with lower exposures[74]. The study also found that exposure after puberty does not increase the risk.

The tragic story of DES shows that exposure to oestrogen mimicking chemicals in the womb can have a devastating impact on the development of the breast later in life. Studies on pregnant rodents using an oestrogen mimicking chemical called bisphenol A (BPA - widely used in consumer products) have also shown that *in utero* exposure can alter the development of the breast tissue in the growing foetus, with possible consequences for breast cancer in later life[75,76]. Indeed, exposure to this oestrogen mimicking chemical makes animals more sensitive to mammary cancer later in life when subsequently exposed to a cancer causing agent[77]. There is not enough evidence to confirm a link in humans yet, but many scientists are increasingly worried because exposure to BPA is so widespread.

These studies show why it is vital to study exposure to potential breast cancer causing chemicals during the critical time period, which may be several decades before the disease occurs. Only then will scientists be able to work out which specific chemicals might be implicated in breast cancer.

Preventing breast cancer: A way forward

Women wishing to reduce the chance of developing breast cancer can make choices about some aspects of their lifestyle, such as alcohol consumption. However, women have no control over many of the established risk factors, such as late age at menopause. Therefore, few proven options for reducing breast cancer exist but bearing in mind the mounting evidence, it can be argued that it would be wise to try to reduce exposure to hormone mimicking chemicals. The Royal Society in the UK[78], with reference to endocrine disrupting chemicals (EDCs), has said...

> *"Despite the uncertainty, it is prudent to minimise exposure of humans, especially pregnant women, to EDCs."*

Similarly, the 2005 Prague Declaration on Endocrine Disruption[79], signed by more than 200 scientific experts from across Europe and the US recommends precautionary action on endocrine disrupting chemicals...

> *"For the foreseeable future, regulation of endocrine disrupters will have to cope with the tension between the biological plausibility of serious, perhaps irreversible damage and delays in generating data suitable for comprehensive risk assessment. In view of the magnitude of the potential risks, we strongly believe that scientific uncertainty should not delay precautionary action for risk reduction."*

Women may choose to limit the unnecessary use of household chemicals, plastic food wrappings, DIY products, and cosmetics. They may also choose to avoid pesticides by eating organically produced fruit and vegetables. But is it really practical for women to have a list of all the known oestrogen mimicking chemicals, and look at each and every label in the supermarket trolley: on toiletries, fruit and vegetables or in all the products in the home including that new smell emanating from the recently replaced shower curtain or kitchen floor?

The answer is that regulatory intervention is needed. CHEM Trust and the Health and Environment Alliance (HEAL) believe it should be the responsibility of regulatory authorities to ensure harmful chemicals, particularly hormone disruptors, are identified and are phased out in favour of safer alternatives.

In the short term, given the number of chemicals potentially involved, and the other confounding factors, it will be impossible to fully elucidate the role chemical exposures are playing in breast cancer. However, in the face of so much human tragedy, well respected international scientists are beginning to raise questions as to how much proof is enough. Some feel that threshold has already been reached.

It is relatively easy for governments to put the ball into the court of the individual and to talk of exercise and weight control. However, the increasing scientific evidence is now demanding that governments also play a part and ensure better control of chemical exposures.

Further Information

CHEM Trust website – Section: ''Diseases: Breast cancer''
http://www.chemtrust.org.uk/

Health and Environment Alliance (HEAL) - Chemicals Health Monitor project website – Section ''Chemicals and Diseases: Breast cancer''
http://www.chemicalshealthmonitor.org/

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The risk factors for breast cancer

Solving the riddle of the missing causes

Only 50% of breast cancers can be linked to specific established or "known" causes. These include genetic predisposition; a woman's total lifetime exposure to oestrogen; the pill and HRT; weight gain and lack of exercise; and, alcohol consumption.

What other factors might be playing a role? Given that exposure to natural and synthetic oestrogens (in the pill and HRT) are both recognised to contribute to the risk, this publication argues that other oestrogenic mimicking chemicals or hormone disrupting chemicals may be playing a role. Modern life is exposing us all to a cocktail of chemicals, some of which are known to disrupt our hormones, including oestrogen. Hormone disrupting chemicals include some pesticides, dioxins which contaminate our food, Bisphenol A that can leak from tin cans and plastic containers, and some UV filters used in sunblock.

Research indicates that better control of such chemicals could make a real difference.

In reading this report it is hoped you will be able to make up your own mind whether breast cancer is possibly more preventable than you had previously thought.

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