

# Environmental contaminants and breast cancer:

*the growing concerns about  
endocrine disrupting chemicals*

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## BACKGROUND: THE ALARMING INCREASE IN BREAST CANCER

The number of new breast cancer cases among women is increasing in almost all Western countries. Thanks to improvements in early detection methods, the chances of surviving the disease have changed for the better, but the continuing rise in the number of new cases places a heavy burden on health services and causes immense private suffering. According to recent figures, the number of women diagnosed with breast cancer in Europe grows continuously, especially in eastern Europe. The risk of contracting breast cancer is highest in northern and western Europe<sup>1</sup>. Throughout their lifetime, around 1 in 9 women in the UK will be diagnosed with breast cancer.

These worrying trends are only partly explained by life choices and changes in lifestyle. For example, it has long been known that breast cancer risks are higher among women who have their first baby late in life, or who do not have children. Around 1 in 20 breast cancer cases are believed to be inherited, but for the overwhelming majority of women the disease is not passed on through genes but acquired during their lifetime<sup>2</sup>. High alcohol consumption<sup>3</sup> and high fat diets<sup>4</sup> also contribute to breast cancer risks. But the sheer number of newly diagnosed cases cannot be explained solely by lifestyle changes, alcohol or poor diet. Experts estimate that more than half of all breast cancers are due to as yet unidentified causes<sup>5</sup>. So what are these additional factors?

## GROWING CONCERN ABOUT ENDOCRINE DISRUPTING CHEMICALS

The realisation that natural hormones play a role in breast cancer has led to renewed concerns about chemicals with hormonal activities found in food, personal care products or as environmental contaminants. It is still not possible to be certain that hormone or endocrine disrupting chemicals play a role in breast cancer, but two findings have emerged from recent scientific research that increase the biological plausibility that this might be the case. These are (a) the importance of the combined action of several chemicals – the “cocktail effect” – and (b) the existence of critical periods early in life and during development in the womb that make women particularly sensitive to breast cancer-causing factors.

In the light of this new evidence, the role of chemicals in breast cancer requires urgent attention, and precautionary action is warranted to reduce exposure. This briefing explains the role of oestrogens in breast development, and the evidence for suggesting that man-made chemicals may be implicated in the increased incidence of breast cancer.

## OESTROGENS AND BREAST DEVELOPMENT

Mammary glands are composed of a tree-like ductal structure for the release of mothers' milk. These structures are not fully developed and functional at birth. Baby girls are born with a duct structure that extends only a small distance from the nipple. Until puberty, these ducts grow in proportion with the rest of the body, but during puberty they experience a massive growth phase. Essential for this growth are steroid oestrogens, natural hormones produced by the ovaries.

Oestrogens act on cells in the blind ends of the ducts, the “end buds”, a process that leads to the elongation and branching of the duct system. With every secretion of oestrogens during ovulation, the entire structure becomes more elaborate and branched. The final phase of development occurs during pregnancy when there is a further massive branching of ducts and

the entire system matures fully. After breastfeeding and weaning, many of the ducts grown in pregnancy are remodelled to resemble the state before pregnancy<sup>6</sup>.

#### NATURAL OESTROGENS AND BREAST CANCER

Paradoxically, natural oestrogens also play a role in breast cancer. It is thought that in promoting the growth of end buds, oestrogens may also contribute to an increase in cells that later in life become prone to cancerous growth. This is borne out by the observation that the majority of breast cancers derive from end buds, the cells most responsive to oestrogens in breast development. During the periods when the duct structures grow, especially during puberty, the breast is particularly vulnerable to cancer-causing influences<sup>7</sup>. Elevated levels of oestrogens during foetal life are also associated with breast cancer<sup>8</sup>. In the womb, the hormone influences the number of end buds in the primitive duct structure of the foetus: higher oestrogen levels induce the growth of more end buds, thereby enlarging the cell pool from which cancer cells derive.

The cyclical secretion of oestrogen during a woman's life is now recognised as a key determinant of breast cancer risk: the more oestrogen reaches the sensitive structures in the breast during her lifetime, the higher the overall risk. Thus, every year of delay in the onset of regular ovulations corresponds to a 5% reduction in breast cancer risk. Conversely, every year of delay in menopause increases the risk by 3%<sup>9</sup>.

On the other hand, pregnancies have a strong protective influence. Each child birth is thought to decrease the risk of breast cancer by 7%, and this effect is even more pronounced before the age of 20<sup>9</sup>. The very high levels of oestrogen and other hormones that are secreted during pregnancy stimulate the full maturation of the duct system of the breast. It is thought that this leads to a reduction in the number of cells in the end buds that are vulnerable to cancer-causing factors, and thus to a decrease in cancer risk.

#### OESTROGENS IN CONTRACEPTIVES AND HORMONE REPLACEMENT THERAPY

The cancer-promoting effects of oestrogens are not limited to natural hormones. External oestrogens administered as oral contraceptives, for the suppression of menopausal symptoms or as anti-miscarriage drugs are also associated with breast cancer. The use of these therapies has increased enormously during the last decades. For example, hundreds of millions of women worldwide have taken oestrogen and progestin as oral contraception<sup>9</sup>. In Britain, one third of all women aged 50-64 use hormone replacement therapy (HRT)<sup>9</sup>.

Combined oestrogen and progestin oral contraceptives lead to a slightly higher breast cancer risk among women who are current users of "the pill" and have been using it for more than 10 years, but there is no detectable increased risk more than 10 years after last use. The excess breast cancer risk among women who have used HRT for five years or longer is estimated to be 35%, but the risk reduces after stopping HRT and is no longer noticeable five years after last use<sup>9</sup>. According to recent estimates, the use of HRT during the last decade has resulted in an extra 20,000 breast cancer cases in the UK alone<sup>10</sup>.

## (A) ENVIRONMENTAL POLLUTANTS AND CHEMICALS IN CONSUMER GOODS THAT MIMIC OESTROGEN, AND THE POTENTIAL ROLE OF THE MIXTURE EFFECT IN BREAST CANCER

Concerns about the possible contribution to breast cancer of environmental pollutants and chemicals found in consumer goods grew with the realisation that many of these substances behaved like steroid oestrogens<sup>11</sup>. The high persistence of some of these chemicals – such as the pesticide o,p'-DDT and its metabolite p,p'-DDE, and polychlorinated biphenyls (PCBs) – combined with their widespread presence in human tissues only added to fears regarding their potential role in the development of breast cancer. Given the good evidence in support of a role for oestrogens in breast cancer, it appeared plausible to suspect that these compounds too should be risk determinants.

However, studies carried out to examine whether persistent chemicals such as o,p'-DDT, p,p'-DDE and PCBs are implicated in breast cancer could neither prove nor rule out a possible link. Some have taken these outcomes as proof to discard a putative relationship between these chemicals and breast cancer risk<sup>12 13</sup>. However, in these studies, too few women were examined to decide the question with certainty, and this factor alone is likely to have produced misleading results.

Furthermore, evidence emerging from recent research shows that two important issues must be fully addressed to avoid wrongly dismissing a role for these chemicals in breast cancer. First, studies in humans have largely focused on single chemicals but have ignored the large number of agents that may act in concert to contribute to breast cancer risks<sup>14</sup>. Second, to understand the role of chemicals in breast cancer, exposures during critical windows of vulnerability, including development in the womb, must be captured. Studies that only examine exposures at the time of breast cancer diagnosis run the risk of overlooking disease-causing factors<sup>15</sup>.

### BREAST CANCER AND THE POLLUTANT "COCKTAIL EFFECT"

Chemicals such as o,p'-DDT, p,p'-DDE and PCBs do not act in isolation in a woman's body, but in concert with natural oestrogens and a large number of other hormonally active chemicals. These include: chemicals released during the preparation of food (for example, during the grilling of meat); a growing plethora of man-made chemicals found as environmental pollutants (dioxins, certain PCBs and pesticides); those used in cosmetics (such as antioxidants, UV-filter agents, and some synthetic fragrances); those that leak from plastics (for example bisphenol A, nonyl phenol); and plant-derived oestrogens in certain food.

The hormonal strength of many of these chemicals is considerably lower than that of natural or pharmaceutical oestrogens. Nevertheless, laboratory experiments have shown that a sufficient number of such chemicals can add to the effects of natural oestrogens, even when they are present at levels that individually do not produce measurable effects<sup>14</sup>. This work highlights that the focus of the previous human studies attempting to investigate the effects of chemicals on breast cancer was wrong. Instead of concentrating on a few, arbitrarily selected substances, the entirety of hormonally active chemicals must be considered.

A recent study among Spanish women demonstrated that breast cancer risk was associated with the body burden of all oestrogenic chemicals, excluding the natural hormones<sup>16</sup>. This is the first evidence that chemicals in our environment, with oestrogenic properties that are 'accidental',

and not just natural hormones or pharmaceutical oestrogens may contribute to the development of breast cancer.

#### (B) BREAST CANCER AND EXPOSURE DURING PERIODS OF INCREASED VULNERABILITY

There are periods in a woman's life when the breast is particularly vulnerable to cancer-causing influences. One such period is puberty, when the breast experiences the first significant growth phase of the ductal system. The increased sensitivity of the breast tissue at this time of life was first noticed in the aftermath of the atomic bombs in Hiroshima and Nagasaki. As a result of the massive levels of radioactivity, breast cancer in Japanese women increased significantly, but only in women who were exposed during puberty. Older women experienced far less pronounced breast cancer risks<sup>7</sup>.

Another key period is during development in the womb, when the origins of the mammary gland ductal system are laid down. Elevated levels of natural oestrogens during this critical time are associated with increased breast cancer risks of daughters later in life<sup>8</sup>.

Very recently, proof was provided that synthetic oestrogens can have similar effects. Between 1953 and 1971, approximately 300,000 women in the UK alone used diethylstilbestrol (DES), an oestrogenic drug, to avoid miscarriages. Not only was the drug ineffective for its intended purpose, it turned out that women whose mothers took DES face twice the normal breast cancer risk<sup>17</sup>. The risk is expected to grow further as these "DES daughters" reach menopausal age. It is thought that DES exposure of the developing foetus in the womb may have promoted the growth of ductal end buds, thereby enlarging the number of cells from which cancer can develop later in life.

Other studies with laboratory animals point in the same direction and suggest that exposure to man-made oestrogen-mimicking compounds in the womb can alter the development of the mammary tissue with possible consequences for breast cancer<sup>18 19</sup>.

Tumour growth is most pronounced when the cancer-causing agent is given to young animals in which the mammary gland is developing, whereas adult animals are almost immune<sup>6</sup>. Some hormonally active chemicals, such as dioxins, can increase the sensitivity of rats to other breast cancer-causing substances when given at critical times during development in the womb<sup>15</sup>. These observations highlight the importance of documenting exposure to potentially cancer-causing chemicals at the appropriate times. For human studies, this poses an enormous challenge: to prove or dismiss a link with breast cancer, exposure to chemicals must be recorded many years before the cancer becomes manifest. Measuring chemicals at a time when the disease is diagnosed will miss important features and will provide a warped picture.

#### IMPLICATIONS FOR SAFETY TESTING OF CHEMICALS

The testing of chemicals for possible carcinogenic effects is usually carried out with laboratory animals after birth, and does not encompass their development in the womb. Although there is evidence that exposure during development will increase the sensitivity with which cancer-causing agents can be detected, this is not incorporated in safety testing strategies. Furthermore, a great deal of carcinogenicity testing focuses on the screening for chemicals that have the ability to cause gene mutations. However, many of the hormonally active chemicals shown to have profound developmental effects on breast cancer risks in animals are not mutagenic and

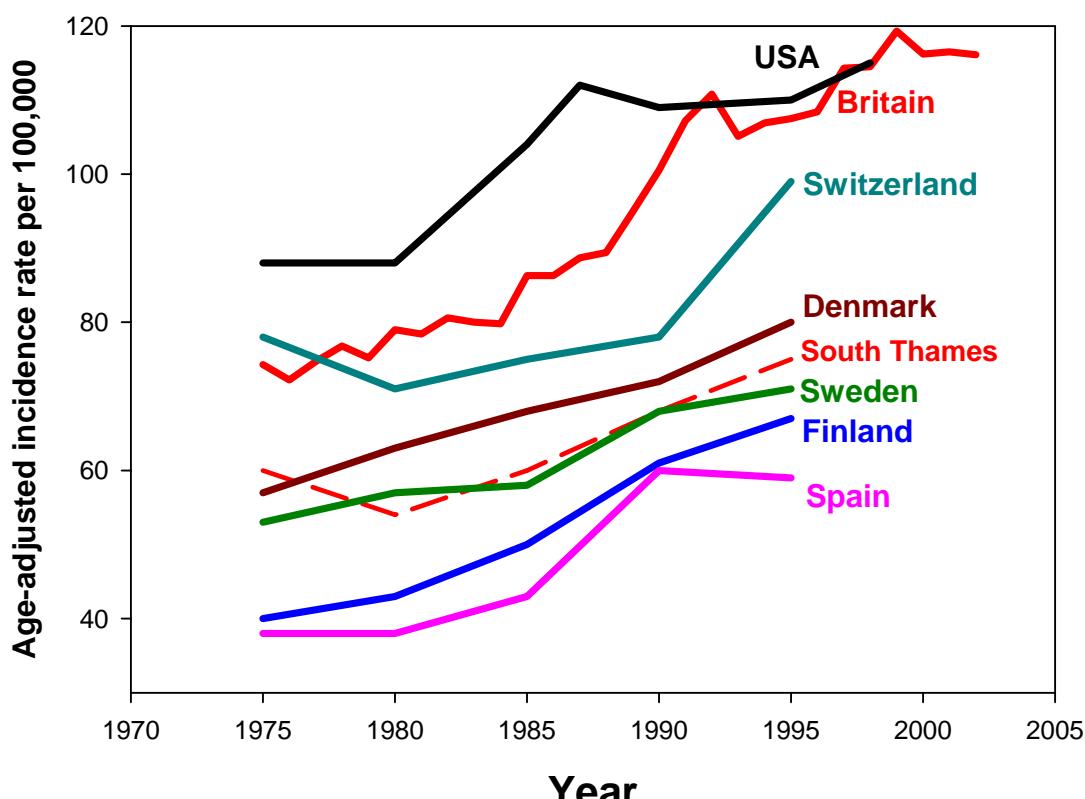
will therefore be missed during screening exercises. These inadequacies have led researchers to question whether, in trying to identify cancer-causing chemicals, they are using the wrong tools, at the wrong times<sup>15</sup>?

## CONCLUSION

Although it is clear that many factors play a role in breast cancer, a contribution of environmental chemicals cannot be dismissed. Indeed, concerns are mounting although positive proof from human studies is missing. Nevertheless, in view of the proven contribution of natural and therapeutically used oestrogens, it is biologically plausible that less potent hormonally active chemicals may also contribute to risks, and the health experience of Spanish women supports this idea<sup>16</sup>. Using targeted research strategies, the issue should be pursued further with urgency. There is also a need to act sooner on evidence available from experimental laboratory studies, because confirmatory data from epidemiological studies would take decades to materialise.

Given the known role of oestrogen in breast cancer, it would be prudent to reduce exposures to chemicals that can mimic oestrogen. Consideration should therefore be given to replacing such chemicals with safer alternatives, where possible.

**Figure: The rise in the number of new breast cancer cases in several countries**



All data from<sup>1</sup>, except data for Britain are taken from Cancer Research UK  
<http://info.cancerresearchuk.org/cancerstats/types/breast/incidence/#source1>

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