breast cancer

Breast cancer and exposure to hormonally active chemicals: An appraisal of the scientific evidence

A background briefing paper
by Professor Andreas Kortenkamp,
Head of the Centre for Toxicology,
The School of Pharmacy,
University of London

April 2008

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/

The Health & Environment Alliance gratefully acknowledge the financial support of the Sigrid Rausing Trust, the Marisla Foundation and the European Commission, DG Environment. The views expressed in this publication do not necessarily reflect the official views of the funders and the EU institutions.

Design: beëlzePub, www.beelzepub.com
Printed at Gillis on recycled paper with vegetable-based ink.

Breast cancer and exposure to hormonally active chemicals:
An appraisal of the scientific evidence

A background briefing paper by Professor Andreas Kortenkamp,
Head of the Centre for Toxicology, The School of Pharmacy, University of London

April 2008

Summary

The number of new breast cancer cases among women is increasing in almost all Western countries. Although late age at first child birth and genetics are shown to contribute to the increase in breast cancer, the sheer number of newly diagnosed cases cannot solely be explained by these factors. Evidence is emerging that environmental influences, including chemical exposure, also play a role.

Studies among identical twins have shown that the most important contributors to the causation of breast cancer are environmental and lifestyle factors that differ between the pair, even under circumstances where the genetic predisposition is very similar. In families with a heritable predisposition to breast cancer, time of birth, physical activity and obesity can profoundly influence risk.

There is overwhelming evidence that oestrogens are strong determinants of breast cancer risks. This is not limited to natural oestrogens formed in a woman's body, but extends to synthetic hormones used as pharmaceuticals, including those employed for the alleviation of menopausal symptoms. The demonstration of breast cancer risks from oestrogen-only and, more pronounced, from combined oestrogen-progesterone regimens is another case in point. Very recent, rapid decreases in breast cancer incidence in the USA, Canada and in parts of Germany have followed a reduction in hormone therapy use.

Given that natural oestrogens and man-made oestrogens used as pharmaceuticals have a role in breast cancer, concerns arise about the potential contribution of industrial chemicals and pesticides with hormonal activity. Such chemicals include several that have been banned already, but can still be found in human tissues, such as polychlorinated biphenyls (PCBs) and compounds related to 1,1,1-trichloro-2,2-bis(4-chloro-phenyl)ethane (DDT). A large number of chemicals currently used in consumer products also fall in this category (phthalates, bisphenol A, UV-filter substances and many more).

To date, the few studies carried out to examine whether certain environmental chemicals are implicated in breast cancer leave much uncertainty about a possible link. But to avoid wrongly dismissing a role for chemicals in breast cancer, two issues must be addressed:

First, the available studies have largely focused on single chemicals and have ignored the possibility that large numbers of agents may act in concert. Recent evidence from Spain suggests that *cumulative* exposure to oestrogenic chemicals is associated with breast cancer risks.

Second, instead of looking at exposures later in a woman's life, when the breast tissue is perhaps less vulnerable, critical periods of vulnerability during puberty and development in the womb must be considered. Very recent studies demonstrating breast cancer risks from exposure to the pesticide DDT before or during puberty, and from in-utero exposure to the oestrogenic anti-miscarriage drug diethylstilboestrol (DES) further underline the importance of early life chemical exposure in breast cancer.

Taken together, there is a case for relinquishing the dominant view of breast cancer as a life-style and genetic disease and for reappraising the role of environmental factors, including chemical exposures. With UK breast cancer incidence at an all time high, risk reduction will not be achievable without considering preventable causes, particularly exposure to chemicals.

Breast cancer incidence rates

With a few exceptions, the number of new breast cancer cases among women is increasing in almost all Western countries. Thanks to improvements in early detection methods and the introduction of large-scale screening, the chances of surviving the disease have changed for the better, but the continuing rise in new cases places a heavy burden on health services and causes immense private suffering. The risk of contracting breast cancer is highest in Northern and Western Europe where incidence rates are rising slowly or are levelling off at high values[1]. Eastern European countries are currently experiencing the fastest rises in breast cancer. In some countries, including the USA and parts of Germany, a down-turn in the number of newly diagnosed women has been noted recently.

The UK has one of the highest breast cancer rates in the world. The number of women who received a diagnosis of breast cancer has risen steadily from 24,174 in 1980 to 43,711 in 2003[1]. As demonstrated by the latest available statistic (44,335 new cases in 2004)[2], there is a continued upwards trend in breast cancer incidence in the UK. Now in the UK, one in nine women will be diagnosed with breast cancer during their lifetime.

The rise in breast cancer incidence in the UK is often attributed to improved diagnosis by screening. There is no doubt that the introduction in 1988 of large-scale screening mammography in the National Health Service has led to a rising number of diagnosed cases, particularly in women aged 50–64 years. Typically however, the additional effect on incidence is only transient and disappears as screening measures reach saturation. In the UK this effect has lasted for 4–7 years, until 1992–1996[3]. Although the upwards trend in incidence has become more pronounced with the introduction of mammography, this has not masked a general increase. The underlying increase in breast cancer incidence in the UK predated screening and continues today. Thus, current rises in incidence are not solely due to screening.

Changes in childbearing contribute to the increase in breast cancer in the UK and in most other countries. For example, it is well established that breast cancer risks are higher among women who have their first baby late in life, or who do not have children at all. Very likely, this plays a role in the current rapid rise of breast cancer in Eastern Europe. Other factors that contribute to increased risks are lack of physical activity, weight gain and obesity after the menopause. Genetics explains a small fraction of breast cancers. Around 1 in 20 cases are believed to be due to an inherited predisposition, but for the overwhelming majority of women the disease is not passed on through genes but acquired during their lifetime[4]. Alcohol consumption[5], but not high fat diets[6] contributes to breast cancer risk.

But the sheer number of newly diagnosed cases cannot be explained solely by childbearing, genetics, lack of physical exercise or alcohol. Experts estimate that more than half of all breast cancers are due to as yet unidentified causes[7]. So what are these unexplained factors? This briefing document will appraise the evidence for a role of environmental factors, particularly chemicals, in breast cancer.

What are "Environmental factors" in breast cancer causation?

The term "environmental factors" is used ambiguously and with different connotations in the medical literature. In its broadest sense, it describes all non-genetic factors in cancer causation, such as life style, diet and infectious agents. Used in this way, the term is not very discriminating and consequently "the environment" can be implicated in the causation of most cancers. More helpful with respect to cancer prevention might be to distinguish between avoidable factors and genetic background. In the interest of avoiding involuntary exposures, this means a focus on the possible role of work place exposures, food contaminants, pharmaceuticals, chemicals in consumer products, air, water, and soil, and physical factors such as radiation. While physical exercise and low alcohol consumption are well established beneficial factors, comparatively less attention has been paid to chemical exposures as avoidable factors.

Setting the scene: what is the contribution of non-genetic factors to breast cancer?

Due to the common genes that are shared by identical twins there is an increased likelihood that the twin of a person diagnosed with cancer will suffer from the same disease. Analyses of differences in the cancer incidence among twins can therefore be used to estimate the relative contributions of heritable and environmental factors to disease causation. Recent studies among Scandinavian twins have produced fascinating insights. For breast cancer in women it was found that heritability accounted for 27% of the variation in susceptibility to this form of cancer. Environmental factors that were shared by both twins explained 6%, and environmental factors

not common to the pair contributed 67%[8]. This means that the most important contributor to the causation of breast cancer is non-genetic or environmental, even under circumstances where the genetic background is very similar.

Studies of families with a heritable predisposition to breast cancer have produced similar results. Women who carry a mutated form of the tumour suppressor genes *BRCA1* and *BRCA2* suffer from a significantly higher risk of developing breast and ovarian cancer than women not afflicted by this genetic change. Among carriers of the altered genes who were born before 1940, the risk of developing breast cancer by the age of 50 is 24%. Interestingly, women harbouring the mutation, but who were born after 1940, have a much higher risk (67%) of being diagnosed with breast cancer at 50 years of age. Similarly, physical activity and leanness delay disease onset significantly in predisposed women when compared with carriers who were obese[9]. Together, these observations show that even in a genetic background that strongly predisposes to breast cancer, non-genetic factors can dramatically modulate risk. This lends further urgency to the question: What are these non-genetic factors?

The role of oestrogens

Prominent among non-genetic risk factors in breast cancer are the female sex hormones, oestrogens. Although essential for breast development, they also play an important role in the causation of breast cancer. This is not restricted solely to natural oestrogens. With the realisation that synthetic oestrogens (e.g. in certain pharmaceuticals) also contribute to risks, concerns are growing over other oestrogen-like chemicals present in the environment, in food or in cosmetics and personal care products.

Oestrogens and breast development

Mammary glands are composed of a tree-like ductal structure for the production and release of mothers' milk. These structures are not fully developed or 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 steroidal oestrogens, natural hormones produced by the ovaries.

Through specialised cellular receptors that regulate the expression of genes important in growth (oestrogen receptors α and β), oestrogens stimulate division of the cells in the blind ends of the ducts, the "end buds". This process 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[10].

Natural oestrogens and breast cancer

Paradoxically, natural oestrogens are not only key players in breast development, but also contribute to breast cancer. It is thought that in promoting the growth of end buds, oestrogens may lead 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 of the ductal lobular units, which are the cells that contain oestrogen receptors and are most responsive to oestrogens in breast development. Consequently, most breast cancers are oestrogen receptor positive and rely on oestrogen for growth.

During the periods when the duct structures grow, especially during development and puberty, the breast is particularly vulnerable to cancer-causing influences[11]. Elevated levels of oestrogens during foetal life are also associated with breast cancer[12]. 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[10].

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%[13].

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[13]. 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, Anti-miscarriage drugs and hormone replacement therapy

The cancer-promoting effects of oestrogens are not limited to natural hormones. External oestrogens administered as oral contraceptives, anti-miscarriage drugs or for the suppression of menopausal symptoms 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[13]. In 2003, one third of all women in Britain aged 50-64 used hormone replacement therapy (HRT)[13].

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 were no detectable increased risks more than 10 years after last use[13].

Between 1953 and 1971, approximately 300,000 women in the UK alone used the oestrogenic drug diethylstilbestrol (DES) to avoid miscarriages. Not only was the drug ineffective for its intended purpose, recent studies have shown that women whose mothers took DES face twice the normal breast cancer risk[14]. The risk is expected to grow further as these "DES daughters" reach menopausal age. These results highlight the risks that stem from exposure to oestrogens at the "wrong" stages of development in the womb.

What led to the widespread use of HRT was the idea that replacing oestrogen lost during menopause might prevent many symptoms of ageing in women, including coronary heart disease and osteoporotic bone fractures. Initially, HRT was "oestrogen-only", but in the early 1980s it became clear that oestrogen-only HRT promoted cancer of the womb (endometrial cancer). But endometrial cancer could be prevented if oestrogen was given in combination with progesterone. Although the cancer causing effects of this HRT combination therapy began to emerge already in the mid 1990's[15], combined oestrogen-progesterone HRT became the most widely prescribed regimen, in Europe and the USA.

The potential benefits and harms of HRT were tested in controlled clinical trials. In 2002, one of these trials, the Women's Health Initiative (WHI) trial, had to be stopped early because oestrogen-progesterone HRT led to increased risks of breast cancer among the participating women. These risks were considered to outweigh the benefits of this form of HRT in terms of reduced bone fractures and reduced colon cancer[16].

Coinciding with the completion of the WHI trial, the results of a very large UK observational study of women receiving mammography screening, the Million Women Study, were published. It showed that all forms of HRT, including oestrogen-only and oestrogen-progesterone, increased breast cancer risks. The study authors estimated that the use of HRT during the last decade in the UK alone had resulted in an extra 20,000 breast cancer cases[17]. A very recent US study found that postmenopausal women taking combined oestrogen and progestin hormone replacement therapy for three years or longer run four times the risk of developing lobular breast cancer. This is shorter than the time associated with an increased risk of other types of breast cancer[53].

Oestrogen-only HRT and breast cancer risks

After the early cessation of the oestrogen-progesterone arm of the WHI trial in 2002, an analysis of the effects of oestrogen-only HRT (also part of the WHI trial) continued and was completed in 2006[18]. In contrast to the UK Million Women Study and other published evidence it revealed decreased breast cancer risks in women who received oestrogen-only HRT. This finding was difficult to explain. Can it be taken to mean that oestrogens, when administered as a synthetic agent (as opposed to synthesised internally and released by a woman's ovaries) are not associated with breast cancer?

In a 2004 interim report, when the downward trend in breast cancer risks had already become apparent, the WHI Steering Committee exercised great care in interpreting their observations[19]. They acknowledged that the risk reduction was not anticipated and was in conflict with the results of other observational studies, most notably the Million Women Study conducted in the UK[17]. While it is clear that combined oestrogen-progesterone HRT has a stronger effect on breast cancer, the Million Women Study found a weaker, albeit significant contribution to risks also with oestrogen-only HRT. A recent meta-analysis of a large number of HRT studies and trials carried out worldwide also supports this notion. It showed that oestrogen-only HRT is associated with breast cancer[20]. Thus, the risks of synthetic oestrogens taken as drugs cannot be dismissed, and some have even argued that the risk reduction in the WHI trial is best interpreted as due to chance[21].

The recent down-turn in breast cancer incidence in the USA and other countries – a consequence of declining HRT use?

With news of a recent sharp decline in breast cancer incidence rates in the USA the association between HRT use and breast cancer has received renewed attention. Between 2002 and 2003 the reported down-turn was between 4% and 7% for women between 50 and 69 years of age[22, 23]. This drop coincided temporally with a pronounced decrease in HRT use. From 2002 onwards the dispensing of HRT in the USA declined by 30–40% [24]. Careful analysis revealed that the changes in breast cancer rates could not be explained by less frequent mammography screenings with a consequent reduction in diagnosed breast cancer cases[24, 25]. One recent Californian study could even demonstrate a quantitative link between changes in HRT use and incidence[25]. This analysis showed that, from 2001 to 2004, the incidence of breast cancer declined by 8.8% in regions with the smallest reductions in HRT prescriptions, by 13.9% in those with intermediate reductions, and by 22.6% in areas with the greatest reductions in combination HRT. The reductions in breast cancer were largely confined to women above the age of 50 and to patients with estrogen receptor positive tumours, both features that lend further support to the idea that changes in HRT use played a role.

A down-turn in breast cancer rates subsequent to reductions in HRT use was also observed in North Germany[26] and in Canada[27]. However, in The Netherlands, Norway and Sweden declines in HRT use were not accompanied by a drop in breast cancer incidence[28, 29]. In these countries, HRT use has been less intensive and was of shorter duration than among US women. Under such conditions decreases in breast cancer incidence are not expected to occur upon discontinuation of HRT[30]. Taken together, the available evidence strongly suggests that the sudden decline in HRT prescriptions may have led to the decrease in breast cancer, but additional, as yet unexplained factors might also have been at play. Very recent data from the USA show that the 2003 drop in breast cancer incidence did not continue in 2004[23].

Phytoestrogens and breast cancer

The possibility that plant-derived oestrogens, so-called phytoestrogens, may have protective effects on breast cancer has attracted considerable attention because of the relatively low incidence rates in East Asia. In these countries diets are rich in soy food, a source of phytoestrogens. Phytoestrogens have biological effects that could potentially reduce breast cancer risks, such as inhibition of surface receptors that tumour cells rely on for growth, that could potentially reduce breast cancer risks. However, these effects occur at pharmacological doses unattainable through consuming soy-rich diets[31]. On the other hand, there are concerns that phytoestrogens, through their ability to activate oestrogen receptors, may promote the growth of latent breast cancers.

The possible protective effects of phytoestrogens on breast cancer have been assessed in numerous epidemiological studies. Comparison of these studies is complicated because researchers used different measures of exposure to soy and phytoestrogens. In a recent meta-analysis of investigations conducted between 1978 and 2004, comparability was achieved by standardisation of phytoestrogen exposure in terms of soy protein intake. The authors came to the conclusion that soy intake is associated with a modest reduction in breast cancer risk[32]. Early life exposures to phytoestrogens may be important: The protective effects of soy-rich diets became more apparent in studies that included women whose consumption began in early childhood[32]. Overall, however, the differences between published studies introduced a great deal of uncertainty, and for this reason, the authors cautioned against over-interpretation and were hesitant to generalise their findings into clinical recommendations.

Some laboratory data suggest that phytoestrogens may promote breast cancer. Research demonstrating that one specific phytoestrogen, genistein, could stimulate the growth of oestrogen-responsive mammary tumours in a mouse model, raised considerable concern[33]. However, the relevance of these animal models for risk extrapolations to humans is the topic of considerable debate (summarised in[31]). For example, unlike women, mice are unable to synthesise sufficient amounts of oestrogen to promote mammary tumours. In summary, neither animal nor human data currently allow firm conclusions about the effects of phytoestrogens on breast cancer risk. Whether the continuous rise in breast cancer experienced by East Asian women since the early 1980s[34] is due to a withdrawal of phytoestrogens through adoption of a more "Westernised" diet is therefore also unresolved.

Growing concerns about chemicals with hormonal activity

There is convincing evidence that natural and synthetic oestrogens play a role in breast cancer. This has led to renewed concerns about chemicals with hormonal activities found in food, personal care products or as environmental contaminants. These substances include organochlorine pesticides such as DDT, polychlorinated biphenyls, polychlorinated dioxins and furans, plasticizers, UV-filter agents in sun creams, widely used preservatives and antioxidants such as parabens. Many of these agents were shown to behave like the female sex hormone oestradiol, although much higher concentrations are usually required to show effects of similar strength[35]. However, their high persistence, combined with their widespread presence in human tissues adds to fears regarding their potential role in the development of breast cancer. It appears plausible to suspect that these compounds too would be contributors to breast cancer risks, just like pharmaceutical oestrogens. What is the evidence for an involvement of synthetic and natural chemicals in breast cancer?

Synthetic chemicals and breast cancer

Studies carried out to examine whether specific persistent chemicals such as 1,1,1,trichloro-2-(p-chlorophenyl)-2-(o-chlorophenyl)ethane (o,p'-DDT), 1,1'-dichloro-2,2'-bis(p-chlorophenyl)ethylene (p,p'-DDE) and polychlorinated biphenyls (PCBs) are implicated in breast cancer could neither prove nor rule out a possible link. Some have prematurely concluded from these studies that there is no relationship between these chemicals and breast cancer risk[36, 37]. However, a variety of methodological limitations in these studies mean that we cannot conclude there is no relationship.

Some study outcomes indicate that women harbouring certain genetic changes in drug metabolising enzymes (cytochrome P450 1A1) may be at increased risk from PCB exposure[38]. The evidence concerning a possible link with dioxin exposure is suggestive. Young women exposed to the polychlorinated dioxin, tetrachlorodibenzo-p-dioxin (TCDD) during the 1975 Seveso accident north of Milan, Italy, suffered a two-fold increase in breast cancer risks[39]. However, these women sustained pronounced exposures resulting in quite high TCDD blood levels, not comparable with those found in other European women.

Epidemiological studies of the effects of plasticizers (e.g. phthalates), UV-filter agents, cosmetic ingredients (e.g. phthalates, parabens) or other widely used chemicals in consumer products are missing. Noteworthy are studies in occupational settings that show elevated breast cancer risks among women exposed to organic solvents for more than 10 years[40].

The uncertainty about an involvement of individual endocrine disrupting chemicals in breast cancer stems in part from the general features of investigations that aim to pinpoint specific risk factors as linked to cancer risks. To be identified as a determinant of risk, the effects of a specific chemical have to be quite pronounced. These difficulties are not limited to studies of the effects of chemicals. Investigations of the role of diet in breast cancer have also failed to show consistent and statistically significant associations between fruit and vegetable intake, or dietary antioxidants and breast cancer[6].

The pollutant "cocktail effect" and exposure timing

Despite these difficulties, evidence emerging from recent research shows that two important issues must be fully addressed to avoid wrongly dismissing a role for chemicals in breast cancer.

First, studies in humans have largely focused on single chemicals but have ignored the large number of agents that occur together in women's tissues and therefore may act in concert to contribute to breast cancer risks[41].

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 or even decades later run the risk of overlooking disease-causing factors[42].

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 and carcinogens. These include: chemicals released during the preparation of food (for example, during the grilling of meat)[43]; 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)[44]; those that leach from plastics (for example bisphenol A, nonyl phenol)[35]; and plant-derived oestrogens in certain foods.

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 significantly enhance the effects of natural oestrogens, even when they are present at levels that individually do not produce measurable effects[45]. There is now good evidence (reviewed in[46]) that combined exposure to hormonally active chemicals can produce additive effects at low doses. Whether the individual doses are effective on their own, is not the key determinant. What also drives the likelihood of mixture effects is the sheer number of chemicals present in a "pollution cocktail". Thus, in principle, combination effects will result from toxicants at or even below threshold doses, provided sufficiently large numbers of components sum up to a suitably high dose. Whether such "cocktail effects" are likely to arise in reality, depends on the nature of hormonally active chemicals, and their number. At present, information about these factors is patchy, but indications are that scores of chemicals may be involved[46] . The recent advances in our knowledge about determinants of mixture effects highlight that the focus of the previous human studies of 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 suggests that cumulative exposure to hormonally active substances is significant. Breast cancer risk was associated with the body burden of lipophylic organohalogen oestrogenic chemicals, excluding the natural hormones[47, 48]. 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. Similar epidemiological studies should be repeated in other countries.

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 other is during development in the womb, when the breast tissue is laid down.

PUBERTY

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 or at an even younger age. Older women experienced far less pronounced breast cancer risks[11].

The importance of exposure to chemicals before or during puberty was very recently highlighted in a US study of breast cancer and DDT exposure at a young age. Previous investigations of a link between DDT and breast cancer have looked at exposures later in life, when the breast tissue is less vulnerable. However, it could be shown[49] that in women born after 1931, high levels of p,p'-DDT were associated with a 5-fold increased breast cancer risk. When DDT came into widespread use, these women were under 14 years of age, and mostly under 20 when DDT use in the USA peaked. Many women exposed to DDT in puberty have not yet reached the age of 50, when breast cancer becomes more common.

DEVELOPMENT IN THE WOMB

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[12].

The recent demonstration of elevated breast cancer risks in the daughters of women who took diethylstilboestrol (DES) to avoid miscarriages[14] shows that synthetic oestrogens can have similar effects. 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[50, 51].

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[10]. 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[42]. 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.

Implications for safety testing of chemicals

Safety testing of chemicals in general faces two fundamental issues that greatly influence test outcomes: Timing and duration of exposure and choice of toxicological effect to be monitored. Recent research has shown that both these issues have not been adequately addressed during the evaluation of hormonally active chemicals.

The testing of chemicals for possible carcinogenic effects in laboratory animals is usually carried out after they are born, 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 two inadequacies have led researchers to question whether, in trying to identify cancer-causing chemicals, they are using the wrong tools, at the wrong times[42].

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 convincing evidence from human studies is missing due to methodological limitations. 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[47]. By adopting targeted research strategies, and with better use of animal studies on mammary carcinogens[52] and *in vitro* data, the issue should be pursued further with urgency.

There is also a need to act sooner to limit exposures. Preventative action should be based on evidence available from experimental laboratory studies, and should not wait for the outcome of human epidemiological studies because confirmatory data from epidemiological studies will take decades to materialise. Given the known role of oestrogens in breast cancer, it would be prudent to reduce exposures to chemicals that can mimic oestrogen. Consideration should therefore be given to amending current chemicals policy so that such chemicals are replaced with safer alternatives, where possible.

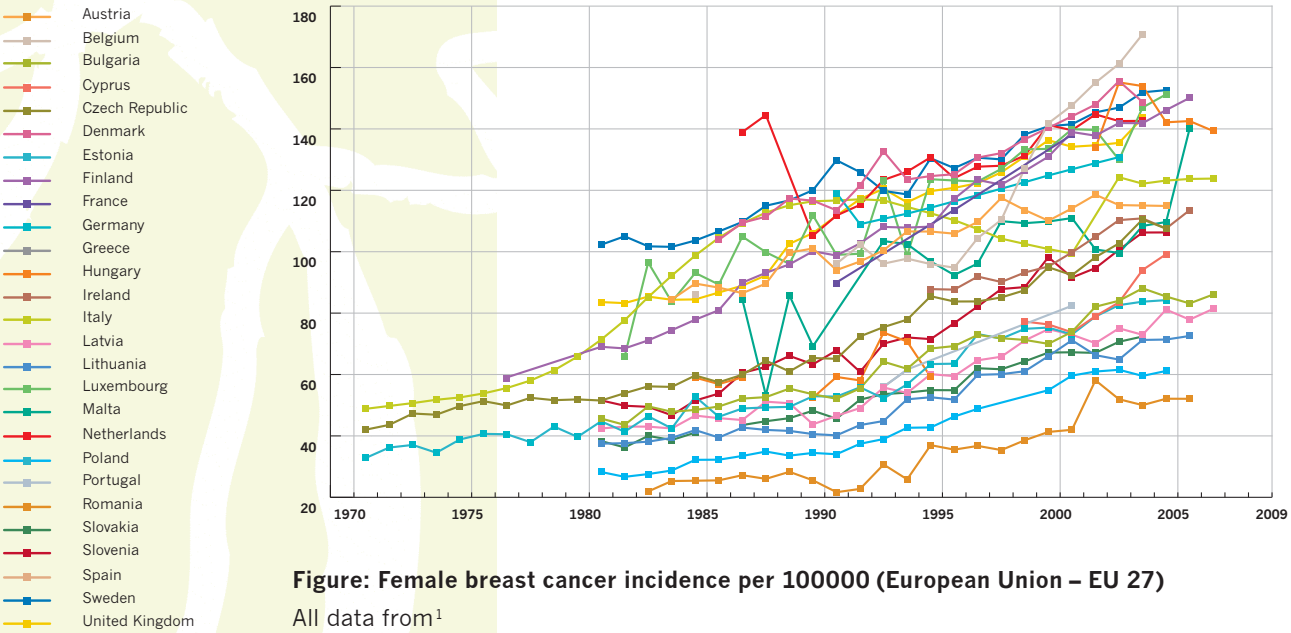

Figure: Female breast cancer incidence per 100000 (European Union – EU 27)

All data from[1]

REFERENCES

[1] World Health Organisation (WHO)/ Europe (2007). Figures and graph from the European health for all database (HFA-DB), World Heath Organisation Regional Office for Europe. Data-base online at http://data.euro.who.int/hfadb/

[2] Office for National Statistics, Cancer Statistics registrations: Registrations of cancer diagnosed in 2004, England. Series MB1 no.35. 2007, National Statistics: London.

[3] Coleman M (2000). Trends in breast cancer incidence, survival, and mortality. *Lancet*, 356 (9229), 590

[4] Colditz GA (1998). Relationship between oestrogen levels, use of hormone replacement therapy, and breast cancer. *J Natl Cancer Inst*, 90, 814-823

[5] Longnecker MP, Newcomb PA, Mittendorf R, Greenberg ER, Clapp RW, Bogdan EF, et al (1995). Risk of breast cancer in relation to lifetime alcohol consumption. *J Natl Cancer Inst*, 87, 923-929.

[6] Michels KB, Mohllajee AP, Roset-Bahmanyar E, et al. (2007). Diet and breast cancer: a review of the prospective observational studies. *Cancer* 109 (12 Suppl), 2712-2749.

[7] Madigan MP, Ziegler RG, Benichou J, Byrne C and Hoover RN (1995). Proportion of breast cancer cases in the United States explained by well-established risk factors. *J Natl Cancer Inst*, 87, 1681-1685.

[8] Lichtenstein P, Holm NV, Verkasalo PK, et al. (2000). Environmental and heritable factors in the causation of cancer - Analyses of cohorts of twins from Sweden, Denmark, and Finland. *N Engl J Med* 343, 78-85.

[9] King MC, Marks JH and Mandell JB (2003). Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. *Science* 302 643-646.

[10] Russo IH and Russo J (1998). Role of hormones in mammary cancer initiation and progression. *J Mamm Gland Biol Neoplasia* 3, 49-61.

[11] McGregor H, Land CE, Choi K, Tokuoka S, Liu PI and Wakabayashi T (1977). Breast cancer incidence among atomic bomb survivors, Hiroshima and Nagasaki, 1950-69. *J Natl Cancer Inst* 59, 799-811.

[12] Weiss HA, Potishman NA, Brinton LA, Brogn D, Coates RJ, Gammon MD, et al (1997). Prenatal and perinatal risk factors for breast cancer in young women. *Epidemiology* 8, 181-187.

[13] Travis RC, and Key TJ (2003). Oestrogen exposure and breast cancer risk. *Breast Cancer Res* 5, 239-247.

[14] Palmer JR, Wise LA, Hatch EE, Troisi R, Titus-Ernstoff L, Strohsnitter W, Kaufman R, Herbst AL, Noller KL, Hyer M and Hoover RN. Prenatal diethylstilbestrol exposure and risk of breast cancer. *Cancer Epidemiol Biomarkers Prev.* 2006 Aug; 15(8):1509-14.

[15] Collaborative group on hormonal factors in breast cancer (1997). *Lancet* 350, 1047

[16] Writing Group for the Women's Health Initiative Investigators (2002). Risks and benefits of estrogen plus progestin in healthy postmenopausal women. *JAMA* 288, 321-332.

[17] Million Women Study Collaborators (2003). Breast cancer and hormone-replacement therapy in the Million Women Study. *The Lancet*, 362, 419-427.

[18] Stefanick ML, Anderson GL, Margolis KL, et al. (2006). Effects of conjugated equine estrogens on breast cancer and mammography screening in postmenopausal women with hysterectomy. *JAMA* 295, 1647-1657.

[19] WHI Steering Committee (2004). Effects of conjugated equine estrogen in post-menopausal women with hysterectomy. *JAMA* 291, 1701-1712.

[20] Greiser CM, Greiser EM and Doeren M (2005). Menopausal hormone therapy and risk of breast cancer: a meta-analysis of epidemiological studies and randomised controlled trials. *Hum Reprod Update* 11, 561-573.

[21] Hulley SB and Grady D (2004). The WHI estrogen-alone trial – do things look any better? *JAMA* 291, 1769-1771.

[22] Kemal A, Ward E and Thun MJ (2007). Recent trends in breast cancer incidence rates by age and tumor characteristics among U.S. women. *Breast Cancer Res* 9, R28, http://breast-cancer-research.com/content/9/3/R28.

[23] Ravdin PM, Cronin KA, Howlander N, et al. (2007). The decrease in breast cancer incidence in 2003 in the United States. *New Engl J Med* 356, 1670-1674.

[24] Glass AG, Lacey JV Jr, Carreon D and Hoover RN (2007). Breast cancer incidence, 1980-2006: Combined roles of menopausal hormone therapy, screening mammography, and estrogen receptor status. *J Natl Cancer Inst* 99, 1152-1161.

[25] Robbins AS and Clarke CA (2007). Regional changes in hormone therapy use and breast cancer incidence in California from 2001 to 2004. *J Clin Oncol* 25, 3437-3439.

[26] Katalinic A and Rajal R (2007). Decline in breast cancer incidence after decrease in utilisation of hormone replacement therapy. *Breast Cancer Prev Treat* in press epub ahead of print 10.1007/s10549-007-9566-z

[27] Kliewer EV, Demers AA and Nugent ZJ (2007). A decline in breast cancer incidence – correspondence. *New Engl J Med* 357, 509-510.

[28] Zahl PH and Mahlen J (2007). A decline in breast cancer incidence – correspondence. *New Engl J Med* 357, 510-511.

[29] Soerjomataram I, Coebergh JW and Louwman MWJ (2007). Does the decrease in hormone replacement therapy also affect breast cancer risk in the Netherlands? *J Clin Oncol* 25, 5038-5039.

[30] Clarke CA and Robbins AS (2007). In reply to Soerjomataram et al. *J Clin Oncol* 25, 5039-5040.

[31] Messina M, McCaskill-Stevens W and Lampe JA (2006). Addressing the soy and breast cancer relationship: Review, commentary and workshop proceedings. *J Natl Cancer Inst* 98, 1275-1284.

[32] Trock BJ, Hilakivi-Clarke L and Clarke R (2006). Meta-analysis of soy intake and breast cancer risk. *J Natl Cancer Inst* 98, 459-471.

[33] Allred CD, Allred KF, Ju YH, et al. (2001). Soy diets containing varying amounts of genistein stimulate growth of estrogen-dependent (mcf-7) tumours in a dose-dependent manner. *Cancer Res* 61, 5045-5050.

[34] Minami Y, Tsubono Y, Nishino Y et al. (2004). The increase of female breast cancer incidence in Japan: emergence of birth cohort effect. *International J Cancer* 108, 901-906.

[35] Soto AM, Sonnenschein C, Chung KL, Fernandez MF, Olea N and Serrano FO (1995). The E-SCREEN assay as a tool to identify oestrogens: an update on oestrogenic environmental pollutants. *Environ Health Perspect*, 103 (Suppl 7), 113-122.

[36] Mendez MA and Arab L (2003). Organochlorine compounds and breast cancer risk. *Pure Appl Chem*, 75, 1973-2012.

[37] Lopez-Cervantes M, Torres-Sanchez L, Tobias A and Lopez-Carrillo L (2004). Dichlorodiphenyldichloroethane burden and breast cancer risk: a meta-analysis of the epidemiologic evidence. *Environ Health Perspect*, 112, 207-214.

[38] Negri E, Bosetti C, Fattore E, La Vecchia C. Environmental exposure to polychlorinated biphenyls (PCBs) and breast cancer: a systematic review of the epidemiological evidence. *Eur J Cancer Prev* 2003;12(6):509-16.

[39] Warner M, Eskenazi B, Mocarelli P, et al. (2002). Serum dioxin concentrations and breast cancer risk in the Seveso Women's Health Study. *Environ Health Perspect* 110, 625-628.

[40] Brody JG, Moysich KB, Humblett O, et al. (2007). Environmental Pollutants and breast cancer – epidemiologic studies. *Cancer* 109 (12 Suppl), 2667-2711.

[41] Kortenkamp, A (2006). Breast cancer, oestrogens and environmental pollutants: a re-evaluation from a mixture perspective. *Int J Androl*, 29, 193-198.

[42] Birnbaum LS and Fenton SE (2003). Cancer and developmental exposure to endocrine disrupters. *Environ Health Perspect* 111, 389-394.

[43] Lauber SN, Ali S, Gooderham NJ (2004). The cooked food derived carcinogen 2-mino-1-methyl-6-phenylimidazo[4,5-b] pyridine is a potent oestrogen: a mechanistic basis for its tissue-specific carcinogenicity. *Carcinogenesis* 25, 2509-2517.

[44] Durrer S, Ehnes C, Fuetsch M et al. (2007). Estrogen sensitivity of target genes and expression of nuclear receptor co-regulators in rat prostate after pre- and postnatal exposure to the ultraviolet filter 4-methylbenzylidene camphor. *Environ Health Perspect* 115 (Suppl 1), 42-50.

[45] Rajapakse N, Silva E and Kortenkamp A (2002). Combining xenoestrogens at levels below individual no-observed-effect-concentrations dramatically enhances steroid hormone action. *Environ Health Perspect* 110, 917-921.

[46] Kortenkamp A, Faust M, Scholze M and Backhaus T (2007). Low-level exposure to multiple chemicals: Reason for human health concern? *Environ Health Perspect* 115 (Suppl 1), 106-114.

[47] Ibarluzea JJ, Fernandez MF, Santa-Marina L, Olea-Serrano MF, Rivas AM, Aurrekoetxea JJ, Exposito J, Lorenzo M, Torne P, Villalobos M, Pedraza V, Sasco AJ and Olea N (2004). Breast cancer risk and the combined effect of environmental oestrogens. *Cancer Causes Control* 15, 591-600.

[48] Fernandez MF, Santa-Marina L, Ibarluzea JM, et al. (2007). Analysis of population characteristics related to the total effective xenoestrogen burden: A biomarker of xenoestrogen exposure in breast cancer. *Europ J Cancer* doi:10.1016/j.ejca.2007.03.010

[49] Cohn BA, Wolff MS, Cirillo PM and Sholtz RI (2007). DDT and breast cancer in young women: new data on the significance of age at exposure. *Environ Health Perspect* epub ahead of print doi 10.1289/ehp.10260 available via http://dx.doi.org

[50] Munoz-de-Toro M, Markey C, Wadia PR, Luque EH, Rubin BS, Sonnenschein C, and Soto AM (2005). Perinatal exposure to Bisphenol A alters peripubertal mammary gland development in mice. *Endocrinology*, doi:10.1210/en.2005-0340 May 26, 2005.

[51] Maffini MV, Rubin BS, Sonnenschein C and Soto AM (2006). Endocrine disruptors and reproductive health: The case of bisphenol-A. Mol Cell. *Endocrinol*. 2006 Jun 14, Available online 15 June 2006.

[52] Rudel RA, Attfiled KR, Schifano JN and Brody JG (2007). Chemicals causing mammary gland tumours in animals signal new directions for epidemiology, chemicals testing, and risk assessment for breast cancer prevention. *Cancer* 109 (12 Suppl) 2635-2666.

[53] Li CI, Malone KE, Porter PL, Lawton TJ, Voigt LF et al. (2008). Relationship between menopausal hormone therapy and risk of ductal, lobular and ductal-lobular breast carcinomas. Cancer Epidemiol Biomarkers Prev 17, 43–50.

Health and Environment Alliance (HEAL)
28 Bld Charlemagne, B1000 Brussels, Belgium
E-mail: info@env-health.org
www.env-health.org

CHEM Trust
PO Box 56842, London N21 1YH, United Kingdom
E-mail: gwynne.lyons@chemtrust.org.uk
www.chemtrust.org.uk