Environmental Science

AIMS Environmental Science, 3(1): 96-114.
DOI: 10.3934/environsci.2016.1.96
Received 24 February 2015,
Accepted 2 February 2016,
Published 23 February 2016

http://www.aimspress.com/journal/environmental

Review

Environmental chemical exposures and breast cancer

E. Stanley, J. Plant, and N. Voulvoulis *

Centre for Environmental Policy, Imperial College London, London SW7 2AZ, UK

*** Correspondence:** Email: n.voulvoulis@imperial.ac.uk; Tel: +44 20 7594 7459.

Abstract: As a hormone-sensitive condition with no single identifiable cause, breast cancer is a major health problem. It is characterized by a wide range of contributing factors and exposures occurring in different combinations and strengths across a lifetime that may be amplified during periods of enhanced developmental susceptibility and impacted by reproductive patterns and behaviours. The vast majority of cases are oestrogen-receptor positive and occur in women with no family history of the disease suggesting that modifiable risk factors are involved. A substantial body of evidence now links oestrogen-positive breast cancer with environmental exposures. Synthetic chemicals capable of oestrogen mimicry are characteristic of industrial development and have been individually and extensively assessed as risk factors for oestrogen-sensitive cancers. Existing breast cancer risk assessment tools do not take such factors into account. In the absence of consensus on causation and in order to better understand the problem of escalating incidence globally, an expanded, integrated approach broadening the inquiry into individual susceptibility breast cancer is proposed. Applying systems thinking to existing data on oestrogen-modulating environmental exposures and other oestrogenic factors characteristic of Westernisation and their interactions in the exposure, encompassing social, behavioural, environmental, hormonal and genetic factors, can assist in understanding cancer risks and the pursuit of prevention strategies. A new conceptual framework based on a broader understanding of the "system" that underlies the development of breast cancer over a period of many years, incorporating the factors known to contribute to breast cancer risk, could provide a new platform from which government and regulators can promulgate enhanced and more effective prevention strategies.

Keywords: breast cancer; environmental exposure; chemicals; evidence; systems thinking

1. Introduction

Cancer has been the focus of intensive research and discussion for over 50 years, during which

period age-standardised (AS) incidence rates of certain cancers, including breast cancer, have risen across the globe [1]. Of the c59 million deaths globally in 2008, 12–13% were from cancer, and it has been estimated that in the United States (US) up to 60% of those can be attributed to eight specific avoidable or modifiable factors; tobacco, alcohol, ionizing and solar radiations, occupations, infectious agents, obesity, and physical inactivity [2]. If this is the case then both the accurate prediction of risk and how to mitigate it in the interests of prevention, depend on a thorough understanding of risk factors not only individually but also in combination.

There remains no consensus on how particular cancers start, although research has identified a number of plausible risk factors correlated to breast cancer, some of which are widely accepted. These are notably sex and age, age at first period, age at first birth, breast cancer in first-degree relatives, and ethnicity [3]. Other identified risks, both modifiable and non-modifiable, include use of HRT [4]; reproductive patterns of behaviour [4,5], alcohol consumption [6-8], height [9] circulating IGF-1 and prolactin levels [11,12], ionizing radiation [13,14], pre and post-menopausal weight-gain/obesity [15,16], dense breast tissue [17,18], dietary protein from red meat [19] and the presence of certain high-penetrance genes (including BRCA1, BRCA2 and TP53), low-penetrance genes (such as the cytochrome P450 genes), DNA repair genes and genes encoding signaling molecules [20,21]. Major reviews conducted by independent groups have endorsed most as risk factors [22-24].

More recently an increasing number of environmental exposures have been the subject of research and intense debate amongst (*inter alia*) scientists, environmentalists, policy-makers and regulators. Women (and men) are exposed to many chemicals in the course of daily life. These range from preservatives in lipsticks to flame retardants in sofas, from plasticizers in water bottles to pesticides on fruits and vegetables. The vast majority have come into existence since the end of World War II, a period which has seen rapid and dramatic industrial development in many regions of the world [25-27].

It has been proposed by many, that such exposures, whether alone or in combination and/or at specific stages over a lifetime, trigger changes in DNA that lead *via* alterations in gene expression to the initiation of breast cancer. Epigenetics is the collective term applied to mechanisms that regulate gene expression but without altering the underlying DNA sequence [28,29]. A growing body of evidence now points to the role of such mechanisms (including the key processes of DNA methylation, histone modifications and post-transcriptional gene regulation by non-coding RNA) as being early events in the initiation of cancer [30-33]. It has been proposed that more than 300 genes and gene products undergo epigenetic alterations in some human cancers [34].

Authoritative scientific reviews by bodies such as the Institute of Medicine (IOM), and Interagency Breast Cancer and Environmental Research Coordinating Committee (IBCERCC) are consistent in their observations that breast cancer is not one disease but a complex group of predominantly hormone-sensitive diseases occurring in an environmentally complex world where perturbations in hormone metabolism are increasingly common. Of these, oestrogen-positive (ER+) breast cancer is the largest group, accounting for more than 75% of all cases currently diagnosed in the US [1] and more than 80% in the UK [35]. In men, breast cancer is rare accounting for c1% of cases but 92% of which are classified ER+ [37,38] underlining the role of hormonal imbalance in the majority of breast cancers.

With the exception only of skin cancer, breast cancer is now the most common form of cancer in women, and the International Agency for Research on Cancer (IARC) reports that incidence is increasing worldwide [38]. It has been proposed for some time that this increase in incidence cannot be explained simply by a growing and ageing population but that, given the preponderance of ER+

cases, it reflects the growing number of environmental exposures that impact on the sensitive workings of oestrogen metabolism [39,40]. Evidence from experimental, ecological and epidemiological research collectively examined by expert committees have led to recommendations that the complexities of breast cancer causation should now be explored using a systems approach in which trans-disciplinary research should also be encouraged [23,24,41]. Sometimes referred to as "team science", trans-disciplinary research is conducted by investigators from a number of disciplines, ranging from the genetic and molecular to the societal and regulatory, working together to devise new conceptual, theoretical and methodological innovations that move beyond discipline-specific approaches towards an integrated solution to a problem [42].

The observation; "We are not students of some subject matter, but students of problems. And problems may cut across the borders of any subject matter or discipline." [43] is exemplified in a recurring hypothesis for breast cancer causation. This proposes that particular characteristics of Westernisation in rapidly developing and newly industrialised countries are contributing to increased incidence in their female populations [44]. "Westernisation" is an umbrella term that attracts mixed and, in many parts of the world, unfavourable reactions. It leads in major changes in cultural behaviours that are protective of health whilst introducing the environmental agents and exposures instrumental to modernization and industrialization. Such agents include large numbers of endocrine disrupting chemicals (EDCs) which have been shown in multiple studies and confirmed in authoritative reviews, as being capable of modulating highly sensitive internal biochemical and hormonal processes [23,24,45].

On-going research contributes greatly to our growing understanding of breast cancer at a molecular and cellular level and has led to the development of drugs including selective oestrogen-receptor modulators as therapeutic and preventative agents. This approach which is reductionist in nature has given rise to a proliferation of specialisations, funding streams, research projects and reporting but which are, by their nature, geared neither to explaining the problem of increasing incidence worldwide nor promoting prevention.

Molecular approaches towards understanding breast cancer whilst they have the capacity to identify preclinical biomarkers and therapeutic interventions to halt progression of the disease are not aimed specifically at prevention. The objective is, essentially, to cure a condition, not to prevent it from arising in the first place. Prevention in its most basic sense requires a different perspective. It has been proposed that developments in computer technology now provide a means of analysing large, disparate bodies of data using a non-linear, systems approach as a means of overcoming the limitations of the reductionist paradigm when it comes to human health and disease [46-49]. These developments provide the opportunity to consider increased incidence of breast cancer in a wider, environmental context.

Whilst it is not the role of reductionism to address the multi-factorial origins of cancer, its findings can validate and inform systems biology and thereby the approach proposed here which would help establish whether cancer is what emerges when human interaction with the environment goes wrong.

2. Breast cancer trends

Global trends since 1973 show increased incidence rates of breast cancer in virtually all regions of the world [38]. The average annual rate of increase in 187 countries between 1980 and 2010 (30 years) has been calculated as 3.1% [50] while incidence worldwide has increased by 20% since 2008. It is now the second most common cancer globally accounting for 12% of all new cancers and 25% of call cancers in women [51].

In the UK, 33% of all new cancers are breast cancers and lifetime risk is currently one in eight [35]. In the US from 2001 to 2010 and notwithstanding a fall of 0.4% in AS and time-adjusted incidence rates in all cancers, breast cancer incidence neither increased nor decreased significantly [52,53]. However, data from the North American Association of Central Cancer Registries (NACCR), show that absolute numbers of breast cancers are currently on the increase [54].

This increase has been argued as attributable to the combination of a growing and an ageing population coupled with more widespread screening [55]. However, accumulating evidence also points to environmentally driven epigenetic changes impacting on endocrine function as a further plausible explanation for the escalation in those breast cancers (the majority) exhibiting hormonal disruption [56]. Rising trends in obesity have been forecast to add significantly to incidence both in the UK and the US especially in post-menopausal women where obesity has been identified as an independent risk factor for ER+ breast cancer [57].

Leaving aside "hereditary" cancers that constitute a distinct, but comparatively small, sub-group of breast cancers the vast majority of cases (>80%) do not display the inherited genetic component exemplified by mutations in the BRACA1, BRACA2 and TP50 genes [58]. It has been proposed that this large majority may reflect instead an accumulation of epigenetic mutations driven by exposures to EDCs [27,45,56,59,60] which amplify the risk of breast cancer *via* their modulating effects on oestrogen metabolism [61-63]. They may also reflect higher use in certain countries of HRT and oral contraception [40,58,64] illustrated by a decline of 8.8% in breast cancer incidence in the US in women aged 40–79 following widespread abandonment of HRT use between 2000 and 2005 [65].

Increases in incidence of breast cancer are not consistent across the globe [38]. The women of East Asia have, traditionally, experienced the lowest rates of breast cancer incidence in the world [62]. However, although rates of incidence are still lower in Asia than in the West, a significant rate of increase has been seen in this region over the past several decades. In Japan and Singapore rates have doubled, and in South Korea tripled, in the past 40 years while China's urban registries have recorded increases in incidence of up to 30% in the decade to 2007 [66-68]. These rapid escalations in incidence require explanation and particularly those in South Korea where, in 2012, breast cancer incidence was the highest in Asia (overtaking Hong Kong), with an AS rate of 52.1 per 100,000 of population [69]. Also noteworthy is that the median age of breast cancer diagnosis in China has been reported as being nearly 10 years younger than in the either the US or Europe [70].

3. Environmental chemical exposures

It has been estimated that there are over 140,000 synthetic chemicals on the market worldwide today with another 1,000 or more being added every year [71]. Over 90% have not been tested for their effects on human health [72]. An estimated 85,000 synthetic chemicals are registered in the United States but with toxicological screening data available for only about 7% [73]. Various bodies, including the President's Cancer Panel (PCP) [74], the IOM [75] and IBCERCC [24] have advocated further study of these environmental chemicals to better understand their potential to cause disease.

The challenges for researchers in doing so are substantial. In some cases, while the impact of an environmental chemical on an adult may be known, its developmental effects on the foetus and in childhood may not be well documented (if at all), and measurable effects in adults may be a reflection of long-term cumulative exposure starting *in utero* [76,77]. This proposition was articulated by Heindle [78] as the "foetal basis of adult disease" which describes the interaction between the external environment and an individual's genes as a determinant of health/disease in later life beginning in the

womb. As well as age at exposure, because some chemicals may be particularly harmful at specific stages of breast tissue development [43], other difficulties arise from duration of exposure and concentrations that can be hard to measure [79], possible effects of "mixing" where a chemical under review may, in combination with another, become toxic [80] and many EDCs exhibit J-type dose response curves [61].

Immigration to an industrialised country, increases exposure to environmental pollutants [80-82] and breast cancer risk in later life may be higher in women whose mothers immigrate from un-developed or developing countries to developed ones during pregnancy or when their daughters are children or adolescent [83]. Migration studies show that women who move from countries with low breast cancer incidence rates soon acquire any higher risk prevailing in the adopted country [84]. Women from Asian countries moving to the United States have been found to experience an 80% increase in risk after just one decade [85,86], a finding replicated in other studies [84,87], while age at immigration is a factor determining whether a woman carries the risk of her country of origin with her or acquires the risk of the country of destination [83].

The proposition that environmental factors may be influencing breast cancer rates has been endorsed in studies of twins. One of the largest of these found that where one twin developed breast cancer the most significant contribution to her risk were the environmental exposures unique to her as opposed to her twin [88]. Inherited genes were found to contribute 27%, shared environmental factors 6% and non-shared environmental factors 67%, of the risk. The study was subsequently re-analysed by others who concluded that "genetic susceptibility makes only a small to moderate contribution" to the incidence of breast cancer [89]. Further studies have since identified more genes that may increase breast cancer risk [90-92] but the most recent research suggests that it is epigenetic alterations that are the primary initiators of cancer development [93-98] and that these "epimutations" may be caused by environmental chemicals with endocrine disrupting potential [60,99].

3.1. Endocrine disrupting chemicals

A large and growing number of studies focusing on endocrine disruption, and specifically oestrogen modulation, point to commonly encountered environmental chemicals as contributing to the increase of oestrogen-positive breast cancer incidence in post-menopausal women [100]. Such studies have been the subject of authoratative and detailed reviews [22,45,101].

An endocrine disrupting compound or chemical (EDC) is defined by the US Environmental Protection Agency (EPA) as "an exogenous agent that interferes with synthesis, secretion, transport, metabolism, binding action, or elimination of natural blood-borne hormones that are present in the body and are responsible for homeostasis, reproduction, and developmental process."

EDCs include oestrogen, rated by IARC as a Group One Carcinogen [102]. The 2009 Endocrine Society Scientific Statement cites a large body of evidence supporting the proposition that EDCs contribute to breast cancer risk *via* their effects on oestrogen metabolism [25].

Both the timing and duration of exposure to EDCs have been proposed as critical in terms of breast cancer incidence [24,101]. It has been observed that in the decades since World War II rates of breast cancer incidence have risen in parallel with the proliferation of synthetic chemicals some now identified as EDCs. A woman's lifetime risk of breast cancer in the US in the 1940's was 1 in 22. Today, the risk is 1 in 8 (12%) [1]. To what extent this increase is attributable to EDCs is the subject of intense debate. However, a woman's risk aged 40 and over has been assessed as 2.5 fold higher in those exposed *in utero* to the synthetic oestrogen diethylstilbestrol (DES) than in women of the same

age who were not exposed, demonstrating the potential of intrauterine events to contribute to the development of cancer in later life [104-106].

A survey in 2007 indicated that 216 chemicals had, by that date, been registered by international and national regulatory agencies as having been shown in at least one study to be implicated in mammary gland carcinogenesis [39]. Of those 216, 25 were from occupational exposures (in more than 5000 women), 10 had been registered with the US Food and Drug Administration (FDA) as food additives, and 73 either had been or were present in consumer products or as contaminants in food [45]. Although only six were directly identified as being EDCs, this class of chemicals have been shown not only to persist in the environment but, being fat-soluble, to accumulate in body fat including breast tissue (which is fatty) where they can remain for long periods [107,108].

Breast tissue cells are considered to be at their most susceptible to the carcinogenic effects of EDCs starting *in utero* and continuing through puberty and adolescence up to the first full-term pregnancy [109]. A study that examined the effects of exposure shortly before birth to polycylic aromatic hydrocarbons (PAHs) from air pollution, vehicle exhaust, tobacco smoke and grilled foods showed altered oestrogen metabolism and an increased risk of breast cancer in the daughters of mothers exposed to higher levels in late pregnancy [110]. The effects of childhood and adolescent exposures to EDCs are difficult to assess but one study in 2007 showed that exposure in childhood or early adolescence to the then widely used but since banned pesticide DDT led to a five-fold increase in breast cancer before the age of fifty [111].

Early, or "precocious" puberty has also been proposed as being a consequence of exposure in preceding years to EDCs [61,112] and which has been demonstrated in animal studies [76,113,114]. Biro and co-workers [115] noted significant increases in early puberty in girls in the US between the early 1990s and 2004–2006 (when their study was conducted) and which the authors propose may be linked to a general increase in BMI over the past 20 years, itself a possible consequence of exposures to environmental agents.

Undisclosed chemicals represent another major potential source of human exposure to EDCs [116-118]. Fragranced consumer goods such as air fresheners, cleaning materials and personal care products (PCPs) contain ingredients that emit EDCs often as volatile organic compounds (VOCs). Despite the coming into force in the European Union in June 2007 of REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) neither this, nor legislation in the US require full disclosure of chemical ingredients in PCPs or other chemically-based consumer products where these are described and classified as a "fragrance" notwithstanding that VOCs emitted from such "fragrances" may be individually regulated as being toxic or hazardous [59,119].

Assessing the risk posed by such EDCs even individually is complex and controversial. Large-scale epidemiological studies of women with breast cancer exploring the effects of environmental chemicals in combination with other factors have produced contradictory results [120-122] serving to illustrate how complex some of the interactions may be and how difficult it is to assign or attribute risk between exposures and in proportion to one another.

3.2. Impacts of EDCs on oestrogen metabolism

Oestrogen is lipophilic and accumulates in fatty tissue [123]. Breast tissue is fatty and therefore a potential storage site both for endogenous oestrogen and for fat-soluble EDCs from the environment. Oestrogen metabolism is central to breast cancer, and elevated levels of oestrogen have been consistently associated with increased risk with numerous animal studies demonstrating that exposure

to environmentally encountered chemicals in general use in developed countries, such as bisphenol-A (BPA), produce measurable effects on oestrogen metabolism [124-126]. Oestrogen receptors (ERs) located in the nucleus of a cell bind with their designated endogenous ligands but can also bind with a range of exogenous synthetic compounds such as BPA which can then impact on cell signaling thorough a number of different pathways [127,128].

The potential for a biological effect is dependent upon the cell type, the concentration of the EDC in the target cell, and the binding affinity of that compound for an ER receptor [129]. Some EDCs exhibit relatively low binding affinities for the ER, suggesting that relatively high concentrations of the compounds are required to induce a response [130]. Studies suggest that EDCs may exert more potent effects during cell growth and particularly *in utero* when the foetus may be more sensitive to low concentrations of oestrogens [131]. Munoz-de-Toro and co-workers [113] argued that the primary target of bisphenol-A (BPA) is the foetal stroma, the only mammary tissue that expresses oestrogen receptors *in utero* and that BPA therefore alters stroma-epithelial interactions that mediate mammogenesis. In addition to this direct effect on mammary gland development, it is further postulated that BPA affects the hypothalamus and therefore the regulation of mammotrophic hormones at puberty, another critical window of susceptibility to endocrine disruption [132].

Studies in the 1960s and 1970s started to indentify the oestrogenicity of a number of industrial compounds and the pesticides o,p-DDT, kepone, methoxychlor, phenolic derivatives and polychlorinated biphenyls (PCBs). In the late 1990s, other environmental chemicals were added to the list including the pesticides toxaphene, dieldrin and endosulphan, several different compounds used in the food industry, antioxidants such a t-butylhydroxyanisole; plasticizers such as benzylbutylphthalate and 4-OH-alkylphenols along with substances used in dental restorations, such as BPA [133]. Later, complex mixtures of pollutants occurring in the environment such as diesel exhaust particles were also shown to have oestrogenic activity and were classified as EDCs [134].

Multiple studies demonstrate the potential of synthetic oestrogens (such as BPA) from environmental exposures to lead to long-term health problems in wildlife where they have been shown to impact on fecundity and fertilisation rates [103,123,135-138]. Oestrogens are important regulators of the metabolic requirements for reproduction and have thereby been implicated in the aetiology *inter alia* of the feminization of fish and testicular dysgenesis including hypospadias, cryptorchidism [139,140] and testicular cancer [141]. In humans, exposure to animal oestrogens is primarily through diet with meat and dairy foods a principal source [142] and it has recently been reported that dietary oestrogens may increase ER+ breast cancer risk in post-menopausal women whose diets are higher in red meat and lower in whole grains and coffee [143].

Exogenous EDCs also include naturally occurring animal, phyto- and mycoestrogens that have the capacity to mimic endogenous oestrogen action and thereby affect hormone levels and/or bind to the ER [144]. Some have been shown to be hormonally active at extremely low concentrations, similar to endogenous hormones [145,146] and as being able to cross the placental barrier and enter foetal circulation [147-150]. It has also been demonstrated that those with smaller molecular structure are able to cross the blood-brain barrier which is still underdeveloped at birth [151].

4. Discussion

Up until now, breast cancer has been approached on the basis that understanding it fully can be achieved by reducing it to manageable components and examining each of them in turn and in depth. Such methods have done much over the past decades to elucidate the processes involved in the

aetiology of the disease at both molecular and cellular level leading to improved treatment and, in consequence, falling mortality rates in most developed countries [38].

Such progress notwithstanding, it cannot be said with certainty that exposure to any one of the established risk factors (or any combination thereof) "causes" breast cancer. This makes an effective strategy for primary prevention difficult both to design and to deliver. In the meantime, incidence continues to rise across the world. A different approach is required, one that is not in competition with the reductionist paradigm but supplemental to it. Systems thinking, which tackles issues that are embedded in complexity and especially those that involve human activity would be appropriate to the task because it addresses the interconnectedness that is usually absent in the reductionist approach.

Many of the problems facing mankind comprise complex, dynamic systems consisting of multiple contributory factors that are both interdependent and self-organising and involve human interactions. A self-organising system has been defined as one "in which elements interact in order to achieve a global function or behaviour. This function or behaviour is not imposed by one or few elements, nor is it determined hierarchically. It is achieved dynamically as the elements interact with one another. These interactions produce feedbacks that regulate the system" [152]. In seeking to understand such problems, science has focused, historically, on understanding and testing individual components of the system rather than developing a more holistic and integrated understanding of "the problem" in its totality. As a consequence, one or more crucial aspects of the system (and particularly their interactions) may be excluded from the formulation of the "solution". This means in turn that management of "the problem" is likely to be less effective as well as encouraging adoption and pursuit of a solution that may, in the absence of a full understanding of the underlying cause, create as many (or more) problems than it solves. A systems approach to problem solving focuses on "the problem" instead of "a solution" and looks at the interactions between its various components [153]. It involves a holistic, step-by-step process the aim of which is to understand the problem in its totality, proposing that the solution will emerge from a fuller understanding of the problem [154] but even where it does not, focus will usefully have been shifted to goals that can be achieved by regulation and policy making [155].

The aetiology of cancer (as distinct from its biological hallmarks once developed) fits this description of a complex system well. Increased incidence of breast cancer (the problem) emerges from the self-organisation of external and internal factors interacting with one another (the system) giving rise to the behaviour (cancer). It has therefore been proposed that by looking for patterns within the exposome that reflect human homeostasis (i.e. the non-cancerous state) and identifying when and what changes or perturbations arise from environmental exposures, some consensus on causation of cancer may be achieved [28]. The exposome, a concept first proposed by Wild [156], represents "the totality of exposures received by a person during life, encompasses all sources of toxicants and, therefore, offers scientists an agnostic approach for investigating the environmental causes of chronic diseases." [157]. This concept of the exposome is consistent with developments in epigenetic research which have shown that cancer is preceded by abnormalities arising from the epigenetic reprogramming of gene expression and specifically those "guardian" genes that have been found to be protective against cancer [158].

Bearing in mind the probable number of environmental EDCs with potential specifically for oestrogenic activity, the biochemical complexities of oestrogen metabolism (including interactions with other agents) and oestrogen's pivotal role in the development of ER+ breast cancer, research into the effects of individual EDCs on breast cancer risk needs to be complemented by a more multi-connected, web-like conceptual framework in which to examine escalating incidence. Focused on

prevention, such an integrated, holistic approach would aim to synthesise knowledge of the molecular and biological processes involved in breast cancer with a growing parallel body of literature on environmental exposures that have been shown to modulate oestrogen metabolism.

A number of models designed to calculate breast cancer risk have been developed over the past three decades. The Gail (1989) model (now incorporated in The Breast Cancer Risk Assessment Tool (BCRAT)) calculates, by reference to five largely non-genetic variables, the probability of developing breast cancer over a given lifespan. Later models include BRCAPR0 (after the BRCA1 and BRACA2 genes) designed to assess probability of germline mutations in high-penetrance genes; the Claus risk tables [159] aimed at estimating risk of breast cancer in women with a first degree family history of ovarian cancer; the Tyrer-Cuzick model and the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADCEA). Between them they incorporate some, but not all, established risk factors and the Claus model does not take into account any non-hereditary factors. Validation studies have produced mixed results [160,161].

What none of these models does, is to take into account potentially modifiable environmental exposures across a lifetime nor assess the potential for their interactions or cumulative effects in the development of breast cancer. A multi-level mathematical model of post-menopausal breast cancer causation addressing these and other factors, including social and behavioural, has been constructed by Hiatt and co-workers for the California Breast Cancer Research Programme (CBCRP) [162]. The model incorporates the strength of evidence for, and the relative strengths of associations arising out of the interactions between, risk factors in four designated and hierarchically constructed domains. What Hiatt's model clearly demonstrates is the complex origins of cancer lending strength to the proposition that breast cancer is the result of interactions between numerous factors over a protracted period that in particular, but as yet unclear, combinations and levels of exposure lead from health to disease.

Whilst aimed specifically at identifying risk of post-menopausal breast cancer in California in response to marked increases in incidence in the preceding years, the CBCRP model (or parts of it) could usefully be applied in the analysis of cancer scenarios in developing countries, particularly in East Asia, which have seen rapid increases in incidence over the past several decades.

This study suggests that prevention of breast cancer depends not only on avoiding and reducing exposure to traditional risk factors but also on recognition and elimination of exposures to carcinogens especially oestrogens and other chemicals in the environment capable of upsetting finely tuned internal hormonal balance. This is made more difficult in developing countries with high rates of incidence where there are conflicting priorities between aspirations for economic development and prosperity on the one hand and concerns over environmental degradation and loss of cultural traditions beneficial to health on the other. Difficult though it may be to achieve, understanding and explaining the dramatic rise in incidence of breast cancer particularly in East Asia, requires assessment of the likely interactions between the established risk factors and the emerging risks posed by EDCs and other environmental exposures characteristic of inustrialsiation.

Reducing exposure to such compounds will require a political and cultural shift so that protection of public health is regarded as paramount. This in turn will demand a comprehensive re-thinking and re-ordering of priorities by science, industry and government together with co-operation between independent organisations and institutions. All share a joint responsibility for delivering primary prevention which is first about identifying and then eliminating the causes of a disease before it affects people. Historically this has been based on a common sense approach together with recognition of

either proved or suspected causative agents. A new conceptual framework incorporating the factors known to contribute to breast cancer risk together with those known to confer protection from it, could provide a new platform from which government and regulators can promulgate enhanced and more effective prevention strategies based on a broader understanding of the "system" that is breast cancer. Systems thinking has evolved to understand the reality of how such interactions affect the whole (in this case increasing incidence) and is therefore consistent with the holistic approach to primary breast cancer prevention proposed here.

5. Conclusion

Current strategies to halt the rise in incidence of breast cancer worldwide have not been effective. In the European Union, where there are more than twice as many new breast cancers annually than in any other site; a woman is diagnosed with breast cancer every 2.5 minutes [38]. Major advances in cancer treatment have not been accompanied by similar achievements in reducing cancer incidence through increased prevention. Globally, rates rose by 20% between 1980 and 2010 and emerging evidence suggests that age of onset is falling. Incidence is projected to continue rising. At the same time, a growing number of compounds in the environment are being shown to have the capacity, whether individually or in combination, to interfere adversely with normal oestrogen metabolism. What is the connection?

We may not be certain what causes breast cancer but there is a good body of evidence to show how risk can be mitigated. What is required is a way of linking that evidence to risk factors so as to identify the best protection "package" for women, deliverable *via* upstream changes in policy-making, aimed at creating a safer environment and better health culture. In setting about this daunting task it should be borne in mind that risk alone is not a cause of illness. Risk is the result of exposure to a hazard. If either hazard or exposure can be removed from the equation there is no risk. Avoiding hazard and reducing exposure are therefore key to decreasing risk and in this regulators and policy-makers will be key.

Conflict of interest

All authors declare no conflicts of interest in this paper.

References

1. IARC (2014) 'World Cancer Report 2014' Ed. BW Stewart & CP Wild ISBN 978-92-832-0429-9.
2. Schottenfeld D, Beebe-Dimmer JL, Buffler PA, et al. (2013) Current perspective on the global and United States cancer burden attributable to lifestyle and environmental risk factors. *Annu Rev Public Health* 34: 97-117.
3. Jemal A, Siegel R, Ward E, et al. (2008) Cancer Statistics, 2008. *CA Cancer J Clin* 58: 71-96.
4. Colditz GA (1998) Relationship between estrogen levels, use of hormone replacement therapy, and breast cancer. *J Natl Cancer Inst* 90: 814-823.
5. Fraumeni JF Jr, Lloyd JW, Smith EM, et al. (1969) Cancer mortality among nuns: role of marital status in etiology of neoplastic disease in women. *J Natl Cancer Inst* 42: 455-468.
6. Britt K, Short R (2012) The plight of nuns: hazards of nulliparity. *Lancet* 379: 2322-2323.

7. Scoccianti C, Lauby-Secretan B, Bello PY, et al. (2014) Female breast cancer and alcohol consumption: a review of the literature. *Am J Prev Med* 46: 16-25.
8. Romieu I, Scoccianti C, Chajès V, et al. (2015) Alcohol intake and breast cancer in the European prospective investigation into cancer and nutrition. *Int J Cancer* 137: 1921-1930.
9. Liu Y, Nguyen N, Colditz GA (2015) Links between alcohol consumption and breast cancer: a look at the evidence. *Womens Health (Lond Engl)* 11: 65-77.
10. Kabat GC, Kim MY, Hollenbeck AR, et al. (2014) Attained height, sex, and risk of cancer at different anatomic sites in the NIH-AARP diet and health study. *Cancer Causes Control* 25: 1697-1706.
11. Arnaldez F, Helman LJ (2012) Targeting the Insulin Growth Factor Receptor 1. *Hematol Oncol Clin North Am* 26: 527-542.
12. Tikk K, Sookthai D, Fortner RT, et al. (2015) Circulating prolactin and in situ breast cancer risk in the European EPIC cohort: a case-control study. *Breast Cancer Res* 17: 49.
13. Ronckers CM, Erdmann CA, Land CE (2005) Radiation and breast cancer: a review of current evidence. *Breast Cancer Res* 7: 21-32.
14. UNSCEAR Sources and effects of ionizing radiation: United Nations Scientific Committee on the Effects of Atomic Radiation: UNSCEAR 2000 report to the General Assembly, with scientific annexes. United Nations; New York: 2000. Scientific Committee on the Effects of Atomic Radiation.
15. Madeddu C, Gramignano G, Floris C, et al. (2014) Role of inflammation and oxidative stress in post-menopausal oestrogen-dependent breast cancer. *J Cell Mol Med* 18: 2519-2529.
16. Li J, Huang Y, Zhang BN, et al. (2014) Body Mass Index and Breast Cancer Defined by Biological Receptor Status in Pre-Menopausal and Post-Menopausal Women: A Multicenter Study in China. *PLoS One* 9: 87224.
17. McCormack VA, Highnam R, Perry N, et al. (2007) Comparison of a New and Existing Method of Mammographic Density Measurement. Intramethod Reliability and Associations with Known Risk Factors. *Cancer Epidemiol Biomark Prev* 16: 1148-1154.
18. Pollán M, Ascunce N, Ederra M, et al. (2013) Mammographic density and risk of breast cancer according to tumor characteristics and mode of detection: a Spanish population-based case-control study. *Breast Cancer Res* 15: R9.
19. Farvid MS, Cho E, Chen W, et al. (2014) Dietary protein sources in early adulthood and breast cancer incidence: prospective cohort study. *BMJ* 348: g3437.
20. Dumitrescu RG, Marian C, Krishnan SS, et al. (2010) Familial and racial determinants of tumour suppressor genes promoter hypermethylation in breast tissues from healthy women. *Cell Mol Med* 14: 1468-1475.
21. Sueta A, Yamamoto Y, Yamamoto-Ibusuki M, et al. (2014) An Integrative Analysis of PIK3CA Mutation, PTEN, and INPP4B Expression in Terms of Trastuzumab Efficacy in HER2-Positive Breast Cancer. *PLoS One* 9: e116054.
22. World Cancer Research Fund (WCRF), Continuous Update Project (CUP). 2007. Available from: http: //www.dietandcancerreport.org/cancer_resource_center/downloads/Second_Expert_Report_full.pdf

23. Institute of Medicine (IOM), Contemporary Issues for Protecting Patients in Cancer Research - Workshop Summary. 2014. Available from: http: //iom.nationalacademies.org/reports/2014/contemporary-issues-for-protecting-patients-in-cancer-research-workshop-summary.aspx#sthash.Kr7ZcQl9.dpuf
24. Interagency Breast Cancer & Environmental Research Coordinating Commitee (IBCERCC), Breast Cancer and the Environment. Prioritising Prevention. 2013. Available from: https://www.niehs.nih.gov/about/assets/docs/breast_cancer_and_the_environment_prioritizing_prevention_508.pdf
25. Diamanti-Kandarakis E, Bourguignon JP, Giudice LC (2009) Endocrine-disrupting chemicals: an Endocrine Society Scientific Statement. *Endocr Rev* 30: 293-342.
26. Kim YJ, Lee E, Lee HS (2015) High prevalence of breast cancer in light polluted areas in urban and rural regions of South Korea: An ecologic study on the treatment prevalence of female cancers based on National Health Insurance data. *Chronobiol Int* 32: 657-667.
27. Soto AM, Sonnenschein C (2010) Environmental causes of cancer: endocrine disruptors as carcinogens. *Nat Rev Endocrinol* 6: 363-370.
28. Holliday R (2006) Epigenetics: a historical overview. *Epigenetics* 1: 76-80.
29. Rodenhiser D, Mann M (2006) Epigenetics and human disease: translating basic biology into clinical applications. *Can Med Assoc J* 174: 341-348.
30. Bell CG, Beck S (2010) The epigenomic interface between genome and environment in common complex diseases. *Brief Funct Genom* 9: 477-485.
31. Paola P (2010) Epigenetic Signatures in Breast Cancer: Clinical Perspective. *Breast Care (Basel)* 5: 66-73.
32. Taioli E (2008) Gene-environment interaction in tobacco-related cancers. *Carcinogenesis* 29: 1467-1474.
33. Kanwal R, Gupta S (2010) Epigenetics and cancer. *J Appl Physiol* 109: 598-605.
34. Kanwal R, Gupta S (2012) Epigenetic modifications in cancer. *Clin Genet* 81: 303-311.
35. Cancer Research UK (CRUK), Breast cancer statistics. 2015. Available from: http: //www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer
36. Anderson WF, Jatoi I, Tse J, et al. (2010) Male breast cancer: A population-based comparison with female breast cancer. *J Clin Oncol* 28: 232-239
37. Kravchenko J, Akushevich I, Seewaldt VL, et al. (2011) Breast cancer as heterogeneous disease: contributing factors and carcinogenesis mechanisms. *Breast Cancer Res Treat* 128: 483-493.
38. Ferlay J, Shin HR, Bray F, et al. (2014) Cancer Incidence and Mortality Worldwide: IARC Cancer Base No. 10 Lyon, France.
39. Brody JG, Moysicj KB, Humblet O (2007) Environmental Pollutants and Breast Cancer: epidemiologic studies. *Cancer* 109: 2667-711.
40. Gray J, Evans N, Taylor B, et al. (2009) State of the evidence: the connection between breast cancer and the environment. *Int J Occup Environ Health* 15: 43-78
41. Urquhart R, Grunfeld E, Jackson L, et al. (2013) Cross-disciplinary research in cancer: an opportunity to narrow the knowledge-practice gap. *Curr Oncol* 20: e512-521.
42. Gehlert S (2013) Turning Disciplinary Knowledge into Solutions. *J Adolesc Health* 52: S98-102.

43. Popper KR (1963) *Conjectures and Refutations: The Growth of Scientific Knowledge*. New York: Routledge and Kegan Paul, p. 88.
44. Leung GM, Thach TQ, Lam TH, et al. (2002) Trends in breast cancer incidence in Hong Kong between 1973 and 1999: an age-period-cohort analysis. *Br J Cancer* 87: 982-988.
45. Rudel RA, Fenton SE, Ackerman JM, et al. (2011) Environmental Exposures and Mammary Gland Development: State of the Science, Public Health Implications, and Research Recommendations. *Environ Health Perspect* 119: 1053-1061.
46. Hoffmann I (2003) Transcending reductionism in nutrition research. *Am J Clin Nutr* 78: 514S-516S.
47. Desiere F (2004) Towards a systems biology understanding of human health: interplay between genotype, environment and nutrition. *Biotechnol Annu Rev* 10: 51-84.
48. Sterman JD (2006) Learning from Evidence in a Complex World. *Am J Public Health* 96: 505-514.
49. Fardet A, Rock E (2014) Toward a new philosophy of preventive nutrition: from a reductionist to a holistic paradigm to improve nutritional recommendations. *Adv Nutr* 5: 430-446.
50. Forouzanfar MH, Foreman KJ, Delossantos AM, et al. (2011) Breast and cervical cancer in 187 countries between 1980 and 2010: a systematic analysis. *Lancet* 378: 1461-84.
51. International Agency for Research on Cancer GLOBOCAN, Cancer Fact Sheets. 2012. Available from: http: //globocan.iarc.fr/Pages/fact_sheets_cancer.aspx
52. Edwards BK, Noone AM, Mariotto AB, et al. (2014) Annual Report to the Nation on the status of cancer, 1975-2010, featuring prevalence of comorbidity and impact on survival among persons with lung, colorectal, breast, or prostate cancer. *Cancer* 120: 1290-1314.
53. Siegel RL, Fedewa SA, Miller KD, et al. (2015) Cancer statistics for Hispanics/Latinos. *Cancer J Clin* 62: 283-298.
54. Weir HK, Thompson TD, Soman A, et al. (2015) The past, present, and future of cancer incidence in the United States: 1975 through 2020. *Cancer* 121: 1827-1837.
55. Edwards BK, Howe HL, Ries LA, et al. (2002) Annual Report to the Nation on the status of cancer, 1973-1999, featuring implications of age and aging on U.S. cancer burden. *Cancer* 94: 2766-2792.
56. Zhang X, Ho S-M (2011) Epigenetics meets endocrinology. *J Mol Endocrinol* 46: 11-32.
57. Macciò A, Madeddu C (2011) Obesity, Inflammation, and Postmenopausal Breast Cancer: Therapeutic Implications. *Sci World J* 11: 2020-2036.
58. Tironaa MT, Sehgala R, Ballestera O (2010) Prevention of Breast Cancer (Part I): Epidemiology, Risk Factors, and Risk Assessment Tools. *Cancer Investig* 28: 743-750.
59. Prüss-Ustün A, Vickers C, Haefliger P (2011) Knowns and unknowns on burden of disease due to chemicals: a systematic review. *Environ Health* 10: 9.
60. Karsli-Ceppioglu S, Dagdemir A, Judes G, et al. (2014) Epigenetic mechanisms of breast cancer: an update of the current knowledge. *Epigenomics* 6: 651-664.
61. McKinlay R, Plant JA, Bell JN, et al. (2008) Endocrine disrupting pesticides: implications for risk assessment. *Environ Int* 34: 168-183.
62. Porter P (2008) "Westernizing" women's risks? Breast cancer in lower-income countries. *N Engl J Med* 358: 213-216.

63. Darbre PD, Harvey PW (2008) Paraben esters: review of recent studies of endocrine toxicity, absorption, esterase and human exposure, and discussion of potential human health risks. *J Appl Toxicol* 28: 561-578.
64. Cogliano VJ, Baan R, Straif K, et al. (2011) Preventable exposures associated with human cancers. *Cancer Inst* 103: 1827-1839.
65. Coombs NJ, Cronin KA, Taylor RJ, et al. (2010) The impact of changes in hormone therapy on breast cancer incidence in the US population. *Cancer Causes Control* 21: 83-90.
66. Ferlay J, Soerjomataram I, Ervik M, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 (Internet). Lyon, France: International Agency for Research on Cancer. 2013. Available from: http: //globocan.iarc.fr
67. Youlden DR, Susanna I, Cramb M, et al. (2014) Incidence and mortality of female breast cancer in the Asia-Pacific region. *Cancer Biol Med* 11: 101-115.
68. Linos E, Spanos D, Rosner BA, et al. (2008) Effects of Reproductive and Demographic Changes on Breast Cancer Incidence in China: A Modeling Analysis. *J Natl Cancer Inst* 100: 1352-1360.
69. Kim YJ, Lee E, Lee HS, et al. (2015) High prevalence of breast cancer in light polluted areas in urban and rural regions of South Korea: An ecologic study on the treatment prevalence of female cancers based on National Health Insurance data. *Chronobiol Int* 32: 657-667.
70. Song QK, Li J, Huang R, et al. (2014) Age of diagnosis of breast cancer in china: almost 10 years earlier than in the United States and the European union. *Asian Pac J Cancer Prev* 15: 10021-10025.
71. United Nations Environment Programme (UNEP), United Nations Environment Programme: Programme Performance Report, 2014. Available from: http: //web.unep.org/ourplanet/september-2015/unep-publications/united-nations-environment-programme-programme-performance-report
72. Sharpe RM, Irvine DS (2004) How strong is the evidence of a link between environmental chemicals and adverse effects on human reproductive health? *BMJ* 328: 447-451.
73. Soto AM, Sonnenchein C, Chung KL (2003) The E-SCREEN Assay as a tool to identify estrogens: an update on estrogenic environmental pollutants. *Environ Health Perspect* 103: 113-122.
74. President's Cancer Panel (PCP). The Future of Cancer Research Panel Annual Report 2010-2011. Available from: http: //web.unep.org/ourplanet/september-2015/unep-publications/united-nations-environment-programme-programme-performance-report
75. Institute of Medicine. Identifying and Reducing Environmental Health Risks of Chemicals in Our Society - Workshop Summary. April 2014. Available from: http: //iom.nationalacademies.org/reports/2014/identifying-and-reducing-environmental-health-risks-of-chemicals-in-our-society.aspx#sthash.ydFX6pHy.dpuf
76. Mahoney MM, Padmanabhan V (2010) Developmental programming: impact of fetal exposure to endocrine-disrupting chemicals on gonadotropin-releasing hormone and estrogen receptor mRNA in sheep hypothalamus. *Toxicol Appl Pharmacol* 247: 98-104.
77. Fenton SE, Birnbaum LS (2015) Timing of Environmental Exposures as a Critical Element in Breast Cancer Risk. *J Clin Endocrinol Metab* 100: 3245-3250.
78. Heindel JJ (2005) The fetal basis of adult disease: Role of environmental exposures--introduction. Birth Defects Research Part A. *Clin Mol Teratol* 73: 131-132.

79. Mouritsen A, Aksglaede L, Sørensen K, et al. (2010) Hypothesis: exposure to endocrine-disrupting chemicals may interfere with timing of puberty. *Int J Androl* 33: 346-359.
80. Mousavi SM, Fallah M, Sundquist K, et al. (2012) Age- and time-dependent changes in cancer incidence among immigrants to Sweden: colorectal, lung, breast and prostate cancers. *Int J Cancer* 131: 122-128.
81. Birnbaum LS, Fenton SE (2003) Cancer and developmental exposure to endocrine disruptors. *Environ Health Perspect* 111: 389-394.
82. Sasco A (2001) Epidemiology of Breast Cancer: An environmental disease? *Apmis* 109: 321-332.
83. Andreeva VA, Unger JB, Pentz MA (2007) Breast cancer among immigrants. A systematic review and new research directions. *J Immigr Minor Health* 9: 307-322.
84. John EM, Phipps A, Koo J (2005) Migration history, acculturation and breast cancer risk in Hispanic women. *Cancer Epidemiol Biomark Prev* 14: 2905-2913.
85. Ziegler RG, Hoover RN, Pike MC (1993) Migration patterns and breast cancer risk in Asian Women. *J Natl Cancer Inst* 85: 1819-1827.
86. Stanford JL, Herrinton LJ, Schwartz SM, et al. (1995) Breast cancer incidence in Asian migrants to the United States and their descendants. *Epidemiology* 6: 181-183.
87. Hemminki K, Li X (2002) Cancer risks in second-generation immigrants to Sweden. *Int J Cancer* 99: 229-237.
88. Lichtenstein P, Niels V, Pai K (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.
89. Baker SG, Lichtenstein P, Kaprio J, et al. (2005) Genetic susceptibility to prostate, breast and colorectal cancer among Nordic twins. *Biometrics* 61: 55-56
90. Boehm JS, Zhao JJ, Yao J (2007) Integrative genomic approaches identify IKBKE as a breast cancer oncogene. *Cell* 129: 1065-1079.
91. Hunter DJ, Kraft P, Jacobs KB (2007) A genome-wide association identifies alleles in FGFR2 associated with risk of sporadic postmenopausal breast cancer. *Nat Genet* 129: 1275-1286.
92. Zuo T, Wang L, Morrison C (2007) FOXP3 is an X-linked breast cancer suppressor gene and an important repressor of the HER-2/ErbB2 oncogene. *Cell* 129: 1275-1286.
93. Polyák E, Gombos K, Hajnal B, et al. (2010) Effects of artificial sweeteners on body weight, food and drink intake. *Acta Physiol Hung* 97: 401-407.
94. Curtis C, Shah SP, Chin SF, et al. (2012) The genomic and transcriptomic architecture of 2,000 breast tumours reveals novel subgroups. *Nature* 486: 346-352.
95. Stephens PJ, Tarpey PS, Davies H, et al. (2012) The Landscape of Cancer Genes and Mutational Processes in Breast Cancer. *Nature* 486: 400-404.
96. Choudhury M, Friedman JE (2012) Epigenetics and microRNAs in Preeclampsia. *Clin Exp Hypertens* 34: 334-341.
97. Byler S, Goldgar S, Heerboth S, et al. (2014) Genetic and epigenetic aspects of breast cancer progression and therapy. *Anticancer Res* 34: 1071-1077.
98. Karsli-Ceppioglu S, Ngollo M, Judes G, et al. (2015) The Role of Soy Phytoestrogens on Genetic and Epigenetic Mechanisms of Prostate Cancer. *Enzymes* 37: 193-221.

99. Martinez-Arguelles DB, Papadopoulos V (2015) Identification of hot spots of DNA methylation in the adult male adrenal in response to in utero exposure to the ubiquitous endocrine disruptor plasticizer di-(2-ethylhexyl) phthalate. *Endocrinology* 156: 124-133.
100. Higley EB, Newsted JL, Zhang X, et al. (2010) Assessment of chemical effects on aromatase activity using the H295R cell line. *Environ Sci Pollut Res Int* 17: 1137-1148.
101. Andersson AM, Soder O, Toppari J, et al. (2012) The impacts of endocrine disrupters on wildlife, people and their environments - The Weybridge+15 (1996-2011) report.
102. International Agency for research on Cancer (IARC), AGENTS CLASSIFIED BY THE IARC MONOGRAPHS, VOLUMES 1-114. 2015. Available from: http: //monographs.iarc.fr/ENG/Classification/
103. Schäfers C, Teigeler M, Wenzel A, et al. (2007) Concentration- and time-dependent effects of the synthetic estrogen, 17alpha-ethinylestradiol, on reproductive capabilities of the zebrafish, Danio rerio. *J Toxicol Environ Health A* 70: 768-779.
104. Gluckman PD, Hanson MA (2006) Changing times: the evolution of puberty. *Mol Cell Endocrinol* 254: 26-31.
105. Odom L, Taylor H (2010) Environmental induction of the fetal epigenome. *Expert Rev Obstet Gynecol* 5: 657-664.
106. Barker DJ, Osmond C, Thornburg KL, et al. (2013) The intrauterine origins of Hodgkin's lymphoma. *Cancer Epidemiol* 37: 321-323.
107. Siddiqui MK, Anand M, Mehrotra PK (2004) Biomonitoring of organochlorines in women with benign and malignant breast disease. *Environ Res* 98: 250-257.
108. Nickerson K (2006) Environmental contaminants in breast milk. *J Midwifery Women's Health* 51: 26-34.
109. Russo J, Russo I (2007) *The role of estrogen in breast cancer*. In: Molecular Basis of Breast Cancer. Berling: Springer-Verlag Chapter 4: 89-136
110. Santodonato J (1997) Review of the estrogenic and antiestrogenic activity of polycyclic aromatic hydrocarbons: relationship to carcinogenicity. *Chemosphere* 34: 835-848.
111. Cohn BA, Wolff MA, Cirillo PM, et al. (2007) DDT and breast cancer in young women: new data on the significance of age at exposure. *Environ Health Perspect* 115: 1406-1414.
112. Partsch CJ, Sippell WG (2001) Pathogenesis and epidemiology of precocious puberty. Effects of exogenous oestrogens. *Hum Reprod Update* 7: 292-302.
113. Muñoz-de-Toro M, Markey CM, Wadia PR, et al. (2005) Perinatal exposure to bisphenol-A alters peripubertal mammary gland development in mice. *Endocrinology* 146: 4138-4147.
114. Gajdos ZK, Hirschhorn JN, Palmert MR (2009) What controls the timing of puberty? An update on progress from genetic investigation. *Curr Opin Endocrinol Diabetes Obes* 16: 16-24.
115. Biro FM, Greenspan LC, Galvez MP, et al. (2013) Onset of Breast Development in a Longitudinal Cohort. *Peadiatrics* 132: 1019-1027.
116. McKelvey W, Brody JG, Aschengrau A, et al. (2004) Association between residence on Cape Cod, Massachusetts, and breast cancer. *Ann Epidemiol* 14: 89-94.
117. Reiner JL, Kannan K (2006) A survey of polycyclic musks in selected household commodities from the United States. *Chemosphere* 62: 867-873
118. Singh K, Oates C, Plant J, et al. (2014) Undisclosed chemicals--implications for risk assessment: a case study from the mining industry. *Environ Int* 68: 1-15.

119. Hauser R, Skakkebaek NE, Hass U, et al. (2015) Male reproductive disorders, diseases, and costs of exposure to endocrine-disrupting chemicals in the European Union. *J Clin Endocrinol Metab* 100: 1267-1277.
120. Millikan R, DeVoto E, Duell EJ (2000) Dichloro-diphenyldichloroethene polychlorinated biphenyls and breast cancer among African-American and white women in North Carolina. *Cancer Epidemiol Biomark Prev* 9: 1233-1240.
121. Laden F, Ishibe N, Hankinson SE (2000) Polychlorinated biphenyls, cytochrome P450 1A1 and breast cancer risk in the Nurses' Health Study. *Cancer Epidemiol Biomark Prev* 11: 1560-1565.
122. Olivier M, Hainaut P (2001) TP53 mutation patterns in breast cancers: searching for clues of environmental carcinogenesis. *Sem Cancer Biol* 11: 353-360.
123. Daxenberger A, Ibarreta D, Meyer HH (2001) Possible health impact of animal oestrogens in food. *Hum Reprod Update* 7: 340-355.
124. Murray TJ, Maffini MV, Ucci AA, et al. (2007) Induction of mammary gland ductal hyperplasias and carcinoma in situ following fetal bisphenol A exposure. *Reprod Toxicol* 23: 383-390.
125. Geens T, Aerts D, Berthot C, et al. (2012) A review of dietary and non-dietary exposure to bisphenol-A. *Food Chem Toxicol* 50: 3725-3740.
126. Dairkee SH, Luciani-Torres MG, Moore DH, et al. (2013) Bisphenol-A-induced inactivation of the p53 axis underlying deregulation of proliferation kinetics, and cell death in non-malignant human breast epithelial cells. *Carcinogenesis* 34: 703-712.
127. Fernandez SV, Huang Y, Snider KE, et al. (2012) Expression and DNA methylation changes in human breast epithelial cells after bisphenol A exposure. *Int J Oncol* 41: 369-377.
128. Patterson AR, Mo X, Shapiro A, et al. (2015) Sustained reprogramming of the estrogen response after chronic exposure to endocrine disruptors. *Mol Endocrinol* 29: 384-395.
129. Gibson DA, Saunders PT (2014) Endocrine disruption of oestrogen action and female reproductive tract cancers. *Endocr Relat Cancer* 21: T13-31.
130. Durmaz V, Schmidt S, Sabri P, et al. (2013) Hands-off linear interaction energy approach to binding mode and affinity estimation of estrogens. *J Chem Inf Model* 53: 2681-2688.
131. Hilakivi-Clarke L, de Assis S, Warri A (2013) Exposures to synthetic estrogens at different times during the life, and their effect on breast cancer risk. *J Mammary Gland Biol Neoplasia* 18: 25-42.
132. Soto A, Brisken C, Schaeberle C, et al. (2013) Does cancer start in the womb? Altered mammary gland development and predisposition to breast cancer due to in utero exposure to endocrine disruptors. *J Mammary Gland Biol Neoplasia* 18: 199-208.
133. Olea N, Pazos P, Exposito J (1998) Inadvertent exposure to xenoestrogens. *Eur J Cancer Prev* 7: S17-23.
134. Takeda K, Tsukue N, Yoshida S (2004) Endocrine-disrupting activity of chemicals in diesel exhaust fumes and diesel exhaust particles. *Environ Sci Technol* 11: 33-45.
135. Maunder RJ, Matthiessen P, Sumpter JP, et al. (2007) Impaired reproduction in three-spined sticklebacks exposed to ethinyl estradiol as juveniles. *Biol Reprod* 77: 999-1006.
136. Coe TS, Söffker MK, Filby AL, et al. (2010) Impacts of early life exposure to estrogen on subsequent breeding behavior and reproductive success in zebrafish. *Environ Sci Technol* 44: 6481-6487.

137. Farmer JL, Orlando EF (2012) Creating females? Developmental effects of 17α-ethynylestradiol on the mangrove rivulus' ovotestis. *Integr Comp Biol* 52: 769-780.
138. Machtinger R, Orvieto R, Bisphenol A (2014) Oocyte maturation, implantation, and IVF outcome: review of animal and human data. *Reprod Biomed Online* 29: 404-410.
139. Pawlowski S, Sauer A, Shears JA, (2004) Androgenic and estrogenic effects of the synthetic androgen 17alpha-methyltestosterone on sexual development and reproductive performance in the fathead minnow (Pimephales promelas) determined using the gonadal recrudescence assay. *Aquat Toxicol* 68: 277-291.
140. Jobling S, Burn RW, Thorpe K, et al. (2009) Statistical modeling suggests that antiandrogens in effluents from wastewater treatment works contribute to widespread sexual disruption in fish living in English rivers. *Environ Health Perspect* 117: 797-802.
141. Boscia F, Passaro C, Gigantino V, et al. (2014) High levels of GPR30 protein in human testicular carcinoma in situ and seminomas correlate with low levels of estrogen receptor-beta and indicate a switch in estrogen responsiveness. *J Cell Physiol* 230: 1290-1297.
142. Macrina AL, Ott TL, Roberts RF, et al. (2012) Estrone and estrone sulfate concentrations in milk and milk fractions. *J Acad Nutr Diet* 112: 1088-1093.
143. Harris HR, Bergkvist L, Wolk A (2015) An estrogen-associated dietary pattern and breast cancer risk in the Swedish Mammography Cohort. *Int J Cancer* 137: 2149-2154.
144. Fucic A, Gamulin M, Ferencic Z (2012) Environmental exposure to xenoestrogens and oestrogen related cancers: reproductive system, breast, lung, kidney, pancreas, and brain. *Environ Health* 11: S8.
145. Kochukov MY, Jeng YJ, Watson CS (2009) Alkylphenol xenoestrogens with varying carbon chain lengths differentially and potently activate signaling and functional responses in GH3/B6/F10 somatomammotropes. *Environ Health Perspect* 117: 723-730.
146. Wozniak AL, Bulayeva NN, Watson CS (2005) Xenoestrogens at picomolar to nanomolar concentrations trigger membrane estrogen receptor-alpha-mediated Ca2+ fluxes and prolactin release in GH3/B6 pituitary tumor cells. *Environ Health Perspect*.113: 431-439.
147. Dorea JG, Cruz-Granja AC, Lacayo-Romero ML, et al. (2001) Perinatal metabolism of dichlorodiphenyldichloroethylene in Nicaraguan mothers. *Environ Res* 86: 229-237.
148. Frederiksen M, Vorkamp K, Mathiesen L (2010) Placental transfer of the polybrominated diphenyl ethers BDE-47, BDE-99 and BDE-209 in a human placenta perfusion system: an experimental study. *Environ Health* 5: 32.
149. Leino O, Kiviranta H, Karjalainen AK, et al. (2013) Pollutant concentrations in placenta. *Food Chem Toxicol* 54: 59-69.
150. Vizcaino E, Grimalt JO, Fernández-Somoano A, et al. (2014) Transport of persistent organic pollutants across the human placenta. *Environ Int* 65: 107-115.
151. Reed CE, Fenton SE (2013) Exposure to diethylstilbestrol during sensitive life stages: a legacy of heritable health effects. *Birth Defects Res C Embryo Today* 99: 134-146.
152. Gershenson C.Self-organising Traffic Lights (2005) *Complex Syst* 16: 29-53.
153. Johnson N (2009) *Simply Complexity*. Oneworld Publications, London.
154. Meadows DH (2008) *Thinking In Systems*. Chelsea Green Publishing Company White River Junction VT 05001.
155. Forrester JW (1971) Counterintuitive Behaviour of Social Systems. *Technol Rev* 73: 52-68.

156. Wild CP (2005) Complementing the Genome with an "Exposome": The Outstanding Challenge of Environmental Exposure Measurement in Molecular Epidemiology. *Cancer Epidemiol Biomark Prev* 14: 1847.
157. Rappaport SM (2011) Implications of the exposome for exposure science. *J Expo Sci Environ Epidemiol* 21: 5-9.
158. Kanwal R, Gupta S (2012) Epigenetic modifications in cancer. *Clin Genet* 81: 303-311.
159. Claus EB, Risch N, Thompson WD (1991) Genetic analysis of breast cancer in the cancer and steroid hormone study. *Am J Hum Genet* 48: 232-242.
160. Amir A, Evans DG, Shenton A, et al. (2003) Evaluation of breast cancer risk assessment packages in the family history evaluation and screening programme. *J Med Genet* 40: 807-814.
161. Amir E, Freedman OC, Seruga B, et al. (2010) Assessing women at High Risk of Breast Cancer: A Review of Risk Assessment Models. Oxford University Press.
162. California Breast Cancer Research Programme (CBCRP), A Model of Breast Cancer Causation. Available from: http: //www.cbcrp.org/causes/index.php

AIMS Press

© 2016 N. Voulvoulis et al., licensee AIMS Press. This is an open access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0)