BREAST CANCER – AN ENVIRONMENTAL DISEASE? THE INCREASED INCIDENCE OF BREAST CANCER WORLDWIDE: A SYSTEMS APPROACH IN INVESTIGATING BIOLOGICALLY PLAUSIBLE OESTROGENIC RISK FACTORS

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ABSTRACT

A growing body of evidence from experimental, body burden and ecological research indicates a link between breast cancer and the environment. Oestrogen metabolism is central to oestrogen receptor positive breast cancer. The vast majority occur in post-menopausal women possibly reflecting oestrogen 'load' leading to emergence of the hypothesis proposing that it is cumulative lifetime exposure to oestrogens that is behind escalating rates of breast cancer across the globe and especially in newly developed and developing countries. Despite all that is known at a molecular level about changes in breast tissue that lead to carcinogenesis there is no consensus on causation. Breast cancer is and remains a self-organising, non-linear and hierarchical system driven by feedback. As such it is both unpredictable and, for the time being, uncontrollable. It may never be fully controllable but by examining and discovering the system's properties, the aim is to work with it. Systems thinking has the capacity to identify links between various exposures and by building networks between them observe how the system that is cancer behaves. An integrated systems approach offers the potential to shift the war against cancer away from treatment towards prevention.

Keywords: breast cancer, systems approach, oestrogenic risk factors, exposure assessment

1. Introduction

Incidence of breast cancer is increasing worldwide with fastest rates of growth in countries generally referred to either as 'developing' or 'recently developed' (Ferlay *et al*. 2015). It accounts for 25% of all new cancers globally (GLOBOCAN, 2015). Two in every three cases in the UK are classified as oestrogen receptor-positive (ER+) (CRUK, 2014). Incidence of this particular type of cancer in the US is predicted to increase by 50% by 2030 (SEER, 2015).

The women of East Asia, particularly Japan and China, have historically experienced the lowest rates of breast cancer incidence (Itoh *et al*. 2009) but the greatest rates of increase are now being seen in Asian countries (Hortobagyi *et al*. 2005). Figures like these have lent strength to the hypothesis proposing that particular characteristics of 'Westernisation' in rapidly developing and newly developed non-Western countries are contributing to increased incidence of breast cancer in their female populations (Troisi *et al*. 2014).

Endocrine-related disease is also increasing globally (Hanson & Gluckman 2014). A body of evidence suggests that environmental exposures, especially to chemicals, play a role (Prüss-Ustün *et al*. 2011). Of particular concern are chemicals with potential to disrupt the endocrine system through their hormone modulating properties via oestrogen mimicry. They are referred to collectively as endocrine disrupting chemicals (EDCs).

Oestrogens have been categorized as carcinogens by since 1987 (IARC). In 2002, oestrogens in HRT and OCs were added to the list of recognized carcinogens (NTP, 2002). In vitro assays have identified >250 chemicals which in interfering with oestrogen metabolism stimulates proliferation of oestrogen-sensitive breast cancer cells (Brody *et al*. 2007).

2. Environmental Oestrogens and Breast Cancer

In the decades since World War II breast cancer incidence has risen in parallel with the proliferation of synthetic chemicals (Breast Cancer Fund, 2008). 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 (Soto, 2013). Evidence is accumulating that exposures to commonly encountered EDCs may be contributing to this increase.

Oestrogen is lipophilic and accumulates in fatty tissue (Daxenberger *et al*. 2001) which therefore constitutes a storage site for endogenous and exogenous hormones as well as fat-soluble EDCs. Multiple studies support the hypothesis that cumulative lifetime exposure to oestrogen is a causal factor in breast cancer risk (Nahleh *et al*. 2011). The most rapid accumulation of risk has been proposed as being between menarche and first pregnancy (Colditz & Rosner 2000) and it is increasingly recognised that early-life exposures, even in utero, can affect lifetime risk (Trichopoulos *et al*. 2008).

3. The Systems Approach

Systems thinking has developed over the past 60 years. It moves away from the division of a problem into the manageable 'chunks' favoured by reductionism and considers instead the dynamics of the whole issue by looking at interactions. Soft systems modelling (SSM) developed as a means of investigating 'messy' problems (Ison 2014) and is now the acknowledged paradigm for the holistic approach to problem solving (Checkland, 2006).

It is argued that systems thinking is both appropriate and useful for tackling issues that are embedded in complexity, especially those that involve human activity, because it addresses interconnectedness in a way that reductionism cannot. In breast cancer, damage to DNA is the initiating step. Drawing back and considering the whole hierarchy is necessary because when a cancer cell in breast tissue starts to replicate uncontrollably it has clearly broken free of its constraints within its designated sub-system with repercussions for other sub-systems in the hierarchy.

A systems approach would draw on the accumulated evidence to flesh-out a conceptual framework aiming to integrate the biological cellular and molecular processes identified in the literature as involved in the aetiology of breast cancer, with the environmental exposures known to modulate oestrogen metabolism. For a system to be properly understood its overall 'shape' must first be established. This can only be achieved by looking at the interconnectedness of the parts because they (the parts) do not display individually the characteristics of the whole (Funtowicz & Ravetz, 1994; Hardeman *et al*. 2013).

Animal and in vitro studies would constitute the system's 'tools' for exploring the health effects, mechanisms of action, and biologic plausibility of oestrogen's association with risk for breast cancer. A preliminary conceptual framework for examining breast cancer incidence in relation to environmental oestrogens is proposed in Figure 1.

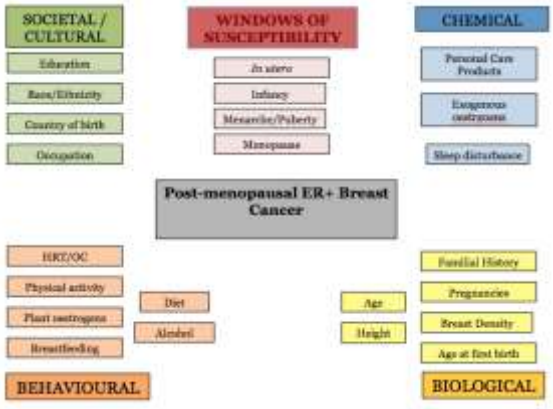

Figure 1: Conceptual framework of an evidence-based model for post-menopausal ER+ breast cancer risk.

4. Conclusion

Systems thinking predicts that people will not change their behaviour and/or thinking until it is proved to them that the current way of doing things is failing (Sterman 2006). On this basis, systems thinking should be regarded not so much as offering 'the' or even 'a' solution but as showing what can or might be achieved.

Breast cancer is and remains a self-organising, non-linear and hierarchical system driven by feedback. As such it is both unpredictable and, for the time being, uncontrollable. It may never be fully controllable but by examining and discovering its properties the aim is to work with it. An integrated systems approach offers the potential to shift the war against cancer away from treatment towards prevention and it is therefore proposed that it should be investigated further.

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