Emerging Contaminants 2 (2016) 204–219

Contents lists available at ScienceDirect

Emerging Contaminants

journal homepage: http://www.keaipublishing.com/en/journals/emerging-contaminants/

Review article

A review of the role of emerging environmental contaminants in the development of breast cancer in women

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ARTICLE INFO

Article history:
Received 12 August 2016
Received in revised form
7 December 2016
Accepted 12 December 2016
Available online 21 December 2016

Keywords:
Breast cancer
Emerging contaminants
Endocrine disrupting chemicals
Toxicology
Epidemiology
BPA
PBDEs

ABSTRACT

The incidence of breast cancer is on a rise worldwide; it is a disease having a complex etiology. Besides genetics, environmental and other lifestyle factors play a role in the development of the disease. There has been a keen interest in studying associations between breast cancer and exposures to emerging environmental chemicals, which mimic estrogens or influence estrogen levels and signaling in the human body. The common consequence of an endocrine disrupting chemical exposure is that it may have an impact on breast cancer etiology by stimulating formation as well as progression of breast cancer. Exposures to selected emerging environmental contaminants such as alkylphenols (APs), bisphenol A (BPA), parabens, perfluoroalkyl substances (PFASs), phthalates, polybrominated diphenyl ethers (PBDEs), synthetic musks and triclosan, and their probable role in breast cancer development are reviewed. Studies evaluated include the experimental *in vitro* and *in vivo* studies as well as human population based studies. In vitro and *in vivo* evidences indicate that a number of emerging environmental contaminants may play a role in the initiation and/or progression of breast cancer. Although exposures have been assessed in some human populations, breast and other cancer risks associated with these exposures are largely unknown. Efforts should be focussed on the evaluation of these environmental exposures in human populations and their interactions with each other and other genetic and lifestyle risk factors.

Contents

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Peer review under responsibility of KeAi Communications Co., Ltd.

http://dx.doi.org/10.1016/j.emcon.2016.12.003

1. Introduction

Breast cancer is a disease with a complex etiology and is the most common invasive malignancy among women worldwide. Incidence rates of breast cancer are approximately 90–130 per 10,000 women in developed countries and 10–60 per 10,000 women in developing countries [1]. In the United States, breast cancer accounts for 25% of cancers among women, and in 2011, approximately 230,480 new cases of invasive breast cancer and 57,650 cases of in situ carcinoma were diagnosed [2]. According to the Canadian Breast Cancer Foundation (2013), breast cancer continues to be the most common cancer diagnosed in Canadian women over the age of 20, representing 1 in 4 cancer diagnoses [3]. It is the second leading cause of cancer deaths in Canadian women, after lung cancer. Worldwide, breast cancer incidence is on the rise in both developed and developing countries, perhaps secondary to dietary and reproductive changes. The incidence of breast cancer is higher in the developed/industrialised nations as compared with developing countries, and may in part reflect differences in population level exposures to environmental contaminants.

The factors involved in the etiology of breast cancer are genetic, reproductive, lifestyle related and environmental. The most common and frequently studied inherited mutations, classified as important susceptibility genes, are BRCA1 and BRCA2, which primarily control homologous recombination and repair of somatic damage to DNA and regulate transcription of genes in the DNA damage response pathway [4]. Inheritance of a mutated form of either of the BRCA genes or of other more moderate susceptibility variants in genes such as PALB2, CHEK2 and ATM [5], is associated with a significantly increased risk for development of breast cancer. However, it is estimated that approximately 20–25% of a woman's risk for developing breast cancer may be attributed to inherited genetic factors [5].

Epidemiological and clinical evidence confirms that cumulative and sustained exposure to estrogen is a well-established risk factor for breast cancer in women [6,7]. Reproductive factors directly associated with increased estrogen levels, such as early menarche, late menopause, nulliparity or late age at first pregnancy, and lack of breast feeding after childbirth (suppresses estrogens), are consistently associated with increased breast cancer risk in observational epidemiologic studies. Late menarche and early menopause reflect reduced estrogen exposures and are associated with a reduced breast cancer risk [8,9]. Other factors, directly and/or indirectly, can affect estrogen levels in the body or act to modify breast cancer risks. These include dietary factors (mediated via obesity or early menarche), alcohol intake, exercise, exogenous hormone consumption (hormone replacement therapies, HRTs), and oophorectomy [10]. These factors, along with a advancing age, family history of breast cancer, and a history of benign breast disease likely account for 25% of breast cancer risk disease [11].

Environmental (including exogenous estrogen exposures) and other lifestyle factors may account for the remainder of breast cancer risk and therefore could play a major role in the development of the disease [5]. Mammary gland development is a complex process extending from gestation through multiple life stages (like puberty and pregnancy). Normal breast development consists of a series of well-orchestrated events that are finely regulated by a balance of hormones, growth factors, and stromal factors. Chemical exposures during susceptible windows of development may alter the mammary gland in ways that increase risk for development of disease later in life.

A number of epidemiological studies have examined breast cancer risks associated with the legacy environmental contaminants, including the organochlorine pesticides [12], dioxins [13], and polychlorinated biphenyls [14]. The biochemical mechanisms of toxicity for these chemicals have been well studied in laboratory animals, and to a lesser extent in humans, and some health effects have been characterized in occupationally exposed individuals. Much less attention has been paid to the adverse health outcomes as a result of exposure to other more contemporary environmental contaminants, and especially for exposures to these contaminants during susceptible windows of development. Environmental pollutants exhibit a high degree of chemical variability, however, a number of environmental compounds with potentially adverse health effects have common structural motifs, such as containing one or more aromatic rings [15]. As a result, unrelated chemicals may have similar molecular functional pathways and influence human disease in similar ways. For example, diverse chemicals may act as carcinogens by causing DNA damage, or may mimic the biological function of the estrogen hormones. Estrogens play an important role in the etiology of breast cancer through two distinct pathways, first, the by-products of estrogen metabolism cause DNA damage by forming DNA adducts and oxidized bases, thereby, leading to mutations in oncogenes and tumor suppressor genes that control normal cell growth and proliferation. Second, estrogens also alter expression of genes which stimulate growth and proliferation of ductal epithelial cells in the breast [16]. Thus, lifetime exposure to estrogen is a well-established risk factor for breast cancer. A survey conducted by Choi and group [17] revealed that 79% of the endocrine disrupting compound (EDCs) studied were shown to produce carcinogenicity (when positive in at least one animal species). They also demonstrated that EDCs showing estrogen-modulating effects were closely related to carcinogenicity or mutagenicity with a high degree of sensitivity. Very recently a review on mechanisms of action of estrogenic EDCs and their role in development of different diseases, including cancer, has been published [18]. One common consequence of the endocrine disrupting chemical exposure is that, it may have a profound impact on breast cancer etiology by stimulating formation as well as progression of breast cancer. The chemicals are present in such varied concentrations, that functionality can be reached in many different ways. Thus, any functionality of chemical concentrations in a tissue would need to take account of the amount of all the chemicals (even their isomers), the relative receptor binding affinity (RBA) values of each and the sum of the estrogenic stimulus generated by all the chemicals in combination. Moreover, using animal (rodent) data to assess human health risk must be approached with caution because the exposure profile and often the body elimination is very different. In animal studies, the exposure is often with single compounds in higher concentrations but over relatively short times, whereas in human the exposure is lifelong with low doses and complex mixtures. The contribution of low-level exposures to chemical mixtures that occur *in utero* and throughout our lifetime is an important factor to consider when evaluating chemical carcinogenicity. It is likely that low-dose carcinogenic effects occur due to exposures to chemical mixtures, at relevant environmental