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PREFACE

Preface

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Over the past several decades, the global incidence rate of breast cancer has increased continuously [1–4] with the most rapid increase occurring in economically developing countries [4]. In 2008, approximately 1.3 million new cases of breast cancer were diagnosed, accounting for 23 % of all cancers [3] and making breast cancer the most commonly diagnosed cancer in women [3, 5]. Approximately, 55 % of breast cancer cases were diagnosed in developed countries and the remaining 45 % of the cases were diagnosed in developing countries [3]. Although breast cancer is the most common cancer in women worldwide, developed countries have a higher overall incidence rate and a three-fold higher age-standardized rate [4]. In Western Europe, the incidence rate is 89.7 per 100,000 women while in Eastern Africa, the incidence rate is 19.3 per 100,000 women [3]. Although the global incidence rate of breast cancer is increasing, the underlying causes of the disease are still largely unknown. During the 1980s, screening practices, access to mammography, and the use of exogenous estrogens and progestins contributed to the high incidence rates in developed countries, but these factors do not explain the increase in these countries before the 1980s or the increase in countries with low rates of screening and use of hormones [6]. It has been suggested that the increasing incidence is due to a combination of an increase in the prevalence of known risk factors and to new unidentified risk factors [2, 7]. Family history is a risk factor for developing breast cancer (8), but only 5–10 % of breast cancers are associated with the highly penetrant BRCA1 and BRCA2 genes [8]. In contrast to family history, endocrine status is a prominent risk factor for developing breast cancer. Early age at menarche [9, 10], late age at menopause [11, 12], and later age at first full-term pregnancy [13] increase the risk of developing the disease. Exposure to exogenous estrogens and progestins after menopause [14–16] and a history of benign breast disease also increase the risk of developing breast cancer. These well established risk factors, i.e., family history, reproductive and menstrual history, and history of benign breast disease, are estimated to account for only about 40 % of breast cancer cases [17]. Childhood exposure to ionizing radiation [18–20], adult alcohol consumption [21], and obesity [7, 22, 23] also increase the risk of developing breast cancer. However, these risk factors are unlikely to account for the remaining cases of the disease [2, 7, 24] suggesting that there are still unidentified causes of breast cancer.

There are many challenges to identifying risk factors for developing breast cancer including, but not limited to, the type of exposure, e.g., environmental estrogens, carcinogens, and mutagens; the influence of genetics on the response to the exposure, a.k.a., gene-environment interactions; and the timing of the exposure. The breast is unique and complex in that it grows and develops throughout the lifetime of a female [25] providing windows of susceptibility to exposures that may increase the risk of developing the disease. Development of the breast begins in fetal life and ends following the first full term pregnancy and lactation. During gestation, the gland develops into a small, branched ductal network with stem cells located at the end of the ducts [26] as well as along the ducts [27]. These stem cells have the potential to generate progenitor cells that proliferate and differentiate into the luminal and basal cells that are necessary for elongation and branching. From birth to the onset of puberty, there is allometric growth of the gland, but with the onset of puberty, there is exponential growth and development. In response to ovarian estrogens and progesterone and pituitary growth hormone, the ducts elongate and branches develop. With each successive menstrual cycle, the gland progressively differentiates. During pregnancy, there is a further increase in the growth and development of the gland and upon lactation, the gland terminally differentiates into a milk secreting organ. Following menopause, the gland regresses due to the absence of ovarian hormones. The central role of estrogens in the growth and

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development of the breast may help us define the windows of susceptibility of the gland to specific environmental exposures. For example, environmental exposures that mimic the biological effects of estrogens may increase the risk of developing breast cancer if the exposure occurs during fetal development or following menopause when the gland is sensitive to small changes in the hormone. During fetal development, exposure to environmental estrogens may reprogram gene expression or alter the stem and/or progenitor cell population predisposing the gland to tumorigenesis, whereas following menopause, exposure to exogenous estrogens may increase the proliferation and expansion of cells that have cumulative DNA damage. In contrast to environmental estrogens, environmental exposures that induce DNA damage may increase the risk of developing breast cancer if the exposure occurs during puberty or pregnancy when the gland is growing and developing. Rapidly replicating cells may not have sufficient time to repair DNA damage leaving the gland vulnerable to carcinogens and mutagens that cause DNA damage. In addition to the timing of exposure, genetics influences the vulnerability of the gland to environmental carcinogens and mutagens. The inherited ability to metabolize carcinogens and mutagens to active and inactive metabolites, to control the progression through the cell cycle, and to repair DNA damage can influence the response of the gland to environmental insults.

As breast cancer is an increasing global health problem, it is important to identify the risk factors for developing the disease. In this issue, experts review our current understanding of suspected, but controversial, risk factors taking into account gene-environment interactions and windows of susceptibility while others review emerging evidence of new potential risk factors. The goal is to provide insight into suspected and potential risk factors for developing breast cancer and provide new testable hypotheses into the underlying causes of the disease.

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