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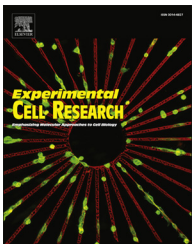

Review Article

Developmental windows of breast cancer risk provide opportunities for targeted chemoprevention ☆

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ABSTRACT

The magnitude of the breast cancer problem implores researchers to aggressively investigate prevention strategies. However, several barriers currently reduce the feasibility of breast cancer prevention. These barriers include the inability to accurately predict future breast cancer diagnosis at the individual level, the need for improved understanding of when to implement interventions, uncertainty with respect to optimal duration of treatment, and negative side effects associated with currently approved chemoprevention therapies. None-the-less, the unique biology of the mammary gland, with its postnatal development and conditional terminal differentiation, may permit the resolution of many of these barriers. Specifically, lifecycle-specific windows of breast cancer risk have been identified that may be amenable to risk-reducing strategies. Here, we argue for prevention research focused on two of these lifecycle windows of risk: postpartum mammary gland involution and peri-menopause. We provide evidence that these windows are highly amenable to targeted, limited duration treatments. Such approaches could result in the prevention of postpartum and postmenopausal breast cancers, correspondingly.

Abbreviations: SERM, selective estrogen receptor modulator; BRCAT, breast cancer risk assessment tool; IBIS, International Breast Cancer Intervention Study Model; NSAID, non-steroidal anti-inflammatory; DCIS, ductal carcinoma in situ; OVX, ovariectomy.

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Rationale for cancer prevention focus

The field of cancer prevention was formalized in the 1970s and coincided with the recognition that most cancers develop through a multi-step process with long latency [1]. Establishing that cancer progression spans from initiation to overt metastasis energized the cancer research community to consider prevention strategies. Based on current incidence rates, the appeal of preventing cancer is self-evident. In the US, it is predicted that almost 50% of men and 33% of women will be diagnosed with cancer in their lifetime [2]. Breast cancer, which is the focus of this review, is a significant health problem worldwide. In 2010 there were an estimated 1.5 million cases of breast cancer diagnosed, representing nearly a quarter of all cancer diagnoses in women. Breast cancer is now the leading cause of cancer death in economically developed countries, a statistic in stark contrast to the low death rate from cervical cancer due to successful prevention [3]. Despite medical advances in breast cancer detection and treatment, mortality remains a global problem and further, access to care is limited in many countries. Thus, breast cancer represents an optimal cancer to target for prevention research, particularly if the outcome is generalizable and inexpensive.

Overview of breast cancer prevention success to date

Conceptually, there are multiple strategies for breast cancer prevention. Primary prevention is focused on blocking tumor cell initiation by minimizing carcinogen exposure or enhancing detoxification. Examples include avoiding the use of ionizing radiation on developing breast tissue, limiting exogenous estrogen exposure, and supplementation with dietary agents such as the cruciferous isothiocyanates, which activate the p450 carcinogen metabolism pathway [4]. The ability to prevent breast cancer through targeted drug therapy, or chemoprevention, has also been successful with the use of selective estrogen receptor modulator (SERMs) [5,6]. Unfortunately, despite research success with SERMs, significant challenges remain [7]. Barriers to the implementation of successful large-scale prevention efforts have been identified from the first generation breast cancer prevention trials and subsequent follow up studies [7]. While a comprehensive summary of these trials is beyond the scope of this short review, we briefly cover many of the salient points, in order to help inform future trials.

Breast cancer was the first malignancy where targeted drug treatment trials in the adjuvant setting demonstrated a concomitant secondary prevention benefit for subsequent contralateral disease. An average 50% reduction in new primary breast cancers was identified among women treated for 5 years with the SERM, tamoxifen [5]. These data supported the ensuing landmark NSABP-P1 randomized clinical trial for the primary prevention of breast cancer, enrolling women over age 35 who had a higher than 1.6% risk of developing breast cancer within the next 5 years [5]. A similar degree of benefit was observed, with a 49% reduction in incidence of estrogen-positive breast cancer, resulting in tamoxifen′s approval as the first chemopreventive agent in 1998 [5]. The second generation SERM, raloxifene, was approved 10 years later, and is approximately 75% as effective as tamoxifen in preventing breast cancer with significantly fewer side effects [6]. More recently, the aromatase-inhibitor exemestane given to high risk post-menopausal women for 5 years reduced annual incidence of invasive breast cancer by 65% [8]. This study confirms efficacy of aromatase-inhibition for prevention in post-menopausal women who are at increased risk for breast cancer [8].

Given the clinical success of anti-hormone based chemoprevention, it is surprising that of the more than 2 million high-risk women in the US alone, the number of women using tamoxifen for prevention is declining, with reports of 120,000 in 2000 to 20,500 in 2010 [7]. Similarly, in 2010, 96,000 postmenopausal women used raloxifene as primary chemoprevention, suggesting it too is not embraced by the vast majority of high-risk women. Data on acceptance of the aromatase inhibitor exemestane is not yet available. So, why do high risk women choose not to take SERMs to reduce risk for breast cancer? Reported barriers to chemoprevention acceptance include lack of risk knowledge among women, toxicity, and selected benefit specific for estrogen receptor (ER) positive tumors.

The toxicity profile and therapeutic index of SERM therapy is a clearly identified detractor to the drug's acceptance among women [6,7]. When the potential benefits of tamoxifen use by high-risk postmenopausal women are examined, estimates indicate that one case of breast cancer is prevented for every 35 women treated, and one breast cancer death prevented by treating 102 women [9]. However, for each 1000 who select tamoxifen as prevention, 3 are anticipated to develop endometrial cancer and 2–3 will experience a significant thromboembolic event [5–7]. There are also a number of other complications from SERM chemoprevention agents that limit the drug's acceptability, including worsening of menopausal symptoms, sexual