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Original article

Breast Cancer Chemoprevention: A Literature Review

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ABSTRACT

Many women at increased risk of breast cancer could get benefit from preventive chemotherapy. Preventive chemotherapy options for breast cancer risk reduction have been expanded in the last few years to include both selective receptor modulators (tamoxifen and raloxifene) and retinoids. Risk factors that place women at high risk for breast cancer, as well as risk calculation models appropriate for the selection of candidates for preventive therapy, are presented, followed by a review of current chemoprevention and results of some chemoprevention trials are reviewed in the present paper. Aromatase inhibitors are not linked to the increase the risk of blood clots or even uterine cancer, as tamoxifen and raloxifene are. As aromatase inhibitors are a new type of treatments, there are not much information is yet known about long term side effects that they might cause. The systemic administration of retinoids however is frequently associated with liver toxicity and abnormalities of serum lipid profiles, which might be related to an increased risk of coronary heart disease as well as the teratogenic effect of all retinoids, which limits their use in women of child bearing potential. Published guidelines on chemoprevention for breast cancer have been updated to raise awareness and encourage discussion between both the patients and their physicians. However, even with increasing the awareness and established benefits of preventive therapy, the use of chemo preventions is still low, with physician and patient barriers identified. It is prudent that these barriers be overcome to enable high-risk women with a favorable risk-to-benefit ratio to be offered chemoprevention to reduce their likelihood of developing hormone receptor-positive breast cancer. In this review article, we aimed to highlight the update on the chemo preventive strategies in breast cancer.

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INTRODUCTION

Breast cancer

Breast cancer is the most diagnosed cancer in women in the UK. One every eight women is estimated to develop breast cancer in their life [1]. The incidence of female breast cancer has increased by 50% over the last 25 years (fig.1). For many women, there is no frightful disease more than breast cancer as it related to loss sexuality, body shape and image and the finally leads to death [2]. While there are certain risk factors like genetics we cannot alter, there are many lifestyles changes we can make to aid the breast cancer prevention. For the majority of women, lifestyle changes such as limiting the amount of alcohol consumption, eating healthy diet staying physically active, weight redaction and breast-feeding may also play an important role in breast cancer prevention [3]**.** To date, the most important strategy in improving survival is still breast cancer screening and early detection [4].

In addition, real prevention for breast cancer has not been found yet even in women at high risk of disease like women with reproductive factors, family history, benign pathology or mammographic density [4]. However, there are some suggestions about primary prevention of breast cancer that might be a realistic objective.

Studies on cancer

To identify studies, we conducted literature searches on the breast cancer prevention Trial (BCPT) were designed to study whether tamoxifen can prevent breast cancer in women who are at an increased risk of developing this disease. The study began in April 1992 and closed to in September 1997 [15].

In their study, 13,389 premenopausal and postmenopausal women were enrolled to 300 centres across the US and Canada and randomly receive tamoxifen or a placebo one per day for 5 years. The study concluded that tamoxifen has ability to reduce the risk of breast cancer in women at increased risk of developing the disease [15].

In 2006, the tamoxifen and raloxifene (STAR) clinical trial study concluded that raloxifene is similarly effective to tamoxifen in reducing the incidence of breast cancer [15], though after an average 4-year follow-up there were 29% fewer blood clots and 36% fewer uterine cancers in women taking raloxifene than in women taking tamoxifen, even though the difference was not statistically significant [15].

Tamoxifen

Tamoxifen is an antagonist of the estrogen receptor in the breast. It blocks the effects of estrogen hormone that induces the growth and development of breast tissue via metabolized it metabolite (hydroxytamoxifen) [6]. Tamoxifen is member of a class of medications known as selective estrogen receptor modulators (SERMs), It has been the standard

endocrine therapy for hormone receptor-positive breast cancer [7]. However, in the uterus, tamoxifen acts like an estrogen and encourages the growth of the lining of the uterus [6]. Tamoxifen binds to the estrogen receptor to prevent estrogen from binding to its receptor (competitive antagonism), therefore breast cancer cell growth is blocked. For breast cancer prevention tamoxifen is normally prescribed as pills are taken once a day by mouth, tamoxifen is usually taken for a total of five years [7]. This drug is used to reduce the risk of invasive breast cancer in high-risk women age 45 and older, whether or not they have gone through menopause. Tamoxifen prevent breast cancer depends on these criteria [8]: Gail model risk scores if it's greater than 1.66 percent. The Gail model is a tool are used by doctors to predict future risk of developing breast cancer, based on factors such as your family history, age and reproductive history. High risk patient for developing breast cancer. For example, a breast biopsy that found precancerous conditions such as atypical ductal hyperplasia, atypical lobular hyperplasia or lobular carcinoma in situ (LCIS). If there is a strong family history of breast cancer. If there are a history of blood clots. Hysterectomy. For breast cancer prevention, we need to balance between the advantage and disadvantage of using tamoxifen and the patient need. So, what is the side effect of using tamoxifen. Common side effects of tamoxifen: Hot flashes,Vaginal discharge, Vaginal dryness, bladder or urinary problems, Blood clots, Endometrial cancer or uterine cancer [9]. Therefore, the potential risks of tamoxifen may outweigh the benefits for it [8]. However, randomized clinical trials of breast cancer therapy for the early-stage have demonstrated a 35% decrease in breast cancers among women receiving tamoxifen.

Raloxifene

Raloxifene is a different kind of medication in the SERMs class [11]. Like tamoxifen, raloxifene works by blocking estrogen's effects in the breast and other tissues [11]. Raloxifene is used to reduce the risk of invasive breast cancer in the high-risk women who are past menopause (postmenopausal) [12]. We consider women at high risk if there score greater than 1.66 percent on the Gail mode [11]. Not like tamoxifen, raloxifene does not cause estrogen-like effects on the uterus [12]. Raloxifene have also used for prevention and treatment of the bone-thinning disease like osteoporosis in postmenopausal women [12]. Common side effects of raloxifene include: Hot flashes, vaginal dryness or irritation, joint and muscle pain or weight gain [13]. Health problem that associated with raloxifene are like to those associated with tamoxifen [14]. As both drugs carry an increased risk of blood clots, though the risk may be lower with using of raloxifene [14]. Nevertheless, raloxifene is associated with fewer cases of endometrial and uterine cancers compared with tamoxifen [14]. In addition, Raloxifene may also link to fewer cases of strokes than

tamoxifen [14]. However, if they have heart disease or multiple risk factors for heart disease, like high cholesterol, obesity, high blood pressure and smoking, raloxifene may really increase their risk of strokes [14].

Retinoids

Due to their major role in the regulation of cell growth and differentiation in lab models, retinoids are being widely evaluated in different clinical trials of cancer prevention [16]. Retinoids, the natural and synthetic derivatives of vitamin A, are known to play a major role in tissue and cellular differentiation. they can suppress tumour promotion and change some properties of totally transformed malignant cells by activating or repressing specific genes [17]. In addition to the nuclear receptors and retinoic acid responding elements, specific cellular retinoid binding proteins link retinoids with high affinity plus regulate their metabolism.

Retinoid receptors are expressed in both normal and malignant epithelial breast cells and they are crucial for normal development. Even though the mechanism that led to breast cell growth inhibition by retinoids hasn't been yet completely explained, experimental evidence proof that it is most likely due to involve multiple signal transduction pathways.

systemic administration of these compounds is frequently associated with mucocutaneous side effects [18], liver toxicity and abnormalities of serum lipid profiles [19], which might be related to an increased risk of coronary heart disease. Of particular concern is the teratogenic effect of all retinoids, which limits their use in women of child-bearing potential Chronic toxicities from long term therapy with retinoids may result in skeletal abnormalities, usually mimicking diffuse idiopathic hyperostosis syndrome.

Aromatase inhibitors

Aromatase inhibitors are usually used to treat breast cancer which hormone receptor positive in post-menopausal women. Aromatase inhibitors are an option drug for breast cancer chemoprevention. Aromatase inhibitors are considered as a class of medicines that reduce the amount of estrogen in the body. There are three aromatase inhibitors are recently approved for use in the treatment of postmenopausal women with breast cancer: anastrozole (Arimidex), exemestane (Aromasin) and letrozole (Femara) [20].

Aromatase inhibitors have shown to be effective in postmenopausal women to treat and prevent breast cancer and to stop breast cancer recurrence [21]. Aromatase inhibitors are not used for preventing breast cancer recurrence in woman who has menstrual cycles.

Aromatase inhibitors, especially exemestane and anastrozole, have been shown if they reduce the risk of breast cancer in high-risk women, like those with a positive family history of breast cancer or any history of precancerous breast lesions. Researchers have shown reduction in the risk of developing breast cancer in these

high-risk women [22]. Additional more studies are underway to look whether aromatase inhibitors could reduce the risk of breast cancer in woman with genetic mutations which increase the risk of breast cancer.

The most Common side effects of aromatase inhibitors include: hot flashes, vaginal dryness, joint and muscle pain, headache, fatigue, also the Aromatase inhibitors increase the risk of bone thinning (osteoporosis).

Aromatase inhibitors are not linked to the increase the risk of blood clots or even uterine cancer, as tamoxifen and raloxifene are [23]. As aromatase inhibitors are a new class of treatments, there are not much information is yet known about long term side effects, like heart disease and broken bones (fractures)[24].

CONCLUSION

Physicians must become more familiar with breast cancer risk assessment.Both tamoxifen and raloxifene decrease breast cancer risk in high risk women. Both have adverse effects which must be weighed against benefits.We must improve communication of risk and benefits to patients and be aware of their perceptions, especially for minority patients.

Published guidelines on chemoprevention for breast cancer have been updated to raise awareness and encourage discussion between both the patients and their physicians. However, even with increasing the awareness and established benefits of preventive therapy, the use of chemo preventions is still low, with physician and patient barriers identified. It is prudent that these barriers be overcome to enable high-risk women with a favorable risk-to-benefit ratio to be offered chemoprevention to reduce their likelihood of developing hormone receptor-positive breast cancer.

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