Chemoprevention of breast cancer: current status and future prospects

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TABLE OF CONTENTS

1. ABSTRACT

Chemoprevention plays an important role in the prevention of cancer. Due to being an estrogen-dependent cancer, breast carcinomas are ideal candidate for chemoprevention. The two main approaches to chemoprevention of breast cancer are to attain a balance in estrogen or to eliminate all estrogens by selective estrogen receptor modulators (SERMs) and aromatase inhibitors (AIs). A series of clinical trials have proven tamoxifene quite useful as a preventive strategy for women at high risk of breast cancer. The third-generation, AIs, hold a great promise in chemoprevention of breast cancer. In this review, the mechanisms, side effects and main clinical trials of SERMs and AIs are discussed. The use of other drugs including $CoQ_{10,}$ retinoids, cyclooxygenase (COX)-2 inhibitors, vitamin E, soy isoflavones, tea polyphenols and statins in chemoprevention is introduced. Since most studies on these drugs were conducted on animal models or cell culture, further studies are needed to determine the efficacy of these drugs in chemoprevention of human cancers.

2. INTRODUCTION

To some extent, prevention of disease is more important than any kind of treatment, for it results in the most benefit with least cost. When it comes to cancer, prevention becomes even more important because it is hard to control the progression of cancer. The best way to solve this problem is to arrest or prevent carcinogenesis. In the United States, breast cancer threatens women's health with the highest incidence and the second highest mortality rate of all cancers (1).This situation calls for an effective way to reduce both the incidence and the mortality rates of the disease.

The term, "chemoprevention" was first introduced by Michael Sporn in 1976(2, 3) to describe the application of drugs to slow or reverse the process of carcinogenesis. However, physicians began to do research on chemoprevention of breast cancer about 100 years ago. Since George Beatson discovered the link between the ovarian activity and growth of the breast cancer in 1896(4), a series of discoveries have been made suggesting that the

occurrence of breast cancer is correlated with estrogens, chemicals produced by the ovaries. In 1936, Antoine Lacassagne suggested that a therapeutic antagonist to estrogen should be developed to block estrogen-induced breast cancer (5). In 1962, Jensen and Jacobsen synthesized radioactive estradiol (6) and proposed the presence of the estrogen receptor (ER) as the link between circulating estrogens and their effects in target tissues, which was identified later (7). The presence of ER was subsequently proven to predict the likelihood that of breast cancer will respond to hormonal manipulation (8). This revealed that breast cancer has an advantage over other solid tumors in that the strategy of chemoprevention is practical. After a number of experiments done in the laboratory, the strategy that estrogen antagonists could be used in chemoprevention for breast cancer in animals was conceived and proven effective, which led to clinical testing.

Tamoxifene, a SERM, was the first drug used in chemoprevention for breast cancer after several random clinical trials. In 1998, results of the National Surgical Adjuvant Breast and Bowel Project (NSABP) P-1 Breast Cancer Prevention Trial (BCPT) showed Tamoxifene achieved a statistically significant 49% reduction in the incidence of invasive breast disease in women at increased breast cancer risk (9). Based on the results of clinical trials, the Food and Drug Administration (FDA) approved tamoxifene for risk reduction in women at high risk of breast cancer in October 1998, marking the historic first FDA approval of any agent for primary cancer prevention. Since then new agents have been emerging, such as AIs, retinoids and so on. In this paper, we mainly emphasize on the recent results of clinical trials about SERMs and AIs as well as the development of new agents.

3. SEARCH STRATEGY AND SELECTION CRITERIA

Data for this review were identified by searches of PubMed, the Internet, and references from relevant articles. Abstracts were included only when the relevant information had not been published in full elsewhere. Only papers published in English were included.

4. DRUGS USED FOR CHEMOPREVENTION OF BREAST CANCER

4.1. SERMs
4.1.1.Mechanism

Selective estrogen receptor modulators, or SERMs, including tamoxifene, reloxifene, toremifene, droloxifene and other related non-steroidal agents, can have ER-agonistic, partial-agonistic, or -antagonistic effect, depending on the species, tissue and specific ER-regulated gene (10). SERMs competitively inhibit the binding of estrogen to ERs through a ligand-receptor protein complex which can interact with an estrogen-response element directly on DNA, or they form a transcription complex through a protein-protein interaction in the promoter region of target genes (11, 12). In this way SERMs can modulate estrogen-regulated genes that influence the growth and apoptosis of breast cells (11). The tissue-selective effects of

the various SERMs depend on the conformation of the ligand-receptor complex and the interaction with other transcription factors through activating functions on the ER complex (13).

Tamoxifene, the trans-isomer of a triphenylethylene derivative, was first used in breast cancer treatment. Animal studies with it showed that tamoxifene prevented breast carcinogenesis (14-16) in rats, and inhibited spontaneous breast carcinogenesis in high-incidence strains of mice (17). These studies resulted in use of tamoxifene in chemoprevention. Another well-studied SERM is raloxifene. Both tamoxifene and raloxifene are reinventions of old medicines. Generally speaking, SERMs' approach to chemoprevention of breast cancer is to strike a balance for the patient.

4.1.2. Clinical Trials

Several clinical trials of SERMs have been conducted. The purpose of BCPT conducted by the NSABP, and one of the most influential trials, was to test tamoxifene versus placebo in women at high risk for breast cancer. The result of BCPT is encouraging: a 49% reduction in the incidence of invasive breast cancer among subjects receiving tamoxifenee, compared with subjects receiving placebo (89 vs 175, $p < 0.00001$), and a 50% reduction in noninvasive breast cancer incidence (69 and 5 cases occurring in the placebo and tamoxifene groups, respectively $p < 0.002$) (18). These results prompted the FDA to recommend tamoxifenee as a chemoprevention drug. The overall protective effect of tamoxifene was due to the reduction in ER-positive tumors. However, side effects with tamoxifene were also found, including endometrial cancer, stroke, transient ischemic attack, pulmonary embolism, deep vein thrombosis and cataracts. Two smaller European (British and Italian) breast cancer prevention trials using tamoxifene did not detect a statistically significant difference between tamoxifene and placebo (19, 20). Considering the much smaller sample sizes of these two trials, the results should be evaluated cautiously. Women with ductal carcinoma *in situ* (DCIS) who were also at high risk for ipsilateral and contralateral breast cancer (21, 22) were not included in the above trials. So the NSABP conducted another trial B-24 to test tamoxifene as adjuvant therapy after resection/lumpectomy and radiation in patients with DCIS (23). In this trial, tamoxifene reduced the incidence of all breast cancers, especially invasive ipsilateral cancers. However, the recently completed trial by the UK Coordinating Committee on Cancer Research (UKCCCR) Ductal Carcinoma *In situ* Working Party put forward some diverse opinions. In the UKCCCR, tamoxifene was not found to reduce the incidence of ipsilateral invasive disease in patients with completely excised DCIS but did reduce the recurrence of overall DCIS compared with radiotherapy (24).

Raloxifene, another SERM, may also be useful for the prevention of breast cancer. The NSABP is presently conducting a cancer prevention trial: the study of tamoxifene and raloxifene (STAR, or P-2). Mutilple Outcomes of Raloxifene Evaluation (MORE) that used

raloxifene for breast cancer risk reduction, provided the main rationale supporting raloxifene in STAR (25). There was a 76% reduction of invasive tumors (90% in ER-positive tumors) in MORE versus the 49% reduction when tamoxifene was used (69% in ER-positive tumors). Moreover, using raloxifene could decrease the incidence of endometrial cancer as well as bone fractures in women with osteoporosis. It is suggested that maybe raloxifene is the better drug for chemoprevention of breast cancer. But to confirm this, further information should be collected in the continuing STAR. According to the research data available now, tamoxifene is still the gold standard drug for chemoprevention of breast cancer.

4.2. Aromatase Inhibitors
4.2.1. Mechanism & effects

AIs are mainly used in the treatment of breast cancer, especially for women whose ovarian function has ceased. AIs inhibit aromatase, a cytochrome P450 enzyme that catalyses the conversion of androgens to estrogens in body fat, liver, breast and muscle cells (26,27), and in the breast tumor tissue (28,29) the last step of the estrogen biosynthetic pathway - by stopping the synthesis of estrogen. In this way AIs can reduce synthesis and output of estrogen in postmenopausal women.

The first two generations of AIs are not for clinical use because of serious side effects, such as rash, drowsiness and minera/ocorticoid suppression (30, 31). The third generation nonsteroidal AIs were recently approved by the FDA for use as first-line agents against estrogen-responsive cancer (32), including anastrozole, letrozole, and exemestane (33). Anastrozole has improven the efficacy and tolerability in the treatment of breast cancer as well as lowering the incidence of contralateral breast cancer compared with tamoxifene (34, 35), suggesting its potential role in chemoprevention. This prompted the International Breast Cancer Intervention Study (IBIS) to start a double-blind, randomized, controlled trial (IBIS-II) to test whether anastrozole would prevent more new breast cancers in women at high risk of breast cancer compared with tamoxifene. The new report of the ATAC (Arimidex, Tamoxifene, Alone or in Combination) trial showed that anastrozole-treated women have better disease-free survival, greater time to recurrence and fewer side effects compared with tamoxifene. It was estimated that anastrozole treatment might prevent 70%-80% of ER-positive tumors in women at high risk of breast cancer (36). The main side effects are metabolic disorders of bones and lipids. As the latest third-generation AI approved by FDA, exemestane is an irreversible AI, producing 98% aromatase suppression (37). Exemestane also showed potential application in chemoprovention with the advantage of having less effect on bone metabolism (38). This leads to the National Cancer Institute of Canada's Clinical Trials Group MAP.3 trial, which evaluates exemestane with or without celecoxib as a preventive therapy (39).

4.2.2. Comparison between SERMs and Ais

It is a controversial decision whether to eliminate all estrogen or to strike a balance for patients, which means making a choice between AIs and SERMs. According to

the research, AIs show advantage in providing more optimal prevention of ER positive breast cancer and less risk of endometrial cancer and blood clots compared with tamoxifene (38, 40, 41). However, the application of AIs in healthy women will affect other estrogen-dependent systems. Thus AIs may accelerate osteoporosis and dementia. SERMs have been involved in a number of clinical trials and tamoxifene, the most investigated chemopreventive drug is still the gold standard in chemoprevention. More large scale clinical trials need to be done in order to erase any doubts about the benefits of AIs. But there is a trend that more physicians prefer AIs based on the favorable outcomes of ongoing clinical trials. Both SERMs and AIs focus on postmenopausal women, while most of the breast cancer that occurs in the 50- to 65- year age group has its genesis in the premenopausal years. That means in the future we need to advance chemoprevention beyond the manipulation of hormones.We need to find ways to prevent carcinogenesis by treating women of reproductive ages.

4.3. Other drugs
4.3.1. Coenzyme Q_{10}

There are several other approaches to prevent breast carcinogenesis. One of these is to use other drugs combined with tamoxifene to improve its efficacy and minimize side effects. It has been proven that adding coenzyme Q_{10} (CoQ_{10}) can achieve this aim in animal experiments (42). Many cancers are accompanied by poor antioxidant defenses. CoQ_{10} is the first antioxidant to disappear from membranes under oxidant stress, and to promote the regeneration of vitamins E and C. Supplementation with CoQ_{10} protects tissue from lipid peroxidation (43, 44), which is related to cell proliferation (45). Higher rates of lipid peroxidation in the cells may cause lower rates of cell division. Researchers observed that tumor cells were more resistant to lipid peroxidation than normal cells (46). Some studies also suggested that CoQ_{10} stimulated the immune system and increased resistance to disease (47). Thus, the combination of tamoxifene and CoQ_{10} would counteract the oxidizing injury by reducing cell proliferation to an appreciable extent and minimizing side effects.

4.3.2. Retinoids

Retinoids, the natural and synthetic derivatives of vitamin A, play a crucial role in cellular and tissue differentiation. Retinoids can suppress tumor promotion and activate and/or repress specific genes to modify some properties of transformed malignant cells. As the most widely studied retinoid, the synthetic amide of retinoic acid fenretinide (4-HPR) is selectively accumulated in the human breast (48). It appears attractive to evaluate this agent in the chemoprevention of breast cancer. A multicentric phase III randomized trial, conducted by the Istituto Nazionale dei Tumori in Milan, began in 1987 and completed in 1993, involved stage I breast cancer patients, aged 33-70 years, who had been operated on for breast cancer within the previous 10 years and had received no systemic adjuvant therapy. Fenretinide was tested for its efficacy as a secondary line of prevention of breast cancer. The result showed fenretinide had a beneficial trend in pre-

menopausal women on both contralateral and ipsilateral breast cancer and a reversed trend on contralateral breast cancer in post-menopausal women (49). These findings suggest that fenretinide acts as a preventive agent at early stages of the breast carcinogenic process, but is useless when the cancer has progresses to a more malignant phenotype, probably because of the loss of retinoid receptor expression (50). The main side effect is nyctalopia. Further studies are needed to confirm above results.

A clinical trial using the combination of fenretinide and tamoxifene had been coordinated by the European Institute of Oncology. Pre-menopausal women with a history of intraepithelial neoplasia or minimally invasive breast cancer or healthy subjects at risk were eligible. This trial was finished in Nov. 2003 with high compliance and a few serious adverse events. The results show the combination of agents is more effective for ER positive cancer (49).

4.3.3. COX-2 Inhibitors

Cyclooxygenase (COX)-1 and COX-2 are inducible enzymes synthesizing prostaglandin. It was found that there was generally no COX-2 expressed in normal breast tissues. The expression of COX-2 was limited and weak in benign breast disease while diffused and strong in breast cancer (50, 51). The increasing activity of COX-2 might result in the progression of breast cancer in the following ways: producing estrogen through aromatase activity, proliferation, protease activity, angiogenesis and resistance to apoptosis (52, 53, 54). It has been proven that chronic use of non-steroidal anti-inflammatory drugs (NSAIDS), which block both COX-1 and COX-2 can reduce the incidence of ER positive breast cancer because of their ability to inhibit the activity of aromatase (55, 56). The side effects of NSAIDS are too many to be neglected, such as gastrointestinal (GI) ulcer, GI bleeding, perforation and obstruction. A more selective drug with fewer side effects is called for.

Experiments done on the pre-clinical stage showed that celecoxib, a COX-2 seclective inhibitor-reduced the incidence of carcinogen-induced ER-positive breast cancer in rats, and ER-negative in HER-2 over-expressing mice with fewer complications compared with NSAIDs (57,58). Several clinical trials using celecoxib as chemoprevention a drug for breast cancer are underway. As rofecoxib, another COX-2 selective inhibitor was withdrawn the market for contributing to increases in cardiovascular disease, the safety of COX-2 selective inhibitors is under discussion (59). The 8 main trials using celecoxib have shown no significant inclination to induce cardiovascular disease up to this point (60, 61).

4.3.4. Vitamin E

Vitamin E is a fat-soluble vitamin that can protect against the adverse effects of free radicals (62). It is postulated that vitamin E inhibits cancer formation through the following mechanisms: quenching of free radicals; direct effects on tumor cells, such as inducing differentiation, inhibiting cell cycle or inducing apoptosis; or increasing the efficacy of the immune system (63).

Research has suggested that vitamin E from dietary sources might provide women with modest protection from breast cancer; however, studies showed that vitamin E supplements provided no protection against breast cancer (64). The protective effects provided by Vitamin E in the diet look promising, but these studies failed to clarify the form of vitamin E used. In fact vitamin E is a general term referring to a group of eight different natural compounds and synthetic vitamin E, including RRR-alpha-, RRR-beta-, RRR-gamma-, and RRR-delta-tocopherols, alpha-, delta-, and gamma-tocotrienols, RRR-alpha-tocopheryl acetate, and RRR-alpha-tocopheryl succinate (65). A comparison of the apoptosis-inducing properties of various vitamin E compounds revealed that alpha-, delta-, and gamma-tocotrienols and the succinate derivative of RRR-alpha-tocopherol were the most potent inducers of apoptosis of human breast cancer cells in culture (66). Among these forms, RRR-alpha-tocopherul succinate shows the best antitumor effects *in vitro* (63, 66) and had chemotherapeutic efficacy in several animal models of cancers including breast cancer (67-69). We know the exact type of Vitamin E that has been shown to have a protective effect at the experimental stage, and this type of Vitamin E is commercially available, so this holds promise for future clinical trials. More specific studies are needed to confirm the efficacy of vitamin E on chemoprevention of breast cancer.

4.3.5. Soy Isoflavones

Soy is rich in isoflavones, which have been suggested to lower the risk for certain diseases: breast and prostate cancers, osteoporosis and coronary heart disease (70,71). Isoflavones contain a phenyl side-chain, with a variable number of hydroxyl or other groups. This structure is similar to estradiol as well as other steroid hormones and steroid hormone antagonists (72). It has been proven that *in vivo* isoflavones could lengthen the follicular phase of the menstrual cycle (73), reduce urinary excretion of 17beta-estradiol, and favor 2-hydroxyestrone formation (74), all of which were associated with a reduced risk for breast cancer. Therefore, isoflavones have been called "natural SERMs". The exact mechanism is still unknown. Other studies *in vitro* found isoflavones act as antioxidants (75), arrest the cell cycle and inhibit topoisomorase II (76), and exert antiproliferative activities (77,78). Isoflavones include daidzein (4', 7-dihydroxyisoflavone), genistein (4', 5, 7-trihydroxyisoflavone) and glycitein (4', 7-dihydrooxy-6-methoxyisoflavone) (79). Most research is concentrated on daidzein and genistein. The experiments done by Hiroyuki confirmed that genistein produced dose- and time-dependent *in vitro* growth inhibition in breast cancer cell lines (DD-762, Sm-MT, MCF-7, MDA-MB-231) and one breast epithelial cell line (HBL-100) (80). Since evident from clinical trials remains absent, the effect of soy isoflavones on prevention of breast cancer needs evaluated in the future.

4.3.6. Tea polyphenols

Tea has been used as a daily beverage and crude medicine in China for thousands of years. There are three classes of teas: green, black and oolong depending on the degree of fermentation involved. Green tea is thought to

exert an inhibitory effect against carcinogenesis and tumor growth because of its effective components, polyphenols (81). A study also suggested that green tea polyphenols inhibited HER2/*neu* signaling, proliferation, and the transformed phenotype of breast cancer cells (82). Other studies showed that black tea had the same effect as green tea in cancer chemoprevention (83,84). In addition, black tea polyphenols have been proven to act as a HER2/*neu* tyrosine kinase inhibitor, and attenuate tamoxifene-resistant breast tumors in estrogen-independent breast cancer cells (85). More research is needed to support tea polyphenols as a chemopreventive agent of breast cancer.

4.3.7. Statins

As a cholesterol-lowering drug, statins are capable of reducing mortality from cardiovascular disease, which is the number one cause of death in the major cancer chemoprevention trials, and the number one cause of death of women following a diagnosis of breast cancer (86). Recently, the potential relationship between certain cancers and dyslidemia has come under investigation. Statins are being considered for use in chemoprevention trials.

5. DISCUSSION

As an estrogen-dependent cancer, breast cancer has an advantage in the prevention stage. The results of the clinical trials referred to here, particularly that of the NSAPB P-1 trial, strongly support the principle of chemoprevention. After decades of clinical trials, tamoxifene is recognized as the gold standard in chemoprevention of breast cancer. These positive outcomes have brought chemoprevention to the forefront of efforts to control breast cancer. However, the substantial risks of chemoprevention cannot be ignored. The development of new SERMs is required. We need a novel SERM with greater effectiveness as well as fewer side effects, which can compete with the third generation of AIs. Can AIs take the place of SERMs? Though there is a trend that AIs are the better choice, SERMs and AIs are two divergent approaches. We can hardly say which has more advantages, for AIs' approach of "no estrogen at all" also brings many problems. SERMs used now were originally developed for the regulation of the sexual cycle, or are newer versions of drugs which failed in earlier attempts to treat breast cancer. For these reasons, a new SERM is needed. Key issue in the development of SERMs is to develop mechanisms to increase the target-site specificity of the compounds. We need to distinguish signal transduction through ER-alpha and ER-beta respectively and this requires a comprehensive model of pharmacological consequences. More specifically targeted SERMs will be more beneficial and will have fewer potential risks for perimenopausal women.

There are several other drugs used in this field, including CoQ_{10}, retinoids, COX-2 inhibitors, vitamin E, soy isoflavones, tea polyphenols and statins. Some of these drugs can be combined with SERMs because they use different mechanisms. Whether the combination improves the preventive effect still needs evaluation. There is something we should pay attention to. The two main drugs used in chemoprevention focus on post-menopausal women. But trials with retinoids suggested that they may be more effective in treating pre-menopausal women. Moreover tea polyphenols show promise in preventing estrogen-independent breast cancers. Further studies of these drugs may fill the gap that remains in SERMs and AIs.

To prevent breast cancer, there are other options we can take into consideration, including a diet low in both carbohydrate and fat, and physical exercise. However, it is difficult to confirm their exact effect on prevention through scientific study. Moreover, preventative ovarianectomy or mastectomy, and recent gene therapy are also choices for preventing breast cancer. The problem we face today is in choosing the therapy most appropriate for the patients. The main risk factors of breast cancer are family history/genetic, reproductive/ hormonal, proliferative benign breast pathology and mamographic density. A complicated and practical model of risk assessment is required to make the right decision for patients. Preventative therapies may be combined to gain the most efficacy.

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Abbreviation: SERMs: selective estrogen receptor modulators; AIs: aromatase inhibitors; ER: estrogen receptor; NSABP: National Surgical Adjuvant Breast and Bowel Project; BCPT: Breast Cancer Prevention Trial; FDA: Food and Drug Administration; DCIS: ductal carcinoma *in situ;* UKCCCR: UK Coordinating Committee on Cancer Research; STAR: study of tamoxifene and raloxifene; MORE: Mutilple Outcomes of Raloxifene Evaluation; IBIS: International Breast Cancer Intervention Study; ATAC: Arimidex, Tamoxifene, Alone or in Combination; $CoQ_{10:}$ coenzyme Q_{10} ; COX-2: cyclooxygenase-2; NSAIDS: non-steroidal anti-inflammatory drugs; GI: gastrointestinal

Key Words Breast Cancer, Chemoprevention, SERMs, AIs, Retinoids, COX-2 inhibitors, Isoflavones, Review

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