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The 4Ps of Breast Cancer Chemoprevention: Putting Proven Principles into Practice

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Abstract

The pioneering Royal Marsden Tamoxifen Prevention Trial, recruited 2471 eligible high risk women to be randomized to either placebo or tamoxifen (20mgs daily) for eight years. Breast cancer incidence was evaluated at a median of 18.4 years from the study start. There was a 32% reduction in estrogen/progesterone receptor (ER/PR) positive breast cancers after tamoxifen treatment finished. Translational research, to study “the good, the bad, and the ugly of tamoxifen” in the 1980’s subsequently ensured women’s safety from possible increases in osteoperosis, coronary heart disease, and endometrial cancer. Other tamoxifen chemoprevention trials followed. The result of laboratory research was the unanticipated discovery of raloxifene to prevent osteoporosis and breast cancer at the same time. A new group of medicines, now known as Selective ER Modulators (SERMs), was established. Indeed, the ability to prevent or delay multiple diseases with a single cheap medicine has the potential to alleviate pressure on healthcare systems that are overwhelmed. It is a priority to educate physicians appropriately to apply recommended proven medicines as preventives.

A century of laboratory and clinical research has proven that estrogen is the female hormone responsible for the development and growth of the majority of breast cancers. (1)

The National Institute for Health and Care Excellence (NICE) in the United Kingdom, recommended that two Selective Estrogen Receptor Modulators (SERMs) tamoxifen and raloxifene and an aromatase inhibitor anastrozole will be available to reduce the risk of breast cancers in women at high risk. This would be distributed cheaply within the National Health Service (NHS). Tamoxifen and raloxifene were approved by the Food and Drug Administration (FDA) in the United States of America for the same indication.

In this issue of Cancer Prevention Research, Detre and coworkers (2) provide the first of two final reports of the pioneering Royal Marsden Prevention Trial (RMPT). The first report of the RMPT was a vanguard study of 200 patients (3) that grew to recruit a total of 2,471 high risk women randomized to placebo or tamoxifen (20mg daily) for eight years. The authors (2) note, after a median of 18.4 years of follow-up, a 32% reduction in ER/PR positive primary breast cancers but only after the 8 years of tamoxifen was complete. This is a demonstration of the consistent “carry over protective effect” of long term estrogen

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deprivation (LTED) therapies used to treat or prevent breast cancer (4). Since tamoxifen is not itself a cytotoxic agent, it is proposed that breast tumor cells with acquired resistance to LTED do not grow with estrogen but are killed by a woman's own estrogen that induces apoptosis (5).

The report by the RMPT (2) states that two publications catalyzed their commitment to consider a chemoprevention trial with the breast cancer treatment medicine tamoxifen (6). The RMPT, under the leadership of Professor Trevor Powles CBE, justified their bold strategy because long-term tamoxifen treatment prevented, almost entirely, ER positive rat mammary carcinogenesis (7). A decade later two years of adjuvant tamoxifen, caused an almost complete prevention of contralateral primary breast cancer (8). The acronym for the trial, referred to as NATO, (9) was conceived to entice American academic clinicians to read the clinical trial results, in the Lancet. In reality NATO stood for "Nolvadex Adjuvant Trial Organization!"

However, in the early 1980s the main questions about the safe use of tamoxifen in women without cancer were 1) if estrogen is important to maintain bone density and regulate cholesterol metabolism, will an anti-estrogenic medicine prevent breast cancer during prolonged therapy, but increase the risk of developing osteoporosis and coronary heart disease (CHD) prematurely? 2) are there any surprises yet to be discovered about the toxicology of tamoxifen?

Actually, several unanticipated surprises from the laboratory were in store in the 1980's that were both good and bad. This drove important clinical studies over the next decade from the Wisconsin Comprehensive Cancer Center and the Royal Marsden Hospital.

An unexpected laboratory finding was that estrogen and two previously discarded "antiestrogens" tamoxifen, a failed morning after pill, and raloxifene, a failed breast cancer drug, each built bone in ovariectomised rats (10). This became the scientific rationale for the Wisconsin Tamoxifen study. One hundred and forty post-menopausal node negative breast cancer patients were randomized to receive tamoxifen (20mg daily) or placebo for 2 years. Changes in circulating cholesterol and bone density were monitored over time. The results showed that low density lipoprotein (bad) cholesterol decreased with tamoxifen. By contrast, high density lipoprotein (good) cholesterol was unaffected (11,12). Bone density was improved significantly in the lumbar spine compared to placebo (13). Professor Powles mobilized parallel clinical studies on bones, cardiovascular safety and lipids (14,15) and most importantly gynecologic side effects (16). The way ahead seemed secure; however new information initially slowed the plan to develop tamoxifen as a breast cancer chemopreventive.

In the laboratory, tamoxifen increased the growth of a human endometrial carcinoma, but prevented the growth of a breast cancer both transplanted into the same immune deficient mouse (17). This was despite the fact that there was no suspicious clinical evidence linking tamoxifen with an increased endometrial cancer risk at that time. A rapid public debate on carcinogenesis issues occurred through the good offices of "Letters to the Editor" in the Lancet(18–20). This resulted in the clinical finding that during 5 years of adjuvant tamoxifen

therapy there was an increased incidence of endometrial cancer but a decrease in contralateral breast cancer (21). The selective estrogen action of tamoxifen switching on or switching off estrogen target sites around the body was unique at that time in the late 1980's, but is now a fundamental mechanism in pharmacology of major clinical significance (22). Almost immediately, package inserts were updated to ensure uterine safety with tamoxifen and, for the first time, gynecologists were required to be involved in breast cancer patient care. This discovery and the rapid resolution of safety issues was timely, as recruitment to the major chemoprevention trials was to start in the 1990's.

The laboratory discoveries with raloxifene and tamoxifen demonstrated that both would prevent decreases in bone density in ovariectomized rats (10) and long-term therapy prevented rat mammary carcinogenesis (23). However raloxifene was less effective than tamoxifen.

When the SERM concept was first proposed (24) it was stated:

> We have obtained valuable clinical information about this group of drugs that can be applied to other disease states. Research does not travel in straight lines and observations in one field of science often become major discoveries in another. Important clues have been garnered about the effects of tamoxifen on bone and lipids so it is possible that derivatives could find targeted applications to retard osteoporosis or atherosclerosis. The ubiquitous applications of novel compounds to prevent diseases associated with the progressive changes after menopause may, as a side effect, significantly retard the development of breast cancer. The target population would be women in general, thereby avoiding the requirement to select a high risk group to prevent breast cancer.

Raloxifene was evaluated in a major registration trial called Multiple Outcomes of Raloxifene Evaluation (MORE). This tested the hypothesis (24) that a SERM could be used to treat and prevent osteoporosis, but reduce breast cancer incidence at the same time. This was found to be correct (25). Nevertheless, a subsequent trial Raloxifene Use for The Heart (RUTH) to determine whether women with preexisting CHD could receive benefit from raloxifene proved unsuccessful (26). There was however, the anticipated decrease in the incidence of breast cancer so some of the science was working. Raloxifene was then compared to tamoxifen in the impressive Study of Tamoxifen and Raloxifene (STAR) Trial (27,28). Tamoxifen and raloxifene were equivalent at reducing invasive breast cancer. By contrast, tamoxifen was superior at reducing indolent lesions of epithelial origin (IDLE). Tamoxifen could be taken for 5 years and remains effective at reducing the incidence of invasive breast cancer, even after stopping treatment, with the "carryover effect." Raloxifene is less effective at creating a "carry over effect" and must be taken continuously. This was predicted in the laboratory (17). The safety profile of raloxifene was better for gynecologic issues and thromboembolic events.

It can be argued that raloxifene and anastrozole (in the UK) are available as a chemo-preventive agent in post-menopausal women at high risk, so issues of endometrial cancer and tamoxifen can be ignored. Probably not, as women need choices. It is now wise to

reconsider the small but worrying association between tamoxifen and endometrial cancer, in light of modern understanding.

In the 1980's no gynecologic examinations occurred for breast cancer patient's prior to taking tamoxifen so no preexisting endometrial cancer was discovered. Now we have a better understanding of endometrial cancer events. They are rare. A thousand 60 year old women can expect to have the detection of one endometrial cancer per year. Women taking five years of tamoxifen will have an excess of three to four extra endometrial cancers detected per thousand women. Not a lot, but enough to worry about, if tamoxifen is **causing** endometrial cancer. Carcinogenesis is a process that takes decades. Of the initial 94 cases of endometrial cancer reported in tamoxifen treated patients only 11 received more than 5 years of treatment. (29). There was another reason. A review of 50,000 female autopsies, found an incidence of 30 occult endometrial cancers, of various stages per 10,000 cases examined (30). That is three times the clinical incidence rate. Tamoxifen is stimulating the growth of preexisting disease that is detected by tamoxifen selective screening. Currently, the standard of gynecologic care is very high for the postmenopausal woman chosing to take tamoxifen. It is also important to note that premenopausal women with a high risk for developing breast cancer have no increased risk of endometrial cancer during tamoxifen treatment (31). Raloxifene or aromatase inhibitor cannot be used. A recent study (32) concluded that women, without obvious endometrial pathologies, have no increase in endometrial cancer with tamoxifen. Indeed endometrial cancer was a rare event (32). The endometrial cancer concerns with tamoxifen continue to be over emphasized currently. The non-existent gynecologic oversight in patients in the late 1980's and early 1990's created the problem through the newly arrived internet.

So what of the future, and can we do better with SERMs as a public health initiative? Osteoporosis and CHD remain the major killers of women after they pass through menopause. Women are continuing to increase their longevity and exceed men. Accumulative health concerns for women are a national priority. The principal risk factor for breast cancer is age and it is estimated that the incidence of IDLE and invasive breast cancer will increase by 50% between 2011 and 2050 (33). The question for health care systems globally is "can we address three diseases (CHD, osteoporosis and breast cancer) in one inexpensive medicine?"

Today there is every reason to believe that the original goal (24) of chosing to address the big diseases of osteoporosis and CHD, but preventing breast cancer as a beneficial side effect, is possible. Unfortunately, despite the fact that tamoxifen and raloxifene reduce LDL cholesterol there is no objective benefit documented in randomized prevention trials of CHD.

A clue to the broad public health utilization of SERMs has recently been noted with lasofoxifene evaluated in clinical trials (34). The agent is not FDA approved.

Lasofoxifene is the chemically engineered derivative of a failed post coital contraceptive (1960s), and also a failed breast cancer drug (1970s). The genealogy would not seem promising! Today lasofoxifene it is a miracle of medicinal chemistry having a high affinity

for the ER, like raloxifene, but unlike raloxifene, which is used at a daily dose of 60mg, lasofoxifene is used at a daily dosage of 0.5mg. A clinical trial recruiting 8,556 post-menopausal women was evaluated after five years of lasofoxifene treatment to prevent or treat osteoporotic fractures (34). This was successful, but lasofoxifene reduced the incidence of breast cancer, did not increase the incidence of endometrial cancers, and decreased CHD and strokes. There is an increase in thromboembolic episodes of the same order as raloxifene (27). The secrets of SERMs continue to surprise us. But how, in the 21st Century, do we move from treating disease to preventing diseases with multipurpose pills?

The lessons learned in the 1970s from the successful introduction of new cytotoxic chemotherapy treatment techniques, in the new discipline of medical oncology, is instructive. In 2016, the German Society of Gynecology and Obstetrics announced that Prof. Hans-Joerg Senn, MD, PhD was recognized as one of the medical pioneer, whose vocation in the 20th century created the standard of cancer care for women's health in the 21st century. Professor Senn traveled from his native Switzerland to the United States in the early 1960s to learn the new methods of breast cancer treatment with cytotoxic chemotherapy. He then returned to Switzerland to bring the latest treatments for breast cancer to the Swiss medical profession. His conviction was that improvement in cancer survivorship can only occur if physicians are educated how to apply the latest proven advances in medical science. This philosophy became the genesis of the bi-annual St Gallen Breast Cancer Meeting. This year is the 30th anniversary of an outstanding educational success story that has improved breast cancer care globally.

I proposed that now is the time to embark upon a focused, but required effort, to educate physicians about the public health potential of medicines proven to prevent multiple diseases. This is, at present, breast cancer and osteoporosis with approved SERMs. For the future, clinical research is showing that the list of diseases that can be prevented will increase. It is the responsibility of professional medical bodies to require the medical education of their members to prevent decease. In particular the Royal Society of Medicine in the United Kingdom and the American College of Physicians in the United States are ideally placed to take the lead. Our knowledge base is established, and medicines are approved and available. There is an increasing need to alleviate the crippling cost of fatal chronic illness. Healthcare systems are overwhelmed. This new strategy would require only a small investment in educational budgets for optimal gain by women. Professor Senn proved that education provides power for the physician to extend lives following a diagnosis of breast cancer. Now is the time to put proven principals into practice to prevent not only breast cancer but also other fatal diseases.

Note added in Proof

The hypothesis that by focusing on GP education in prevention this will reduce the burden of cancer care on healthcare, was confirmed with the simultaneous publication by Smith and coworkers [35]. These investigators surveyed 1000 GPs and noted the shocking results that 50% did not know that tamoxifen was proven to reduce the risk of breast cancer in high risk women. Additionally, only 25% were aware that NICE had recommended the use of tamoxifen to reduce breast cancer incidence in high risk populations. Fewer breast cancers,

fewer patients being treated for breast cancer, less stress on the family unit, reduced burden on health care and social services nationwide. The words of the motto for the RSM ring true *"Non est vivere sed valere vita est"* ("Life is not being alive but being well").

Acknowledgments

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