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Current Perspective

Optimising endocrine approaches for the chemoprevention of breast cancer
Beyond the Study of Tamoxifen and Raloxifene (STAR) Trial ☆

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ABSTRACT

The completion of the Study of Tamoxifen and Raloxifene (STAR) [Vogel VG, Costantino JP, Wickerham DL, et al. The Study of Tamoxifen and Raloxifene (STAR): Report of the National Surgical Adjuvant Breast and Bowel Project P-2 Trial. JAMA 2006;295:2727-2741.] and the ongoing studies with aromatase inhibitors [Goss PE. Breast cancer prevention–clinical trials strategies involving aromatase inhibitors. J Steroid Biochem Mol Biol 2003;**86**(3-5):487-93.] to assess their worth for the chemoprevention of breast cancer, creates an opportunity to consider the realistic future for chemoprevention as an option for women's healthcare and to identify strategies for future progress in an era of targeted therapeutics, managed healthcare and soaring costs.

What did the STAR Trial achieve?

Nineteen thousand seven hundred and forty seven postmenopausal women (mean age 58.8 years) with an increased 5 year Gail risk (mean 4.03) were randomised to receive either tamoxifen 20 mg or raloxifene 60 mg for 5 years. A final analysis was initiated after at least 327 invasive breast cancers were diagnosed. There were 163 and 168 invasive breast cancers observed in women assigned to tamoxifen and raloxifene respectively. Thus, the conclusion of the study was that raloxifene was equivalent to tamoxifen at reducing the risks of breast cancer in postmenopausal women at high risk. However, the side effect profile favoured raloxifene. There were 36 and 23 cases of uterine cancer with tamoxifen and raloxifene respectively, fewer hysterectomies with raloxifene, and fewer thromboembolic events occurred with raloxifene when compared with tamoxifen. Similarly, there were fewer cataracts and cataract surgeries noted in women taking raloxifene but there was the same number of osteoporotic fractures in both groups. Thus, raloxifene, a drug that has been extensively investigated and used for the treatment and prevention of osteoporosis for the past 7 years, has now been shown to be a useful agent with reduced side effects to prevent breast cancer in high risk postmenopausal women.

To achieve the goal of practical progress in the chemoprevention of breast cancer which can truly enhance public health, three interdependent issues must be addressed satisfactorily: whom to treat, what agent to use and is the process affordable?

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Whom to treat?

The Gail model[3] has been used satisfactorily to select pre and postmenopausal women for inclusion in the NSABP P-1 Trial which compared tamoxifen versus placebo[4] and subsequently used to recruit high risk women into the STAR P-2 Trial.[1] However, it is interesting to note that in the Nurses Health Study[5] where 81,209 women have now been followed for several decades, that of the 1354 breast cancers that have been recorded, 44% of these tumours occur in women with the Gail risk of $\geqslant$1.67 a cut off for high risk but 54% of the cancers occur in women who would not be considered to have a risk for breast cancer. Clearly strategies need to be developed that are cost effective both for high risk and normal risk women.

To this end, in this era of targeted therapies for the treatment of cancer, it seems only reasonable to target specific populations with chemoprevention of breast cancer so we can enhance the value to public health. By simple analogy, it would be considered of no value to treat breast cancer patients with antihormone therapy if their tumour did not have the oestrogen receptor. Patients would then be treated when there was no possibility of any benefit. The BRCA1 and 2 genes are used as markers for familial breast cancer but unfortunately there are no equivalent markers to pre-select for spontaneous breast cancer. Therefore, either the high risk group should be considered for chemoprevention specifically or for breast chemoprevention where the strategy embraces the idea of additional benefits for public health.

Let us place this concept into perspective by examining the best agent that could be used as a chemopreventive. The link between oestrogen and breast cancer has been known for more than a century therefore creating 'a no oestrogen at all' state in postmenopausal women by using an aromatase inhibitor seems an entirely logical approach to provide the best results to prevent breast cancer. The idea is not new as Lacassagne proposed this general prevention strategy in 1936.[6] The evidence for choosing aromatase inhibitors as the agent of choice is readily available from the clinical trials literature that has used either tamoxifen or an aromatase inhibitor as adjuvant therapies for the treatment of oestrogen receptor positive breast cancer. In all cases, tamoxifen has performed well, producing an estimated 50% decrease in contralateral breast cancer,[7] (the same decrease noted in the P-1 trial.[4]) Nevertheless, aromatase inhibitors all produce greater decreases in contralateral breast cancer[8–11] and it can be stated that these agents are undoubtedly superior to tamoxifen.

Can the concept of using the best agent available to prevent breast cancer be put into practice? If Gail high risk postmenopausal women are selected for treatment under circumstances similar to the STAR trial,[1] it would be anticipated that with no treatment, 8 per 1000 women per year would develop breast cancer and the aromatase inhibitors would perform optimally preventing three out of four of the breast cancers. Unfortunately, looking at this projection another way, it means that to prevent six breast cancers in 1000 women, 992 additional women must be treated for the year. With apologies to Winston Churchill, 'Never in the field of cancer therapeutics has so much been given to so many to benefit so few'.

An alternative approach is to use a selective oestrogen receptor modulator and use it selectively in appropriate patient populations to provide the best results for the right women.

What to use?

Selective oestrogen receptor modulation was first recognised in the late 1980s[12] when it was realised that the then named nonsteroidal antioestrogens, tamoxifen and raloxifene (then known as keoxifene) would not only prevent mammary cancer in rats but would also maintain bone density.[13,14] The class of drugs were antioestrogenic at some sites (breast, uterus) but oestrogenic at other sites (bone, circulating cholesterol). These laboratory findings subsequently translated to the clinic.[15,16] However, it was immediately clear that the idea of selective oestrogen receptor modulation could be applied to advance the chemoprevention of breast cancer.[17] The initial strategy [17] was subsequently refined, and defined as follows 'important clues have been garnered about the effects of tamoxifen on bone lipids so it is possible that derivatives could find targeted applications to retard osteoporosis and atherosclerosis. The ubiquitous application of novel compounds to prevent disease associated with the progressive changes after menopause, may, as a side effect, significantly prevent breast cancer'.[18]

It is now possible to test this evidenced based[17,18] hypothesis by examining clinical studies of raloxifene used to treat osteoporosis while monitoring the impact of breast cancer incidence at the same time. The first proof of principle was noted by Cummings and coworkers[19] but the initial 4 year osteoporosis study with raloxifene has now been extended out to 8 years in the Continuing Outcomes Relative to Evista (CORE). Martino and coworkers[20] found that in the placebo arm (2576 osteoporotic women) that there were 4.2 cases of breast cancer per 1000 women per year. In contrast, in the women treated with raloxifene (5129 osteoporotic women), there were only 1.4 cases of breast cancer per 1000 women per year. It is now possible, using these figures, to evaluate the progress made in chemoprevention over the last 20 years by calculating the approximate incidence of breast cancer in women being treated for osteoporosis (Fig. 1). It is estimated that 500,000 women are taking raloxifene worldwide[1] so this is a reasonable starting point to discover the potential impact on public health. If half a million women were using bisphosphonates to treat osteoporosis over a 10 year period then 21,000 women would develop breast cancer. If these same women had been appropriately treated for osteoporosis during the 1990s, using hormone replacement therapy (HRT), there would be a significant increase in the incidence of breast cancer based upon the Women's Health Initiative[21] and the Million Women's Study.[22] On average 500,000 women would develop 34,230 breast cancers over a 10 year period. In contrast, if those same women now take raloxifene for 10 years, there would only be 7000 women who will develop breast cancer; a net decrease of 27,320 breast cancers from those women that would have been taking HRT during the 1990s.

There is between a 75% and 65% decrease in breast cancer in women when raloxifene is used for the prevention of osteoporosis[19,20] However, by reference to the STAR trial[1] there appears to be only a 50% decrease in the incidence[4] of breast

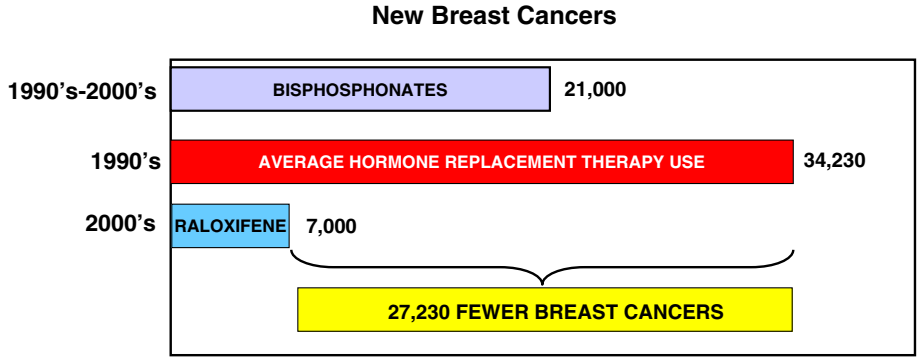

Fig. 1 – An estimation of breast cancer incidence in a population of 500,000 postmenopausal women with the same risk for osteoporotic fractures as participants in the CORE trial[20] treated for a 10 year period with a bisphosphonate, hormone replacement therapy (HRT) based on the average breast cancer risk between the Women's Health Initiative [21] and the Million Women's Study [22] or currently with raloxifene. The overall change in prescribing practices from the former practice of HRTwould be the standard treatment to the current practice of prescribing raloxifene will produce a net decrease of 27,230 breast cancers.

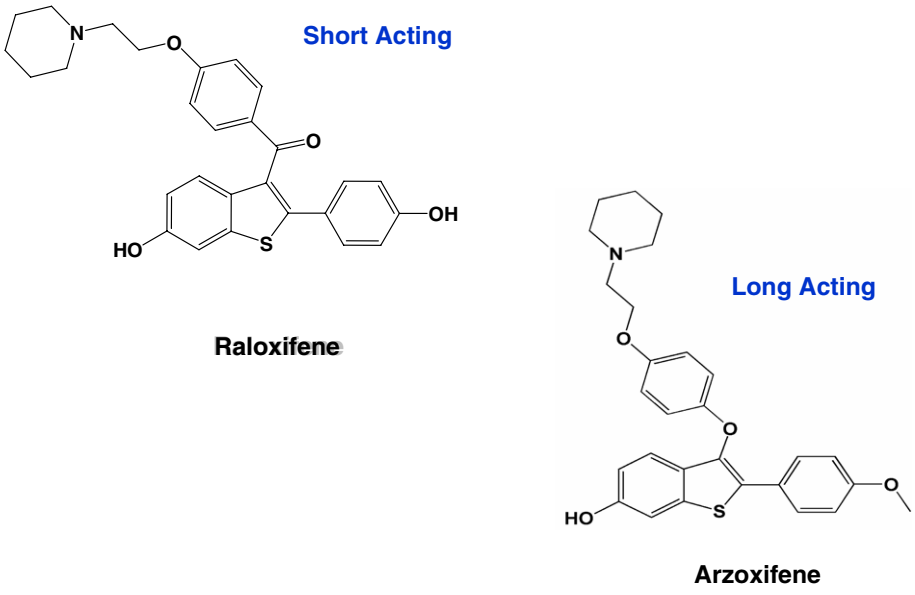

Fig. 2 – The formula of the short acting SERM raloxifene and its long acting derivative arzoxifene.

cancer. This is an assumption because there was no control group in STAR,[1] however, tamoxifen is known to produce a 50% decrease in breast cancer incidence and raloxifene was equivalent to tamoxifen in STAR. What could account for these differences? One possible explanation could be that raloxifene performs very well in the low oestrogen environment noted in osteoporotic women. In contrast, healthy women not suffering from osteoporosis undoubtedly have higher circulating levels of oestrogen. It has been know for about 20 years that drugs of the raloxifene class are very short acting and have very poor bioavailability.[13,23,24] Indeed, raloxifene is only 2% bioavailable in women and is rapidly excreted.[25] Clearly, compliance will be essential to maintain the antitumour actions of raloxifene. If no raloxifene is present, oestrogen will cause breast carcinogenesis. Thus, in the STAR trial, the actions of raloxifene as a chemopreventive could become undermined by poor compliance which would explain the inability of raloxifene to control invasive and noninvasive breast cancer optimally.[1] Clearly, new long acting selective oestrogen receptor modulators (SERMs) need to be developed and tested in the clinic. One such compound arzoxifene is completing clinical studies as a preventive for osteoporosis and has already been shown to be superior to raloxifene in the prevention of rat mammary carcinogenesis (see Fig. 2).[26] Finally, it must be asked how cost effective will chemopreventive interventions be if they are to improve the standards of healthcare.

Affordable?

A strategy to create a public health policy that will reduce the incidence of breast cancer can now be examined based on the application of different agents targeted to specific populations. In the same examination, it is appropriate to consider which agent is targeting which population and then attempt to create an approximate cost to prevent a standard number of breast cancers. There are three appropriate applications

Table 1 – Appropriate populations for SERMs use as chemopreventives for breast cancer

Agent	Targeted group	Alternative?
Tamoxifen	Very high risk[a] premenopausal women[27]	Not aromatase inhibitors
Raloxifene	Osteoporotic women	Not aromatase inhibitors
New long acting SERMs or raloxifene	Very high risk postmenopausal women	Aromatase inhibitors

The only alternative of aromatase inhibitor is also stated.
a Atypical hyperplasia, LCIS 2 > 1st degree relatives or GAIL risk > 5.[29]

Table 2 – The relative monthly costs per person of antihormonal agents potentially useful as chemopreventive agents in select groups of high risk women

Medicine	Monthly cost[a]	5 year course cost[a]	Cost to prevent 300 breast cancers[a]
Anastrozole	68.56	4114	41,140,000
Exemestane	88.80	5328	53,280,000
Letrozole	83.16	4989	49,890,000 + bisphosphonate costs (approx. 3,600,00)
Tamoxifen pre	2.39	143.40	2,145,000 Approx. 750,000 bulk buying
Raloxifene post	19.86	1193.60	17,910,000 Bonus: prevents fractures
Raloxifene osteo	19.86	1193.60	23,880,000 Bonus: prevents fractures

Based on the cost of a 5 year course, the actual cost of preventing 300 breast cancers during that time period is estimated based on incidence of breast cancer. The high risk postmenopausal or premenopausal women is calculated at 8 breast cancers per 1,000 women per year. The risk for osteoporotic women was estimated based on the article by Martino and coworkers.[20]
a NHS cost in GB pounds.

where a SERM can be targeted to reduce the incidence of breast cancer (Table 1). Each of these populations have been evaluated in clinical trial so this fact minimises speculation. Firstly, the best risk benefit ratio for tamoxifen is to target very high risk premenopausal women.[27] Tamoxifen is an effective chemopreventive but endometrial cancer and blood clots are not increased in premenopausal women.[4] In a recent evaluation [28] of potential mortality outcomes, populations of Gail Risk >3 are calculated to the best benefit but only in countries with cheap tamoxifen. It should be noted that tamoxifen is the only agent available for this application as raloxifene and aromatase inhibitors *cannot* be used in premenopausal women. Raloxifene has not been tested in this application and the manufacturer recommends against this application. Aromatase inhibitors are ineffective in premenopausal women with an intact hypothalamo-pituitary-ovarian axis. Secondly, raloxifene when it is used specifically to prevent osteoporosis in postmenopausal women effectively prevents breast cancer as a beneficial side effect.[20] Bisphosphonates do not alter the incidence of breast cancer and aromatase inhibitors are inappropriate for use in this application. Finally, the case for the use of raloxifene in very high risk postmenopausal women is complex. Raloxifene provides a significant benefit[1] but as noted in the previous section, it seems appropriate that new long acting SERMs are developed to provide optimal chemoprevention. Aromatase inhibitors will clearly be beneficial in this category but are they affordable?

Table 2 summarises costs to the National Health Service in GB pounds of the three leading aromatase inhibitors, anastrozole, exemestane and letrozole that are currently being evaluated as chemopreventives for breast cancers.[2] Table 2 illustrates the monthly costs and the cost of an appropriate 5 year course for each individual choosing this strategy for chemoprevention. To standardise a comparison of the cost to the health service in prevention, an approximate calculation has been made to prevent 300 breast cancers for the appropriate risk group i.e. eight breast cancers per 1000 women per year. The costs are very large ranging between 40 and 50 million pounds but there is an additional hidden cost for the supply of bisphosphonates to approximately 1/3 of women who may develop osteopenia and osteoporosis during the 5 year course of an aromatase inhibitor. In contrast, tamoxifen is exceptionally cheap with the cost of preventing 300 breast cancers in high risk premenopausal women of around 2 million pounds. That being said, this cost drops in many Trusts because of the bulk buying of generic drugs. Thus tamoxifen is extremely affordable in this targeted application as has been noted previously.[28,29] The other SERM, raloxifene, when used as a chemopreventive in high risk postmenopausal women is less than half the cost noted for the aromatase inhibitors when preventing the 300 breast cancers. However, the hidden bonus is that a significant number of women will not be developing osteopenia or osteoporosis so there will be fewer fractures in this high risk breast cancer group. Finally, when raloxifene is used to prevent osteoporosis, although the cost to the health service is higher because more women will need to be treated to prevent the same standard 300 breast cancers (i.e. low risk group), the significant bonus to public health will be an approximate 30% decrease in fractures in this patient population.

Conclusions

Clinical trials data are providing strong evidence that SERMs are affordable and cost effective when applied to targeted patient populations of the highest risk for developing breast cancer. Again, it is clear from their clinical applications that SERMs are more versatile than aromatase inhibitors for pre-

venting breast cancer. Despite the fact that raloxifene is now known to be ineffective in reducing the risk of coronary heart disease[30] the SERMs are progressing appropriately in fulfilling their promise to prevent multiple diseases.[17,18] The best evidence for this is the application of SERMs to prevent osteoporosis but at the same time preventing breast and endometrial cancer.[20]

Conflict of interest statement

None declared.

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