Clinical strategies for chemoprevention of breast cancer (Part 2)

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This is the second of a two part article on chemoprevention which will focus on national and international guidelines for chemoprevention of breast cancer and consider optimal approaches to maximise uptake and benefit from potential reductions in breast cancer incidence.

Assessment of breast cancer risk

Chemoprevention should only target women at substantially elevated risk of developing breast cancer. This includes all women aged 35 years or older with a breast cancer risk ≥1.66% in the next five years, based on the Gail Model or those with lobular carcinoma in situ (LCIS) [1]. Several societies and organisations have evaluated the evidence for chemoprevention and endorsed its implementation, including the American Society of Clinical Oncology (ASCO) [2], United States Preventive Services Task Force (USPSTF) [3] and the National Comprehensive Cancer Network [4]. Most consider a Gail Model risk score of at least 1.66% to be an appropriate level of risk for chemoprevention, and the National Cancer Institute has developed a risk assessment tool for identification of women at increased risk [www.cancer.gov/bcrisktool]. Freedman and colleagues employed a retrospective analysis to compile risk tables incorporating not only conventional risk assessment data, but factors such as age, race, ethnicity and uterine status [5]. Based on these amended risk estimations, the USPSTF have recently suggested that the risk:benefit calculation for women aged over 50 years favours a five-year risk of 3%, greater than the present norm of 1.66% [3]. All chemotherapeutic agents have some level of adverse side-effects and the risk:benefit ratio in the chemopreventive setting is more delicate when these agents are administered to otherwise healthy women where there is no measurable biomarker to act as a predictor of efficacy (c.f. statins and LDL levels). Post-menopausal women are more susceptible to side-effects of chemopreventive agents, namely SERMS. Tools for risk assessment in the United Kingdom differ from the United States where the Gail model is popular and based on five key factors – current age, age at first live birth, age at menarche, number of first degree relatives with breast cancer and benign breast biopsies [1]. Other instruments for risk assessment of proven clinical value include Tyrer-Cuzik [6] and the Manchester scoring system [7]. Tyrer-Cuzik is a user-friendly web-based model that includes a more detailed family history, as well as body mass index and LCIS. Genetic testing is now being offered to women with a strong family history of breast cancer when the combined BRCA1/BRCA2 carrier probably is ≥10% rather than the previous threshold of 20%.

Recommendations for chemoprevention based on current guidelines

ASCO published updated guidelines on use of pharmacological interventions for breast cancer reduction in July 2013 [2]. These represented a watershed in chemoprevention as the phrase 'may be offered' was replaced with 'should be discussed as an option', thereby implying some incumbency on the part of clinicians to consider chemoprevention as a management option for higher risk women. Thus tamoxifen (20mg per day orally for five years) should be discussed as an option to reduce the risk of oestrogen receptor-positive invasive breast cancer in premenopausal and postmenopausal women, whereas a similar recommendation applies to raloxifene (60mg per day orally for five years) for postmenopausal women only. Furthermore, these most recent updates acknowledge the aromatase inhibitor, exemestane (25mg per day orally for five years), as an additional option for breast cancer risk reduction in postmenopausal women (ER-positive disease only). These recommendations apply to women aged ≥35 years with an estimated five-year risk of breast cancer of 1.66 based on the aforementioned NCI risk assessment tool, but not to those with a personal history of breast cancer or a known BRCA gene mutation. It should be noted that no trials have specifically examined the effect of chemoprevention in mutation carriers, although trials of high risk groups would inevitably include some mutation carriers who may also be more susceptible to the teratogenic effects of tamoxifen. The USPSTF concur with these key recommendations, but have suggested that a five-year risk for invasive breast cancer of 3% may ensure that women derive greater benefit than harm from pharmacological intervention for risk reduction [3]. Ultimately all women must individually discuss risk and benefits with healthcare professionals prior to making a final decision. Exemestane is an appropriate agent for higher risk women who have a history of deep vein thrombosis, pulmonary embolus, stroke,

Table 1: Recommendations for chemoprevention in higher risk women		
	PRE-MENOPAUSAL WOMEN	POST-MENOPAUSAL WOMEN
USA	TAMOXIFEN * (20mg daily for 5 years)	TAMOXIFEN * (20mg daily for 5 years)
		RALOXIFENE** (60mg daily for 5 years)
		EXEMESTANE (25mg daily for 5 years)
UK	TAMOXIFEN* (20mg daily for 5 years)	TAMOXIFEN * (20mg daily for 5 years)
		RALOXIFENE** (60mg daily for 5 years)
* – no significantly increased risk of endometrial cancer or blood clots ** – no significantly increased risk of endometrial cancer [tamoxifen, raloxifene and exemestane taken as oral preparations]		

transient ischaemic attack or current prolonged immobilisation. Moreover, exemestane might be considered to lower the risk of contralateral disease in women who have undergone unilateral mastectomy for diffuse DCIS. These chemopreventive agents should not be combined with HRT, although this was permitted in the IBIS-1 trial [8].

The National Institute for Health and Care Excellence (NICE) recommends offering tamoxifen and raloxifene (as above) to high risk (>30%) postmenopausal women and considering chemoprevention in moderate risk (>17%; <30%) women with no personal history of breast cancer (Table 1). This excludes those women without a uterus who have a past history of endometrial cancer or an intact uterus and risk of thromboembolic or endometrial cancer. Tamoxifen can also be offered to premenopausal women ≥35 years and the overall reduction in breast cancer incidence is calculated to be 3% (or 408,000 women in the UK population) [8].

Uptake of chemoprevention among at risk women

Thus far, uptake of chemoprevention strategies in the United States (where tamoxifen has been licensed for this use for over a decade) has been low, with a survey conducted in 2010 indicating that <1% of women were using tamoxifen or raloxifene for breast cancer prevention [9]. There is a need for healthcare professionals to promote this method of cancer prevention as the magnitude of risk reduction is substantial for some women who may also be at low risk of adverse side-effects. Tamoxifen is associated particularly with thromboembolism and uterine cancer, but these are not shared by either raloxifene or aromatase inhibitors. Furthermore, side-effects reported in recent trials of aromatase inhibitors in the chemopreventive setting are not severe, with no major adverse events in the MAP3 trial and only minimal impairment of health-related quality of life [11]. Despite this new directive from professional organisations, the United States Food and Drug Administration (FDA) has not approved any aromatase inhibitors for reduction of breast cancer risk. Neither tamoxifen nor raloxifene are licenced as chemopreventive agents in Europe. There is probably a need for better education of patients and healthcare workers about the risk:benefit for chemoprevention, with shared decision-making that incorporates a woman's personal values and preferences.

Combining SERMS and aromatase inhibitors for chemoprevention

Hitherto, trials of aromatase inhibitors as chemopreventive agents have compared one of these agents against a placebo rather than a head-to-head comparison with another chemopreventive agent. NICE have emphasised that there are no randomised controlled trials comparing tamoxifen or raloxifene (SERM) with an aromatase inhibitor. It would seem sensible to undertake a randomised comparison of an aromatase inhibitor (anastrozole, letrozole or exemestane) with either tamoxifen or raloxifene, which could better inform women about the best approach for chemoprevention of breast cancer. Raloxifene has much attenuated ureterotrophic activity and is probably a more appropriate agent for any direct head-to-head comparison with an aromatase inhibitor. Randomised, controlled trials have shown benefit in disease-free survival in postmenopausal women receiving aromatase inhibitors as adjuvant therapy. The oral aromatase inhibitors, anastrozole, letrozole and exemestane, are of comparable anti-tumour efficacy and are potentially interchangeable. Longer term data for side effect profiles and toxicities must be awaited before definitive recommendations on clinical use.

The most appropriate sequencing with or without tamoxifen, long-term toxicity, and any overall survival benefit for adjuvant treatment with aromatase inhibitors have yet to be determined. A recent patient-level meta-analysis examined randomised trials of five years of tamoxifen versus continuous aromatase inhibition, or sequenced with an aromatase inhibitor for a total duration of five years. On average, for postmenopausal breast cancer a switch strategy incorporating an aromatase inhibitor significantly reduced recurrence (RR 0.56 in years two to four; 0.97 after five years) and fewer deaths (RR 0.84) compared with 5 years of tamoxifen monotherapy. There were more fractures (RR 1.40) in patients receiving aromatase inhibitors but fewer cases of endometrial cancer (RR 0.37) [12].

In the chemopreventive setting, there may be advantages of using an early switch policy in terms of maintaining bone health and minimising musculoskeletal symptoms (which can be a nuisance to women who are otherwise fully healthy). Patient-reported outcomes from the STAR trial showed that those treated with raloxifene experienced more musculoskeletal symptoms, weight gain and dyspareunia, whereas patients treated with tamoxifen had more vasomotor symptoms, leg cramps, and bladder control problems and gynaecologic problems [13]. An optimal trial design for chemoprevention of breast cancer might be an aromatase inhibitor after initial therapy with tamoxifen or raloxifene for two to three years, for which there is some biological rationale. Thus hormone-dependent breast cancer cells in vitro develop oestrogen hypersensitivity and upregulation of aromatase when grown in oestrogen poor media, whereas in animal models there is initial regression of tumours in response to tamoxifen, but subsequent stimulation by the agonist component of this SERM. Therefore sequential administration of an aromatase inhibitor would be a logical approach as these agents would both negate the

oestrogen agonist effect of tamoxifen, and reduce local and circulating levels of oestrogen. It remains unclear whether any early switch sequence with a SERM and aromatase inhibitor would be associated with a 'carry-over' effect, as witnessed for tamoxifen (and raloxifene) whereby the benefits continue beyond the treatment period. The duration of follow-up should be a minimum of 10 years in order to identify potential longer term sequelae of interventions with agents that induce hypoestrogenic states which affects bone mineral density, cardiovascular deaths (elevated cholesterol) and neurocognitive function. There is no evidence to date of any reduction in mortality from chemoprevention strategies, and breast cancer specific/overall survival will be important outcomes to measure.

Conclusions

The development of a SERM that combines risk reduction for breast cancer with incidental benefits in other tissues may be a more promising approach to chemoprevention than aromatase inhibitors, which induce a hypoestrogenic state that could be associated with more intense adverse sequelae in the longer term. Newer SERMs have shown promising results with favourable risk:benefit ratios (namely absence of thromboembolic events and uterotrophic effects). A combination using a SERM and aromatase inhibitor sequentially for chemoprevention might be an optimal strategy at the present time and maximise cost-effectiveness with least side-effects. Furthermore, a single pulse of treatment for five years has been advocated for chemoprevention, but this recommendation is based to some extent on concerns about the longer-term stimulatory effects of tamoxifen. Aromatase inhibitors may be potential candidates for longer chemoprevention, notwithstanding issues of safety and quality of life relating to oestrogen deprivation. Further clinical trials are essential to evaluate aromatase inhibitors as chemopreventive agents in high risk postmenopausal women. These agents are associated with a greater reduction of contralateral breast cancer in adjuvant trials than tamoxifen, and are not associated with increased risks of thromboembolism or uterine malignancy. Nonetheless, follow-up is mandatory to determine longer term effects on bone mineral density and musculoskeletal symptoms, as well as cognitive function. Aromatase inhibitors could potentially be combined with a gonadotrophin releasing hormone agonist as a chemopreventive strategy in premenopausal women, but there are concerns about side effects of profound oestrogen deprivation and the optimum duration of therapy is unknown.

It is important to take account not only of the clinical efficacy of individual agents and their potential to reduce both incidence and mortality of breast cancer, but the selection of patients at greatest risk who are least susceptible to the adverse sequelae of pharmacological intervention. New approaches for communication of risk must be developed that are commensurate with race, ethnicity and levels of educational attainment. Ultimately, an ideal chemopreventive strategy will target the most appropriate "at risk" groups with the most effective agents that can be monitored with biomarkers and administered for a finite period of time with minimum side-effects and at low cost (Figure 1).

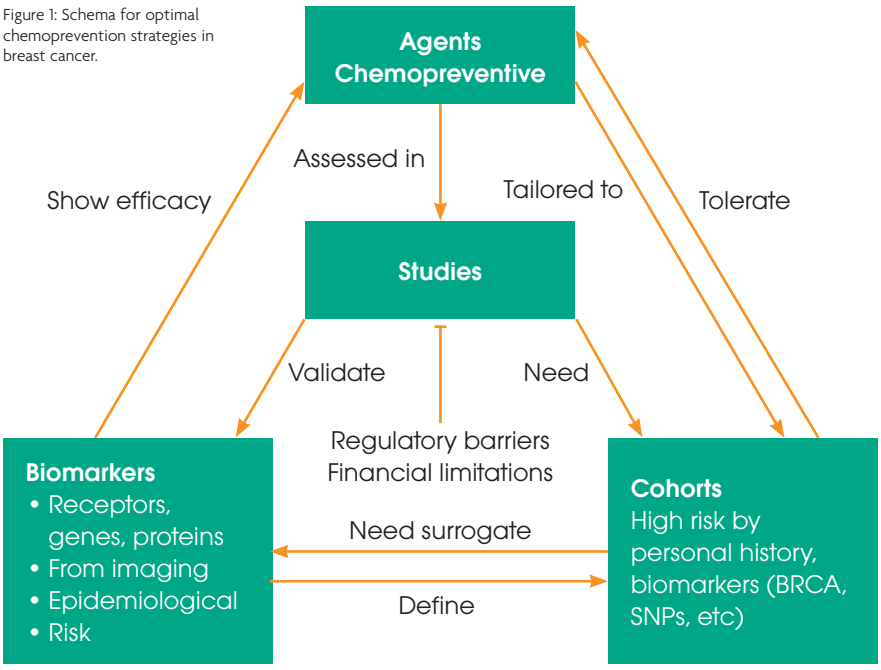

Figure 1: Schema for optimal chemoprevention strategies in breast cancer.

References

1. Gail MH, Brinton LA, Byar DP, et al. *Projecting individualized probabilities of developing breast cancer for white females who are examined annually.* J Natl Cancer Inst 1989; 81:1879–86.
2. Visvanathan K, Hurley P, Bantug E, et al. *Use of pharmacological interventions for breast cancer risk reduction: American Society of Clinical Oncology Clinical Practice Guideline.* J Clin Oncol 2013; DOI: 10.1200/jco.2013.49.3122
3. *Breast Cancer: Medication for Risk Reduction* USPSTF 2013
4. *National Comprehensive Cancer Network Guidelines* http://www.nccn.org/professionals/physician_gls/f_guidelines.asp
5. Freedman AN, Yu B, Gail MH, et al. *Benefit/risk assessment for breast cancer chemoprevention with raloxifene or tamoxifen for women aged 50 years or older.* J Clin Oncol 2011;29:2327–33.
6. Tyrer J, Duffy SW, Cuzik J. *A breast cancer prediction model incorporating familial and personal risk factors.* Stat Med 2004;23:1111–30.
7. Evans DGR, Eccles DM, Rahman N, et al. *A new scoring system for the chances of identifying a BRCA1/2 mutation outperforms existing models including BRCAPRO.* J Med Genet 2004;41:474–80.
8. Cuzik J, Sestak I, Cawthorn S, et al. *Tamoxifen for prevention of breast cancer: extended long term follow of the IBIS-1 breast cancer prevention trial.* Lancet 2015;16:67–75.
9. *National Institute for Health and Care Excellence: Familial Breast Cancer: Classification and Care of People at risk of Familial Breast Cancer and Management of Breast Cancer and Related Risks in People with a Family History of Breast Cancer.* London. National Institute for Health and Care Excellence. 2013. http://publications.nice.org.uk/familial-breast-cancer-cg164
10. American Cancer Society. *Medicines to Reduce Breast Cancer Risk.* Atlanta, GA. American Cancer Society,2013. www.cancer.org/cancer/breastcancer/moreinformation/medicinestoreducebreastcancer/medicines-to-reduce-breast-cancer-risk-toc
11. Goss PE, Ingle JN, Ales-Martinez JE, et al. *Exemestane for breast cancer prevention in post-menopausal women.* N Eng J Med 2011;364:2381–91.
12. Forbes JF, Dowsett M, Bradley R, et al. *Patient-level meta-analysis of randomized trials of aromatase inhibitors (AI) versus tamoxifen (Tam).* J Clin Oncol 2014;32:5s (Suppl; abstr 529).
13. Vogel VG, Costantino JP, Wickerham DL, et al. *Effects of tamoxifen versus raloxifene on the risk of developing invasive breast cancer and other disease outcomes: The NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial.* JAMA 2006;295:2742–51.