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Preventing invasive breast cancer using endocrine therapy

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ABSTRACT

Developments in breast cancer treatment have resulted in reduction in breast cancer mortality in the developed world. However incidence continues to rise and greater use of preventive interventions including the use of therapeutic agents is needed to control this burden. High quality evidence from 9 major trials involving more than 83000 participants shows that selective oestrogen receptor modulators (SERMs) reduce breast cancer incidence by 38%. Combined results from 2 large trials with 8424 participants show that aromatase inhibitors (AIs) reduce breast cancer incidence by 53%. These benefits are restricted to prevention of ER positive breast cancers. Restricting preventive therapy to high-risk women improves the benefit-harm balance and many guidelines now encourage healthcare professionals to discuss preventive therapy in these women. Further research is needed to improve our risk-prediction models for the identification of high risk women for preventive therapy with greater accuracy and to develop surrogate biomarkers of response. Long-term follow-up of the IBIS-I trial has provided valuable insights into the durability of benefits from preventive therapy, and underscores the need for such follow up to fully evaluate other agents. Full utilisation of preventive therapy also requires greater knowledge and awareness among both doctors and patients about benefits, harms and risk factors. Healthcare professionals should routinely discuss preventive therapy with women at high-risk of breast cancer.

1. Introduction

Breast cancer is by far the commonest cancer in women today and is a major cause of cancer death. Its incidence continues to rise with an estimated 1.6 million cases occurring worldwide each year [1]. We have, through significant improvements in cancer treatments over past few decades, have reduced breast cancer mortality in the well-developed regions of the world. In comparison, our cancer prevention efforts have been very modest. With incidence still rising, breast cancer is a prime candidate to focus our prevention efforts on, particularly given the availability of agents with well-proven efficacy backed by a large body of evidence [2–5].

In 1985, Cuzick and Baum first reported a reduction in contralateral breast cancers in women taking tamoxifen [6]. This paved the way for evaluation of tamoxifen as a preventive therapy [7]. The original observation was also confirmed later in the EBCTCG overview of adjuvant tamoxifen trials [8]. A similar observation of a larger reduction in contralateral breast cancers in women receiving anastrozole as compared with tamoxifen in the ATAC trial [9] led to evaluation of aromatase inhibitors (AIs) as preventive therapy [3,5]. Results from 9 large phase III trials (Fig. 1) have demonstrated that preventive therapy with selective oestrogen receptor modulators (SERMs) reduces breast cancer incidence by about 38% [2], whereas 2 large phase III trials have shown that preventive therapy with AIs reduces breast cancer incidence by at least 50% [3,5].

The effectiveness of prophylactic therapy for breast cancer prevention as a public health strategy requires that it is used in a large proportion of women who are at an increased risk of breast cancer. Women with a significant family history of breast cancer, mammographically dense breasts, certain precursor lesions such as atypical ductal hyperplasia (ADH), lobular carcinoma *in situ* (LCIS) or ductal carcinoma *in situ* (DCIS) are obvious candidates. Several risk-prediction models, particularly the Breast Cancer Risk Assessment Tool (also known as the Gail Model) [10] and IBIS Breast Cancer Risk Evaluation Tool (also known as the Tyrer-Cuzick Model) [11], assist stratification of women into different risk categories to facilitate appropriate use of preventive therapy. In this article, we review the current evidence for prevention of invasive breast cancer using endocrine therapy, discuss barriers to a wider use of preventive therapy and identify research priorities to move the

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Abbreviations

AIs	Aromatase Inhibitors
ATAC	Arimidex, Tamoxifen, Alone or in Combination
AH	Atypical Hyperplasia
ADH	Atypical Ductal Hyperplasia
BCRAT	Breast Cancer Risk Assessment Tool
DCIS	Ductal Carcinoma *in situ*
EBCTCG	Early Breast Cancer Trialists' Group
HR	Hazard Ratio
LCIS	Lobular Carcinoma *in situ*
NSABP	National Surgical Adjuvant Breast and Bowel Project
OR	Odds Ratio
SERMs	Selective Oestrogen Receptor Modulators

field forward.

2. SERM trials

Selective oestrogen receptor modulators (SERMs) are a class of drugs that compete with endogenous oestrogen to bind to oestrogen receptor and after binding modulate (either inhibit or potentiate) the ligand-receptor action in a tissue-specific manner [12]. The value of four SERMs for breast cancer prevention has been evaluated in large randomised trials (Fig. 1); these are tamoxifen, raloxifene, lasofoxifene and arzoxifene. SERMs have been evaluated not only in women at an increased risk of breast cancer, but also in those with an average risk of breast cancer. An individual patient data meta-analysis for 83399 women with 306617 years of follow-up from 9 randomised trials showed a 38% reduction (hazard ratio [HR] 0·62, 95% confidence interval [CI] 0·56–0·69) in breast cancer incidence (including DCIS) and the number needed to treat to prevent one invasive ER positive breast cancer in 10 years was 53 [2]. This meta-analysis included data from three trials of tamoxifen in women at an increased risk of breast cancer, viz. the Royal Marsden trial [7,13], the IBIS-I trial [14–16] and the NSABP-P1 trial [17,18] as well as one trial in those at average-risk women, viz. the Italian Tamoxifen Prevention Study [19,20]. Data from the STAR trial [21,22] comparing tamoxifen versus raloxifene in women at an increased risk of breast cancer, as well as data from trials of raloxifene in average-risk women (those conducted in fracture prevention and cardiovascular prevention settings) viz. MORE [23]/CORE [24] and RUTH [25] were included. Data from trials of two other SERMs, viz. the PEARL trial [26,27] evaluating lasofoxifene and the GENERATIONS trial [28,29] evaluating arzoxifene in average-risk women with osteoporosis were also included, thus covering a range of drugs in a broad population mix.

2.1. Royal MARSDEN trial [7,13]

The Royal Marsden trial was the first randomised prevention trial of tamoxifen. Between 1986 and 1996, it recruited 2494 (2471 eligible, 1238 in the tamoxifen arm and 1233 in the placebo arm) healthy women aged 30–70 years, with a family history of breast cancer to take tamoxifen or placebo for 5–8 years. Although after a median follow-up of 13 years and 2 months, the trial did not observe a statistically significant reduction in all invasive breast cancers (82 on tamoxifen and 104 on placebo; HR = 0.78, 95% CI 0.58–1.04; P = 0.1), the number of ER positive invasive breast cancers was significantly lower in the tamoxifen arm (53 versus 86; HR = 0.61, 95% CI 0.43–0.86; 0.005). Importantly, this benefit mainly accrued in the post-treatment period (HR = 0.48, 95% CI 0.29–0.79; P = 0.004).

2.2. IBIS-I [14–16]

The first International Breast Intervention Study (IBIS-I) trial recruited 7154 women at increased risk of breast cancer between April 1992 and March 2001. Women were randomly allocated to 5

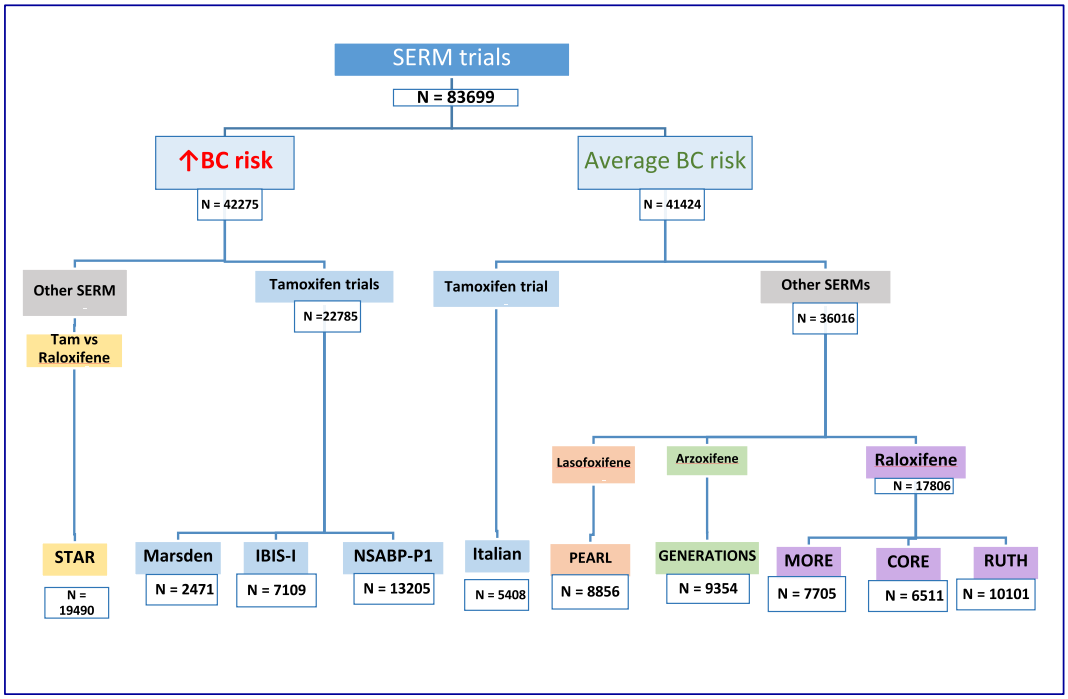

Fig. 1. Overview of trials of Selective Oestrogen Receptor Modulators (SERMs).

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