# Chemoprevention of Breast Cancer

# 32

Jack Cuzick

## 32.1 Chemoprevention of Breast Cancer[1]

Prospects for the prevention of breast cancer have never been greater. We are beginning to find the lifestyle factors that can reduce the risk for women of average risk, and targeted chemoprevention for high-risk women is developing on a number of fronts. Likewise the need for prevention has never been greater. There are 1.2 million new cases of breast cancer worldwide every year, which far exceeds the number of any other cancers, with cervix now being a distant second at about 400,000 [1]. Not only is breast cancer the commonest cancer in women, but it is also rapidly increasing, especially in the developing world.

While population-based programmes, based on reducing obesity and increasing exercise, are likely to be effective for breast cancer [2, 3] just as they have been for heart disease (Fig. 32.1). However, as in cardiovascular disease, targeting individuals at increased risk is likely to be a key part of an effective overall policy. Over the last 50 years cardiac deaths have been reduced by more than 50 % in the US and death from strokes has been reduced by more than two-thirds (Fig. 32.1). Much of this can be attributed to the identification of high-risk individuals by measuring blood pressure and cholesterol levels, and offering them targeted preventive treatment. This is not yet widely done for any cancer, but breast cancer is leading the way, and we now have some important risk factors/biomarkers with a high population attributable risk, which can be used to identify high-risk women. While risk factors only identify individuals most likely to develop a disease, a key requirement for a biomarker is that it responds to treatment in a way that predicts quantitatively the extent of risk reduction for an individual. At present, we have only candidate biomarkers for a few cancers, notably breast cancer and prostate cancer. Mammographic density is the most promising biomarker for breast cancer, and more than 40 studies that date back to the original work by Wolfe [4] have shown an increased risk for women with radiographically dense breasts [5]. Since then other researchers [6] have shown that quantification of the proportional area of the breast that is covered by mammographic dense tissue is the best measure available. We can expect further improvements in measurement of density through the use of computerised assessments, volume measurement, and identification of other radiologic features, such as diffuse disease versus nodular pattern, or structured densities. However, even using current techniques breast density is a common, readily measurable factor that indicates an appreciable increase in risk in both premenopausal and postmenopausal women [7, 8]. Although much remains to be learned about how changes in density affect risk, the fact that breast density is reduced by tamoxifen [9] and increased by hormone-replacement therapy [10] suggests that we might be able to predict the effect on risk from modification of breast density.

## 32.2 Chemoprevention Agents

### 32.2.1 Tamoxifen

Tamoxifen was first shown to prevent new contralateral tumours in women with breast cancer in 1985 [11]. This, plus supporting animal studies [12], led to the proposal to use this drug in primary prevention of high-risk women [13]. Four prevention trials have now been completed (Table 32.1). The combined results of these trials [14] indicated that about half of oestrogen receptor positive tumours can be prevented with 5 years of prophylactic tamoxifen (Fig. 32.2a), but this agent

[1]Chapter reproduced from Cuzick J. Chemoprevention of breast cancer. Breast Cancer. 2008;15(1):10–6 with kind permission of Springer Science + Business Media.

J. Cuzick (✉)
Wolfson Institute of Preventive Medicine, Queen Mary University of London, Centre for Cancer Prevention, Charterhouse Square, London, EC1M 6BQ, UK
e-mail: j.cuzick@qmul.ac.uk



I. Jatoi and A. Rody (eds.), *Management of Breast Diseases*, DOI 10.1007/978-3-319-46356-8_32

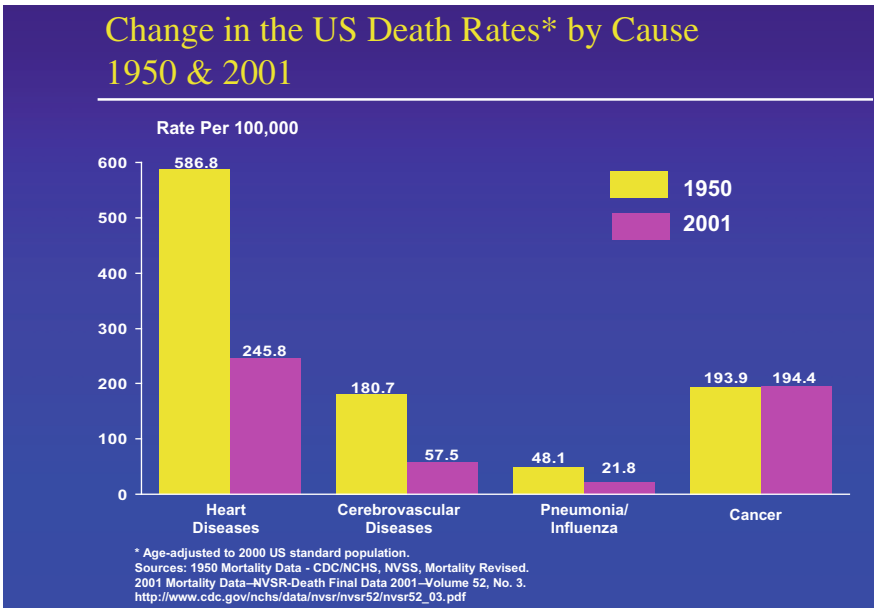


**Fig. 32.1** Change in the US death rates by cause, 1950 and 2001. Note age-adjusted to 2000 US standard population. *Sources* 1950 Mortality Data—CDC/NCHS, NVSS, mortality revised. 2001 Mortality Data-NVSR-Death Final Data 2001-Volume 52, No. 3 http://www.cdc.gov/nchs/data/nvsr52/nvsr52_03.pdf

has no impact on oestrogen receptor negative women (Fig. 32.2b). Overall this amounts to a 38 % reduction in the risk of breast cancer.

On the other hand, there were two major side effects of tamoxifen—increases in endometrial cancer, and venous thromboembolic events during the active treatment phase. The former is increased about 21/2-fold whereas the latter is approximately doubled. In simple terms giving 5 years of tamoxifen to 1000 women aged 50 at double the population risk would lead to 11 fewer breast cancers, six additional deep vein thromboses and three extra endometrial cancers in the first five years of follow-up (Table 32.2). Given that breast cancer is the most serious of these events, the balance appears reasonably favourable.

However, a key question will be the extent to which benefits and side effects extend beyond the 5 year treatment period. Recent reports [15, 16] show that the benefits extend well beyond the active treatment period, but the side effects largely do not. In particular in years 5–10, after 5 years if tamoxifen in the IBIS-I trial, the risk of new ER-positive breast cancer was reduced by 44 %.

In addition, endometrial cancer and thromboembolic events were not in excess after completion of treatment. Thus one can expect that another 11 cancers will be prevented in this period and there will be no additional major side effects, so that the 10 year risk-benefit ratio will be substantially improved over the 5 year estimate currently available. Furthermore, as there was no diminution of benefit even at year

**Table 32.1** Breast cancer prevention trials using tamoxifen

| Trial (Entry dates) | Population | Number randomised | Agents (vs. placebo) and daily dose (mg) | Intended duration of treatment (years) |
|---|---|---|---|---|
| Royal Marsden (1986–1996) | High-risk | 2471 | Tamoxifen 20 | 5–8 |
| | Family history | | | |
| NSABP-P1 (1992–1997) | High-risk women | 13,388 | Tamoxifen 20 | 5 |
| | >1.6 % 5 years risk | | | |
| Italian (1992–1997) | Normal risk | 5408 | Tamoxifen 20 | 5 |
| | Hysterectomy | | | |
| IBIS-I (1992–2001) | >twofold relative risk | 7139 | Tamoxifen 20 | 5 |
| Adjuvant overview (1976–1995) | Women with ER + operable breast cancer in 11 trials | ~15,000 | Tamoxifen 20–40 with or without chemotherapy in both arms | 3 or more (average ~5) |

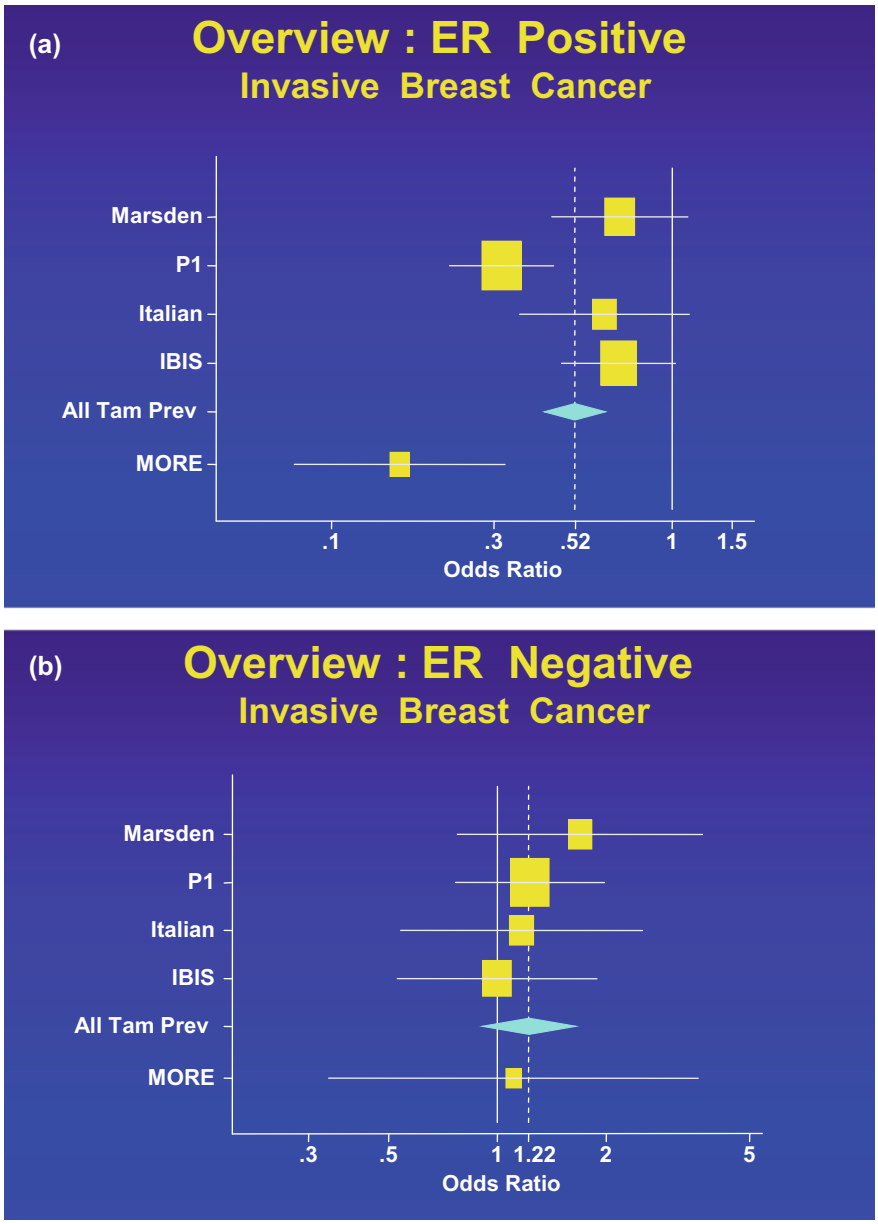


**Fig. 32.2** **a** Overview of impact of tamoxifen in prevention trials for ER-positive invasive breast cancer. **b** Overview of impact of tamoxifen in prevention trials for ER-negative invasive breast cancer

**Table 32.2** Predicted outcome in 1000 women aged 50 at high-risk of breast cancer followed for 5 or 10 years

| | Follow-up period (years) | No treatment | Tamoxifen for 5 years |
|---|---|---|---|
| Breast cancer | 5 | 30 | 19 |
| | 10 | 60 | 38 |
| VTE | 5 | 6 | 12 |
| | 10 | 12 | 18 |
| Endometrial cancer | 5 | 2 | 5 |
| | 10 | 5 | 8 |

**Table 32.3** Prevention trials using raloxifene

| Trial (Entry dates) | Population | Number randomised | Agents (vs. placebo) and daily dose (mg) | Intended duration of treatment (years) |
|---|---|---|---|---|
| MORE (1994–1999) | Normal risk | 7705 | Raloxifene 60 or 120 (3 arm) | 4 |
| | Postmenopausal women with osteoporosis | | | |
| CORE (2000–2004) | Normal risk | 4011 | Raloxifene 60 | Additional 4 |
| | Postmenopausal women with osteoporosis | | | |
| RUTH (1998–2000) | Postmenopausal women ≥55 years with CHD or risk factors | 10,101 | Raloxifene 60 | 5 |
| STAR (2001–2005) | High-risk postmenopausal women >1.6 % 5 years breast cancer risk | 19,747 | Raloxifene 60 versus tamoxifen (20) | 5 |

10, the benefits could persist even longer, making tamoxifen chemoprevention even more attractive, especially for women in the late premenopausal years, where life-expectancy is long. Raloxifene four trials have reported on the use of raloxifene for breast cancer prevention (Table 32.3). Two independent parts of the MORE/CORE trial have reported on the reduction of breast cancer in osteoporotic women. The original intent of this trial was to reduce bone fracture rates [17]. After 4 years of treatment a 65 % reduction in all breast cancer was found in the MORE segment [18]. This led to another 4 years of blinded treatment in the CORE study, where breast cancer was the primary endpoint. Results here were also very favourable with a 50 % reduction in breast cancer [19]. Raloxifene appears to be associated with some increase of thromboembolic complications, as with tamoxifen, but it does not stimulate the endometrium, so that there are no excess of endometrial cancers or other gynaecologic problems.

The RUTH study, which is evaluating the impact of raloxifene on cardiovascular endpoints in 10,101 women at increased risk of cardiovascular events [20] found reductions in breast cancer similar in size to that seen for tamoxifen in other studies. Also the STAR trial comparing raloxifene directly to tamoxifen in 19,747 women at high-risk for breast cancer recently found similar efficacy for the two drugs, but fewer gynaecologic and thromboembolic side effects with raloxifene [21]. Based on these results, one can safely anticipate that raloxifene will become a useful part of the armitarium for preventing postmenopausal breast cancer.

## 32.2.2 Aromatase Inhibitors

### 32.2.2.1 Efficacy

Most of what we know about the potential use of AIs in prevention derives from adjuvant studies in women with early breast cancer, where the development of isolated contralateral tumours as a first event is a good model for prevention of new tumours in healthy women. This has proved a reliable source for estimating the qualitative effects of tamoxifen in prevention, both in terms of major side effects, and in terms of efficacy. This approach has generally been more reliable than animal models or observational epidemiologic studies, although randomised intervention studies in the prevention setting remain essential for directly quantifying effectiveness in this setting and balancing risks and benefits.

To date, eight different adjuvant trials have reported on the use of three different AIs for postmenopausal women with breast cancer [22–29]. In these trials, adjuvant AIs have been found effective in three clinical settings, as initial treatment, after 2–3 years of tamoxifen, or as extended treatment after 5 years of tamoxifen.

In these trials, a consistent reduction in the rates of contralateral breast cancer has been observed in the group receiving the AI (Fig. 32.3). For example, in the ATAC trial, the number of contralateral breast cancers was reduced from 59 in the tamoxifen arm to 35 on anastrozole, a 42 % reduction (95 % CI, 12–62 %; $P = 0.01$). A larger reduction of 53 % (95 % CI, 27–71 %; $P = 0.001$) was seen in the hormone receptor-positive patients [22]. Tamoxifen itself is known to reduce the incidence of contralateral tumours by 46 % in women with mostly ER-positive primary tumours, suggesting that the overall reduction of receptor-positive breast cancer associated with anastrozole compared to no treatment may be around 70–80 %. Information on the receptor status of the second cancers in this trial is not yet available, but one would expect the preventive effect to be restricted to ER-positive contralateral tumours, and to be greater for this group than for new breast tumours overall.

### 32.2.2.2 Side Effects

The profound oestrogen depletion associated with AIs produces a new state of human existence, and this is bound to have other effects beyond those related to breast

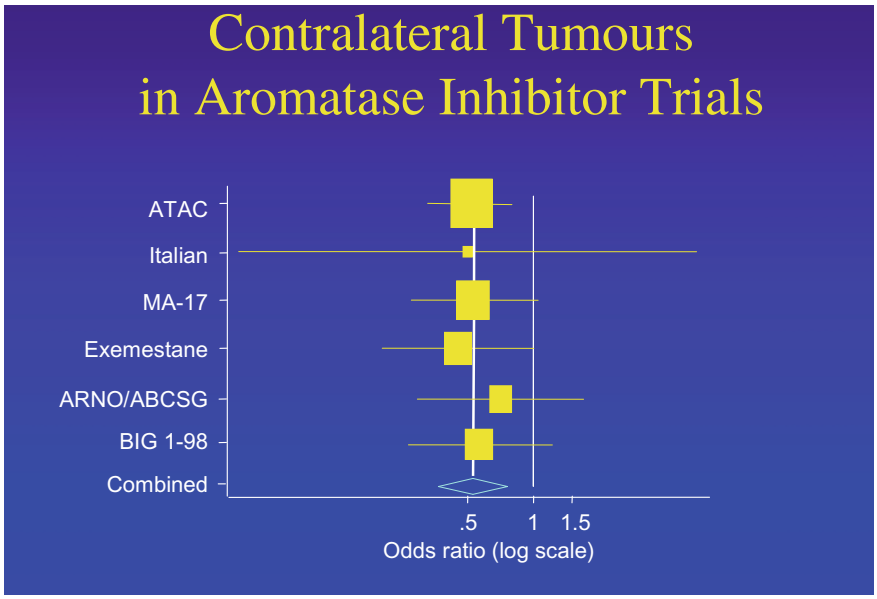


**Fig. 32.3** Contralateral tumours in aromatase inhibitor trials. Combined odds ratio is 0.53 (95 % CI [0.41, 0.68])

carcinogenesis. These effects can most reliably be studied in prevention trials where a placebo is employed, allowing a direct determination of the effect of the AI. There are suggestions from adjuvant trials comparing AIs to tamoxifen, that AIs may also reduce endometrial cancer and cerebrovascular events to below baseline rates, but full evaluation is difficult because there is no untreated comparison group. Bone loss leading to increased fracture rates appear to be the most serious side effect of AIs, and methods for combating them will be essential if these drugs are to be used prophylactically [30]. Generally similar side-effect profiles are seen for all AIs and the results for anastrozole from the ATAC trial are shown in Tables 32.4 and 32.5.

## 32.3 Prevention Trials

Two primary prevention trials using AIs are currently in progress. One uses anastrozole while the other uses exemestane.

### 32.3.1 International Breast Cancer Intervention Study-II

The international breast cancer intervention (IBIS)-II trial began in February 2003 and is comparing anastrozole to placebo on 6000 postmenopausal women at increased risk of

**Table 32.4** ATAC: predefined adverse events. From [22]

| | Completion analysis (%) | | *P* value |
|---|---|---|---|
| | *A* | *T* | |
| Hot flushes | 35.7 | 40.9 | <0.0001 |
| Vaginal bleeding | 5.4 | 10.2 | <0.0001 |
| Vaginal discharge | 3.5 | 13.2 | <0.0001 |
| Endometrial cancer[a] | 0.2 | 0.8 | 0.02 |
| Ischaemic cerebrovascular event | 2.0 | 2.8 | 0.03 |
| Venous thromboembolic events | 2.8 | 4.5 | 0.0004 |
| Deep venous thromboembolic events | 1.6 | 2.4 | 0.02 |
| Joint symptoms | 35.6 | 29.4 | <0.0001 |
| Total fractures[b] | 11.0 | 7.7 | <0.0001 |

Adverse events on treatment or within 14 days of discontinuation
[a]Excludes patients with prior hysterectomy and includes on- and off-therapy AEs
[b]Fractures occurring at anytime prior to recurrence (includes patients no longer receiving treatment)

**Table 32.5** Non-predefined adverse events during treatment or within 14 days of discontinuation. From [31]

| | Treatment first received (*n* [%]) | | Odds ratio[a] (99 % Cl) | *P* value |
|---|---|---|---|---|
| | Anastrozole (*n* = 3092) | Tamoxifen (*n* = 3094) | | |
| Hypertension | 402 (13) | 349 (11) | 1.18 (0.96–1.44) | 0.04 |
| Diarrhoea | 265 (9) | 216 (7) | 1.25 (0.98–1.60) | 0.02 |
| Dry mouth | 113 (4) | 73 (2) | 1.57 (1.06–2.32) | 0.003[b] |
| Reduction in libido | 39 (1) | 12 (<1) | 3.28 (1.4–7.7) | 0.0001[b] |
| Dyspareunia | 28 (1) | 9 (<1) | 3.13 (1.16–8.42) | 0.002[b] |
| Gynaecological events[c] | 95 (3) | 324 (10) | 0.27 (0.20–0.37) | <0.0001 |
| Hysterectomy[d] | 30 (1) | 115 (5) | 0.25 (0.15–0.43) | <0.0001 |
| Vaginal moniliasis | 38 (1) | 136 (4) | 0.27 (0.17–0.44) | <0.0001 |
| Urinary incontinence | 74 (2) | 133 (4) | 0.55 (0.37–0.80) | <0.0001 |
| Urinary-tract infection | 244 (8) | 313 (10) | 0.76 (0.60–0.96) | 0.002 |
| Osteopenia or osteoporosis | 325 (11) | 226 (7) | 1.49 (1.18–1.88) | <0.0001[b] |
| Muscle cramps | 132 (4) | 235 (8) | 0.54 (0.41–0.72) | <0.0001 |
| Carpal-tunnel syndrome | 78 (3) | 22 (1) | 3.61 (1.93–6.75) | <0.0001[b] |
| Paresthaesia | 215 (7) | 145 (5) | 1.52 (1.14–2.02) | 0.0001[b] |
| Thrombocytopenia | 13 (<1) | 28 (1) | 0.46 (0.19–1.10) | 0.03 |
| Anaemia | 113 (4) | 159 (5) | 0.70 (0.51–0.97) | 0.005 |
| Nail disorder | 54 (2) | 92 (3) | 0.58 (0.37–0.91) | 0.002 |
| Fungal infection | 23 (1) | 45 (1) | 0.51 (0.26–0.99) | 0.01 |
| Increase in alkaline phosphatase | 55 (2) | 8 (< 1) | 6.99 (2.63–18.56) | <0.0001[b] |
| Hypercholesterolaemia | 278 (9) | 108 (3) | 2.73 (2.02–3.69) | <0.0001[b] |

[a]Refers to anastrozole versus tamoxifen
[b]Favours tamoxifen
[c]Includes endometrial hyperplasia, endometrial neoplasia, cervical neoplasm, and enlarged uterine fibroids
[d]Recorded in 2229 patients assigned anastrozole and 2236 assigned tamoxifen (excluding those with hysterectomy at baseline)

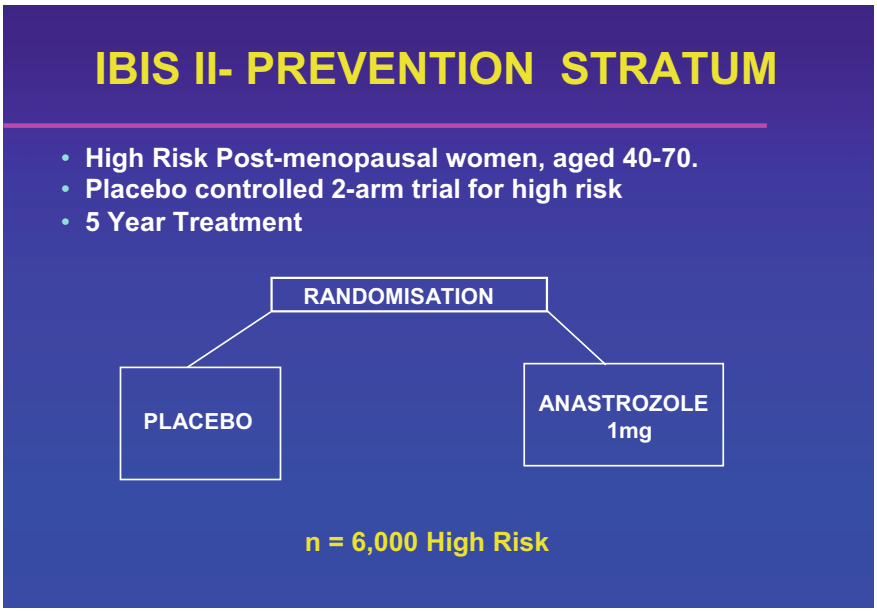


**Fig. 32.4** IBIS II: prevention stratum

breast cancer (Fig. 32.4). This study is still open to recruitment. Entry criteria are similar to IBIS-I, except that only postmenopausal women are eligible and women with mammographic density covering at least 50 % of the mammogram, are also eligible. A parallel study of anastrozole versus tamoxifen in 4000 postmenopausal women with locally resected ER-positive DCIS is also being conducted as part of this activity.

### 32.3.2 Map.3

Another prevention trial with AIs is currently underway using exemestane. This trial sponsored by the NCIC-Clinical Trials Group compares exemestane for 5 years placebo in 3000 postmenopausal women at increased risk. Risk factors needed for eligibility include a Gail score >1.66, age >60 years, prior atypical ductal or lobular hyperplasia, or DCIS treated with mastectomy.

### 32.3.3 New Agents

Several lines of investigation for improved agents are underway. One approach is to search for SERMs that have an even more favourable profile that raloxifene, which still has thromboembolic concerns and leads to vasomotor symptoms such as hot flushes and night sweats. However, its lack of gynaecologic symptoms has stimulated the search for a perfect SERM which would be anti-oestrogenic for the breast, endometrium, and lipid profile, but have oestrogenic effects on bones and brain (vasomotor symptoms). Two compounds have completed stage III human testing, arzoxifene and lasofoxifene, and several more are in early development.

Oestrogen receptor negative tumours remain a challenge for prevention, and new targets will be needed to prevent these tumours. There is interest in EGFR blockers [gefitinib (sp.)] and agents targeting HER2 such as trastuzamab, and joint blockers of both targets (lapatinib), but these current agents are too toxic for prevention. NSAIDs [32, 33], COX-2 inhibitors [34, 35], retinoids, rexinoids [36], and statins [37–39] may also protect against both receptor positive and receptor negative tumours, but only results from observational studies or adjuvant studies or trials with other primary endpoints are available at the moment, and the results still have inconsistencies.

## 32.4 Conclusions

Approaches to prevent receptor positive are well established, and the challenge now is to reduce side effects and find agents with very favourable benefit to risk ratios. Raloxifene achieves a better side-effect profile than tamoxifen, but the efficacy is similar. The AIs hold promise for greater efficacy and fewer, but different side effects from SERMs. Unfortunately, a direct comparison of raloxifene versus letrozole in the NSABP P-4 trials looks unlikely to be funded, so decisions about which to use will have to be based on indirect comparisons of the other trials looking at AIs or SERMs separately. The side effect profiles will be critical in determining which to use both overall and for individual patients.

Good biomarkers will greatly accelerate our ability to evaluate new agents, and breast density is currently the most attractive candidate. However, its ability to predict the degree of risk reduction still needs validation and good serum markers are still awaited. The prevention of oestrogen receptor negative breast cancer remains an unmet challenge, but new agents offer an approach to preventing these cancers as well.

## References


1. Parkin DM, Bray F, Ferlay J, et al. Global Cancer Statistics, 2002. CA Cancer J Clin. 2005;55(2):74–108.
2. Bernstein L, Patel AV, Ursin G, et al. Lifetime recreational exercise activity and breast cancer risk among black women and white women. J Natl Cancer Inst. 2005;97(22):1671–9.
3. Eliassen AH, Colditz GA, Rosner B, Willett WC, Hankinson SE. Adult weight change and risk of postmenopausal breast cancer. JAMA. 2006;296(2):193–201.
4. Wolfe JN. Risk for breast cancer development determined by mammographic parenchymal pattern. Cancer. 1976;37:2486–92.
5. Warner E, Lockwood G, Tritchler D, Boyd NF. The risk of breast cancer associated with mammographic parenchymal patterns: a meta-analysis of the published literature to examine the effect of method of classification. Cancer Detect Prev. 1992;16(1):67–72.
6. Brisson J, Diorio C, Masse B. Wolfe's parenchymal pattern and percentage of the breast with mammographic densities: redundant or complementary classifications? Cancer Epidemiol Biomarkers Prev. 2003;12(8):728–32.
7. Boyd NF, Byng R, Jong E. Quantitative classification of mammographic densities and breast cancer risk: results from the Canadian national breast screening study. J Natl Cancer Inst. 1995;87:670–5.
8. Boyd NF, Guo H, Martin LJ, et al. Mammographic density and the risk and detection of breast cancer. N Engl J Med. 2007;356(3):227–36.
9. Cuzick J, Warwick J, Pinney E, et al. Tamoxifen and breast density in women at increased risk of breast cancer. J Natl Cancer Inst. 2004;96(8):621–8.
10. Greendale GA, Reboussin BA, Slone S, et al. Postmenopausal hormone therapy and change in mammographic density. J Natl Cancer Inst. 2003;95:30–7.
11. Cuzick J, Baum M. Tamoxifen and contralateral breast cancer. Lancet. 1985;2(8449):282.
12. Jordan C. Tamoxifen for the prevention of breast cancer. In: DeVita, et al editors. Cancer prevention. 1990. p. 1–12.
13. Cuzick J, Wang DY, Bulbrook RD. The prevention of breast cancer. Lancet. 1986;2(8472):83–6.
14. Cuzick J, Powles T, Veronesi U, et al. Overview of the main outcomes in breast cancer prevention trials. Lancet. 2003;361(9354):296–300.

15. Cuzick J, Forbes JF, Sestak I, Cawthorn S, Hamed H, Holli K, Howell A. Long-term results of tamoxifen prophylaxis for breast cancer—96-month follow-up of the randomized IBIS-I trial. J Natl Cancer Inst. 2007;99:272–82.
16. Powles TJ, Ashley S, Tidy A, Smith IE, Dowsett M. Twenty-year follow-up of the Royal Marsden randomized, double-blinded tamoxifen breast cancer prevention trial. J Natl Cancer Inst. 2007;99(4):283–90.
17. Ettinger B, Black DM, Mitlak BH, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) investigators. JAMA. 1999;282(7):637–45.
18. Cummings SR, Eckert S, Krueger KA, Grady D, Powles TJ, Cauley JA, Norton L, Nickelsen T, Bjarnason NH, Morrow M, Lippman ME, Black D, Glusman JE, Costa A, Jordan VC. The effect of raloxifene on risk of breast cancer in postmenopausal women: results from the MORE randomized trial. Multiple Outcomes of Raloxifene Evaluation. JAMA. 1999;281(23):2189–97.
19. Martino S, Cauley JA, Barrett-Connor E, Powles TJ, Mershon J, Disch D, Secrest RJ, Cummings SR. CORE Investigators. Continuing outcomes relevant to Evista: breast cancer incidence in postmenopausal osteoporotic women in a randomized trial of raloxifene. J Natl Cancer Inst. 2004;96(23):1751–61.
20. Barrett-Connor E, Mosca L, Collins P, et al. Effects of raloxifene on cardiovascular events and breast cancer in postmenopausal women. N Engl J Med. 2006;355(2):125–37.
21. Vogel VG, Costantino JP, Wickerham DL, Cronin WM, Cecchini RS, Atkins JN, Bevers TB, Fehrenbacher L, Pajon ER Jr, Wade JL 3rd, Robidoux A, Margolese RG, James J, Lippman SM, Runowicz CD, Ganz PA, Reis SE, McCaskill-Stevens W, Ford LG, Jordan VC. Wolmark N; National Surgical Adjuvant Breast and Bowel Project (NSABP). Effects of tamoxifen vs. 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(23):2727–41.
22. ATAC Trialists' Group. Results of the ATAC (Arimidex, Tamoxifen Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. Lancet. 2005;365 (9453):60–2.
23. Boccardo F, Rubagotti A, Puntoni M, et al. Switching to anastrozole versus continued tamoxifen treatment of early breast cancer: preliminary results of the Italian Tamoxifen Anastrozole Trial. J Clin Orthod. 2005;23(22):5138–47.
24. Coates AS, Keshaviah A, Thurlimann B, et al. Five years of letrozole compared with tamoxifen as initial adjuvant therapy for postmenopausal women with endocrine-responsive early breast cancer: update of study BIG 1–98. J Clin Oncol. 2007;25(5):486–92.
25. Coombes RC, Kilburn LS, Snowdon CF, Paridaens R, Coleman RE, Jones SE, Jassem J, Van de Velde CJ, Delozier T, Alvarez I, Del Mastro L, Ortmann O, Diedrich K, Coates AS, Bajetta E, Holmberg SB, Dodwell D, Mickiewicz E, Andersen J, Lonning PE, Cocconi G, Forbes J, Castiglione M, Stuart N, Stewart A, Fallowfield LJ, Bertelli G, Hall E, Bogle RG, Carpentieri M, Colajori E, Subar M, Ireland E, Bliss JM; Intergroup Exemestane Study. Survival and safety of exemestane versus tamoxifen after 2–3 years' tamoxifen treatment (Intergroup Exemestane Study): a randomised controlled trial. Lancet. 2007;369(9561):559–70.
26. Goss, et al. A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. N Engl J Med. 2003;349:1793–802.
27. Jakesz R, Jonat W, Gnant M, et al. Switching postmenopausal women with endocrine-responsive early breast cancer to anastrozole after 2 years' adjuvant tamoxifen: combined results of ABCSG Trial 8 and ARNO 95 trial. Lancet. 2005;366 (9484):455–62.
28. Jakesz R, Samonigg H, Greil R, et al. Extended adjuvant treatment with anastrozole: results from the Austrian Breast and Colorectal Cancer Study Group Trial 6a (ABCSG-6a). Proc Am Soc Clin Oncol. 2005;23:10 s abstract 527.
29. Mamounas E, Jeong J-H, Wickerham DL, et al. Benefit from exemestane (EXE) as extended adjuvant therapy after 5 years of tamoxifen (TAM): Intent-to-treat analysis of NSABP B-33. abstract for the San Antonio breast cancer symposium, December 2006.
30. Eastell R, Hannon RA, Cuzick J, et al. Effect of an Aromatase inhibitor on bmd and bone turnover markers: 2-year results of the Anastrozole, Tamoxifen, Alone or in Combination (ATAC) trial. J Bone Miner Res. 2006;21(8):1215–23.
31. The ATAC Trialists' Group, Buzdar A, Howell A, Cuzick J, Wale C, Distler W, Hoctin-Boes G, Houghton J, Locker GY, Nabholtz JM. Comprehensive side-effect profile of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: long-term safety analysis of the ATAC trial. Lancet Oncol. 2006;7 (8):633–43.
32. Rahme E, Ghosn J, Dasgupta K, et al. Association between frequent use of nonsteroidal anti-inflammatory drugs and breast cancer. BMC Cancer. 2005;5:159.
33. Swede H, Mirand AL, Menezes RJ, et al. Association of regular aspirin use and breast cancer risk. Oncology. 2005;68(1):40–7.
34. Harris RE, Beebe-Donk J, Alshafie GA. Reduction in the risk of human breast cancer by selective cyclooxygenase-2 (COX-2) inhibitors. BMC Cancer. 2006;6:27.
35. Mazhar D, Ang R, Waxman J. COX inhibitors and breast cancer. Br J Cancer. 2006;94:346–50.
36. Wu K, Zhang Y, Xu XC, et al. The retinoid X receptor-selective retinoid, LGD1069, prevents the development of estrogen receptor-negative mammary tumors in transgenic mice. Cancer Res. 2002;62(22):6376–80.
37. Bonovas S, Filioussi K, Tsavaris N, et al. Use of statins and breast cancer: a meta-analysis of seven randomized clinical trials and nine observational studies. J Clin Oncol. 2005;23(34):8606–12.
38. Cauley JA, Zmuda JM, Lui LY, et al. Lipid-lowering drug use and breast cancer in older women: a prospective study. J Womens Health (Larchmt). 2003;12(8):749–56.
39. Eliassen AH, Colditz GA, Rosner B, et al. Serum lipids, lipid-lowering drugs, and the risk of breast cancer. Arch Intern Med. 2005;165(19):2264–71.