REVIEW ARTICLE

Current concepts in breast cancer chemoprevention

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KEY WORDS

aromatase inhibitors, breast cancer, chemoprevention, raloxifene, tamoxifen

ABSTRACT

In Western countries, breast cancer is the most common cancer in women but available interventions can reduce risk. The aim of the paper was to review the available evidence regarding breast cancer chemoprevention trials. A systematic literature search was conducted to identify all full-scale, randomized prospective chemoprevention trials as well as similarly conducted randomized trials with breast cancer as the primary monitoring endpoint. In full-scale, randomized chemoprevention trials, the selective estrogen receptor modulators (SERMs), tamoxifen and raloxifene, reduce breast cancer incidence. In a direct comparison, tamoxifen resulted in greater breast cancer reduction than raloxifene but with greater endometrial cancer risk. The aromatase inhibitors, exemestane and anastrozole, also reduce breast cancer incidence in breast cancer prevention trials. In the Women's Health Initiative hormone therapy trials, in postmenopausal women with no prior hysterectomy, estrogen plus progestin increased breast cancer incidence and deaths from breast cancer, while estrogen alone, in women with prior hysterectomy, reduced breast cancer incidence and reduced deaths from breast cancer. For premenopausal women at increased breast cancer risk, tamoxifen is a proven option with favorable side effect profile. For postmenopausal women, while no direct comparison of SERMs and aromatase inhibitors for chemoprevention are available, cross-study comparisons suggest greater efficacy and more favorable side effect profile for aromatase inhibitor use, especially for older women. The opposite effects of estrogen plus progestin compared with estrogen alone on breast cancer incidence and outcome should factor into risk-benefit consideration when these agents are considered for climacteric symptom management.

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Introduction Breast cancer is the most common cancer in women. The term "chemoprevention" describes interventions used in women with no prior breast cancer to reduce breast cancer risk.[1] However, given that breast cancers take years to develop and become clinically detectable, can chemoprevention administered for a relatively short time of 3 or 5 years interfere with such a long-term process? Santen et al.[2] addressed this issue using a clinically based model, an average 200-day time of breast cancer doubling, 1.16 cm breast cancer detection threshold for mammography, and a 7% prevalence of subclinical breast cancer in postmenopausal women based on autopsy series. This model was applied to a population from the Women's Health Initiative (WHI) randomized trial evaluating estrogen plus progestin,[3] which involved a population quite similar to that participating in most breast cancer chemoprevention trials (50–79 years of age with a negative baseline mammogram). Using the model, the number of invasive breast cancers diagnosed during the 5.6 years of hormone intervention in the trial was calculated as being already established preclinical breast cancers in 94% of the cases and being new cancers in only 6% of the cases. Thus, breast cancer chemoprevention in prevention trials is almost exclusively therapy of already established but preclinical disease.[2] Implications of these findings will be discussed later in this document.

Selective Estrogen Receptor Modulators Breast Cancer Prevention Trial Interest of breast cancer chemoprevention was generated by the finding that the selective estrogen receptor modulator (SERM), tamoxifen, when used as adjuvant therapy of both pre- and postmenopausal women with

TABLE 1 Breast cancer chemoprevention trials of selective estrogen receptor modulators and aromatase inhibitors

	No. of participants	Eligibility summary	Duration of intervention, y	Median follow-up, mo	IBC (total)	Invasive BC RR (95% CI)
tamoxifen (20 mg/d) vs. placebo						
NSABP P-1, 2005	13,388	pre- and postmenopausal and 5-year Gail risk >1.66%	5	84	395	0.57 (0.46–0.70)
IBIS-1, 2007	7145	pre- and postmenopausal, at increased risk	5	96	292	0.74 (0.58–0.94)
Royal Marsden Trial, 2007	2494	pre- and postmenopausal, at increased risk	8	158	186	0.78 (0.58–1.04)
Italian Study, 2007	5408	pre- and postmenopausal, average BC risk, hysterectomy	5	132	119	0.80 (0.56–1.15)
raloxifene (60 mg or 120 mg/d) vs. placebo						
MORE, 1999	7705	postmenopausal, osteoporosis	3	40	NR	0.24 (0.13–0.44)
CORE, 2004	5213	MORE cohort subset	4	95	92	0.41 (0.24–0.71)
RUTH, 2006	10,101	postmenopausal, CHD or at CHD risk	5	67	110	0.56 (0.38–0.83)
raloxifene (60 mg/d) vs. tamoxifen (20 mg/d)						
STAR, 2010	19,747	postmenopausal, 5-year Gail risk ≥1.66%	5	81	557	1.24 (1.05–1.47)[a]
exemestane (25 mg/d) vs. placebo						
ExCel/MAP3, 2011	4560	postmenopausal, age >60 y or 5-year Gail risk ≥1.66%	5	35	43	0.35 (0.18–0.70)
anastrozole (1 mg/d) vs. placebo						
IBIS-II, 2013	3864	postmenopausal at increased risk	5	60	96	0.50 (0.32–0.76)

a RR for raloxifene effect relative to tamoxifen

Abbreviations: IBC – invasive breast cancer, CHD – coronary heart disease, CI – confidence interval, RR – relative risk

early-stage hormone-receptor-positive breast cancer, substantially reduced new contralateral breast cancers.[4] As a result, tamoxifen was compared with placebo in 4 randomized, full-scale clinical trials, all of which have been presented and updated.[5-12] In addition, the SERM, raloxifene, approved as therapy for bone loss in postmenopausal women, has been compared against placebo in 2 randomized trials in women with osteoporosis[13,14] and in 1 trial in women with established or at risk of heart disease.[15] In these trials, while breast cancer risk was not evaluated at entry, breast cancers were recorded. Finally, raloxifene was directly compared with tamoxifen in the National Surgical Adjuvant Breast Project (NSABP) chemoprevention trial in postmenopausal women where breast cancer incidence was the primary study outcome.[16,17] Updated outcomes from these trials, including their influence on breast cancer prevention and side effects, have been presented in an updated meta-analysis of individual participant data[18,19] with results summarized below and in **TABLE 1**.

In the 4 tamoxifen trials, while eligibility requirements varied between the trials and only the NSABP P-1 trial[5] excluded use of menopausal hormone therapy, when analyzed together, a significant reduction in breast cancer incidence of 33% (P <0.0001) was seen. The result largely reflects the influence on estrogen-receptor-positive invasive breast cancers with a much lower, nonsignificant increase in estrogen-receptor-negative breast cancers.[19] In terms of the side effects, tamoxifen increased endometrial cancer (hazard ratio [HR], 2.18; 95% confidence interval [CI], 1.39–3.42; P = 0.001), thromboembolic disease (HR, 1.60; 95% CI, 1.21–2.12; P = 0.001), and modestly increased cataracts (HR, 1.10; 95% CI, 1.01–1.21; P = 0.04). Tamoxifen did not affect the incidence of myocardial infarction, stroke, or fracture.

In the raloxifene trials compared with placebo, a significant reduction in the incidence of invasive breast cancer was also observed (P <0.0001), reflecting a large effect on estrogen-receptor-positive breast cancer with a nonsignificant increase in estrogen-receptor-negative cancers.[19] In the Multiple Outcomes of Raloxifene Evaluation (MORE),[13] Continuing Outcomes Relevant to Evista (CORE),[14] and Raloxifene Use for The Heart (RUTH)[15] trials, a somewhat greater raloxifene effect in reducing breast cancers was seen compared with the tamoxifen effects in placebo trials. However, in the STAR trial, directly comparing tamoxifen to raloxifene with long-term follow-up, tamoxifen had greater influence on reducing the incidence of invasive breast cancer (HR, 0.81; 95% CI, 0.70–0.93).[17] Endometrial cancer was not increased in the raloxifene trials (HR, 1.09 95%; CI, 0.74–1.62, P = 0.7) and significant decrease in fractures was seen with raloxifene use.

To summarize, both tamoxifen and raloxifene result in an overall reduction of invasive breast cancer incidence by significantly reducing estrogen-receptor-positive cancer but with a modest, nonsignificant increase in estrogen-receptor-negative breast cancers. Tamoxifen has a somewhat greater effect on reducing invasive

TABLE 2 Women's Health Initiative trials of menopausal hormone therapy with breast cancer as a primary monitoring endpoint

	No. of participants	Eligibility summary	Duration of intervention, y	Median follow-up, mo	Invasive BC no. (total)	IBC HR (95% CI)	Deaths from BC HR (95% CI)
estrogen plus progestin vs. placebo (2010)							
CEE (0.625 mg/d) + MPA (2.5 mg/d)	16,608	postmenopausal women aged 50–79 y, no prior hysterectomy, no prior breast cancer	5.6 y	11.0 y	678	1.25 (1.07–1.46)	1.96 (1.00–4.04)
estrogen alone vs. placebo (2012)							
CEE (0.625 mg/d) + MPA (2.5 mg/d)	10,739	postmenopausal women, aged 50–79 y, prior hysterectomy, no prior breast cancer	5.9 y	11.8 y	350	0.77 (0.62–0.95)	0.37 (0.13–0.91)

Abbreviations: CEE – conjugated equine estrogen, HR – hazard ratio, MPA – medroxyprogesterone acetate, others – see TABLE 1

breast cancers than raloxifene, and only tamoxifen reduces ductal carcinoma in situ. However, only raloxifene reduces fractures. Both tamoxifen and raloxifene increase thromboembolic events while only tamoxifen increases endometrial cancer and cataracts.

Despite the positive breast cancer findings, use of tamoxifen and raloxifene for breast cancer chemoprevention in the United States is extremely limited. Based on a 2010 survey, only about 21,000 women aged from 35 to 79 years were using tamoxifen and only 97,000 women aged from 50 to 79 years were using raloxifene for breast cancer chemoprevention in the United States.[20] Concerns about side effects and lack of public awareness are possible explanations.[20] To guide appropriate use, Freedman et al.[21] have developed a benefit-risk index to quantify benefits from chemoprevention using tamoxifen or raloxifene. The baseline rates of health outcomes, absent raloxifene and tamoxifen, were estimated from breast cancer chemoprevention trial control groups, from the Surveillance, Epidemiology and End Results Program results, and from the WHI cohort. Tamoxifen and raloxifene effects were then estimated from the NSABP P-1 Study[16,17] and other breast cancer prevention trials. For women aged 50 years and older with a uterus, raloxifene had a more favorable benefit-risk index than tamoxifen but in most risk circumstances only moderate benefits over risk were seen (TABLE 2). For women without a uterus, the risk-benefit profile for raloxifene and tamoxifen was similar and, while more women would be candidates for chemoprevention use, strong evidence of benefit outweighing risks was seen mainly in younger postmenopausal women and those at substantial 5-year breast cancer risk.[21]

Third-generation selective estrogen receptor modulators and breast cancer Two- and third-generation SERMs have been evaluated in phase III clinical trials in women with osteoporosis. The PostmEnopAusal and risk-Reduction with Lasofoxifene (PEARL) trial compared 2 doses of lasofoxifene to placebo and a significant reduction in breast cancer incidence was seen with a higher lasofoxifene dose of 0.5 mg but not with a dose of 0.25 mg.[22] While the higher dose also reduced risk of coronary heart disease and stroke, a trend towards more deaths in a lower-dose lasofoxifene group was seen compared with placebo (65 deaths vs. 90 deaths, $P = 0.05$),[23] reducing overall enthusiasm for this agent and an application for regulatory approval was withdrawn.[24] The SERM, arzoxifene, was also evaluated in a multicenter placebo controlled trial comparing a 20 mg/d dose with placebo in 9354 postmenopausal women with osteoporosis or low bone mass. While vertebral fractures and invasive breast cancers were significantly lower in the arzoxifene group, nonvertebral fractures were not significantly reduced. Based on these results, the sponsoring company agency decided not to seek regulatory approval.[25,26] These 2 trials, which failed to show unequivocal improvement over the results with tamoxifen and raloxifene, may signal an end to a search for an improved SERM that lasted several decades.

Women's Health Initiative hormone therapy trials with breast cancer as primary monitoring endpoint While not initiated as breast cancer chemoprevention trials, 2 WHI trials have major implications for breast cancer risk for a large population of postmenopausal women. The WHI has conducted 2 randomized, placebo-controlled clinical trials to assess the effects of estrogen alone (in women with prior hysterectomy) and of estrogen plus progestin (in women with an intact uterus) on life-threatening chronic disease risk.[3,27,28] In both trials, coronary heart disease (CHD) was the primary monitoring endpoint for benefit and invasive breast cancer was the primary monitoring endpoint for harm. A major study endpoint was a prospectively identified global index representing time to first event of clinical conditions felt to be under potential influence of menopausal hormone therapy including CHD, invasive breast cancer, hip fracture, stroke, pulmonary embolism, and endometrial and colorectal cancer.

In the WHI clinical trial evaluating estrogen plus progestin, where 16,608 postmenopausal women with a uterus were randomized, intervention ended early, after a mean of 5.6 years, when a significant increase in breast cancer incidence was seen and overall harms exceeded benefits for

A

5-year projected risk of IBC (%)	tamoxifen vs. placebo (with uterus)			raloxifene vs. placebo (with uterus)		
	50–59 y	60–69 y	70–79 y	50–59 y	60–69 y	70–79 y
1.5	–144	–319	–349	–25	–68	–108
2.0	–117	–292	–322	–3	–46	–86
2.5	–89	–264	–294	19	–24	–64
3.0	–62	–237	–267	41	–3	–43
3.5	–36	–211	–241	62	19	–21
4.0	–9	–184	–214	83	40	–1
4.5	18	–157	–187	105	62	22
5.0	45	–130	–160	126	83	43
5.5	72	–105	–135	147	104	64
6.0	98	–78	–108	169	126	86
6.5	124	–51	–81	190	146	106
7.0	151	–25	–55	211	168	128
5-year projected risk of IBC is ≥1.67%	using BCPT data and WHI baseline reports			combining RR from BCPT and STAR using WHI baseline reports		

B

5-year projected risk of IBC (%)	tamoxifen vs. placebo (without uterus)			raloxifene vs. placebo (without uterus)		
	50–59 y	60–69 y	70–79 y	50–59 y	60–69 y	70–79 y
1.5	3	–53	–93	27	2	–4
2.0	31	–26	–66	49	23	18
2.5	57	2	–39	71	45	40
3.0	84	29	–12	92	67	62
3.5	111	56	15	114	88	82
4.0	138	83	42	134	109	104
4.5	164	109	69	156	131	126
5.0	191	136	96	178	152	147
5.5	218	163	121	199	173	168
6.0	244	189	148	220	195	190
6.5	270	215	175	242	216	210
7.0	297	242	201	262	237	232
5-year projected risk of IBC is ≥1.67%	using BCPT data and WHI baseline reports			combining RR from BCPT and STAR using WHI baseline reports		

strong evidence of benefits outweighing risks

moderate evidence of benefits outweighing risks

benefits do not outweigh risks

FIGURE Benefit and risk balance for tamoxifen and raloxifene use for breast cancer risk reduction by 5-year invasive breast cancer risk in white women by age group for those with a uterus (**A**) and those without a uterus (**B**). The numbers in each box indicate the net number of life threatening events (invasive breast cancer, hip fracture, endometrial cancer, stroke, and pulmonary embolism scored as 1 and in situ breast cancer and peripheral thromboembolism scored as 0.5). For example, in FIGURE 1A, among 10,000 white women with a uterus aged 60 to 69 years with a 5-year invasive risk of 3.5%, 202 life-threatening equivalent events would be caused in 5 years by taking tamoxifen instead of placebo, strongly indicating that risk outweighs benefits in this setting. One can see the relatively modest groups of women with a uterus who would benefit from tamoxifen or raloxifene chemoprevention. The number benefiting is larger in women with prior hysterectomy as seen in FIGURE 1B where tamoxifen and raloxifene appear equivalently effective. Freedman AN, et al. J Clin Oncol. 2011; 29: 2327-2333.
Abbreviations: BCPT – breast cancer prevention trial, RR – relative risk, WHI – Women's Health Initiative, STAR – Study of Tamoxifen And Raloxifene, others – see TABLE 1

the combined hormone therapy group.[3,29] Combined hormone therapy significantly increased invasive breast cancers[30,31] (HR, 1.24; 95%, CI 1.01–1.53), significantly interfered with mammogram detection performance,[30,32] and significantly increased deaths from breast cancer.[31] In contrast, in the WHI placebo-controlled clinical trial evaluating estrogen alone in 10,749 postmenopausal women with prior hysterectomy, estrogen alone significantly decreased breast cancer incidence[33,34] and significantly decreased deaths from breast cancer.[34]

In response to the initial reports from the WHI trial,[3] a substantial drop in menopausal hormone therapy, particularly in combined hormone therapy, occurred in the United States and many countries.[35,36] This change was temporarily associated with a sharp decrease in breast cancer incidence in the United States, which was attributed to the decrease in menopausal hormone therapy[37,38] and was subsequently supported by observations from other countries.[36] The feasibility of a rapid decrease in breast cancer occurring shortly after cessation of hormone therapy was supported by findings from the WHI trial, where participants were informed to stop study medications on the day the main trial findings were announced.[39] As menopausal hormone therapy is still commonly used throughout the world, change in use of estrogen plus progestin as well as estrogen alone could be expected to impact on breast cancer incidence in opposite ways.

Aromatase inhibitor breast cancer prevention trials

Two full-scale clinical trials have compared aromatase inhibitors with placebo in primary breast cancer prevention settings. In the Mammary Protocol 3 (MAP.3) trial,[40] postmenopausal women, 35 years of age or older, were eligible based on age alone (≥60 years of age) and nearly half were entered on this basis. Also eligible were postmenopausal women at an increased risk of breast cancer.

A total of 4560 women at a median age of 62.5 years were randomized to 25 mg of exemestane plus placebo, 25 mg of exemestane plus celecoxib, or placebo plus placebo for a planned 5-year intervention. Early in the trial, the celecoxib arm was discontinued because of cardiovascular concerns.[41]

The sample size was based on an anticipated 65% reduction in breast cancer incidence with exemestane. At the final analysis, 43 invasive breast cancers were diagnosed (annual incidence, 0.19% vs. 0.55; HR, 0.35, favoring exemestane; 95% CI, 0.18–0.70, $P = 0.002$ by stratified log test). While numbers in the subgroups are limited, a positive exemestane effect was seen in estrogen-response-positive cancers (HR, 0.27; 95% CI, 0.12–0.60, $P < 0.001$) but not estrogen-receptor-negative cancers (HR, 0.80; 95% CI, 0.21–2.98; nonsignificant).[40]

Side effects were as expected for an aromatase inhibitor that reduces estrogen levels. However, the frequency of severe side effects was lower than that reported in adjuvant trials. For example, grade 2 or grade 3 joint pain was reported in 7% of the exemestane group but also in 5% of the placebo group. Hot flashes and fatigue were more common in the exemestane group. Importantly, no differences in clinical fractures, cardiovascular events, or other malignancies were seen between the groups.[40] The quality of life did not appear to be negatively altered by exemestane.[42] While the treatment period was relatively short, in an adjuvant setting, aromatase-inhibitor therapy was associated with continued reductions in contralateral breast cancer incidence even after the aromatase inhibitor was discontinued.[43]

In the International Breast Cancer Intervention Study II (IBIS-II), the aromatase inhibitor, anastrozole, was compared with placebo for the effect on breast cancer in a primary prevention setting. This multicenter trial randomized 3864 postmenopausal women at increased breast cancer risk to daily oral anastrozole (1 mg) or matching placebo for 5 years. The sample size was based on an anticipated 50% reduction in breast cancer incidence.[44]

After median 5-year follow-up, there were significantly fewer total invasive breast cancers in the anastrozole compared with the placebo group (32 vs. 64 cases; HR, 0.50; 95% CI, 0.32–0.76; $P = 0.001$), and fewer estrogen-receptor-positive cancers (HR, 0.42; 95% CI, 0.25–0.71; $P = 0.001$) and fewer ductal carcinomas in situ (HR, 0.30; 95% CI 0.12–0.74; $P = 0.009$) but not fewer receptor-negative cancers (HR, 0.78; 95% CI 0.35–1.72, nonsignificant). Again, the side effect profile was as expected for an aromatase inhibitor that lowers estrogen levels. While musculoskeletal adverse events were common in the anastrozole group, they were mostly of moderate severity. Vasomotor symptoms were commonly seen in both groups but the incidence was higher in women on anastrozole. No increases in fractures, myocardial infarction, or cardiac failure were seen between the groups. Of note, there were significantly fewer other cancers diagnosed in the anastrozole group including skin cancers and colorectal cancers (overall risk ratio, 0.53; 95% CI, 0.28–0.99).[44]

The MAP.3 and IBIS-II placebo-controlled aromatase inhibitor chemoprevention trials provide new insight regarding the side effect profile of these agents. In the adjuvant therapy setting, where aromatase inhibitors were commonly compared with tamoxifen or placebo, a greater number of fractures was seen with aromatase inhibitor use.[45] These studies were initiated several decades ago where there was limited understanding of bone health. Subsequently, the benefit of bone mineral density (BMD) monitoring and use of therapies such as bisphosphonates to increase BMD have been proved effective in reducing fracture incidence in clinical trial settings and have been incorporated in routine clinical practice. Both the MAP.3 and IBIS-II prevention trials were initiated when bone health maintenance

strategies were integrated into routine clinical practice. While neither study mandated monitoring of BMD or use of bisphosphonate therapy, bisphosphonates were used to some degree (16%–24% of the participants), initiated largely by primary physicians. As a result, neither trial identified an increased fracture incidence with aromatase inhibitor use.[40,44] Thus, aromatase inhibitor use for chemoprevention would not be expected to increase fractures in a population of women receiving current medical management.

In these aromatase inhibitor trials, many expected side effects associated with estrogen deprivation were, in fact, only modestly increased compared with placebo. For example, in IBIS-II, joint stiffness was reported in 7% of the anastrozole group and 5% of the placebo group. In MAP.3, grade 2 or 3 musculoskeletal/arthritis complaints were seen in 6.4% of the exemestane group and 4.4% of the placebo group participants. Of interest, early discontinuation of protocol treatments for "toxic effects" in MAP.3 was reported by 15.4% of the participants in the exemestane group but also by 10.8% of the women receiving placebo. In neither MAP.3 nor IBIS-II was an increase in cardiovascular events seen in the aromatase inhibitor groups.[40,44] Thus, the side effect profile of aromatase inhibitors is quite favorable for use in breast cancer prevention.

In summary, as no trial has directly compared aromatase inhibitors with SERMs for breast cancer prevention, comparisons are based on inferences across trials. Compared with placebo, aromatase inhibitor appeared to reduce breast cancer incidence to a greater degree than tamoxifen or raloxifene. In addition, in the aromatase inhibitor trials, there was no suggestion of an increase in estrogen receptor negative breast cancers. Taken together with consideration of the side effect profile, an aromatase inhibitor should generally be favored for chemoprevention in postmenopausal women. For premenopausal women at increased risk, tamoxifen, which has a relatively favorable side effect profile in younger women, is the only available intervention for breast cancer prevention.

Breast cancer chemoprevention: the near future

When we examine clinical trial experience with tamoxifen and the aromatase inhibitors, exemestane and anastrozole, a linear pattern emerges. As adjuvant therapy, tamoxifen reduces breast cancer recurrences and new contralateral breast cancers. In prevention trials, tamoxifen reduces breast cancer incidence. Similarly, aromatase inhibitors in adjuvant trials reduce breast cancer recurrence and new contralateral breast cancers. In prevention trials, aromatase inhibitors reduce breast cancer incidence. Given that the effect of relating short-term chemoprevention regimens is almost exclusively on established preclinical cancer, such linear relationships are not surprising. Therefore, a hypothesis can be posed that any agent that can reduce breast cancer recurrence and reduce contralateral cancers in adjuvant trials will also be an effective chemoprevention agent given a favorable side effect profile.

An agent which could benefit from such concept is metformin. Metformin has been used for decades as therapy for diabetes and glucose intolerance and has an acceptable and well-established safety profile.[46,47] Currently, an adjuvant breast cancer trial has randomized over 2500 early-stage breast cancer patients to receive conventional cancer management incorporating surgery, and as-needed radiation therapy, chemotherapy, and hormonal therapy with a randomization to 5 years of metformin or placebo.[46] If, in this trial, metformin reduces breast cancer recurrence and new contralateral breast cancers, it could well be considered an additional chemoprevention agent.

Therapeutic advances in breast cancer therapy are now creating economic "side effects" that may impact chemoprevention interest. As an example, studies incorporating pertuzumab, a novel anti-HER2 antibody, have demonstrated improved outcome for breast cancer patients with advanced disease.[48] More recently, improved pathological complete responses have been seen with pertuzumab addition to neoadjuvant therapy,[49] leading to a Federal Drug Administration approval for its use in this setting. As a result, a 6-cycle neoadjuvant regimen for a breast cancer patient with HER2-positive disease may cost upwards of $50,000. The AFFINITY adjuvant trial which has completed accrual includes a regimen pertuzumab given for a full year[50] at a cost of about $200,000. Against this background, in the MAP.3 primary prevention trial evaluating exemestane, an interesting signal has emerged. There were 6 HER2--positive cancers diagnosed in the placebo group but no HER2-positive cancers diagnosed in the exemestane group.[40] The potential to reduce the risk of some cancers where their diagnosis entails substantial cost could potentially increase future interest in chemoprevention strategies.

Attempts to improve the ability to reliably identify individual women at increased breast cancer risk have included assessment of breast mammogram density and search for additional genetic risk factors through the Genome Wide Association Studies with arguably no or only modest improvement to date.[51,52] However, despite the increasingly recognized complexity of the mechanisms driving breast cancer growth,[53] it is remarkable that a single intervention, namely, reduction in estrogen levels using aromatase inhibitors, can reduce breast cancer incidence by 50% to 65%.[40,44]

Thus, despite great diversity and complexity among individual breast cancers, relatively straightforward interventions can prove effective. While issues of toxicity remain, we have signals from clinical trials in advanced, hormone--receptor-positive breast cancer that over 50% improvement over that achieved with aromatase inhibitors can be seen with new oral agent targeting additional pathways driving breast cancer growth.[48,54-56] While the currently identified

agents have more toxicity than would be acceptable in a prevention setting, such findings provide optimism for the future. At present, there are effective agents for use in today's clinical practice.

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ARTYKUŁ POGLĄDOWY

Współczesne koncepcje – chemoprewencja raka piersi

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STRESZCZENIE

Rak piersi jest najczęstszym nowotworem u kobiet w krajach zachodnich, ale niektóre interwencje pozwalają na zmniejszenie ryzyka jego występowania. Celem pracy jest przegląd dostępnych dowodów naukowych pochodzących z badań klinicznych z zastosowaniem chemoprewencji raka piersi. Przeprowadzono systematyczny przegląd piśmiennictwa w celu znalezienia prowadzonych na pełną skalę prospektywnych badań klinicznych z randomizacją, dotyczących chemoprewencji raka piersi oraz badań klinicznych z randomizacją przeprowadzonych w podobny sposób, w których pierwszorzędowym punktem końcowym był rak piersi. W prowadzonych na pełną skalę badaniach klinicznych z randomizacją dotyczących chemoprewencji, wybiórcze modulatory receptora estrogenowego (*selective estrogen receptor modulator* – SERM), tamoksyfen i raloksyfen, zmniejszały częstość występowania raka piersi. Bezpośrednie porównanie obu leków wykazało, że tamoksyfen zmniejszał ryzyko raka piersi w większym stopniu niż raloksyfen, ale zwiększał ryzyko raka endometrium. W badaniach nad zapobieganiem rakowi piersi inhibitory aromatazy, eksemestan i anastrozol, także zmniejszają częstość jego występowania. W badaniach klinicznych prowadzonych przez Women's Health Initiative z zastosowaniem terapii hormonalnej u kobiet w okresie po menopauzie bez wcześniejszej histerektomii wykazano, że skojarzenie estrogenu z progestynami zwiększało częstość występowania raka piersi oraz liczbę zgonów z powodu raka piersi, podczas gdy sam estrogen zmniejszał zarówno częstość występowania raka piersi, jak i liczbę zgonów z powodu tego nowotworu u kobiet po histerektomii. U kobiet przed menopauzą ze zwiększonym ryzykiem raka piersi tamoksyfen ma potwierdzoną wartość terapeutyczną, przy korzystnym profilu działań niepożądanych. Bezpośrednie porównania SERM i inhibitorów aromatazy w chemoprewencji u kobiet po menopauzie nie są dostępne, jednak porównanie między badaniami sugeruje większą skuteczność i korzystniejszy profil działań niepożądanych inhibitorów aromatazy, szczególnie u starszych kobiet. W ocenie równowagi ryzyka i korzyści, w trakcie wyboru sposobu leczenia objawów związanych z menopauzą należy uwzględnić odwrotne działanie skojarzenia estrogenu z progestynami i samego estrogenu na częstość występowania raka piersi i liczbę zgonów.

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