Chemoprevention for Breast Cancer

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Rurina Watanuki, Aiko Nagayama, Tetsu Hayashida, and Yuko Kitagawa

Abstract

Cancer chemoprevention is defined as the use of natural, synthetic, or biochemical agents to reverse, suppress, or prevent carcinogenic processes in neoplastic diseases. Although the precise mechanisms that promote breast cancer are not fully understood, several recent clinical trials suggest that chemoprevention is a rational and attractive strategy for selected high-risk populations in a prophylactic setting. Conventionally, endocrine interventions using selective estrogen receptor modulators and aromatase inhibitors have already been applied clinically in high-risk populations. In particular, the chemoprevention approach for *BRCA* germline mutation carriers is drawing attention as an alternative option to invasive prophylactic mastectomy. Although the evidence from prospective clinical studies was limited, this review aims to provide an up-to-date overview of the biological mechanisms and the efficacy of various chemopreventive agents, including new promising candidates that target *BRCA* deficiency, and discuss future challenges and prospects for breast cancer chemoprevention.

Keywords

Breast cancer · Chemoprevention · *BRCA* mutation carriers · Selective estrogen receptor modulators · Denosumab · Poly ADP-ribose polymerase (PARP) inhibitors

R. Watanuki · A. Nagayama · T. Hayashida (✉) · Y. Kitagawa
Department of Surgery, Keio University School of Medicine, Shinjuku, Tokyo, Japan
e-mail: rurina.w.629@keio.jp; anagayama@keio.jp; tetsu@keio.jp; kitagawa@a3.keio.jp

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9.1 Introduction

Given the increasing incidence and mortality of cancer worldwide as well as the rising cost of medical treatment, there is a growing interest in developing strategies for disease prevention. One of the approaches with enormous potential is chemoprevention. In 1976, Sporn defined the term "chemoprevention" as the use of natural, synthetic, or biological agents to reverse, inhibit, or prevent either the initial phases of carcinogenesis or the progression of premalignant cells to invasive disease [1]. The process of breast carcinogenesis begins with the accumulation of an unspecified number of genetic events, followed by the emergence of progressive dysplastic cells with genotypic and phenotypic alterations that lead to deregulated cell growth. Chemoprevention aims to reduce the incidence of disease by arresting or modifying these mechanisms.

Those at increased risk for developing breast cancer could benefit from preventive therapy, as it is the most prevalent malignancy in women. The risk factors for breast cancer are described in various available risk calculation models, including the Tyrer-Cuzick and Gail models, to provide a numeric risk that can be used to help quantify the level of individual risk. Other individual risk factors for the selection of candidates for preventive therapy include the presence of premalignant diseases, such as lobular carcinoma in situ (LCIS), atypical ductal hyperplasia (ADH), and atypical lobular hyperplasia (ALH); high mammographic density; use of hormone replacement therapy; and presence of either high-risk penetrant genes, including *BRCA1/BRCA2* mutation carriers or less penetrant genes, but higher-frequency polygenic risk score SNPs [2, 3]. The National Comprehensive Cancer Network (NCCN) guidelines and the United States Preventive Services Task Force (USPSTF) have stated and recommended the use of breast cancer risk-reducing agents in high-risk populations. However, there is insufficient evidence showing the efficacy of chemopreventive agents in women who are carriers of pathogenetic *BRCA1/BRCA2* mutations. Hence, herein, we reviewed the current risk-reducing agents for breast cancer and pathogenetic *BRCA1/BRCA2* mutation carriers suitable for chemopreventive therapy.

9.2 Chemopreventive Drugs for Breast Cancer

9.2.1 Selective Estrogen Receptor Modulators

Hormones play a significant role in almost 70% of breast cancer cases [4], and current chemopreventive strategies have targeted hormonally responsive breast cancers. The two major classes of antiestrogenic drugs, selective estrogen receptor modulators (SERMs) and aromatase inhibitors (AIs), have been recently used for breast cancer prevention. A list of prospective trials regarding the use of SERMs and AIs as primary preventive treatments for breast cancer is provided in Table 9.1 [5–14].

Estrogen is the main factor that stimulates the development and growth of breast cancer. Deprivation of estrogenic signaling has been the primary form of hormonal

Table 9.1 Prospective trials for the primary prevention of breast cancer using selective estrogen receptor modulators and aromatase inhibitors

Trial	Study design	Participants	Interventions	End point	Major results
Royal Marsden trial [5]	Placebo-controlled, double-blind, randomized trial (n = 2,471)	• High-risk women • Family history of breast cancer • Age: 30–70 years	TAM 20 mg/day vs. placebo (for 8 years)	• Occurrence of invasive breast cancer • Occurrence of ER-positive invasive breast cancer	• Median follow-up: 13 years • Invasive breast cancer HR: 0.78, 95% CI: 0.58–1.04, P = 0.1 • ER-positive invasive breast cancer HR:0.61, 95% CI: 0.43–0.86, P = 0.05
NSABP-P1 trial [6]	Placebo-controlled, double-blind, randomized trial (unblinded after 5 years) (n = 13,388)	• High-risk women • Age: ≥60 years • Age: 35–59 years with a Gail model 5-year breast cancer risk of ≥1.66% • Age 35–59 years with a history of LCIS	TAM 20 mg/day vs. placebo (for 5 years)	• Cumulative rate of invasive breast cancer • Cumulative rate of noninvasive breast cancer	• Median follow-up 7 years • Invasive breast cancer RR: 0.57, 95% CI: 0.46–0.70, P < 0.001 • Noninvasive breast cancer RR: 0.63, 95% CI: 0.45–0.89, P < 0.008
IBIS-1 trial [7]	Placebo-controlled, double-blind, randomized trial (n = 7,154)	• High-risk women • Age: 35–70 years • ≥2-fold relative risk of breast cancer	TAM 20 mg/day vs. placebo (for 5 years)	• Incidence of breast cancer including DCIS • Side effects	• Median follow-up: 8 years • All breast cancer RR: 0.73, 95% CI: 0.58–0.91, P = 0.004 • The risk-reducing effect persisted for at least 10 years • Most side effects do not continue after a 5-year treatment period
Italian trial [8]	Placebo-controlled, double-blind, randomized trial (n = 5,408)	• Normal-risk women • Age: 35–70 years • Total hysterectomy	TAM 20 mg/day vs. placebo (for 5 years)	• Incidence of breast cancer including DCIS • Side effects	• Median follow-up: 11 years • The incidence rates of breast cancer were similar in both groups of women with low risk • Much lower in the tamoxifen group among women at high risk

(continued)

Table 9.1 (continued)

Trial	Study design	Participants	Interventions	End point	Major results
MORE trial [9]	Placebo-controlled, double-blind, randomized trial (n = 7,705)	• Postmenopausal women with osteoporosis (aged up to 80 years)	RAL 60 mg/day or 120 mg/day vs. placebo (for 4 years)	• Incidence of invasive breast cancer • Incidence of ER-positive breast cancer	• Median follow-up: 4 years • Invasive breast cancer 72% risk reduction with RAL (RR: 0.28, 95% CI: 0.17–0.46) • ER-positive breast cancer 84% risk reduction with RAL (RR = 0.16, 95% CI: 0.09–0.30)
CORE trial [10]	Placebo-controlled, double-blind trial (n = 4,011)	• Postmenopausal women with osteoporosis (aged up to 80 years)	RAL 60 mg/day or 120 mg/day vs. placebo (for 8 years)	• Incidence of invasive breast cancer • Incidence of ER-positive breast cancer	• Four-year incidence rates of invasive breast cancer 59% risk reduction with RAL (HR: 0.41, 95% CI: 0.24–0.71) • Four-year incidence rates of ER-positive breast cancer 66% risk reduction with RAL (HR: 0.34, 95% CI: 0.18–0.66) • Over the 8 years of MORE and CORE trial Invasive breast cancer: 66% risk reduction (HR = 0.34, 95% CI: 0.22–0.50) ER-positive breast cancer: 76% risk reduction (HR: 0.24, 95% CI: 0.15–0.40)
RUTH trial [11]	Placebo-controlled, double-blind, randomized trial (n = 10,101)	• Postmenopausal women (≥55 years old) with CHD or multiple risk factors for CHD	RAL 60 mg/day vs. placebo (for 5 years)	• Incidence of coronary events • Incidence of invasive breast cancer	• Median follow-up: 5.6 years • RAL had no significant effect on the risk of primary coronary events (HR: 0.95, 95% CI: 0.84–1.07) • RAL reduced the risk of invasive breast cancer (HR: 0.56, 95% CI: 0.38–0.83)

STAR trial [12]	Double-blind, randomized trial (n = 19,747)	• Postmenopausal women (≥35 years old) • 5-year risk of breast cancer ≥1.66%	RAL 60 mg vs. TAM 20 mg (for 5 years)	• Incidence of invasive breast cancer • Incidence of noninvasive breast cancer • Toxicity	• Median follow-up: 6.8 years • Invasive breast cancer RR (RAL: TAM): 1.24, 95% CI: 1.05–1.47 • Noninvasive breast cancer RR (RAL: TAM): 1.22, 95% CI: 0.95–1.59 • RAL is far less toxicity (highly significantly less endometrial cancer)
MAP.III trial [13]	Placebo-controlled, double-blind, randomized trial (n = 4,560)	• Postmenopausal women (≥35 years old) • Gail 5-year risk of breast cancer ≥1.66%	EXE 25 mg/day vs. placebo (for 5 years)	• Incidence of invasive breast cancer • Toxicity	• Median follow-up: 3 years • Invasive breast cancer: 65% risk reduction with EXE (HR: 0.35, 95% CI: 0.18–0.70, P = 0.002) • EXE was associated with no serious toxic effects
IBIS-II trial [14]	Placebo-controlled, double-blind, randomized trial (n = 3,864)	• Postmenopausal women • Age: 40–70 years • High risk of breast cancer	ANA 1 mg/day vs. placebo (for 5 years)	• Incidence of all breast cancer • Incidence of invasive breast cancer	• Median follow-up: 5 years • All breast cancer HR: 0.47, 95% CI: 0.32–0.68, $P < 0.0001$ • Invasive breast cancer HR: 0.50, 95% CI: 0.32–0.76, P = 0.001

TAM tamoxifen, *ER* estrogen receptor, *HR* hazard ratio, *CI* confidence interval, *LCIS* lobular carcinoma in situ, *RR* risk ratio, *DCIS* ductal carcinoma in situ, *RAL* raloxifene, *CHD* coronary heart disease, *EXE* exemestane, *ANA* anastrozole

therapy for patients with estrogen receptor (ER)-positive and/or progesterone (PgR)-positive disease. Over the past three decades, tamoxifen, a type of SERM, is an antiestrogen drug that inhibits the binding of estrogen to its receptors and has become the mainstay of hormone therapy [15]. Figure 9.1 illustrates the mechanism of estrogen deprivation [15].

Four large historical studies [5–8] evaluating the efficacy of tamoxifen as a primary chemopreventive drug have been conducted, and long-term follow-up data are available. An integrated analysis of tamoxifen primary prevention trials, including these studies, showed a 38% (95% confidence interval [CI] = 28–46; $P < 0.0001$) reduction in breast cancer incidence [16]. However, this drug was not effective in patients with ER-negative breast cancers (hazard ratio [HR] = 1.22, 95% CI = 0.89–1.67; $P = 0.21$); nonetheless, tamoxifen prevention trials reported that the incidence of ER-positive cancers decreased by 48% (95% CI = 36–58; $P < 0{\cdot}0001$) [16]. The data from these studies, particularly the National Surgical Adjuvant Breast and Bowel Project (NSABP) Breast Cancer Prevention trial (P-1 trial), led to the US Food and Drug Administration (FDA) approval of tamoxifen in 1998 for breast cancer risk reduction in high-risk women. A large-scale study on tamoxifen and raloxifene (STAR) trial, which directly compared tamoxifen with raloxifene, found that tamoxifen was more effective in reducing the breast cancer risk than raloxifene after a long-term follow-up [17]. Data from the STAR trial and the other raloxifene/placebo trial (MORE-CORE and RUTH) resulted in the approval of raloxifene by the US FDA for risk reduction of invasive breast cancer in postmenopausal women

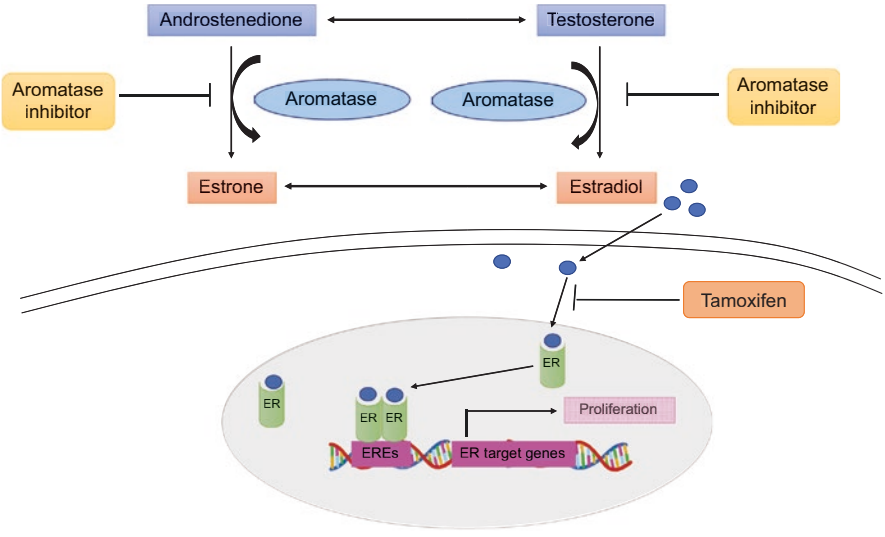

Fig. 9.1 Mechanism of estrogen deprivation by tamoxifen and aromatase inhibitor
Estradiol binds to estrogen receptors (ERs), causing receptor dimerization and subsequent binding to estrogen-responsive elements upstream of estrogen-responsive genes, including genes involved in proliferation. Tamoxifen competes with estradiol for binding to the ER, and aromatase inhibitors decrease the synthesis of estrogen from androgen precursors

with osteoporosis as well as for risk reduction of invasive breast cancer in postmenopausal women at high risk of invasive breast cancer. Cuzick et al. performed a meta-analysis using individual data from nine randomized double-blind trials comparing the efficacy of four SERMs with placebo or another drug in women with no history of breast cancer. They showed a 38% reduction in the overall breast cancer incidence, including that of ductal carcinoma in situ (DCIS) [18]. Interestingly, the impact of reduction was larger in the first 5 years of follow-up than in the 5–10 years of follow-up (42% vs. 25%). Treatment with all types of SERMs increased the incidence of venous thromboembolic events, whereas treatment with tamoxifen alone resulted in an increase in the incidence of endometrial cancers. Despite a 10–20% reduction in LDL cholesterol after treatment with SERMs, no reduction in cardiovascular disease was noted. Moreover, a significant reduction of 34% in the incidence of vertebral fractures was reported in this analysis.

Only a subgroup analysis of the NSABP P-1trial evaluated the effect of tamoxifen on breast cancer risk in women with *BRCA1/BRCA2* pathogenic variants [19]. Tamoxifen reduced the breast cancer risk by 62% in *BRCA2* carriers (relative risk [RR]: 0.38, 95% CI: 0.06–1.56), but not in *BRCA1* carriers (RR: 1.67, 95% CI: 0.32–10.07). However, this analysis is limited by the small number of participants carrying pathogenic variants; among 288 women with breast cancer, only 8 had *BRCA1* pathogenic variants and 11 had *BRCA2* pathogenic variants. To date, no primary prevention trials using tamoxifen or raloxifene have been conducted among women with *BRCA1/BRCA2* mutations. Although not validated as a chemopreventive agent for primary breast cancer in *BRCA1/BRCA2* mutation carriers, tamoxifen prevents contralateral breast cancer by up to 50% [20–22]. In a recent meta-analysis, tamoxifen was significantly associated with a reduced risk of contralateral breast cancer among *BRCA1/BRCA2* mutation carriers (summary RR, 0.56; 95% CI, 0.41–0.76) [23]. Similar findings were observed in *BRCA1* mutation carriers (summary RR, 0.47; 95% CI, 0.37–0.60) and *BRCA2* mutation carriers (summary RR, 0.39; 95% CI, 0.28–0.54), respectively [23]. Gronwald et al. demonstrated that the use of tamoxifen for 1 year was associated with a 63% reduction in the risk of contralateral breast cancer (95% CI, 0.37–0.75; $P = 0.003$) [22]. They suggested that short-term use of tamoxifen for chemoprevention in *BRCA1/BRCA2* mutation carriers may be as effective as a conventional 5-year course of treatment.

Previous data suggest a role for tamoxifen in estrogen receptor blockade and the prevention of contralateral breast cancer, even among *BRCA1* mutation carriers who have a tendency to develop hormone receptor-negative disease. Although the underlying mechanisms mediating the protective role of tamoxifen in contralateral breast cancer remain unclear, a reduction in mammary cell proliferation [24], the number of mammary stem cells, and mammographic density [25] have been proposed. Premenopausal carriers of *BRCA1/BRCA2* mutations usually exhibit higher titers of estradiol and progesterone [26], which is one of the reasons for developing cancer prevention strategies in premenopausal women.

De Censi et al. conducted a multicenter randomized phase III trial evaluating the effectiveness of 5 mg/day tamoxifen or placebo administered for 3 years in women with breast intraepithelial neoplasia, including those with ADH, DCIS, and LCIS

[27]. Low-dose tamoxifen reduced the risk of breast cancer development by 52%, and the incidence of side effects in the tamoxifen arm was not higher than that in the placebo arm [27]. This study indicated that low-dose tamoxifen may be an effective chemopreventive method with good tolerability.

9.2.2 Aromatase Inhibitors

In premenopausal women, aromatase and estrogen are produced by the granulosa cells in the functional ovaries and are also present in other normal tissues, including the mesenchymal cells of subcutaneous fat, breast, and bone [15, 28]. After menopause, estrogen is no longer produced in the ovaries, but aromatase activity and production of estrogen persists in all the other sites [15].

Tamoxifen competes with estradiol for ER binding, whereas AIs reduce the synthesis of estrogens from androgenic precursors (Fig. 9.1). A significant association exists between breast cancer risk and plasma levels of the common circulating estrogens in postmenopausal women [29], and AIs achieve almost complete inhibition of aromatase in vivo and suppression of plasma estrogen levels. The significant reduction in contralateral breast cancer in adjuvant AI clinical trials [30] has led to the increased interest in the use of these agents for primary prevention, especially due to the less incidence of toxicities, such as thrombotic events and endometrial cancer compared with SERMs. Two landmark studies were conducted to evaluate the efficacy of AI for the primary prevention of breast cancer (Table 9.1).

In the National Cancer Institute of Canada Mammary Prevention 3 (MAP.3) trial, after 35 months of follow-up, treatment with exemestane reduced the breast cancer risk by 65% in high-risk postmenopausal women [13]. Similarly, the European IBIS-II trial reported a 53% reduction in the breast cancer risk in women at increased risk of breast cancer after treatment with anastrozole [14]. Neither exemestane nor anastrozole was associated with an increased risk of thromboembolic or cardiovascular events or other cancer types. The MAP.3 trial showed that short-term use of exemestane exacerbated the age-related bone loss despite calcium and vitamin D supplementation, but long-term follow-up is needed to assess its impact on the risk of fracture in the prevention population [31]. The side effects of exemestane, including vasomotor, sexual, and musculoskeletal symptoms, had limited impact on patients' quality of life [32]. In addition to vasomotor symptoms, musculoskeletal events were more common in the anastrozole arm [14]. In the NCCN guidelines and the USPSTF, AI is recommended as a risk-reducing agent for breast cancer. However, it remains unclear whether SERMs or AIs are preferred agents for the prevention of breast cancer because of the absence of head-to-head comparisons and differences in patient characteristics between studies.

Retrospective data suggested that AIs could reduce the risk of ER-positive contralateral breast cancer in *BRCA1/BRCA2* mutation carriers who are receiving AIs as adjuvant therapy [33]; however, data on the effectiveness of AIs as well as tamoxifen for primary prevention in *BRCA* mutation carriers are insufficient.

9.2.3 Denosumab

The receptor activator of nuclear factor κB (RANK), its cytokine ligand (RANKL), and the soluble receptor osteoprotegerin (OPG) form a functional triad in the tumor necrosis factor (TNF) and TNF receptor superfamily [34, 35]. RANK and RANKL are known for their involvement in bone metabolism [34]. The binding of RANKL to RANK on osteoclast precursors induces osteoclast maturation and activation, thereby promoting bone resorption, whereas the binding of RANKL by OPG inhibits its RANKL-mediated signaling pathways, resulting in the inhibition of bone resorption and maintenance of bone density (Fig. 9.2) [34, 36]. Denosumab, a human anti-RANKL monoclonal antibody, is approved for the treatment of osteoporosis and for the prevention of skeletal damage due to bone metastases in patients with breast cancer and other types of solid tumors [37]. Various experimental data have demonstrated that progesterone-mediated upregulation of RANK/RANKL may also play a critical role in mammary gland epithelial cell proliferation, mammary stem cell expansion, and carcinogenesis, particularly in *BRCA1* mutation carriers [38–42].

A precancerous *BRCA1*$^{mut/+}$ tissue harbors an aberrant population of luminal progenitor cells [43], and deregulated progesterone signaling has been implicated in *BRCA1*-associated oncogenesis [44–46]. Nolan et al. showed that a highly proliferative subset of luminal progenitor cells that gives rise to basal-like breast cancer, constitutively expresses RANK and is hyper-responsive to RANKL (Fig. 9.3) [47]. They proposed that this finding suggests an exciting opportunity for the precision

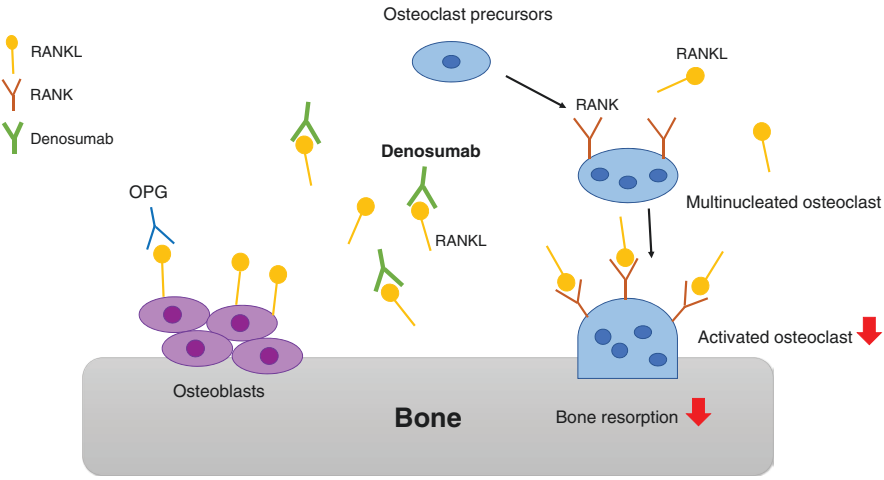

Fig. 9.2 Mechanism of action of denosumab
Binding of RANKL to RANK on osteoclast precursors induces osteoclast maturation and activation, thereby promoting bone resorption. Conversely, the binding of RANKL by osteoprotegerin inhibits the RANKL-mediated signaling pathway, thereby inhibiting bone resorption. Denosumab binds to RANKL and reduces osteoclasts by directly inhibiting the RANK-RANKL signaling pathway

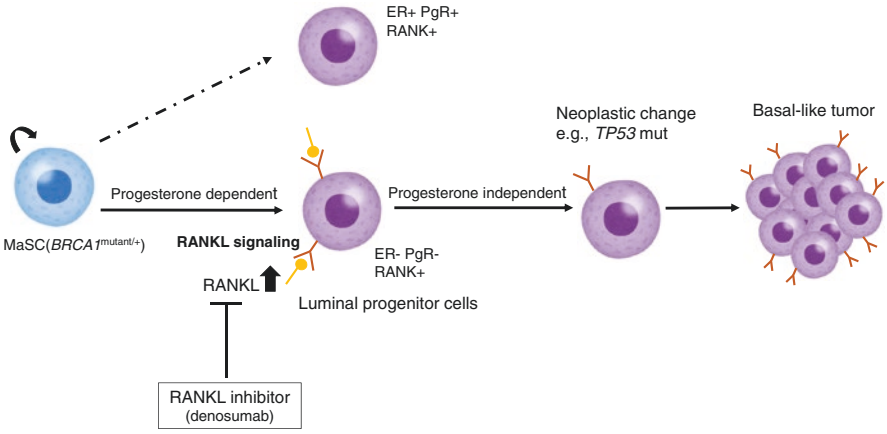

Fig. 9.3 Progression of *BRCA1*$^{mut/+}$ RANK+ luminal progenitor cells to basal-like tumors *BRCA1*$^{mut/+}$ RANK+ subset of mammary luminal progenitor cells give rise to basal-like tumors. Progesterone-dependent RANK signaling in luminal progenitor cells is responsive to RANKL inhibition. Denosumab abrogates progesterone-dependent signaling of RANK+ *BRCA1*$^{mut/+}$ luminal progenitor cells to prevent the progression to basal-like tumors. *MaSC* mammary stem cell, *ER* estrogen receptor, *PgR* progesterone receptor

cancer prevention in *BRCA1* mutation carriers [47, 48]. Important preclinical studies relevant to women with *BRCA1* mutations demonstrated that genetic or pharmacological inhibition of RANKL significantly suppressed mammary tumorigenesis in *BRCA1*-deficient mice [47, 49]. In *BRCA1*-deficient mice, the loss of RANKL reduced the progression of mammary tumors, and the inhibition of RANKL suppressed the development of mammary tumor [47]. Furthermore, the proliferation of mammary progenitor cells in *BRCA1*-mutant mice was suppressed by inhibiting RANK, supporting the paracrine activity of RANKL on RANK expression in ER-negative and PR-negative cells [50, 51]. Evidence from studies using human breast cells of *BRCA1* mutation carriers consistent with the data of animal trials supports the inhibition of the RANK pathway as a new target for prevention. Among the mammary progenitor cells of *BRCA1* mutation carriers, RANK-positive cells had significantly higher clonogenic potential than RANK-negative cells [47]. In a three-dimensional organoid model constructed using *BRCA1* mutant breast cancer cells, exposure to progesterone increased the expression of Ki67, but treatment with denosumab inhibited this progesterone-induced increased expression of Ki67 [47]. A pilot window study was conducted in three women within this research, and biopsies taken before and after denosumab treatment showed a significant decrease in Ki67 expression after treatment [47].

OPG is an endogenous decoy receptor of RANKL that antagonizes RANK/RANKL-mediated signaling [34]. Interestingly, women with *BRCA1* mutations may have inherently lower circulating OPG levels than those with baseline risk. Widschwendter et al. reported significantly lower free serum OPG levels among premenopausal *BRCA* mutation carriers compared with non-carrier controls

throughout the menstrual cycle [52]. In addition, the difference was more pronounced in *BRCA1* mutation carriers than in *BRCA2* mutation carriers. Oden et al. conducted a prospective study in 206 *BRCA* mutation carriers with an average follow-up period of 6.5 years [53]. They found a significant inverse relationship between circulating OPG levels and breast cancer risk among women with either a *BRCA1* or *BRCA2* mutation. Women with high plasma OPG levels had a significantly decreased risk of developing breast cancer compared with women with low OPG levels (HR: 0.25; 95% CI: 0.08–0.78; $P = 0.02$) [53]. These data suggest that OPG may be a promising biomarker to help identify women who are at a higher risk of developing breast cancer and who would be ideal candidates for RANKL-based chemopreventive therapy.

As a clinical trial, the ABCSG 18 study provided important results supporting that targeting the RANKL pathway improves the outcomes for breast cancer patients. In this prospective, double-blind, placebo-controlled phase III trial, 3420 postmenopausal breast cancer patients with early hormone receptor-positive disease were treated with an aromatase inhibitor and randomized to receive denosumab 60 mg or placebo biannually [54]. The study reported a reduction in clinical fractures in the denosumab group compared with the placebo group, with no additional toxicities [54]. Moreover, a follow-up analysis showed improved disease-free survival in women who received adjuvant denosumab with an acceptable safety profile [55]. Following the preclinical study that revealed the role of the progesterone/RANK/RANKL pathway in mammary carcinogenesis, which is thought to be particularly relevant in women with *BRCA1* mutations, a randomized, double-blind, placebo-controlled, multicenter, international phase III trial (BRCA-P trial) is now underway to determine the primary preventive effect of denosumab on breast cancer in healthy women with mutations in the *BRCA1* gene. Osteonecrosis of the jaw is one of the adverse events of denosumab treatment, although it is less frequent. In the ABCSG 18 trial, none of the participants reported osteonecrosis of the jaw. If the safety of denosumab can be demonstrated in the BRCA-P trial, in which denosumab is administered to healthy *BRCA1* mutation carriers, it could be used for RAKL-based chemoprevention, which represents a plausible, non-surgical prevention of breast cancer in *BRCA* mutation carriers.

9.2.4 Poly ADP-Ribose Polymerase Inhibitors

Poly ADP-ribose polymerases (PARPs) are a family of enzymes that play a key role in the repair of DNA damage [56]. In particular, PARP-1 and PARP-2 are the most important enzymes used in the treatment for *BRCA1* or *BRCA2* mutation carriers [57, 58]. An important role of PARP-1 and PARP-2 is to maintain genomic integrity, particularly through base excision repair of single-stranded DNA damage [59]. The inhibition of these enzymes leads to the accumulation of DNA single-strand breaks, which can result in the occurrence of DNA double-strand breaks at replication forks [60]. In *BRCA* mutant cells, the function of BRCA protein, which is required for homologous recombination repair against

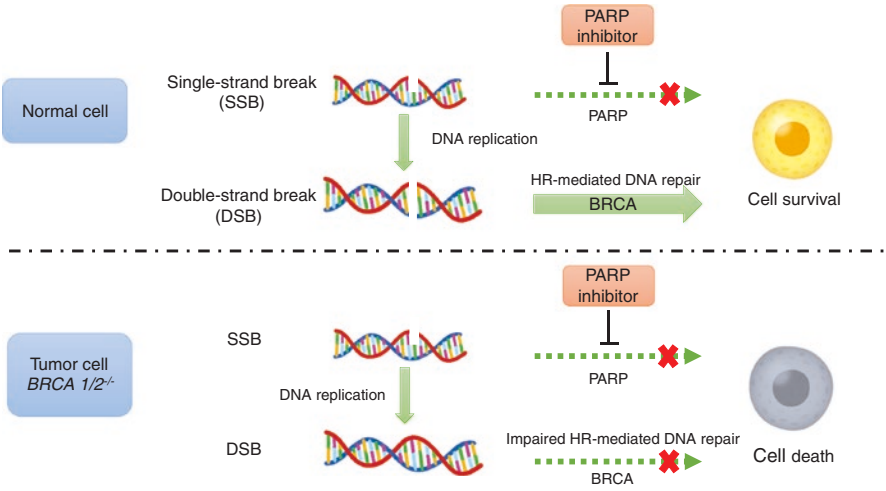

Fig. 9.4 Mechanism of synthetic lethality in *BRCA1/BRCA2*-deficient tumor cell
PARP inhibitors selectively induce cell death in *BRCA1/BRCA2*-deficient cells through the mechanism of synthetic lethality, where cancer cells cannot tolerate the loss of both single-strand break and double-strand break repair machinery. HR; homologous recombination

double-strand breaks, is lost. Therefore, when PARPs are inhibited in *BRCA* mutant cells, the DNA repair mechanism is disrupted and cell death is selectively induced (Fig. 9.4), resulting in an antitumor effect [61, 62]. The concept of synthetic lethality has paved the way for the development of PARP inhibitors for cancer patients with defects in homologous recombination repair, particularly those with *BRCA1* and *BRCA2* bi-allelic loss [63, 64]. This new strategy has led to major advances in the treatment of patients with ovarian cancer and, subsequently, in those with pancreatic, prostate, and breast cancers. Currently, there are two PARP inhibitors approved for treatment in HER2-negative metastatic breast cancer patients with *BRCA*1/*BRCA*2 mutations: olaparib and talazoparib. Both have demonstrated improvements in progression-free survival compared with chemotherapy, overall better tolerability, and low discontinuation rates documented in the trials that led to the approval of these agents [65, 66]. The results of the OlympiA trial, a double-blind, randomized controlled, phase III trial that aimed to evaluate the efficacy of olaparib as adjuvant therapy in patients with high-risk HER2-negative breast cancer and germline *BRCA* mutations, are underway.

Thus, PARP inhibitors have emerged as promising agents for the treatment of cancer patients with *BRCA* mutations via synthetic lethality, but their role in chemoprevention has not been elucidated. Although preclinical data showed that veliparib and olaparib are effective in delaying mammary tumor development and extending the lifespan of *BRCA1*-deficient mice [67], the possible long-term effect of PARP inhibitor treatment on normal tissues in a patient without any cancer or even a high-risk individual needs further clinical evaluation [68].

9.2.5 Nonsteroidal Anti-inflammatory Drugs

In experimental animal models, nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit tumor growth [69, 70]. Aspirin may influence the cancer risk primarily through its effect on the cyclooxygenase (COX) activity. Like other NSAIDs, aspirin inhibits the COX enzyme that converts arachidonic acid into prostaglandins [71]. Aspirin is presumed to have an effect on the tumor growth due to the inhibition of the cyclooxygenase-2 (COX-2) enzyme, which is associated with inflammation, apoptosis, cell migration, and angiogenesis [72]. Aspirin is also thought to be an effective antioxidant [71] and helpful in modulating estrogen biosynthesis [73].

Aspirin and NSAIDs are reported to be effective in preventing colon cancer [74, 75]. Epidemiological studies showed accumulating evidence regarding the cancer-preventive effects of these agents, and the long-term use of aspirin could also reduce the risk of breast cancer by approximately 14% [76, 77]. However, the efficacy of aspirin in the primary prevention of cancer remains controversial, because results from a large-scale, randomized control study suggested that alternate-day use of low-dose aspirin (100 mg) within a period of 10 years did not lower the risk of total, breast, colorectal, or other site-specific cancers [78]. Recently, a prospective study examined the association between regular NSAID use and breast cancer risk in a large cohort of women with a family history of breast cancer, including 1054 *BRCA1* or *BRCA2* mutation carriers [79]. This study found that regular use of aspirin and COX-2 inhibitors was associated with a reduced risk of breast cancer (39% and 61%, respectively) in women with either familial or genetic risk [79]. However, in a series of subgroup analyses, the strength of these associations did not differ by family risk profile or mutation status; although not nominally significant, negative associations were found for both *BRCA1* and *BRCA2* mutation carriers [79]. Similarly, the association was not modified by ER status [79].

The use of aspirin and other NSAIDs for primary breast cancer prevention can be an attractive strategy because they are inexpensive and widely available, but the benefits of NSAIDs need to be weighed against the potential harm of long-term use. Secondary prevention trials in women affected by breast cancer, such as the Aspirin for Breast Cancer (ABC) trial and the Add-Aspirin trial [80, 81], are ongoing and the results are awaited.

9.2.6 Retinoids

Retinoids have been studied as chemopreventive agents due to their role in regulating cell growth, differentiation, and apoptosis in preclinical models [82]. Fenretinide (N-(4-hydroxyphenyl) retinamide), a synthetic derivative of all-trans-retinoic acid, has been the most studied retinoid in clinical trials of breast cancer chemoprevention owing to its selective accumulation in breast tissue and its unique ability to inhibit cell growth proliferation through the induction of apoptosis rather than differentiation [83, 84]. A multicentric phase III randomized trial evaluating the efficacy of fenretinide was initiated in 1987. The participants were stage I breast cancer

patients aged 33–70 years who had undergone surgery for breast cancer within the previous 10 years. Women were randomly assigned to receive either no treatment or 200 mg/day of fenretinide orally for 5 years. The main outcome measure was the occurrence of contralateral breast cancer as the first malignant event. A statistically significant beneficial trend was observed in premenopausal women with contralateral and those with ipsilateral breast cancer (HR: 0.66 and HR: 0.65, respectively), compared with an opposite trend in postmenopausal women (contralateral breast cancer HR: 1.32; ipsilateral breast cancer HR: 1.19), when the analysis was stratified by menopausal status [85]. This result was confirmed after a 15-year follow-up. Fenretinide has demonstrated a favorable toxicological profile, which mainly includes reversible skin dryness and rashes and dark adaptation difficulties, often overcome by a regular 3-day/month suspension of the drug. However, teratogenicity remains a major issue, and contraception is required [86].

This agent has shown antitumor activity in ovarian cancer animal models [87]. In the phase III breast cancer prevention trial, the incidence of ovarian cancer during the 5-year intervention period was significantly lower in the fenretinide group (no cases vs. six in the control group) [85, 88], although no significant difference was shown in the long-term follow-up [89]. Moreover, fenretinide was highly effective in inhibiting the growth of *BRCA1* mutant breast cancer cell lines [90]. Considering the protective effect of fenretinide in young women with second breast cancer and a similar trend in ovarian cancer, it can be used for chemoprevention in women with *BRCA1* or *BRCA2* mutations [83].

9.3 Future Challenges

We reviewed the current candidate drugs for the chemoprevention of breast cancer. Among them, endocrine intervention is considered as the standard of care for breast cancer with relatively few side effects; thus, it is most likely considered as a starting point for chemoprevention in high-risk breast cancer populations. However, despite the recommendation of chemopreventive therapy for breast cancer in some guidelines, many women do not prefer to take chemopreventive agents, and chemoprevention strategies are not widely used in clinical practice. In terms of primary prevention for breast cancer, the most important consideration is the balance between adverse events and their effects. A recent retrospective study in the United States indicated that the use of chemoprevention among women at increased risk for breast cancer remains low, especially among those aged below 50 years, largely because of the fear of adverse events [91]. In particular, teratogenic drugs, such as tamoxifen, may not be a good option for young women of childbearing age who are well aware of the possibility of chemoprevention. Given the low chemoprevention uptake among high-risk populations, healthcare providers must be encouraged to provide appropriate counseling to women who are eligible for chemoprevention, which includes further education about the adverse effects and recruitment of women to participate in a trial regarding chemoprevention when appropriate [91].

Given the aforementioned limitations, chemoprevention options should be offered to women who have a significantly higher risk of breast cancer with germline *BRCA* mutations. This is because prophylactic mastectomy is still the gold standard risk reduction method for women with *BRCA* mutations, but it is an invasive procedure and requires psychological considerations because of its impact on cosmetic appearance. Therefore, further evidence regarding the specific chemoprevention options for these women should be obtained. A particularly promising approach is to focus on the differences in the mechanisms of carcinogenesis and phenotypes between *BRCA1*-deficient and *BRCA2*-deficient breast cancers, and to develop strategies for chemoprevention in *BRCA1* and *BRCA2* mutation carriers. Considering these differences, subtype-based approaches are expected, such as endocrine therapy for *BRCA2* mutation carriers and denosumab for *BRCA1* mutation carriers. In addition, PARP inhibitors may be suitable agents for both *BRCA1* and *BRA2* mutation carriers.

There is insufficient evidence to confer an optimal duration of administration in chemoprevention. However, the administration of chemopreventive treatment may require the suspension of prophylactic mastectomy, thus avoiding the potential harm from surgery in healthy women with *BRCA* mutations.

Although several steps must be overcome to ensure the feasibility of chemoprevention in the clinical setting, an individualized treatment using the recently developed molecularly targeted drugs will help improve the efficacy of chemopreventive strategies in both research and clinical settings. The development of rational, effective, and minimally toxic prophylactic drugs with the ability to modify carcinogenesis at an early stage is needed to improve the clinical outcome of chemoprevention.

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