Chemoprevention

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Andrea De Censi, Bernardo Bonanni,
and Massimiliano Cazzaniga

9.1 Introduction

In 1976, Sporn defined the term "chemoprevention" as the use of natural, synthetic, or biologic chemical agents to reverse, suppress, or prevent carcinogenic progression to invasive cancer [1].

Although the precise mechanisms promoting the development/progression of breast cancer are not completely established, the success of several clinical trials in preventive settings, mainly in selected high-risk populations, suggests that chemoprevention is a rational and an appealing strategy (Fig. 9.1).

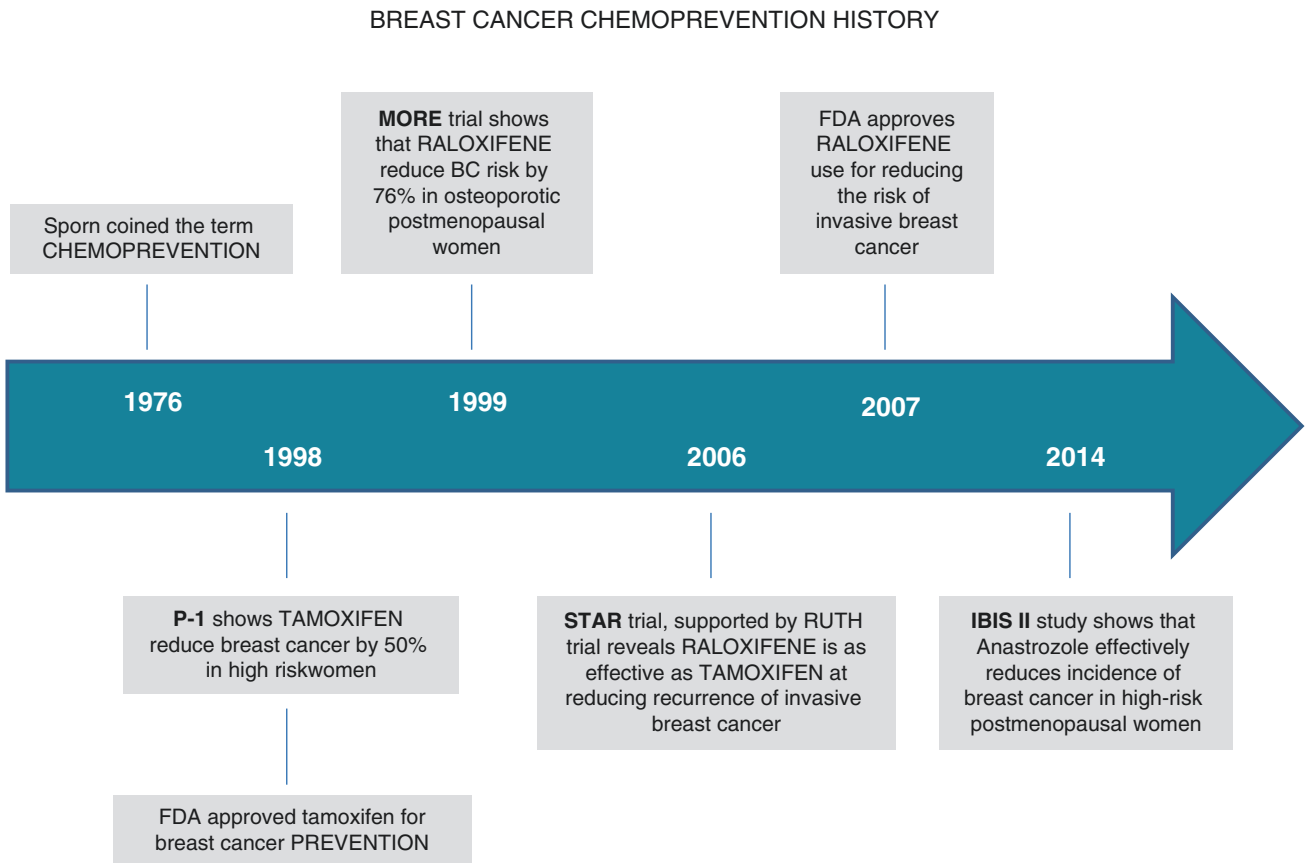

Fig. 9.1 Breast cancer chemoprevention history

A. De Censi (✉)
Division of Medical Oncology, EO. Ospedali Galliera,
16128 Genoa, Italy
e-mail: andrea.decensi@galliera.it

B. Bonanni • M. Cazzaniga
Division of Cancer Prevention and Genetics, European Institute of Oncology, 20141 Milan, Italy

U. Veronesi et al. (eds.), *Breast Cancer*, DOI 10.1007/978-3-319-48848-6_9

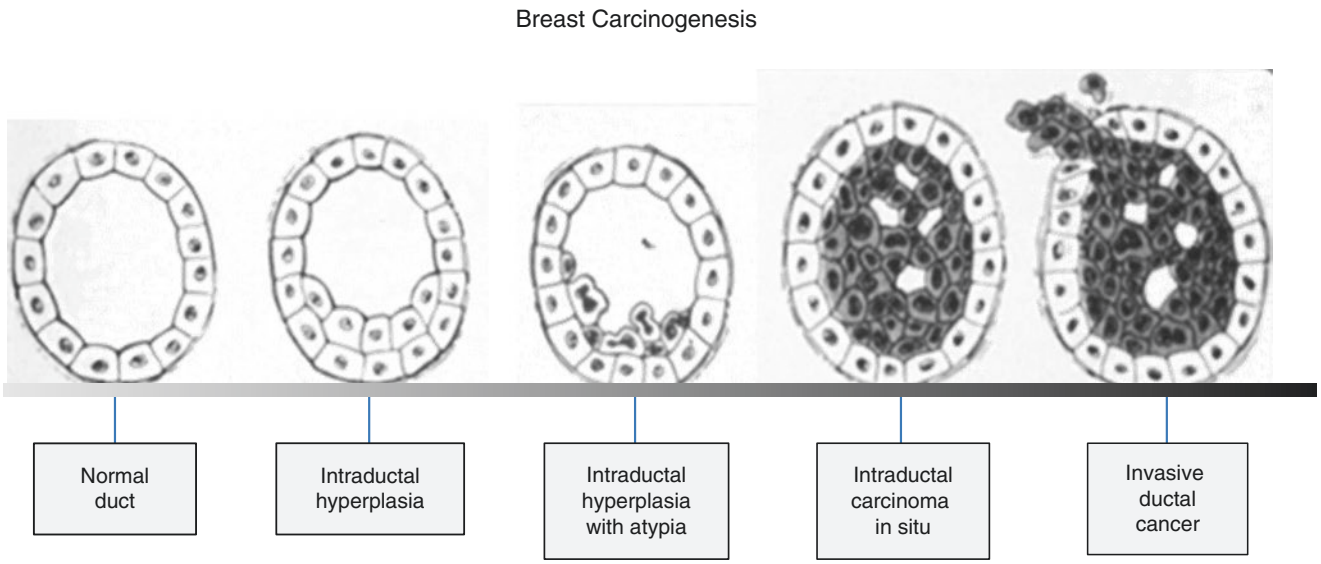

Fig. 9.2 Breast cancer carcinogenesis

Breast carcinogenesis is a multistep, multipath, and multiyear disease of progressive genetic and associated tissue damage. It spans the continuum from simple hyperplasia without atypical cells to intraepithelial neoplasia (IEN) and finally to invasive cancer (Fig. 9.2) [2].

In detail, the carcinogenetic process starts with unspecified accumulations of genetic events leading to a progressive dysplastic cellular appearance with genotypic and phenotypic alterations, deregulated cell growth, and finally cancer. Chemoprevention is just part of these mechanisms and works with the aim to arrest or modify them, thus resulting in a decrease in the incidence of the disease.

In the last few decades, following the therapeutic paradigm for the treatment of cardiovascular diseases that began to include a chemopreventive risk reduction approach [3], preventive therapy for several kinds of cancers, including breast cancer, is currently oriented toward the reduction of modifiable risk factors. The first task, of course, is to identify modifiable factors that would influence the development and progression of the disease in order to tailor prevention strategies on the basis of the individual risk. However, it is now accepted that therapeutic cancer prevention is an effective and essential tool in the fight against cancer, although the use of preventive therapy is sadly still inadequate.

Many subjects at increased risk for breast cancer could benefit from preventive therapy. Defining breast cancer risk incorporates knowledge of individual risk factors known to be associated with increased risk. These risk factors are included in various available risk calculation models, mainly Tyrer-Cuzick and Gail model, 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 are substantially the presence of premalignant disease (LCIS, ADH, ALH), the presence of mammographic density, and/or the use of HRT, the high-risk penetrant genes (BRCA mutation carriers) or the less penetrant but higher frequency polygenic risk score SNPs [4, 5].

9.2 Breast Cancer Chemoprevention

9.2.1 Prevention of ER-Positive BC

Although the precise mechanism causing breast cancer is not fully established, it is well known that hormones play a significant role in almost 70% of cases [6] 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 their activity in breast cancer prevention.

The SERM tamoxifen was proven extremely effective on recurrent and new contralateral tumors, hence showing a good toxicity profile in the treatment of hormone receptor-positive breast cancer [7]. Tamoxifen has therefore been an obvious candidate for assessment as a preventive agent.

Four historical large trials [8–11] on tamoxifen effectiveness were undertaken, and long-term follow-up data are available. An overview of these trials has shown a 43% reduction in estrogen receptor (ER)-positive invasive breast cancer, but no effect on ER-negative disease [12]. The data from these studies and, in particular, from NSABP P-1 trial led to the 1998 US Food and Drug Administration (FDA) approval of tamoxifen for reduction of breast cancer incidence in high-risk women.

Furthermore, the direct comparison of tamoxifen with raloxifene (a second-generation SERM) in the STAR trial showed that raloxifene is less effective than tamoxifen (mainly on in situ breast cancer), but with fewer side effects. The initial report from 2006 found raloxifene to be as effective as tamoxifen in preventing invasive breast cancer, but with fewer associated toxicities. In the recent update [13], raloxifene has retained approximately 81% of the effectiveness of tamoxifen in preventing invasive breast cancer and continued to grow closer to tamoxifen in preventing noninvasive breast cancer. Raloxifene has also maintained a better profile with respect to uterine disease, thromboembolic events, and death.

Data from the STAR trial and the other raloxifene/placebo trial (MORE-CORE and RUTH) resulted in the approval of this drug by the US FDA for a reduction in the risk of invasive breast cancer in postmenopausal women with osteoporosis as well as a reduction in the risk of invasive breast cancer in postmenopausal women at high risk of invasive breast cancer. Finally, another recent meta-analysis by Cuzick [14] of nine randomized double-blind trials comparing various SERMs with placebo or another drug on women without breast cancer showed a 38% reduction in breast cancer incidence overall, including ductal carcinoma in situ (Fig. 9.3). The reduction appears larger in the first 5 years of follow-up than in years 5–10. Authors reported a reduction in both year groups, though with a minor effect in the 5–10-year group. No evidence of heterogeneity was found between trials. Moreover, the analysis recorded a significant 34% reduction in vertebral fractures.

While all SERMs increased venous thromboembolic events, only tamoxifen showed a clear increase in endometrial cancers. The large amount of extended follow-up available for this analysis has provided a clear overview of the benefits and harms of these drugs.

The fear of incurring some adverse effects of this drug has hampered its uptake by women at increased risk, and a relative recent route of administration of tamoxifen seems to have solved the question. A simple and economic approach to retain tamoxifen efficacy while reducing the risks was to diminish its dose. The effects of these different doses on proliferation were analyzed using the Ki-67 expression, as the

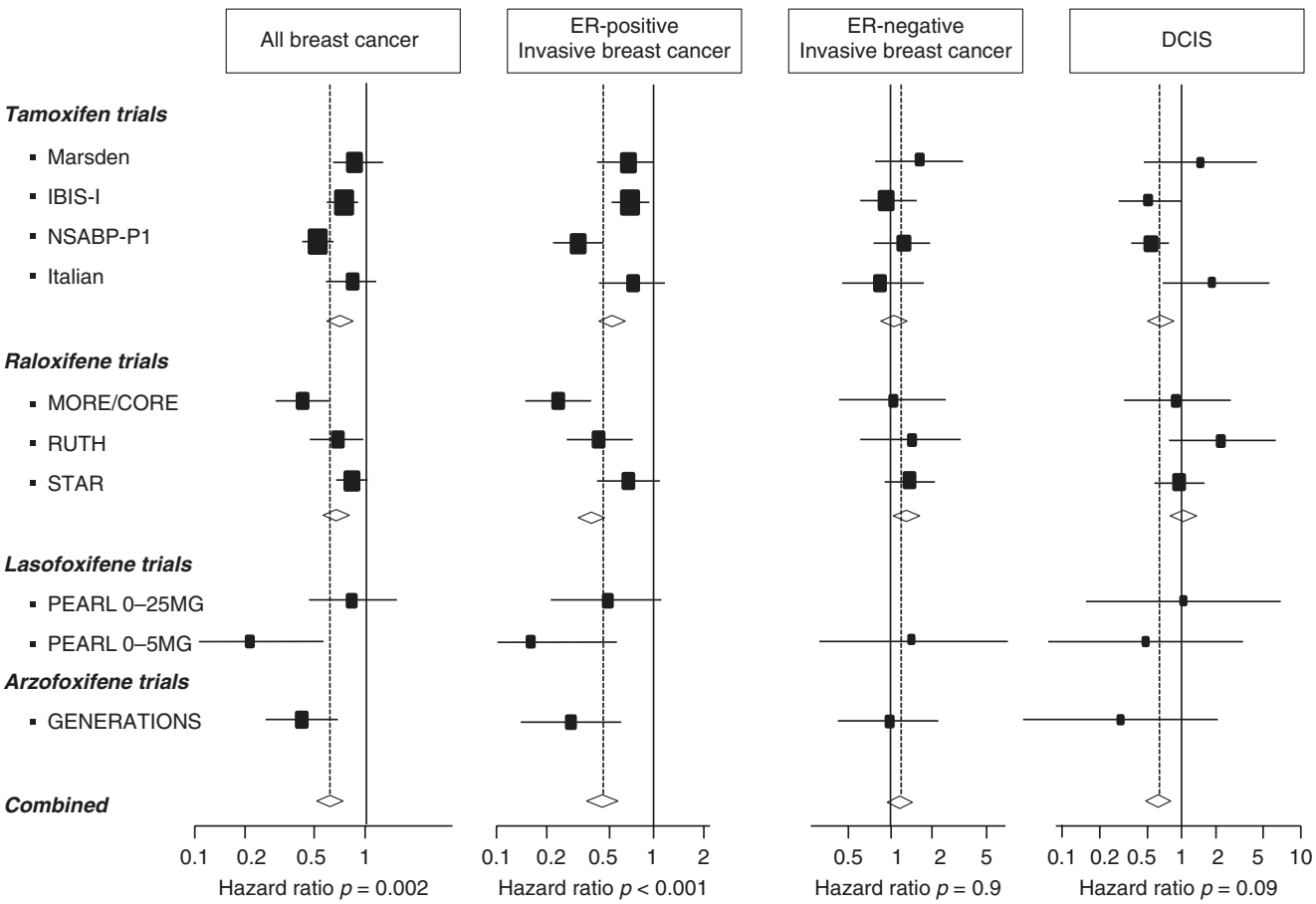

Fig. 9.3 SERMs efficacy in all breast cancer (invasive and in situ) in 10-year follow-up

main surrogate end point marker in several studies [15–18]. The change of the marker expression induced by lower doses of tamoxifen was confirmed to be comparable to that obtained with the standard dose.

Each of the three third-generation AIs used in adjuvant BC trials is effective in suppressing aromatase activity by 97–99% [19], thus achieving near-complete inhibition of aromatase in vivo as well as near-complete suppression of plasma estrogen levels. The significant reduction in contralateral BCs found in adjuvant AI clinical trials [20] has raised interest in these agents for primary prevention, in particular because they may be associated with a less adverse effect profile, specifically in thrombophilic events and endometrial cancer, compared with SERMs. There have been two landmark studies of AIs for BC primary prevention.

The National Cancer Institute of Canada Clinical Trials Group Mammary Prevention 3 (MAP.3) trial was an international prospective, randomized, placebo-controlled, double-blind study, designed to detect a 65% relative reduction in IBC with 25 mg of exemestane compared with placebo [21] In addition, the combined incidence of IBC and DCIS was reduced by 53% in the exemestane group compared with placebo. The IBIS-II [22] was a double-blind, randomized, placebo-controlled study that aimed to assess the efficacy and safety of anastrozole for BC prevention in high-risk postmenopausal women. A total of 3864 postmenopausal women were randomized to either 1 mg of anastrozole daily or placebo. This study showed that anastrozole significantly reduced IBC (mainly high-grade tumors) and DCIS diagnoses.

The MAP.3 and IBIS-II results demonstrate that exemestane and anastrozole were associated with a greater magnitude of BC risk reduction compared to SERMs. However, we should also consider their less adverse effect (especially in thrombophilic and gynecological events) and their simultaneous associated reduced bone mineral density leading to an increased fracture risk, an increase in musculoskeletal side effects, and also, most likely, an increase in cardiovascular events [23, 24]. Relevant issues for both types of chemoprevention, i.e., appropriate duration of therapy, dose optimization, target population, and, ultimately, effects of primary prevention on mortality, still remain unanswered. Finally, because of the absence of head-to-head comparisons and inter-study differences in patient characteristics, it remains unclear whether SERMs or AIs are the preferred agents for BC chemopreventive risk reduction.

9.3 Prevention of ER-Negative BC

Estrogen receptor-negative and triple-negative breast cancers are types of aggressive tumors that account for approximately 30 and 15% of total breast cancers, respectively [25]. Selective estrogen receptor modulators and aromatase inhibitors are unable to treat and prevent these subtypes of mammary tumors, and other approaches are, therefore, needed. Notably, around 90% of breast cancers arising in BRCA-1 mutation carriers are triple negative or estrogen receptor negative [26]. For these reasons, available preventive strategies are urgently needed in BRCA mutation carriers and, in general, in young high-risk population.

It is therefore worth identifying new pathways, biomarkers, and agents that are effective in the treatment and prevention of these subtypes. With the accumulating knowledge in understanding the biology of cancer development, several classes of a new generation of chemopreventive agents modulating the non-endocrine biochemical pathways have been developed, and many of these are still currently under investigation (Table 9.1).

These agents include retinoids, poly(ADP-ribose) polymerase (PARP) inhibitors, EGFR tyrosine kinase inhibitors (for HER2-positive tumors), metformin, cyclooxygenase-2 (COX-2) inhibitors, bisphosphonates, and peroxisome proliferator-activated receptor (PPAR) inhibitors. Due to their lack of proven efficacy or to an unacceptable risk-benefit ratio for healthy subjects, several of these agents are currently on standby. Only the following most apparently promising agents are described.

Table 9.1 Class, specific pathways, and agents actually involved in the treatment and prevention of ER-negative breast cancer

Class	Targets	Drugs or agent
Nuclear receptors	Retinoid acid receptor RXR	Fenretinide (4-HPR) 9 cis-retinoic acid (Targretin)
	VDR	VIT D3 analogues
	$PPAR_Y$	Troglitazone, rosiglitazone, pioglitazone
Membrane receptors and signal transduction	HMG-CoA	Statins
	Tyrosine kinase	Gefitinib (Iressa)
	HER-1, HER-2	Trastuzumab (Herceptin), lapatinib, genfitinib, neratinib
	IGF-R, IGF-1, IGFBP3	Metformin
Anti-inflammatory and antioxidant	COX-2	Celecoxib,rofecoxib, NSAIDs
Angiogenesis	VEGF	Bevacizumab
DNA modulation	BRCA1-BRCA2\	PARP-inhibitors

4-HPR N-(4-hydroxyphenyl) retinamide, *COX* cyclooxygenase, *ER* oestrogen receptor, *HMG-CoA* 3 hydroxy-3 methylglutaryl coenzyme A, *NSAIDs* nonsteroidal anti-inflammatory drugs, *PARP* poly (ADP-ripose) polymerases, *PPAR* peroxisome-activated receptor, *RXr* retinoid X receptor, *VDR* Vitamin D receptor

9.4 Retinoids

Retinoids (either natural or synthetic compounds structurally related to vitamin A) have long been studied for their chemotherapeutic effect and for their chemopreventive potential in breast cancer setting. They are able to regulate cell growth, differentiation, and apoptosis [27] in ER-positive and ER-negative breast cancer cells. The most promising retinoid in chemoprevention setting is fenretinide, N-4-hydroxyphenyl retinamide (4-HPR). The first important study where 4-HPR was administered as a single agent was an Italian multicentric phase III randomized trial, started in 1987. Stage I breast cancer patients were randomly assigned to receive either no treatment or fenretinide given orally at a dose of 200 mg/day for 5 years. The main outcome measure was the occurrence of contralateral breast cancer as first malignant event. Also, a different effect was noticed when the analysis was stratified by menopausal status, with a beneficial trend in premenopausal women on both contralateral and ipsilateral breast cancer (38%) and a reversed trend on contralateral breast cancer in postmenopausal women. Importantly, the protective effect persisted for up to 15 years (i.e., 10 years after retinoid cessation) [28]. Such benefit was associated with a remarkable 50% risk reduction in women aged 40 years or younger. This phase III trial suggested a possible role of fenretinide as a preventive agent acting at different levels of breast carcinogenesis. This protective effect was suggested also in women with a high probability of carrying a BRCA mutation.

9.5 Metformin

Epidemiological studies have strongly suggested that metformin can reduce cancer risk and mortality in diabetic subjects. A recent meta-analysis [29] on 47 independent studies and 65,540 cancer cases in diabetic patients showed that metformin reduced the overall cancer incidence by 31%, while mortality was reduced by 34%. Several preclinical studies have confirmed the effect of metformin in vitro and in vivo and showed a significant reduction of both breast epithelial cell proliferation and protein synthesis [30, 31].

Because of these promising epidemiologic and preclinical data, several phase I and II trials were conducted to investigate its breast cancer preventive effects [32–34]. Most of these were neoadjuvant "window of opportunity" studies among women with operable breast cancer and investigated a variety of biomarker changes after metformin administration. Metformin reduced proliferation (KI67) and increased apoptosis (TUNEL staining) in invasive tumor tissue, in particular in patients with a metabolic unbalanced condition [32, 35]. Phase II and III clinical trials are currently in progress to further elucidate the cancer preventive effect of metformin [36–39]. The most important one is a currently ongoing phase III study (the NCIC-MA.32 trial), testing 5 years of metformin versus placebo among women with early-stage breast cancer [36].

Metformin's antineoplastic mechanisms of action involve several pathways through which the drug acts in direct or indirect mode. In particular, metformin regulates the AMPK/mTOR pathway implicated in the control of protein synthesis and cell proliferation [40]. It has been confirmed that metformin produces a significant repression of cell proliferation and this effect was found to be different in human breast cancer cell lines if related to either positive or negative ERs. A complete cell growth repression was detected in ER-positive cell lines, although only a partial inhibition was detected in ER-negative phenotypes [41]. These data suggest that although ER-negative cells are not as sensitive as ER-positive ones, both of them show a reduction in cell growth under metformin treatment.

9.6 Bisphosphonates

Bisphosphonates are commonly used in patients with breast cancer to reduce skeletal-related events in metastatic disease and to mitigate bone loss associated with cancer therapy in early-stage disease. Antiresorptive agents, including bisphosphonates such as ibandronate, risedronate, and zoledronic acid and the receptor activator of nuclear factor kappa B ligand (RANKL) inhibitor denosumab, have been shown to mitigate aromatase inhibitor-associated bone loss in a series of trials [42]. In addition, adjuvant breast cancer trials evaluating the oral bisphosphonate clodronate suggested a reduction in cancer recurrence and prevention with a direct antitumor effects involving anti-angiogenic, antiproliferative, and proapoptotic mechanisms [43]. Recent adjuvant trials suggest that bisphosphonates may also delay disease recurrence in some populations of estrogen-depleted women in early breast cancer setting supporting a potential anticancer effect. Two large cohort studies reported reductions in breast cancer incidence of around 30% in bisphosphonate users [44, 45]. Both studies reported similar benefits for ER-negative breast cancers.

9.7 EGFR Tyrosine Kinase Inhibitors (TKIs)

Researchers have recently focused their attention on EGFR-HER-1 and EGFR-HER-2 pathways and consequently on TK inhibitors, because the mechanism of resistance to antiestrogen therapy is usually associated with an increased expression of HER-1 and HER-2 receptors.

EGFR is one of a family of four closely related receptors (EGFR or erbB-1, HER-2/neu or erbB-2, HER-3 or erbB-3, and HER-4 or erbB-4) that uses tyrosine kinase activity and contributes to a large number of processes involved in tumor survival and growth, including cell proliferation and inhibition of apoptosis and angiogenesis [46], thus making it an attractive target for cancer prevention. There are two different and concomitant strategies able to inhibit erbB activity. One involves blockade of this activity with monoclonal antibodies (trastuzumab), whereas the second involves the TKIs. TKIs have several advantages over monoclonal antibodies, such as oral bioavailability and potentially less toxicity, and these make them attractive preventive agents [47]. There are two agents tested in this setting, lapatinib and gefitinib.

Lapatinib has been evaluated in several phase II and III trials in various types of breast cancer [48, 49]. Moreover, in prevention setting, it showed a significant delay in the development of ER-negative mammary tumors [50]. This preventive action was seen in premalignant mammary lesions, and this suggests its effectiveness also in the initiation and progression of breast carcinogenesis. Gefitinib showed the ability to suppress ER-negative mammary tumor formation in MMTV-ErbB2 transgenic mice [46], and, despite the results of preclinical and clinical studies, gefitinib recognized ability to inhibit proliferation in early-stage breast cancers and in normal adjacent epithelium remains controversial. This could be the rationale for the use of this compound in prevention trial.

Finally, a mention must be done to neratinib, another irreversible tyrosine kinase inhibitor of HER1, HER2, and HER4, which has recently shown [51] clinical activity in patients with HER2-positive metastatic breast cancer. Neratinib for 12 months significantly improved 2-year invasive disease-free survival when given after chemotherapy and trastuzumab-based adjuvant therapy to women with HER2-positive breast cancer. Disease-free survival including ductal carcinoma in situ was also significantly improved with neratinib compared with placebo after 2 years, and this action about early phases of cancinogenesis should be promising in the preventive settings too.

9.8 Limited Uptake of BC Chemoprevention

Despite the availability of several efficacious agents, the utilization of preventive therapy has been poor due to various barriers, such as the lack of physician and patient awareness, fear of side effects, and licensing and indemnity issues. For preventive therapy, we cannot identify those individuals whose cancer was prevented or risk was substantially reduced because of the lack of measurable biomarkers of efficacy, which currently exist for other diseases, including cardiovascular diseases, prevention of diabetes complications, or osteoporotic bone fractures.

Therefore, from those persons' point of view, they either have taken unnecessary medication or, worse, they have unnecessarily suffered the adverse effects of such therapy. Preventive therapy for cancer is often discounted as overtreatment and used as an example of overmedicalization. Understanding and overcoming such perception differences, along with other barriers, are essential if we are to realize the full potential of this approach for cancer control. New strategies are needed in order to improve this condition, and they include improving physician awareness and countering prejudices by highlighting the important differences between preventive therapy and cancer treatment. Researchers in the last few decades have discussed about the important barriers to therapeutic cancer prevention and the strategies to overcome these barriers and future research needs (Table 9.2).

Several reasons seem to be the causes that complicate the spread of the use of preventive therapies, although the most important often seems to be the fear of side effects. Moreover, future research to improve therapeutic cancer prevention needs to include improvements in the prediction of benefits and harms and improvements in the safety profile for new or existing agents by experimentation with dose.

Table 9.2 Barriers to preventive therapy and strategies to overcome these barriers

Barriers	Strategies to overcome barriers
Underestimation of benefits and/or overestimation of harms	• Acknowledging different needs of risk prediction for different diseases and agents • Refining risk prediction and risk communication • Development of biomarkers than can be frequently monitored by non-invasive means
Adverse effects of agents	Exploring strategies to reduce adverse effects, e.g., dosing modifications
Individual lack of knowledge	Improving physician-patient communication and information sharing; educational interventions
Individual's fear of side effect	Exploring re-purposing of commonly used agents with well-documented safety profile
Physicians' lack of knowledge/prejudices	Increasing physician awareness and countering prejudices
Licensing and off-label use issues	Policy engagement
Lack of well-proven agents for several cancers	Increased focus on preventive research, particularly in academia

9.9 Natural Compounds

Lifestyle changes do offer an important strategy for cancer prevention [52]. They generally include diet and nutrition modifications as well as a regular and suitable physical activity. Moreover, recent attention has been given to the use of natural products in a preventive setting, especially in trying to counteract the concern of drugs' side effects, in addition to making a possible preventive approach intriguing [53]. Some of the most promising compounds include catechins (e.g., epigallocatechin gallate (EGCG), green tea extract), curcumin, carotenoids, omega-3 fatty acids, resveratrol, soy isoflavones, and vitamin D. Unfortunately, none of these dietary agents has been shown to consistently prevent breast cancer. So, in spite of the fact that natural products are a promising alternative strategy for cancer prevention, their potential efficacy in the prevention of ER-negative and, particularly, triple-negative breast cancer will be determined in the near future. In particular, it might be useful to identify those natural products that cannot act directly on carcinogenic mechanisms but on the main risk factors. Since the properties of some carcinogenic pathways, such as inflammation, cholesterol, metabolic syndrome, and hyperinsulinemia, are already known, natural products could successfully be used in the regulation and/or control of these pathways and could also indirectly act on the risk of developing the disease.

One simple strategy is to combine nutraceuticals which are in common use as food ingredients to make a single cancer polypill. This was done with success for antihypertensive agents in the polypill for stroke prevention in the general population [54].

Conclusions

The success of several recent clinical trials in the preventive setting in selected high-risk populations suggests that chemoprevention is an effective strategy. New pathways, biomarkers, and agents are actively searched in this subgroup of cancers and have been recently put under investigation in order to improve the effectiveness and reduce the toxicity. These strategies accompanied by a serious lifestyle and nutrition changes could be a decisive step to breast cancer prevention and treatment.

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