The rationale and potential of cancer chemoprevention with special emphasis on breast cancer

Matteo Puntoni[a], Andrea Decensi[a,b]

[a]*Medical Oncology Unit, Galliera Hospital, Genoa, Italy*
[b]*Division of Cancer Prevention and Genetics, European Institute of Oncology, Milan, Italy*

Introduction

Substantial preclinical and epidemiological data indicate that cancer can be prevented, or at least significantly delayed. The key concept underlying chemoprevention is that carcinogenesis is multistep (i.e. it results from accumulated genetic and epigenetic alterations), multipath (i.e. multiple functional pathways are involved, such as self-sufficiency in growth signals, insensitivity to antigrowth signals, apoptosis evasion, limitless replicative potential, tissue invasion and metastasis and sustained angiogenesis), and multifocal (both multi-clonal, that is, 'field cancerisation' occurs, and clonal, that is, cloning expansion leading to intraepithelial spread occurs) (Fig. 1) [1].

The rationale is based on the hypothesis, as originally proposed by Sporn and colleagues in 1976, that the use of natural, synthetic or biological chemical agents can reverse, suppress or prevent either the initial phase of carcinogenesis or the progression of neoplastic cells to cancer [2].

Chemoprevention can be divided into primary (to prevent the onset of disease in healthy individuals at risk), secondary (to treat a population with a premalignant condition in order to arrest the development of cancer) or tertiary (to protect subjects cured of an initial cancer against second primary tumours).

This definition encompasses a major aspect of clinical cancer chemoprevention: the use of pharmacological interventions to reduce the risk of invasive cancer after the onset of intraepithelial neoplasia (IEN) [3,4].

IEN is a premalignant lesion occurring in most epithelial tissues as moderate-to-severe dysplasia. Accumulating mutations (i.e. genetic progression)

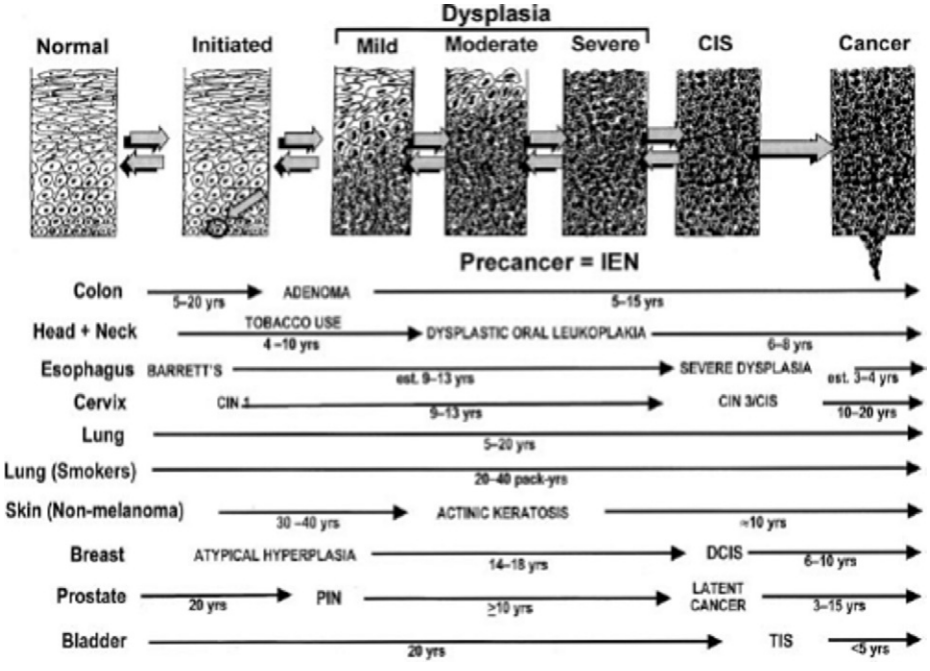

Fig. 1. Human carcinogenesis is a multiyear process. From O'Shaughnessy JA, et al. [3].

Table 1
Characteristics of neoplasia and associated molecular biomarkers

Characteristics of neoplasia	Possible molecular targets
Self-sufficiency in cell growth	Epidermal group factor, platelets-derived growth factor, MAPK, PI3K
Insensitivity to antigrowth signals	SMADs, pRb, cyclin-dependent kinases, MYC
Limitless replicative potential	hTERT, pRb, p53
Evading apoptosis	BCL-2, BAX, caspases, FAS, tumour necrosis factor receptor, DR5, IGF/PI3K, mTOR, p53, PTEN, ras, interleukin-3, NF-κB
Sustained angiogenesis	VEGF, basic fibroblast growth factor, $\alpha_v\beta$, thrombospondin-1, hypoxia-inducible factor-1α
Tissue invasion and metastasis	Matrix metalloproteinases, MAPK, E-cadherin

NOTE: Data from Hanahan and Weinberg [13].

and loss of cellular control functions are observed as the phenotype changes from normal histology to early dysplasia then to increasingly severe IEN, superficial cancers, and finally invasive disease [5] (Fig. 1). Although the progression of severe dysplasia to cancer may happen within months to a few years in situations where the process is relatively aggressive (e.g. in the presence of a DNA repair-deficient genotype or a viral transformant such as human papilomavirus (HPV)), these changes generally appear to occur over a long time period. For example, in the breast it is estimated that progression from atypical hyperplasia through ductal carcinoma *in situ* (DCIS) to adenocarcinoma requires 10–20 years or more [6,7]. The results are that IEN is a precursor to invasive cancer and occurs at a relatively late stage in the pathway leading from normal tissue to cancer. Consequently, subjects with IEN, particularly severe IEN, are at significantly higher risk than unaffected populations for developing invasive cancer in the same tissues. This risk in fact exceeds other measurable risk factors with the exception of germ-line mutations that occur in genetic syndromes. The invasive cancer risk associated with IEN can be illustrated by two notable examples, colon (adenomas) and prostate (prostatic intraepithelial neoplasias (PIN)). Colorectal adenomas may form over a period as long as 5–20 years, and progression from adenoma to colorectal carcinoma usually requires another 5–15 years [8–11]. PIN may develop over approximately 20 years. From PIN to early latent cancer may take 10 or more years, and clinically significant carcinoma may not occur until 3–15 years later [12].

Moreover, many IENs (for example, grades 2 and 3 cervical IEN, breast ductal and lobular carcinoma *in situ* and colorectal adenomas in patients with familial adenomatous polyposis) are recognised as diseases requiring treatment in their own right, independent of cancer prevention objectives.

Chemoprevention drugs customarily must reduce cancer incidence in a clinical trial before being considered for standard of care but the cancer endpoint and its reduction make trials long, large and costly. Therefore, an important component of chemopreventive agent development research in recent years has been to identify biomarkers that accurately predict an agent's clinical benefit or cancer incidence-reducing effect. Establishing IEN as a surrogate endpoint for cancer chemoprevention trials reduces the number of subjects (by thousands), the time (by a decade or more) and countless costs from the logistics of chemoprevention trials. In 2002, the American Association for Cancer Research recommended the development of chemoprevention strategies that are focused on carcinogenesis, not necessarily invasive cancer, as a measure of clinical benefit. This recommendation specified the prevention and regression of clinical/histopathological IEN [3]. A 2006 update of these recommendations [4] highlighted the importance of molecular IEN (that is, molecular alterations detected early in the target histopathological IEN) as a potential surrogate marker for invasive cancer and an endpoint for chemoprevention studies [13] (Table 1).

In the present paper, we review most phase III clinical trials showing an association between use of chemoprevention agents and risk reduction of breast cancer.

Breast Cancer Epidemiology

Breast cancer is the most common cancer in women excluding basal cell carcinoma and spinocellular carcinoma of the skin and the second most common cause of cancer deaths in women. Worldwide breast cancer incidence and mortality rates are 1,151,298 and 410,712, respectively, and in the US alone 182,460 cases of invasive breast cancer among women were estimated to occur in 2008, with the expectation

Table 2
Phase III trials of tamoxifen versus placebo with reduction of breast cancer as endpoint

Trial	Start year	n	Effect (tamoxifen vs placebo)	Ref
NSABP P-1	1992	13,388	RR = 0.51 (95%CI: 0.4–0.7)	[20]
Royal Marsden Chemoprevention Trial	1986	2494	RR = 1.06 (95%CI: 0.7–1.7)	[23,24]
Italian Tamoxifen Prevention Study	1992	5408	HR = NS	[25,26]
IBIS-I	1992	7152	RR = 0.67 (95%CI: 8–50)	[27]

NSABP-1: National Surgical Adjuvant Breast and Bowel Project Protocol-1; IBIS-I: International Breast Cancer Interventional Study; n=: number; RR: relative risk; CI: confidence interval; HR: hazard ratio; NS: non-significant; ref: reference.

that 40,480 women would die of this disease [14]. Female breast cancer incidence rates levelled off from 2001 to 2003 after increasing since 1980, reflecting the saturation of mammography utilisation and reduction in the use of hormone-replacement therapy (HRT) [15]. Mortality from breast cancer has declined since 1990; this has been attributed, in part, to early detection [16] and the increased use of hormonal and adjuvant chemotherapies [17], resulting in an increase in survival of 13% since the mid-1970s [15]. Despite these improvements, breast cancer still remains a major cause of morbidity and mortality and breast IEN, which spans the continuum from simple hyperplasia without atypia to DCIS, is a recognised risk factor for invasive cancer [18,19].

The majority of breast cancers are sporadic and risk factors are primarily related to oestrogen exposure. Selective oestrogen receptor (ER) modulators (SERMs) have an established role in the treatment and chemoprevention of hormone-related breast cancer. These agents antagonise oestrogens in some tissues and mimic their action in others. The mechanism for tissue selectivity appears to be related to differences in their molecular and three-dimensional structures, which affect the transcriptional activity of the activated oestrogen receptor. For example, tamoxifen and toremifene act as oestrogen antagonists in breast tissue and as oestrogen agonists in the endometrium. Conversely, raloxifene behaves as an oestrogen antagonist in both the breast and the endometrium.

Tamoxifen studies

The rationale for using tamoxifen for the prevention of breast cancer relied on several different biological lines of evidence, considering also that it is an inexpensive non-patented drug, well-tolerated and with a known side-effect profile. Studies of tamoxifen have shown that chemoprevention can successfully cover all three settings of prevention: (a) primary chemoprevention, as shown in the NSABP P-1 trial in healthy women at increased risk according to the Gail model ([20], http://bcra.nci.nih.gov/brc/); (b) secondary chemoprevention, as described in the NSABP B-24 trial, in which patients with DCIS benefited from tamoxifen for prevention of ipsilateral and contralateral breast cancer [21]; and (c) tertiary chemoprevention, as demonstrated in the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis, wherein tamoxifen was associated with prevention of contralateral breast cancer in definitively treated breast cancer patients [22]. In the following review we will focus on primary chemoprevention trials (Table 2).

The NSABP P-1 study

This study [20] recruited 13,388 women with a Gail model breast cancer risk $\geqslant$66% in 5 years, which is on average equivalent to a 60-year-old woman's risk or to the risk of a woman with history of lobular carcinoma *in situ*. Women were randomised to receive either tamoxifen 20 mg/day or placebo. This trial gave such positive results that an interim analysis led to early closure. It was shown that tamoxifen reduces the risk of invasive and non-invasive breast cancer by 49% and 50%, respectively (two-sided $P < 0.00001$ and $P < 0.002$) and decreases the occurrence of ER-positive tumours by 69%, with no effect on ER-negative tumours. The protective effect of tamoxifen was seen in women of all age groups. Risk was also reduced in women with a history of lobular carcinoma *in situ* by 56% and by 86% in those with atypical hyperplasia. All women in any category of predicted 5-year risk had a risk reduction with tamoxifen.

Interestingly, tamoxifen produced an overall 20% reduction in the incidence of osteoporotic bone fractures. However, women aged 50 or older had a 4-fold increased risk of early stage endometrial cancer, a 3-fold increased risk of pulmonary embolism and a significant excess of cataract [20]. Based on the trial results, the US Food and Drug Administration approved the use of chemopreventive tamoxifen in

high-risk individuals. This study provides the first example of a medication approved and marketed as a cancer preventive agent. However, the striking results of the NSABP P-1 trial were only partially confirmed in European trials [23–26].

The Royal Marsden Chemoprevention trial

In this ground-breaking study [23], 2494 healthy women aged between 30 and 70 years, at increased risk of breast cancer because of family history, were accrued and randomised in a double blind fashion to receive either tamoxifen 20 mg/day or placebo for up to 8 years. The initial analysis after a median follow-up of 70 months, when the study had adequate power to detect a 50% reduction of breast cancer in the tamoxifen arm, reported the same overall frequency of breast cancer in both arms ($P = 0.8$). Interestingly, women who were already on HRT, mostly by oral route, at the time of recruitment showed an increased risk of breast cancer compared to non-HRT users, whereas those who started HRT while on trial had a significantly reduced risk. There were four cases of endometrial cancer in the tamoxifen arm versus one in the placebo arm and seven cases versus four of vascular thrombo-embolic events (VTE) and pulmonary embolism. In an updated analysis after a median follow-up of 123 months, there was still no significant reduction of breast cancer on tamoxifen (69 on tamoxifen versus 82 on placebo), despite a trend for risk reduction in women on HRT who took tamoxifen (Hazard ratio (HR) 21%; $P = 0.12$) [24].

The Italian Tamoxifen Prevention study

This study recruited 5408 healthy women aged 35–70 years who had had prior hysterectomy for non-malignant conditions [25]. At a median follow-up of 81.2 months, there was a non-significant trend to fewer cases on tamoxifen (34 versus 45 events). Tamoxifen significantly reduced the incidence of breast cancer in the high-risk group (3 versus 15 events; $P = 0.003$), defined on the basis of baseline as well as reproductive and hormonal characteristics, whereas no such effect was seen in the low-risk group ($P = 0.89$). No difference was observed in the subset of women who had never taken HRT. Conversely, women who had taken HRT at some point before or during the study ($n = 1.584$) had fewer breast cancers in the tamoxifen arm (6 on tamoxifen versus 17 on placebo; HR 0.35; 95% confidence interval (CI) 0.14–0.89). There were 28 VTE on placebo and 44 on tamoxifen (HR 1.63, 95%CI 1.02–2.63), 80% of which were superficial phlebitis, accounting for all the excess due to tamoxifen within 18 months from randomisation. In multivariate regression analysis, age $\geqslant$60 years, height $\geqslant$165 cm and diastolic blood pressure $\geqslant$90 mmHg had independent detrimental effects on VTE risk during tamoxifen, whereas transdermal oestrogen therapy during tamoxifen was not associated with any excess of VTE (HR 0.64, 95%CI 0.23–1.82) [26].

The IBIS-I trial

In the IBIS trial [27], 7152 women aged 35–70 years at increased risk for breast cancer were recruited for a double-blind, placebo-controlled, tamoxifen study. Nearly all participants (97%) had a family history of breast cancer. At a median follow up of 50 months, tamoxifen treatment resulted in a 33% reduction of breast cancer incidence compared to placebo ($P = 0.01$). A non-significant two-fold relative increase (11 versus 5) of endometrial cancer was observed ($P = 0.20$) in the tamoxifen arm. VTE were significantly increased in the tamoxifen arm ($P = 0.001$). Major VTE increased significantly on tamoxifen within 3 months of major surgery, immobilisation or fracture. No differences in bone fractures and cataract were observed.

In a summary of all the randomised tamoxifen prevention trials, including several European studies and the NSABP P-1 trial, Cuzick and colleagues [28] confirmed a 38% overall decrease in breast cancer, with a 48% decrease in ER-positive breast cancers but no effect on ER-negative cancers, as the mechanism of action would predict.

Tamoxifen at lower doses

A simple and economic approach to retain tamoxifen efficacy while reducing the risks may be a dose reduction. The rationale for this approach is summarised in Table 3 and supported by several observations.

In a study conducted by us, standard dose tamoxifen (20 mg/day) and two different lower doses (10 mg/day and 10 mg on alternate days) were administered for 2 months to a cohort of 127 healthy women [29] and changes in serum biomarkers regulated by the ER were evaluated, including lipid profile, blood cell count, fibrinogen, antithrombin III, osteocalcin and insulin growth factor (IGF)-I. No evidence for a concentration-response relationship was observed for most of the biomarkers. The concept of a dose reduction was further supported by the observation that tamoxifen has very high tissue distribution, ranging from 5 to 60 times its blood concentrations [30,31], and a prolonged half-life (9 and 13 days for tamoxifen and metabolite X, respectively) [30,32]. Also, the

Table 3
Rationale for a dose reduction in tamoxifen use for chemoprevention

- Binding to oestrogen receptor follows saturation kinetics
- Twenty milligram per day is as effective as 30–40 mg/day in the global meta-analysis
- The endometrial effect is dose-dependent
- Animal data show complete inhibition of tumour formation at a dose equivalent to 1 mg/day in humans
- Preoperative clinical trials show similar anti-proliferative effects of 1 mg and 5 mg/day compared to 20 mg/day

Table 4
Phase III trials of raloxifene with reduction of invasive breast cancer as an endpoint

Trial	Comparison arm	*n*	Effect	Ref
MORE	vs placebo	7705	RR = 0.24 (95%CI: 0.13–0.44)	[35–37]
CORE	vs placebo	4011	HR = 0.41 (95%CI: 0.24–0.71)	[38]
RUTH	vs placebo	10,101	HR = 0.56 (95%CI: 0.38–0.83)	[39,40]
STAR	vs tamoxifen	19,747	RR = 1.02 (95%CI: 0.82–1.28)	[41,42]

CORE: Continuing Outcome Relevant to Evista; MORE: Multiple Outcomes of Raloxifene Evaluation; RUTH: Raloxifene Use for The Heart; STAR: Study of Tamoxifen and Raloxifene; *n*=: number; RR: relative risk; CI: confidence interval; HR: hazard ratio; NS: non-significant; ref: reference.

breast tissue level attainable with 10 mg per alternate days still exceeds the *in vitro* growth inhibitory concentration of tamoxifen in breast cancer cell lines. Interestingly, a recent cross-sectional study conducted in older, nursing home residents in New York State long-term facilities has shown a significant reduction of bone fracture rate among breast cancer women taking tamoxifen 10 mg/day [33]. The concept of a dose reduction has further been assessed in a preoperative trial [34] in which 120 women with breast cancer were treated with either 20 mg or 5 mg or 1 mg/day of tamoxifen for 4 weeks before surgery. The effects of different doses of tamoxifen on breast cancer proliferation were studied using Ki-67 expression as the main surrogate endpoint marker. The change in Ki-67 expression induced by lower doses of tamoxifen was comparable to that achieved with the standard dose, implying that tamoxifen at low doses retains anti-proliferative activity. Several blood biomarkers of tamoxifen oestrogenicity associated with the risk of breast cancer, cardiovascular disease and bone fracture showed a dose–response relationship, suggesting that low doses of tamoxifen may be associated with reduced, favourable and unfavourable, oestrogenic effects of tamoxifen.

Taken together, these findings provide a strong rationale for the formal assessment of low dose tamoxifen in a preventive context. For this reason, two phase III randomised placebo controlled trials are underway to assess the efficacy of tamoxifen 5mg/daily in women on HRT (the HOT study) and in women with breast IEN.

Raloxifene studies (Table 4)

The Multiple Outcomes of Raloxifene Evaluation (MORE) trial

The study randomised 7704 postmenopausal women with osteoporosis and a mean age of 66.5 years to the SERM raloxifene versus placebo. Results showed that raloxifene for 8 years reduced the incidence of newly diagnosed breast cancer by 66%, with a marked effect on ER-positive tumours (risk reduced by 76%) and no effect on ER-negative tumours and non-invasive cancers [35–37]. There is no reported increase of endometrial cancer so far, whereas the effects on VTE look similar to those of tamoxifen [28].

Continuing Outcomes Relevant to Evista (CORE) trial

The Continuing Outcomes Relevant to Evista (CORE) trial [38] examined the effect of an additional 4 years of raloxifene (60 mg orally daily) therapy on the incidence of invasive breast cancer in women in the MORE trial who agreed to continue therapy. After 4 years participation in this trial, the risk of invasive breast cancer was reduced by 69%. No increase in the risk of endometrial cancer was observed with raloxifene in either the MORE or CORE trials but

both studies showed a significant increase in the risk of VTE, similar to the NSABP P-1 study.

Raloxifene Use for The Heart (RUTH) trial

The Raloxifene Use for The Heart (RUTH) trial randomised 10,101 postmenopausal women (mean age: 67.5 years) with coronary heart disease (CHD) or multiple risk factors for CHD to raloxifene 60 mg orally daily versus placebo; participants were followed for a median period of 5.6 years [39]. The study showed no difference between the two study arms with regard to the cardiac primary outcomes. In terms of breast cancer, a 46% risk reduction for invasive breast cancer was documented with raloxifene. In contrast, there was a 49% increase in fatal stroke and a 44% increase in VTE. These results raised the possibility that the protective effects of raloxifene, such as breast cancer reduction, were not large enough to balance the impact of the serious venous and arterial thrombo-embolic adverse events. It should be taken into consideration that the RUTH trial was focused on elderly women with a high risk for coronary artery disease events, and therefore its result should not be automatically generalised to the entire postmenopausal population [40].

NSABP Study of Tamoxifen and Raloxifene (STAR) trial

Raloxifene is being evaluated in comparison with tamoxifen in the STAR study, a large primary prevention trial of tamoxifen 20 mg/day versus raloxifene 60 mg/day for 5 years. The study population includes postmenopausal women at high risk based on the Gail model and women with previous lobular carcinoma *in situ*. It evaluated 19,747 postmenopausal women over the age of 35 years, with a 5-year predicted breast cancer risk $\geqslant$1.66% based on the Gail model [41], and women with lobular carcinoma *in situ*. Women were randomised to receive daily tamoxifen 20 mg or raloxifene 60 mg. After a median follow up of 3.9 years, no difference was found in the incidence of invasive breast between arms, both decreasing the incidence by 50%. However, despite the fact that raloxifene did not provide protection against non-invasive carcinoma while tamoxifen decreased the incidence by half, the rate of endometrial cancer was 38% lower in the raloxifene group and the incidence of VTE disease was lower in the raloxifene group, showing a better side-effect profile for raloxifene [42].

Despite its impressive efficacy, and having been given a US Food and Drug Administration labelling indication for breast cancer risk reduction, tamoxifen has never gained widespread acceptance in breast cancer prevention due to increased risk for the incidence of endometrial cancer, stroke, pulmonary embolism and deep-vein thrombosis, even if there were no significant differences in important adverse events between tamoxifen and placebo in women under 50 years of age.

Aromatase inhibitors

Another method to reduce or eliminate oestrogen-dependent processes important in the development and progression of breast cancer is to simply reduce the amount of oestrogen by interfering with its production, via ovarian ablation in premenopausal women and use of aromatase inhibitors or inactivators (AIs) in postmenopausal women. Because of their effectiveness, AIs are quickly becoming the most frequently used anti-hormonal treatment for breast cancer in postmenopausal women. Further, AIs are now being tested in breast cancer prevention trials.

Superior disease-free survival of AIs compared with tamoxifen in the adjuvant setting, including a lower risk of contralateral breast cancer [43–45], and the lack of increase in thrombo-embolic events or uterine cancer has led to the initiation of multiple primary-prevention trials in postmenopausal high-risk women in which an AI is being compared with placebo (International Breast Cancer Intervention Study II, Aromasin Prevention Study, National Cancer Institute of Canada Clinical Trials Group MAP.3 Breast Cancer Prevention Trial). The serious concern for prevention is the increase in risk of bone fracture and cardiovascular disease related to long-term oestrogen depletion with AIs even if arthralgias, fatigue, dyspareunia, reduced libido and hot flashes may result in poor uptake and/or compliance [43–45]. Ongoing phase III prevention trials will define the incidence of these adverse events relative to placebo in a healthy population, and potential solutions to avoid some of these problems in the prevention setting are already being explored.

Retinoids

Retinoids and natural or synthetic vitamin A analogues can regulate cell growth, differentiation and apoptosis in various cell types. The regulation of cell growth by retinoids is thought to result from direct and indirect effects on gene expression [46]. Both naturally occurring and synthetic retinoids have been shown to inhibit the growth of breast cancer cells. Retinoids have long been studied for their

chemotherapeutic effect, as well as chemopreventive potential in breast cancer; unfortunately, their side effects, including hyperlipidaemia and muco-cutaneous and liver toxicity, have limited their extensive use in humans [47]. A Phase III clinical trial initiated in 1987 assessed the efficacy of 5-year treatment with fenretinide, a synthetic derivative of all-trans-retinoic acid, in reducing contralateral or second ipsilateral breast cancer in patients aged 30–70 years with early breast cancer who had received no systemic treatment after primary treatment [48]. The main results of the study after 8 years showed no difference in contralateral or ipsilateral breast cancer, but a post hoc analysis suggested a significant treatment interaction with menopausal status (or age), with a 35% reduction in premenopausal women (or women aged <50 years) and an opposite trend in postmenopausal women (or women aged >50 years) [18]. The 15-year follow-up of the trial with 1739 women, representing 60% of the initial cohort of 2867 women [49], shows a 17% borderline significant reduction of second breast cancer associated with the retinoid. Most importantly, the risk reduction is of the order of 50% in women aged 40 years or younger, and persists for 10 years after retinoid cessation. The results of 83,234 women (aged 33–60 years) who were participating in the Nurses' Health Study revealed that premenopausal women who consumed five or more compared with two or fewer fruits, vegetables or supplements of β-carotene or vitamins A, C and E, had a reduction in the relative risk of breast cancer of 0.77 (95%CI 0.58–1.02) [50].

Novel selective synthetic retinoids offer the advantage of less toxicity by their specific actions on retinoid X receptors, bexarotene or targetrin; a member of this class is currently being assessed in a study to determine whether it can modify immunophenotypic markers related to breast cancer progression in breast tissue from genetically identified high-risk patients [51].

Non-steroidal anti-inflammatory drugs (NSAIDs)

Since different epidemiological studies on NSAIDs and breast cancer have produced mixed results, a direct relationship between breast cancer risk and use of NSAIDs cannot be demonstrated yet.

Incident invasive cases of breast cancer from the Multi-ethnic Cohort of 98,920 women were identified from 1993 to 2002. Data on aspirin, acetaminophen, and other NSAIDs (ibuprofen, naproxen, indomethacin) use were based on a self-administered questionnaire at baseline (1993–1996). Using the Cox Multivariate model, there was no association between breast cancer risk and duration of aspirin use for current or past users (HR 1.05, 95%CI 0.88–1.25 and HR 1.04, 95%CI 0.84–1.27 for ⩾6 years of use, respectively) compared with non-users. However, duration of current other NSAID use was protective (HR 0.70, 95%CI 0.51–0.95 for ⩾6 years of use; $P(\text{trend}) = 0.01$) against the risk of breast cancer, while past use was not (HR 0.90, 95%CI 0.62–1.30 for ⩾6 years of use). Analyses by ethnicity and hormone receptor status showed that the protective effect of current other NSAID use was limited to Caucasians and African Americans and to women with at least one positive hormone receptor [52].

The Iowa Women's Health Study [53] found no associations between breast cancer risk and duration of aspirin and non-aspirin NSAID use for current or past users in a cohort of 22,507 women (HR 1.05, 95%CI 0.88–1.25 and HR 1.04, 95%CI 0.84–1.27 for ⩾6 years of use, respectively) compared with non-users.

A prospective study, based on a cohort of 2292 early-stage breast cancer survivors, found an inverse association between current, regular ibuprofen use and breast cancer recurrence (relative risk (RR) 0.56, 95%CI 0.32–0.98), but not with aspirin (RR 1.09, 95%CI,0.74–1.61) [54].

Evidence for an interaction of a genetic polymorphism of COX-2 (allele 8473) with NSAIDs to reduce risk of hormone receptor-positive breast cancer has been found in a population-based case-control study, in which 1067 breast cancer cases and 1110 controls were genotyped [55]. Eight distinct haplotypes and 18 diplotypes were observed in the population. Overall, no significant associations between COX-2 haplotypes/diplotypes and breast cancer risk were observed. Among women who used aspirin or any NSAID there was little evidence for an interaction with the at-risk COX-2 genotypes, with one exception. Among women with hormone receptor-positive breast cancer, the reduced risk for any NSAID use was only evident among those who had at least one variant C allele of COX-2 8473 (odds ratio (OR) 0.7, 95%CI 0.5–1.0; P for the interaction = 0.02).

The association of NSAID use with risk of breast cancer has been further investigated in the California Teachers Study cohort, with special attention paid to the risk of a specific breast cancer subtype and to the type of NSAID used. Long-term daily use of NSAIDs was not associated with breast cancer risk overall. Ibuprofen use was associated with an increased risk of breast cancer, and long-term daily aspirin use was

associated with an increased risk of ER/progesteron receptor (PR)-negative breast cancer [56].

Conclusions

Both real and perceived toxicity concerns strongly affect the acceptability of chemopreventive agents and their ability to be used in mainstream clinical practice. Clinical efficacy has been shown in several breast cancer prevention trials but an incremental approach of improving efficacy and toxicity profiles through processes that span from preclinical to phase I–III clinical testing will probably be needed for cancer prevention strategies to become safe and widely used.

Conflict of interest statement

None declared.

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