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BREAST

Breast cancer and sex steroids: Critical review of epidemiological, experimental and clinical investigations on etiopathogenesis, chemoprevention and endocrine treatment of breast cancer

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Abstract

There is strong epidemiological, experimental and clinical evidence that the etiology of breast cancer is closely related to long-term exposure of breast epithelium to sex steroid hormones. Estrogens can enhance the development of breast cancer by stimulating cell proliferation rate and thereby increasing the number of errors occurring during DNA replication, as well as by causing DNAdamage via their genotoxic metabolites produced during oxidation reactions. Anti-estrogenic drugs, including tamoxifen, raloxifene and anastrozole, have been tested with promising results in the chemoprevention of breast cancer in high-risk women. As for the use of exogenous sex-steroids in the gynecological practice, data about breast cancer risk associated with oral contraception are reassuring, and available data on oral hormone replacement therapy (HRT) use for not more than 5 years have failed to detect a significant increase in the risk of developing a breast cancer. Long-term HRT administration increases the incidence of this tumor slightly, with a relative risk ranging from 1 to 2 depending on hormone preparation. Estrogens alone, even if taken for long periods of time, seem to be safer than estrogen/progestin combinations. New administration routes and novel hormone regimens are currently under evaluation,.and these new HRT modalities could have different impact on breast cancer risk because of their metabolic and pharmacodynamic effects.

As for the management of hormone sensitive breast cancer, anti-estrogen drugs have been used both for adjuvant therapy of early disease and for treatment of advanced and metastatic disease. The standard drug for adjuvant endocrine therapy is tamoxifen. However, recent studies appear to suggest a possible role for anastrozole and letrozole in adjuvant setting. First-line hormonal treatment of advanced or metastatic breast cancer consists of tamoxifen plus a gonadotropin-releasing hormone (GnRH) agonist in premenopausal patients, and anastrozole, letrozole or exemestane in postmenopausal ones. The establishment of an optimal sequence of endocrine therapies should give significant clinical benefits to breast cancer patients.

Keywords: *Breast cancer, sex steroid, estrogen, propestin, selective estrogen receptor modulator*

Introduction

In developed countries breast cancer is the most common malignancy in women, who have an overall lifetime risk for developing this tumor of approximately 1:8 [1]. There is strong biological and experimental evidence that the etiology of breast cancer is closely related to long-term exposure of breast epithelium to sex steroid hormones [2,3]. In several animal models, estrogens alone, without any additional chemical carcinogens, are sufficient to increase the incidence of mammary tumors, whereas the removal of ovarian steroids substantially reduces tumor risk [4]. For instance, the inhibition of estrogen production with aromatase inhibitors abrogates the development of spontaneous breast tumors in aging Sprague–Dawley rats [5]. Pooling data from nine prospective studies assessing the relationship between serum endogenous sex steroids and breast cancer in postmenopause found that the relative risk (RR) for women with increasing quintile of estradiol concentration, relative to the lowest quintile, was 1.42 (95% confidence interval (CI) 1.04–1.95), 1.21 (95% CI 0.89–1.66), 1.80 (95% CI 1.33–2.43) and 2.00 (95% CI 1.47–2.71) ($p < 0.001$) [6]. Similarly, the RR for women with increasing quintile of free estradiol was 1.38 (95% CI 0.94–2.03), 1.84 (95% CI 1.24–2.74), 2.24 (95% CI 1.53–3.27) and 2.58 (95% CI 1.76–3.78) ($p < 0.001$).

Whereas in premenopause ovarian estradiol is the main estrogen, in postmenopause estrogen synthesis consists mainly of aromatization of adrenal precursors by aromatase present in many extraglandular tissues, including adipose tissue, muscles and liver

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[7,8]. After the aromatization of androstenedione to estrone, the enzyme 17β-hydroxysteroid dehydrogenase type 1 (17β-HSD-1) converts estrone to estradiol in peripheral tissues. Approximately 40% of plasma estrone and estradiol are converted by the enzyme sulfotransferase to estrone sulfate, a compound with slow metabolic turnover. Plasma estrone sulfate may provide an important source of precursors for local estrogen production within breast cancer tissue that can release estrone from estrone sulfate via sulfatase. Breast cancer tissue also contains aromatases able to convert biologically relevant amounts of androgens to estrogens, but quantitative evaluation shows that estrone sulfate via sulfatase is a much more likely precursor for estradiol than is androstenedione via aromatase [9].

The effects of progestins on normal and malignant breast cell growth are contrasting. The mitosis rate of breast cells is higher during the luteal phase of the menstrual cycle than during the follicular phase, suggesting either that progesterone and estrogen together induce more mitosis than estrogen alone or that estrogen alone induces mitosis in a dose-dependent manner and that progesterone has no effect [3]. Progestins have been found to inhibit, stimulate or have no effect on the proliferation of either normal breast epithelium or breast cancer cell lines [9]. For instance, by evaluating the influence of sex steroids on the growth fraction of 35 primary human breast cancers, Jones and Russo [10] found that progesterone treatment increased growth fraction in 30% of tumors treated with low doses compared with 14% of those treated with high doses, whereas estrogen/progestin treatment markedly depressed the growth of 85% of the tumors.

Reproductive variables and breast cancer risk

Early age at menarche, late age at menopause and short interval between age at menarche and age at which menstruation becomes regular represent risk factors for breast cancer, probably because regular cycling maximizes the exposure of breast epithelium to sex steroids [4]. The heavier a woman in postmenopause, the higher are her serum estrogen levels and the greater is her breast cancer risk, whereas in premenopause estrogens from adipose tissue give a minimal contribution to the overall estrogen production. These observations explain why several authors [11,12] reported an increased risk of postmenopausal breast cancer in obese patients, whereas a meta-analysis of data from 23 studies showed a modest inverse association between body mass index and premenopausal breast cancer risk [13].

As for the effect of pregnancy, there is a transient increase in breast cancer risk in the first 3 or 4 years after delivery of a baby, but afterwards lifetime risk appears to be lower than that of nulliparous women [14]. The early increased risk is probably due to the high serum sex steroid levels, whereas the long-term protective effect is mediated in part by pregnancy-induced terminal differentiation of breast epithelium with consequent reduction of cell proliferation rates [4]. Recent experimental data in rat and mouse models of mammary cancer suggested that the *p53* gene could play a pivotal role in the protective effect of pregnancy [15].

The risk for premenopausal breast cancer is reduced with lactation, especially for women with extended periods of breastfeeding during their lifetime [14]. A recent collaborative reanalysis of individual data from 47 epidemiological studies, including 50 302 women with breast cancer and 96 973 controls, showed that the RR of breast cancer decreased by 4.3% (95% CI 2.9–5.8%; $p < 0.0001$) for every 12 months of breastfeeding in addition to a decrease of 7.0% (95% CI 5.0–9.0%; $p < 0.0001$) for each birth [16]. The size of the decline in the RR of breast cancer associated with breastfeeding did not differ significantly by age, ethnic origin, parity and woman's age at first delivery.

Experimental investigation by Forster and colleagues [17] suggested that mammary gland develops normally until puberty in mice homozygous for the mutated *estrogen receptor-β* gene (ER$\beta^{-/-}$), whereas *ERβ* is essential for complete gland differentiation during pregnancy and lactation. The levels of adhesion molecules, such as E-cadherin and integrin-α_2, were reduced whereas Ki67 and β-catenin expression were increased in luminal epithelial cells in ER$\beta^{-/-}$ mice compared with wild-type animals. Therefore *ERβ* may contribute to cellular differentiation, homeostasis and growth control, thus being involved in the protection offered by pregnancy and lactation against breast cancer.

Pharmacological effects of estrogens in breast carcinogenesis

Estrogens can enhance the development of breast cancer by stimulating cell proliferation rate and thereby increasing the number of errors occurring during DNA replication, as well as by causing DNA damage via their genotoxic metabolites produced during oxidation reactions [2,18–21] (Table I).

Table I. Pharmacological effects of estrogens in breast carcinogenesis.

Stimulation of transcription of genes involved in cell proliferation (via ER)
Induction of growth factor expression
Enhancement of hTERT transactivation
Induction of matrix metalloprotease expression
Induction of VEGF expression
DNA damage via genotoxic metabolites (via estrogen oxidative metabolism)

ER, estrogen receptor; hTERT, human telomerase reverse transcriptase; VEGF, vascular endothelial growth factor.

Estrogens, growth factors and breast cell proliferation

As for the most commonly supported hypothesis, estrogens bind to ER and stimulate the transcription of genes involved in cell proliferation [19]. Errors in DNA replication may occur in each cell cycle, and if not repaired these errors may result in point mutations. When these mutations involve critical regions for cell proliferation, DNA repair and apoptosis, neoplastic transformation can occur [22]. Moreover, estrogens may induce growth factors and interact with them in a complex manner [23–26]. Functional cross-talk between estrogen-mediated and growth factor-mediated signaling pathways has been detected in breast cancer cells. For instance, epidermal growth factor (EGF), insulin-like growth factor (IGF)-I and heregulin-β_1 can modulate the expression and activity of ERα via the phosphatidylinositol 3-kinase/Akt pathway in the ERα-positive breast cancer cell line MCF-7 [24]. Several data are available on the importance of the IGF system in growth regulation of breast cancer cell lines, showing that the IGF receptor (IGF-R) and IGF function as survival factors while IGF-binding protein (IGFBP) acts as a growth inhibitor [25]. Estrogens enhance IGF-I activity, mainly by increasing the expression of IGF-R and by decreasing the expression of IGFBP-3 that modulates IGF-I bioavailability [26]. In a case–control study within the prospective Nurses' Health Study cohort, IGF-I levels were measured in blood samples collected in 1989–1990 from 397 women who had a diagnosis of breast cancer after this date and from 620 age-matched controls [27]. In postmenopausal women no relationship was detected between IGF-I levels and breast cancer risk, whereas in premenopausal women the RR of this tumor was associated with IGF-I concentrations (top vs. bottom tertile: RR 2.33; 95% CI 1.06–5.16; $p = 0.08$). Such relationship became significant among premenopausal women younger than 50 years at the time of blood collection (RR 4.58; 95% CI 1.75–12.0; $p = 0.02$). A recent meta-analysis of 16 epidemiological and clinical studies confirmed a positive relationship between circulating IGF-I levels and breast cancer risk among premenopausal but not postmenopausal women [28].

Estrogens have been also found to enhance transactivation of the telomerase catalytic subunit, termed human telomerase reverse transcriptase [29], and to induce the expression of matrix metalloproteases [30] and vascular endothelial growth factor [31] in human breast cancer cells.

Estrogen oxidative metabolism pathway

The main support for the genotoxicity hypothesis of estrogen oxidative metabolism derives from animal models in which the administration of estrogens was found to induce malignant tumors such as renal cancer in male Syrian hamsters [32] and endometrial cancer in CD-1 mice [33]. Recent experimental data obtained from the ERα-positive hamster kidney tumor H301 and from the breast cancer cell line MCF-7 showed that 17β-estradiol, a strongly carcinogenic estrogen, has a stronger oxidant potential than 17α-ethinyl estradiol, a weakly carcinogenic estrogen, which could suggest that metabolic activation and subsequent generation of oxidative stress play a critical role in estrogen-induced carcinogenesis [34].

The oxidative pathway starts with hydroxylation of estradiol to the catechol estrogen metabolites, termed 2-hydroxy (OH)-estradiol and 4-OH-estradiol, by cytochrome P450 (CYP) enzymes [2,18–21,35]. These enzymes further oxidize the catechol estrogens to unstable semiquinone/quinone intermediates, that in turn form adducts with deoxynucleosides. Furthermore, catechol estrogens and their semiquinone/quinone metabolites undergo redox cycling, which results in the production of reactive oxygen species able to cause DNA oxidative damage and to induce mutations [36,37].

By using quantitative reverse-transcriptase polymerase chain reaction to assess mRNA expression levels of different CYP in human breast cancers, Modugno and associates [38] detected only four CYP, termed CYP1A1, CY1PB1, CYP2C9 and CYP3A4, in breast tumor or adjacent tissues and each of these was expressed in at least 75% of the samples. CYP1A1, CYP1B1 and CYP3A4 are involved in estradiol hydroxylation, whereas CYP2C9 is involved in the conversion of estrone sulfate to the 16-OH sulfate metabolite. Therefore the local activation of estrogens into potentially reactive metabolites by the CYP may play a role in breast carcinogenesis.

In a population-based, case–control study including 1521 breast cancer cases and 1498 controls, Rylander-Rudqvist and co-workers [39] found that *CYP1B1* gene polymorphism does not influence overall breast cancer risk but it may modify the risk after long-term exposure to hormone replacement therapy (HRT). In fact, women who had taken HRT for 4 years or longer and carried a particular *CYP1B1* genotype (CYP1B1 *3/*3) had RR of breast cancer of 2.0 (95% CI 1.1–3.5) compared with long-term HRT users without this genotype.

Two phase-II enzymes, catechol-*O*-methyltransferase (COMT) and glutathione-*S*-transferase (GST), can interfere with estrogen oxidative metabolism pathway [40–44]. Specifically, COMT catalyzes the methylation of catechol estrogens to methoxy estrogens, thus reducing the amount of catechol estrogens that can be converted to estrogen quinones and lessening the potential genotoxicity of estrogens [40]. This enzyme has isoforms with low and high activity, and some epidemiological studies found an increased risk of breast cancer in women with low COMT activity and consequently with a low rate of inactivation of catechol estrogens [41,42]. Moreover catechol estrogens may undergo oxidation and glutathione conjugation either non-enzymatically

or catalyzed by GST, and this conjugation could further lower DNA damage risk [43,44].

Chemoprevention of breast cancer

Cancer chemoprevention is defined as the use of natural, synthetic or biological chemical agents in order to reverse, suppress or prevent carcinogenic progression to invasive cancer [45]. As for breast cancer, tamoxifen has been widely investigated in phase-III trials for prevention of this malignancy in high-risk women [46–50] and interesting data have recently emerged about the chemopreventive effect of raloxifene [51], anastrozole [52] and fenretinide [53] (Table II).

Tamoxifen

Tamoxifen is a triphenylethylene derivative able to arrest the growth in the G_1 phase of the cell cycle of ER-positive human breast cancer cells [54]. This agent blocks estrogen binding to ER, and moreover it decreases the secretion of EGF, transforming growth factor (TGF)-α and IGFs, stimulates the production of TGF-β, blocks protein kinase C and calmodulin activation, and enhances natural killer cell activity [23,54].

The National Surgical Adjuvant Breast and Bowel Project (NSABP)-P1 study recruited 13 388 women at high risk for breast cancer according to the Gail model, who were randomly allocated to receive tamoxifen 20 mg daily versus placebo for 5 years [46]. After a median follow-up of 69 months, tamoxifen was found to reduce invasive breast cancer risk by 49% ($p < 0.00001$) (cumulative incidence: 43.4/1000 women in the placebo group vs. 22/1000 women in the treatment arm) and non-invasive breast cancer risk by 50% ($p < 0.002$). Compared with the placebo group, women aged 50 years or older enrolled in the tamoxifen arm experienced a fourfold increased risk of endometrial cancer and a threefold increased risk of pulmonary embolism. Conversely, tamoxifen use did not increase the risk of ischemic heart disease, liver cancer, colorectal cancer, ovarian cancer or other tumors, and moreover, it was associated with a 19% reduction in the incidence of osteoporotic fractures of the hip, radius and spine. The good results observed at the interim analysis led to an early closure of the trial that was criticized by those who argued that the long-term effects of tamoxifen on the incidence of breast cancer would not be known. Based on these findings, the Food and Drug Administration (FDA) has approved the use of tamoxifen to reduce the risk of breast cancer in women at elevated risk according to the Gail model. However, European trials [47–50] achieved less striking benefits than the NSABP-P1 study [46].

Table II. Chemoprevention of breast cancer.

Tamoxifen
Raloxifene
Low-dose tamoxifen and hormone replacement therapy
Aromatase inhibitors
Fenretinide

The Royal Marsden trial enrolled 2494 healthy women aged between 30 and 70 years at increased risk of breast cancer for family history, who were randomized to receive tamoxifen 20 mg daily or placebo for up to 8 years [47]. After a median interval time of 70 months, the overall frequency of breast cancer was the same for both arms (tamoxifen vs. placebo: RR 1.06; 95% CI 0.7–1.7; p not significant (NS)). Women who were given HRT when they entered the study had an increased risk of breast cancer compared with non-HRT users, whereas women who started such therapy while on trial had a reduced risk. As for safety profile, there were four cases of endometrial cancer and seven cases of deep vein thrombosis or pulmonary embolism in the tamoxifen arm compared with one and four cases, respectively, in the placebo group.

The Italian study enrolled 5408 healthy women aged 35–70 years who had previously undergone hysterectomy for benign disease and who were randomly allocated to be treated with either tamoxifen 20 mg daily or placebo for 5 years [48,49]. At a median follow-up of 81 months, tamoxifen was not found to reduce breast cancer risk in the whole series, but a subset analysis detected a protective effect of the drug only in women who were given HRT.

The International Breast Cancer Intervention Study (IBIS)-I was a double-blind, placebo-controlled randomized trial assessing tamoxifen 20 mg daily for 5 years in 7152 women aged 35–70 years who were at increased risk of breast cancer [50]. After a median interval time of 50 months, the RR of breast cancer for the tamoxifen arm was 0.68 (95% CI 0.50–0.92) and age, degree of risk and HRT use did not change this protective effect. A non-significant twofold excess of endometrial cancer was found in the tamoxifen group (RR 2.20; 95% CI 0.80–6.06; p = NS), and cancers other than those of breast and endometrium were equally distributed between the two arms. Conversely, the RR of venous thromboembolic events for tamoxifen was 2.5 (95% CI 1.5–4.4; $p = 0.001$), and such events occurred particularly within 3 months of major surgery or after long-duration immobility. Therefore a wise precaution would be to discontinue tamoxifen before any surgery and to give appropriate antithrombotic therapy until full mobility has returned.

Very few data are currently available about the effect of tamoxifen on breast cancer incidence among *BRCA1* or *BRCA2* mutation carriers [55–57]. In a matched case–control study enrolling 209 women with bilateral breast cancer and *BRCA1* or *BRCA2* mutation and 384 women with unilateral disease and

BRCA1 or *BRCA2* mutation as controls, tamoxifen protected against contralateral breast cancer in both *BRCA1* mutation carriers (RR 0.38; 95% CI 0.19–0.74) and *BRCA2* mutation carriers (RR 0.63; 95% CI 0.20–1.50) [55]. Conversely, recent data from the NSABP-P1 trial showed that tamoxifen reduced breast cancer incidence among healthy *BRCA2* mutation carriers by 62%, whereas tamoxifen use beginning at age 35 years or older had no protective effect among healthy *BRCA1* mutation carriers [56].

Raloxifene

Raloxifene is a selective estrogen receptor modulator (SERM) that binds to ER with high affinity, and exerts estrogen agonistic effects on bone and estrogen antagonist actions on breast and uterus. The Multiple Outcomes of Raloxifene Evaluation (MORE) trial enrolled 7705 osteoporotic women who were randomly allocated to receive raloxifene (60 or 120 mg daily) or placebo [51]. After a median follow-up of 40 months, 13 cases of breast cancer were diagnosed among the 5129 women assigned to raloxifene versus 27 cases among the 2576 women assigned to placebo, with RR of this tumor for the raloxifene arm of 0.24 (95% CI 0.13–0.44; $p < 0.001$). In detail, raloxifene significantly decreased the risk of ER-positive breast cancers (RR 0.10; 95% CI 0.04–0.24), but not the risk of ER-negative tumors. This SERM increased the RR (3.1; 95% CI 0.5–6.2) of venous thromboembolic disease, but did not increase the RR (0.8; 95% CI 0.2–2.7) of endometrial cancer. A subsequent analysis of the MORE trial showed that, in the placebo group, women with estradiol levels > 2.7 pg/ml had a 6.8-fold higher rate of breast cancer than did women with undetectable estradiol levels [58]. It is noteworthy that women with estradiol levels > 2.7 pg/ml in the raloxifene arm had a breast cancer rate that was 76% lower than that of women with estradiol levels > 2.7 pg/ml in the placebo arm, whereas women with undetectable estradiol levels had similar breast cancer risk whether or not they were given raloxifene. Therefore serum estradiol assay appears to be able to identify the subset of postmenopausal, high-risk women who might benefit most from raloxifene use. The Continuing Outcomes Relevant to Evista (CORE) trial examined the effect of 4 additional years of raloxifene therapy on invasive breast cancer incidence in women from the MORE trial who agreed to continue in the CORE trial [59]. Women who had been randomized to receive raloxifene in the MORE trial were assigned to receive raloxifene 60 mg/day in the CORE trial, and women who had been assigned to the placebo arm in MORE continued on placebo in CORE. Data analysis revealed that during the CORE trial the 4-year incidences of invasive breast cancer and ER-positive invasive breast cancer were reduced significantly by 59% and 66%, respectively, in the raloxifene group compared with the placebo group.

The Study of Tamoxifen and Raloxifene (STAR) is a large, ongoing prevention trial aiming to compare tamoxifen 20 mg daily versus raloxifene 60 mg daily for 5 years in postmenopausal women with high breast cancer risk according to the Gail model or with a previous lobular carcinoma *in situ* [60].

The ongoing Raloxifene Use for The Heart (RUTH) trial is a double-blind, placebo-controlled, randomized study designed to assess whether raloxifene 60 mg daily compared with placebo lowers the risk of coronary events and reduces the risk of invasive breast cancer in women at risk for a major coronary event [61]. The trial, which should enroll more than 10 000 postmenopausal women aged 55 years or more from 26 countries, will be terminated after a minimum of 1670 women experience a primary coronary endpoint.

Currently, there are no published data regarding the sequential use of tamoxifen and raloxifene as well as the combined use of raloxifene and HRT. Preclinical studies demonstrating raloxifene-induced stimulation of tamoxifen-resistant breast cancer in athymic mice [62], as well as clinical data showing a modest activity of high-dose raloxifene in selected postmenopausal patients with advanced breast cancer [63], appear to suggest caution in administering raloxifene to breast cancer women after the completion of adjuvant therapy with tamoxifen.

A recent meta-analysis [64] included the four major primary prevention trials of tamoxifen [46–50], the MORE trial [51] and an overview of the 11 trials of adjuvant tamoxifen for early breast cancer that also assessed the effect of this anti-estrogen agent on contralateral breast cancer risk [65]. The tamoxifen prevention trials showed a 38% (95% CI 28–46%) reduction of breast cancer incidence, with ER-positive cancers decreased by 48% whereas no effect was seen for ER-negative tumors. The rates of endometrial cancer were increased in all tamoxifen prevention trials (RR 2.4; 95% CI 1.5–4.0) as well as in adjuvant tamoxifen trials (RR 3.4; 95% CI 1.8–6.4), whereas no increase was seen with raloxifene. Venous thromboembolic events were increased in all tamoxifen studies as well as in the MORE trial.

Low-dose tamoxifen and hormone replacement therapy

A simple approach to retain the efficacy of tamoxifen while decreasing its risks might be a dose reduction, since the effect on the uterus seems to be dose- and time-dependent. In fact, the meta-analysis of all adjuvant tamoxifen trials showed a clear relationship between the length of tamoxifen treatment and endometrial cancer incidence [65]. Decensi and co-investigators [66] showed that the treatment of healthy women with tamoxifen for 2 months at a dose of 10 mg daily or 10 mg every other day did not affect drug activity on serum biomarkers of cardio-

vascular disease and appeared to have a more favorable safety profile than the dose of 20 mg daily. Moreover, these authors randomized 120 women with ER-positive breast cancer to receive tamoxifen at the dose of 1 mg, 5 mg or 20 mg daily for 4 weeks before surgery, and found that tumor Ki67 expression decreased in all three tamoxifen arms, with no difference in the magnitude of reduction according to drug dose [67].

The combination of HRT and tamoxifen may reduce the risks while retaining the benefits of either agent [60]. In particular, the slightly increased risk of breast cancer associated with HRT is mainly related to the mitogenic effect of estrogens and thus the addition of a SERM able to decrease this growth-promoting effect could prevent breast carcinogenesis. Chang and colleagues [68] found no significant adverse interactions between tamoxifen and HRT on serum cholesterol, coagulation factors and bone mineral density in healthy postmenopausal women. A placebo-controlled phase-III trial has recently been planned to assess benefits, risks and compliance of the combination of HRT and low-dose tamoxifen in healthy postmenopausal women – The HRT Opposed by Tamoxifen (HOT) [69].

Aromatase inhibitors

The two hypothesized pharmacological mechanisms through which estrogens enhance breast carcinogenesis (i.e. increased cell proliferation and genotoxic metabolite formation) could act in an additive or synergistic fashion [18,19]. Therefore aromatase inhibitors could be more effective than anti-estrogens as chemopreventive agents, because aromatase inhibitors block both processes whereas anti-estrogens inhibit ER-mediated effects only. The new third-generation aromatase inhibitors, including anastrozole, letrozole and exemestane, have shown good clinical efficacy in postmenopausal patients with ER-positive advanced breast cancer [52,70–77]. Moreover, the Arimidex, Tamoxifen Alone or in Combination (ATAC) trial revealed that anastrozole had superior efficacy and a better safety profile than tamoxifen as adjuvant treatment of postmenopausal women with early-stage breast cancer [78,79]. Contralateral breast cancer incidence data favored anastrozole (RR 0.62; 95% CI 0.38–1.02; $p = 0.06$), and statistical significance was achieved in the ER-positive subgroup (RR 0.56; 95% CI 0.32–0.98; $p = 0.04$). Data from the ATAC trial could be interpreted in the light of the genotoxic hypothesis and could suggest further investigation on this topic. A number of chemopreventive trials with aromatase inhibitors are currently underway or in planning in healthy women with dense mammography or a high-risk genetic and/or histocytopathologic profile [80]. For instance, the Italian Consortium of Hereditary Breast Ovarian Cancer recently planned a double-blind, randomized, placebo-controlled phase-III study aimed to assess the effect of exemestane versus placebo given for 3 years as chemopreventive agent in postmenopausal *BRCA1*/*BRCA2* mutation carriers [81].

Fenretinide

Fenretinide or *N*-(4-hydroxyphenyl)-retinamide is a vitamin A analog that selectively induces apoptosis rather than differentiation in several tumor cell systems [53,82]. This retinoid shows preferential accumulation in breast instead of liver, is effective in the inhibition of chemically induced mammary carcinoma in rats, and appears to be a potent inhibitor of the IGF system in human breast cancer cell lines [83]. Veronesi and associates [53] randomly assigned 2972 women with surgically removed stage I breast cancer or ductal carcinoma *in situ* to receive for 5 years either fenretinide 200 mg daily orally or no treatment, and detected no statistically significant differences in the occurrence of contralateral breast cancer or ipsilateral breast cancer between the two arms after a median follow-up of 97 months. However, by analyzing data by menopausal status, the authors found a possible beneficial effect of fenretinide in premenopausal women (contralateral breast cancer: RR 0.66; 95% CI 0.41–1.07; ipsilateral breast cancer: RR 0.65; 95% CI 0.46–0.92) and an opposite effect in postmenopausal women (contralateral breast cancer: RR 1.32; 95% CI 0.82–2.15; ipsilateral breast cancer: RR 1.19; 95% CI 0.75–1.89). It is noteworthy that modulation of serum IGF-I levels by fenretinide followed a similar pattern, i.e. IGF-I levels were lowered in premenopausal women only. However, the clinical relevance of IGF-I modulation by fenretinide is still debated [84].

Exogenous hormone use and breast cancer risk

Oral contraception

Oral contraceptives have represented the mainstay in birth regulation programs since the 1960s. Apart from their reversible contraceptive action, they offer evident and different advantages on dysmenorrhea, endometriosis, menstrual cycle dysfunctions and pelvic inflammatory disease. The safety of oral contraceptive administration has been thoroughly investigated, and its impact on carcinogenesis is one aspect of greatest interest in clinical practice as well as clinical research.

The supposed correlation between pill use and breast cancer is still one of the most studied topics and highly debated for evaluation of the risk–benefit relationship of hormonal contraception. In 1996, the Collaborative Group on Hormonal Factors in Breast Cancer [85] published a reanalysis of data from 54 epidemiological studies performed in 25 countries, for a total of 53 297 patients with breast cancer and

100 239 controls. The RR of breast cancer among oral contraceptive ever users compared with never users was 1.07 and the excess was statistically significant ($p = 0.00005$). The risk was associated mainly with the time interval since the last pill administration. In fact the RR was 1.24 (95% CI 1.15–1.33; $p < 0.00001$) for current users, 1.16 (95% CI 1.08–1.23; $p = 0.00001$) 1–4 years after stopping, 1.07 (95% CI 1.02–1.13; $p = 0.009$) 5–9 years after stopping, and 1.01 (95% CI 0.96–1.05; $p = 0.00001$) 10 or more years after stopping pill use. Moreover, there was a weak trend of increasing risk with increasing total duration of use ($p = 0.05$), whereas there was no significant trend with increasing age at first use. Conversely, results from the Women's Contraceptive and Reproductive Experience (CARE) study [86] on 4575 breast cancer women and 4682 controls aged 35–64 years did not show any increase in risk for both women who were currently taking oral contraceptives (RR 1.0; 95% CI 0.8–1.3) and those who had used them previously (RR 0.9; 95% CI 0.8–1.0).

In a large population-based, case–control study, current oral contraceptive use was associated with increased risk of lobular carcinoma (RR 2.6; 95% CI 1.0–7.1), whereas pill use was not clearly associated with ductal carcinoma (RR 1.2; 95% CI 0.8–1.9) [87].

The Collaborative Group on Hormonal Factors in Breast Cancer study found that breast cancers diagnosed in women who had previously taken oral contraceptives were less advanced clinically than those detected in never users [85]. It is still debated whether this depends on either a direct influence of estrogens/progestins on tumor growth and metastasis, or simply an earlier diagnosis.

Data about the clinical relevance of estrogen and progestin types and doses are still conflicting and inconclusive. Although the Collaborative Group on Hormonal Factors in Breast Cancer study [85] did not show any difference in risk associated with the type of compound employed, the Norwegian Women and Cancer study (NOWAC) reported that, classifying progestins according to chemical groups, the RR increased significantly with increasing cumulative dose of levonorgestrel [88]. Moreover, a significant increased risk was found with increasing mg-months of estrogen exposure ($p = 0.002$). In a recent US population-based case–control study [89], women who recently took oral contraceptives containing > 35 μg ethinyl estradiol had a higher risk of breast cancer than users of low-dose preparations compared with never users (RR = 1.99 and 1.27, respectively, $p < 0.01$). This relationship was more marked among women younger than 35 years, in whom the RR associated with high- and low-dose ethinyl estradiol use was 3.62 and 1.91, respectively. Significant trends of increasing breast cancer risk were observed for pills with higher progestin and estrogen potencies ($p < 0.05$), which were most pronounced among women younger than 35 years ($p < 0.01$).

Hormone replacement therapy

Hormone replacement therapy and breast cancer risk. Most epidemiological studies published in the last ten years have shown that HRT usage for a few years does not increase breast cancer risk and that tumor incidence increases progressively only after 5 years of hormonal treatment. Results obtained in 1997 from the Collaborative Group on Hormonal Factors in Breast Cancer study [90], that reanalyzed more than 95% of all epidemiological data available at that time, have been confirmed by more recent studies [91–98]. In the Collaborative Study [90], 80% of hormone users had received unopposed estrogen replacement. The duration of treatment and the time elapsed since the last administration influenced breast cancer risk. The increase in risk for each year of HRT use was 1.023 (95% CI 1.01–1.03), slightly lower than expected for each year of delayed menopause in women who have never used HRT (RR 1.028; 95% CI 1.02–1.03). Overall, the RR of breast cancer was 1.14 (95% CI 1.11–1.17) among ever users and 1.35 (95% CI 1.21–1.49) among women taking hormones for 5 years or longer. The increase in breast cancer risk appeared to be limited to lean women, since obese postmenopausal women have already achieved the maximum hormone-related risk due to their endogenous estrogen production. In North America and Europe the cumulative incidence of this malignancy between the ages of 50 and 70 years in never HRT users is approximately 45/1000 women. The cumulative excess number of breast cancers diagnosed between these ages per 1000 women who started HRT at the age of 50 years and took it for 5 years, 10 years or 15 years was estimated to be respectively 2, 6 and 12. After 5 years of treatment discontinuation, the risk became similar to that of never users. This is an interesting observation, since the impact of reproductive risk factors, such as late menopause, does not appear to decrease after a period of time [99].

The more recent studies, including the Women's Health Initiative (WHI) and the Million Women Study published with great resonance between 2002 and 2004, have shown an RR of developing breast cancer for HRT users ranging from 1 to 2, with differences related to the treatment regimen [91–98].

Different dosages, different routes of administration and different preparations (estrogen alone or estrogen plus progestin) may have a significant impact on the risk of developing breast cancer. With regard to estrogens, it is important to note that most of the epidemiological studies have analyzed the use of oral estrogens, generally conjugated equine estrogens (CEE), given at standard (0.625 mg daily) or elevated dosage (1.25 mg daily). Data about the effect on the breast of low-dose regimens

(< 0.625 mg daily of CEE or equivalent) or alternative routes of estrogen administration (i.e. transdermal or the recent nasal spray formulation) are not yet available. Oral estrogens are associated with a significant reduction of circulating IGF-I levels, as they inhibit hepatic IGF-I production, whereas IGF-I modifications during transdermal estrogen administration tend to be biphasic, since the levels decrease in women with high basal values and increase in those with low basal values [100,101]. Therefore transdermal estrogens may have peculiar pharmacokinetic and metabolic properties compared with oral estrogens, and this could modify the hormone effects on breast tissue proliferation. The consensus report from the North American Menopause Society remarkably underlines the need to concentrate research efforts also in this direction [102].

In recent years all studies seem to have detected a negative effect of estrogen plus progestin associations on breast cancer risk compared with estrogens alone, even if data are still contradictory [91–93,96,98,103]. The WHI reported that after a mean follow-up of 5.2 years women treated with continuous combined oral CEE 0.625 mg daily + - medroxyprogesterone acetate (MPA) 2.5 mg daily had RR of breast cancer of 1.26 (95% CI 1.00–1.59) [96]. The risk increased only after 4 years of consumption, and it is noteworthy that women who never used HRT before enrolment in the study had RR of about unity (1.06; 95% CI 0.81–1.38), while RR was increased to 2.13 (95% CI 1.15–3.94) for women who had taken HRT for less than 5 years and to 4.61 (95% CI 1.01–21.02) for those who had received HRT for 5–10 years before starting the WHI trial. In the recent paper reporting data on the estrogen-alone component of the WHI trial in postmenopausal hysterectomized women, the risk of breast cancer for women who were given unopposed oral CEE 0.625 mg daily was not different from that of women who took placebo [98]. In fact, after a median follow-up of 6.8 years, the RR for hormone users even appeared to be reduced (0.77; 95% CI 0.59–1.01).

Also, the observational Million Women Study [97] conducted in the United Kingdom has evidenced a twofold increased risk of breast cancer for estrogen/progestin combinations as compared with estrogen alone, without any significant differences associated with specific types of estrogen and progestin or their doses. In detail, current HRT users had an adjusted RR of 1.66 (95% CI 1.58–1.75; $p < 0.0001$) of developing breast cancer compared with never users, whereas past users had no increased risk. The RR for current hormone users was 1.30 (95% CI 1.21–1.40; $p < 0.0001$) for estrogen alone, 2.00 (95% CI 1.88–2.12; $p < 0.0001$) for estrogen/progestin regimen and 1.45 for tibolone (95% CI 1.25–1.68; $p < 0.0001$). It has been calculated that 10 years' use of HRT results in five additional breast cancers per 1000 estrogen users and 19 additional breast cancers per 1000 estrogen/progestin users.

Regarding progestins, some studies have shown a certain variability of results that may be attributed to different biological actions of these compounds, especially linked to the androgenic activity of some of them, like 19-nortestosterone derivatives [104]. In the study of Magnusson and colleagues [91], breast cancer risk appeared to be higher only among women treated with androgenic progestins, with an increase of 8% for each year of use and RR of 3.41 (95% CI 1.91–6.08) after 10 years of treatment.

The relationship between tumor risk and type of combined hormonal treatment (continuous vs. cyclic sequential) has not been yet clarified. In the US Breast Cancer Detection Demonstration Project study, the RR of developing breast cancer was higher for estrogen/progestin associations (1.4; 95% CI 1.1–1.8) than for estrogen alone (RR 1.2; 95% CI 1.0–1.4), with an increase in risk for each year of use of 0.08 and 0.01, respectively [92]. In this study most women were treated with sequential MPA for 10 days per month. Also the study of Ross and associates [93] reported that breast cancer risk for each 5 years of hormone use was higher for combined estrogen/progestin therapy (RR 1,24; 95% CI 1.07–1.45) than for unopposed estrogen therapy (RR 1.06; 95% CI 0.97–1.15). It is noteworthy that the RR was higher for sequential therapy (1.38; 95% CI 1.13–1.68) than for continuous combined therapy (1.09; 95% CI 0.88–1.35), but this difference was not statistically significant. Conversely, data from a US population-based, case–control study on 1870 cases and 1953 controls aged 35–64 years revealed an increased breast cancer risk for current users of 5 or more years of continuous combined HRT (RR 1.54; 95% CI 1.10–2.17), while the use of estrogen alone or sequential associations even for long periods did not determine any meaningful increase in risk [95].

The importance of the type of progestin used has recently been underlined in two French cohort studies [105,106]. In the first study of De Lignières and co-workers [105] including 3175 postmenopausal women, the large majority of HRT users were receiving exclusively or mostly a combination of transdermal estradiol and a progestin other than MPA. The adjusted RR of breast cancer for women taking HRT was 0.98 (95% CI 0.65–1.5) and the RR per each year of use was 1.005 (95% CI 0.97–1.05). In the recent E3N–EPIC study, including 54 548 postmenopausal women, the adjusted RR of breast cancer was 0.9 (95% CI 0.7–1.2) for the group receiving estrogens combined with micronized progesterone and 1.4 (95% CI 1.2–1.7) for women using estrogens combined with synthetic progestins [106]. In the first group, there was no evidence of increasing risk with increasing duration of hormone exposure.

Prognosis of breast cancer diagnosed in hormone replacement therapy users. Many epidemiological studies

showed a more favorable prognosis of breast cancer developed in women who have consumed in the past or are taking HRT at the time of tumor diagnosis compared with never HRT users [90,107–110]. The Collaborative Group on Hormonal Factors in Breast Cancer study reported that breast cancer detected in HRT users gave less frequently lymph node or distant metastases when compared with controls [90]. Although this positive effect might derive from earlier diagnosis as a consequence of improved breast surveillance among hormone users, the large majority of the studies have shown that women treated with HRT develop breast cancers with better histological differentiation, lower proliferation rate and more favorable clinical course, thus suggesting a biological effect of HRT on the growth of less aggressive tumors [107–110]. In a Swedish cohort study conducted on 22 597 women receiving HRT, the standardized mortality ratio for breast cancer among hormone users was 0.5 (95% CI 0.4–0.6) [107]. Similarly, Jernstrom and colleagues [110] reported that HRT use before breast cancer diagnosis was significantly related to longer survival. In fact, ever HRT use prior to diagnosis was associated with an RR of death of 0.78 (95% CI 0.65–0.93; $p = 0.006$) in breast cancer women aged 50 years or older.

However, some conflicting data have been reported in the literature [96,97,111–113]. The Nurses' Health Study [111] reported an increase in mortality from breast cancer among long-term hormone users (after 10 or more years), and similar results have been obtained in the Million Women Study showing that current users of HRT at recruitment had an increased risk of dying from breast cancer compared with never users (adjusted RR 1.22; 95% CI 1.00–1.48) [97]. The WHI could not assess the risk of death due to breast cancer because of the relatively short follow-up time and the low number of women who died of breast cancer in both arms [96]. As for biological characteristics, there is no clear relationship between HRT use and ER status in breast cancer, and some authors have even reported a lower rate of ER-positive tumors among HRT users [113]. Cobleigh and co-investigators [112] observed a greater frequency of breast cancers with high S-phase fraction in women who were taking HRT compared with never hormone users (RR 2.82; 95% CI 1.04–7.66), and this greater rate of highly proliferating tumors appeared to be limited to women with ER-positive disease.

HRT can early cause a diffuse or focal increase of breast density, thus reducing the sensitivity and the specificity of screening mammography [114–117]. Different hormonal regimens may have different impacts on this mammographic finding, and an increase in breast density is much more frequent among women on combined estrogen/progestin treatment than among those receiving unopposed estrogen therapy [116]. For instance, Greendale and associates [115] assessed mammographic parenchymal density in 307 women enrolled in the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial. After 12 months of treatment, the rates of women with increased mammographic density were 0% (95% CI 0.0–4.6%) for the placebo group, 3.5% (95% CI 1.0–12.0%) for the CEE group, 23.5% (95% CI 11.9–35.1%) for CEE plus cyclic MPA group, 19.4% (95% CI 9.9–28.9%) for CEE plus daily MPA group and 16.4% (95% CI 6.6–26.2%) for CEE plus cyclic micronized progesterone group. In the WHI, tumors occurring in women who were given continuous combined HRT were found to have greater diameter and to be at a more advanced stage compared with those detected in the placebo group, probably because the early diagnosis was more difficult in women with dense breasts [117].

Some authors [94,118] underline that women consuming HRT have a higher increase of lobular than of ductal breast cancer. These data could have clinical relevance, since both the radiological diagnosis and the conservative surgery of lobular cancer are more difficult than for the ductal histotype. In any case, review of the literature data appears to suggest that breast cancers arising in HRT users generally have better prognostic characteristics and better clinical outcome compared with those detected in non-users [113].

Tibolone

Tibolone is a synthetic steroid with a weak estrogenic, progestational and androgenic activity, available in over 70 countries for the treatment of menopause-associated symptoms and osteoporosis prevention [119]. The drug's effects on bone density, hot flushes and vaginal dryness are similar to those of HRT. Moreover, tibolone has the same endometrial protection profile as continuous combined HRT, and it appears to have better clinical effectiveness on sexual disorders probably due to its androgenic properties. There are no epidemiological studies about the risk of developing cardiovascular disease in women taking tibolone. *In vitro* studies have found this drug to reduce the activity of sulfatase, increase the activity of sulfotransferase and inhibit the activity of 17β-HSD-1, and to promote apoptosis in breast cancer cells [9,120,121]. Experimental studies on ovariectomized cynomolgus macaques showed that tibolone did not stimulate breast, in contrast to distinct proliferative responses of the breast to CEE and CEE + MPA [122].

Breast tenderness, which is relatively frequent in HRT users, is rare in tibolone-treated women [116]. A recent prospective, randomized, double-blind placebo-controlled study on 166 postmenopausal women showed that an increase in mammographic density was much more common among women receiving continuous combined HRT (46–50%) than in women receiving tibolone (2–6%) or placebo (0%) [123]. In particular, the RR of increased breast

density for estradiol 2 mg/norethisterone acetate 1 mg versus tibolone was found to be 8.3 (95% CI 2.7–25.0).

Unlike for HRT, there are few epidemiological data on breast cancer incidence in tibolone-treated women. In the Million Women Study only 6% of participants had recently taken tibolone; nevertheless, an increased RR of developing breast cancer was seen also in these women (1.45; 95% CI 1.25–1.68), even if lower compared with the RR observed in women receiving combined HRT [97]. This result is still to be confirmed, since it might simply reflect the English physicians' propensity to prescribe tibolone mainly to women at higher risk of developing the disease.

In 2002, a multicenter, randomized, placebo-controlled trial was launched in over 170 centers throughout the world with the goal of assessing the safety and effectiveness of tibolone in breast cancer survivors who suffer from menopause-associated symptoms. Following the publication of the Million Women Study, the protocol committee decided to carry on enrolling women, provided that they are properly informed about the new data.

Endocrine therapy for breast cancer

The last decade has been a successful era in the development of endocrine therapy for breast cancer. Two-thirds of breast cancers are ER-positive, and a significant percentage of these will respond to endocrine therapies based on the reduction of estrogen-induced growth stimulation [7,8,54,124]. Response rates to hormonal manipulation range from approximately 60% for women whose tumors are both ER- and progesterone receptor (PgR)-positive, to 30–40% for those whose tumors are either ER- or PgR-positive, to 5% for those whose tumors are both ER- and PgR-negative.

Reduced stimulation of hormone-sensitive breast tumors can be achieved either by agents that block estrogen signals at the receptor level or by drugs that inhibit estrogen synthesis. Tamoxifen is able to arrest the growth of breast cancer cells mainly by blocking ER [7,8,54,124]. A modulation of ER can be obtained by a series of new drugs belonging to the SERM category, such as toremifene, raloxifene, arzoxifene and droloxifene, or to the selective estrogen receptor down-regulator (SERD) category, like fulvestrant [8]. The new aromatase inhibitors are able to reduce estrogen synthesis in postmenopausal women by inhibiting the conversion of androgens to estrogens [7,8,52,70–77,125]. These compounds are classified in two major classes: the type I steroidal inhibitors (such as exemestane and formestane) and the type II non-steroidal inhibitors (such as letrozole, anastrozole and vorozole).

Furthermore, in premenopausal women, the ovarian estrogen synthesis can be suppressed by gonadotropin-releasing hormone (GnRH) agonists [126].

Adjuvant endocrine therapy of early breast cancer

Tamoxifen. The standard drug for the adjuvant endocrine therapy of ER-positive breast cancer is tamoxifen [65] (Table III). Tamoxifen was approved by the FDA in 1986 and was the only agent so accepted until September 2002 when the FDA approved anastrozole, based on the results of the ATAC trial, as an option for adjuvant endocrine therapy in women with contraindication to tamoxifen use [78].

Data from an overview of 55 randomized clinical trials showed that 5 years of tamoxifen use was associated with a reduction in the risk of recurrence and death of 47% and 26%, respectively [65]. Furthermore, tamoxifen was able to reduce the risk of contralateral breast cancer by 47%. However, in a trial conducted by the NSABP, women who continued to receive tamoxifen after 5 years had worse outcomes than women in whom it was discontinued at 5 years [127]. On the basis of these results, the National Cancer Institute has recommended that tamoxifen treatment should be limited to 5 years [128].

Moreover, approximately 30% of postmenopausal women with ER-positive early breast cancer treated with tamoxifen fail to survive 10 years, many as a consequence of tamoxifen resistance [129].

New aromatase inhibitors. The good clinical results obtained with the new aromatase inhibitors in advanced breast cancer have suggested their assess-

Table III. Endocrine therapy of ER-positive breast cancer.

	Premenopause	Postmenopause
Adjuvant setting	Tamoxifen ± GnRH agonist	Tamoxifen Anastroxole (if contraindication to tamoxifen) Sequential tamoxifen and anastrozole/letrozole (investigational)
Advanced or metastatic disease	Tamoxifen + GnRH agonist	Anastrozole, letrozole (first-line) Exemestane, tamoxifen (second-line) Fulvestrant (third-line)

ER, estrogen receptor; GnRH, gonadotropin-relasing hormone.

ment as adjuvant endocrine therapy for early disease in postmenopausal women. The ATAC trial was designed as a randomized, double-blind, multicenter study for postmenopausal women with invasive operable breast cancer who had completed primary therapy and who were candidates to receive adjuvant endocrine therapy [78]. Nine thousand three hundred and sixty-six patients were randomly assigned to receive anastrozole or tamoxifen or anastrozole plus tamoxifen. After a median follow-up of 33.3 months, 3-year disease-free survival was 89.4% for anastrozole and 87.4% for tamoxifen (RR 0.83; 95% CI 0.71–0.96; $p = 0.013$), and results with the combination were not significantly different from those with tamoxifen alone (3-year disease-free survival 87.2%; RR 1.02; 95% CI 0.89–1.18; $p =$ NS). Improvements in disease-free survival with anastrozole were only seen in patients with ER-positive disease. Moreover, the incidence of contralateral breast cancer was lower with anastrozole than with tamoxifen (RR 0.42; 95% CI 0.22–0.79; $p = 0.007$). After 47 months of follow-up, 4-year disease-free survival was still better for anastrozole than for tamoxifen (86.9% vs. 84.5%; $p = 0.03$), and the benefit associated with anastrozole was even greater in ER-positive tumors ($p = 0.014$) [79]. Anastrozole showed several tolerability benefits over tamoxifen for hot flushes ($p < 0.001$), vaginal bleeding and discharge ($p < 0.001$ for both), cerebrovascular events ($p < 0.001$), thromboembolic events ($p < 0.001$) and endometrial cancer ($p = 0.007$), whereas musculoskeletal disorders and fractures were less frequent in the tamoxifen arm ($p < 0.001$ for both).

Two smaller studies conducted by Boccardo and co-workers [130,131] evaluated the effects of switching a patient from tamoxifen to an aromatase inhibitor before the completion of 5 years of adjuvant therapy, and both trials suggested that sequential treatment might be better than tamoxifen alone. In the first trial, 380 postmenopausal breast cancer patients who had received adjuvant tamoxifen for 3 years were randomized either to continue tamoxifen for 2 more years or to switch to low-dose aminoglutethimide (250 mg daily) for 2 years [130]. A statistically significant ($p = 0.005$) overall survival advantage was found for the sequential arm, whereas the aromatase inhibitor failed to impact on disease-free survival. In the second trial, investigators enrolled 448 postmenopausal breast cancer patients who had been given adjuvant tamoxifen for 2 or 3 years and who were randomly assigned to receive tamoxifen for additional 2 or 3 years or to switch to anastrozole for the same time period [131]. The results demonstrated that switching patients from tamoxifen to anastrozole might improve both disease-free survival ($p = 0.0002$) and event-free survival ($p = 0.0004$).

Goss and colleagues [132] conducted a double-blind, placebo-controlled trial to assess the effectiveness of 5 years of letrozole therapy (2.5 mg daily) in 5187 postmenopausal women with early-stage breast cancer who had completed 5 years of adjuvant tamoxifen therapy. Patients who received letrozole had a 43% reduction in disease recurrence rate and a 46% reduction in contralateral breast cancer incidence compared with placebo. Women in the letrozole arm showed slight but statistically significant increases of hot flushes (47.2% vs. 40.5%), arthralgia (21.3% vs. 16.6%) and muscle pain (11.8% vs. 9.5%), while vaginal bleeding occurred more often in the placebo arm (6% vs. 4.3%). No significant difference in the rate of cardiovascular events was detected between letrozole and placebo (4.1% vs. 3.6%), even if a longer follow-up is needed to draw a firm conclusion. The incidence of new-onset cases of osteoporosis was 5.8% for the letrozole arm and 4.5% for the placebo arm ($p = 0.07$) and the rate of fractures was 2.9% and 3.6% ($p =$ NS), respectively. However, these data may underestimate the long-term effects of letrozole on bone metabolism because of the early discontinuation of the study. The effectiveness of adding biphosphonates to aromatase inhibitors is under assessment, and until the results of this evaluation become available it is recommended that women receiving long-term letrozole therapy take calcium and vitamin D.

Currently tamoxifen remains an appropriate choice for adjuvant endocrine therapy, whereas aromatase inhibitors represent a useful alternative for patients with intolerance to tamoxifen [133]. However, the panel of experts of the American Society of Clinical Oncology suggests that optimal adjuvant endocrine therapy for a postmenopausal woman with ER-positive breast cancer includes an aromatase inhibitor as initial therapy or after treatment with tamoxifen [134].

The ongoing International Breast Cancer Study Group (BIG) trial is a randomized, double-blind study designed to compare four different adjuvant hormonal regimens: tamoxifen for 5 years, letrozole for 5 years, tamoxifen for 2 years followed by letrozole for 3 years and letrozole for 2 years followed by tamoxifen for 3 years [129]. The trial results should provide more definite guidance about the standard initial agent for adjuvant endocrine therapy and about the efficacy and safety of switching from one hormonal agent to another during the early years of adjuvant therapy.

Gonadotropin-releasing hormone agonists. In premenopausal women with early ER-positive breast cancer, the addition of a GnRH agonist such as goserelin to standard treatment (surgery with or without tamoxifen, chemotherapy or radiotherapy) appears to give a significant benefit in terms of recurrence free-survival and overall survival [135]. The current treatment guidelines from the St Gallen Conference and the European Society of Mastology recommend the use of a GnRH agonist plus tamoxifen in this clinical setting.

Endocrine therapy of advanced and metastatic breast cancer

Advanced and metastatic breast cancer is considered incurable and the goal of therapeutic strategy consists of prolonging survival and optimizing palliative care. The management of the disease is generally focused on systemic treatment, and hormonal agents represent important therapeutic tools for their effectiveness and excellent tolerability (Table III).

Tamoxifen. Over the past 25 years tamoxifen has been the endocrine treatment of choice for postmenopausal patients with hormone-sensitive metastatic breast cancer. A comprehensive review on tamoxifen reported a complete or partial response in approximately one-third of patients with advanced disease [124]. Objective responses were detectable after 6–8 weeks and lasted on average 24 months. Response rates ranged from 12% for patients with ER-negative tumors to 50% for those with high ER content tumors.

Selective estrogen receptor modulators. The results obtained with the new SERMs in metastatic breast cancer patients are disappointing. A multicenter randomized trial comparing tamoxifen 20 mg daily versus toremifene at different dosages (60 and 200 mg daily) failed to show any differences among treatment arms [136]. In a phase-III trial droloxifene 40 mg daily was significantly less effective than tamoxifen 20 mg daily [137]. Also, idoxifene failed to show therapeutic superiority or a better toxicity profile than tamoxifen. In a phase-II randomized trial comparing two doses of arzoxifene in patients with locally advanced or metastatic breast cancer, response rate was higher in the 20-mg arm compared with the 50-mg arm among tamoxifen-sensitive patients, whereas the response rate was similar in the two arms among tamoxifen-refractory patients [138].

Aromatase inhibitors. The new aromatase inhibitors were initially studied in comparison with progestins and aminoglutethimide in patients with advanced disease who progressed on tamoxifen [7]. Use of these drugs was charged by moderate to severe side-effects, such weight gain, edema, hypertension, heart failure, hyperglycemia and thrombophlebitis for progestins, as well as lethargy, skin rush and ataxia, besides the need for corticosteroid administration, for aminoglutethimide.

The introduction of the steroidal inhibitor formestane and the non-steroidal inhibitor fadrozole resulted in a modest improvement in therapeutic index compared with the old hormonal agents [139,140]. For instance, fadrozole has been shown to be equivalent to tamoxifen [140] but inferior to letrozole [141] in advanced breast cancer and will not be discussed further, as drug approval is restricted to Japan.

Conversely, both non-steroidal (anastrozole and letrozole) and steroidal (exemestane) aromatase inhibitors appeared to provide superior efficacy and a better toxicity profile than megestrole and aminoglutethimide as second-line hormone treatments in advanced or metastatic breast cancer [52,70–72]. These new drugs were subsequently compared with tamoxifen as first-line endocrine treatment in postmenopausal women with ER-positive and/or PgR-positive or unknown receptor status advanced breast cancer [73–77,142]. In a North American study, anastrozole 1 mg daily was superior to tamoxifen 20 mg daily in terms of both clinical benefit rate (59% vs. 46%; $p = 0.0098$) and time to progression (11.1 vs. 5.6 months; $p = 0.005$) [73]. The identical European study showed similar results [74]. Combined data analysis from the two studies enrolling 1021 patients showed that, after a median follow-up of 18.2 months, anastrozole was equivalent to tamoxifen in respect of time to progression in the whole series but it obtained a longer time to progression (10.7 vs. 6.4 months) in the subgroup of patients with receptor-positive tumors [75].

In a randomized, double-blind trial including 907 patients, letrozole 2.5 mg daily was more effective than tamoxifen 20 mg daily in terms of response rate (30 vs. 20%; $p = 0.0006$) and median time to progression (41 vs. 26 weeks; $p = 0.0001$) [76]. A recent update of the study with a median follow-up of 32 months confirmed the superiority of letrozole over tamoxifen regarding response rate (32 vs. 21%; $p = 0.0002$), median time to progression (9.4 vs. 6.0 months, $p < 0.0001$) and median time to treatment failure (9.0 vs. 5.7 months; $p < 0.0001$) [142]. Conversely, the median overall survival was similar for the two arms (34 vs. 30 months). In a randomized phase-II trial, exemestane 25 mg daily achieved a higher response rate than tamoxifen 20 mg daily, with a lower incidence of severe flushing, sweating and edema, as first-line endocrine therapy in postmenopausal patients with metastatic breast cancer [77]. Exemestane is the only hormonal agent that has been studied in a phase-II trial to determine efficacy in patients with prior exposure to non-steroidal aromatase inhibitor [143]. Two hundred and forty-one patients were treated with the currently approved dose of 25 mg daily followed, at the time of progression, by exemestane 100 mg daily, and an objective response and disease stabilization longer than 6 months were detected in 6.6% and 17.7% of patients, respectively. Increasing the dose of exemestane to 100 mg upon the development of progression achieved only one (1.7%) partial response among 58 patients. In April 2002 the FDA approved the use of the SERD fulvestrant to treat hormone receptor-positive metastatic breast cancer in postmenopausal women with disease progression after anti-estrogen therapy [144]. Approval was based on results of two phase-III trials enrolling 851 patients who were randomly allocated to receive either fulvestrant

250 mg intramuscularly monthly or anastrozole 1 mg daily. Ninety-six percent of patients had previously been treated with tamoxifen for early (adjuvant treatment) or advanced breast cancer. Response rates were 17% for both fulvestrant and anastrozole in the North American trial, and 20% for fulvestrant and 15% for anatrozole in the European trial, and moreover, there were no differences between the two arms with respect to time to progression or survival. No phase-II trials of fulvestrant after progression on an aromatase inhibitor have been completed, but preliminary data from interim analyses of two ongoing clinical trials showed a low response rate (6–7%) but a relatively high rate of disease stabilization (28–43%) [145].

Gonadotropin-releasing hormone agonists. GnRH agonists are effective in reducing serum estrogen concentrations below postmenopausal levels within 21–28 days in premenopausal women [126]. The use of a GnRH agonist can shrink metastatic disease in about 30% of unselected premenopausal women. In a phase-III randomized trial, goserelin was approximately equivalent to surgical oophorectomy in terms of response rate (31% vs. 27%) and median overall survival (37 vs. 33 months) in premenopausal women with ER-positive metastatic breast cancer [146]. The meta-analysis of four randomized trials showed that the combination of a GnRH agonist and tamoxifen is superior to GnRH agonist alone in terms of progression-free survival ($p = 0.0003$) and overall survival ($p = 0.02$) in premenopausal women with advanced breast cancer [147].

Conclusions

Epidemiological, experimental and clinical data have detected that estrogens play a major role in the development and progression of breast cancer. Anti-estrogenic drugs, including tamoxifen, raloxifene and anastrozole, have been tested with promising results in the chemoprevention of this malignancy in high-risk women. As for the use of exogenous sex steroids in gynecological practice, data about cancer risk associated with oral contraception are reassuring, even if results of studies on long-term use of more recent formulations are still lacking. Available data on oral HRT use for not more than 5 years have failed to detect a significant increase in the risk of developing a breast cancer. Long-term HRT administration increases the incidence of this tumor slightly, with an RR ranging from 1 to 2 depending on hormone preparation. These data have also been substantially confirmed by the recent WHI study, and can be considered on the whole reassuring. Estrogens alone, even if taken for long periods of time, seem to be safer than estrogen/progestin combinations. In recent years the number of preparations available for HRT has increased, and new administration routes and novel hormone regimens are currently under evaluation. These new treatment modalities could have different impacts on breast cancer risk because of their metabolic and pharmacodynamic effects.

As for the treatment of hormone-sensitive breast cancer, anti-estrogen drugs have been used both for adjuvant therapy of early disease and in the management of advanced and metastatic disease. The standard drug for adjuvant endocrine therapy is tamoxifen. However, recent studies appear to suggest a possible role for anastrozole and letrozole in the adjuvant setting. First-line hormonal treatment of advanced or metastatic breast cancer consists of tamoxifen plus a GnRH agonist in premenopausal patients, and anastrozole, letrozole or exemestane in postmenopausal ones. The establishment of an optimal sequence of endocrine therapies should give significant clinical benefits to breast cancer patients [8,145]. A better knowledge of the molecular basis of resistance to endocrine agents could lead to the development of a series of hormonal therapy/signal transduction inhibitor combinations tailored according to the biology of the individual tumor [148].

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