Hormonal prevention of breast cancer

Prévention hormonale du cancer du sein

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Abstract

Breast cancer prevention can be provided by using SERMs or aromatase inhibitors depending on the ovarian status, with a global risk reduction of 50 to 60%. Prophylactic annexectomy offered to reduce ovarian risk in BRCA mutation carriers also lowers breast cancer risk by 50%. Main side effects include deep vein thrombosis for SERMs, hot flushes and joint pain (although less frequently than initially suspected) with aromatase inhibitors. Other strategies based on progesterone, insulin or prolactin signaling modulation may be offered in the future. Criteria for candidate selection remain to be established.

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Keywords: Cancer; Breast; Prevention; Antihormones

Résumé

La prévention du cancer du sein peut être assurée par l’utilisation thérapeutique de modulateurs sélectifs des récepteurs des œstrogènes (SERM) ou d’inhibiteurs de l’aromatase, selon l’état de la fonction ovarienne, avec une réduction globale du risque de 50 à 60 %. Une ovariectomie peut également être proposée pour réduire de 50 % le risque de cancer de l’ovaire chez les patientes porteuses des mutations des gènes BRCA1 et BRCA2. Les principaux effets indésirables des SERM sont le risque de thrombose veineuse et les bouffées de chaleur. Et, pour les anti-aromatase, l’ostéopénie avec douleurs osseuses, moins fréquentes cependant que l’on craignait initialement. D’autres stratégies de prévention concernant les voies de signalisation de la progestérone, de l’insuline et de la prolactine devraient être disponibles dans l’avenir. Les critères de sélection pour ces traitements restent à déterminer.

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Mots clés : Cancer du sein ; Inhibiteur de l’aromatase ; SERM ; Prévention

1. Introduction

Breast cancer (BC) is the first cancer in women as it affects 50,000 women per year and causes 10,000 deaths per year. Surgical prophylaxis still remains the only strategy validated in the world and in France. This mutilating management often requires several procedures and is associated with an estimated residual risk of cancer of 5–10%, depending on the technique used. Non-surgical prevention means are thus eagerly awaited for.

Current strategies are based on what is known and progressively discovered about BC physiology. Some targets are already used in routine care while others are still more speculative (Table 1).

Breast cancer is a hormone-dependent disease with estrogens and more recently progestins having been the two promoters mainly investigated and modulated in therapeutic. Progesterone and estradiol are the main actors in development and differentiation of breast tissue.

The growth of lobular ducts is under the control of estradiol through its alpha receptor (ERα). The role of ERβ in breast...
tumorigenesis is now better known [1] and suggests that ERβ modulation may play a role in the treatment of tumors. Models of homozygous progesterone receptor-deficient mice (both PRA and PRB isoforms) showed that PRB is sufficient to allow normal growth and differentiation under the influence of progesterone [2]. The PRA isoform is over expressed in cancers with poor prognosis occurring in women from the general population [3]. It is also over expressed in normal cells surrounding the tumor of women having BRCA1 mutation operated for BC [4]. More recently, a central role of insulin and its signalization pathways has been suspected in breast carcinogenesis [5]. Clinical trials using metformin are currently ongoing for BC treatment and prevention [6,7]. The rational of those will be briefly exposed. The role of prolactin in the development of BC remains uncertain and will be quickly exposed. The numerous modulations implicated in the concept of hormonoprevention related to hormonal environment and maturation of the breast such as the beneficial effect of pregnancy before 30 years, the role of oral contraceptives and the treatment of menopause, which will not be addressed here. The two main drugs currently used in hormonal prevention of BC are selective estrogen receptor modulators (SERMs) and aromatase inhibitors (AI) that target estrogen signaling and production. The benefits of surgical castration in specific situations will also be discussed. Selective progesterone receptor modulators (SPRMs) also have potential impact in this context and will be briefly addressed. Primary prevention of BC targets healthy women. Therefore, essential questions such as defining the population needed to treat and the risk-benefit balance (medical and economic) will also be discussed.

2. Estrogen signaling modulation: a current application in BC prevention

SERMs and aromatase inhibitors are currently used for breast cancer prevention, in particular in the USA. Since they have been used for many years in breast cancer treatment the clinical body of evidence is very rich.

2.1. SERMs

The significant reduction in the risk of contralateral BC in women taking tamoxifen initially suggested that SERMs could be used for primary prevention of BC [8,9]. Studies on other SERM in prevention of osteoporotic fractures also suggested a beneficial effect of this therapeutic class on the risk of developing breast cancer. Although SERMs have different chemical structures (Fig. 1) possibly affecting their biological effects, they all act by binding to the estrogen receptor and inhibit cell division in breast cells. Jordan detailed these effects in his review [10]. The effects of tamoxifen and raloxifene have been analyzed for the first time with a relatively short follow-up from various primary prevention studies in the meta-analysis of Cuzick et al. in 2003 [11]. The results showed an overall reduction in the risk of BC expressing the estradiol receptor (HR+) of 48%, but no effect was noted for tumors not expressing the estradiol receptor (HR−).

Updated data in 2013 [12] reported long-term follow-up after preventive treatment with tamoxifen and raloxifene and provided data with short-term follow-up after treatment with lasofoxifene and arzoxifene (Fig. 1). Data from 83,399 women corresponding to 306,617 years of patient follow-up were analyzed. The average follow-up was 65 months (range: 54–93 months). An overall reduction of 38% (hazard ratio [HR]: 0.62, 95% CI: 0.56–0.69) in the incidence of BC was observed. Forty-two women should be treated in order to avoid the occurrence of one BC in the next 10 years. The risk reduction was significant for HR+ tumors, whereas a non-significant increased risk was observed for HR− tumors. This effect was observed with all SERMs and notably there was no difference of efficacy between raloxifene and tamoxifen. For lasofoxifene, risk reduction was observed with the highest dose tested (0.5 mg/day). The risk reduction was more pronounced during the first 5 years of

Table 1
Potential targets for hormonal breast cancer (BC) prevention.

<table>
<thead>
<tr>
<th>Targets</th>
<th>Molecule(s)</th>
<th>Current state of the art</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER and estrogen signaling</td>
<td>SERMs: Tamoxifen, Raloxifene, Lasofoxifene and arzoxifene</td>
<td>Routinely used for ER positive BC treatment In discussion in France Clinical trials for BC treatment: published and ongoing</td>
<td>[8,9,65] [10–12] [12]</td>
</tr>
<tr>
<td>Estrogen production</td>
<td>Aromatase inhibitors: Non-steroidal: anastrozole, letrozole Steroidal: exemestane</td>
<td>Routinely used for ER positive postmenopausal BC treatment Clinical trials for BC prevention in high risk patients: ongoing and published</td>
<td>[21,66] [16,18,22]</td>
</tr>
<tr>
<td>PR</td>
<td>SPRMs: mifepristone, onapristone, ZK 230211</td>
<td>Clinical trials for BC treatment: ongoing</td>
<td>[33,67,68]</td>
</tr>
<tr>
<td>Insulin receptor and signaling</td>
<td>Metformin</td>
<td>Clinical trial as second line adjuvant therapy in BC treatment: ongoing</td>
<td>[6,7]</td>
</tr>
<tr>
<td>PRL receptor</td>
<td>PRL antagonists: cabergolin</td>
<td>Under development</td>
<td>[69–71]</td>
</tr>
</tbody>
</table>

SERMs: selective estrogen receptor modulators; SPRMs: selective progesterone receptor modulators.
Fig. 1. Structure of currently used and evaluated SERMs. From [14].

post-treatment follow-up than in the last 5 years of follow-up (42%, HR: 0.58, 0.51–0.66, \( P < 0.0001 \) versus 25%, HR: 0.75, 0.61–0.93, \( P = 0.007 \)).

These results need to be balanced with the side effects of SERMs as compared to aromatase inhibitors, which are analyzed in a specific paragraph.

2.2. Aromatase inhibitors

Tamoxifen and raloxifene are poorly accepted in primary prevention, particularly because of thromboembolic side effects (Fig. 2). Four percent of American women at risk and 0.08% of American women aged 40 to 79 years have accepted this concept in a recent study [13].

Aromatase inhibitors (Fig. 2) are steroidal (exemestane, Aromasin®) or non-steroidal ligands (anastrozole, Arimidex®, letrozole, Femara®) of cytochrome P450 (CYP 450) of the aromatase complex [14,15]. Steroidal inhibitors bind to the catalytic site of CYP 450 and have more pronounced effects than non-steroidal inhibitors. The latter bind to the iron residue of the heme radical, and act on the reductase resulting in more temporary and reversible effects. They significantly decrease estradiol levels in postmenopausal women and have antitumor effects in animal models [16,17]. In studies conducted in women with breast cancer, a decrease in the risk of contralateral cancer was observed with both AI types and it was greater than with tamoxifen [18].

Moreover, AIs show greater performance in secondary prevention (reducing the risk of contralateral cancer) and cause fewer side effects than tamoxifen in women with BC in early stage [19–21].

A study of primary prevention of BC published in 2011 [22] was conducted in postmenopausal women with a moderate risk of breast cancer. These women showed no deleterious mutation constitutive BRCA1 and -2, had a history of benign breast lesion at risk in 11% of cases, 49% had an age greater than 60 years or a score of gail \( > 1.66 \) (40%).

In this prospective randomized study, 4560 women with a median age of 62.5 years old were included and received exemestane or placebo during 5 years. After a median follow-up of 35 months, 11 invasive cancers occurred in patients treated with exemestane and 32 cancers in patients receiving the placebo, which led to discontinue the study. The risk reduction in the treated group was 65% (annual incidence 0.19% versus 0.55%; HR: 0.35, 95% CI: 0.18 to 0.70, \( P = 0.002 \)) [22].

A study is currently ongoing [23] in France in postmenopausal women with a deleterious mutation of the constitutive genes BRCA1 and -2. This randomized study versus placebo assesses the effects of treatment with letrozole administered during 5 years. Similarly, the IBIS I prevention study [24] is also an ongoing international study evaluating the secondary effects of anastrozole and tamoxifen in women with a family history of breast or ovarian cancer.

2.3. Castration

For many years, associated castration was standard protocol in the treatment of breast cancer, whether with surgery or radiation. It is now recommended only for women with a high risk of breast and ovarian cancer due to a constitutive deleterious mutation in BRCA1 or BRCA2. The main objective of this action is to prevent adnexal cancers. The procedure performed thus consists
in bilateral oophorectomy and salpingectomy. In this particular context, there is also a reduced risk of BC of approximately 50% [25].

2.4. Adverse effects with SERM and aromatase inhibitors

In the meta-analysis of Cuzick et al. [12], the main side effect of SERMs are thromboembolic events which are significantly increased under treatment whatever the molecule used (odds ratio: 1.73, 95%CI: 1.47–2.05, \( P < 0.00001 \)). No increase in the risk of coronary or cerebral arterial incident has been observed. The risk of endometrial cancer is also increased under tamoxifen therapy and during the first 5 years of follow-up (HR: 1.64, 1.14–2.36, \( P = 0.007 \)), but this increase disappears over the next five years (0.85, 0.38–1.89, \( P = 0.7 \)). This was not observed with raloxifene. The available data do not allow to conclude on losaxifene, and a two- to three-fold risk of endometrial cancer was observed under arzoxifene (2.26, 0.70–7.32, \( P = 0.2 \)).

In the study of Goss et al. [22] comparing exemestane and placebo, side effects were observed in 88% of exemestane and 85% for placebo (\( P = 0.003 \)), without significant differences in the rate of fracture, cardiovascular events, non-breast cancer or deaths in relation to treatment. Minimal differences in quality of life (hot flashes, ligament and articular pains) were observed.

3. Alternative signaling pathways as potential targets for BC prevention

Different signaling pathways involved in BC development may be targeted for BC prevention, although in that case the body of evidence is far less developed, mainly based on epidemiological data and preclinical research.

3.1. Selective progesterone receptor modulators (SPRMs)

The controversy about the effects of progestins in breast was revived in 2002 by the publication of the results of the WHI study [26] showing an increased risk of BC in the group of women receiving conjugated equine estrogens and synthetic progestins in comparison to the group of women with prior hysterectomy, receiving only estrogen. These potential adverse effects of synthetic progestins on the postmenopausal breast had already been suggested by previously published data [27–31] on cohorts of treated women. In addition, the effects of progesterone and its receptor are now better understood physiologically and suggest a real potential for the modulation of this receptor in the treatment and prevention of BC [32].

Progesterone treatment of human BC cell lines provide conflicting results depending on cellular contexts and the cellular function studied. The available data on the proliferation of breast tumor cells MCF-7, T47 D and MDA 231 show a decrease of the proliferation with mifepristone [33]. In MCF-7 cells resistant to tamoxifen, mifepristone alone or in combination with tamoxifen can induce apoptosis and inhibit cell proliferation [34,35].

Treatment by antiprogestins (mifepristone and onapristone) allows the reduction of subcutaneous nodules and lymph node metastasis in an experimental model of grafts of breast ductal tumor, ER and PR positive, C7-2-HI-2 [36,37]. Poole et al. have developed a mouse model of genetic BC [38]. These mice have a conditional invalidation of BRCA1 and p53 limited to the mammary gland. After administration of mifepristone, none of the treated mice developed tumors at 12 months, whereas all untreated control mice developed tumors between 4 and 7 months.

Positive results were obtained with mifepristone in the treatment of BC [33,39]. These studies were conducted in treated women with metastatic BC from the general population. Data suggest that mifepristone administered in first line (before any other hormone) or in second line (after anti-estrogen) is effective in the stabilization and/or regression of the disease. These successes were mostly observed when the initial breast tumor expressed progesterone receptors [33,40].

Since mifepristone exerts antiglucocorticoid activity as well, the mechanism of action of this molecule in the breast may be mediated by the glucocorticoid receptor. Neoadjuvant mifepristone administration has recently been proposed by Skor et al. in the treatment of triple-negative tumors which frequently exhibit high rates of chemoresistance [41]. In fact this group has shown,
in a BC cell line xenograft model, that mifepristone inhibits the antiapoptotic signaling pathways of GR and may increase the cytotoxic effects of chemotherapy.

Patients carrying mutations in the BRCA1 or BRCA2 genes might be putative good candidates for prevention by SPRMs as shown by Poole et al. in their mouse model [42]. However BRCA1 mutations may be associated to the loss of expression of GR [43], suggesting that in this particular situation the mechanism of action of mifepristone is not mediated by this receptor. In clinical trials response to mifepristone was limited to PR positive tumors [33]. In the mouse model by Poole et al. [42], PR was expressed in tumors in untreated mice while no tumors appeared in mifepristone treated mice. This suggests that SPRMs act through PR. This is consistent with the data obtained with SERMs, reducing ER positive tumors, as previously discussed.

3.2. Insulin signaling pathways and metformin

The role of insulin in carcinogenesis was first suggested in type 2 diabetes patients cohort studies, showing an increase in BC risk. In the most recent meta-analysis [44], the increase appears to be limited in terms of amplitude (1.16 after adjustment for body mass index), and observed only in postmenopausal women. Similar data has been reported with metabolic syndrome [45].

Further data on the impact of type 2 diabetes treatment suggested an impact on BC risk and survival rates. In a recent meta-analysis [46], this impact was not observed for metformine or sulfonylureas, possibly because of the high-level of heterogeneity between studies, while another review showed a significant risk reduction in patient treated with metformin (RR: 0.83) [47]. In parallel, an impact of thiazolidinedione has been reported [48]. The authors of these contrasted results insist on the heterogeneity of the studies, their retrospective design and the absence of prospective randomized trials.

Conversely, animal and in vitro data have accumulated on the role of insulin signaling in BC progression [6]. These include loss of insulin receptor down regulation in cancer cells, and therefore hyperactivation of the downstream, AMP kinase-mediated transduction pathway; increase in IGF1 levels in diabetes; mediation of inflammatory process leading to increased adipokine levels, which in turn increases insulin resistance and insulin levels.

In vitro and animal models suggest that metformin may reduce breast cancer cells proliferation, possibly by activating a lethal AMPK-dependent response which can adversely affect survival of BC cell lines by inhibiting a PI3K/Akt/mTOR signaling pathway involved in cell proliferation [49,50]. Apart from its AMP kinase-mediated activity metformine may also interact with non-genomic estrogen signaling through the membrane ERα or its variants [51,52] and GPR30 [53] which are able to activate PI3K/Akt pathway directly.

Clinical trials are currently ongoing using metformin as an adjuvant therapy in BC patients [6] or in a preventive strategy [7].

3.3. Prolactin receptor modulators

Prolactin is involved in breast development and lactation. It is a ubiquitous and pleiotropic peptide hormone whose molecular characteristics are close to those of growth hormone. Prolactin is also able to activate its own receptors, present in different forms, the GH and IGF1 receptors, which are potent growth factors. It can also interact with other intracellular signaling pathways involved in tumorogenesis, particularly with signalizations of sexual steroids and HER2 [54,55]. Finally, prolactin exists in different molecular forms, one of its fragments playing an angiogenic role which could possibly be involved in tumor processes [56].

There is debate regarding its role in breast tumorogenesis due to potential differences between animal models and human disease. The data in murine models show a pro-tumor role of prolactin and clinical studies in the 1980s showed hyperprolactinemia to be a poor prognosis marker [57,58]. However, the few studies available have not established a link between onset of mammary tumors and circulating prolactin levels [57].

Currently it is known that prolactin may be produced locally in the breast tumor and be responsible for particular pro-tumoral effects. Physiological arguments also exist in humans for this mechanism. Moreover, the existence of variant forms of the prolactin receptor, endowed with an increased activity and linked with breast tumorigenesis activity has also contributed to the understanding of these mechanisms [59].

The search for therapeutic strategies relies on specific inhibitors of prolactin receptors. The role of prolactin in resistance to systemic treatment of BC is also being explored.

4. BC prevention: to whom should we offer it? Is it affordable?

4.1. Patient selection

Different statistical methods are available to calculate risk scores of breast cancer. These relate to either the general population (score Gail-NCI) or a context of genetic risk (scores Claus, BRCAPRO, IBIS and IBIS changed BCPCG, BOADICEA) (Table 2). Whether it is a general or a familial context, these models estimate the risk, that is to say the probability of being diagnosed with BC during life.

The possible use of these tools requires a good knowledge of the data considered and limitations of the model. The interpretation at the individual level of the calculated probability should be limited to the medical practitioners to guide follow-up recommendations in the specific context of each patient. They are of unequal value in predicting risk in women with a genetic risk. Introducing the characteristics of any prior tumor in these models improves their relevance [60]. These tools have not yet been evaluated for their predictive value regarding response to preventive treatment.

4.2. Temptative cost-benefit evaluation

The medical and economic evaluation of prevention is difficult to drive [61]. Apart from the obvious psychological and
Table 2
Models for breast cancer (BC) risk calculation.

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<tbody>
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<td>Genetic</td>
<td>Genetic</td>
<td>Genetic</td>
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<tr>
<td>Family history</td>
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<td>Second</td>
<td>Second</td>
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<td>BRCA1 prevalence</td>
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<td>0.05%</td>
<td>0.07%</td>
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<td>BRCA2 prevalence</td>
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<td>0.07%</td>
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<tr>
<td>Number of breast biopsies</td>
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<td>Number of children</td>
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<td>Hormone therapy treatment</td>
</tr>
<tr>
<td>In situ lobular carcinoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Atypical hyperplasia</td>
</tr>
</tbody>
</table>

Reviewed in [73].

human cost of BC for the patient and his family, the cost of therapeutic care is important. Medical treatment is estimated between 7700 and 14,900 euros [62]. The surgical management for the heaviest strategies (mastectomy, lymphadenectomy) reaches 10,800 euros, breast reconstruction can reach 29,000 euros [63]. Radiation treatments cost about 750 euros each.

Prophylactic surgery involves the surgical costs already mentioned. The residual risk being evaluated and discussed above leads centers to propose radiological monitoring relatively close to that made in the absence of prophylaxis, with costs that are maintained. This is currently discussed on a national basis.

Drug prevention includes medical treatment, which can be estimated for example at 33,600 euros for a daily treatment with letrozole from 40 to 80 years, and monitoring. In a study in the GENEPSO cohort of women mutated in France [64], the cost of screening for BC in this population including annual breast MRI was estimated at 9200 euros by cancer detected versus 5600 euros if no MRI was performed (unpublished data). In comparison, the cost of screening for BC in the screening program of the Lower Rhine between 1990 and 1997 was 13,800 euros. As mentioned above, these costs are currently at least partially maintained even after prophylactic surgery. Monitoring of treatment with letrozole also includes monitoring of lipid and bone and possible prevention of demineralization by vitamin and calcium supplementation. The cost of bone densitometry is 50 euros, carried out every two years from 40 to 80 years, the cost would amount to 1000 euros. The annual cost of lipid and vitamin calcium treatment is low.

Given the treatment costs of breast cancer, drug prevention strategies appear to be potentially interesting from a purely economic point of view, after non-specific rough analysis.

5. Conclusion

Hormonal prevention of BC is currently based on the modulation of estrogenic effects by SERMs or aromatase inhibitors. Recent data on the use of exemestane show significantly better tolerance than had been feared. Modulating the effects of progesterone is an option being evaluated. Candidate selection for primary prevention remains unclear.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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