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Editorial

Endocrine treatment and prevention of breast and gynaecological cancers

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1. Introduction

The first international Flemish Gynaecologic Oncology Group (FGOG) meeting in 1997 was on tamoxifen and the uterus. Thereafter, all the international meetings from FGOG updated the audience biannually on the latest developments in 'endocrine treatment and prevention', mainly in breast, but also in other gynaecological cancers. The 4th meeting held in 2004 was built around the following four topics: (1) prevention of breast cancer; (2) the oestrogen receptor (ER) and factors interfering with anti-oestrogen activity; (3) adjuvant and metastatic endocrine therapy; (4) hormone replacement therapy (HRT). Over 400 delegates from 20 different countries attended this meeting. Each invited presentation and selected abstract for oral presentation was offered an extended abstract in this supplement of *European Journal of Cancer*. This accompanying Editorial provides you 'in a nutshell' the meeting's highlights.

2. Prevention of endocrine-responsive gynaecological cancers

Selective oestrogen receptor modulators (SERMs), like tamoxifen and raloxifene, have the potential to reduce mammographic breast density [1,2]. They also lower the incidence of breast cancer and ductal carcinoma *in situ* [3–5]. Although breast cancer risk reduction with SERMs seems higher in women with high circulating oestradiol levels [6,7], the protective effect is also seen in a low breast cancer risk population, such as in postmenopausal women with established osteoporosis in the Multiple Outcomes of Raloxifene Evaluation (MORE) trial [5]. After four years of use, continuing raloxifene for another four years further reduces the breast cancer risk by 59% as reported in the CORE trial, an extension of the MORE trial. They studied 3510 women continuing on raloxifene and 1703 continuing on a placebo. Less than 1% of the women taking raloxifene developed invasive breast cancer, compared with 1.6% of the women taking placebo [8]. Women with a proven 'premalignant' breast lesion such as 'atypical ductal hyperplasia' or 'lobular carcinoma *in situ*' benefitted most from prevention and both conditions are currently predictors for being offered chemoprevention in the United States (US) [9,10]. Following the National Surgical Adjuvant Breast and Bowel Project (NSABP) P1 data [9], the American Food and Drug Administration (FDA) registered tamoxifen for breast cancer prevention in women with a five-year breast cancer risk of at least 1.67% according to the Gail model. Freedman and colleagues [11,12] have calculated that 15% of the US population is at risk, but that only 4.9% of all white US women would have a positive benefit/risk index for breast cancer chemoprevention using tamoxifen. According to a survey carried out in 2000, two years after the FDA's approval, only, and this is probably an overestimated number, 0.2% of white women age 40–79 years in the US without a previous history of breast cancer were taking tamoxifen for chemoprevention [12]. In women with such a high breast cancer risk, tamoxifen would prevent or defer this disease in 1%. According to data from the MORE trial, the estimated number needed to treat or prevent one breast cancer

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for raloxifene users varies according to circulating oestradiol levels between 48 and 111 [6]. It is also unclear which is best, tamoxifen or raloxifene, but this is currently being tested in the NSABP-P2 trial, which has almost completed the accrual of 19000 women [13]. Absence of a uterus is already one important factor in determining differences between tamoxifen and raloxifene with regard to the risk/benefit ratio. Apart from potential uterine side-effects, like irregular periods, postmenopausal vaginal bleeding, polyps, cancer and sarcoma [14,15], other potential risks may outweigh any benefit like hot flushes, pulmonary embolism, stroke, deep vein thrombosis and eye problems such as cataracts [16]. Whether side-effects from SERMs are different or predictable in different breast cancer risk groups is still unknown. Pre-existing endometrial disease and the size of intra-uterine masses measured by ultrasonography are risk factors for endometrial pathology on tamoxifen [17,18] but this is currently being assessed prospectively within ATAC (anastrazole, tamoxifen, alone or in combination) [19], where less endometrial side-effects are expected with oral aromatase inhibitors [20]. Risk factors for thrombo-embolic events from tamoxifen are less clear. Being overweight and Factor V Leiden and prothrombin mutations were not associated with thrombosis, but immobilisation, fractures and prior surgery predict for developing venous thromboembolic events on tamoxifen [21]. The relative effects of tamoxifen's benefits and harms should also take into account that risk reduction is only seen for oestrogen receptor (ER)-positive breast cancers and that follow-up data like survival from breast cancer beyond those published for P1 at the interruption of this positive trial were never updated [5,9]. Many other questions remain unanswered: Are breast cancers prevented permanently or is clinical presentation only delayed; how long will a carry-over effect of tamoxifen in the preventive setting last? According to a hypothetical calculation, in a population of 1000 women age 50 years with a breast cancer risk profile as in the P1-trial, 25/1000 SERM users instead of 50/1000 non-SERM users will develop breast cancer during a 15-year period. The survival benefit of tamoxifen for chemoprevention, which remains hypothetical, is defined by the delayed therapeutic effect of tamoxifen on tamoxifen-sensitive breast cancers that appear in the non-treated group. An estimated 10% survival benefit from tamoxifen on mortality rates means that 2–3 women in a thousand high breast cancer risk women will not die of the disease thanks to tamoxifen. This figure compares favourably with the effect of breast cancer screening on breast cancer mortality in this age group and over the same time period, where between one and two thousand women are needed to prevent one woman from dying of breast cancer [22]. What about newer SERMs, currently in Phase III clinical studies for postmenopausal health, like lasofoxifene, bazedoxifene and arzoxifene? We will have to wait until our 2006 meeting for this evidence to be reported.

The effect of tamoxifen on the genital tract was the topic of the first international FGOG meeting in 1997; only one oral presentation highlighted today's 'state of the art' on this issue [23] 'There is no place to screen for asymptomatic endometrial lesions while on tamoxifen and baseline uterine assessment may be more important'. The molecular mechanisms of tamoxifen's carcinogenic effect on the endometrium were summarised [24,25]. The Dutch Tamarisk (risk of tamoxifen-associated malignancies) study was presented [26]. Uterine sarcomas are more frequently seen (estimated at an extra case of 1/10 000 users/year) in long-term tamoxifen users, but this may be of less clinical relevance since tamoxifen is only given for five years [14]. This certainly is informative for trials considering tamoxifen use for long-term prevention and if current ongoing trials like adjuvant tamoxifen longer against shorter (ATLAS) or adjuvant tamoxifen treatment offer more (aTTom) decide more than five years should become the standard. Tamoxifen's agonistic and antagonistic effects on the female genital tract depend on the ambient oestradiol concentration and the menopausal status of the patient. In postmenopausal women, tamoxifen has a potential oestrogen agonistic effect on the vaginal epithelium, the uterine myometrium and the endometrium, although in some women, atrophic findings do not change on tamoxifen. Tamoxifen induces in most women benign cystic hyperplasia of the endometrial stroma and in a few, it causes endometrial polyps. The risk of endometrial cancer increases 2–3-fold (estimated at an extra case of 1/1000 users/year) after an exposure of up to 5 years. In asymptomatic tamoxifen users, gynaecological surveillance is therefore not recommended. Any postmenopausal bleeding, independent of tamoxifen use, requires an endometrial histology. Despite its gynaecological side-effects, the benefits of tamoxifen in breast-cancer treatment outweighs the risks. A non-hysterectomised patient with a history of endometrial polyps or other endometrial disease should be treated with an oral aromatase inhibitor.

Because of long-term side-effects with SERMs, the 'at-risk' population should have the highest possible benefit-to-risk ratio and the Gail model, which only delineates a population with a doubling/tripling of breast cancer risk, needs to be reconsidered [27]. Goldstein urged a modification of the Gail model that also takes other risk factors into account, such as circulating postmenopausal oestrogens, alcohol use and breast/bone density. He also suggested omitting a number of previous breast biopsies because these are no longer relevant in this era of core-needle/open breast biopsies following an abnormal screening mammogram. A further fine-tuning of the risk factors for breast cancer may be-

come apparent from studying the breast cancer cases in the Nurses Health Study. Risk factors for breast cancer differ when divided by ER/progesterone receptor (PR) status into four groups. Colditz and colleagues [28] recently showed different associations with age, history of pregnancy, postmenopausal hormone use, and body mass index (BMI) after menopause comparing oestrogen-sensitive with oestrogen-independent tumours. There is clearly a need to combine risk factors to provide a better overall determination of the breast cancer risk.

Although some risk models include genetic and family histories, personal factors such as reproductive and medical history should also be taken into account. However, none have incorporated personal risk factors with a detailed genetic analysis. The discovery of the *BRCA1* and *BRCA2* genes has explained some of the genetic determinants of breast cancer risk, but these genes alone do not explain all of the familial aggregation of breast cancer. Mutation in genes that leads to an inheritable high sensitivity to oestrogens may also play a role [29]. Among the candidate genes are low penetrance genes coding for proteins involved in steroidal hormone metabolism and oestrogen receptors leading to risk modification, as recently suggested for the response of high-density lipo-protein (HDL)-cholesterol to HRT [30]. As shown in twin and family studies, bone and breast density have a strong heritable component [31,32]. Women with a familial history of breast cancer also have a higher risk of breast cancer at a given level of bone density compared with women without such a family history of the disease. If susceptibility factors within such families could be identified, it would be possible to identify women by their genetic profile leading to targeted breast cancer prevention and tamoxifen may play a more important role than in carriers of mutated BRCA genes [33]. In the meantime, risk modifiers for carriers of mutated BRCA genes have been identified, such as a lack of obesity in adolescence, physical exercise, reproductive history and oral contraceptives [34,35]. Hormone replacement is not a proven risk modifier, but bilateral salpingo-oophorectomy helps to reduce the breast cancer risk [36].

Such risk factors or risk modifiers should be included in currently available risk models' such as the Gail/Claus models. Tyrer and Cuzick [37] recently developed such a model incorporating the BRCA genes, a low penetrance gene and other personal risk factors; following its validation, it seems to be the most consistently accurate model for the prediction of breast cancer [38]. The Gail, Claus and Ford models all significantly underestimate risk, although the accuracy of the Claus model may be improved by adjustments for other risk factors. Once such models are approved, the acceptability and efficacy of prevention strategies need to be validated taking the effects of such genetic risk into consideration [39]. If strategies for prevention have a higher efficacy than, for example, the long-term use of tamoxifen, it will be easier to modify hormonal 'milestones' in a woman's life. These 'milesones' are age at first pregnancy, long-term use of hormonal contraception and substitution, long-term use of SERMs, aromatase inhibitors, bilateral salpingo-oöphorectomy and prevention of early age and postmenopausal obesity [39].

As for the treatment of cancer, the psychosocial impact of any prevention strategy in women at a high risk of breast cancer should not be underestimated [40]. Should not we improve quality of life when performing 'prevention'? Prophylactic bilateral mastectomy, bilateral salping-oophorectomy, long-term use of tamoxifen and regular surveillance will all affect the woman's quality of life. Tamoxifen-related side-effects are well described with a four-year follow-up in two placebo-controlled double-blind randomised trials investigating tamoxifen for chemoprevention. They do not include anxiety, psychological distress, depression or sexual dysfunctioning [41]. Only vasomotor symptoms were more frequently reported. Raloxifene does not seem to differ from tamoxifen in this respect [42,43]. Prophylactic breast surgery will decrease the fear of developing cancer, but will affect body image and sexuality [44]. Bilateral salpingo-oophorectomy may be more acceptable [45]. Not only prevention, but also treatment modalities, affect quality of life. Chemotherapy compares unfavourable with hormonotherapy regarding quality of life issues [46]. However, women will choose chemotherapy for a proven 1% gain in survival benefit. The arrival of the oral aromatase inhibitors for the treatment and prevention of breast cancer implies there will be new and different side-effects [47]. Many of the strategies for breast cancer prevention involve severe oestrogen deprivation and it is important to consider the acute and long-term effects of an early induced menopause followed by a further lowering of circulating oestrogens in young women (at high risk for) with breast cancer. Musculo-skeletal events, fractures and sexual dysfunctioning show how important low levels of oestrogens are for a normal functioning in the menopause. Cuzick presented his proposed solutions for these 'new' side-effects [47].

3. The oestrogen receptor and interfering factors

The ovarian hormones, oestrogen and progesterone induce a complex tissue-specific response throughout the body. Significant progress has been made in defining the molecular mechanisms by which cells distinguish between agonists and antagonists and how some receptor modulators (co-activators and co-repressors) can manifest their actions in a cell-selective manner [48]. Predispositions to the risks of hormones for developing breast and other oestrogen-related cancers may be

genetic in origin, but also could be influenced by environmental factors. Ligand binding to the nuclear receptor leads to conformational changes within the receptor and to interaction with DNA-response elements activating co-regulators. McDonnell [49] examined how we should incorporate recent advances in our understanding of the molecular pharmacology of oestrogens and progestins into medical practice. He also presented evidence on how xenobiotics or environmental compounds affect steroid hormone signalling and peoples's sensitivity/responsiveness to hormones. Methoxyacetic acid and the commonly prescribed anticonvulsant, valproic acid, both short-chain fatty acids, dramatically increase cellular sensitivity to oestrogens, progestins, and other nuclear hormone receptor ligands [50] and also enhance tamoxifen-mediated ER-α transcriptional activity. Different factors influence the molecular pharmacology of ER-ligands; such as the expression of the PR and the relative expression level of the two ER subtypes, the different impact of 'ligands' on the structure of the receptors and the ability of differently conformed receptors to interact with other factors that are needed for activity [49].

A tumour's global microarray gene expression profile may be able to classify breast cancers into biological subgroups that differ with regard to patient prognosis and response to therapy. Gruvberger and colleagues [51] have previously shown that ER-positive and ER-negative breast cancers have remarkably distinct gene expression profiles when a hierarchical clustering of the top 113 genes is analysed [52]. They are also able to predict ER-protein values on a continuous scale from the gene expression profiles that are switched on in ER-positive tumours enabling a cut-off threshold for ER-status to be set [52]. So far, no study has shown whether this approach predicts better the response to hormonal treatment compared with other measures which differentiate between ER status, such as immunohistochemistry. Finally, she also showed a consistent reciprocal relationship (no overlap) in the expression levels of certain genes that are important for the prediction of ER-protein and the fraction of cells in S phase [53].

Stephen Johnston [54] showed how various growth pathways in cancer cells 'cross-talk' with the ER-pathway and he showed how resistance to endocrine therapy can be linked to HER-2/neu and ER co-expression. Peptide growth factor receptors and their associated downstream pathways appear to be intimately involved in the mechanisms of acquired resistance [54]. New drugs, like farnesyl transferase inhibitors (FTI) and tyrosine kinase inhibitors (TKI) may disrupt this cross-talk between ER and growth factor signalling. A number of these small molecule signal transduction inhibitors are in the early stages of clinical development for the treatment of breast cancer. Pre-clinical evidence suggests that these drugs may be most effective when they are used in combination with endocrine therapy due to synergy between these two types of agents with regard to activity [55,56]. It was also shown from laboratory data how ER-sensitive cells adapt over time to low levels of circulating oestrogens and thereby escape from oestrogen deprivation using alternative intra-cellular signalling pathways. Mechanisms for acquired resistance to tamoxifen may allow aromatase inhibitors to work. New monoclonal antibodies, like gefitinib, will target alternative pathways delaying the development of resistance to tamoxifen. This hypothesis is currently being tested in the tamoxifen-/gefitinib trial for first-line metastatic or locally advanced inoperable breast cancer. Again, the question remains as to whether these therapies translate into a further improvements in clinical outcome.

Fuqua [57] stated that both ER-α coregulators and a specific ER-α mutation are upregulated in metastatic deposits of ER-positive breast cancer. The presence of such an ER is a poor prognostic marker. The group generated a monoclonal antibody for the detection of ER-β in archival, formalin-fixed breast tumours and have examined its expression using immunohistochemistry in over 300 breast cancer patients. Coexpression of ER-β and ER-α was found in most of the tumours. ER-α, but not ER-β, was strongly associated with PR expression. Although ER-α expression was positively correlated with a good patient prognosis, ER-β expression showed a trend towards an association with aneuploidy and no association with tumour grade or S-phase fraction was seen. High ER-β also predicted for a greater benefit from tamoxifen treatment and this was reflected by a better DFS and OS. ER-β therefore, seems to be an additional and independent predictor of response to tamoxifen treatment [58].

Recent evidence confirms that both steroid hormone receptors when considered on their own have only short-term prognostic value [59]. When their joint expression is considered, patients who are ER- and PR-positive have a better outcome than those with a ER-positive/PR-negative phenotype [59–61]. Twenty five percent of all ER-positive breast cancers are PR-negative and this proportion is menopausal-related. A premenopausal patient with an ER-positive breast cancer is less likely to be PR-negative (12.8%) than after the menopause (28.1%). A negative PR in a woman with an ER-positive breast cancer is an independent predictor for a positive lymph node status in women under the age of 50 years, independent of the grade of the breast cancer, but not in women after 50 years of age [60]. The ER-positive PR-negative phenotype is more common after the menopause and this is probably related to the lower levels of circulating oestrogens observed after the menopause, but may also indicate another pathway for tumour growth, especially in premenopausal women where oes-

Table 1
Proportion of breast cancers being HER-2/neu-positive by age and PR in women with an ER-positive breast cancer

HER-2/neu 2+/3+ (%)	<50 years	>50 years
ER+PR+	14.7%	9.9%
ER+PR−	23.8%	20.5%

trogens are abundantly present. An ER-positive breast cancer which is PR-negative is more likely to be HER-2/neu-positive compared with an ER-positive breast cancer that also expresses PR (Table 1) [62]. This may explain resistance to tamoxifen in women with an ER-positive breast cancer when PR is not expressed [63]. On hormonal therapy, disease-free curves between the phenotypes ER^+PR^+ and ER^+PR^- widen referring to a better response to hormone therapy in cases of an ER^+PR^+ breast cancer [59]. Dowsett [55] also presented evidence that the ER-positive/PR-negative phenotype of breast cancer benefits more from anastrazole than from tamoxifen therapy.

Many other molecules are involved in the biology of breast cancer and studied for their potential as predictive markers for hormonal therapy [64–66]. Overexpression of cyclin E or its low molecular weight forms is associated with a poor prognosis and may also explain resistance to anti-oestrogens [64]. They are overexpressed in 25% of breast cancers, where two-thirds were ER-positive. These molecules bypass the inhibitory effects of p21 and p27 induced by anti-oestrogen treatment and may thereby lead to *de novo* or acquired resistance to anti-oestrogens. Results from the clinic are awaited. Further studies are also warranted to explain the underlying resistance to endocrine therapy when urokinase plasminogen activation: plasminogen activator inhibitor-I (uPA:PAI-I) levels are high [65]. The levels of evidence for most molecular markers are currently being studied and these markers are still unsuitable to make individual patient treatment choices.

Gene microarrays have been successfully used to classify breast cancers into subtypes with specific gene expression profiles and to evaluate prognosis [67,68]. Reverse transcriptase-polymerase chain reaction (RT-PCR) has also been used to evaluate the expression of multiple genes in archival tissue. Berns and colleagues [68] used glass arrays with approximately 18 000 spotted human cDNAs to identify a gene expression pattern that predicts the type of response to anti-oestrogen therapy. These microarrays have identified and validated a set of classifier genes that can distinguish primary breast tumours from patients who responded and who did not respond to anti-oestrogen treatment [69]. However, as yet, gene microarrays for prognostic or predictive purposes are still experimental. Several groups are currently exploring the possibility of using these prognostic gene expression profiles to guide adjuvant therapy, especially to identify those who may not need this therapy, i.e. the lymph node-negative patients. Proteomic technologies, the study of the complete set of proteins expressed in a cell, are in development and will also be used to predict response. Serial biopsies, that compare the protein profile before and after hormonal therapy, may allow us to determine particular protein profiles that predict for ultimate clinical outcomes [70].

4. Adjuvant therapy

What is the ideal hormone therapy for a premenopausal woman with an ER-positive breast cancer? Can we leave out chemotherapy? Is (temporary) amenorrhoea better; is there a place for aromatase-inhibitors or can we continue to use tamoxifen? Where polychemotherapy is the only option for women with an ER-negative breast cancer, polychemotherapy, tamoxifen, and ovarian ablation all reduce the risk of recurrence and death from ER-positive breast cancer by at least a quarter [71]. The meeting recognised that tamoxifen is always needed, either alone or in combination with the other modalities: chemotherapy or ovarian ablation. There are enough data to support this assumption and the Early Breast Cancer Trialists' Cooperative Group (EBCTCG) has confirmed this in their latest published overview analysis, which was updated during this symposium: Tamoxifen is better than no tamoxifen and its combination with ovarian ablation is better than ovarian ablation alone, independent of whether chemotherapy was given [71,72]. The FGOG meeting in Brussels asked the following two questions:

(1) Do we still need to give adjuvant chemotherapy? Today, almost all premenopausal women with high-risk, ER-positive breast cancer receive polychemotherapy followed by hormone therapy. Endocrine therapy alone with suppression of ovarian function plus tamoxifen may be sufficient to achieve the same outcomes as chemotherapy, especially for patients at a low risk of recurrent disease. The ablation or suppression of ovarian function was equivalent to chemotherapy in at least eight randomised trials [73]. Among the many studies that have compared adjuvant chemotherapy with endocrine therapies, one of the largest has been the International Breast Cancer Study Group (IBCSG) [74] and Austrian Breast and Colorectal Cancer Study Group (ABCSG) Trial 5 [75,76], which yielded similar results for LHRH alone and better results for LHRH plus tamoxifen than with chemotherapy alone. However, despite the fact that these trials favour the use of combined hormonotherapy this does not justify the systematic replacement of adjuvant chemotherapy followed by hor-

monal therapy with ovarian suppression and tamoxifen in all premenopausal patients with endocrine-responsive tumours. We lack data on the efficacy of ovarian ablation plus tamoxifen compared with regimens shown to be superior to 6X cyclophosphamide, methotrexate, 5-fluorouracil (CMF) or 4X doxorubicin, cyclophosphamide (AC). The ideal adjuvant hormone therapy will have to be compared with the best available combination of chemotherapy sequentially followed by the best hormone therapy. This may be tamoxifen, or ovarian suppression plus tamoxifen or ovarian suppression plus an aromatase inhibitor. The answer to the question for the need of adjuvant chemotherapy is currently being investigated in the Premenopausal Endocrine Responsive Chemotherapy (PERCHE) trial, which compares suppression of ovarian function plus chemotherapy followed by tamoxifen or exemestane versus suppression of ovarian function and tamoxifen or exemestane without chemotherapy for patients with ER-positive tumours [77].

(2) Do we need to add ovarian ablation to tamoxifen or to chemotherapy plus tamoxifen? The question is an old one [78], but we still do not have the answer. Several studies like the ZIPP-trial have compared the additional effect of ovarian ablation to tamoxifen, but, unfortunately, no decent published data are available. A surrogate marker for ovarian suppression is 'post-chemotherapy amenorrhoea'. Whether chemotherapy-induced amenorrhoea has a prognostic effect remains unclear [76], as prospective studies do not exist. Some retrospective analyses show that women who continue to have menses have less benefit from chemotherapy with regard to a reduced risk of recurrence and death, especially if they are aged less than 40 years and node-positive [79–81]. The recently published data from the IBCSG also show that only young women may benefit from post-chemotherapy ovarian suppression, but do not answer the question of whether this is also the case if tamoxifen is added to CMF – the chemotherapy regimen used in this study [74]. Pooling all retrospective data, more evidence is compatible with an additional adjuvant effect of amenorrhoea after chemotherapy, particularly in women aged < 40 years but level 1 evidence is lacking. We also agree that the time has come to examine whether an aromatase inhibitor will prove to be a superior alternative, because the results of recent trials indicate that complete suppression of oestrogen production for five years may be a better strategy than blocking its action at the receptor level [82,83]. This question of ovarian suppression and aromatase inhibitors is now being addressed by the global Suppression of Ovarian Function Trial (SOFT; coordinated by the IBCSG on behalf of the Breast International Group (BIG) and the North American Breast Cancer Intergroup) [77]. SOFT compares tamoxifen alone versus suppression of ovarian function (by either the Gonadotrophin-releasing hormone (Gn-RH) analogue triptorelin or bilateral oophorectomy or ovarian irradiation) plus tamoxifen versus suppression of ovarian function plus exemestane (a steroidal aromatase inhibitor) for patients with hormone receptor-positive tumours who remain premenopausal after adjuvant chemotherapy or for whom tamoxifen alone is considered a reasonable treatment option. The complementary Tamoxifen and Exemestane Trial (TEXT) compares the Gn-RH analogue triptorelin, plus tamoxifen versus triptorelin plus exemestane for patients who receive the Gn-RH analogue, with or without chemotherapy from the start of their adjuvant therapy programme (77). Thus, the roles of ovarian function suppression and of an aromatase inhibitor are being prospectively studied in the adjuvant setting for premenopausal patients with endocrine-responsive breast cancer.

Postmenopausal women with a lymph node-negative breast cancer expressing high levels of ER have no survival advantage above 1% from adding chemotherapy to tamoxifen [84]. Those fit enough for chemotherapy and at a high risk of relapse (node-positive disease) do gain some benefit from CMF according to some [85], but not all studies [86]; benefit of chemotherapy plus tamoxifen versus tamoxifen alone has been reported if chemotherapy contains an anthracycline [87] or a taxane [88,89]. Within these trials, some higher risk subgroups, such as those with N2a lesions [88], or women with an ER-positive breast cancer, did not necessarily benefit from the added taxane [89,90]. If tamoxifen is started after completion of chemotherapy, chemotherapy is more efficient because tamoxifen seems to antagonise chemotherapy [87]; by contrast, there is no need to wait until the end of radiotherapy before starting tamoxifen. Some patients with an ER-positive tumour and also expressing HER-2/neu may not benefit at all from adjuvant tamoxifen, as has been suggested from results in a neoadjuvant clinical trial comparing tamoxifen with letrozole in postmenopausal women [91]. So far, the true predictive value of HER-2/neu can only be estimated from prospective randomised clinical trials [92,93]. A lot of as yet unknown data from adjuvant trials comparing tamoxifen with these three oral aromatase inhibitors are still awaited. All three oral aromatase inhibitors offer the clinician more choices when deciding the adjuvant hormone therapy in postmenopausal breast cancer patients [82,94–96]. From the efficacy viewpoint, only data on disease-free but not overall survival are available. In the adjuvant setting, five years of anastrazole is currently the only aromatase inhibitor to have proven superior efficacy over five years of tamoxifen [82]. There is no place for combined anastrazole and tamoxifen treatment [82]. Statistically significant reductions in serum letrozole and anastrazole levels of 37% and 27%, respectively, have been observed in patients receiving these drugs in combination with tamoxifen. A second possible expla-

nation for the lack of improvement with the combination of tamoxifen with anastrazole or letrozole is that the elimination of 99% of oestrogens from the body with oral aromatase inhibitors causes the partial oestrogen agonistic effects of tamoxifen to become apparent.

As said before, the subgroup of ER-positive breast cancer patients not expressing PR may benefit more from anastrazole than from tamoxifen compared with those expressing PR [94]. Ferno and colleagues [97] already found prolonged tamoxifen therapy for five years instead of two years was beneficial for patients with ER-positive and PR-positive breast cancer, whereas three extra years of tamoxifen had little or no effect for patients with ER-positive, but PR-negative tumours. Furthermore, recent evidence shows that following two years of tamoxifen treatment, switching to exemestane is superior to continued tamoxifen in postmenopausal women with an ER-positive breast cancer. Also, women with a lower risk of disease recurrence and independent of the PR-status seem to benefit. This confirms previous data recently presented for the switch to anastrazole after 2 years taking tamoxifen [96,98]. Data for letrozole against tamoxifen from baseline or following two years of tamoxifen and *vice versa* are awaited from the BIG-98 trial, but starting letrozole after five years of tamoxifen is better than stopping tamoxifen with a small survival advantage in node-positive patients, as presented during the last American Society of Clinical Oncologists' (ASCO) meeting [95,99]. Letrozole is the first and only treatment to achieve a significant disease-free survival (DFS) benefit in the extended adjuvant setting after early use of adjuvant tamoxifen. However, there was no survival benefit in node-negative patients, the follow-up is short and the optimal duration of use of letrozole after five years of tamoxifen is still unknown [95,100]. In a trial of extended adjuvant therapy, adverse events were reported more frequently following letrozole treatment than placebo including hot flushes, arthralgia, myalgia and arthritis.

So far, only tamoxifen, toremifene and anastrazole are approved for adjuvant therapy of breast cancer, but others will follow. Some subgroups may do better with an oral aromatase inhibitor from baseline, or after two or five years of tamoxifen, but specific guidelines have not yet been drawn. New treatments also imply new side-effects and some will be more specific for one compound than for another. The steroidal structure of exemestane, and especially its 17-hydro-metabolite may induce less bone loss than the non-steroidal aromatase inhibitor [101]. However, Lonning and colleagues [102] showed that after two years of therapy, compared with placebo, exemestane, like anastrazole [101], also increases bone loss, especially at the femoral neck, but not in the spine.

Neoadjuvant hormone therapy can reduce the tumour volume making inoperable tumours operable or enabling patients (who would have required a mastectomy) to undergo breast-conserving surgery [91,103,104]. The biological differences between tamoxifen and aromatase inhibitors with regard to their effect on proliferation [105] are reflected in the clinic. Responses with each of the available aromatase inhibitors appeared greater than those with tamoxifen, with higher rates of conversion from mastectomy to breast-conserving surgery. Recent data from Edinburgh confirm that anastrazole is also effective in the neoadjuvant setting in HER-2/neu-overexpressors [103]. Results from direct comparisons of anastrazole and letrozole are underway regarding quality of life and side-effects, ability to down-regulate proliferation, PR expression, effects on lipids, clotting and bone metabolism.

5. Metastatic cancer

The combination of tamoxifen and suppression of ovarian function remains the best 1st line therapy for premenopausal patients with an ER-positive metastatic breast cancer [106]. We do not know whether substitution of tamoxifen by an aromatase inhibitor in this situation is better. We do know that the substitution of tamoxifen by anastrozole as second-line therapy in combination with castration, still produces a significant clinical response [107]. For postmenopausal women, recent clinical trials have shown that all three third-generation aromatase inhibitors present significant efficacy advantages over traditional tamoxifen in first-line [108–111] and over progestins or aminoglutethimide for second-line after tamoxifen [106]. Starting with an oral aromatase inhibitor instead of starting with tamoxifen will prolong the total duration of endocrine therapy before chemotherapy has to be used and this improves the patient's quality of life. Two first-line phase III trials of letrozole versus tamoxifen [108] and anastrazole versus tamoxifen [111] showed the aromatase inhibitors to be superior to tamoxifen in short-term survival measures only. These data suggest that aromatase inhibitors may replace tamoxifen in the first-line hormonal management of this disease in postmenopausal women. Comparative trials of anastrozole versus letrozole [112] or anastrazole versus exemestane [113] for second-line hormonal therapy in metastatic breast cancer have also been performed. In an open label trial [112], letrozole was found to be superior to anastrazole with regard to the overall response rate, but the other clinical endpoints like time to progression which was the primary endpoint were not different.

Tumours progressing on tamoxifen remain sensitive to second-line therapy with oral aromatase inhibitors. Although tumours take a longer time to progress on aromatase inhibitors, once they do, they are less responsive to tamoxifen [108,114]. However, recent data

suggest that tamoxifen remains effective in a small group after relapse on an aromatase inhibitor [115].

Several clinical trials are ongoing to determine whether the addition of monoclonal antibodies, like trastuzumab, or ErbB-specific TKI's, like Iressa, or inhibitors of downstream signal transducers, like FTI's, to anti-hormone agent will also provide breast cancer patients with benefits in clinical practice [116].

Fulvestrant is the first of a new type of ER-antagonist that downregulates the ER and PR. It is devoid of the partial agonist properties of tamoxifen when tested in laboratory models. This unique mode of action means that it is important that fulvestrant is placed optimally within the sequence of endocrine therapies to ensure that patients gain maximum benefit [117]. Fulvestrant has shown efficacy in patients heavily pretreated with prior endocrine therapy, such as tamoxifen or anastrozole in postmenopausal women with advanced breast cancer [118]. Recently published data also confirms its activity in the first-line [119]. After progression on fulvestrant, subsequent endocrine treatments can still produce responses, demonstrating that fulvestrant does not lead to cross-resistance with other endocrine therapies [120]. Other hormonal agents, like the newer SERMs, are being compared with tamoxifen for their efficacy in metastatic breast cancer [121].

In metastatic endometrial cancer, although no proven benefit in the adjuvant setting, progestogens have been the 'cornerstone' of the hormonal treatment of recurrent, advanced or metastatic endometrial cancer [122]. Like in breast cancer, response to progestogens is related to PR-status. The ideal dose is 200 mg medroxyprogesterone acetate which is equally effective with less side-effects than the 1 g dose [123]. Tamoxifen also has a small benefit in the metastatic setting of endometrial cancer. A regimen of alternating megestrol acetate and tamoxifen is active in treating endometrial cancer and may result in a prolonged complete response in some patients [124,125]. Locally-released levonorgestrel, that is cost-effective when compared with hysterectomy for menorrhagia [126], has also been reported to be effective in grade I endometrial cancers and premalignant endometrial conditions, but only data from case reports are available [127–129]. This should not become standard practice, but may be an option for inoperable obese women or those wanting to preserve fertility [130]. Other agents, like the newer SERMs such as arzoxifene [131], and aromatase inhibitors, like exemestane, are being or will be tested in women with advanced or recurrent endometrial cancer. Endometrial stromal sarcomas and uterine adenosarcomas [132] contain high levels of steroid receptors; c-erbB-2 is also expressed, but only in a quarter of undifferentiated uterine sarcomas [133]. Letrozole at a daily dose of 2.5 mg has been shown to be effective in low-grade endometrial stromal sarcomas with positive oestrogen receptors [134]. Aromatase inhibitors, like letrozole, also show some activity and limited toxicity in relapsed ovarian cancer patients; there is no association between response and hormonal receptor expression, so the underlying mechanisms of letrozole action have still to be elucidated [135].

6. Hormone replacement therapy

Women on continuous oestradiol valerate for secondary prevention of cardiovascular disease in the ESPIRIT Trial had a large rate of non-compliance because of vaginal bleeding in 57%. The rate of atypical hyperplasia in the group of bleeders was only 4% which means that bleeding preceeded the endometrial premalignant abnormalities [136]. Women on HRT for the menopause do risk more gynaecological interventions than those on placebo [137] or raloxifene [138,139]. Low doses of oestrogens such as oestradiol 1 mg, conjugated equine oestrogens 0.3 mg orally per day or transdermally applied oestradiol 25 μg per 24 h have been shown to be effective for the treatment of vasomotor symptoms and for prevention of bone loss. Little long-term data on endometrial safety are available, the longest study has only two years of follow-up [140]. Levonorgestrel-intrauterine device (LNG-IUD) appears an effective method of counteracting the stimulatory effect of oestrogen on the endometrium. Long-term endometrial and breast safety with the combination of systemic oestrogens and local LNG-IUD are promising, but require longer follow-up [141]. In addition, data on the endometrial safety of quarterly administration of progestins are missing [142]. In our opinion, progestogens are always required for endometrial protection, even if one considers low doses of oestrogens for postmenopausal health [143]. Another solution may be fulvestrant which may be protective against oestrogen stimulated growth of the endometrium, at least in preclinical models. Fulvestrant at a dose of 250 mg significantly inhibited the oestrogen-stimulated thickening of the endometrium compared with placebo [144]. Tibolone, a selective oestrogen enzyme modulator (SEEM), or now called selective tissue oestrogenic activity regulator (STEAR), is a synthetic steroid with oestrogenic, androgenic and progestogenic properties, which has been successfully used as an alternative to oestrogen replacement therapy in several countries [145,146]. Vaginal bleeding rates on tibolone are higher than placebo, but lower than HRT, especially if taken early in the menopause. One of its outstanding features is that it does not stimulate endometrial proliferation in the short-term, although endometrial polyps and cancers have been reported in long-term tibolone users [147]. The THEBES trial currently evaluates tibolone's long-term endometrial effects.

It has been estimated that all types of HRT, including tibolone, increase the risk of breast cancer within 1–2

years of initiating treatment [148–152]. The increased risk is related to the duration of HRT use, but not to the age at which HRT is started and this excess risk disappears within about five years of stopping. Approximately 32 in every 1000 women aged 50–65 years not using HRT have breast cancer diagnosed over a 15–20 year period. In those using *oestrogen-only*, data are controversial. In the Women's Health Initiative (WHI), 10 739 women were exposed to either CEE or placebo. Estimated Hazard Ratios (95% Confidence Intervals) for CEE vs placebo for breast cancer was 0.77 (0.59–1.01) with data from 218 cases. This translates into a possible reduction of breast cancer [149]. These data were not confirmed in the Million Women's Study (MWS) where five years of oestrogen use was proposed to lead to 1.5 extra cases of breast cancer in 1000 and approximately five extra cases in 1000 after 10 years use [151]. Differences between both studies have been explained by differences in proportions of women with a high body mass index. Therefore, women with a low body mass index may also have an elevated risk for breast cancer if they are exposed to oestrogens although this risk appears to be small.

Using oestrogen and progestogen *combined HRT* for five years, breast cancer was diagnosed in six extra cases in 1000 and 19 extra cases in 1000 after 10 years use [150]. For E-P HRT, WHI [150] and MWS [151] agree on an increased breast cancer risk. Such tumours are not necessarily associated with better patient's prognoses [152,153]. Tibolone increases the risk of breast cancer, but to a lesser extent than *combined E–P HRT* [151,154]. Women already treated for breast cancer should not be exposed to HRT. In the HABITS trial, there was an increase in risk in those breast cancer patients on HRT [155]. The safety of tibolone in this setting is currently being tested. The LIBERATE trial continues because preliminary evidence on a small number of new or relapsed cases in this study suggests it is safe in this high-risk population (at least over the short-term) [154]. During this meeting, we have also seen data presented that HRT may affect screen-detected breast cancers differently than non-screen-detected cancers [156].

We should also not forget the advantages of HRT during the menopause [157,158]. Long term use of E–P HRT is associated with a decreased risk of osteoporotic fractures and colorectal cancer [158]. However, colorectal cancers in women who took E-P HRT were diagnosed at a more advanced stage than those in women who took placebo.

Rozenberg [159] reviewed existing literature on the menopausal management of patients treated for breast cancer. He stressed the need for better, more efficient, non-hormonal alternatives for menopausal women with a breast cancer because HRT is not safe. Phyto-oestrogens, marketed for use by postmenopausal women as natural and safe alternatives to HRT, are not effective for menopausal vasomotor symptoms [160]. The beneficial effects of phyto-oestrogens on bone are promising, but still have to be confirmed [161]. A diet high in isoflavonoids (soy) is associated with a lower endometrial cancer risk in Asian populations [162], but studies regarding the important role of dietary intake of phyto-oestrogens and breast cancer risk in European populations remain controversial [163,164]. Phyto-oestrogens have also not been tested for their safety. Do they affect growth of pre-existing breast or endometrial tumours? Cell culture studies report both the oestrogenic stimulation of ER-positive breast cancer cell lines and the antagonism of tamoxifen activity at physiological phyto-oestrogen concentrations. A recent report from a breast cancer chemoprevention study suggests red clover does not increase breast density [165]. Possible interaction with other non-hormonal alternatives for menopausal symptoms in breast cancer patients on tamoxifen have also to be considered as was recently done for paroxetine [166]. Clonidine, venlafaxine, paroxetine, fluoxetine and gabapentin are non-hormonal agents that have demonstrated efficacy in small controlled and uncontrolled trials in reducing hot flashes. These should be considered in patients who are unwilling or unable to take hormonal therapies but clearly are less effective than oestrogens [167].

7. Others

Pregnancy affects breast cancer risk, diagnosis and treatment. Breast cancer also has an impact on subsequent pregnancy [168]. Young age at first full-term pregnancy is protective, but miscarriage on its own has no effect [169]. Breast cancer is not more frequently diagnosed during pregnancy, but pregnancy implies a short-term increase in the risk of breast cancer which protects thereafter, although this protective effect is age-related. Pregnancy delays the diagnosis of breast cancer, but should not interfere with surgery and some types of chemotherapy are justified. Prognosis is thought not to be significantly different from non-pregnancy-associated breast cancer, except in cases where a delay in diagnosis is associated with more advanced disease. Prognostic markers are not differently expressed, although numbers are limited. Treatment is similar to non-pregnant cases, with the exception of radiotherapy, which is contraindicated throughout pregnancy. Chemotherapy is contraindicated during the first trimester and last couple of weeks of pregnancy. Antihormone therapy can easily be delayed until after full-term pregnancy. Few breast cancer survivors go on to conceive, but those who do have no worse breast cancer or pregnancy outcomes. The superior survival for those conceiving after treatment for breast cancer may merely

reflect a healthy patient selection bias, but may also be consistent with an antitumour effect of the pregnancy.

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