Consensus paper

The EMAS 2008 update on clinical recommendations on postmenopausal hormone replacement therapy

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1. Overview

Most postmenopausal women who are treated with hormone replacement therapy (HRT), use a combined form of estrogen-progestogen therapy but women who have had hysterectomy use generally estrogen-only treatment.

The use of HRT to relieve menopausal symptoms and the consequences of estrogen deficiency after the menopause is since long established as an effective option for women. The decision process is complex and benefits needs to be balanced vs. risks and well explained to women.

During the last year several important publications from randomised trials and of some observational studies have been published concerning the benefits and risks of hormone replacement therapy (HRT) in postmenopausal women, necessitating an update of the earlier recommendations of EMAS [1–3]. This statement presents, below, an updated assessment of this complex body of evidence and opens with a clear statement of the EMAS position in the light of this evidence. The randomised controlled trial data on HRT predominantly based on the use of conjugated equine estrogen (CEE) alone or CEE plus medroxyprogesterone acetate (MPA).

The observational studies involve a much wider range of HRT formulations.

2. Updated EMAS statement

In view of the recent available information EMAS conclude as following:

- The main indication for HRT use in postmenopausal women remains the relief of menopausal symptoms.
- Treatment significantly decreases bone loss and risk of osteoporotic fractures.
- In 50–59-year-old women a “window of opportunity” for a benefit in cardiovascular disease displays a high plausibility.
- The risk of stroke is mildly increased by both estrogen-only and estrogen-progestogen treatment but remains of low clinical impact in women <70 years.
- The risk in breast cancer increases according to the duration of treatment and is higher with estrogen-progestogen than estrogen-only HRT. However selecting patients with low baseline risk factors may decrease the risk of breast cancer as suggested by the randomized and observational data. One of the indirect benefits of women treated by HRT is that they have more access to screening. The decrease in mortality observed in observational study from combined HRT treated women suggests that more
differently differentiated tumours with lower aggressive profiles are promoted by the treatment and that they are diagnosed at lower stages. The knowledge of increased risk in lobular cancers also indicates a clinical survey of these patients since lobular tumours are under diagnosed by mammograms.

- In addition, it is not clear how the previous treatments may have influence the various risks. This has been published for the WHI trial in 2006 but not for the oestrogen only trial where as reported in the last publication almost 60% of women were treated previously. It is important to include in the evaluation of the balance between benefits and risks of HRT the increase in quality of life and climacteric symptoms. It can be speculated, in view of this reappraisal of HRT effects in the WHI trials, that prescribing HRT to symptomatic women using more natural hormones and route of administration may even improve the beneficial effects.

- EMAS strongly recommend evaluating individual risks factors before prescription of an HRT. Lifestyle counselling is also strongly recommended since exercise, loosing weight and low alcohol intake can decrease the risk of breast cancer. This might improve the tolerance of HRT when appropriate HRT is given after an individual clinical evaluation, the benefits will far outweigh any potential risks by respecting contraindications. In addition it is recommended to perform an annual clinical examination of women especially after 50 years even without a uterus, whether or not under HRT since the risk of cancer and other disease increase. This consultation is also the time to monitor cardiovascular risk factors, quality of life, and the accuracy of the HRT indication. This could help decreasing the incidence of some of diseases and offer an opportunity for educational and lifestyle recommendations which may contribute to a better prevention of severe diseases.

- Tibolone is an effective treatment and prevention for osteoporotic fractures but increase the risk of stroke in aging women. Its use is submitted to the same contraindications in women with cardiovascular risk factors than other oral HRT.

2.1. An assessment of the updated evidence

2.1.1. HRT and cardiovascular disease

The hypothesis that HRT use was associated with reduced long-term risk of coronary heart disease, which was based on the study of patho-physiological and epidemiological evidence, was not confirmed by the overall results of the Women’s Health Initiative randomised controlled trials. However, debate has continued on whether use of HRT in the first postmenopausal decade may be associated with a beneficial cardiovascular balance.

2.1.1.1. New evidence on the cardiovascular balance. Several publications are supportive of a theoretical “window of opportunity” of HRT decreasing the risk of CHD

- In a sub-analysis of the Women's Health Initiative trial using oestrogen only vs. placebo (WHI-estrogen trial), it was shown in 1064 women aged 50–59 years, that the coronary calcified plaque progression (measured as the mean coronary-artery calcium score, using tomography), was less severe among women receiving oestrogen therapy vs. placebo [4].

- Furthermore, this hypothesis is sustained by another sub-analysis of the WHI trial, showing that when HRT was initiated shortly after menopause, a reduced CHD risk tended to exist as compared with an increased CHD risk, when HRT was given late as after the onset of the menopause [5]. Since in the two WHI trials most of the postmenopausal women were over 60 years of age, and also at least at 10 years beyond menopause, a beneficial effect of HRT can have been missed within the smaller group of younger postmenopausal women because of limited statistical power. This reanalysis concerned 27,374 women by aggregating the oestrogen only (CEE only) and the combined oestro-progestin trials (CEE + MPA). The primary outcomes were CHD and stroke and the other outcomes were mortality and a global index including negative effects (breast cancer, endometrial cancer, and thromboembolism) and benefits (osteoporotic fractures and colorectal cancer). The models used were different from the previous publications in that age and years since menopause were categorised rather than treated as continuous variables. The main result is that mortality was significantly decreased among women between 50 and 59 years of age, HR = 0.70 [CI 95% 0.51–0.91] using HRT as compared to placebo and that the global index was not increased in the same age population 0.96 [CI 95% 0.81–1.14]. In the whole population, Coronary Heart Death (CHD) was not significantly altered pooling both trials, HR = 1.07 [CI 95% 0.92–1.23], neither if analysing independently the CEE group, HR = 0.95 [CI 95% 0.78–1.16] nor with CEE + MPA, HR = 1.23 [CI 95% 0.99–1.53]. The increase in the global index and CHD were only significantly increased in women over 70 years or who were 20 years beyond the menopause. The factor ‘years since menopause’ was more sensitive than age considering the effect of HRT on CHD.

- An increased risk of stroke was observed, however (HR = 1.33; CI 95%: 1.12–1.56), whether the data were analysed as pooled data or as a separate set using CEE alone or CEE + MPA.

- This publication also reports interesting information about the difference in baseline characteristics between the two trials. Women using CEE had a more adverse cardiovascular profile than women under CEE + MPA. Previous use of HRT was higher in the CEE vs. placebo trial (61% in women with bilateral oophorectomy, 41% in women without bilateral oophorectomy) than in the CEE + MPA trial (26%). These differences strongly suggest that a comparison of the results between the two trials is not accurate due to baseline different characteristics of the patients.

- A new release from the observational “Nurses” study reevaluated the use of HRT in relation to the risk of stroke and to time of HRT initiation, its delay since menopause, and the CEE dose used [6]. These authors observed a significantly and equivalent increased risk of stroke when using CEE or CEE + MPA, respectively of RR: 1.39 [CI 95% 1.18–1.63] and RR: 1.27 [CI 95% 1.04–1.56]; There was no difference in the risk whether the treatment was initiated soon after menopause or more than 10 years after it and was again similar in CEE users or in CEE + MPA users. In women of less than 55 years of age and/or taking HRT for less than 5 years, no increased risk was observed. However, the attributable fraction of stroke was increasing with age due to the increase in basal risk with age: from 0.9 case/10,000 person-years in women over 50 years, 1.5 in women between 50 and 54, 2.2 in women aged 55–59, 2.8 in women between 60 and 64 and 7.2 in those who were older than 64 years old. Considering only the users, however, the attributable fraction was somehow higher, i.e. for 1 year of treatment an extra 2.2 cases/10,000 persons occurred in women 50–54 years old and 0.21 in women over 65 years. A possible dose effect was observed: no risk increase was observed in women who used 0.3 mg CEE, but the number of users was limited.

Comment: This new analysis of the WHI by pooling the data from both trials shows a benefit in terms of mortality in women under HRT between 50 and 59 years and no increase in the global index before the age of 70 years. This increase in the global index of risk after 70 years is essentially due to the increase in CHD and to a lesser extend thromboembolism.

Finally “The Estrogen Replacement and Atherosclerosis trial” provides evidence that is consistent with the possibility of a “window of opportunity” hypothesis. This is a randomized study
involving 309 postmenopausal women with established coronary atherosclerosis (mean age, 65.8 ± 6 years), who’s endothelial-dependent flow-mediated vasodilatation (FMD) were measured using two-dimensional ultrasound. This study showed that after an average of 3.2 years of treatment with unopposed oestrogen or oestrogen plus progestin vs. placebo, no improvement in endothelial vasodilatation could be observed in older postmenopausal women with established coronary heart disease, while oestrogen has been shown to enhance FMD in healthy and younger women in the past [7].

The effect of HRT on stroke, however, remains consistently elevated throughout the different studies in terms of relative risk (RR). Nevertheless, the absolute risk remains low in younger postmenopausal women. These data suggest that lower doses of oestrogens might offer a safer alternative than conventional ones. It is also very likely that treatments which do modify the coagulation to a lesser extend or the blood pressure may decrease its occurrence.

2.1.1.2. Ovarian cancer. A recent release from the observational Million Women Study (MWS) reported an increased risk of ovarian cancers among HRT users [8]. During the study, 2273 incident ovarian cancers and 1591 deaths from the malignancy were recorded. Current users were significantly more likely to develop (RR: 1.20; 95% CI: 1.09–1.32) and to die from ovarian cancer than never users (RR: 1.23; 95% CI: 1.09–1.38). The risk increased with duration of HRT use, but past use was not associated with an increased risk. The risk also varied according to the histologic type of cancer; it increased significantly for the serous type (RR: 1.53; 95% CI: 1.31–1.79), but not for mucinous, endometroid, or clear cell tumours (respectively RR: 0.72; 95% CI: 0.52–1.00; RR: 1.05; 95% CI: 0.77–1.43; RR: 0.77; 95% CI: 0.48–1.23). Over 5 years, the standardised incidence rates for ovarian cancer in current and never users of HRT were 2.6 [95% CI 2.4–2.9] and 2.2 [95% CI 2.1–2.3] per 1000, and death rates were 1.6 [95% CI 1.4–1.8] and 1.3 [95% CI 1.2–1.4] per 1000. This could account for one additional case of ovarian cancer for 12,500 women per year and one additional death in 16,600 women per year. Oestrogen-only and oestrogen–progestogen therapy carried similar levels of risk at 1.34 and 1.14, respectively. Similarly the various regimens studied did not show differences. The risk was increased in women who had had a hysterectomy compared to women with an intact uterus RR: 1.47 [95% CI 1.18–1.83] vs. 1.12 [95% CI 1.00–1.25] (p = 0.03). This difference was attributed to a longer duration of treatment in the hysterectomised women than in non-hysterectomised women who were treated using oestrogen-progestin combinations (9.3 vs. 6.9 years). A meta-analysis of this study pooled with nine other studies provided a RR of 1.28 (95% CI 1.20–1.36).

Comment: The MWS is an observational study, which studied a cohort British women undergoing mammographic screening. Use of HRT was as reported by the women by questionnaire at the time of the mammography. There was no clinical examination and the cancer diagnoses were reported through cancer registrations after an interval of time. For example the diagnosis for ovarian cancer was reported after an average of 2.4 years later than the date of reporting HRT use. In this study, the risk increase ceased after the cessation of the hormone therapy. This is surprising, since if a treatment acts like a promoter and increases tumorigenesis, it is likely that its effect will persist several years after the cessation of the treatment, corresponding to continuing growth of the tumours that have been initiated.

In observational studies it is necessary to attempt to correct for imbalances in potential confounding factors. In this report from MWS, authors have taken into account factors such as BMI, socioeducative level, parity, alcohol intake, and OC use in the paper or in subsequent correspondence [10] but the potential for systematic bias remains since it is difficult to adjust for all confounding factors relying on a questionnaire as the principal source of clinical information. It is therefore not excluded that, in observational studies, an observed increase of risk is at least partially due to bias between treated and untreated populations. In particular, the rate of clinical examinations and references to health providers have been reported to strongly influence the rate of ovarian carcinoma [9]. This could explain why women without a uterus, who are presumably less examined, could also have an increased risk. Alternatively, these women were more often prescribed oestrogen only treatment which may carry a moderately increased risk as compared to combined E-P.

The Nurse Health Study has also reported a mildly increased ovarian cancer risk in current and in past HRT users who used it for more than 5 years (RR: 1.41 [95% CI 1.07–1.86] and RR: 1.52 [95% CI: 1.01–2.27], respectively [10]. Use of unopposed oestrogen was associated with a significant increase in the risk of epithelial ovarian cancer (P for trend <0.001); RR for 5-year increment of use: 1.25 [95% CI 1.12–1.38]. While use of E-P (RR for 5-year increment of use: 1.04 [95% CI 0.82–1.32]) was not significantly associated with an increased ovarian cancer risk. Where risk was increased the histological type involved was endometriotic ovarian cancer, possibly consistent with a higher sensitivity to oestrogens. Overall, the role of hormones in the ovarian cancer pathophysiology remains obscure. The beneficial effects of OC are usually attributable to ovulation inhibition but the effects of the hormone per se before and after menopause remains unclear [11,12]. Alternatively, a differential role of oestrogen and combined E-P could be explained by the effect of progesterone on ovarian epithelial cells and ovarian cell cultures [13]. Both observational studies on HRT report some increase in ovarian cancer in women who received oestrogen only HRT but no increase in the risk using combined HRT. The meta-analysis performed at the end of the MWS publication is strongly influenced by the weight of the MWS itself and thus reflects predominantly its results. Finally the causality between HRT and ovarian cancer is not firmly demonstrated by these observations.

2.1.1.3. Breast cancer.

- Decrease in breast cancer incidence and HRT. The relation between HRT and breast cancer has been assessed in a range of studies.

Several publications have reported for the first time a decrease in breast cancer incidence which appears to coincide with the fall in the levels of HRT use, for instance in the US following the WHI publication in 2002.

- Ravdin et al. [14] reported a 6.7% fall in breast cancer incidence using the national Cancer’s Institute Surveillance, Epidemiology and End results (SEER). These registries concerned about 13% of the breast cancers occurring in the US. The decrease concerned women aged 50 years of age and over. Between 2001 and 2004, an 11.8% decrease in breast cancer incidence was observed in women between the ages of 50–69-year. The decrease concerned only ER positive tumours. The authors stated that the decrease paralleled the decrease in HRT use.

Another report was published using the Kaiser Permanente cohort [15]. It concerned 7386 cases of breast cancer diagnosed between 1980 and 2006. These authors also observed a decline in breast cancer diagnosis. However, the decrease concerned all the age groups (pre and postmenopausal women) and mostly started around 1998–1999. In the latter series, an important 10% decrease was also observed in ER negative cases. Similarly, Jemal et al. using
the SEER data and Li and Daling using data from 13 cancer registries that participate in the SEER, reported that the decrease (3–4%) in breast cancer incidence could be detected as early as 1999 [16,17]. In the San Francisco Bay area a decrease of 3.6% per year [95%
CI, 1.6–5.6%] was recorded in 1999–2004. There was an additional reduction after 2002. These authors suggested that both screening and the HRT reduced use, influenced the observed decreased breast cancer incidence. It is notable that breast cancer incidence remains almost stable in the European countries where the screening is stable for several years (see below).

Comment: There should be caution in drawing conclusions and suggesting a causal relation between the decreased breast cancer incidence and reduced HRT use.

First of all, the number of breast cancer cases in these studies referred to the number of diagnosed cases through screening programs and individual follow-up, which is an estimation of the incidence but not necessarily the real incidence. Secondly, even in the publication by Ravdin, the decline in the incidence of breast cancer started before the first WHI publication. In addition, in some publications, the decrease concerned women over 70-year. This last population is not the one which mainly used HRT. This suggests that there is a decline in breast cancer incidence due to several components: modification in screening politics and compliance, in risk factors for breast cancer.

Role of the screening

• Decrease in adherence to screening.
  A 3.2% decrease in screening adherence was reported in women for the year 2003 by Radvin et al. [14] and, Glass et al. [15] reported a 4–5% decrease during the period 2001–2004 in the Kaiser Permanente cohort corresponding to the decrease in breast incidence at the same period.
• Increase in in situ vs. invasive carcinoma.
  Another possibility is the modification in the number of invasive breast cancer diagnoses as a result of screening during the previous years. There is an initial increase in diagnosis of invasive and in situ carcinoma and after a certain lag-time, the screening is “saturated” by the already diagnosed and (over?) treated breast cancers and the “incidence“ seems to decrease, as reported in several publications in the US [15–17]. The observations that these declines were more pronounced for localized disease and tumours of small size support the latter hypothesis [17].
• First screening effect.
  A study from Italy exemplified the effect of the first screening on the fluctuation of breast cancer diagnoses [18]. The population of Turin is covered by a cancer registry operating since 1985, and since 1992 by a centrally organized mammography screening program for women aged 50–69 years. In this population there was a fall in breast cancer diagnoses in 2003. The decrease was steeper during the period 1999–2001 and restricted to older groups of patients. However, when cases detected at the first screen were excluded, both the increasing time trend (due to increase in initial diagnosis) and the subsequent decrease in breast cancer incidence almost completely disappeared.

In Europe, the decline is not observed everywhere but the screening is also variable

• Significant decreases in breast cancer rates were not observed in several other European countries where the screening program are stable (UK, Sweden, NDL) [19,20]. In Scotland, the screening was stable since the last 80 s and the use of HRT quite important (30% of the population) whereas in NDL, the use of HRT was less than 10%.

• In Canada, the decrease concerned only women over 75 years and was not seen in younger women [21].
• In Norway two publications reported different conclusions [22,23]. One looking at the 40% of the population of all ages did not record any variation [22] whereas the other one looked at women 50–69-year and reported an increase following the screening program and a more recent small decrease [23].
• In France, a recent publication has shown a breast cancer incidence decrease, starting in 2004, following an increase between 2000 and 2004 [24]. In this country the organized screening was generalized only in 2000, in addition to the previously voluntary spontaneous screening. The excess in the number of diagnosed breast cancer cases was very likely related to the first screening effect as in Italy and it is thus very difficult to attribute the small drop in the incidence only to the decrease in the HRT use in France. The age of the women with new diagnosed breast cancer will help to interpret these data and determine whether a causality of HRT use is likely.

Because the mammography screening and the breast cancer rates varies largely between regions in the US and in Europe, it remains difficult to determine which part of this breast cancer incidence decrease should be attributed to the decrease in HRT use.

• WHI new releases: risk of cancer 3 years after end of the trial
  Furthermore, a recent publication from the WHI [25] has shown that, after an average of 2.4 years, following the end of the combined HRT trial, the increase in risk of breast cancer was not modified, suggesting a promoter effect of HRT in breast cancer. Although, it is possible that in the future a drop in breast cancer incidence, following the important fall in HRT use will be observed, so far it is not possible to determine its amplitude.

The WHI time since menopause and breast cancer risk
  Two publications from the WHI reanalyzed the WHI data in relation to the risk of breast cancer, that was observed in those two randomized trials [26,27]. The aim of these reanalyzes were to study why the observed breast cancer RR in the combined HRT and the CCE alone trials, were lower than in observational studies of the WHI.

By pooling the data from the WHI combined HRT trial with a subset of patients receiving combined HRT in the WHI observational study, the observed breast cancer RR was 1.64 [95% CI: 1.00–2.68] over a 5-year period of use and 2.19 [95% CI: 1.56, 3.08] over a 10-year period of use when HRT was initiated shortly after menopause, i.e. an excess of 28 cases of invasive breast cancer/10,000 persons-years for the first 5 years of use and 61 cases over 10 years of HRT use. This level of the risk is similar to what has been observed in most observational studies. The results from this study suggest, however, that when HRT was initiated after a delay of at least 5 years following the menopause, no increase in breast cancer risk was observed.

In the group of women using CEE alone, a similar analysis showed a very different age-adjusted annualized rate of breast cancer between the randomized trial and the observational cohort with a lower rate in the clinical trial among women using CEE (0.22% vs. 0.37% in the placebo group, in women with no prior treatment before the beginning of the study and no decrease in the observational population (0.43% vs. 0.39%). There was no indication of any protective effect from CEE treatment except in women without prior treatment and starting HRT who were 5 years post-menopausal. The distribution of the time gap since menopause for initiation of the HRT was very different in the observational study where the vast majority started it soon after menopause in contrast to the clinical trial.
Comment: These publications suggest that the lower risks of breast cancer observed in the two WHI randomized trials might be due to the women being older than in the observational studies which correspond much more to real life where HRT is predominantly used in younger postmenopausal women. These studies suggest a lower risk of breast cancer in older women using HRT at a distance from menopause. However when looking at the crude numbers of breast cancer cases they appear very low to get enough power for such an assertion to be convincing. Indeed most of the cases in 50–59-year-old women came from the observational study where confounding factors were not controlled as in a randomized trial and especially as shown in the publication concerning combined HRT, the effect of mammography screening is important, higher in treated than untreated women and can modify the observed incidence in breast cancer.

- Histological types of breast cancer:
  Two recent reports also confirmed about ten previous studies by showing that a predominant promoting effect of combined HRT on lobular or mixed lobular than ductal cancers [28,29]. In addition in the French cohort study, no increase risk with oestradiol combined with progesterone was observed confirming the previous publication of this group [30]. In this study, the effect of synthetic progestins combined with oestrogens were observed only on ER+ tumours.

- Mortality and HRT use:
  A case-control study population based in the US of 12,269 cases of breast cancer was established to analyse breast cancer risk factors [31]. During an average follow-up of 10.3 years, a total of 3953 deaths including 1690 deaths from breast cancer were recorded. Mortality from breast cancer was significantly lower in women who used combined HRT than in non-users HR: 0.73 [95% CI 0.59–0.91]. This decrease was limited to current users. In oestrogen only users no decrease was observed. The greater benefit of mortality reduction was observed in long-term users of combined HRT HR: 0.60 [95% CI 0.43–0.84]. The lower risk was limited to cancer diagnosed at a regional stage. Deaths from all causes were significantly lower both in current users and former HRT users HR: 0.75 [95% CI 0.68–0.83] and HR: 0.87 [95% CI 0.78–0.96]. The all causes mortality was significantly lower in the combined HRT treated women than in the CEE only HRT (P < 0.0001). HRT was not associated with cerebrovascular diseases or other cancer deaths. Both treatment were associated with lower deaths from cardiovascular diseases, HR: 0.62 [95% CI 0.48–0.80] for CEE alone and HR: 0.27 [95% CI 0.12–0.57] for combined HRT.

Comment: These data on mortality are encouraging for the use of HRT in “real life”. They indeed correspond to an observational cohort where women with lower risk have been selected for the treatment. In addition, an increase in mammography screening is also likely in women under treatment. In this study only 10% of HRT users had never been screened compared with 30% of never users. But this is exactly what is operating in clinical practice where the clinician is supposed to select indications according to the treatment and to tailor it to the individual patient. It is thus extremely striking to see that women who received the treatment and especially the US combined HRT (something is missing in the past sentence).

- Tibolone.
  A randomized trial "The Lift study" was recently published on the effect of 1.25 mg of Tibolone on osteoporotic fractures [32]. This study also looked at the risk of stroke, CHD, breast cancer, and colon cancer. 4935 women between 60 and 85 years with a low T score and no more than one vertebral fracture were recruited and followed up for 3 years. A significant decrease in the risk of fractures was observed: for vertebral fracture, RR: 0.55 [95% CI 0.41–0.74], and non-vertebral fracture (RR: 0.74; [95% CI 0.58–0.93]. A decreased risk of invasive breast cancer (RR: 0.32 [95% CI 0.13–0.80] and colon cancer, RR: 0.31 [95% CI 0.10–0.96]. However, the Tibolone group had an increased risk of stroke RR: 2.19 [95% CI 1.14–4.23]. No difference in the RR of CHD and venous thrombosis. Endometrial cancers were diagnosed in four of the Tibolone treated group and none of the placebo group. Endometrial thickness was increased in 533 women under Tibolone and 168 under placebo at some point in the trial. Vaginal bleeding occurred in 9.8% of the women under Tibolone and 2.5% under placebo. Endometrial biopsies were performed in 499 women under Tibolone and 136 under placebo. Two cases of hyperplasia were observed in the treated group and one in the placebo.

Comment: The most surprising result of this study is the decrease in breast cancer risk. The studied population is quite old and with a lower risk of breast cancer; in a recent publication from the WHI, it was reported that a low T score is predictive of a low risk of breast cancer [33]. The basal risk of the Lift population was in the placebo group 2.8/1000 person-years which is much lower than the WHI one (around 4). Twenty percent of the population had had a previous treatment for menopause, of an unknown type. The results were however based on a follow up of 3 years which is probably too short to see an increase in breast cancer risk and on a small number of events: 6 breast cancers in the treated group and 19 in the placebo group. It is thus difficult to extrapolate this positive result for a longer treatment and in different population. Similarly, the number of venous events (5 vs. 9) and of colon cancers (4 vs. 13) do not constitute robust data.

References


