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Rationale for a study adding tamoxifen to HRT

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Tamoxifen can be classified as a first generation Selective Oestrogen Receptor Modulator (SERM). It is widely used for palliative endocrine treatment of advanced breast cancer and as adjuvant therapy to control micrometastatic relapse and new primaries in women treated surgically for early breast cancer [1]. Tamoxifen has also been investigated in three large cooperative phase III trials for breast cancer prevention in at-risk women. While the preliminary results of two European studies, conducted in Italy (Italian Tamoxifen Prevention Study) and in the United Kingdom (Royal Marsden Tamoxifen Chemoprevention Trial) [2,3], have shown no significant differences so far, the American (National Surgical Adjuvant Breast and Bowel Project, NSABP-P1) trial has shown an approximately 50% reduction of the risk of both invasive and non-invasive breast cancer and a 69% reduction of the occurrence of oestrogen receptor-positive tumours [4].

The Italian Tamoxifen Prevention Study included 5408 healthy hysterectomised women aged 35–70 years who were randomised to receive either 20 mg/day of tamoxifen or placebo for 5 years. After 81.2 months median follow-up, tamoxifen increased the risk of venous vascular events (38 women on tamoxifen versus 18 women on placebo, $P = 0.0053$), mainly consisting of superficial phlebitis.

Women entering the Italian trial were allowed to use Hormone Replacement Therapy (HRT) for the treatment of climacteric symptoms (ERT, mostly transdermal). Among women who never used HRT, there was no discernible difference between women allocated to the tamoxifen or placebo arm ($P = 0.986$). 56 of the 79 breast cancers occurred among women who never used HRT at any point during the trial, with equal numbers of cases of breast cancer occurring among women on each arm.

Among women who used HRT at some point during the study, either at baseline or during the study, 23 breast cancers occurred: 17 on placebo and 6 on tamoxifen ($P = 0.022$). The difference was also statistically significant when the analysis was restricted to women who were continually using HRT, of whom there were 11 cases in the placebo group and 3 on tamoxifen ($P = 0.048$).

After 8 years of follow-up, the cumulative incidence of breast cancer among women who never used HRT was 1.78% on placebo and 1.55% on the tamoxifen arm. In women who used HRT at least some time during the trial, the cumulative incidence of breast cancer was 1.41% among women on the tamoxifen arm and 2.74% on women assigned to placebo.

Withdrawal rate (mainly due to menopausal symptoms) differed according to ERT use, compliance being 78 and 75% at 3 and 5 years, respectively, for women who never took ERT and 92 and 88% at 3 and 5 years, respectively, for women not on ERT at baseline, but who took ERT at some time during the trial. Pharmacokinetic and pharmacodynamic (surrogate endpoint biomarkers) studies showed that a lower dose of tamoxifen (such as 5 mg/day) does not affect the drug's activity on several biomarkers of both cardiovascular and breast cancer risk [5].

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Taking into account all of the above-mentioned considerations, it seems reasonable to test prospectively whether the combination of HRT and low doses of tamoxifen may retain the benefits, while reducing the risks of either agent. We are therefore setting up a multicentre placebo-controlled phase III trial in postmenopausal healthy women currently on HRT (no more than 3 years are allowed) or in *de novo* users. Women will be randomised to tamoxifen 5 mg/day or placebo for 5 years. The study is powered to detect a 40% reduction in the incidence of invasive breast cancer and ductal carcinoma *in situ* in the tamoxifen arm. Secondary endpoints will be the incidence of other non-invasive breast disorders, endometrial cancer, bone fractures, cardiovascular events, venous thromboembolic events, cataracts, all other cancers (in particular, colorectal and ovary) and overall mortality. In addition, an ancillary study has already started to assess the minimal active dose and the best treatment schedule of tamoxifen, through the modulation of a set of surrogate endpoint biomarkers (SEBs) of breast carcinogenesis of 200 postmenopausal healthy women undergoing HRT. Women are randomised to one of the following arms: tramoxifen 5 mg/day + placebo/week or tamoxifen 1 mg/day + placebo/week or placebo/day + tamoxifen 10 mg/week or placebo/day + placebo/week. Treatment duration is 1 year. The primary endpoint is the change in Insulin-like Growth Factor-1 (IGF-I) at 12 months.

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