RAZOR: a phase II open randomized trial of screening plus goserelin and raloxifene versus screening alone in pre-menopausal women at increased risk of breast cancer.

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Running title: Breast cancer prevention using goserelin and raloxifene.

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Abstract

Background

Ovarian suppression in premenopausal women is known to reduce breast cancer risk. This study aimed to assess uptake and compliance with ovarian suppression using the LHRH analogue, goserelin, with add-back raloxifene, as a potential regimen for breast cancer prevention.

Methods

Women at ≥30% lifetime risk breast cancer were approached and randomized to mammographic screening alone (C-Control) or screening in addition to monthly subcutaneous injections of 3.6mg goserelin and continuous 60mg raloxifene daily orally (T-Treated) for two-years. The primary endpoint was therapy adherence. Secondary end points were toxicity/quality of life, change in bone density and mammographic density.

Results

75/950 (7.9%) women approached agreed to randomization. In the T-arm, 20/38 (52%) of women completed the two-year period of study compared with the C-arm (27/37, 73.0%). Drop-outs were related to toxicity but also the wish to have established risk-reducing procedures and proven chemoprevention. As relatively few women completed the study, data are limited, but those in the T-arm reported significant increases in toxicity and sexual problems, no change in anxiety and less cancer worry. Lumbar spine bone density declined by 7.0% and visually assessed mammographic density by 4.7% over the two-year treatment period.

Conclusion
Uptake is somewhat lower than comparable studies with tamoxifen for prevention with higher drop-out rates. Raloxifene may preserve bone density but reduction in mammographic density reversed after treatment was completed.

Impact
This study indicates that breast cancer risk reduction may be possible using LHRH agonists, but reducing toxicity and preventing bone changes would make this a more attractive option.

Introduction

Observational studies of women who undergo premenopausal bilateral oophorectomy, both in the general population and in the majority of studies in those with inactivating mutations in the BRCA1 and BRCA2 genes, have a reduction in breast cancer risk of as much as 50% with a greater effect the younger the age of operation (1, 2, 3, 4, 5, 6, 7).

Surgical oophorectomy was widely used as a breast cancer treatment, but clinical trials indicated that surgery could be replaced by the use of either intranasal or subcutaneous administration of luteinizing hormone releasing hormone (LHRH) agonists for breast cancer treatment (8,9T). Recently it has been shown that combining treatment with the LHRH agonist goserelin increased the effectiveness of adjuvant tamoxifen in premenopausal women with breast cancer (10)
In 1989 Pike and his colleagues (11) suggested that LHRH analogues might be used for the prevention of breast cancer primarily by the reduction of cyclical ovarian hormones. Subsequently this group reported two small trials exploring this approach where toxicity was reduced by add-back oestrogen, medoxyprogesterone acetate and testosterone (12,13).

In order to develop this approach to prevention in women at high risk of breast cancer we designed three randomized trials of treatment with the LHRH agonist goserelin were designed with different add-back regimens (raloxifene, tibolone or ibandronate). The primary aims of these studies were to assess uptake of and adherence to treatment with secondary aims of assessing toxicity/quality of life, bone density and mammographic density. The results using add-back ibandronate were reported previously (14). We now report the study with add-back raloxifene (previously reported in abstract form (15). The trial with tibolone was not initiated because of ethical issues in Holland (Klijn, personal communication).

Participants and methods

Study design

This was an open-label phase II, randomised trial which compared screening by mammography plus treatment with goserelin and raloxifene (T-arm) with screening by mammography only (C-arm). The initial protocol included only women with ≥40% lifetime risk of breast cancer but was amended to include ≥30% risk because of slow recruitment. Women between the ages of 30 and 46 years with normal ovarian function and high risk of familial breast cancer (≥30% lifetime risk) were invited to participate in the RAZOR (RAloxifene and ZOladex Research Study) trial in
Manchester, London and Southampton, all in the UK. Treatment was subcutaneous goserelin, 3.6 mg once every 4 weeks (supplied by Astrazeneca UK), and raloxifene, 60mg orally daily (supplied by Lilly), both for 2-years. Delays in treatment visits were recorded. No dose or schedule modifications were permitted.

Approvals from the three relevant ethics committees were obtained and the study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. Each participant gave written informed consent before randomisation. The trial number is NCT00031850.

**Patient Eligibility**

All participants were required to use non-hormonal contraception and have an estimated life expectancy of more than 10-years. Women with the following were excluded: current pregnancy or planning a pregnancy in the next 2-years, lactation, current treatment with anticoagulants, history of deep vein thrombosis or pulmonary embolism, being postmenopausal, mastectomy or bilateral oophorectomy and no prior history of breast cancer or other invasive malignancy except basal cell carcinoma or *in situ* cervix or basal cell carcinoma.

**Endpoints**

The primary endpoint of the trial was compliance with adherence to treatment. Secondary endpoints were: occurrence of toxicity and change in impact on quality of life, change in bone mineral density and change in serum lipids.

**Toxicity and quality of life**

Toxicity and quality of life were assessed using four standardised patient reported outcome
measures (FACT-Endocrine Subscale [ES], Sexual Activity Questionnaire [SAQ], the State-Trait Anxiety Inventory [STAI] and the Cancer Worry Scale [CWS] given at baseline and one month and three monthly from baseline for 2 years.

The FACT-ES comprises 20 items: (I have) hot flushes, cold sweats, night sweats, vaginal discharge, vagina itching/irritation, vaginal bleeding or spotting, vaginal dryness, pain or discomfort with intercourse, lost interest in sex, gained weight, light-headed/dizzy, vomiting, diarrhea, headaches, bloated, breast sensitivity/tenderness, mood swings, irritable, lack of energy, nausea. Respondents state how bothered they have been over the previous 7 days using Likert type categorical scoring: not at all, 1; somewhat, 2; moderately, 3; and very much, 4. The overall ES score is the sum of 20 single scores between 0 and 4 thus total scores ranged from 0 to 80. As negatively framed questions are reversed higher scores correspond to a less severe symptoms and better QoL (16). The Sexual Activity Questionnaire (SAQ) is a validated self-report questionnaire divided into 2 sections: 1) a screening section to establish whether or not the patient is sexually active, and reasons for sexual inactivity if appropriate, 2) 10 items regarding sexual functioning 17). The Speilberger State/Trait Anxiety Inventory (STAI) has 20 items: (I feel/am) calm, secure, tense, strained, at ease, upset, worrying over misfortune, satisfied, frightened, comfortable, self-confident, nervous, jittery, indecisive, relaxed, content, worried, confused, steady, and pleasant. Respondents use Likert-type categorical scoring: not at all, 1; somewhat, 2; moderately, 3; and very much, 4. An overall anxiety score is the sum of 20 single scores (range 20 to 80). Higher scores correspond to higher anxiety (18). The CWS (19) is a six item scale designed to measure worry about the risk of developing cancer and the impact of worry on daily functioning. The scores were: 1, rarely or never; 2, sometimes; 3, often; 4, all the time. The overall score is a range from 6 to 24.
Patients also completed study specific exit interviews.

Standard laboratory methodology was used to measure serum progesterone, SHBG, CTX and lipids. Serum oestradiol levels were measured using a highly sensitive assay (detection limit 3pmol/l), as previously described (20).

**Bone density**

Bone mineral density (BMD) was measured at the lumbar spine, femoral neck, and total hip using a Hologic scanner and was reported as gm/cm², T- and Z-scores. The scanner was calibrated daily with a spine phantom to ensure all measurements were reliable. Reports were obtained from the Department of Clinical Radiology, Imaging Science and Biomedical Engineering, University of Manchester.

**Mammographic density**

Breast density was assessed using a visual assessment score (VAS) as previously described (21, 22) This was formed by taking the mean percent density that was assessed by two radiologists who scored up to 4 mammographic views from each visit by eye.

**Statistical considerations**

Blinding was not possible since it was not considered ethical to give placebo monthly injections, and the onset of amenorrhoea would amount to unblinding. Randomization was performed centrally at the Centre for Cancer Prevention, London. Stratification occurred within each participating institution. Analyses were conducted on an intent-to-treat basis. All participants who were randomized and received treatment or screening were evaluated by treatment arm. Nonparametric methods were employed for analysis due to small numbers in the study. The $\chi^2$
test was used to compare nominal data, and Fisher’s Exact test was used for 2 x 2 tables. P values must be interpreted with caution due to the small numbers compared. Missing or inapplicable measures were excluded when calculating P values. P values in the tables refer to the comparison of only those with measures at the correct time points. Differences in mammographic density between the two arms were assessed using a linear mixed model (see supplementary material), and a non-parametric bootstrap for mean density differences between time points. In the quality of life analyses the majority of total scores were not normally distributed, therefore non-parametric Mann-Whitney and Wilcoxon tests were used and, because of multiple testing significance, was taken as a P value of <0.01.

Results

Baseline characteristics

Between June 2000 and March 2004, 75 invited women agreed to be randomised in the trial (Figure 1 shows a consort diagram). Women were seen face to face, but were also sent a mail shot. Initially 32 women at the originally protocolled ≥40% risk were recruited in Manchester from 601 eligible women (5.2%). The risk threshold was reduced to ≥30% because of slow recruitment. Overall, at least 950 women were contacted in order to recruit the final 75 women, giving an uptake of at most 7.9% (Figure 1). The reasons for non-participation were assessed in a subset of 89 women. Fear of side effects (81%), wish to wait to join a projected larger study (48%), concern about the possibility of permanent amenorrhoea (32%), no time (30%) and dislike of pills (16%) were the major reasons for non-entry. No woman declined because of the randomisation process.
Characteristics of women who agreed to randomisation were well matched (table 1). The median age at entry was 36 years (range 30 to 44 years); 79% of entrants were parous. The most frequent past medical problems were gynaecologic, five (13%) in the T-arm and six (16%) in the C-arm. Six subjects had previous breast biopsies, all of which were benign. All women had at least 2 relatives with breast cancer (table 2).

Primary endpoint – adherence

Of the 38 participants in the T-arm, 20 completed the two year treatment period and of the 37 women in the C-arm, 27 completed treatment (Figure 1). Reasons for non-adherence in the T-arm were side effects in 13 (all vasomotor symptoms or mood disorders), three wished to have risk reducing surgery, one stopped treatment to become pregnant and one was lost to follow up. Of the 10 women who did not complete observation, four elected for risk reducing surgery, two wished to take tamoxifen, one developed breast cancer, one became pregnant and two were lost to follow up. Of the 38 subjects in the T-arm, ten (26%) completed the 24 month schedule with no deviations. A further ten (26%) had some deviations but continued on to complete the 24 months. The reasons for deviation ranged from simply forgetting to take a few tablets, stopping to go on holiday or delaying because of operations.

Secondary end points

Side Effects/Quality of Life

The number of women completing evaluable questionnaires (ES, SAQ, STAI and CWS) at each time point ranged from 61-100% (Table S1). There were no appreciable differences between the overall scores at baseline between the two arms of the study (Table S2)
ES (Endocrine Symptoms)

The ES questionnaire captures the severity of 20 of the most common symptoms associated with endocrine therapy. The ES score decreased (i.e. women experienced more severe problems) from baseline to month 3 onwards in T-arm, but significantly only by the 12 month time point (p=0.01). The range for T-arm was <23,72> and for (C) was <40,72>, (Figure 2A). The major toxicity was the expected large increase in vasomotor symptoms (hot flushes, cold sweats and night sweats) (Figure 2B). All other symptoms were highly variable between T-arm and C-arm, but weight gain and headaches were prominent in T-arm (Figures 1S, 2S and 3S).

Effects on Sexual Activity: At baseline, 33/37 (89%) in the T-arm and 32/36 (89%) in the C-arm were married or having an intimate relationship. Pleasure was significantly decreased and discomfort significantly increased in the T-arm (Figure 2C and 2D).

Anxiety/worry scores: There was no significant change in trait (Table 3S) or state anxiety (Figure 2E). There was significantly less cancer worry in T-arm at 3, 6 and 12 months from baseline (Figure 2F).

Lipids

There were no significant changes in serum lipids between the two arms of the trial.

Bone density

Bone density measurements were made in the T-arm only. We report the nine women who had measurements at the appropriate times at baseline, one year and at the end of study at two years (Supplementary Table). There were small decreases between from baseline after two
years for DXA measures of the lumbar spine (P=0.015) and total hip (P=0.011) but no significant change for femoral neck (P=0.11). Medians and ranges are used because of the small number of subjects. There was a highly significant decline in all measures at year one, with some recovery during year two. The reduction of bone in the lumbar spine was 10.9% by year one but some recovery occurred during year 2 (7.0%). Four women became osteopaenic (t-score <-1.0) in the lumbar spine at the end of year one and two remained osteopaenic by year two. During the study, four subjects developed fractures, three in T-arm (tibia at six months, metatarsal at six months and metatarsal at 13 months) and 1 in C-arm (scaphoid at 24 months).

Sixty-one subjects had at least two serum measures of CTX and 53 had between 3 and 5 measurements over two years. CTX for the T-arm rose significantly from median of 1168 pmol/L to 2831 pmol/L over the first six months (p<0.005) and remained significantly higher at 12 months returning to a median of 1342 pmol/L at 18 months. This was not the case for the C-arm where the median stayed reasonably stable over the 18 months between 1000 pmol/L and 1500 pmol/L, thus giving a significant difference between the arms at both 6 and 12 months (p<0.005).

**Mammographic density**

Percent density was assessed by two readers using a visual analogue scale. The Spearman correlation between the two readers was 0.93 (Figure 1A). Mammograms were available for both T- and C-arms at baseline, during (Year 1 and 2) and after treatment (Year 3 and 4); 58 of the 67 women entered in Manchester had 2 or more mammograms available (2 n=11, 3 n=15, 4 n=20 and 5 n=10)). Inspection of the data suggested that there was a decline in breast density during treatment which tended to return to baseline after cessation of treatment (Figure 1B).
We first compared change in density over four years in 22 subjects (13 treatment, 9 control) who had all four mammograms at baseline and years 1, 2 and 3. In C-arm there was a slight linear decline in mean density, whereas in the T-arm there was a steeper decline of density during treatment and an increase when treatment was stopped after 2 years.

We then considered all subjects with density measurements (Figure 3). Mean breast density during years 1 and 2 was compared with that before and after treatment (baseline and years 3 and 4) (Figure 3C). During the treatment period (years 1 and 2) there was a 4.7% (95% CI 0.9 - 8.7%) reduction of mean density in the T-arm, but a non-significant difference in c-arm (mean density increase 2.0% (95% CI -2.3 to 6.4%)). The density reduction in the T arm was particularly marked in younger women (Figure 2D). A repeated measures statistical model indicated that both the treatment effect on density (P=0.0003) and age (P=0.0013) were important (supplementary table).

The median duration of follow up in the study is 9 years. There have been two Invasive and two DCIS cancers in the control arm and one Invasive and one DCIS in the T-arm. These arose at 19, 22, 30 and 48 months from baseline in C-arm and 36 and 43 months in T-arm.

Discussion

We report a randomised trial of ovarian suppression and raloxifene and screening versus screening alone. Both uptake of randomization and subsequent adherence were low. Quality of life was largely maintained in those who completed treatment, but patients in the T-arm experienced severe vasomotor complaints, and decreased pleasure and more discomfort from sexual activity. At the exit interview 9 of 23 patients in the T-arm said that they would not
consider the option of further treatment for 5 years because of the side-effects. There were no significant changes in serum lipids. Treatment was associated with reduced bone density and mammographic density.

Uptake was approximately 7.5% of all women approached. In the sub-group at particularly high risk (≥40% lifetime risk) recruited on the initial protocol, the uptake was 5.3%. The overall uptake of 7.5% is similar to the companion GISS randomised trial in Germany; 31 women were randomized out of 322 approached (9.6%) (14). In the trial reported by Spicer et al (1993)(12), 21 women at high-risk were recruited, but the number approached was not reported, nor in a subsequent study of 9 subjects with BRCA1/2 mutations (13). In prevention studies using tamoxifen in the same clinic we find that uptake averages about 10-12% (23,24). In an overview of all tamoxifen prevention trials/studies the uptake varied between 0.08 and 42% depending on the type of recruitment and centre (24).

Fifty two percent of women competed the two year treatment period which compares with 66% in the GISS-Study. The main reason for non-completion was toxicity in 33% of RAZOR patients but none of the 15 women on treatment dropped out for this reason in the GISS study (14). A number of women wished to opt-out and undertake risk-reducing breast surgery (four in each arm) and a wish of two women in C arm begin tamoxifen reduced compliance in the control T-arm to 73%. Thus in women at high-risk in prevention trials there is attrition not only because of toxicity, but also the wish to have proven treatments such as surgery or chemoprevention. The drop-out rate of 48% at two years compared unfavourably with trials of SERMs and aromatase inhibitors, where the estimated drop-out two years into these studies is approximately 20-30% (25, 26). It is of interest that there were practically no reported drop-outs
over a two-year period in two trials of LHRH agonists and add-back oestrogen to control vasomotor symptoms (12, 13).

Toxicity of the interventions was measured using an specially developed and validated scale for women having endocrine therapy (Endocrine Subscale [ES])(16,27). It consisted of twenty of the most frequent toxicities reported by women on therapy. As expected there was a significant change in symptoms in both the RAZOR and GISS trials. Virtually all women on treatment had marked vasomotor symptoms as is also seen post oophorectomy and other studies of LHRH analogues given for breast cancer treatment (Figure 2B) (28,10). Symptoms other than vasomotor were uncommon but included weight gain and headaches. With the exception of the brief periods of hot flushes or vaginal dryness, which were eliminated by increasing the dose of CE, subjects in the two trials of add-back sex steroids were reported to have minimal symptoms.

The Sexual Activity Questionnaire (SAQ) was developed to investigate the impact of long-term tamoxifen on the sexual functioning of women at high-risk of developing breast cancer (17). The SAQ was first assessed in women in the general population and in women at increased risk of breast cancer where acceptability was equally high and no difference was found between women at high risk and population controls. The majority of variance in sexual functioning can be explained by three factors: pleasure from sexual intercourse, discomfort during sexual intercourse and habit. We found a significant reduction in sexual pleasure and an increase in discomfort during intercourse in treated women in the RAZOR trial and this was also noted in GISS study. Studies after oophorectomy in BRCA1/2 carriers have reported similar results (29, 30, 31). The use of HRT appears to reduce discomfort but not improve reduction in pleasure (31, 32) which may be helped by add-back androgens (35, 12, 13). There were no significant
differences in scores for pleasure or discomfort over this treatment time period. Since studies have shown little difference in sexual activity between use of raloxifene and control, albeit in postmenopausal women, we assume that the reduction in pleasure and increase in discomfort found in this study reflect the effect of goserelin (36).

There were no significant differences in state or trait anxiety between the two arms of the study but a significant reduction in the CWS in T-arm. The CWS was also reduced after prophylactic oophorectomy in women with BRCA1/2 mutations who were at high risk of ovarian cancer (29, 37). Only 3 women in RAZOR had a BRCA1/2 mutation and thus the majority were not at known elevated risk of ovarian carcinoma and suggests that CWS is also reduced for perceived breast cancer risk reduction.

Bone mineral density did not decline in the GISS study where add-back ibandronate was used. In RAZOR we were testing whether add-back raloxifene might maintain bone density. However, at one year there was a loss of 10.7% of bone in the lumber spine which is more than in studies post bilateral oophorectomy, where losses of 6.7% (38) and 3.0% (39) were reported. However there was a rise in bone density in the second year which may have been a delayed effect of raloxifene. In premenopausal women treated with goserelin after surgery for breast cancer, tamoxifen was not associated with preservation of bone density. At three years the loss in the lumber spine was 11.6% (40). It is of interest that add-back treatment with oestrogen and testosterone was effective in preserving bone density in the studies of Spicer et al. (1993) (12) and Weitzel et al. (2007) (13), and this has also been reported in a study of the treatment of endometriosis with the LHRH agonist Desorelin (41). It is important to maintain bone density not only to reduce fracture risk but observational studies suggest that early menopause affects long term survival if hormone replacement therapy is not used (31, 42, 43).
Mammographic density was shown to be reduced in the Spicer and Wietzel studies (12, 13) using various measures. In the study reported here, percentage mammographic density was estimated by two expert radiologists with good correlation between the two readers. The main result was that, in agreement with the Californian studies, we demonstrated a significant reduction in density and a recovery of density after treatment was stopped at two years. Visually assessed density is also reduced after treatment with tamoxifen and may be an indication of responsiveness to the effectiveness of tamoxifen as a preventive agent (44).

The strengths of this study are that we have a clear indication that, even in women at high risk, ovarian suppression is not likely to be acceptable as a preventive option based on low uptake for treatment and subsequent poor adherence. Furthermore, the magnitude of any reduction in breast cancer risk following bilateral oophorectomy in BRCA1 mutation carriers has recently been questioned (6, 7). The poor adherence is due not only to vasomotor side effects but also to the perceived need for surgical prophylaxis in this group of women at particularly high risk. The limitations of the study include the failure to enter 80 women as planned and small numbers upon which we base comments on the effect of treatment on bone and mammographic density. In the modest number of women that maintained treatment side-effects were as expected less severe or better tolerated, but prospectively identifying those as a target population would be very difficult.

In conclusion, treatment with goserelin and raloxifene, as a nonsurgical option for breast cancer prevention, was shown to have low uptake and adherence and thus, in its current form, is not likely to be widely accepted, even if effective. Uptake is lower compared with many studies using tamoxifen (24). Other measures than raloxifene may be necessary to maintain bone density and it remains to be demonstrated that short term mammographic density reduction is
beneficial. Trials aimed at chemoprevention in healthy women at high cancer risk may benefit from involving patients to improve the selection of acceptable intervention strategies and the design of information, physician training and study support materials aimed at improving recruitment and retention. The safety of ovarian suppression with add-back oestrogen and testosterone might be explored in future longer duration prevention trials.

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Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.
References


Table 1. Baseline characteristics of women randomised

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<th>Screening only n=37</th>
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<td>36 &lt;30, 44&gt;</td>
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<td>Age at menarche</td>
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<td>12 &lt;9, 15&gt;</td>
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<td>Parous</td>
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<td>14 (38)</td>
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Table 2. Breast cancer risk categories at the beginning of the study

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<th>Screening only n=37</th>
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<td>BRCA-1 germ-line mutation</td>
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</tr>
<tr>
<td>BRCA-2 germ-line mutation</td>
<td></td>
<td>2 (5)</td>
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<tr>
<td>First degree relative known to carry the BRCA1/BRCA2 mutation</td>
<td></td>
<td>2 (5)</td>
</tr>
<tr>
<td>First degree female relative diagnosed with breast cancer below the age of 40</td>
<td>11 (29)</td>
<td>15 (41)</td>
</tr>
<tr>
<td>First degree female relative with bilateral breast cancer, with first cancer diagnosed before age 50</td>
<td>4 (11)</td>
<td>3 (8)</td>
</tr>
<tr>
<td>Two first degree or one first and one second degree female relative from the same side of the family, both diagnosed with breast cancer before age 60.</td>
<td>22 (58)</td>
<td>22 (59)</td>
</tr>
<tr>
<td>Two first degree or one first and one second degree female relatives, both diagnosed with breast cancer before age 60 and ovarian cancer at any age</td>
<td>1 (3)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>One first and one second degree female relative with breast and ovarian cancer diagnosed before age 60</td>
<td>36 (95)</td>
<td>36 (97)</td>
</tr>
</tbody>
</table>
Figure 1. Consort flow diagram of numbers approached and study participants

Enrollment

Assessed for eligibility (n~1,000)

Declined to participate (n= 925)

Randomized (n=75)
Manchester (n=67), RMH (n=1), Southampton (n=7)

Allocation

Allocated to intervention (n=38)
Goserelin + raloxifene + screening
Completed allocated intervention (n=20)

Allocated to intervention (n=37)
Screening only
Completed allocated intervention (n=27)

2 Year Follow-Up

Discontinued intervention (n=18)
Reasons 13 side effects, 2 prophylactic mastectomy, 1 BSOH, 1 pregnancy, 1 emigration

Discontinued intervention (n=10)
Reasons 1 prophylactic mastectomy, 3 BSOH, 2 other treatments, 1 breast cancer, 1 pregnancy, 1 lost to follow up, 1 emigration

Analysis

Analysed (n=38)
Excluded from analysis (n= 0)

Analysed (n=37)
Excluded from analysis(n=0)
Figure 2 Results from toxicity/quality of life measures. Treated in blue and control in pink. A Endocrine Symptom scale all 16 measures. B Endocrine Symptom scale vasomotor symptoms of 3 and 4 severity. C Sexual Activity Questionnaire – pleasure. D Sexual Activity Questionnaire – discomfort. E State Anxiety Score. Cancer Worry Scale. (The numbers of women at each time point for all measures are shown in table S1). F Median cancer worry scores.
Figure 3 A. Mean density change (VAS from two readers; o control, triangle treatment, | standard error) in women who had yearly mammograms available from baseline to year 3. B. Reduction in mean density from years 1 and 2 (o control, triangle treatment) compared with baseline and years 3,4. C. Younger women were more likely to see a change in density: VAS difference (mean VAS in years 1&2 minus mean VAS at baseline and years