A hormonal contraceptive approach to reducing breast and ovarian cancer risk: an update

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Abstract

Epidemiological studies have consistently found that bilateral oophorectomy at a young age substantially reduces breast cancer risk. Such surgical menopause around age 35 has been found to reduce risk by 60 to 75%. A reversible medical oophorectomy using an agent such as a gonadotropin-releasing hormone agonist (GnRHA) should achieve a similar reduction in risk. Although the use of GnRHA alone is unacceptable because of the associated hypoestrogenic side-effects, these can be satisfactorily prevented by add-back low-dose estrogen treatment with intermittent progestin to protect the endometrium. It is estimated that a regimen of GnRHA plus add-back ultra low-dose estrogen and progestin would prevent some two-thirds of current breast cancer if used from age 30. If used from age 20 almost nine out of ten current breast cancer cases would be avoided. If, as is likely, these estimates also apply to women at high genetic risk of breast cancer because of possession of a BRCA1 or BRCA2 gene, their breast cancer risk would be reduced to below that of ‘normal’ women. The protective effects on ovarian cancer are calculated to be greater than the protective effects on breast cancer. Practical chemoprevention of breast and ovarian cancer using this approach should be possible within 5 years.

Surgical menopause and breast cancer risk

Epidemiological studies have found that breast cancer risk decreases with decreasing age at menopause (Table 1) (Lilienfeld 1956, Hirayama & Wynder 1962, Feinleib 1968, Trichopoulos et al. 1972, Kelsey 1979). This is the key epidemiological observation on the relationship of ovarian hormones to breast cancer risk. Most importantly, surgical menopause (bilateral oophorectomy) has an effect which is at least as large as that associated with natural menopause (Table 1). Hirayama & Wynder (1962) found a 59% reduction in breast cancer risk in women who had a surgical menopause before age 37 in their case-control study. Feinleib (1968) noted in his cohort study that women with surgical menopause before age 40 had a 75% reduction in breast cancer risk, and in the case-control study of Trichopoulos et al. (1972) surgical menopause below age 35 was associated with a 64% reduction in breast cancer risk. The findings are very consistent and there is a large decrease in breast cancer risk with early bilateral oophorectomy. The situation is illustrated in Fig. 1 which shows the age-incidence curve of breast cancer for ‘normal’ women with menopause around age 50 and the age incidence for women with bilateral oophorectomy at age 35.
Table 1 Age and type of menopause and breast cancer risk.

<table>
<thead>
<tr>
<th>Type of menopause</th>
<th>Age at menopause (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;45</td>
</tr>
<tr>
<td>Bilateral oophorectomy</td>
<td>0.77</td>
</tr>
<tr>
<td>Natural menopause</td>
<td>1.00</td>
</tr>
</tbody>
</table>

*Derived from Trichopoulos et al. (1972).

Gonadotropin-releasing hormone agonists

Complete inhibition of ovarian steroid production (and inhibition of ovulation) can be achieved by the chronic use of a sufficient dose of a gonadotropin-releasing hormone agonist (GnRHA). Chronic administration of a GnRHA which achieves this blocking of ovarian function (a reversible ‘medical oophorectomy’) should have the same effects as a bilateral oophorectomy and, in particular, should achieve the same protective effect on breast cancer risk.

Figure 1 shows the age-incidence curve of breast cancer for ‘normal’ women and the predicted curves for women who use a GnRHA from ages 20, 30 or 40 until age 50. The predicted reductions in breast cancer incidence from use of the GnRHA are very significant and are shown numerically in Table 2. If a GnRHA is used only from age 40 the lifetime risk (cumulative incidence to age 75) of breast cancer should be reduced by 35%. If, however, a GnRHA is used from age 30 the risk should be reduced by 83%. If a GnRHA is used from age 20 the risk is predicted to be reduced by 98%, i.e. the risk of breast cancer is reduced to 2% of ‘normal’. (The calculations for Fig. 2 and Table 2, and other predicted effects given below were made using our published mathematical model (Pike et al. 1983, Pike 1987); this model accurately describes the most important known epidemiological risk factors for breast cancer.)

Use of a GnRHA alone is, however, unacceptable except for brief periods because of the associated...
side-effects, including hot flushes, dyspareunia, and loss of bone mineral density (BMD). These side-effects, and other side-effects that have been reported in some women, appear in the main to reflect the hypoestrogenic state induced by the GnRHA and can be prevented by add-back low-dose estrogen treatment. It is also necessary to use add-back intermittent progestin to protect the endometrium from the add-back estrogen treatment. We have carried out a small randomized trial of such a GnRHA plus add-back estrogen/progestin (GEP) regimen in women at high risk of breast cancer (Spicer et al. 1993, 1994).

**Table 2** Predicted reduction in cumulative breast cancer risk with use of GnRHA alone.

<table>
<thead>
<tr>
<th>GnRHA use</th>
<th>Reduction in risk</th>
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<tbody>
<tr>
<td>From age 20</td>
<td>98%</td>
</tr>
<tr>
<td>From age 30</td>
<td>83%</td>
</tr>
<tr>
<td>From age 40</td>
<td>35%</td>
</tr>
</tbody>
</table>

**Add-back estrogen/progestin**

The regimen we used in our GEP pilot trial is shown in Table 3. The required add-back estrogen dose appeared, at the time we designed the pilot trial, to be 0.625 mg conjugated estrogens (CEs)/day or equivalent, since a CE dose of 0.625 mg/day appeared to be the minimum estrogen required as estrogen replacement therapy (ERT) in postmenopausal women and we could find no reason to think that this dose would not also suffice in women using a GnRHA (see Pike et al. 1989, Spicer et al. 1991 for details). We calculated that use of such a GnRHA plus estrogen regimen would achieve a major reduction in breast cancer risk, although not so great as would be achieved by GnRHA alone. Endometrial hyperplasia is a significant clinical concern with ERT use in postmenopausal women, and will be so with a GnRHA plus estrogen regimen. In postmenopausal women, progestin therapy for 13 days appears to be the minimum necessary to completely control ERT-induced endometrial hyperplasia. We presumed that the same would apply to women using a GnRHA plus estrogen regimen. There was also evidence that a small proportion of women would develop hyperplasia if progestins were not given every 28-day cycle, but few would develop symptoms, and a progestin course every fourth 28-day cycle would eliminate any hyperplasia that did develop. It was therefore decided to prescribe the progestin medroxypregesterone acetate (MPA) for 13 days at a dose of 10 mg/day only every fourth 28-day cycle. With this schedule it was predicted that no endometrial problems would arise. The main reason for not using a progestin every 28-day cycle was because we considered that the currently available evidence suggests that progestins are mitogenic to breast tissue and that their more frequent use would further decrease the beneficial effect of the GnRHA on breast cancer risk. These estrogen and progestin doses are much lower than those in modern low-dose oral contraceptive (OC) regimes: we estimate that the cumulative estrogen dose is reduced by 62% and the cumulative progestin dose by 85% compared with a 30 µg ethinylestradiol plus 1 mg norethisterone OC. The regimen is thus a GnRHA plus ultra low-dose estrogen/progestin contraceptive regimen (GEP).

**Table 3** Pilot GEP contraceptive regimen.

<table>
<thead>
<tr>
<th>Agent and administration</th>
<th>Rationale</th>
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<tbody>
<tr>
<td>GnRHA</td>
<td>Leuprolide acetate depot (Lupron Depot®)</td>
</tr>
<tr>
<td></td>
<td>Prevent ovulation, and ovarian sex-steroid production, reducing risk of breast, ovarian and endometrial cancer</td>
</tr>
<tr>
<td>Estrogen</td>
<td>Conjugated estrogens (0.625 mg/day p.o.; Premarin®) 6 days out of 7</td>
</tr>
<tr>
<td></td>
<td>Prevent bone mineral loss; Prevent possible rise in cardiovascular disease risk; Prevent menopausal symptoms; Prevent urogenital atrophy</td>
</tr>
<tr>
<td>Progestogen</td>
<td>MPA (10 mg/day p.o.; Provera®)</td>
</tr>
<tr>
<td></td>
<td>Reverse any endometrial hyperplasia, and prevent any possible increased risk of endometrial cancer</td>
</tr>
</tbody>
</table>

**GEP and reduction in breast cancer risk**

Studies of postmenopausal ERT use suggest that breast cancer risk is increased approximately 2.2% for every year that ERT is used at a dose of 0.625 mg
CE/day, and that this risk will endure after the ERT use is stopped (Steinberg et al. 1991, Pike et al. 1993a). There is some evidence to suggest that adding a progestin to an ERT regimen will increase the breast cancer risk (Bergkvist et al. 1989, Persson et al. 1992, Pike et al. 1993b), and we estimated (and still estimate) that an estrogen/progestin regimen such as we were using may increase the breast cancer risk of postmenopausal women by 2.7% per year of use. This is a much smaller increase in risk than is associated with continuing ovarian function (see Table 1).

![Figure 3](image)

**Figure 3** Age-incidence curve of breast cancer (nulliparous women): comparison of natural menopause at age 50 and predicted effects of GEP regimen over various age ranges. The inflection in the GEP curves at age 50 is because it is assumed that HRT is not used after age 50.

To estimate the effect on breast cancer risk of the GEP regimen in premenopausal women we assumed that the GnRHA use would induce a reversible ‘medical oophorectomy’ and that the effect of the estrogen and progestin was the same as that described above in postmenopausal hormone replacement therapy (HRT) users.

Figure 3 shows the age-incidence curve for ‘normal’ women and the predicted curves for women who use the GEP regimen from ages 20, 30 or 40 until age 50. The predicted reductions in breast cancer incidence are less than with GnRHA alone, but they remain very substantial, and are shown numerically in Table 4. If the GEP regimen is used only from age 40, the lifetime risk of breast cancer should only be reduced by 16%. If, however, the regimen is used from age 30 the risk of breast cancer should be reduced by 64%, i.e. some two-thirds of breast cancer would be prevented. If the regimen is used from age 20 the risk of breast cancer should be reduced by 89%, i.e. almost nine out of ten breast cancer cases would be avoided. (If there is, in fact, no increased breast cancer risk from ERT and progestin use in the postmenopausal period, as a number of authors maintain, then the GEP regimen should reduce breast cancer risk to the extent illustrated in Fig. 2 and shown in Table 2. We prefer to make a more conservative prediction of the reduction in breast cancer risk.)

Although it may be objected that these figures (Table 4) were calculated from a mathematical model, they can be seen to be probably close to correct by comparing the figure for starting at age 30 to the known effects of early oophorectomy. We noted above that epidemiological studies have found that early surgical menopause with no HRT is associated with a 60% to 75% reduction in breast cancer risk. The figures calculated for the GEP regimen are effectively simply these figures reduced slightly to account for the relatively small increased risk of breast cancer associated with HRT use.

The predicted effect on breast cancer risk of using the GEP regimen for a limited length of time and then stopping is illustrated in Fig. 4 for 10 years of use from age 30 to 40. Essentially the slopes of the incidence curve are as shown in Fig. 3 for the period

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**Table 4** Predicted reduction in cumulative breast cancer risk with use of GEP regimen.

<table>
<thead>
<tr>
<th>GEP use</th>
<th>Reduction in risk</th>
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<tr>
<td>From age 20</td>
<td>89%</td>
</tr>
<tr>
<td>From age 30</td>
<td>64%</td>
</tr>
<tr>
<td>From age 40</td>
<td>16%</td>
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in view of her poor compliance with the oral CE. All other women remained on the study.

**Effect on the breast**

Mammographic densities of women on the contraceptive regimen were quite dramatically decreased after 1 year on the regimen (Fig. 5) (Spicer *et al.* 1994). This is precisely what happens at menopause and, as we have noted, early menopause is associated with a much reduced risk of breast cancer. The statistically highly significant reductions in mammographic densities at 1 year suggest that the aim of the regimen to reduce breast cancer risk has been accomplished.

(Menopause is associated with reduced breast cell mitotic activity, and we believe that the associated decreased mammographic densities reflect this. The majority of the breast consists of adipose and fibrous tissue. In the premenopausal breast, less than 15% of the volume of the breast consists of epithelial cells, and this decreases to less than 5% by age 60. The relative amounts of fibrous and adipose tissue are what determine the appearance of the mammographic image. Increased fibrous tissue equates to increased mammographic densities. Since estrogen and progesterone receptors in the breast appear to exist only in epithelial cells, the reduced sex-steroid levels of postmenopausal women are likely to affect fibrous tissue secondarily to their effect on epithelial cells.)

**Table 5** Predicted reduction in breast cancer risk with use of GEP regimen for various durations before age 40.

<table>
<thead>
<tr>
<th>Duration of regimen (years)</th>
<th>Reduction in risk</th>
</tr>
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<tr>
<td>5</td>
<td>33%</td>
</tr>
<tr>
<td>10</td>
<td>57%</td>
</tr>
<tr>
<td>15</td>
<td>73%</td>
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In an editorial accompanying the report (Spicer *et al.* 1994) of the effect of the GEP regimen on mammographic densities, Feig (1994) suggested that finding early cancers in mammograms from women on such a regimen would be much easier than in ‘normal’ premenopausal women. This could lead to a greatly improved efficacy of screening mammography in young women.

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**Figure 4** Age-incidence curve of breast cancer (nulliparous women): comparison of natural menopause at age 50 and predicted effect of GEP from age 30 to age 40.

**GEP pilot study**

We have tested the prototype GEP regimen (Table 3) in a pilot clinical trial (Spicer *et al.* 1993, 1994). Fourteen premenopausal women were randomized to the regimen and seven to the control arm. We removed one woman randomized to the regimen arm from the study following the second dose of GnRHA
Other effects

Women on the regimen had significantly fewer 'symptoms' on the regimen than before they started the regimen (Spicer et al. 1993). This was mainly due to the sharp reduction of the symptoms associated with premenstrual syndrome. Cyclical breast symptoms were effectively eliminated, and no other changes in the breasts were noted. The few occurrences of hot flushes or vaginal dryness were eliminated by increasing the estrogen dose to 0.9 mg CE. Unscheduled bleeding or spotting was infrequent and decreased with time on the regimen. A beneficial rise in high-density lipoprotein cholesterol was seen. However, despite the use of an estrogen dose which is known to prevent loss of BMD in normally postmenopausal women, a small (2-3%) loss of spinal and femoral BMD was seen in the women on the GEP regimen at 1 year.

The reason for this loss of BMD appears to be inhibition of ovarian androgen production by the GnRHA, which may also account for the changes in libido occasionally reported with GnRHA use. Women in the regimen group had a 62% drop in non-sex hormone binding globulin-bound testosterone. In contrast, during the early naturally postmenopausal period testosterone levels are stable. This provides an explanation of why the CE dose we used has been found adequate for preventing bone loss in naturally menopausal women, but not in our volunteers. The addition of testosterone to the regimen to replace that lost by the action of the GnRHA should eliminate this problem. Preliminary results with low-dose oral methyl-testosterone showed no further bone loss in women on the regimen. However, use of oral methyl-testosterone is an unsatisfactory approach as it has unwanted first pass effects and we are currently conducting studies with non-oral testosterone.

GEP and reduction in ovarian cancer risk

The suppression of ovulation and ovarian function by a GEP regimen should protect against ovarian cancer to at least the same extent as has been found to occur with use of OCs. If the GEP regimen is used only from age 40 the subsequent risk of ovarian cancer is calculated to be reduced by 67% (Pike 1987). If the regimen is used from age 30 the risk should be reduced by 92%, i.e. more than nine out of ten ovarian cancer cases would be prevented. If the regimen is used from age 20 the risk of ovarian cancer should be reduced to less than 1% of current rates. Use for only 5 years is predicted to reduce the lifetime risk of ovarian cancer by 41%, use for 10
years to reduce risk by 67%, and use for 15 years to reduce risk by 84%. These predicted effects are even greater than the predicted effects on breast cancer risk.

GEP and endometrial cancer

Our original estimates of the effect of the GEP regimen on endometrial cancer risk were that there would be a modest 18% reduction in risk of endometrial cancer with 5 years use of the proposed regimen, that use for 10 years would reduce risk by 33%, and 15 years use would reduce risk by 45%. These estimates were partly based on very incomplete information about the effects of the addition of intermittent progestins to menopausal ERT on endometrial cancer risk. Recent data suggest that the regimen may reduce endometrial cancer risk more than we originally estimated. First, Ettinger et al. (1994) showed that the addition of a progestin for 14 days every third 28-day cycle to postmenopausal women on ERT was associated with no more hyperplasia than when the progestin was given every cycle. Secondly, we found in a large epidemiological study of endometrial cancer and HRT that the addition of a progestin for 10 days per 28-day cycle was associated with effectively no increase in risk of endometrial cancer (MC Pike, RK Peters, W Cozen, N Probst-Hensch, JC Felix, PC Wan & TM Mack, unpublished observations). Extrapolating the latter result to a modified GEP regimen in which the progestin is given every 28-day cycle would imply that such a regimen would produce a large decrease in endometrial cancer risk (Pike 1987). When this is then taken together with the results of Ettinger et al. (1994), it appears that we may have significantly underestimated the beneficial effects of the proposed GEP regimen on endometrial cancer risk. Studies on the possible mechanism of the profound protective effect of the 10-day progestin regimen on the risk of postmenopausal endometrial cancer are planned to further elucidate the mechanism of the effect. These studies should provide a firm basis on which to predict the effect of the GEP regimen on endometrial cancer risk.

The main reason we originally had for using progestin only every fourth cycle was to minimize the exposure of the breast to progestin, because we believed that such exposure would decrease the beneficial effects of the GEP regimen on breast cancer risk. Whether progestins do act as mitogens in breast tissue is still not satisfactorily resolved. Recent reports of experimental data relevant to this issue have been published by Laidlaw et al. (1995) and by Cline et al. (1996).

Laidlaw et al. (1995) implanted normal human breast tissue into athymic nude mice and found that cell proliferation was proportional to estradiol dose up to a dose of a 2 mg pellet, but a further increase to a 6 mg pellet had no additional effect. When a progesterone pellet was added to the maximally effective dose of estradiol (i.e. the 2 mg pellet) no further increase in cell proliferation was noted. This was interpreted in the paper as implying that 'progestosterone does not affect proliferation'. The results, however, only support the much weaker statement that 'the addition of progesterone to a maximally stimulatory dose of estradiol does not further increase cell proliferation' (Pike et al. 1996).

Cline et al. (1996) gave surgically postmenopausal adult female cynomolgus macaques either no treatment, CE, or combined therapy with CE and the progestin MPA. Drugs were administered in the diet, at doses equivalent on a caloric basis to 0.625 mg/ woman per day for CE and 2.5 mg/woman per day for MPA, for 30 months. In this model, combined therapy with estrogen and the progestin MPA induced greater proliferation than did estrogen alone. The increased proliferation occurred in the alveoli and major breast ducts but not in the terminal ducts, so that the interpretation of these results is regarding human breast cancer is not completely clear.

If the addition of progestins does not affect breast cancer risk, there would still likely be a benefit as regards cardiovascular disease risk of not adding more progestin than is absolutely necessary to the regimen, but these arguments would need to be balanced against the greater confidence one would have of protecting the endometrium. Our view remains that progestin may well decrease the beneficial effect of the GnRHA-based regimen on breast cancer risk, and should be used no more than is needed to protect the endometrium.

GEP and genetic risk of breast cancer

The rationale for the GEP regimen is based on the overwhelming evidence that decreasing breast exposure to ovarian hormones leads to a significant
decrease in breast cancer risk. The main evidence comes from studies of the effects of surgical menopause, in which a 60 to 75% reduction of breast cancer risk is observed if the bilateral oophorectomy is done around age 35. Would a bilateral oophorectomy reduce the subsequent risk of breast cancer in a woman at high genetic risk of breast cancer because of a mutant BRCA1 or BRCA2 gene? The answer to this question is not yet clear. However, breast cancer in such carriers remains an essentially female disease, and we would certainly predict that the disease in these women is affected by hormones in much the same way that it is in ‘normal’ women. If this is true, then their use of a GEP regimen from age 20 would reduce their breast cancer risk below that of ‘normal’ women. It is clearly of great importance to establish the effects of ovarian hormones on breast cancer risk (age incidence) in these women. This is difficult but not impossible to do with family studies, but a more direct approach is also possible. The direct approach is to evaluate the biology (including cell proliferation) of the breast in a BRCA1 carrier before and after bilateral oophorectomy or use of a GnRHA. If ovarian hormones are important we would, of course, predict that mammograms obtained 1 year after oophorectomy (or after being on a GEP regimen for a year) will have significantly reduced mammographic densities compared with mammograms obtained before the surgery (or starting the regimen). These studies need to be done as a matter of some urgency.

**Proposed developments**

In order to make a GEP with replacement testosterone regimen practical it will be necessary to make its administration simple and to produce it at a reasonable cost. The latter does not appear, at least in the long term, to be a major issue. An injectable depot regimen using ultra low-dose ethinyl-estradiol is likely to be acceptable to many women. This depot contraceptive would deliver all four hormone components in a single injection to be given three (or possibly four) times per year. The depot will deliver, with approximately constant release characteristics, the GnRHA, estrogen and testosterone continuously. The progestin would be released for 2 weeks at a high enough dose to completely control endometrial hyperplasia. A non-injection non-depot regimen also appears technically quite feasible. Practical chemoprevention of breast and ovarian cancer using this approach should be possible within 5 years.

**Declaration of interest**

The authors are associated with Balance Pharmaceuticals, Inc., a company set up to develop the contraceptive regimens discussed here.

**References**


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