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THE PREVENTION OF BREAST CANCER THROUGH REDUCED OVARIAN STEROID EXPOSURE

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Analysis of epidemiologic data on cancers of the breast, ovary and endometrium; the effects of endogenous hormones on cell proliferation; and current carcinogenesis concepts, suggest that hormonal contraceptives can be developed that will reduce lifetime risk of all 3 cancers. The 'unopposed-estrogen hypothesis' accounts for endometrial cancer risk factors. Ovarian cancer risk is closely related to the total frequency of ovulation. The risk of breast cancer can be explained by an 'estrogen-plus-progestogen hypothesis'. On the basis of this analysis an hormonal contraceptive regimen has been developed consisting of a gonadotropin-releasing hormone agonist (GnRHA) plus continuous low-dose add-back estrogen and a short course of progestogen every fourth month. The total dose of add-back estrogen is estimated to be approximately 38% that in present-day low-dose combination-type oral contraceptives (COCs). The total dose of progestogen is approximately 15% that in COCs. This regimen prevents ovulation and should thus reduce ovarian cancer risk. It also reduces the exposure of the endometrium to unopposed estrogen, and the exposure of the breast to estrogen-plus-progestogen. It is estimated that use of such a regimen for 10 years will only reduce lifetime risk of endometrial cancer by one-sixth, but lifetime risk of ovarian cancer is estimated to be reduced by two-thirds, and lifetime risk of breast cancer is estimated to be reduced by one-half.

Key words: Breast cancer, ovarian cancer, prevention, hormonal contraceptives.

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A substantial body of knowledge is now available concerning the epidemiology of breast, ovarian and endometrial cancer. When the epidemiological data are considered in conjunction with the results of studies of the physiology of the epithelial tissues from which these cancers arise and our current concepts of carcinogenesis, it is clear that interventions can now be planned to reduce a woman's risk of all 3 cancers. Use of combination-type oral contraceptives (COCs) is known to significantly reduce a woman's risk of both endometrial and ovarian cancer, and the reasons for these effects are essentially understood. Our understanding of normal breast epithelial physiology, and our ability to develop approaches to prevent breast cancer, have trailed significantly behind our understanding of the endometrium and ovary. However, as we argue below, the critical mass of knowledge now exists to permit the design of a hormonal contraceptive that will reduce breast cancer risk.

The incidence of most non-hormone dependent adult cancers rises continuously and increasingly rapidly with age; and a plot of the logarithm of incidence against the logarithm of age produces a straight line (Fig. 1) (1). In contrast, the incidence of cancers of the breast, ovary and endometrium show a sharp slowing of the rate of rise at the age of menopause (Fig. 2) (2–4). The simplest interpretation of this phenomenon is that the key etiologic

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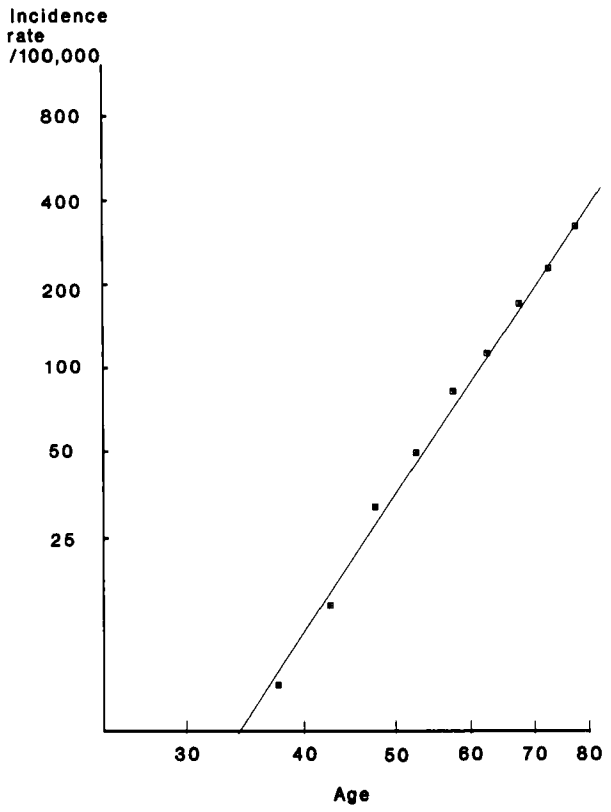

Fig. 1. Age-incidence curve of colorectal cancer (from data for US white women, 1969–1971).

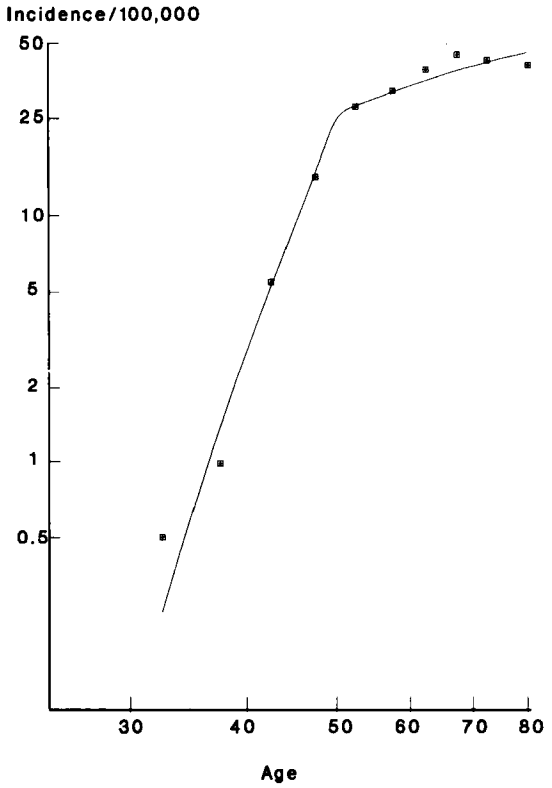

Fig. 2. Age-incidence curve of endometrial cancer (from data for West Midlands Region of England, 1968–1972).

elements are present in premenopausal women, but are reduced following the menopause. For endometrial and breast cancer, ovarian steroid hormones are the key factors (5, 6). For ovarian cancer, ovulation is the key factor (7).

Cell proliferation and carcinogenesis

An extensive body of evidence from the fields of chemical carcinogenesis, molecular genetics, and epidemiology, demonstrates that cell proliferation is central to the process of carcinogenesis (7–11). Cell proliferation, stimulated by exposure to mitogens, increases the risk of tumorigenesis by accelerating the accumulation of stochastic somatic genetic errors, including mutations, translocations, and reduction to homozygosity of tumor suppressor genes.

Studies of chemical carcinogenesis have identified a large group of substances that induce cancer in animal bioassays, but are not genotoxic (8–10). This evidence has resulted in much rethinking of the concepts of chemical carcinogenesis, and has led to the idea that many non-genotoxic carcinogens (such as hormones) act by increasing cell proliferation (12). Recent studies in molecular genetics provide a mechanism to explain the importance of cell division in carcinogenesis (10). Cellular DNA is subject to damage from a variety of sources with great frequency, but such damage is generally rapidly repaired. If, however, DNA replication and cell division occur before repair, the damage may be converted into a stable genetic error. Thus, an agent that increases mitotic activity will increase the probability of converting DNA damage (however caused, i.e., both exogenously and endogenously induced damage) into mutations (12). More profound DNA changes, including non-disjunction and gene conversions, also require cell division and occur with increased frequency with increased cell division (13). The prevention of (i.e. the reduction in risk of) breast, endometrial and ovarian cancer can all be achieved by reducing the rate of cell division in the relevant epithelial tissue.

Endometrial cancer

The 'unopposed estrogen hypothesis' has been highly successful in explaining the risk factors associated with endometrial cancer; this hypothesis states that endometrial cancer risk is increased by exposure to estrogen that is not 'opposed' by a progestogen. Estrogen stimulates endometrial-cell mitosis, but only in the absence of progestogen, and the hypothesis is that the increased risk of endometrial cancer associated with such estrogen exposure is caused by the increased mitotic activity of the endometrium induced by such exposure. During a normal menstrual cycle (Fig. 3a and b) endometrial-cell mitotic activity peaks during the early follicular phase (5). Following ovulation, serum

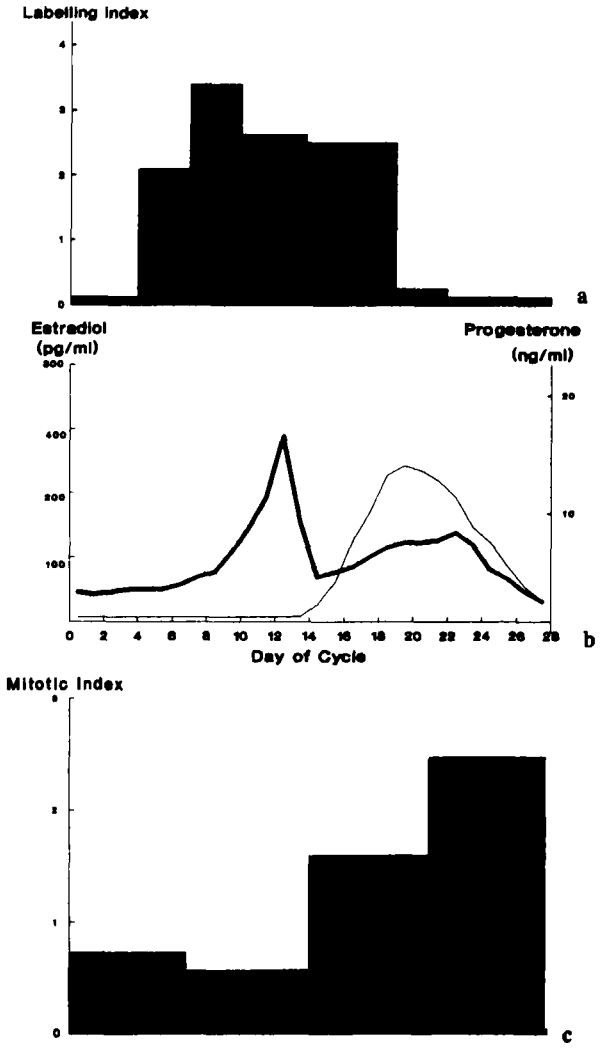

Fig. 3. Cyclical change in endometrial and breast cell proliferation of premenopausal women. a) Cyclical changes in endometrial cell mitotic activity; peak proliferative activity occurs in the follicular phase. b) Serum levels of the ovarian hormones estradiol and progesterone. Thick line is of estradiol; thin line is of progesterone. c) Cyclical changes in breast epithelial cell mitotic activity; in contrast to the endometrium, peak proliferative activity occurs in the late luteal phase.

progesterone rises and endometrial-cell proliferation ceases, despite continued estradiol levels in excess of 50 pg/ml. In contrast, at low serum estradiol concentrations (5 pg/ml), as occur in slender postmenopausal women, endometrial cell mitotic activity is very low, and the endometrium is atrophic.

Epidemiologic studies have shown that endometrial cancer risk decreases with decreasing age at menopause, with increasing parity, and with COC use (5). Increasing body weight in both pre- and postmenopausal women, and estrogen replacement therapy (ERT) in postmenopausal women, increase endometrial cancer risk (5).

Early menopause reduces risk by reducing the unopposed estrogen concentration to the low level of the postmenopausal period. During pregnancy there is no unopposed estrogen, so increasing parity is associated with decreasing risk. In premenopausal women, obesity increases risk through the progesterone deficiency associated with the increased anovulation frequency of such obese women, and the serum estrogen level is sufficiently high to cause maximal endometrial cell proliferation (5). In obese postmenopausal women, serum estrogen is increased and serum sex-hormone-binding globulin (SHBG) is decreased, so that there is an increase in unopposed non-SHBG bound (bioavailable) estrogen (5). In a postmenopausal woman, conjugated equine estrogens (CEE) as ERT increase the exposure of the endometrium to unopposed estrogen and the endometrial mitotic activity of a postmenopausal woman is much increased by CEE use. Other estrogens, as ERT, act in a similar manner.

COCs contain an estrogen and a high dose of progestogen; endometrial cells are, thus, exposed to unopposed estrogen only during the 7 days in 28 during which the COC is not taken, and the endogenous estrogen level during these 7 days is very low. COC use reduces the cancer risk as endometrial mitotic activity is near zero (5).

Breast cancer

In contrast to the endometrium, studies of the effects of endogenous or exogenous hormones on breast epithelial-cell proliferation have been difficult, since breast biopsies are not as readily performed as endometrial biopsies. However, over the last decade thymidine labelling and mitotic counts have been used to study normal breast tissue removed at mastectomy, biopsy, reductive mammoplasty or forensic autopsy (14–16). The epithelial cells of the terminal duct lobular unit (TDLU) from which the vast majority of breast cancers arise, undergo significant changes during the menstrual cycle. TDLU cell proliferation is lowest during the follicular phase and then increases some 4-fold to peak in the mid to late luteal phase (Fig. 3c). This suggests that estradiol induces some cell division, but that estradiol and progesterone together induce considerably more—the 'estrogen-plus-progestogen hypothesis'. In the postmenopausal period, when estradiol levels are low, and progesterone is absent, rates of TDLU cell proliferation are very low (14).

Epidemiologic studies have demonstrated that breast cancer risk decreases with increasing age at menarche and decreasing age at menopause. The protective effect of a late menarche is readily explained by the estrogen-plus-progestogen hypothesis; it delays the time to onset of breast epithelial-cell mitotic activity. During the postmenopausal period, serum estradiol falls to a low level and progesterone is absent; as a result breast epithelial-cell proliferation is profoundly lower than during the premenopausal period. Thus the incidence of breast cancer, that increases steeply during the premenopausal years, rises at a much diminished rate postmenopausally (Fig. 4).

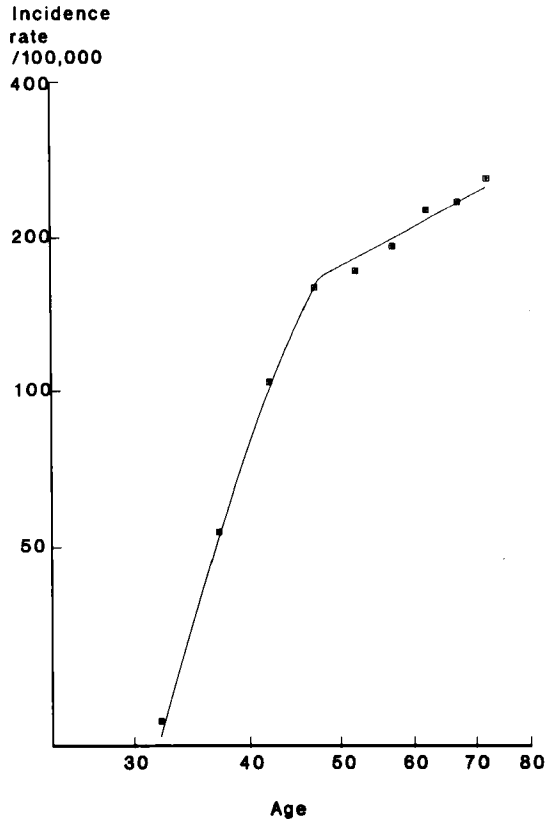

Fig. 4. Age-incidence curve of breast cancer (from data for US white women, 1969–1971).

Obesity during postmenopausal years increases breast cancer risk, but obesity during the premenopausal years actually reduces risk. These contradictory effects of obesity are predicted by the estrogen-plus-progestogen hypothesis. The increased anovulation associated with premenopausal obesity will decrease breast exposure to both estradiol and progesterone. After menopause, the decreased risk associated with premenopausal obesity is gradually eliminated and an increased risk finally achieved by the increased bioavailable estrogen levels associated with postmenopausal obesity (6).

Use of ERT only marginally increases breast cancer risk, but there is evidence that the use of ERT plus progestogen in the postmenopausal period may increase risk substantially (17). The reason that risk is only slightly increased by ERT is the relative low-dose of estrogen used in ERT (CEE use is associated with a bioavailable estradiol level only some 2/3rds that of the early follicular phase) and the absence of progestogen. The addition of a relatively high-dose progestogen to ERT is, of course, predicted to substantially increase the risk associated with ERT (6).

Studies of COC use and breast cancer have found either no effect or a slight increase in risk (6). This is entirely consistent with the estrogen-plus-progestogen hypothesis. COCs contain an estrogen and a progestogen. COCs inhibit gonadotropin secretion thus reducing ovarian steroidogenesis to very low levels and preventing ovulation, but the ovarian steroid loss is compensated for by the synthetic estrogen (ethinyl estradiol) and progestogen making up the COC. Studies using thymidine labelling of TDLU cells in COC users, confirm that breast epithelial-cell mitotic rates in women using COCs are in the premenopausal range (18).

The recent demonstration of low serum levels of ovarian estrogens in women at low risk of breast cancer in China and Japan (19–21) shows that the estrogen-plus-progestogen hypothesis can explain the large differences in breast cancer risk between these Asian countries and the West (3, 22). This adds considerably to the evidence supporting this hypothesis as holding the key to breast cancer prevention.

Ovarian cancer

The tissue from which ovarian cancer arises is the surface epithelium. The major impetus to ovarian epithelial-cell replication is the repair of the ovarian surface after each ovulation (7, 23). Increasing parity, early menopause and use of COCs all reduce the risk of developing ovarian cancer; and all reduce the frequency of ovulation. Any factor or intervention that reduces ovulation will reduce ovarian cancer risk (7).

Cancer prevention through hormonal contraception

Table 1 summarizes the design requirements of a hormonal contraceptive to reduce the risks of endometrial, ovarian and breast cancer based on the above analysis of the risk factors associated with these cancers, the significance of cell-proliferation rate to carcinogenesis, and the factors associated with epithelial-cell mitotic rate in the 3 structures.

Present day COCs fulfill the requirements for the prevention of endometrial and ovarian cancer, but they do not provide protection against breast cancer. This is, as we discussed above, because COCs deliver estrogen plus progestogen to the breast in quantities sufficient to replace the action of the natural estrogen plus progesterone of the normal menstrual cycle. The dose of sex steroids in present-day COCs is close to the lowest dose possible while still maintaining their contraceptive effect of preventing

Table 1

Design requirements of a hormonal contraceptive to reduce cancer risk

Organ	Design aim
Endometrium	Reduce exposure of the endometrium to 'unopposed' estrogen
Breast	Reduce exposure of the breast to 'estrogen plus progestogen'
Ovary	Reduce the frequency of ovulation

ovulation. Achieving a reduction in breast cancer risk using the approach of conventional COCs does not therefore appear possible.

COCs achieve two separate goals. The first is to prevent ovulation, and the second is to counteract the effects of the hypoestrogenemia caused by the ovarian 'failure' associated with the first goal. The progestogen component of COCs has a vital role in suppressing ovulation, but it only has a minor role (as regards bone metabolism) in dealing with the associated hypoestrogenemia. The hypoestrogenemia is dealt with by the estrogen component of the COC. The lowest estrogen dose in conventional COCs is 30 μg of ethinyl estradiol (EE_2). If the first goal of COCs, i.e., preventing ovulation, could be achieved by some other means, could this dose of estrogen be reduced further? This issue can be addressed by studying the dose of estrogen found to be required to control menopausal hypoestrogenemia, in particular hot flushes and adverse changes in serum cholesterol and calcium balance.

CEE is the estrogen most frequently used as ERT in the US, but CEE is not used in contraceptive formulations. EE_2 is almost the only estrogen used in COCs, but it is not much used as ERT; and, as a consequence, less is known about the dose of EE_2 required as ERT. A daily dose of 5 to 10 μg of EE_2 has been suggested as adequate (24, 25). Studies of small numbers of women indicate that 5 μg may be sufficient to control hot flashes (26) and vaginal atrophy (24), and that 10 μg is more than sufficient to achieve the required effect on serum lipoproteins (27, 28). Detailed studies of the minimal effective dose of EE_2, when not administered with the progestogen, to prevent loss of bone mineral content appear, however, to be lacking. The studies that are available suggest that the required dose will be in the 5 to 15 μg range (29, 30), i.e., at most half the dose used in current low-dose COCs.

Gonadotropin-releasing hormone agonists (GnRHAs), when given chronically, inhibit pituitary release of FSH and LH, reversibly inhibit ovulation and reduce ovarian sex-steroid production to postmenopausal levels (31–34). Thus, the reversible ovulation inhibiting function of COCs can be achieved by using a GnRHA. This enables one to concentrate solely on finding the combination of add-back sex steroids of greatest benefit to a woman's health. We noted above, that a daily dose of approximately 10 μg of EE_2 appears likely to be all the estrogen needed to deal with the hypoestrogenemic effects of ovarian failure. Some progestogen is needed to control any endometrial hyperplasia which may be caused by the unopposed EE_2: we show below that this can be achieved satisfactorily by giving a progestogen for 13 days once every 4 months. It would thus appear to be quite possible to significantly reduce the dose of estrogen and progestogen in COCs while achieving the second anti-hypoestrogenemic goal of COCs, if the first goal of preventing ovulation is achieved by a GnRHA.

A prototype contraceptive regimen is shown in Table 2, and is currently in clinical trial at our institution (35). We have chosen to use CEE rather than EE_2, as so much more data exist for this form of ERT. There is ample data suggesting that 0.625 mg per day of CEE for 24 days per 28-day cycle will be sufficient to prevent hot flashes and to prevent loss of bone-mineral content (36, 37), other than that simply associated with aging; and this dose should induce the necessary beneficial effect on cholesterol (38, 39); 0.625 mg of CEE is roughly equivalent to 5 to 10 μg of EE_2 (40). The administration of a progestogen only every fourth cycle is to minimize exposure of the breast epithelium to progestogen, and to preserve the maximum beneficial effects of the ERT on cardiovascular disease risk, while retaining a beneficial effect on the endometrium. Currently, we are using the GnRHA leuprolide acetate depot. Alternate GnRHAs, that are administered less frequently, will be more desirable for long-term use.

We have previously estimated (41) that such low-dose CEE as in the prototype contraceptive regimen will have an associated effective endometrial mitotic rate only half

Table 2

Prototype contraceptive regimen

Agent	Rationale
GnRHA – Leuprolide acetate depot Day 1 every 28-day cycle	induce a reversible medical oophorectomy, reducing risk of breast, ovarian and endometrial cancer
Estrogen-conjugated equine estrogens 0.625 mg PO, 24 days per 28-day cycle Monday through Saturday	prevent bone mineral loss prevent possible rise in cardiovascular disease risk prevent menopausal symptoms prevent urogenital atrophy
Progestogen-medroxy-progesterone acetate 10 mg PO for 13 days, every fourth cycle	reverse any endometrial hyperplasia, and prevent any possible increased risk of endometrial cancer

that attained during the unopposed estrogen (follicular) phase of the menstrual cycle; if this dose is given for 24 days in each 28-day cycle the associated cumulative effective mitotic rate will be approximately 86% that of a normally cycling premenopausal woman (half the daily rate but for 24 days in every 28 rather than 14 days in every 28). Even if this is an underestimate, it is very unlikely that the total endometrial-cell mitotic rate during such a CEE regimen would be greater than that occurring during a normal menstrual cycle: this is especially so if this regimen is supplemented with a progestogen every fourth cycle, as is proposed. The minimum duration necessary to control endometrial hyperplasia completely (42, 43), appears to be 12–13 days of progestogen therapy but there is evidence to suggest that such a regimen is not required every cycle (44). A small proportion of women will develop hyperplasia if progestogens are not given every cycle, but few will develop symptoms, and a 13-day progestogen course every 4 cycles will likely eliminate any hyperplasia that has developed (44).

In the prototype regimen shown in Table 2 we have chosen for convenience to use medroxyprogesterone acetate (MPA) as progestogen rather than the usual progestogens used in COCs. Ten mg of MPA has been estimated to be equivalent to the usual 1 mg dose of norethindrone used in COCs (45). MPA is the usual progestogen used with CEE in the US.

If we equate 0.625 mg of CEE to 10 μg of EE_2 then this prototype contraceptive regimen has 38% $[(10 \times 24)/(30 \times 21)]$ the total estrogen dose of a 30 μg EE_2 COC. Similarly, the total progestogen dose of this prototype contraceptive regimen is 15% $[13/(21 \times 4)]$ that of a 1 mg norethindrone COC.

The effect of the prototype contraceptive on breast cancer risk may be estimated from relevant epidemiological studies. Numerous reports have documented the protective effect of early menopause on breast cancer risk (46–49). From these studies one may estimate that bilateral oophorectomy at age 35 is associated with a relative risk of 0.30 when compared with a natural menopause at age 50, i.e., that 15 years of ovarian 'failure' is associated with a 70% reduction in breast cancer risk. The administration of a GnRHA alone should accomplish the same risk reduction as early oophorectomy, i.e. a relative risk of 0.30 with 15 years' use. If ERT use in the postmenopausal period increases breast cancer risk (as seems likely), the 0.30 value must be increased slightly. In the recent meta-analysis of ERT and breast cancer risk, it was concluded that postmenopausal ERT use for 15 years increased breast cancer risk 1.30-fold (50). Thus one may estimate that the relative risk of 0.30 (15 years' use of GnRHA alone) will be increased by a factor of 1.30 (associated with ERT use) to become 0.39; a 61% reduction in lifetime breast cancer risk. Administration of a progestogen would be expected to reduce the benefit slightly, however a substantial protective effect should persist, as it is given only every fourth cycle.

Previously we employed mathematical models to calculate the protective effects of the prototype contraceptive on cancers of the breast, endometrium, and ovary (35, 41). These models are based on estimated mitotic rates of the relevant tissues. The relative risks shown in Table 3 are calculated assuming that the contraceptive is used only after a first full-term pregnancy; and that the computed effective mitotic rates of postmenopausal women on ERT would apply to a premenopausal woman taking GnRHA plus ERT. Table 3 shows that the calculated relative risk of breast cancer after 15 years' use is 30%, which is remarkably similar to that estimated from the epidemiological data above (i.e. 39%). Due to the difficulty with precisely estimating from epidemiological studies the protective effect of a 'reversible oophorectomy' during the years when a woman would be regularly ovulating, the values calculated using the mathematical model may be more accurate. Table 3 also shows the predicted lifetime relative risks for breast cancer, if the prototype contraceptive was used for 5 or 10 years after first full-term pregnancy. The estimates in Table 3 were calculated making allowance for the effect of the progestogen. Use before first full-term pregnancy should have an even greater effect.

Table 3

Predicted relative reduction in lifetime cancer risk with proposed contraceptive regimen

	Duration of regimen (yrs)		
	5	10	15
Breast	31%	53%	70%
Endometrium	18%	33%	45%
Ovary	41%	67%	84%

Table 3 also shows the predicted relative risks for ovarian cancer using the prototype contraceptive; use for 5 years is predicted to reduce the lifetime risk of ovarian cancer by as much as 40%. The predicted reduction in risk of endometrial cancer is much less, but is still of some note.

In addition to its effects on cancer risk, the prototype contraceptive regimen should reduce either the incidence or severity of a number of hormonally mediated benign gynecologic disorders, including cyclical mastodynia, premenstrual syndrome, uterine fibroids and endometriosis.

While validation of the concepts presented here is certainly required, there is more than sufficient evidence available to justify substantial efforts being made along these lines. These efforts should be regarded as complementary to other breast cancer prevention strategies currently under consideration or study, including: dietary interventions aimed at reducing fat intake and/or increasing fiber intake (51); and the use of long-term tamoxifen in postmenopausal women.

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