Hormonal Chemoprevention of Cancer in Women

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The use of oral contraceptives in the United States during the past three decades has led to a dramatic decline in the incidence of cancers of the ovary and endometrium. The magnitude of these declines was predictable both from epidemiologic data and from the biologic effects of oral contraceptives on these tissues. Although the incidence of breast cancer has not been substantially affected by current oral contraceptives, it may be possible to develop alternative forms of contraception that provide protection against all three cancers. The major goal of hormonal chemoprevention of cancer is to reduce cell proliferation in the relevant epithelial tissue. New chemopreventive agents such as tamoxifen exemplify the application of this principle.

A substantial body of experimental, clinical, and epidemiological evidence indicates that hormones play a major role in the etiology of several human cancers (*1*). Specific hormones have been linked to development of cancers of the breast, endometrium, and prostate, and the process of ovulation (or follicle development) induced by gonadotropins has been linked to cancer of the ovary. This form of carcinogenesis may result from the ability of hormones to stimulate cell division in certain target organs. The repeated cell divisions may in turn lead to the accumulation of random genetic errors that ultimately produce the neoplastic phenotype (*2*, *3*).

Hormone-related cancers account for more than 20% of all newly diagnosed male and more than 40% of all newly diagnosed female cancers in the United States (*4*). Because of the evidence that endogenous hormones directly affect the risk of these cancers, chemoprevention through administration of "antihormones," agents that reduce the rate of cell division in the relevant epithelial tissue, has become an important focus of cancer prevention research. Several types of antihormones are already available, and these vary in their precise mode of action (Table 1). The acceptability of a given antihormone for widespread use in cancer prevention depends on the balance of benefits and risks derived from its use.

In considering prevention strategies for breast, ovary, and endometrium cancers, it is important to recognize the role of hormonal events during the reproductive years in determining the risk of these cancers. The incidence of most non-hormone–dependent adult cancers rises continuously with age, and a plot of the logarithm of incidence against the logarithm of age produces a straight line. In contrast, the age-incidence curves of these three cancers of women show a different pattern (*5*). The age-incidence curve rises with age as for other adult cancers until menopause, and then there is a distinct slowing of the rate of rise (Fig. 1). These curves emphasize that the key etiologic events for these cancers occur in the premenopausal period. Prevention strategies that intervene during the premenopausal period can be expected to have a bigger long-term impact in reducing risk than those implemented for an equivalent length of time in the postmenopausal years.

Use of exogenous hormones clearly has an impact on the risk of certain cancers and in some cases hormonal "chemoprevention" is already occurring as result of such use. In addition to addressing the potential of exogenous hormones as chemopreventive agents, we discuss the impact on cancer incidence of the two forms of exogenous hormones widely used in the United States today—oral contraceptives and hormone replacement therapy. We limit our discussion to chemoprevention strategies in women, although similar principles and strategies for chemoprevention apply to prostate cancer in men.

Table 1. Hormone chemopreventive agents in clinical use.

Chemopreventive agent	Cancer site	Mechanism of action
Oral contraceptives	Endometrium	Anti-estrogen
	Ovary	Inhibit ovulation
GnRH agonists	Breast, Endometrium	Inhibit ovarian steroid hormone production
	Ovary	Inhibit ovulation
Progestogens (HRT)	Endometrium	Anti-estrogen
Tamoxifen	Breast	Anti-estrogen
Finasteride	Prostate	5α-reductase inhibitor

GnRH, Gonadotropin-releasing hormone; HRT, Hormone replacement therapy.

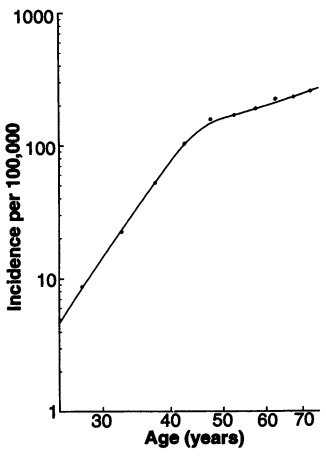

Fig. 1. The incidence rate of breast cancer is plotted against age at diagnosis with data from the United Kingdom (U.K.) Birmingham Cancer Registry for the years 1968–1972 (*6*). More recent age-specific incidence data for U.K. and U.S. cancer registries are altered by the growing impact of screening (primarily mammography), which produces artificially inflated rates in the older age groups. The solid line represents the model predicted from breast cancer risk factors by Pike (*5*), and the dots are the actual incidence data. For most non-hormone–dependent cancers the relationships between incidence, I, and age, t, can be represented by the equation $I(t) = axt^k$, which produces a straight line of slope k when the logarithm of incidence is plotted against the logarithm of age. The hormone-associated cancers can be reconciled with a linear log-log plot of incidence against age if t in the formula is considered to be the cumulative "effective mitotic rate" of the relevant tissue. The fundamental idea is that "aging" of a tissue relates directly to its cell kinetics. When the tissue is not undergoing cell division the rate of aging is zero, whereas aging is maximal when the mitotic rate is maximal. For breast, endometrial, and ovarian cancer, the rate of aging is greatest during the years of active ovulation and slows, or essentially ceases in the case of the ovary, at the menopause. If women continued to ovulate until old age, then at age 70, breast cancer risk would be increased some sixfold, endometrial cancer risk some eightfold, and ovarian cancer risk some 4.5-fold over present rates.

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Oral Contraceptives

Epidemiological studies of endometrial cancer have revealed that obesity is a major risk factor throughout life (*1, 2, 7*) and that use of sequential oral contraceptives substantially increases risk (*8–12*). In premenopausal women, obesity is often associated with anovulatory cycles characterized by normal (nonpeak) pre-ovulatory (follicular phase) estrogen levels throughout the cycle and low levels of progesterone. In postmenopausal women, adipose tissue is the major source of endogenous estrogen. Use of sequential oral contraceptives, which were removed from sale in the United States in 1976, was associated with a twofold increase in risk of endometrial cancer (*8–12*). Sequential formulations induced a menstrual cycle that began with a 14- to 16-day proliferation phase (this mimicked the follicular phase of the cycle and was triggered by administration of an estrogen without a progestogen), followed by a 7-day secretory phase (this mimicked the luteal phase and was triggered by administration of an estrogen-progestogen combination), and ending with a 5- to 7-day period without treatment in which endometrial proliferation restarted because of low levels of endogenous unopposed estrogen. These pieces of evidence, combined with the strong evidence that estrogen replacement therapy (ERT) increases risk of endometrial cancer (discussed below), led to the development of the "unopposed estrogen" hypothesis: that endometrial cancer risk is directly related to the amount of exposure of endometrial tissue to estrogen that is unopposed by progesterone or a synthetic progestogen (*1, 2, 7*).

In contrast with sequential oral contraceptives, which have adverse effects on the endometrium, combination oral contraceptives (COCs) markedly decrease the risk of endometrial cancer (*9–11*). COCs contain an estrogen and a high-dose progestogen; thus, endometrial cells are exposed to unopposed estrogen only during the 7 days in 28 during which the COC is not taken, and even during these 7 days the endogenous estrogen level remains quite low. The unopposed estrogen hypothesis predicts an inverse association between COC use and the risk of endometrial cancer. In fact, epidemiologic studies overall show a remarkable reduction in endometrial cancer risk of ~11.7% per year of COC use (*13*).

The unopposed estrogen hypothesis has been expressed as a mathematical model that incorporates the known risk factors for endometrial cancer and their impact on endometrial cancer risk by age (*5*). The results of the epidemiologic studies of COC use and endometrial cancer can most easily be comprehended by expressing them in terms of the effect of COC use on the age-incidence curve of endometrial cancer. The results strongly suggest that the slope of the age-incidence curve is reduced during COC use but once COCs are discontinued the slope increases again to the pre-COC rate. A plot of this relationship illustrates that the protective effect of COC use should be lifelong (Fig. 2A). Epidemiologic data confirm that the protection lasts for at least 15 years after cessation of COC use (*9*).

Epidemiologic studies have shown that the major factor determining ovarian cancer risk is parity; increasing parity decreases risk. The parity effect has been explained by the "ovulation" hypothesis, which posits that ovarian cancer risk is increased by each ovulation (*14, 15*). The major impetus to ovarian epithelial cell replication is the repair of the ovarian surface after each ovulation. If ovarian cancers arise in these surface epithelial cells, or in crypts where the surface epithelium may grow after ovulation, any factor or intervention that reduces ovulation should reduce ovarian cancer risk.

Because COCs suppress ovulation, the use of these agents would be predicted to reduce the risk of ovarian cancer. Epidemiological studies demonstrate a reduction in ovarian cancer risk of ~7.5% per year of COC use (*13*). Expression of these results in terms of the age-incidence curve illustrates a pattern comparable to that for endometrial cancer (Fig. 2B). Epidemiologic data again confirm that women who had stopped using COCs more than 15 years ago have retained the protection against ovarian cancer (*16*). The same epidemiologic data (*16*) suggest that follicle development rather than ovulation may be the important determinant of ovarian cancer. Follicle development is suppressed by both pregnancy and COC use.

Breast cancer risk increases with increasing age at menopause, with decreasing age at menarche, and with obesity during the postmenopausal years; obesity during the premenopausal years actually reduces risk (*1, 2, 17*). From studies of breast cell mitotic rates (*18*) it is clear that 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. The TDLU cell proliferation rate is relatively low during the follicular phase (estrogen alone) and then increases by a factor of two in the mid-to-late luteal phase (estrogen plus progesterone). Thus, the combination of estrogen and progesterone appears to have a greater stimulatory effect on cell division than estrogen alone. These findings have led to the development of an "estrogen-augmented-by-progestogen" hypothesis regarding breast cancer etiology (*17*); this hypothesis posits that breast cancer risk is increased by estrogen alone but is increased further by simultaneous exposure of breast epithelium to estrogen and progestogen.

In postmenopausal women, in whom estrogen levels are low and progesterone is absent, the rate of TDLU cell proliferation is low and breast cancer incidence increases at a slow rate relative to the rate of increase in premenopausal women (Fig. 1). The protective effects of late menarche and early menopause on breast cancer risk are readily explained by the estrogen-augmented-by-progestogen hypothesis; early establishment

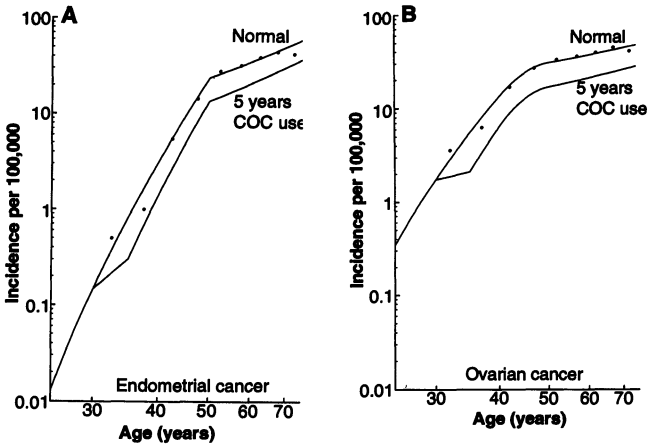

Fig. 2. Age-specific incidence rates for cancers of the endometrium (**A**) and ovary (**B**) in "normal" women and in women using COCs for 5 years. The data are from the same registry and time period as in Fig. 1. These data largely avoid the problems arising from the high hysterectomy and oophorectomy rates in the U.S., which artificially distort the age-incidence curves. The dots are the actual incidence data and the solid lines marked "normal" represent mathematical models predicting incidence rates from the major known risk factors for these cancers (*5*). On the basis of these models and the reduction in cancer risk associated with COC use observed in epidemiological studies, it is possible to calculate how these age-incidence curves will be altered by COC use; these predicted age-incidence curves are also shown (lower solid lines in A and B). The latter curves produce the observed reduction in risk observed in epidemiological studies of COC use over the age range so far studied. It has not yet been possible to study older women who have used COCs but stopped using them 25 or more years ago. However, our general understanding of the relationship of aging to cancer incidence (see Fig. 1) suggests that the protective effects will be lifelong, and this reduction as calculated from our mathematical model is what is shown in the graphs.

or late cessation of ovulatory cycles increases risk, as predicted. The contradictory effects of obesity on risk are also explained by this hypothesis. The increased anovulation associated with premenopausal obesity will decrease breast exposure to both estrogen and progesterone; after menopause, the decreased risk associated with premenopausal obesity is gradually eliminated and an increased risk is achieved by the elevated levels of bioavailable estrogen associated with postmenopausal obesity (*2*).

Studies of COC use and breast cancer have produced mixed results. There is evidence of a modest increase in breast cancer risk in women diagnosed under age 45 of ~3.1% per year of COC use. The few studies in women diagnosed over age 45 find no change in risk with COC use (*13*). The basis of these discrepant results by age at diagnosis is not understood. The absence of any marked reduction in risk is predicted by the estrogen-augmented-by-progestogen hypothesis. COCs inhibit gonadotropin secretion, thus reducing ovarian steroidogenesis to low levels, but the ovarian steroid loss is compensated for by the synthetic estrogen and progestogen making up the COC. As a result, the simultaneous presence of estrogen and progestogen in COCs is not protective against breast cancer, as is the case for cancers of the endometrium and ovary.

Secular Changes in Incidence and Mortality

To estimate the overall impact of COC use on national cancer patterns, we have compared the incidence and mortality rates of cancer of the ovary, endometrium, and breast in two groups of women—those under age 50 around 1970 and those under age 50 in the mid-1980s (Table 2) (*19*). The cancer rates around 1970 essentially represent women who had not used COCs, whereas the rates in the mid-1980s represent women of whom some 60% had used COCs for an average of about 5 years (*20, 21*). Given the decreased risk per year of COC use noted above for cancer of the ovary (7.5%) and endometrium (11.7%), 60% of the women in the latter group would be expected to show an average reduction in risk of ~32% and ~46%, respectively, whereas the remaining 40% would experience no change in risk. Thus, COC use during this period should have produced a reduction in incidence of ~19% for ovarian cancer and ~28% for endometrial cancer. The observed changes in incidence are remarkably close to these figures. We predict that these decreases in incidence of ovarian and endometrial cancer will extend to older women as the group of young women who have used COCs extensively begins to age. This reduction in incidence can already be seen in women up to age 60. Similar calculations suggest that COC use should have produced an ~9% increase in breast cancer incidence in women under age 50. There are currently no data indicating that any COC-induced increase in breast cancer risk in these young women will extend in time to older women.

Comparison of mortality and incidence rates suggests that treatment improvements (or earlier diagnosis) have been occurring for all three cancers. Mortality rates have decreased more than incidence rates for ovarian and endometrial cancers; breast cancer mortality rates have also declined slightly during this period of increasing incidence (*22*).

Toward a Contraceptive That Prevents All Three Cancers

Despite the enormous contributions of COCs in reducing incidence of cancers of the ovary and endometrium, as currently formulated they clearly do not protect against breast cancer. COCs are designed to achieve two major related goals. The first is to prevent pregnancy by suppressing 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 little if any role in achieving the second goal. The lowest estrogen dose in conventional, currently marketed COCs is 30 μg of ethinyl estradiol (EE_2), but it appears likely that if ovulation could be prevented through some other means, the hypoestrogenemia could be effectively counteracted with a lower dose of estrogen (*23*). Much data are available on this issue through studies of the minimal ERT doses required to control symptoms of menopausal hypoestrogenemia—in particular, hot flashes, adverse changes in serum cholesterol, and bone loss.

EE_2 is now almost the exclusive estrogen component in COCs, but it is rarely used in the United States as ERT. As a consequence, the dose of EE_2 required as ERT has not been studied intensively, but the available data suggest that it will be in the 5- to 15-μg range (*23*); this is at most half the dose used in current low-dose COCs.

Gonadotropin-releasing hormone agonists (GnRHAs) offer an alternative hormonal approach for reversibly inhibiting ovulation and reducing production of ovarian steroid hormones to low (postmenopausal) levels. Such an approach allows for careful titration of add-back steroid hormones to maximize the benefit to a woman's health while still achieving the primary goal of hormonal contraception. A daily dose of approximately 10 μg of EE_2 appears to be the maximum estrogen dose required. Some progestogen is also needed to control any endometrial hyperplasia that may be caused by the unopposed EE_2; a low dose progestogen given for 13 days once every four months may satisfactorily fulfill this requirement (*23*).

A prototype GnRHA contraceptive regimen constructed according to these principles is currently in phase I clinical trial (*23*). It has been estimated that such a regimen could reduce lifelong breast cancer risk by 31% if used for 5 years, 47% if used for 10 years, and 70% if used for 15 years. The protection against ovarian cancer is estimated to be identical with or (if follicle development is important) greater than, that afforded by COCs. The protection could be as large as 41% if the contraceptive is used for 5 years, 65% if it is used for 10 years, and 79% if it is used for 15 years. The corresponding reductions in risk from COC use are 32%, 54%, and 69%, respectively. There should also be a reduction in the risk of endometrial cancer relative to women not using a hormonal contraceptive, but not as great a reduction as that afforded by COCs. The GnRHA regimen is projected to reduce endometrial cancer risk by 18% if used for 5 years, 33% if used for 10 years, and 45% if used for 15 years; the comparable figures for COC use are 46%, 71%, and 85%. The expected reduction in endometrial cancer benefit is due to more limited use of progestogen. Because endometrial cancer

Table 2. Age-adjusted incidence and mortality rates for women less than 50 years of age (*19*).

	Incidence			Mortality		
	Average rate*		Change (%)	Average rate		Change (%)
	1973–1974	1986–1987		1973–1974	1986–1987	
Ovary	4.8	3.9	−19.9	1.9	1.2	−37.0
Endometrium	5.1	3.7	−28.1	0.5	0.3	−44.1
Breast	30.6	33.6	9.6	6.9	6.4	−8.2

*The cancer rates in 1973–1974 essentially represent women who had not used COCs; that is, the rates reflect the cancer burden of women who would not have had access to COCs during the majority of their child-bearing years. By contrast, women who were 49 years old or younger in 1986–1987 could have had access to COCs since 1962 or since they were in their early twenties.

has a low mortality rate, this may be an acceptable trade-off for the added benefit of a substantial reduction in breast cancer. Before such a regimen is fully tested, a convenient formulation is required, and short-term studies need to be completed to establish that the regimen successfully compensates for the induced hypoestrogenemia.

Hormone Replacement Therapy

The use of hormone replacement therapy (HRT) to provide short-term relief of symptoms related to menopause and long-term protection from the consequences of estrogen deficiency constitutes the other major setting in which exogenous steroid hormones are widely used in essentially healthy women. As with COCs, use of HRT has had a remarkable impact on cancer incidence and mortality. As strategies for delivering HRT have evolved, however, the nature of this impact has dramatically changed. In particular, the ever-expanding use of a combination regimen, in which a progestogen is added continuously or sequentially to estrogen during a monthly cycle, has not only highlighted the importance of progestogens but also raised important issues concerning the risk-benefit balance of various HRT formulations.

There is a strong association between ERT and endometrial cancer risk that is related to both dose and duration of therapy (*24*). The endometrial cell mitotic activity in a woman on continuous high-dose ERT is approximately equal to that observed during the follicular phase of the menstrual cycle, and the total mitotic activity over a 28-day period is thus roughly double that of a premenopausal woman because there is no opposition by progesterone at any time. On the basis of this mitotic rate, the predicted effect of 5 years of ERT use starting at menopause on the risk of endometrial cancer (Fig. 3A) (*5*) is to increase the premenopausal slope of the incidence curve for the 5 years of ERT use. This effect is comparable to the decrease that normally occurs at menopause. Endometrial cancer risk is calculated to increase by a factor of ~3.5 and will be of long-term (lifelong) duration after 5 years of such ERT use, in agreement with actual epidemiologic observations.

The benefit of adding a progestogen to ERT in reducing endometrial mitotic activity has been clearly established (*25*). Therefore, in response to the "epidemic" of endometrial cancer that followed the rise in estrogen prescriptions in the 1960s and 1970s, progestogens were added to the estrogen in various doses and schedules (typically 5 to 10 mg of medroxyprogesterone acetate for 10 to 12 days per month). Such combination therapy has been shown to reduce the estrogen-enhanced risk of endometrial cancer (*26*). As a second response, the average daily dose of the most commonly used form of estrogen, conjugated equine estrogen (CEE), was lowered from 1.25 mg to 0.625 mg. Noncontraceptive estrogen prescriptions in the United States declined almost 50% in the mid-1970s as it became clear that ERT caused endometrial cancer. This decline led to a decrease in endometrial cancer incidence and mortality in the late 1970s, after the substantial increases that had occurred in the preceding decade. The reduced dosages of ERT and the addition of a progestogen to HRT have sustained these decreases into the 1980s. Incidence and mortality from endometrial cancer in postmenopausal women declined 27.9% and 14.4%, respectively, between 1973 and 1987.

The addition of a progestogen to ERT has implications not only for endometrial cancer, but also for other components of the risk-benefit equation. Because of the importance of these other health effects, we discuss them in detail below, together with comparative data for ERT alone.

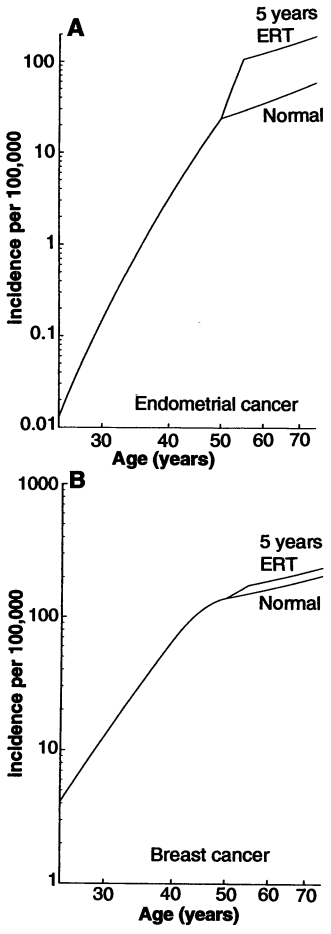

Fig. 3. Age-specific incidence rates for endometrial cancer (**A**) and breast cancer (**B**) in "normal" women and in women using ERT for 5 years. Calculation of the effects of ERT follows the same logic as that described in Fig. 2.

Breast cancer incidence increases with age at ~2.1% per year in postmenopausal women. If this rise is attributable solely to endogenous estrogens, as appears likely, the risk of breast cancer associated with ERT use can be predicted by comparing endogenous serum estrogen levels with the serum estrogen levels achieved while a woman uses ERT. In postmenopausal U.S. women, the serum level of bioavailable estradiol (E_2), the fraction of E_2 that is not bound to sex hormone binding globulin (SHBG), is ~12 pg/ml (*7*). The serum level of non-SHBG-bound E_2 in women receiving 0.625 mg CEE per day is approximately double the normal postmenopausal level (~26 pg/ml) (*7*). On the assumption that E_2 is the most important estrogen both from endogenous serum and from ERT, the incremental increase in breast cancer risk due to ERT should be approximately equal to that due to endogenous estrogens (an additional 2.1% per year). The risk estimates from population-based epidemiologic studies (*27*) show an increase in breast cancer risk of 3.1% per year of ERT use, for all formulations combined (*28*). When only CEE in a dose of 0.625 mg is considered, however, the increase in breast cancer risk is estimated to be slightly less than 2% per year of ERT use (Fig. 3B) (*28*), almost precisely as predicted.

Nearly all the breast cancer studies to date have evaluated risk attributable to ERT alone, not to combination HRT. Data from a prospective study in Sweden have suggested that risk associated with combination HRT is higher than any found for ERT alone (*29*), as the breast mitotic rate data would suggest. Further data on the effects of adding a progestogen to ERT are urgently needed not just for breast cancer but also for other components of the risk-benefit equation.

The most important long-term health effect of ERT is to lower cardiovascular disease morbidity and mortality (*30*). Largely because of this profound effect, the reduction in overall mortality (from all causes) for ERT users is 20% or more in some populations, with an even greater reduction in mortality for current long-term users. In addition to the likely adverse effect on breast cancer risk, progestogens may negate some of this cardiovascular benefit of ERT. Nonetheless, these predicted adverse effects of an added progestogen have not yet had a substantial impact on HRT prescribing patterns (*31*).

Twelve to 13 days of progestogen therapy is the minimum duration necessary for effective control of endometrial hyperplasia (*32*). Such a regimen may not be required each month. A small proportion of women develop hyperplasia if progestogens are not given every cycle; few of these women develop symptoms, however, and a 13-day

progestogen course every four to six cycles will likely eliminate the hyperplasia (*33*). Such an intermittent progestogen regimen warrants serious investigation, given the potential adverse effects associated with progestogen treatment. An even more desirable delivery system would allow for delivery of progestogen continuously, directly, and solely to the endometrium. This regulated delivery is possible through use of a progestogen-containing intrauterine device (*34*). Solutions to the problems associated with such a delivery system (intermittent bleeding, difficulties with insertion, and a relatively short efficacy period requiring reinsertions) are being actively pursued. The ideal device would, after the initial insertion, deliver an adequate local progestogen dose for up to 5 years and would be specifically designed for postmenopausal women.

A final caution is in order regarding the ever-changing practices of prescribing HRT. CEE produces substantial benefit in preventing cardiovascular disease, an effect most likely mediated by an increase in serum levels of high-density lipoprotein and a decrease in serum levels of low-density lipoprotein, although other mechanisms such as altered blood flow may be involved. At the same time, however, it causes a small increase in breast cancer risk, most likely mediated by an increase in serum levels of E_2 tempered by a substantial (50%) rise in SHBG levels. Certain other oral formulations of ERT, as well as most forms of ERT delivered either cutaneously or subcutaneously, raise circulating levels of E_2 well above 50 pg/ml and even as high as 150 pg/ml (*35*). The latter figure is at least twice the E_2 level associated with CEE in the commonly prescribed dosages, and the nonoral routes, in particular, are not accompanied by concomitant increases in SHBG levels. If progestogen in the usual dose is added to these regimens, the amount of circulating steroids approaches that associated with the normal ovulatory cycle. The rate of increase of breast cancer with age in women on such regimens could approximate that of premenopausal women.

Tamoxifen

A key proposal for the hormonal chemoprevention of breast cancer was made by Cuzick and colleagues in 1986 (*36*). The goal was to treat healthy postmenopausal women at high risk of breast cancer with the anti-estrogenic drug, tamoxifen. Since the mid 1970s, tamoxifen has been a mainstay of breast cancer therapy. A summary analysis in 1988 of 28 randomized clinical trials showed a significant reduction in the mortality from breast cancer in women treated with this agent (*37*).

At least among women with a prior history of breast cancer and those at elevated risk by virtue of a strong family history or a biopsy demonstrating atypical hyperplasia, the use of CEE requires caution if indeed it is not totally contraindicated (*38*). Tamoxifen appears to offer an attractive alternative to ERT in such women.

The most compelling argument for extending the use of tamoxifen to healthy women at high risk of breast cancer is the lower risk of contralateral primary breast cancer that has been observed among women receiving adjuvant tamoxifen therapy for an initial primary breast cancer. A summary of data from eight randomized trials of tamoxifen-treated versus control breast cancer patients (*39, 40*) showed a 35% reduction in risk of contralateral breast cancer after an average treatment duration of two years.

An ongoing concern that has guarded optimism about the efficacy of such a regimen in primary breast cancer prevention is the possible adverse effect of tamoxifen on other organ systems (*41*). Of particular note is the possible anti-estrogenic effect of tamoxifen on lipid and bone metabolism. In the most authoritative analysis of lipid metabolism to date (*42*), Love and colleagues found that low-density lipoprotein levels declined ~18% after instituting tamoxifen therapy and that this decline persisted for at least 1 year of treatment. High-density lipoprotein levels were reduced by 7% at 1 year compared with baseline values. The Scottish Adjuvant Tamoxifen Trial (*43*) has provided some preliminary evidence that tamoxifen, like ERT, may have a beneficial effect on coronary heart disease risk; in this trial, tamoxifen-treated women had a statistically significant reduction in mortality due to acute myocardial infarction compared with control women. Thus far, this is the only tamoxifen trial reporting an effect on heart disease risk. Studies of tamoxifen and bone mineral density have yielded mixed results but do not suggest an adverse effect. Two studies have reported slight increases in the density of the lumbar spine during tamoxifen treatment for postmenopausal breast cancer (*44*), but rates of osteoporotic fractures in tamoxifen-treated women have not yet been evaluated.

Other potential side effects of tamoxifen have been discussed extensively elsewhere (*39, 45*). Tamoxifen may be associated with a substantially elevated risk of endometrial cancer, of a magnitude comparable to that associated with ERT (*39*). Although not every tamoxifen trial has reported such an effect, the totality of evidence supports a causal relationship between tamoxifen and endometrial cancer. Liver tumors have been produced in rats that have been treated with large doses of tamoxifen over an extended period (*46*). However, no statistically significant increase in primary liver tumor incidence has been reported among tamoxifen-treated patients in any clinical trial to date, and there have been only two case reports of hepatocellular carcinoma developing in tamoxifen-treated patients (*47*). Small decreases in antithrombin III levels occur in postmenopausal women receiving long-term adjuvant tamoxifen therapy (*48*), but thromboembolism associated with tamoxifen therapy is uncommon (*49*). A retinopathy characterized by lens opacities, macular edema, and (occasionally) a reduction in visual acuity, has long been known to occur with supraclinical dosages of tamoxifen (*50*). Recently this retinopathy, which appears to be reversible, has been reported to occur in dosages commonly used to treat breast cancer (*51*).

A chemoprevention trial of tamoxifen in American women at an elevated risk for breast cancer is currently under way. Among postmenopausal women, we predict that tamoxifen will level off the continued slow rise in breast cancer incidence after age 50 (Fig. 4); there is no convincing evidence that the risk of a hormone-related cancer can decline after removal of (or blocking of) a hormone stimulant. The 35% reduced risk of contralateral breast cancer observed after just 2 to 3 years of tamoxifen treatment in postmenopausal women is substantially greater than this predicted benefit of 2% per year (*52*). This observation suggests to us that most of the tumors being diagnosed as primary incident contralateral cancers in the control arms of the clinical trials are metastatic cancers or preexisting contralateral primaries. Although we believe that the actual benefit of

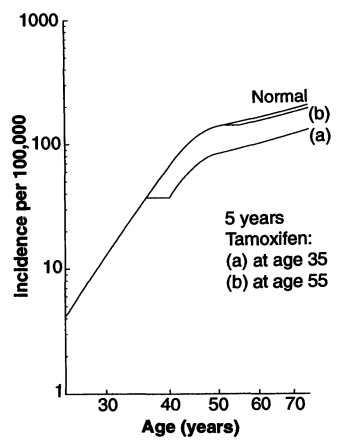

Fig. 4. Age-specific incidence rates for breast cancer in "normal" women, and the predicted effects of tamoxifen use for 5 years starting at age 35 (a) and at age 55 (b). Calculation of the predicted effects of tamoxifen follows the same logic as that described in Fig. 1. The "effective mitotic rate" is assumed to cease during the time of tamoxifen administration.

tamoxifen therapy in healthy postmenopausal women is likely to be close to 2% reduction in risk per year (10% in 5 years), the impact in the premenopausal years could be greater. In premenopausal women, breast cancer rates increase much more rapidly, and, if tamoxifen totally blocked this increase, 5 years of use would result in an ~60% reduction in breast cancer risk, an effect that should continue for life.

Breast cancer is not only the most common serious cancer in women, it is also a disease with enormous psychosocial ramifications. With the widespread use of oral contraceptives, we inadvertently entered the era of hormonal chemoprevention. With tamoxifen, we have now entered the era of controlled trials of hormonal chemoprevention. Because of the experience and knowledge gained through use of oral contraceptives and hormone replacement therapy, we can enter this new era confident of success. As some 10% of women in the United States will develop breast cancer in their lifetime, the implications of a successful trial are extraordinary.

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