

Progestins and breast cancer

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The relationship between the use of menopausal hormone therapy (ERT, unopposed estrogen therapy; HRT, combined estrogen and progestin therapy) and the development of breast cancer remains controversial. Mechanistic studies examining progestins in human breast cancer cell lines have demonstrated a biphasic cellular response to progesterone; initial exposure to hormone results in a proliferative burst with sustained exposure resulting in growth inhibition. To date, there is no definitive evidence that progestins act in the pathogenesis of breast cancer. Epidemiologic studies have produced inconsistent results, and data from randomized, placebo-controlled trials are limited. Although recent results from the continuous combined therapy arm of the Women's Health Initiative trial showed a small increase in the risk of invasive breast cancer in women on therapy for 5 years or more, a clear consensus regarding the relationship between HRT and breast cancer risk cannot yet be drawn from existing data. Studies have consistently documented that HRT use is associated with improved mortality and survival rates for women with breast cancer. Large-scale, randomized studies on different progestin regimens are needed to critically assess the effect of progestin on breast cancer. (*Am J Obstet Gynecol* 2003;188:1123-31.)

Key words: Progestins, breast cancer, estrogen replacement therapy, hormone replacement therapy, estrogen

Other than skin cancer, breast cancer is the prevailing cancer in women and the second leading cause of cancer-related deaths among women in the United States.¹ Approximately 15% to 25% of all breast cancers occur in women with a positive family history of breast cancer in a first-degree relative (mother, sister, or daughter).² Two breast cancer genes (*BRCA1* and *BRCA2*) have been identified^{3,4} and account for approximately 5% of cancers. To date, however, the etiology of most human breast cancers is still unknown. Established risk factors include early age at menarche, nulliparity, late age at first birth, and late age at menopause. The relationship between these risk factors and normal ovarian function have led some to hypothesize that exposure to ovarian hormones may increase a woman's risk for breast cancer, but a specific role for estrogen and/or progesterone is unclear.

The use of unopposed estrogen replacement therapy (ERT) for the relief of menopausal symptoms in postmenopausal women has been widespread for several decades. In the 1970s, hormone replacement therapy (HRT, combined estrogen and progestin therapy) was

recommended for protection from endometrial cancer. In postmenopausal women, ERT/HRT is effective in alleviating clinical manifestations of estrogen deficiency, including vasomotor and urogenital symptoms,⁵ bone loss,⁶⁻⁹ cardiovascular risk factors,¹⁰ and acute cognitive decline.^{11,12}

Because of the influence of ovarian function on breast cancer, there has been extensive examination of a possible correlation between menopausal hormone therapy and breast cancer risk. Some researchers have proposed that unopposed ERT modestly increases the risk of breast cancer, and the addition of progestin further increases this risk¹³⁻¹⁵; however, a broad review of the literature does not uphold these suppositions. Despite reports to the contrary,^{14,15} any association of progesterone with breast cancer risk remains controversial. This article reviews the current understanding of the role of progesterone in breast cancer, with special attention paid to its association with breast cancer risk, survival, and underlying cellular processes.

Cellular response to progesterone

The requirement for progesterone in normal mammary gland development is well established,^{16,17} but its role in the precancerous and cancerous breast remains poorly defined. Studies with knockout mice have demonstrated that progesterone acts through its nuclear receptor to control normal mammary development and

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differentiation in preparation for lactation.^{18,19} Interestingly, disruptions of mammary development are also observed in mice on deletion of a series of other cellular genes, including cell cycle regulatory proteins such as cyclin D1²⁰ and transcription factors.^{21,22} Taken together, results from knockout studies emphasize that overall control of breast cell proliferation results from a complex balance of hormonal, growth factor, and convergent cell-signaling pathways.²³ The relative role of progesterone in this complex equilibrium is difficult to quantitate.

Research has demonstrated that progesterone can act both as a proliferative and antiproliferative agent in breast tissue. Evidence that progesterone is a proliferative hormone in breast tissue includes the *in vivo* observations that progesterone levels are greatest during the late luteal phase of the menstrual cycle, a period of high mitotic activity, and that the high progesterone levels during pregnancy induce breast development.¹⁶ However, *in vivo* observations are inconsistent with results from several randomized clinical trials. In these trials, progesterone was administered topically to women's breasts before lumpectomy²⁴ or esthetic breast surgery,²⁵ and epithelial cell cycles in the removed tissue were evaluated. Both studies found that percutaneous progesterone acts in normal breast as an antiproliferative agent by decreasing the number of cycling epithelial cells. *In vitro* studies of the cellular response to progesterone have also produced inconsistent results, with progesterone capable of acting as a proliferative^{26,27} or an antiproliferative agent,^{16,28-30} depending on study parameters.

There is growing evidence that the key to understanding inconsistent data regarding the cellular effects of progesterone lies in the duration of hormone exposure. Cell culture studies with human breast cancer cell lines have demonstrated that the proliferative effects of progesterone are biphasic.³¹⁻³³ A single initial pulse of progesterone results in a short-lived induction of genes associated with cell growth, with acceleration through one mitotic cycle.^{34,35} However, subsequent pulses of progesterone are inhibitory and result in growth arrest in the second cell cycle.^{23,31-33} The finding that the rate and duration of progesterone treatment controls the cellular response to progestin can reconcile disparate *in vitro* results found in the literature. These studies have led some to propose that transient or intermittent doses of progesterone are growth stimulatory in breast cells, whereas continuous or sustained progesterone is growth inhibitory.^{23,32} The biphasic growth response has important implications for the timing of progestin treatments and stresses the need for careful examination of sequential versus continuous administration of progestin in postmenopausal hormone therapy with regard to breast cancer risk. The *in vitro* studies cited here indicate that continuous, daily administration of progestins may be advantageous.

Progestins and the biosynthesis of estrogen

Although the ovary serves as the primary source of estrogen for premenopausal women, after menopause estrogen biosynthesis from circulating precursors occurs in some peripheral tissues by the action of several enzymes—17 β -hydroxysteroid dehydrogenases (17 β -HSD), aromatase, and sulfatases. In the breast, both adipose tissue and malignant tumors have been shown to be capable of synthesizing estrogen,^{36,37} and estrogen production by mammary adipose tissue, specifically the stromal component,³⁸ has been implicated in the development of breast tumors.³⁹ At present, aromatase inhibitors are successfully used as second-line treatment for breast cancer in postmenopausal women,^{40,41} and other compounds, including progestins, are being investigated as potential therapeutic options because of their ability to modulate enzymes involved in estrogen biosynthesis.⁴²

17 β -HSD consists of a complex group of enzymes⁴³ that catalyze the bidirectional conversion of inactive estrone to the biologically active estrogen, estradiol. Both in normal breast tissue⁴⁴ and in hormone-independent breast cancer cell lines,⁴⁵ 17 β -HSD activity is in the oxidative direction (promoting the conversion of estradiol to estrone), whereas in hormone-dependent breast cancer cell lines, reductive 17 β -HSD activity predominates.^{45,46} A series of progestins have been tested *in vitro* for their ability to affect the relative oxidative/reductive activities of 17 β -HSD. Although early data from human breast tumors suggest that progestins can increase oxidative 17 β -HSD activity,⁴⁷ results from cell culture studies are contradictory. For example, in the hormone-dependent breast cancer cell line T-47D, nomegestrol acetate and medrogestone were shown to significantly decrease reductive 17 β -HSD activity.⁴⁸⁻⁵⁰ In T-47D cells, however, promegestone has no effect on the reductive activity but can increase the oxidative 17 β -HSD activity.^{45,46} In MCF-7 breast cancer cells, progestins have been shown to increase both reductive and oxidative 17 β -HSD activities.^{51,52}

Although it has been shown that aromatase activity in breast tissue is influenced by systemic elements such as growth factors and hormonal status,^{36,53} studies on the effect of progestins on aromatase are very limited. With use of human breast carcinoma cell lines, Perel et al⁵⁴ have demonstrated that promegestone can inhibit aromatase activity by as much as 30%.

Minimizing the production of estradiol with antiaromatase compounds has provided significant therapeutic benefits for women. Importantly, though, in human breast cancer cells, estrone sulfates, and not androgens, are quantitatively the most important precursor of estradiol.⁴² Estrone sulfates themselves have no estrogenic effect because they do not bind to the estrogen receptor. The degree of conjugation of estrone is dependent on the balance of estrone sulfatase and estrogen sulfotrans-

ferase activities. Various progestins, including nomegestrol acetate, promegestone, and medrogestone, have been shown to inhibit estrone sulfatase activities^{48,49,55} and stimulate sulfotransferase activity^{55,56} in hormone-dependent breast cancer cell lines, effectively increasing the formation of biologically inactive sulfate derivatives.

Essentially all the data on progestins and estrogen biosynthetic enzymes have been obtained from studies on breast cancer cell lines. Future analysis of the effect of progestins in breast cancer patients, specifically the inhibition of 17 β -HSD and sulfatases and the stimulation of sulfotransferases, could provide insight into a potential role for these compounds in the treatment of the disease.

Progestins and breast cancer risk

Epidemiologic studies. The relationship of postmenopausal hormone use to breast cancer risk has been examined in many epidemiologic studies, with mixed and inconclusive results.⁵⁷⁻⁶⁰ In the past 25 years there have been more than 50 epidemiologic studies and at least 6 meta-analyses relating to breast cancer risk and hormone therapy.⁵⁷ The majority of these studies contain robust data for unopposed ERT⁶¹; in comparison, few studies specifically address progestins and breast cancer risk. In the large Collaborative Group on Hormonal Factors in Breast Cancer analysis of 51 published studies involving a total of 52,705 women with breast cancer, the majority of women (80%) had used estrogen-only regimens and, therefore, data for progestin and breast cancer could not be extracted.⁶¹ Of the published studies that have assessed the association between combined estrogen and progestin regimens with breast cancer risk,^{14,15,62-81} only four have demonstrated significant differences. Two studies demonstrated a significantly higher breast cancer risk with long-term use of HRT (≥ 6 years, relative risk [RR] = 1.7 for both studies),^{64,71} but in one of those the increased risk was significant only in a subpopulation of lean women.⁶⁴ The two other observational studies with significant differences have reported a protective effect with HRT use, with reported RRs of 0.3⁶² and 0.5.⁶³

Two recent epidemiologic studies^{14,15} have garnered extensive attention because of their reported modest increase in breast cancer risk in select subpopulations of HRT users. In a reanalysis of Breast Cancer Detection Demonstration Project data, Schairer et al¹⁴ concluded that HRT results in a greater risk of breast cancer than ERT. This conclusion, however, was based on few data associated with progestin use and was limited to a small group of lean women who used progestins for fewer than 15 days; the RRs did not achieve statistical significance. Similarly, Ross et al¹⁵ reported results of a population-based, case-control study that suggest a greater risk of breast cancer with HRT compared with ERT; again, the number of data available for HRT was very limited and comparisons were not statistically significant. Other re-

cent studies that have not received as much attention have demonstrated no significant effect on breast cancer risk.^{74,81} For example, a cohort study monitored 5761 postmenopausal women for up to 22 years and reported a lower incidence of breast cancer in women who had used HRT compared with women who had never used HRT (RR = 0.8, 95% CI 0.6-1.1).⁸¹ The lack of consistency from a large number of epidemiologic studies suggests either no effect of combined hormone therapy on breast cancer risk, or at best, a modest but not significant effect with long-term use in a select population of women.

Data from randomized controlled trials examining progestins and breast cancer were very limited until recently. A small, 22-year-long, placebo-controlled clinical trial of HRT use found a significantly lower incidence of breast cancer in women receiving combined therapy (0% incidence) compared with placebo (11.5% incidence, $P > .01$).⁸² The results of the continuous combined arm (conjugated equine estrogens [CEE], 0.625 mg/day, with medroxyprogesterone acetate [MPA], 2.5 mg/day) of the Women's Health Initiative (WHI) study involving >16,000 postmenopausal women were published in July 2002.⁸³ After a mean follow-up of 5.2 years, WHI investigators reported a hazard ratio for risk of invasive breast cancer of 1.26 (95% CI, 1.00-1.59). In absolute terms, after 5.2 years they found that there were eight more breast cancers per 10,000 women per year among HRT users; the absolute increased risk of breast cancer was 0.4%. However, when the investigators performed a subgroup analysis, they found that the only group that had a significantly increased risk of breast cancer was that group of women who had been on HRT before entering the study. In other words, the results from WHI are consistent with previously published observational data^{64,71} suggesting that there may be a slightly increased risk of breast cancer after 5 years' use of combined HRT. There was no increased risk of death from breast cancer. The estrogen-alone arm of the WHI is still continuing.

Further, two forms of CIs are presented in the WHI report, nominal and adjusted. The nominal intervals describe the variability in the risk estimates that would arise from a simple trial for a single outcome; for invasive breast cancer these intervals were 1.00-1.59. The adjusted CIs accounted for a Bonferroni correction. The Bonferroni CIs for the breast cancer data were not significant (0.83-1.92).⁸³

HRT in high-risk women. If HRT does increase breast cancer risk, this outcome would likely be exacerbated in women at high risk for development of the disease. However, several studies examining tumor incidence in women with a family history significant for breast cancer⁷⁸ or tumor recurrence in breast cancer patients⁸⁴⁻⁹⁰ have failed to demonstrate an association between HRT use in high-risk women and increased incidence of breast cancer. For example, a large prospective cohort study in-

volving >41,000 women with a family history of breast cancer found that women who were receiving HRT did not have a significantly higher breast cancer risk than women who had never used hormones.⁷⁸

Although HRT has traditionally been withheld from women with a personal history of breast cancer,^{88,89,91} a few studies in women previously diagnosed with breast cancer have suggested that HRT may have beneficial effects.^{87,88,92} A nested, case-controlled study in Australia examined 1122 women with surgically proved breast cancer and found that ERT/HRT use after diagnosis resulted in a significant reduction in recurrence compared with nonuse (RR = 0.62; 95% CI, 0.43-0.87).⁹² Also, all-cause mortality (RR = 0.34; 95% CI, 0.19-0.59) and death from primary tumor (RR = 0.40; 95% CI, 0.22-0.72) were both reduced for the subjects using ERT/HRT. The majority of women used continuous combined HRT; the median daily dose of progestin was 50 mg of MPA or 5 mg of norethisterone, a higher dose than commonly given with estrogen, in an attempt to elicit an antiestrogen effect on the breast. To my knowledge, this approach has not been tried previously.

Another study that examined 2755 women diagnosed with breast cancer observed a rate of breast cancer recurrence of 17 per 1000 person-years in women who used ERT/HRT after diagnosis and 30 per 1000 person-years in nonusers; it also demonstrated a significantly lower risk of recurrence for ERT/HRT users (RR = 0.50; 95% CI, 0.30-0.85).⁸⁷ In contrast to the Australian study, most patients (79%) used estrogen without a progestin. These data suggest that HRT use after breast cancer diagnosis may be protective. Although these results must be considered preliminary, the possibility that HRT can improve survival in patients with breast cancer would necessitate major re-evaluation of hormonal treatment of these patients.⁹³

Effect on breast density. Many studies have demonstrated that women tend to have an increase in parenchymal breast density with HRT use.⁹⁴⁻¹⁰⁴ This increase in density occurs soon after initiation of hormones^{94,97,99,102} and is sustained throughout therapy^{99,105}; however, the effect reverses quickly with cessation of HRT,¹⁰³ typically within 2 weeks.¹⁰⁶ Although some data have suggested that increased breast density is associated with a greater breast cancer risk,¹⁰⁷⁻¹⁰⁹ no studies to date have established a link between the rapidly reversible progestin-induced changes in breast density and increases in cancer risk.

Effect of progestin schedule. The controversy surrounding progestins and breast cancer risk is compounded by the various progestin regimens currently available. Comparisons of different dosage or duration therapies are not well studied but may prove necessary to obtain an accurate assessment of any role of progestin in breast cancer risk. Because the use of continuous combined progestin is relatively recent, data for this treatment schedule are

few. For example, in the reanalysis of the large Nurses' Health Study data set, the number of women using continuous progestin was too low to evaluate any relationship to breast cancer risk.⁶⁵

Of the *in vivo* studies that have examined breast cancer risk and treatment regimen, several have demonstrated an increased risk for breast cancer with cyclic progestin in comparison with continuous progestin. For example, results from an early population-based, case-control study in Denmark involving 1486 breast cancer patients showed an increased risk with sequential HRT therapy (RR = 1.36; 95% CI, 0.98-1.87), whereas continuous progestin therapy resulted in a nonsignificant reduction in risk (RR = 0.63; 95% CI, 0.26-1.53).⁶⁶ A reduction in risk with continuous progestin was also suggested in a cohort study involving 1150 premenopausal women with benign breast disease, where use of continuous 19-nortestosterone derivatives significantly reduced the risk for development of breast cancer (RR = 0.48; 95% CI, 0.25-0.90) over other regimens.⁸⁵ More recently, Ross et al¹⁵ and Schairer et al¹⁴ both reported a lower risk estimate with continuous progestins compared with sequential progestins, but the differences in risk between regimens were not statistically significant. In contrast, a large case-control study in Sweden reported that a continuous regimen of HRT was associated with a greater risk of breast cancer compared with a sequential regimen⁶⁴; however, some have argued that statistical considerations weaken this conclusion.¹¹⁰

Although no data have linked hormone-induced changes in mammographic density with breast cancer risk, some studies have demonstrated differences in density effects between progestin regimens. In contrast to reports from studies that cite a greater increase in breast density with continuous progestin over sequential progestin,^{95,97,98,104,111} the large Postmenopausal Estrogen/Progestin Interventions trial observed no difference in mammographic densities between continuous progestin regimens and sequential progestin regimens.⁹⁴

Effect of progestin dose. The use of lower-dose progestins in HRT formulations is relatively recent; therefore, there is little information on their effects. For example, the extensive Collaborative Group on Hormonal Factors in Breast Cancer meta-analysis of epidemiologic data from 51 studies provided no information on progestin dose effects.⁶¹ Although direct examination of lower doses of progestins has not yet been reported, some investigators have suggested that the data linking continuous combined therapy to a lower risk of breast cancer may be explained by the fact that continuous regimens typically use lower doses of progestin (MPA 2.5 mg) than sequential progestin therapy (typically MPA 5 to 10 mg).¹⁵ Indeed, in a study of mammographic density, a 2.5-mg dose of MPA combined continuously with 0.625 mg of CEE resulted in mean density increases of approx-

imately 50% of those observed with a 5-mg dose of MPA,⁹⁵ demonstrating that dose effects are highly probable. Given that the introduction of new progestin formulations has complicated analysis of progestin's effects, better-designed investigations are necessary to elucidate any role of progestin dose.¹¹²

Progestins and breast cancer survival

Although results from epidemiologic studies remain inconsistent, most of the studies that have examined breast cancer outcome in women who had used ERT/HRT have consistently documented improved mortality^{78,87,113-116} and survival rates.¹¹⁷⁻¹²³ For example, in the Breast Cancer Detection Demonstration Project, breast cancer mortality for women who were receiving hormones at the time of cancer diagnosis was half the mortality of nonusers (RR = 0.5; 95% CI, 0.3-0.8) up until 10 years after diagnosis.¹²⁰ The increase in survival may be due in part to surveillance bias, including a greater frequency of mammography and breast examinations among HRT users,^{124,125} but early detection may not be the only explanation. Improved survival has also been attributed to observed hormonal influences on tumor biology. Numerous studies have demonstrated that HRT users have smaller tumors^{78,121,122,126-130} that are more well differentiated^{60,126-133} and more localized^{61,113,126,127,130,131,134} than tumors in nonusers of HRT. In addition, histologic studies have shown that breast tumors in HRT users have a lower proliferation rate (S-phase fraction) than do tumors in nonusers,^{127,128,131} although one report demonstrated the opposite effect.¹³⁵ The favorable tumor characteristics observed with HRT use imply that exogenous hormones may promote the controlled growth of a malignant locus already in place. In general, breast cancer in HRT users is less aggressive than cancer in nonusers; therefore, prior HRT use is associated with a more favorable clinical outcome for breast cancer patients.

Conclusions

To date, there is conflicting epidemiologic evidence about the role of progestins in breast cancer. The majority of observational studies have examined estrogen-only regimens and those that were able to deduce progestin effects have differing results. Although two recent epidemiologic studies that garnered significant attention reported slightly elevated risks with HRT, the statistical strength of these conclusions is weak, and a clear consensus on progesterone and breast cancer risk is lacking. In the large, randomized WHI trial, the relationship between the small increase in risk of breast cancer after 5.2 years seen in the HRT arm and the progestin used is not clear. Despite the commercial introduction of new progestin regimens involving varied doses or treatment

schedules, there has been little examination of the different effects of these formulations on breast cancer risk.

Although a consensus regarding the relationship between HRT and breast cancer risk cannot be drawn from existing epidemiologic data, studies have clearly demonstrated that prior or current HRT use results in a paradoxically improved survival for patients with breast cancer. This improved outcome may be due in part to surveillance bias but may also be due to hormone-induced tumor characteristics that result in a more favorable prognosis.

Progesterone action in a normal and neoplastic breast cell is not isolated; a series of important regulatory proteins work in concert to decide cell fate. Results from mechanistic studies with breast cancer cell lines have demonstrated both proliferative and antiproliferative effects of progestins. This disparity in response is thought to result in part from a biphasic cellular response to progestin that depends on duration of treatment. Progestins are proliferative when administered in a transient or sequential manner but sustained treatment results in growth arrest. The timing and dose of progesterone treatment, therefore, is likely to influence any biologic response. The implication that sustained progestin may be inhibitory to malignancies already in place corroborates the favorable tumor biology observed in breast cancer patients who use HRT. The cellular effects of progestins on modulating enzymes involved in the localized biosynthesis of estrogens may also prove advantageous for women at risk for breast cancer or as a treatment option.

Despite *in vivo* consonance between progesterone levels and high mitotic activity in the breast, results from epidemiologic studies are inconsistent and mechanistic studies have not provided a physiologic foundation to implicate progestin in the pathogenesis of breast cancer. It is clear that rigorous, large-scale, double-blind, randomized trials are necessary to clarify the role of progestins and breast cancer risk. Given the variety of formulations available today, differences between progestin doses or treatment schedule must also be carefully examined. Because progestins are now widely used in postmenopausal hormone therapy, it is becoming critically important that their specific effect on breast cancer be clearly understood.

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