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Risk of Breast Cancer with Progestins in Combination with Estrogen as Hormone Replacement Therapy

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Two recent studies have suggested that progestins substantially increase the relative risk (RR) of breast cancer when added to estrogens as hormone replacement therapy (HRT) (1–2) (see Figs. 1 and 2). If correct, this information could substantially change clinical practice. Here, we review biological, epidemiological, and clinical data regarding the effects of progestins on the breast. From this analysis, we conclude that no definitive proof exists to establish a causal relationship between progestins and breast cancer risk. However, a wide range of biological and clinical data provides strong supportive evidence of such an effect. Based on this, we believe that it is prudent to inform patients that progestin use may add to the increased risk imparted by estrogens. Patients should understand, however, that this increased risk is small, particularly when associated with the short-term use of HRT.

Data linking estrogens with an increased breast cancer risk

Before examining the effects of progestins, it is first necessary to question whether estrogen alone increases the risk of breast cancer. Substantial data from animal and human studies provide support for a link between estrogen use and breast cancer risk. Administration of exogenous estrogen to rodents results in a high incidence of breast cancer (3). The use of antiestrogens or blockers of estrogen biosynthesis (aromatase inhibitors) abrogates the development of breast tumors that occur spontaneously or are induced by carcinogens in rats (4–5). In women, early menarche, late menopause, and increased endogenous circulating estrogen levels increase the RR of developing breast cancer (3, 6, 7). Removal of both ovaries before age 35 lowers the risk of breast cancer by 75% over a 25-yr period of observation (8–9). Finally, antiestrogens such as tamoxifen and raloxifene reduce the incidence of newly diagnosed breast cancer as demonstrated by randomized, placebo-controlled trials in women (10–11).

More than 50 observational studies in patients have examined whether estrogens cause an increased risk of breast cancer. Individual studies report an increase, decrease, or no change in the risk of breast cancer in menopausal women taking estrogen replacement therapy (ERT) (6). A recent meta-analysis from the Collaborative Group on Hormonal Factors in Breast Cancer (CGHFBC) (6) identified several objective factors that potentially explain differing conclusions among these studies. We draw the following conclusions from this meta-analysis. First, the RR of breast cancer from ERT is small and very large numbers of women must be studied to minimize type I and type II statistical errors.[1] Second, the risk of breast cancer seems to increase linearly with duration of use. Consequently, studies comparing "ever users" of estrogen with "never users" have limited validity because they do not consider duration of estrogen use. Third, the increased risk of breast cancer imparted by estrogens seems to dissipate within 4 yr of cessation of therapy. Accordingly, only women using estrogen within 4 yr of study might be found to be at increased risk. Fourth, breast cancer risk seems to diminish over the 4-yr period following the menopause, presumably as a reflection of decreased estrogen levels. As a result, analyses of observational studies need to match users *vs.* nonusers as to time following menopause. Finally, the increased risk of breast cancer seems to be limited to nonobese women [*i.e.* body mass index (BMI), <25 kg/m^2]. Inclusion of a large proportion of obese women might obscure the association between estrogen use and breast cancer risk.

The CGHFBC meta-analysis (6) was sufficiently large (*i.e.* 52,705 women with breast cancer and 108,411 without) to take each of these five factors into account. The key finding was a linear 2.3% increase in the RR of breast cancer for each year of HRT use for up to 25 yr. Both the slope of this linear increase in risk and the overall risk of breast cancer among HRT users was found to be highly statistically significant. In the authors' opinion, the CGHFBC meta-analysis provides substantial evidence that ERT increases the risk of breast cancer. However, the inferences from this study must be

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[1] The type I error or false positive error is the probability of concluding that a specified difference exists when, in truth, it does not. The type II error or false negative error is the probability of concluding that a specified difference does not exist when, in truth, it does (Piantadosi, 1997). The power of a study is 1 minus the type II error. (Piantadosi, S., Clinical Trials: A Methodologic Perspective, 1997, Wiley & Sons, Inc.)

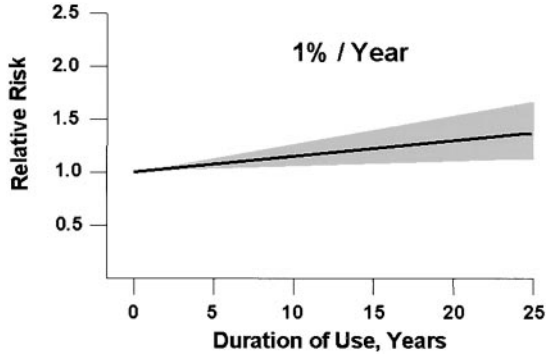

FIG. 1. Estimated increase in RR of breast cancer as a function of taking estrogen alone as HRT. The *shaded area* represents the confidence limits of the percent increase in risk per year. Redrawn from Ref. 1.

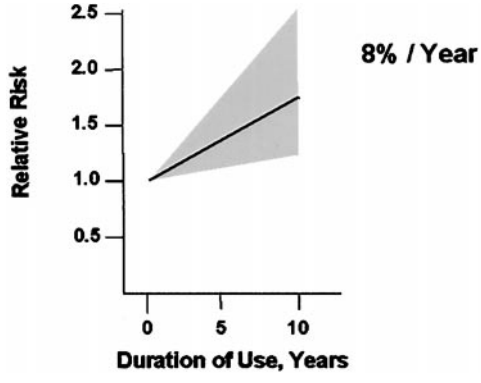

FIG. 2. Estimated increase in RR of breast cancer as a function of taking estrogen plus a progestin. The *shaded area* represents the confidence limits of the percent increase in risk per year. Redrawn from Ref. 1.

considered provisional because they are based on observational data and are subject to various biases.

Relationship between cell proliferation and breast cancer

A general theory of carcinogenesis holds that agents that increase the rate of cell proliferation can enhance the development of new genetic mutations (12). Mutations are thought to be necessary for the process of initiation of cancer. Once mutations are present, they need to be propagated by cell replication, a process considered to be responsible for tumor promotion. Estrogens are known to enhance the rate of cell proliferation in glandular tissue of the breast and, thus, could potentially act both in the initiation and promotion of breast cancer.

Effect of progestins on human breast proliferation

A key issue is whether progestins exert proliferative or antiproliferative effects on the human breast. Progestins oppose the proliferative effects of estrogens on the human endometrium and reduce the risk of endometrial cancer. Gambrell (13) has hypothesized that progestins might abrogate the carcinogenic effects of estrogen on the breast through a similar antiproliferative action. Others argue that progestins exert proliferative and, thus, procarcinogenic effects on the breast (14). This controversy has stimulated a wide range of *in vitro* and *in vivo* studies to delineate the effects of progestins on breast tissue. The resulting reports highlight various complexities underlying the effects of progestins on breast tissue.

It is important to understand that not all progestins are alike in structure and function. Progestins can be classified into two major subtypes, the 17α-acetoxyprogesterone and the nortestosterone derivatives (15). The 17α-acetoxyprogesterone derivatives, such as medroxyprogesterone acetate (MPA), possess glucocorticoid-like as well as progestational activity. The group of 19-nortestosterone compounds includes two subclasses, the estranes and gonanes. The estranes, such as norethindrone acetate and ethynodiol diacetate, are more androgenic, and the gestanes, such as gestodene and desogestrel, are more progestational. Depending on their structure and the tissues in which they are studied, the various progestins can exert either androgenic, synandrogenic, antiandrogenic, estrogenic, glucocorticoid-like, or progestational effects (16–28).

These disparate actions of progestins on human breast cells in culture have confounded interpretation regarding effects on proliferation. For example, various studies report that human breast cancer cell lines such as MCF-7, T47-D, and ZR-75–1 can be either stimulated or inhibited by progestins through their androgenic, estrogenic, or progestational effects (17–28). Normal human breast cells obtained at reduction mammoplasty and grown in primary culture also respond to various progestins with either proliferative or antiproliferative responses.

A recent series of studies by Horwitz and colleagues (29–31) highlight the complexity of mechanisms whereby progestins regulate the proliferative process. They demonstrated that progestins act to up-regulate growth factor and cytokine receptors and interact with key downstream cell cycle mediators such as cyclin D. Substantial cross-talk between progesterone receptors and growth factor-related pathways occurs. Progestins increase the level of epidermal growth factor receptors, activate the transcription factor stat 5, and result in stimulation of several factors involved in regulating the proliferative process such as mitogen-activated protein kinase, p38 kinase, and c-*jun*-NH_2-kinase. Whereas much is now known about the *in vitro* effects of progestins from these studies, critical evaluation of these data do not establish whether the predominant effect of progestins is to stimulate or inhibit breast cell proliferation.

Clinical studies regarding progestin effects in patients

A clearer understanding that the predominant effects of progestins on breast are to induce proliferation has emerged from patient studies. Anderson and colleagues (14, 32) examined breast biopsies taken from women during the follicular phase when estradiol is the predominant circulating hormone and again during the luteal phase when progesterone increases. They found a substantial increase in tritiated thymidine uptake in association with luteal phase progesterone increments and with use of progestin containing oral contraceptives. These observations were confirmed by an additional study using fine-needle aspiration and markers

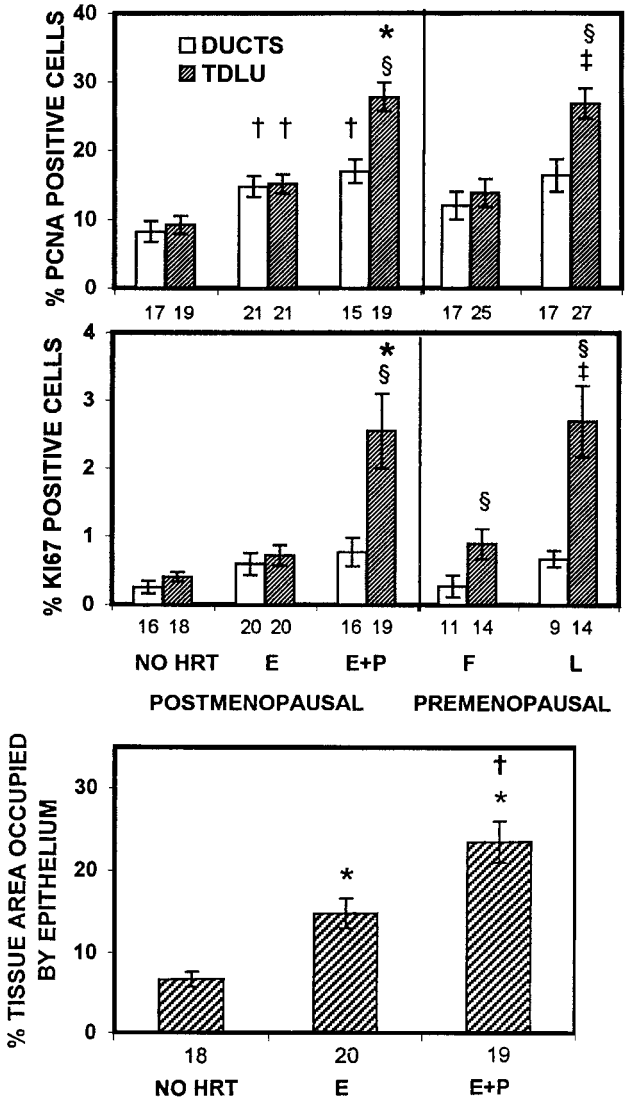

FIG. 3. *Top*, The percentage of cells that stain positively for the proliferation marker PCNA in ductal tissue and in TDLUs. The *number under each bar* represents the number of individuals from whom ducts or TDLUs could be analyzed. *, $P < 0.002$ that the percentages of PCNA-positive cells in the TDLUs of the E+P group were significantly greater than in the TDLUs or ducts of the no HRT group or E alone group; +, $P < 0.007$ that the percentages of PCNA-positive cells in the TDLUs or ducts of the E group or ducts of the E+P group were significantly greater than in the TDLUs or ducts of the no HRT group; ±, $P < 0.005$ that the percentages of PCNA-positive cells in the TDLU of the luteal phase group were significantly greater than in the TDLUs of the follicular phase group; §, $P < 0.05$ that the percentages of PCNA-positive cells were greater in TDLUs than in the ducts of the same group. E, Estrogen; P, progestin; L, luteal phase; F, follicular phase. *Middle*, The percentage of cells that stain positively for the proliferation marker Ki67 in ductal tissue and in TDLUs. The *number under each bar* represents the number of individuals from whom ducts or TDLUs could be analyzed. *, $P < 0.002$ that the percentages of Ki67-positive cells in the TDLUs of the E+P group were significantly greater than in the TDLUs or ducts of the no HRT group or E alone group; +, $P < 0.007$ that the percentages of Ki67-positive cells in the TDLUs or ducts of the E group or ducts of the E+P group were significantly greater than in the TDLUs or ducts of the no HRT group; ±, $P < 0.05$ that the percentages of Ki67-positive cells in the TDLUs of the luteal phase group were significantly greater than in the TDLUs of the follicular phase group; §, $P < 0.05$ that the percentages of PCNA-positive cells were greater in TDLUs than in the ducts of the same group. *Bottom*, Effects of HRT on breast epithelial density in postmenopausal women. The *number under each bar* represents the number of individuals for whom epithelial density was determined. *, $P < 0.001$ that the percentages of epithelial area in the E or E+P groups were significantly greater than that of the no HRT group; + $P < 0.02$ that the percentage of epithelial area in the E+P group was significantly greater than that of the E alone group.

of cell proliferation (Ki67 or MIB 1) to assess differences between follicular and luteal phase proliferation (33). Some doubt persisted, however, as a result of findings from topical administration of progestins that reduced breast epithelial cell proliferation. However, the amounts of topical progestin used were sufficient to increase tissue levels to pharmacological levels and, thus, may not reflect normal physiology (34).

More compelling data regarding the proliferative effects of progestins resulted from histological studies of breast tissue in postmenopausal women receiving either estrogen alone, estrogen plus a progestin, or no HRT for varying periods of time up to 10 yr. Hofseth *et al.* (35) examined breast tissue from women undergoing excisional biopsy for mammographic lesions. Tissue for assessment was taken from areas distant from the focal lesion. These investigators assessed proliferation by proliferating cell nuclear antigen (PCNA) and Ki67 measurements and quantitated the percent area of breast occupied by glandular tissue with computer-assisted morphometry. The results demonstrated that long-term estrogen use increased the rate of cell proliferation, the number of cells present in terminal ductal lobular units, and the percentage of breast tissue made up of glandular tissue as opposed to adipose and stromal tissue (Fig. 3). Notably, the addition of a progestin to estrogen replacement enhanced the rate of cell proliferation, terminal duct lobular units (TDLUs), and glandular mass. These effects of progestins appeared to increase linearly with time.

Further evidence of the proliferative effect of progestins derives from quantitative studies of mammographic density in women receiving HRT (36–40). Glandular tissue enhances the density of mammograms, and adipose tissue reduces it. Thus, breast density can serve as a surrogate marker for long-term glandular cell proliferation. The Postmenopausal Estrogen/Progestin Interventions trial analyzed mammographic density (36) in 307 eligible candidates out of a total of 875 women in the entire trial. Eligibility criteria required having a baseline mammogram; a follow-up mammogram at 12, 24, or 36 months available for review; 80% compliance with the assigned medication; and no use of estrogen for 5 yr before the baseline mammogram. At 12 months, the percentage of women with density grade increases was 0% [95% confidence interval (CI), 0.0–4.6%] in the placebo group; 3.5% (95% CI, 1.0–12.0%) in the conjugated estrogens alone group; 23.5% (95% CI, 11.9–35.1%) in the conjugated estrogens plus cyclic MPA group; 19.4% (95% CI, 9.9–28.9%) in the conjugated estrogens plus daily MPA group; and 16.4% (95% CI, 2.4–73.3%) with the conjugated estrogens plus cyclic micronized progesterone group. Mammographic density may be a marker for increased risk for breast cancer. If so, the above incremental changes seen when a progestin is added to estrogen therapy may be important. These results are

consistent with other studies (37–40) and provide compelling evidence of the proliferative, as opposed to the antiproliferative, effects of the progestins on human breast tissue *in vivo*.

Recent data regarding progestin use and breast cancer

The two recent studies, published within 1 month of each other in the winter of 2000 (1–2), reported that progestins add to the risk of breast cancer attributable to ERT. Although these studies are observational with a potential for inherent biases, they are remarkably consistent and supported by most, but not all, prior studies. To evaluate the validity of the conclusions from these studies, we have chosen to review existing data from prior studies meeting certain very stringent criteria. We believe that demonstration of the concordance of findings among these key studies provides the best means of reaching tentative conclusions from presently available data. We do not believe that a point-by-point analysis of potential biases in each individual study will serve to override these conclusions.

In our opinion, the experience gained from the CGHFBC meta-analysis allows identification of certain stringent criteria required for study validity (6). First, the study must be large enough to compare risks among various subgroups. Second, women must have used HRT within at least 4 yr before assessment of breast cancer risk. Third, the duration of HRT use must be taken into account. For these reasons, we have chosen to focus on individual studies meeting the following criteria: 1) involvement of at least 1500 women with breast cancer; 2) inclusion of data on women receiving HRT within 4 yr of breast cancer risk assessment; 3) examination of risk after long duration (*i.e.* at least 4 yr) of HRT exposure; and 4) comparison of estrogen alone with the combination of estrogen plus a progestin. Five studies met these four criteria (Table 1).

The study published in the *Journal of the American Medical Association* in January 2000 by Shairer *et al.* (1) represents a cohort study of 46,355 postmenopausal women followed long term in a mammographic screening program. The investigators report that the RR of breast cancer from estrogen alone was 1.2 (95% CI, 1.0–1.4) and that the RR from estrogen plus a progestin was 1.4 (95% CI, 1.1–1.8). Strikingly, the RR increased by 1% (95% CI, 0.2–3%) per year of estrogen use alone and 8% (95% CI, 2–16%) per year of use of estrogen plus a progestin (Figs. 1 and 2). No increase in risk was observed in women with a BMI (kg/m^2) greater than 24.4. However, in women with a BMI equal to or less than 24.4, the yearly increase in risk was 3% (95% CI, 1–6%) with estrogen alone and 12% (95% CI, 2–25%) with estrogen plus a progestin.

The study by Ross *et al.* (2) used the case control method and compared HRT use in a group of 1897 postmenopausal women with diagnosed breast cancer and 1637 controls. The risk of breast cancer with ERT alone was only increased for women taking this medication for 15 yr or more (odds ratio, 1.24; no CI listed). With continuous estrogen plus a progestin, the odds ratio after 10 yr was 1.51 (no CI listed). Expressed as a yearly increase in odds ratio, ERT was associated with a 1.2% per year increment, whereas estrogen in combination with a progestin was associated with a 4.8% per year increment. These were reported as risks per 5 yr with confidence limits indicated (ERT alone 1.06 with 95% CI 0.97–1.15; estrogen-progestin combination 1.24 with 95% CI 1.07–1.45). The risk of sequential progestin use seemed to be higher (but was not significantly different statistically) than that associated with continuous progestin use. After 10 yr, the odds ratio for the sequential regimen was 1.79 *vs.* 1.23 for the continuous regimen.

The Nurses Health Study, reported only in abstract form, involved 980,000 person years and 16 yr of follow-up (41). In all, 2035 women developed breast cancer and provided information regarding use of hormones. Yearly breast cancer risk increased with estrogen use alone by 3.3% (SEM, 0.84%) and with estrogen plus a progestin by 9.0% per year (SEM, 2.5%).

A Swedish case control study (42) reported on 3345 postmenopausal women with invasive breast cancer. After 10 yr of use, the odds ratio for breast cancer risk associated with estrogen alone was 2.7 (95% CI, 1.47–4.96), whereas that associated with estrogen plus a progestin was 2.95 (95% CI, 1.84–4.72). The yearly risk was 3% (95% CI, 0.98–1.08) with estrogens alone and 7% (95% CI, 1.02–1.11) for estrogen plus a progestin. This study also compared thin with obese women. The risks of HRT taken for more than 10 yr (either estrogen alone or estrogen plus a progestin) were not increased for those with a BMI more than 27 kg/m^2 (odds ratio, 1.33; 95% CI, 0.62–2.85) as opposed to those with BMIs of 22–27 kg/m^2 (odds ratio, 3.12; 95% CI, 2.09–4.66), and BMIs of less than 22 kg/m^2 (odds ratio, 1.97; 95% CI, 1.05–3.70). The final study (43), the results of which conflicted with those of the other four, reported that the RR associated with estrogen

TABLE 1. Summary of data from five key studies of estrogens (E) alone *vs.* E plus a progestin (P)

Study	Breast cancer cases	RR		Yearly incremental RR	
		E alone (duration)[a]	E & P (duration)[a]	E alone	E & P
Schairer *et al.*	2082	1.2 (10.3 average mean person yr)	1.4 (3.6 average mean person yr)	1% (0.2%–3%)[b]	8% (2%–16%)[c]
Ross *et al.*	1897	0.93 (>10)	1.79 (>10)[d]	1.2%[d]	7.6%[d]
Colditz *et al.*	2035	1.1 (>10)	1.58 (>10)	3.3% (± 0.84%)[e]	9.0% (± 2.5%)
Magnussen *et al.*	3345	2.7 (>10)	2.95 (>10)[f]	3% (−2%–8%)	7% (2%–11%)
Newcomb *et al.*	3130	0.81 (>5)	1.06 (>5)	Not calculated	Not calculated

[a] Years.
[b] 95% CIs.
[c] Combined and sequential.
[d] Sequential prog, CIs reported only for 5-yr estimates.
[e] SEM.
[f] Testosterone-derived P.

use alone was 0.81(95% CI, 0.65–1.00), whereas that associated with estrogen plus a progestin was 1.06 (95% CI, 0.68–1.64).

Other reported studies not meeting the stringent criteria defined above are generally consistent with an adverse effect of progestins. Persson *et al.* (44, 45) reported two studies from Sweden within the past 5 yr. One reported a RR of 1.4 (95% CI, 1.1–1.8) for an estrogen-progestin (levonorgestrel) combination for 10 yr *vs.* a RR of 0.8 (95% CI, 0.6–1.1) for estrogen alone (44). The other reported a RR of 2.4 (95% CI, 0.7–8.6) for the estrogen-progestin combination *vs.* a RR of 1.3 (95% CI, 0.5–3.7) for estrogen alone (45). Another study reported a RR of 1.7 (95% CI, 0.9–3.3) for estrogen plus a progestin *vs.* 1.2 (95% CI, 1.0–1.4) for estrogen alone (46). In contrast, four additional studies including relatively large numbers of women with breast cancer (1486, 742, 800, and 660 women respectively) (47–50) detected no increased risk of adding progestins to estrogens. Several other studies included too few women with breast cancer to detect trends (*i.e.* all <100 breast cancer cases) (51–53). Interestingly, the CGHFBC meta-analysis contained minimal information regarding estrogen plus progestin use, and no conclusions were drawn regarding the added effects of progestins on breast cancer risk (6).

Unanswered questions regarding progestins and breast cancer risk

Biological data suggest that synthetic progestins may exert various hormonal actions in addition to their progestational effects. Accordingly, the various synthetic progestins used by patients could exert divergent actions depending on their intrinsic properties. Clinical data will be required to determine whether there are differences in breast cancer risk associated with the use of these compounds. The case control study of Magnussen *et al.* (42) suggests that this might be the case. They noted a trend toward greater risk of breast cancer in association with the 19-nortestosterone derivatives as opposed to the 17-α-derived progestins.

The schedule of progestin administration may also alter breast cancer risk. Available clinical data relate primarily to use of cyclic progestins, whereas clinical practice now favors use of continuous estrogen-progestin combinations. A trend observed in the study by Ross *et al.* (2) indicated that the cyclic regimen, after 10 yr of use, incurred a RR of 1.79 whereas the RR for the combined regimen was 1.23. Finally, the beneficial reduction of endometrial cancer with progestins may be offset by the increased risk of breast cancer. Careful risk/benefit analyses need to readdress the recommendations regarding long-term progestin use to prevent endometrial cancer. Notably, should progestins be avoided in HRT regimens? The increased risk of breast cancer from progestins may outweigh its beneficial effects to prevent endometrial cancer.

Attributable risk of breast cancer from HRT with estrogens plus a progestin

Epidemiological data examining the risk of breast cancer from HRT report "relative risk" statistics to determine statistical significance (6). This methodology provides substantial statistical power to detect the effects of these agents that might be quite small in magnitude. As discussed extensively in a prior publication (54), the lay press, patients, and many physicians confuse the term " relative risk" with "attributable risk." An understanding of the precise definitions of these terms, as detailed below, is important to judge the actual magnitude of risks involved.

RR represents the ratio of the risk of breast cancer in women taking HRT to those not taking HRT. The term does not take into account the actual frequency of breast cancer in the group being considered. Absolute risk is determined by multiplying the usual rate of breast cancer in the group being considered by the RR. For example, average 50-yr-old women have an average risk of developing breast cancer of 2.52 per 100 women over a 10-yr period. A 10% increase in RR from estrogens alone would increase the absolute chance of getting a breast cancer over a 10-yr period to 2.77 per 100 women. Attributable risk refers to the number of women who would develop a breast cancer that would not have otherwise occurred without use of estrogen replacement. Using the example above, the difference between breast cancer risk of 2.52 per 100 and 2.77 per 100 represents the increased risk attributable to estrogen, or 0.252 per 100 women. Stated in another way, 1 in 397 women taking ERT over 10 yr would develop a breast cancer that would not have ordinarily occurred if ERT were not used (Table 2).

What are the attributable risks of breast cancer from estrogen alone vs. an estrogen-progestin combination?

Calculation of attributable risk requires data regarding the age-specific incidence of breast cancer in the population under consideration and the increase in RR with duration of hormone use. One can use the data of Schairer *et al.* (1) (Figs. 1 and 2) to calculate attributable risk. In 50-yr-old women, use of estrogen for only 2 yr increases the RR of breast cancer by 2% (1% per year over 2 yr). According to Surveillance,

TABLE 2. Attributable risks and benefits from HRT

Hormone	Age initiated	Duration of use	Attributable risk of breast cancer		Attributable benefit for preventing first cardiovascular event	
			Per 100 women	As numerical chance	Per 100 women	As numerical change
Estrogen alone	50 yr old	2 yr	0.0101	1:9925	0.04	1:2500
Estrogen/progestin	50 yr old	2 yr	0.0806	1:1241	0.04	1:2500
Estrogen alone	50 yr old	10 yr	0.252	1:397	0.37	1:270
Estrogen/progestin	50 yr old	10 yr	2.016	1:50	0.37	1:270
Estrogen alone	60 yr old	10 yr	0.350	1:286	0.66	1:152
Estrogen/progestin	60 yr old	10 yr	2.780	1:36	0.66	1:152

Epidemiology, and End Results (SEER) data, 2.02 in 400 50-yr-old women will have a new breast cancer diagnosed over a 2-yr period. With a 2% increase in RR, the 50-yr-old patient taking ERT would then have a 2.06 in 400 chance of getting a breast cancer. The attributable risk due to HRT is then 0.04 per 400 women. Stated in another way, 1 in 9925 women would develop a breast cancer as a direct result of taking estrogen. Similar calculations for an estrogen-progestin combination indicate an attributable risk of 1 in 1241 women. This small absolute increase in risk occurs even though the RR is increased by 8% per year over 2 yr, or 16% in total.

The use of HRT over a 10-yr period increases the attributable risk substantially. The cumulative incidence of breast cancer increases over this time period, and the risk increases linearly per year. For estrogen alone, the risk is increased by 1% per year or 10% over 10 yr. The reported rate of breast cancer in a 50-yr-old woman is 10 per 400 women at 10 yr. A 10% increase would make the rate of breast cancer 11 per 400 over 10 yr. The attributable risk related to estrogen is, thus, 1 in 397. With the combination of estrogen plus a progestin, the RR increases by 8% per year or 80% overall. The attributable risk for this group is now 1 in 50.

Practical use of attributable risks and benefits in decision making

Short-term use of ERT/HRT for menopausal symptoms. Use of ERT or HRT for less than 2 yr causes only a negligible increase in risk of breast cancer in a 50-yr-old woman (1 in 9925 attributable risk from estrogen alone and 1 in 1241 for estrogen plus a progestin). Consequently, a woman could be encouraged to take short-term ERT or HRT for menopausal symptoms without a great deal of concern regarding risk of breast cancer.

Long-term use of ERT/HRT to prevent heart disease or osteoporosis. The longer a woman takes estrogen, the greater is her risk of developing breast cancer attributable to this hormone. The attributable risk associated with estrogen alone, when taken by the average 50-yr-old woman for 10 yr, is a 1 in 397 increase in the chance of getting a breast cancer. For 60-yr-old women, the respective risk is 1 in 286. If we accept the data of Schairer *et al.* (1) as valid, the RR of breast cancer increases by 8% per year with use of an estrogen plus a progestin. Using these data, we may calculate that, for the 50-yr-old taking HRT for a 10-yr period, the breast cancer risk attributable to hormonal therapy would be 1 in 50. For the 60-yr-old, the risk increases to 1 in 36.

In the average woman, this risk of developing breast cancer would exceed the benefits of preventing a cardiovascular event. If one accepts the Nurses Health Study data (55), HRT prevents a new cardiovascular event in only 1 of 270 50-yr-old women taking this medication for 10 yr. In the 60-yr-old women taking HRT for 10 yr, 1 in 152 will have a cardiovascular event prevented. However, this must be interpreted in light of recent information from the Heart and Estrogen/Progestin Replacement study, the Estrogen and Atherosclerosis study, and other trials that raise valid questions whether estrogen usage actually results in primary cardiovascular prevention (56–58).

Weighing the pros and cons of HRT, many women will still choose hormonal therapy because the risk of breast cancer is relatively small in absolute terms. For example, based on the worst case analysis, a 50-yr-old women taking an estrogen/progestin combination as HRT for 10 yr has only a 4% chance of getting breast cancer. Without HRT, her risk would be 2%. These statistics sound more reassuring if expressed as the number of women remaining free of breast cancer. For example, women taking HRT for 10 yr have a 96% chance of remaining free of breast cancer *vs.* 98% of those not taking HRT.

Other factors which influence decision making

The two most recent studies of HRT and breast cancer risk suggest that only thin patients (*i.e.* BMI of <24.4 in one study and <27 in the other) experience an increased risk of breast cancer from either estrogen alone or the combination of estrogen and a progestin (1, 6). When limiting analysis to thin women, only those taking HRT long term (*i.e.* greater than 5 yr) had a statistically significant increase in breast cancer risk. Obese women did not have an increased risk of breast cancer attributable to HRT. A family history of breast cancer, early age of menarche, late age of child bearing, a high-fat diet, obesity, increased breast density on mammograms, and certain benign breast lesions increase the underlying risk of developing a breast cancer. Finally, several studies suggest that the breast cancers that develop in women receiving HRT are less aggressive in type and are associated with a better prognosis (59).

Alternatives to use of ERT or HRT in women at high risk of developing breast cancer

A number of alternatives exist that can be used in place of systemic estrogen to ameliorate problems related to estrogen deficiency in women concerned about breast cancer risk (60). Vaginal estrogen can be used to treat the symptoms of urogenital atrophy without increasing systemic estrogen levels to a measurable degree. The selective serotonin reuptake inhibitor class of drugs can alleviate symptoms of depression. Preliminary data from a randomized, controlled trial indicate that the selective serotonin reuptake inhibitors also cause 75% relief of hot flashes (61–62). Other trials demonstrated that clonidine is more effective than placebo in relieving hot flashes. For maintenance of bone mineral density and prevention of osteoporosis and fractures, the bisphosphonates, raloxifene (a selective estrogen receptor modulator), and calcitonin can be beneficial. In some postmenopausal patients at high risk for breast cancer, tamoxifen may be used both for prevention of breast cancer as well as maintenance of bone density. A series of recent publications report the surprising finding that the "statins" increase bone formation and reduce fracture risk (63–69). Randomized, controlled, prospective studies will now be required to confirm these observational studies. For prevention of heart disease, the HMG-CoA-reductase inhibitors (statins) are proven to be effective. These can be chosen in place of estrogens alone or estrogen–progestin combinations in patients at high risk of breast cancer or fearful of taking HRT. Aspirin, anti-inflammatory agents, and vitamin E are being studied as possible

alternatives for the prevention of Alzheimer's disease, colon cancer, or macular degeneration—diseases for which there is preliminary but not definitive evidence that HRT may influence the rates of development.

Conclusions

Biological, epidemiological, and clinical data support the concept that progestins enhance cell proliferation of breast tissue but inhibit cell division in the uterus. Based on this reasoning, it is plausible to postulate that progestins may increase the risk of breast cancer over and above that resulting from estrogens alone. The attributable risk from estrogen plus a progestin is minimal for short-term use but may be substantial in the setting of long-term replacement. Recent data suggest that the risks of breast cancer associated with HRT relate primarily to thin but not obese women. We recognize that there is still much to learn and the picture is confusing. Nonetheless, until definitive data from randomized, prospective trials are available, it is prudent to present the "worst case" analysis to patients and inform them of their actual level of risk from estrogens with or without a progestin. Based on this assessment, short-term use of HRT is associated with negligible risk whereas the risks and benefits of long-term use requires more analysis and careful consideration and discussion of risks and benefits.

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