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INSIDE

Influence of Estrogen Plus Progestin on Breast Cancer and Mammography in Healthy Postmenopausal Women

ABSTRACT & COMMENTARY

Synopsis: *In an intent-to-treat analysis, the use of conjugated equine estrogen combined with continuous medroxyprogesterone acetate by menopausal women increased the hazard ratio of invasive breast cancer to 1.24.*

Source: Chlebowski RT, et al. *JAMA*. 2003;289:3243-3253.

THE AIM OF THE PRESENT ANALYSIS IS TO "BETTER UNDERSTAND the relationship between breast cancer and exposure to estrogen plus progestin." The data are from the Women's Health Initiative. A total of 8506 women were randomized to the conjugated equine estrogen plus continuous medroxyprogesterone acetate arm, and 8102 women started in the placebo arm. The data from the women who are receiving conjugated equine estrogen alone are not available for this analysis. Randomization appears to have been achieved for important variables such as smoking, alcohol use, prior hormone use, age of menarche, parity, risk of breast cancer, and so forth. There were 349 incident invasive breast cancers and 84 in situ breast cancers; 42% of the participants using CEE+MPA and 38% of those using placebo stopped their medication. Also, 6.2% of those in the CEE+MPA arm and 10.7% in the placebo arm started using another hormone preparation while in the study (drop-ins). Participants were followed regardless of adherence.

The hazard ratio for invasive breast cancer was 1.24 with an unweighted confidence interval of 1.01-1.54 (P = .003) and an adjusted confidence interval of 0.97-1.59 (nonsignificant). When nonadherent women were omitted from the analysis, the hazard ratio became 1.49 (CI, 1.13-1.96). The hazard ratio for in situ breast cancer was 1.18 (CI, 0.77-1.82), which is statistically nonsignificant. The breast cancers in the women using CEE+MPA were slightly larger (1.7 vs 1.5 cm), but the biological significance of this is unknown because only 4 women who had breast

VOLUME 20 • NUMBER 4 • AUGUST 2003 • PAGES 25-32

cancer died in each arm. More disturbing is the finding that women in the CEE+MPA arm were more likely than those in the placebo arm to have advanced stage (regional/metastatic 25.4% vs 16.0%, $P = .04$) and to be node positive (25.9% vs 15.8%, $P = .03$). Also, more women in the CEE+MPA arm had abnormal mammograms (9.4% vs 5.4%). Histologic type and estrogen and progesterone receptor status were similar in both groups. More reliable molecular markers of tumor prognosis such as cyclins were not determined. Prior hormone users were at somewhat lower risk of breast cancer when compared to those without prior use (refer to Table 2 in the source article). Chlebowski and colleagues favor the interpretation that CEE+MPA stimulates breast cancer growth and delays breast cancer diagnosis by mammography. However, they note in the discussion that the data and safety monitoring board indicated on May 31, 2002, that there was not an increase in breast cancer in the conjugated equine estrogens-only arm.

OB/GYN Clinical Alert, ISSN 0743-8354, is published monthly by Thomson American Health Consultants, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

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Registration Number: R128870672.
Periodicals postage paid at Atlanta, GA.

POSTMASTER: Send address changes to ***OB/GYN Clinical Alert***, P.O. Box 740059, Atlanta, GA 30374.

Back issues: $42.

Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

Subscriber Information

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Subscription Prices

United States
1 year *with* free AMA Category 1 credits: $299
(Resident/Student rate: $149).
Multiple Copies
1-9 additional copies: $224 each; 10 or more copies: $199 each
Canada
Add GST and $30 shipping
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Term of approval covers issues published within one year from the beginning distribution date of Jan. 1, 2003. This volume has been approved for up to 25 Prescribed credit hours. Credit may be claimed for one year from the date of this issue.

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Statement of Financial Disclosure

In order to reveal any potential bias in this publication, and in accordance with Accreditation Council for Continuing Medical Education guidelines, we disclose that Dr. Speroff is involved as a consultant, and does research for Wyeth Ayerst, Pfizer, Ortho, and Novo Nordisk. Dr. Berga is a consultant for Pfizer, Organon, and Women First, Inc., and is involved in research for Berlex and Health Decisions, Inc. Dr. Gershenson is involved in research for Pharmacia-Upjohn, Oncotech, Genetech, SmithKline Beecham, Atairigen, and the National Cancer Institute. Dr. Hobbins reports no relationships related to this field of study.

■ COMMENT BY SARAH L. BERGA, MD

The results of this study need to be considered in conjunction with the manuscript that follows next in this issue of *JAMA* (*see the following abstract & commentary*). The present manuscript is carefully and clearly written. The discussion is interesting and balanced. Chlebowski et al note that the data "cannot inform questions regarding risk associated with other oral or topical menopausal hormone therapies" and that "the rates of discontinuation of study medications in both study groups are limitations." Figure 1 in the article suggests a divergence of risk for invasive breast cancer that appears by year 4 of use, but the hazard ratio for year 6 is lower in the CEE+MPA arm than that observed in years 4 and 5, so it is not clear if this early risk is sustained. If not, then it might not be "real." Also, while the data suggest that the risk for a breast cancer with a poor prognosis is increased by CEE+MPA use, the lack of data regarding mortality and the absence of more reliable molecular markers of prognosis preclude a firm interpretation. As I recently noted in an earlier review,[1] clinical staging does not correlate well with outcome, while the tumor marker cyclin E does.[2] In short, this detailed analysis of the WHI data suggests that use of CEE+MPA modestly increases the risk of invasive breast cancer. We are told that as of last year, there was not an increased risk of invasive breast cancer in the CEE-only arm. If true, this would strongly implicate the progestin component as the source of the increased risk of invasive breast cancer. Even if the risk of death is not increased in those with invasive breast cancer, women with more advanced stages will be subjected to more aggressive evaluation and intervention for the treatment of breast cancer. Given that we cannot guarantee that other hormonal approaches do not carry the same risk, the increased probability of more procedures alone might serve as a deterrent to use other hormonal preparations. On the other hand, if other types of menopausal hormone therapy confer some of the putative benefits of menopausal hormone use, such as neuroprotection from dementia or preservation of habitus and sexual responsivity but with a null risk of breast cancer, it would be tragic that fear alone could motivate so many women to be denied these and other benefits. Clearly, this is not a time for dogmatism. ■

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Relationship Between Long Durations and Different Regimenes of Hormone Therapy and Risk of Brest Cancer

ABSTRACT & COMMENTARY

Synopsis: *The data in this case-control study of combined estrogen plus progestin therapy revealed an increased risk of breast cancer, particularly invasive lobular tumor, regardless of whether the progestin component was taken sequentially or continuously. There was no increased risk of breast cancer in those exposed postmenopausally to estrogen only.*

Source: Li CI, et al. *JAMA*. 2003;289:3254-3263.

THE AIM OF THIS STUDY WAS TO INVESTIGATE THE role of progestin use in the risk of postmenopausal breast cancer. Li and colleagues conducted a thorough case-control study in which hormone use was carefully ascertained. The subject population was women living in 3 counties in the Seattle-Puget Sound metropolitan area. There were 1007 control women and 975 cases of breast cancer. More than 95% of all incident cancer cases were entered into a registry. Control women were culled from the same population using HFCA records. The designation of ERT use was restricted to women who were exclusive users of ERT. The 2 groups were comparable in almost all regards except that those with breast cancer were more likely to have a family history of breast cancer and higher levels of alcohol consumption. Those diagnosed with invasive ductal breast carcinoma were more likely to have never used oral contraceptives, while those diagnosed with invasive lobular breast cancer were more likely to have used oral contraceptive for greater than 5 years.

Compared to ERT-only users, exclusive users of combined HRT (CHRT) had a 1.8-fold (CI, 1.3-2.2) increased risk of breast cancer of all types. When examined by histologic type, ever users of CHRT had an increased risk of both invasive ductal (OR, 1.5; CI, 1.1-2.0) and invasive lobular carcinoma (OR, 2.7; CI, 1.7-4.3). The increases were greatest for those using CHRT the longest. The increased risk associated with ever and current use of CHRT differed little by progestin regimen (continuous vs sequential). In contrast, the OR for current use of only ERT was 1.0 (CI, 0.7-1.3) and in those using ERT ≥ 25 years (101 cases), the OR was 1.0 (CI, 0.7-1.5).

■ COMMENT BY SARAH L. BERGA, MD

This study complements the recent WHI data reviewed above and buttresses the notion that the progestin component of menopausal hormone therapy may explain the excess risk of breast cancer seen in the CEE+MPA arm of the WHI. If the data from these 2 studies are true, then they suggest that we ought to be doing all that we can to minimize progestin exposure in women who take hormone therapy after menopause. As I noted herein last month, if there is an increased risk of dementia as was purportedly observed in the WHI in the CEE+MPA arm, it may also be attributed to the progestin component abrogating the neuroprotective effects of estrogen or via direct effects of progestins on neurons or glia. As far as I know, there are no known benefits associated with progestin use other than protection of the endometrium from hyperplasia and cancer. Progestins cause many symptoms, including dysphoria in some and bleeding in others.

What can we do to minimize progestin exposure in postmenopausal women who want to take estrogen? For years, there were some practitioners who advocated estrogen-only use even when the uterus was intact. However, the PEPI trial demonstrated high rates of hyperplasia in women given the standard dose of CEE of 0.625 mg. This led some to suggest the use of much lower estrogen doses, in the hope that this approach would confer benefits but avoid the risk of overstimulating the endometrium. In select individuals who consent to monitoring, this plan may have merit. The use of a progestin-containing intrauterine device also has merit, although some have raised concerns that even the small amount of progestin in the circulation that results from this approach may increase the risk of breast cancer. It is also possible that not all progestin preparations carry the same risk. The study by Li et al did not specify the type of progestin used by the cases, although medroxyprogesterone acetate is by far the most commonly used progestin. With regard to the vascular bed, it appears that synthetic progestins induce vasospasm while progesterone does not. Can we expect differential tissue responses to progestins in the breast and brain as well? Only ongoing research on this topic will tell us. In summary, taken together, these 2 studies strongly link the progestin component of CHRT to the increased risk of invasive breast cancer. One could also counter that, taken together, these 2 studies exonerate estrogens, but this latter statement is more controversial. In the meantime, it is abundantly clear that we need to explore the notion that not all progestins are the same while we simultaneously explore methods to give unopposed estrogen. The concept of "chemoamelioration" of aging

has merit, but we must continue to refine the approaches with an eye toward safety and enhanced efficacy. ■

Perinatal Outcomes in Twins: The Effect of Placental Abruption

ABSTRACT & COMMENTARY

Synopsis: *Birth weight discordancy of ≥ 15% for same sex and ≥ 30% for different sex confer greatest risk of adverse perinatal outcomes in the absence of abruption. In the presence of placental abruption, these risks are further compounded. The results underscore the need for careful monitoring of twin pregnancies.*

Source: Ananth CV, et al. *Am J Obstet Gynecol*. 2003; 188:954-960.

In obstetrical texts much has been made of the poor pregnancy outcomes associated with twin weight discrepancies of more than 20%. In a recent report, Ananth and colleagues have thrown another factor into the mix, placental abruption.

They looked at data from a "matched multiple birth file" for the United States from 1995 to 1997. The data involved 269,287 patients. Since information on zygosity was not available, they broke their results into same sex vs opposite sex twins.

The relative risk of abruption was 1.2 (CI, 1.1-1.4) for same sex twins with a 20% or greater discordance and 2.2 (CI, 1.7-2.8) for opposite sex twins with a 40% discordance. In nonabruptions, there was an increase in stillbirth, preterm births, and neonatal deaths when birth weight discordance exceeded 15% in same sex and 30% in different sex twins. Not surprisingly, abruption increased the risk for perinatal death even when discordance was a little as 5%.

■ COMMENT BY JOHN C. HOBBINS, MD

Twins are emerging as one of the largest problems in obstetrics. Older figures indicated a prevalence of spontaneous twinning to be 1 in 80 pregnancies—one third of these being identical. Now, through ovulation stimulation and assisted reproductive techniques, the prevalence of twins is around 1 in 40 and much higher in those older than 35 years of age. The overwhelming majority of this increase is contributed by dizygous twinning.

This trend is alarming because, although couples desperately seeking fertility help are happy to have any kind of pregnancy, the chance of problems during and after pregnancy more than doubles. Also, we have shown from our own studies that the cost of maintaining twin pregnancies is 6 times that of a singleton, a fact that has substantial impact on the cost of health care.

There are 2 major reasons why twins require so much attention:

1. They tend to deliver earlier (10% of monozygotic twins and 5% of dizygotic twins deliver prior to 32 weeks); and
2. They have a higher rate of intrauterine growth restriction, with all its accompanying morbidity.

The good news is that, in the absence of anomalies (twins have a higher rate), intrauterine growth retardation (IUGR), and preterm birth, the majority of patients with twins sail through pregnancy without a hitch. The thrust of our attention should be directed toward identifying early which patients would be in the at-risk categories so that we can concentrate on them, while leaving the others alone so that they might enjoy a singleton-like pregnancy. Also, this could generate substantial cost savings.

The best time to assess this risk for preterm birth and IUGR is between 20 and 24 weeks. A cervical length examination by transvaginal ultrasound will give the clinician a better idea of risk for very early delivery (< 32 wks). For example, in a study by Souka and colleagues the risk of preterm birth at less than 32 wks with a cervix of < 2.5 was 47%.[1] However, the risk of very early preterm birth with a cervix of > 4.0 is remarkably low with a negative predictive value exceeding 98%.

The twin IUGR story is just starting to unfold. Our yet unpublished data suggest that a 20% discordance is of much less importance if it does not involve IUGR of at least one twin. A 20% discordance in appropriate for gestational age (AGA) twin weight had little effect on time of delivery or days in the nursery. However, when the > 20% discordance involved a fetus that was below the 10th percentile, there was a significant decrease in age at delivery and a substantial increase in days spent in the nursery. Also, those with discordance in biometry at 20-24 weeks had far more morbidity than those in which the discordance occurred after 30 weeks, the latter having outcomes similar to concordant AGA twins.

Buried in the Ananth study data was an interesting fact: 63% of twins with a birth weight discordance of > 20% involved at least one twin with IUGR. This risk was much further elevated in the presence of placental abruption.

All of the above observations suggest there is a primary placental reason for IUGR and abruption

that can be suspected early (20-24 wks) in pregnancy by biometry alone. Our recent research thrust has been in honing in on the placenta with new color Doppler techniques to identify the placentas that are struggling during a critical stage in branching angiogenesis.

Better yet, it is hoped that with a comprehensive examination in twins at 20-24 weeks, using biometry, transvaginal ultrasound, and sophisticated 2-D and 3-D Doppler methods, clinicians will be able to pick out the majority of patients whom we can leave alone. ■

Reference

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Radiation Therapy With or Without Extrafascial Hysterectomy for Bulky Stage IB Cervical Carcinoma

ABSTRACT & COMMENTARY

Synopsis: *Following radiation therapy, adjuvant extrafascial hysterectomy decreased the risk of relapse for patients with "bulky" stage IB cervical cancer without improving survival.*

Source: Keys HM, et al. *Gynecol Oncol*. 2003;89: 343-353.

KEYS AND COLLEAGUES HAVE REPORTED A STUDY OF the Gynecologic Oncology Group in which the principal objective was to evaluate, in a randomized trial, the role of adjuvant hysterectomy after standardized radiation in improving progression-free survival and survival for patients with "bulky" stage IB cervical cancer. A total of 256 eligible patients with exophytic or "barrel" shaped tumors measuring > 4 cm were randomized to either external and intracavitary irradiation (RT, n = 124) or attenuated irradiation followed by extrafascial hysterectomy (RT + HYST; n = 132). Tumor size was the most pronounced prognostic factor, followed by performance status 2 and age at diagnosis. Hysterectomy did not increase the frequency of reported grade 3 and 4 adverse effects (both groups, 10%). The majority of these adverse effects were from the gastrointestinal or genitourinary tracts exclusively. There was a lower cumulative incidence of local relapse in the RT + HYST group (at 5 years, 27% vs 14%). There was no statistical difference in outcomes between regimens except for the adjusted comparison of progression-free survival, although all indicated a lower risk in the adjuvant hysterectomy regimen. Keys et al concluded that, overall, there was no clinically important benefit with the use of extrafascial hysterectomy. However, there is good evidence to suggest that patients with 4-, 5-, and 6-cm tumors may have benefited from extrafascial hysterectomy.

■ COMMENT BY DAVID M. GERSHENSON, MD

Adjuvant hysterectomy after preoperative irradiation rather than irradiation alone in patients with bulky stage IB cervical cancer was first highlighted in a series of reports from M.D. Anderson Cancer Center in the 1960s and 1970s. The rationale of this strategy was based on the premise that tumor hypoxia within a large cervical tumor would be better treated with surgical resection than brachytherapy following external therapy. Of course, the principal objectives of such an approach were to reduce the incidence or local pelvic relapse and to thereby improve overall survival. Following these reports, this treatment approach became widely used throughout the United States without any definitive evidence to support its use. Although the approach was essentially abandoned at M.D. Anderson Cancer Center by the early 1980s, its popularity continued to increase. Amazingly, this GOG trial was conducted between 1984 and 1991, but it was only reported in June 2003. Although Keys et al provide a very positive spin to their conclusions, this study should really signal the death knell for adjuvant extrafascial hysterectomy, except in very specific clinical scenarios. There was only a modest improvement in pelvic control, only a trend toward improvement in progression-free survival, and no improvement in overall survival. Potential indications for adjuvant extrafascial hysterectomy would include patients who have poor anatomy for brachytherapy, those with poor tumor response to irradiation, those with large uterine leiomyomata, and patients in whom there is confusion regarding the primary site of cancer (cervix vs endometrium). The accompanying editorial authored by a well-respected radiation oncologist, Dr. Anthony H. Russell, is very thoughtful and puts this article in the proper perspective.[1] ■

Reference

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Special Feature

Alternatives for Hot Flushing

By Leon Speroff, MD

THE VASOMOTOR FLUSH IS VIEWED AS THE HALLMARK of the female climacteric, experienced to some degree by most postmenopausal women. In the Massachusetts Women's Health Study, the incidence of hot flushes increased from 10% during the premenopausal period to about 50% just after cessation of menses.[1] In a community-based Australian survey, 6% of premenopausal women, 26% of perimenopausal women, and 59% of postmenopausal women reported hot flushing.[2] Although the flush can occur in the premenopause, it is a major feature of postmenopause, lasting in most women for 1-2 years but in some (as many as 25%) for longer than 5 years. In cross-sectional surveys, up to 40% of premenopausal women and 85% of menopausal women report vasomotor complaints.[3]

The treatment of choice for vasomotor symptoms is hormone therapy. However, there exists a substantial number of women who either cannot or will not accept hormone therapy. The alternative choices that have been available in the past offered only a modest benefit. Transdermal clonidine, applied with the 100-µg dose once weekly was a common choice, but the reduction in hot flushing was only slightly better than that obtained with placebo treatment.[4,5] Clonidine, bromocriptine, and naloxone given orally are only partially effective for the relief of hot flushes and require high doses with a high rate of side effects. Bellergal treatment (a combination of belladonna alkaloids, ergotamine tartrate, and phenobarbital) is slightly better than a placebo and a potent sedative in the short-term; however, one study documented a similar response with bellergal and placebo after 8 weeks.[6,7] Veralipride, a dopamine antagonist that is active in the hypothalamus, is relatively effective in inhibiting flushing at a dose of 100 mg daily but is associated with major side effects, including mastodynia and galactorrhea.[8-10] Medroxyprogesterone acetate (10-20 mg daily) and megestrol acetate (20 mg b.i.d.) are also effective, but concerns regarding exogenous steroids (especially in patients who have had breast cancer) would apply to progestins as well.[11,12] Vitamin E, 800 IU daily, is barely more effective than placebo.[13] Isoflavones (including soy protein) have been demonstrated to have little clinical difference compared with placebo treatment.

In the last few years, selective serotonin reuptake inhibitors (SSRIs) have gained a reputation for significant efficacy in treating hot flushing. The drugs that have been studied include fluoxetine (Prozac), paroxetine (Paxil), and venlafaxine (Effexor). In addition, an antiseizure medication, gabapentin (Neurontin), has been demonstrated to reduce vasomotor symptoms.

In the study with paroxetine (the controlled-release product), 61% of the treated group (a general population of postmenopausal women with only 12 individuals who were breast cancer survivors) at the end of the study had at least a 50% reduction in frequency and severity of flushing, an effect that was about 2.5 times better than placebo with the higher dose.[14] An important feature of this study was that individuals with clinically significant mood disorders were excluded. Venlafaxine was studied in breast cancer survivors; although the optimal dose was 75 mg, an appreciable response with 37.5 mg indicated that it would be worthwhile to begin treatment with the lower dose.[15,16] The response was very rapid, within days, and therefore the dose can be increased in 1-2 weeks. The main side effects were mouth dryness, anorexia, nausea, and constipation. The efficacy of venlafaxine was demonstrated to be the same in women taking or not taking tamoxifen. Fluoxetine was also studied in breast cancer survivors; its effect appeared to be more modest.[17]

Gabapentin is a g-aminobutyric acid analogue that has been used for seizures since 1994. It is also effective for migraine headaches, tremors, and panic disorder. In the gabapentin clinical trial, 67% of the treated women experienced more than a 50% reduction in flushes at week 12, compared with 38% in the placebo group.[18] The most common side effects were som-

Table

New Drugs for Hot Flushing—Randomized Clinical Trials

Drug	# of Patients	Study Length	Dose	Dose Reduction in Flushing	
				Drug	*Placebo*
Fluoxetine (Prozac)	81	4 wks	20 mg/d	50%	36%
Paroxetine (Paxil)	165	6 wks	12.5 mg/d	62%	38%
			25 mg/d	65%	
Venlafaxine (Effexor)	191	4 wks	37.5 mg/d	37%	27%
			75 mg/d	61%	
			150 mg/d	61%	
Gabapentin (Neurontin)	59	12 wks	900 mg/d	50%	29%

nolence (20%) and dizziness (13%). Peripheral edema occurs occasionally because of an induced decrease in serum protein. The potency of this agent appears to be more modest than the SSRIs.

Important Questions Remain Unanswered:

1. The available studies are all very short in duration (4-12 weeks); will long-term therapy maintain its efficacy? An open-label continuation of the venlafaxine trial documented maintenance of efficacy, but the length of the study was only 8 weeks.[19]
2. How does the potency of the SSRIs compare with hormone therapy? No comparative trial has been reported.
3. What is the lowest effective dose of each SSRI?
4. Is venlafaxine more effective than the other SSRIs (because it is both a serotonergic and a noradrenergic drug)? Conclusions regarding potency require appropriately designed studies comparing the effects of the drugs in the same population.

The published reports have indicated that larger and longer clinical trials are under way, and perhaps answers to these questions will emerge. Until then, it seems to me that the SSRIs are the best choice after hormone therapy. It is worth trying to titer the dose down to its lowest effective level because of a low but bothersome incidence of decreased libido. The SSRIs may be the best choice for flushing due to tamoxifen treatment. In a report at the most recent San Antonio Breast Cancer Symposium, hormone therapy was ineffective in reducing the flushing associated with tamoxifen.[20] Either the presence of tamoxifen blocks hormone action or the mechanism of tamoxifen-induced flushes is different than those associated with a reduction in estrogen. Nevertheless, SSRIs are effective for flushing secondary to both tamoxifen and hypoestrogenemia. An added advantage of the SSRIs is the fact that the clinical studies have also reported improvements in depression, anxiety, and sleep. ■

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CME Questions

3. The recent report on breast cancer differs from the original WHI report by all of the following *except*:

a. The diagnoses were adjudicated by a central facility.
b. Data on stage of disease are presented, indicating a later stage in hormone users.
c. The hazard ratio in the updated report is higher.
d. The increased risk appears early and then declines.

4. Recent studies on postmenopausal hormone therapy and the risk of breast cancer have indicated all of the following *except*:

a. The use of combined estrogen-progestin is associated with a higher risk of breast cancer.
b. The use of a daily, continuous regimen is definitely associated with a higher risk than a sequential regimen of estrogen-progestin.
c. Users of estrogen only do not have an increased risk of breast cancer.
d. About 25% of women using a daily, continuous regimen of estrogen-progestin develop increased breast densities on mammography.

5. The following statements are true regarding the treatment of hot flushes *except*:

a. Phytoestrogens effectively suppress hot flushing.
b. All of the serotonin reuptake inhibitors are equally effective.
c. Estrogen is probably the most effective treatment, but comparative studies have not been performed.
d. Other drugs, such as clonidine, bellergal, and veralipride, have some efficacy, but a high rate of side effects.

Answers: 3 (c); 4 (b); 5 (a)

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