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Hormone Replacement Therapy After a Diagnosis of Breast Cancer in Relation to Recurrence and Mortality

ABSTRACT & COMMENTARY

There is no compelling evidence that hormone replacement therapy (HRT) use by women who have survived breast cancer increases the likelihood of recurrence. However, it has been a general assumption, based on our mental cartoon of the pathogenesis of breast cancer, that its use carried a significant, if undefined, likelihood of harm. Breast cancer survivors, therefore, have generally been discouraged from taking HRT. No one argues that the proscription of HRT is of no clinical consequence. It has just seemed the lesser of 2 evils. As O'Meara and colleagues highlight, prior studies attempting to address this issue were seriously limited by sample size or inherent biases. Nonetheless, 4 of 5 previous studies found no increased risk of breast cancer recurrence among users of HRT compared to nonusers. The present study came to the same conclusion and it clearly used the best methodology so far. Data were assembled from 2755 women aged 35-74 years who were diagnosed with incident invasive breast cancer while they were enrolled in a large health maintenance organization from 1977 through 1994. Pharmacy data identified 174 users of HRT after diagnosis. Each HRT user was matched to 4 randomly selected nonusers of similar age, disease stage, and year of diagnosis. O'Meara et al considered and controlled for every conceivable confounding variable, including route of administration, total exposure (dose and duration), and use of a progestin. The duration of HRT use before the diagnosis of breast cancer was greater among users of HRT after the diagnosis of breast cancer. While concurrent HRT use has been linked to better survival in women who subsequently develop breast cancer, O'Meara et al state that the magnitude of this potential confounding variable is not large enough to conceal a true adverse effect of HRT use after diagnosis. The rate of breast cancer recurrence was 17 per 1000 women-years in HRT users vs. 30 in nonusers, adjusted relative risk (RR) = 0.50, confidence interval (CI) 0.30-0.85. Total mortality rates were 16 per 1000 women-years in HRT users and 30 in nonusers, adjusted RR = 0.48; CI 0.29-0.78.

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INSIDE

Beyond the first year of use, the adjusted RR = 0.37; CI 0.13-1.04 for breast cancer recurrence and 0.50; CI 0.31-0.83 for total mortality. Among women with estrogen receptor-positive tumors, the unadjusted RR for HRT use = 0.31; CI 0.10-0.98 for breast cancer recurrence, 0.16; CI 0.02-1.19 for breast cancer mortality, and 0.30; CI 0.11-0.82 for total mortality. (O'Meara ES, et al. *J Natl Cancer Inst*. 2001;93:754-761).

COMMENT BY SARAH L. BERGA, MD

I was thrilled to find that someone had finally done this study. However, after reading the report, I was even more intrigued. The present study begs the issue as to whether estrogen use by breast cancer survivors with estrogen receptor-positive tumors is protective. O'Meara et al chose not to position their results as indicating increased survival for women with breast cancer who use HRT after diagnosis, but the results could be interpreted in this way. It appears that O'Meara et al chose the more conservative interpretation due to the inherent limitations of the study design. After all, this was not a randomized, prospective trial. Likely O'Meara et al also recognized the tremendous implications of suggesting that HRT use might promote survival. The current dogma suggests that anti-estrogens like tamoxifen increase survival because they are anti-estrogens. This study would seem to contradict that dogma. Sadly, given what we now know about estrogen receptors and the multiple ligands that interact with them, it becomes increasingly difficult to hold onto the simplistic worldview that there are 2 discrete classes of steroid ligands, agonists and antagonists. Based on the presumption that anti-estrogens both exist and are needed, The National Surgical Adjuvant Breast Project (NSABP) is now conducting what is referred to as the STAR trial, Study of Tamoxifen and Raloxifene, in an attempt to determine which anti-estrogen is better as adjuvant therapy for women with recently diagnosed breast cancer. I had the privilege of addressing the NSABP last summer to talk about the risks and benefits of estrogen use by postmenopausal women. After a thorough review of the data, I wondered why the STAR trial was not the STARE trial, Study of Tamoxifen, Raloxifene, and Estrogen. I concluded it was because no one felt brave enough to challenge the underlying paradigm that supports the use of anti-estrogens. The aim of the study is simply to determine which of the 2 "anti-estrogens" is best for women who have had breast cancer. The operating assumption of the STAR trial is that anti-estrogen use by women who have breast cancer is of benefit and all we lack is data about which anti-estrogen is better. The concluding line of the discussion of the present report, however, advocates for a study like the STARE. The results of the report reviewed herein further increase the justification for such a trial. Given the multiplicity of benefits that accrue from long-term HRT use, it is literally vital to know if we should continue to deny HRT use to women who have survived breast cancer. ❖

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MSAFP

ABSTRACT & COMMENTARY

Synopsis: *Pregnant women with extreme MSAFP values in the second trimester have an increased risk of fetal and infant deaths.*

Source: Krause TG, et al. *Obstet Gynecol*. 2001;97(2): 277-282.

Krause and colleagues reviewed data from 77,149 pregnancies screened with maternal serum alpha feto-protein (MSAFP). Armed with a powerful Danish national database, Krause et al were able to

obtain comprehensive follow-up with regard to spontaneous abortion, fetal demise, infant death, delivery timing, and birth weight. Since MSAFP elevation could well have represented a sign of fetal demise or imminent demise at the time of sampling, Krause et al plotted spontaneous abortions according to weeks post-sampling and found, not surprisingly, a high rate of abortion soon after the patients' bloods were drawn. However, after 3 weeks the rate plateaued. For this reason, Krause et al focused particularly on fetal death after 3 weeks as a more clinically relevant variable against which to compare high (> 2.5 MoM) and low (< 0.25 MoM) levels of MSAFP. Krause et al arbitrarily chose 28 weeks as a cutoff below which fetal death was labeled as an "abortion."

These results indicated that having an MSAFP above 2.5 MoM predisposed patients to a higher risk of preterm delivery (PTD) (relative risk [RR], 4.8; 95% confidence interval [CI], 4.1-5.5%), small-for-gestational age (SGA) (RR, 2.8; CI, 2.4-3.2%), low birth weight (LBW) (RR, 5.8; CI 9.7-16.1%), spontaneous abortion (SAB) (RR, 12.5; CI 9.7-16.1%), and infant death (RR, 1.9; CI 1.2-2.8%). Patients with MSAFP values below 0.25 MoM had a RR of PTD of 2.2; CI 1.3-3.8%, and a SAB RR of 15.2; CI 9.3-24.8%. The RR of stillbirth (after 28 weeks) was 4.0 with a low MSAFP and 2.9 for high MSAFP, but neither achieved statistical significance after adjusting for LBW.

COMMENT BY JOHN C. HOBBINS, MD

MSAFP screening for fetal neural tube defects (NTD) came into being in the 1970s. A decade later, estriol (E3) and human chorionic gonadotropin (HCG) were added to the screening armamentarium to identify pregnancies at high risk for fetal Down syndrome (DS). In the later 1980s and early 1990s, reports began to emerge suggesting higher rates of adverse outcome (unrelated to fetal anomalies) in patients having elevations of MSAFP and HCG in the second trimester. The outcome that seemed to generate the most attention was a higher rate of stillbirth. Because of this, many patients with elevated MSAFPs, having made it through the anxiety-provoking amniocentesis and/or ultrasound testing to rule out NTD or ventral wall defects, were then subjected to a regimen of once or twice weekly nonstress testing (or biophysical profiles) after 28-30 weeks of gestation.

When our antenatal testing center became flooded with these patients (representing 5% of our pregnant population), I reviewed the literature looking for instances where high MSAFP was associated with stillbirth in the absence of fetal growth restriction (SGA), and could find few cases where the stillborn fetus was appropriately grown. In the above Danish study, only 10 of the 282 nonanomalous stillbirths in the study were in patients whose MSAFP was > 2.5 MoM. The RR of stillbirth in this category was 2.9, but, after adjusting for LBW, the RR was not statistically significant (0.9). Unfortunately, Krause et al did not account for how many of the LBW stillbirths in the high-MSAFP category were SGA, but from other studies one could assume that a large proportion was.

The study tells us that patients with extremely low-MSAFP levels (0.025 MoM) are at greater risk for preterm birth, low birth weight, and spontaneous abortion. Although a few reports in the literature have shown similar results, low MSAFP has gotten far less attention than high MSAFP, and interestingly, elevated HCG, which may be an even better predictor of adverse outcome than high or low MSAFP, has barely raised a ripple of interest.

It is not completely clear why elevations of MSAFP and HCG portend trouble. However, it is likely the placenta is the culprit responsible for the adverse outcomes. Since AFP is produced almost exclusively by the fetus, whatever is in the maternal circulation (in microgram amounts compared with milligram amounts in the fetus) gets there across the placenta. Usually the placenta grudgingly allows AFP across, but when it acts as an inefficient excluder of AFP in the second trimester, it undoubtedly is giving a warning that it may be a poor supplier of oxygen and nutrients in the third trimester. On the other hand, HCG is a product of the placenta and elevations of HCG represent either greater production or release of the substance from placental cells. In vitro studies have shown that the placenta releases HCG under the influence of hypoxia.

The big question is what to do when components of a triple screen suggest a higher rate of adverse outcome? Although our record so far for preventing preterm birth is dismal, with "raised antennas" we might possibly do better. Certainly spontaneous abortion would be difficult to prevent, and infant death often results from factors that cannot be controlled, even when caregivers are forewarned. Perhaps because of this, many have concentrated on preventing stillbirth (through timely delivery) as a way to have a positive impact. However, doing serial nonstress tests on every patient with an abnormal triple screen is an inefficient way to identify fetuses most apt to be snatched from death's jaws. A better way would be to narrow down the group to be watched by performing 1 ultrasound after 30 weeks on those with worrisome triple screens and identifying those that have small-for-dates fetuses. By performing umbilical artery Dopplers in those fetuses with estimated fetal weights below the 10th percentile (or abdominal circumferences below the 5th percentile) one could more precisely identify the truly compromised fetus that would benefit from timely delivery.

By concentrating on the undergrown fetus one could

prevent fetal death in those most likely to be stillborn and, perhaps, through improvement in uterine blood flow by lateral recumbent positioning and by optimizing the timing of delivery through comprehensive fetal Doppler testing, we could also improve overall neurological outcome.

Not only would this "coned down" version of fetal surveillance most efficiently prevent most stillbirths in patients with elevated MSAFP, but it would be more cost effective. About 5% of all patients will have an MSAFP above 2.5 MoM. Weekly NSTs or biophysical profiles starting at 30 weeks would result in an average of 8 to 10 tests per pregnancy (that might not provide the clues to a fetal death 5 to 6 days later). Doubling up on the testing (biweekly) would result in 16 to 20 investigations per patient. On the other hand, 1 third-trimester ultrasound should identify most, if not all, of the SGA fetuses in the at-risk group. Using the Danish RR of 2.8 in high MSAFP, one would expect an incidence of SGA of 28%, at most, leaving the remaining 72% to have a test-free remainder of their pregnancies. The SGA pregnancies would then be followed with serial Doppler evaluations, which, by providing early evidence of fetal compromise as shown in many studies, including 2 meta-analyses, is far more efficient in optimizing perinatal survival than NSTs. And from a public health standpoint, the cost savings would be prodigious. ❖

Suggested Reading

1. Waller DK. *Obstet Gynecol*. 1996;88:816-822.
2. Divon M. *Am J Obstet Gynecol*. 1996;174:10-14.
3. Benn PA, et al. *Obstet Gynecol*. 1996;87(2):217-222.
4. Marsal K. *Baillieres Clin Obstet Gynaecol*. 1988;2: 125-144.

Malignant Potential of Positive Peritoneal Cytology in Endometrial Cancer

ABSTRACT & COMMENTARY

Synopsis: *Evidence suggests that endometrial cancer cells found in the peritoneal cavity usually disappear within a short time and seem to have a low malignant potential.*

Source: Hirai Y, et al. *Obstet Gynecol.* 2001;97: 725-728.

Hirai and colleagues report a study of 50 patients with clinical stage I-II endometrial cancer in whom the disease was completely surgically resected and positive peritoneal cytology was found at surgery. The purpose of the study was to investigate the malignant potential of positive peritoneal cytology in endometrial cancer. A tube for cytologic analyses was inserted into the peritoneal cavity when closing the abdomen. The peritoneal cavity was irrigated with physiologic saline, and washings were obtained through the tube 7 and 14 days after the operation. Persistence of positive peritoneal cytology was observed in 4 of 7 patients with adnexal metastasis, 0 of 9 patients with nodal disease, and 1 of 34 patients with disease confined to the uterus, for a total of 10% (5 of 50). In the remaining 45 (90%) patients, no malignant cells were found in any of the washings. Hirai et al concluded that the current series suggests that endometrial cancer cells found in the peritoneal cavity usually disappear within a short time and seem to have a low malignant potential. They also theorized that only malignant cells from special cases, such as adnexal metastasis, may be capable of independent growth, and are possibly associated with intraperitoneal recurrence.

COMMENT BY DAVID M. GERSHENSON, MD

The influence of positive peritoneal cytology in patients with endometrial cancer has been a topic of great controversy over the past several years. Although several early studies strongly suggested that positive peritoneal cytology had an independent adverse effect on relapse and survival, findings from more recent studies have indicated that peritoneal cytology is not an independent prognostic or risk factor. In other words, other prognostic factors—depth of myometrial invasion, histologic grade, histologic type, and lymph node status—are much more important in determining outcome. If a patient has positive peritoneal cytology but no other unfavorable risk factors, current philosophy dictates that no adjuvant therapy is recommended. The current study gives some credence to this therapeutic strategy. Even though peritoneal cytology may be positive, the cells may not have metastatic potential or be viable for long periods of time. As Hirai et al also point out in their article, these findings also have implications for the debate about dissemination of endometrial cancer cells at the time of hysteroscopy. Current evidence strongly suggests that malignant cells can be disseminated into the peritoneal cavity at the time of hysteroscopy, but this study lends support to the theory that those cells have low malignant potential. I find this study to be simplistic in its design but potentially important in elucidating the true meaning of positive peritoneal cytology in patients with endometrial cancer. ❖

Combined Bisphosphonate and Hormone Treatment

ABSTRACT & COMMENTARY

Synopsis: *Estrogen combined with risedronate increased bone mineral density slightly more than estrogen alone.*

Source: Harris ST, et al. *J Clin Endocrinol Metab.* 2001;86:1890-1897.

Harris and colleagues report the results of a multicenter, 1-year, double-blind, placebo-controlled study of the effect on bone mineral density of risedronate (5 mg daily) combined with conjugated estrogens (0.625 mg daily) compared with estrogen alone in a total of 524 women. Forty-eight percent of the patients also received medroxyprogesterone (5 mg) in a sequential regimen. At the end of 1 year, both treatment groups increased bone mineral density. (*See Table*).

The only differences that achieved statistical significance were those in the femoral neck and midshaft radius. Bone biopsies in a subset of patients demonstrated normal bone structure and mineralization in both groups. After 1 year, there were 4 new vertebral fractures (2.6%) in the hormone-only group and 3 (1.8%) with the combined treatment; however, this study had insufficient power to detect meaningful differences in fractures.

Table

Gain in BMD with Treatment

	Lumbar spine	Femoral neck	Midshaft Radius
Hormone therapy alone	4.6%	1.8%	0.4%
Combined risedronate & hormone therapy	5.2%	2.7%	0.7%

COMMENT BY LEON SPEROFF, MD

There is growing recognition that not all postmenopausal women respond to treatments aimed at the prevention of bone loss. Clinicians have rapidly assumed that the solution is to combine treatments. There are 2 important questions:

1. Will a slightly better gain in bone density mean better protection against fractures?
2. Will a poor responder to 1 treatment respond to an alternative treatment?

Adding alendronate or risedronate to postmenopausal hormone therapy produces a gain in bone density that is about 1-2% greater than with single treatment, indicating that each works through a different mechanism. There is no doubt that both lack of bone loss and a gain in bone mineral density correlate with a reduction in fractures. However, that does not mean that a 7% gain protects against fractures better than a 5% gain. One piece of evidence that suggests a difference in bone density is not the whole story is the fact that raloxifene produces a smaller increase in vertebral bone density compared with estrogen and alendronate, yet the 3 agents are associated with essentially identical reductions in vertebral fractures. No study, thus far, has had a sufficient number of patients followed long enough to provide reliable fracture information with combined therapy compared to single agent treatment.

The percentage of postmenopausal women who respond poorly to single agent treatment varies from 5-20% in various studies. This is a substantial number, and underscores the recommendation to screen 65-year-old women with bone density measurements even if they are on osteoporosis prevention treatment. This would detect the poor responders and provide the opportunity for intervention. However, studies of this group of women have yet to appear in the literature. At this time we can only provide the proper intervention, follow the patient, and learn from the patients.

Recommended Evaluation and Intervention for Poor Responders:

1. Rule out other causes of osteoporosis.
2. Make sure calcium and vitamin D supplementation is adequate.
3. Make sure compliance with the treatment is appropriate.
4. Add another antiresorptive agent to the treatment regimen.
5. After 2 years, assess bone density response.

The bone world has expressed concern that combining 2 agents that both inhibit bone resorption might over time interfere with the dynamics of bone remodeling and ultimately yield more fragile bone. This is speculation at the present time, and the biopsy results in this study indicating normal bone morphology and mineralization are reassuring. This has also been reported with combined alendronate and estrogen treatment.[1] In addition, tetracycline labeling appeared in the biopsy specimens indicating that the necessary bone turnover to repair microdamage was

taking place.

At the present time, it is premature to assume that combined agent therapy will yield better fracture protection. We need evidence from bigger studies with longer follow-up. ❖

Reference

1. Bone HG, et al. *J Clin Endocrinol Metab.* 2000;85: 720-726.

Outcome of Surgical Treatment for Superficial Dyspareunia from Vulvar Vestibulitis

ABSTRACT & COMMENTARY

Synopsis: *Approximately 80% of patients with vulvar vestibulitis are improved following surgery.*

Source: Schneider D, et al. *J Reprod Med*. 2001;46(3): 227-231.

Between 1993 and 1997 schneider and colleagues performed 69 vestibulectomy procedures for women with dyspareunia. Although it is unclear from the text, it appears that almost all of these women would fit into the classification of chronic vulvar vestibulitis. Unfortunately, only 54 of the patients responded to the questionnaire that was mailed.

Schneider et al divided the patients into "primary" vestibulitis and "secondary" vestibulitis. Primary included those women who had always had painful intercourse, and secondary included those who developed it later. Four of 5 women had received medical therapy of some type prior to surgery.

There were no intraoperative problems, but 15% of the patients had postpartum complications. Except for 1 patient with heavy bleeding, the complications were mild. Nine patients required repeat surgery to excise a remaining piece of tissue that caused pain with intercourse. Thirty-four percent of the women who had surgery found it necessary to seek medical therapy for continuing dyspareunia of some degree.

Schneider et al noted that those women who had the most severe disease prior to surgery were most likely to benefit from it. That is, 96% of those women who were unable to have intercourse preoperatively reported moderate to excellent results, but only 70% of those who could occasionally have intercourse prior to surgery had a similar improvement.

Schneider et al conclude that surgery is probably the most effective method of therapy for vulvar vestibulitis, but that all women should have conservative methods attempted prior to resorting to surgical therapy.

COMMENT BY KENNETH L. NOLLER, MD

The chronic vulvar vestibulitis saga continues. While medical therapies come and go, there is certainly no doubt that the single most effective therapy for this condition is vestibulectomy. However, it is also clear that vestibulectomy is not 100% successful. While different success rates have been reported in the literature (including 1 with no failures) it has been my observation that only 60-80% of women have marked benefit from the procedure.

I particularly like this paper. It has one main flaw (see next paragraph), but overall is a fair appraisal of the results of surgery for vulvar vestibulitis. The fact that Schneider et al emphasize that women with more severe problems that have not been helped by medical therapy respond better than women with more minor symptoms is an important fact for clinicians who treat this condition to note.

A shortcoming to this study is that it tells us nothing about the success of medical therapy. That is, it is a study only of those women who failed medical therapy and had surgery. While Schneider et al make this point clear in their paper, casual reading of the manuscript might lead some clinicians to assume medical therapy has no role in the treatment of vulvar vestibulitis. Indeed, it has been my experience that patients who are immediately offered surgical therapy have minimal relief of symptoms postoperatively far more commonly than women who have tried all medical measures first. ❖

Special Feature

Comparison Groups and Generalization

By Kenneth L. Noller, MD

During the past several years, i have tried to draw attention to the extreme importance of study design in clinical investigation in my comments to articles, and in a few of these special features. In this piece I want to focus on aspects of study planning and interpre-

tation I have not previously covered.

There are 3 important questions to ask each time you read a paper:

1. What type of study is this?
2. If comparison (control) groups are used, are they appropriate?
3. Are the authors' conclusions appropriate, or have they generalized results that are applicable only to a small group?

There is a fourth important consideration that is largely beyond the ability of most of us to decipher—the appropriateness of the statistical analyses. In general, we must rely on the journal to have considered this aspect of the publication.

In a previous piece I dealt with the various types of studies that are commonly presented in the medical literature and their relative ratings. In this article I will deal with the concept of comparison (control) groups and generalization of results.

The Myth of Randomization and Controls

There is no doubt that the Random Clinical Trial (RCT) is the most powerful type of study currently published in the medical literature. In this type of study the investigators recruit study participants and, typically, assign them either to treatment or nontreatment (placebo agents). In many chemotherapy studies patients are randomly assigned to a new drug protocol or a standard drug protocol. Various versions are possible. Although there are occasional mistakes made in randomization, it is a rather simple task that can be accomplished by the use of any table of random numbers, whether printed or generated by a computer. The more important aspect of random assignment is recruitment of the study participants who will be randomized. In virtually all cases, the group to be randomized is not representative of the general female population. For example, if a chemotherapy agent is to be evaluated, perhaps only women with ovarian cancer would be eligible for recruitment.

Another subtlety is that those women who volunteer to be in a RCT may not be representative of all women with the disease. For example, if an ovarian cancer chemotherapeutic regimen is to be tested, it is possible that only women who were feeling better (or worse) or women who were highly educated (or less well educated) would tend to volunteer. The point is that there are multiple ways to invalidate a randomized trial. Since results of such RCTs might result in new medications (for example, antibiotics) being widely used (and not just in patients with similar histories to those in the trials), the chance that error might result in appropriate drug usage is significant.

The other type of study which directly compares groups is the case-control study. This is an efficient and widely used study design methodology. A group of women with a given disease or a given exposure, or a given surgical outcome, are compared to a group of women without the disease, exposure, or surgery. In almost all cases, there is no problem establishing the "case" group. For example, an investigator might choose to study the differences between women with and without endometrial adenocarcinoma. The group of women with the disease is easy to establish, although even there the investigator must be aware that bias can be introduced (for example, the patient seen at a tertiary referral center might not be representative of all women with endometrial adenocarcinoma). The real problem in a case-control study is the development of an appropriate comparison (control) group. In our example, what would be the appropriate comparison group to women with endometrial adenocarcinoma? Certainly, there should be some age matching as younger women virtually never develop the disease. The investigators must struggle with many decisions regarding matching. In general, it is better to match on very few variables because no statement can be made regarding a matched variable. For example, if those with and without uterine cancer were matched for the use of hormone replacement therapy (HRT) it would not be possible to draw any conclusion regarding the role of HRT since it would be present to an equal extent in both groups.

I have never encountered a "perfect" control group in any case-control study. It is virtually always possible to quarrel with some of the decisions made by the investigators in developing their controls. However, thoughtful investigators can come close, and can adjust for some variables with appropriate statistical analyses. Overall, I like the case-control study design, but know it has limitations.

Generalization of Results

Let's assume that you have carefully reviewed an article, you have determined the type of study that is being presented, you have carefully examined the comparison group and found it satisfactory, what then remains? The answer, of course, is that the results of the study must be carefully applied to the appropriate population base when drawing conclusions.

Perhaps an example would be helpful to make my point. Recently I was asked by a major OB/GYN journal to review an article in which the stated purpose of the study was to determine whether it is appropriate to follow women with minimally abnormal Pap smears. It was a cohort study, and followed the women in the study pop-

ulation for 3 years. They concluded that it was inappropriate to follow women with minimally abnormal Pap smears because so few return for follow-up visits. Their blanket conclusion was applied to all women. However, the study population consisted of extremely poor, itinerant women in a rural setting. Many of the women did not speak English and had virtually no education. It was clearly inappropriate for the authors to conclude that longitudinal follow-up of women with minimally abnormal Pap smears was inappropriate. Rather, they should have concluded that such follow-up of poor, itinerant women, and poorly educated women in a rural setting might not be managed appropriately with cytology follow-up. That conclusion might also be true for rich urban women, but the authors did not study that segment of the population

Because so much emphasis recently has been placed on study design, I am finding that over-generalization of study results is the most common major error in published manuscripts. ❖

CME Questions

1. **Which of the following is *not* likely for women with estrogen receptor-positive breast cancer who then decide to take HRT?**
   a. Lower overall mortality
   b. Decreased risk of dementia
   c. Lower risk of breast cancer recurrence
   d. Increased risk of osteoporosis

2. **In the study by Hirai et al, in which 50 patients with endometrial cancer and positive peritoneal cytology were reported, persistence of positive peritoneal cytology was observed most frequently in association with:**
   a. disease confined to the uterus.
   b. adnexal disease.
   c. lymph node involvement.
   d. cervical involvement.
   e. upper abdominal disease.

3. **According to the paper by Schneider et al, which one of the following groups of women with vulvar vestibulitis is most likely to benefit from vestibulectomy?**
   a. Those who have surgery before other treatment
   b. Those who have failed antifungal therapy
   c. Those who are totally unable to have intercourse
   d. Those who have previously failed surgical treatment

4. **The following statements are true regarding osteoporosis prevention therapy *except* :**
   a. Bisphosphonate and estrogen treatment produce comparable effects on bone density.
   b. It is worthwhile to try to gain as much bone density as possible.
   c. All the currently approved agents for the prevention of osteoporosis produce comparable effects on reduction of vertebral fractures.
   d. There is concern that long-term follow-up of treated patients will yield different results than short-term bone density studies.

Readers are Invited. . .

Readers are invited to submit questions or comments on material seen in or relevant to *OB/GYN Clinical Alert*. Send your questions to: Robert Kimball, *OB/GYN Clinical Alert*, c/o American Health Consultants, P.O. Box 740059, Atlanta, GA 30374. For subscription information, you can reach the editors and customer service personnel for *OB/GYN Clinical Alert* via the internet by sending e-mail to robert.kimball@ahcpub.com. ❖

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