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INSIDE

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Decline in Breast Cancer and Reduced Use of Hormone Therapy

ABSTRACT & COMMENTARY

By Leon Speroff, MD, Editor

Synopsis: *Breast cancer statistics indicate a rapid decrease in prevalence immediately after the publicity surrounding the reports from the Women's Health Initiative.*

Source: Ravdin PM, et al. A sharp decrease in breast cancer incidence in the United States in 2003. San Antonio Breast Cancer Symposium, December 14, 2006.

Ravdin and colleagues from the University of Texas M.D. Anderson Cancer Center reported a 7% decrease (14,000 fewer cases) in the incidence of breast cancer in 9 regions of the U.S. in 2003.[1] This decrease occurred in women over age 50 and consisted of two to three times as many estrogen receptor positive tumors. The steepest decline was observed in women ages 50-69. Clarke and colleagues from California reported the breast cancer incidence for the years 2003 and 2004 in the Northern California Kaiser program and for the 13-county Kaiser catchment area.[2] Coincident with the post-Women's Health Initiative decline in postmenopausal hormone use, the breast cancer incidence declined 10% in Kaiser members and 11% in the area's population.

COMMENTARY

These reports highlight the currently most important unanswered question: Does postmenopausal hormone therapy cause an increase in breast cancer or do the epidemiologic data reflect an impact of hormone therapy on pre-existing tumors? The most striking feature of these recent reports is the short latent period between discontinuation of hormone therapy and a reduction in prevalence. This is consistent with the uniform findings in case-control and cohort studies of an increase in breast cancer risk only in current users, with a rapid reduction after cessation of treatment. The current reports are consistent with breast cancer statistics derived from

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the area around Geneva, Switzerland, indicating the other side of the coin. Beginning in 1997, the peak of breast cancer incidence in the Geneva area increased in a younger group of women (ages 60-64), and the increase occurred only in Stage I and Stage II disease with estrogen receptor positive tumors in hormone users.[3]

These effects of hormone therapy are in keeping with the multiple reports of better outcomes in hormone users diagnosed with breast cancer because of better-differentiated tumors,[4, 5] an effect that can be interpreted as a beneficial consequence. Another finding that is consistent with an effect on pre-existing tumors is the fact that not a single study thus far has reported a risk increase for non-invasive disease. If hormone therapy were initiating (causing) new tumor formation, one would expect to see an increase in in-situ disease.

Even the M.D. Anderson Cancer Center authors pointed out that their data most likely primarily reflect existing cancers just below the detection limit in 2002 that slow or stop their growing. Thus, a serious question is raised: What will the statistical data show in the coming years? Will some of the pre-existing tumors be overcome by body defenses and disappear? Will tumors that emerge later be of later stage and grade disease with poorer outcomes? At this point in time, we must recognize that hormone therapy could be having a favorable effect on breast cancers. ■

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Breast Cancer Risk in Finnish Women Using Estrogen-Only Therapy

ABSTRACT & COMMENTARY

By Leon Speroff, MD, Editor

Synopsis: *A cohort study from Finland concludes that long-term users of oral and transdermal estradiol have an increased risk of breast cancer.*

Source: Lyytinen H, et al. Breast cancer risk in postmenopausal women using estrogen-only therapy. *Obstet Gynecol.* 2006;108:1354-1360.

Lyytinen and colleagues from Helsinki reported the results of a cohort study assessing the risk of breast cancer in postmenopausal Finnish women using oral, transdermal, and vaginal estrogen products containing either estradiol or estriol.[1] The women were identified as those who purchased any type of estrogen in 1994-2001. Women who used conjugated equine

estrogens (387) and women who used estrogen for less than 6 months (172,309) were excluded, leaving 110,984 women in the final cohort. Breast cancer was recorded to the end of 2002. The use of estradiol for 5 or more years was associated with an increased risk of 1.44 (CI = 1.29-1.59). The risk was similar comparing oral and transdermal estradiol therapy. An increase was observed in both localized and metastatic disease. A statistically significant increase was noted with carcinoma-in-situ, 2.43 (CI = 1.66-3.42).

COMMENTARY

Only 7% of Finnish postmenopausal women use hormone therapy for more than 5 years. This study reports an increase in breast cancer risk in this long-term user group of women. No increase in breast cancer risk was detected either in association with estriol given orally or with vaginal estrogen products. It is inappropriate to conclude, as the authors do, that these formulations can be used without risk. To make this conclusion, users and nonusers of these formulations would have to be identical in terms of breast cancer risk factors, and to be comparable in terms of bioequivalent blood levels of estrogen. Only then could a valid comparison be made. This study cannot and does not adjust for these factors.

The use of estradiol patches was associated with a statistically significant increase with doses of 30 to 60 µg per day, used for 5 years or more. However, neither lower doses nor higher doses demonstrated a statistically significant change. Because there were only 599 lower-dose users and 611 higher-dose users compared with 6845 using the standard dose, the power was not sufficient to reveal a dose-response relationship. The authors interpreted their findings as indicating that both oral and transdermal routes of administration shared an increased risk of breast cancer in long-term users. There is a major strength in this study. The use of postmenopausal hormone therapy in Finland can be accurately recorded because all treatments must be prescribed and then paid for by the National Social Insurance Institution. However, the study is affected by an overwhelming problem: the results are questionable because of an inability to control for confounders.

This is the first epidemiologic study, to my knowledge, to report a statistically significant increase in the risk of in-situ breast cancers. But before we accept that conclusion, consider that there were only 141 in-situ cancers in the cohort, and the increased ratio of 2.43 (CI=1.66-3.42) reported for use of 5 years or more was based on only 13 cases. The authors themselves caution us that hormone users visited physicians at a greater rate and more regularly, and thus, the increase in in-situ disease may reflect a detection bias. In this paragraph, they raise the real possibility of confounders in the hormone users, but then they argue to the contrary in another paragraph. You can't have it both ways.

The major problem with this study is that the risk was expressed as incidence ratios, calculated by dividing the observed number of cases by the numbers expected (based on the general statistics in Finland). Therefore, the study could not be controlled for confounders. It is well demonstrated that hormone users differ when compared to non-users in terms of recognized risk factors for breast cancer. The differences include a greater prevalence of mammography among hormone users. A good example can be found in the report from the Nurses' Health Study that, like the cohort from Finland, indicated an increased risk of breast cancer with long-term users of estrogen-only.[2] The long-term users in the Nurses' Health Study had more bilateral salpingo-oophorectomies, more nulliparity, more benign breast disease, greater alcohol consumption, and they were thinner—all factors that make a comparison of users to nonusers very difficult.

The authors of the Finnish report argue that "there are no socioeconomic differences between postmenopausal hormone therapy users and the general population in Finland," citing a previous report. It is a bit mind boggling that this citation is not totally accurate. The report in 1999 was based on population surveys and measured only two things: length of education and rural vs. urban living.[3] The authors concluded that a lack of socioeconomic differences was present in Finnish women under the age of 55, but older postmenopausal had more years of education. In addition, there were regional differences at all ages, with the current use of hormone therapy being most common in the Helsinki area (especially among older women). Therefore, the 1999 study does not imply a lack of differences in hormone users in Finland; in fact, just the opposite. Age information is not provided in the current report, but I would expect the longer-term hormone users to be an older group of women, and according to the 1999 Finnish report, they do differ when compared to the general population of Finland. Remember, this cohort study is not comparing users with nonusers. It compares users to general population statistics. Therefore, we cannot know whether the results of this study reflect long-term use of estrogen, or whether the results of this study reflect a greater prevalence of risk factors and mammography in the hormone-using group.

The accompanying editorial is written by a distinguished statistician.[4] He reviews the results in the Women's Health Initiative (WHI) and, to my surprise and disappointment, he offers no criticisms of the current report from Finland. He concludes that "longer use of combined estrogen-progestin therapy undeniably increases" breast cancer risk "likely to a greater extent than exposure to estrogen alone." He further argues that estrogen-progestin therapy "causes" (his word) more breast cancers than the number of endometrial cancers prevented.

In the latest report from the estrogen-progestin arm of the WHI, the overall risk of breast cancer in the treated estrogen-progestin group was the same as previously reported by the WHI (1.24; CI=1.02-1.50).[5,6] However, after adjusting for the multiple factors recognized to influence the risk of breast cancer, the hazard ratio was 1.20, and no longer statistically significant (CI=0.94-1.53). The WHI results are not consistent with a large effect, and the results are finding it hard to escape the influence of differences in risk factors and personal characteristics. This further emphasizes the weakness in the current Finnish cohort study: the inability to control for confounding risk factors. Thus, in my view, the article and the editorial both overstate the case, and we still don't know whether hormone therapy is associated with a small risk of breast cancer or whether the epidemiologic data reflect an impact on preexisting tumors. ■

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Pregnancy after Uterine artery embolization for uterine fibroids

ABSTRACT & COMMENTARY

By John C. Hobbins, MD

Professor and Chief of Obstetrics, University of Colorado Health Sciences Center, Denver

Dr. Hobbins reports no financial relationship to this field of study.

Synopsis: *Uterine artery embolization has become an increasingly popular procedure for treatment of uterine fibroids, but there are only a few studies in the literature dealing with the outcomes of pregnancy following this form of modestly invasive therapy.*

Source: Walker WJ, et al. Pregnancy after uterine artery embolization for leiomyomata: A series of 56 completed pregnancies. *Am J Obstet Gynecol.* 2006;195:1266-1271.

In a recent paper, Walker and McDowell contacted 1200 patients having had this procedure since 1996 at either the Royal Surrey County Hospital or the London clinic. One hundred eight women had tried to become pregnant and 33 succeeded at least once. In total, the authors had data on 56 completed pregnancies.

There were 33 live births (58.9%) in this group of patients. Also, there were 17 (30.4%) miscarriages, 6 preterm births (18.2%), 2 (3.6%) stillbirths, and 1 ectopic pregnancy.

■ COMMENTARY

Since embolization works quite well in shrinking fibroids by starving them, one cannot help but wonder what the temporary interruption of a portion of the uterine circulation will do to a uterus that is later being asked to support a fetus and placenta that are substantially larger and more demanding than the fibroid that was embolized. In fact, in a recent review of fibroid embolization by Olive et al in 2004, it was recommended that, until further evidence is available, those contemplating later pregnancy should have another form of therapy for uterine fibroids.

A glance at the results in which the incidence of miscarriage, preterm birth, and, simply, the chances of not having a successful pregnancy, are well above that of the overall population, might well raise some concern about the procedure. However, those having this procedure are not the "overall population." For example, the average age

of the patients in the study was 37.5 years and 58% of these pregnancies were in those who were never pregnant before (a loaded deck for pregnancy-related complications). The average age of those having miscarriages was close to 39 years. Although the rate of spontaneous abortion is stated to be 10 to 15%, this increases two- to three-fold for those who are 40 years of age or older. Also, one would expect at least a 2 fold increase in preterm birth in women over 35, so the 18% rate in this study roughly matches up to what would be expected in this population.

Last, the Cesarean section rate is quite high at 72.7 % in these patients. However, the major indication for the Cesarean sections was "fibroid"—a self-fulfilling situation. I would guess that in the USA the Cesarean section rate in a group of women in their first pregnancies, whose average age is 38, would be close to that figure.

So, my take on this study is that the glass is a little more than half full for patients wishing to become pregnant after uterine artery embolization, but whatever problems they will encounter are less about the embolization of their fibroids and more about their inherently greater predisposition toward adverse pregnancy outcome. ■

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Additional support OCP's reduce ovarian cancer risk

ABSTRACT & COMMENTARY

By Robert L. Coleman, MD

Associate Professor, University of Texas; M.D. Anderson Cancer Center, Houston

Dr. Coleman is on the speaker's bureau for GlaxoSmithKline, Bristol-Myers Squibb and Ortho Biotech.

Synopsis: *Reproductive risk factors for ovarian cancer in carriers of BRCA1 of BRCA2 mutations: a case-control study.*

Source: McLaughlin JR, et al. *Lancet Oncol.* 2007;8:26-34.

Women with pathogenic mutations in BRCA1 or BRCA2 are known to be at substantially higher lifetime risk for ovarian and breast cancer than the general population. The degree to which reproductive factors affect this risk has been estimated but is limited by studies of small sample size or faulty methodology. McLaughlin and colleagues conducted a matched case-control study in women who were known BRCA carriers. Case patients were 799 women with ovarian cancer who were carefully matched (median 3:1) with 2424 control patients without ovarian cancer on the basis of age, BRCA mutation, country of residence, and history of breast cancer. Each completed a questionnaire detailing their reproductive history. The authors identified that use of oral contraceptives reduced the risk of ovarian cancer in BRCA1 (odds ratio: 0.56, 95% CI: 0.45-0.71, $p < 0.0001$) and BRCA2 (0.39, 0.23-0.66, $p = 0.0004$) mutation carriers. Breastfeeding reduced the risk of ovarian cancer in BRCA1 mutation carriers but not BRCA2 mutation carriers. Parity was associated with a protective effect on BRCA1 mutation carriers (0.67, 0.46-0.96, $p = 0.03$) but was detrimental for BRCA2 mutation carriers (2.74, 1.18-6.41, $p=0.02$). Tubal ligation had no apparent association with ovarian cancer risk. The authors concluded that oral contraceptives could be used as a means to prevent ovarian cancer in carriers of BRCA1 and BRCA2 mutations. The reason for the observed increased risk of ovarian cancer in patients with deleterious BRCA2 mutations is unknown.

COMMENTARY

It has been previously documented that the use of oral contraceptives represents one of the few chemoprevention strategies available for women to alter their risk for ovarian cancer. In unselected populations, investigators have documented that "ever" use was associated with an approximately 50% reduction in lifetime ovarian cancer risk and trending analyses support the contention that the longer the duration of use the better protection. Fortunately, ovarian cancer is rare in the population, therefore recommendations for use of steroidal contraception as a chemoprotective agent was largely focused in "high-risk" settings. However, clear documentation that similar effects could be realized in these women is lacking. In addition, other reproductive factors such as parity, breastfeeding and tubal ligation have had a suggested role in reduction of ovarian cancer risk primarily through factors related to ovulation and ovarian steroidogenesis. However, the degree to which these factors modify risk in patients with substantially higher lifetime risk of cancer is largely unknown.

The investigators of the current report represent one of the few large Study Groups who are gathering data in population-based studies to address these issues in women

who carry deleterious mutations in BRCA1 or BRCA2. Limitations of retrospective analyses are widely known and appreciated in the context of making cause and effect statements. However, carefully controlled analytical studies, such as the current report, aid in making valuable inferences into populations being studied. That being said, there are a few important considerations that should be borne in mind in interpreting the results outlined in this excellent report; first, both incident and prevalent cases of ovarian cancer are included. Some of the women included in the risk assessment were diagnosed 10 years or longer following enrollment. The potential bias here is that these women may not represent the general population of ovarian cancer patients. If the risk factors under study are related to overall cancer survival, information from these patients may misrepresent the impact of risk reduction in the general population. To their credit, the authors did repeat the analysis restricting enrollment to those completing the questionnaire within 3 years of diagnosis and similar results (with wider confidence limits) were found. Second, no pathological review was undertaken on the case patients. This means the confidence of diagnosis (including epithelial, borderline and metastatic) is based on patient reporting and natural incidence. However, the "softest" data in the report relates to information regarding duration of use, which is a limitation in retrospective reports. Women in this study were asked to estimate the temporal use of oral contraceptives and the duration of breastfeeding. Trending was seen in use of oral contraceptives and parity but not in breastfeeding. Interestingly, ovarian cancer risk is increased with increasing parity for patients with BRCA2 mutations, but decreased in BRCA1 patients. In fact, when compared to each other there is a significant difference, suggesting the hypothesis that parity affects ovarian cancer risk primarily through ovulation interruption may be faulty and related to other factors.

Overall, the report adds confidence that there may be an effective risk-reducing strategy for ovarian cancer in truly high-risk women. Prospective data are desperately needed to define this effect further. ■

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How Best to Medically Manage Ectopic Pregnancy?

ABSTRACT & COMMENTARY

by Frank W. Ling, MD

Clinical Professor, Dept. of Obstetrics, University of Colorado Health Services, Denver

Dr. Ling reports no financial relationship to this field of study.

Synopsis: *Single dose and multi-dose regimens for methotrexate treatment of ectopic pregnancy are equally efficacious.*

Source: Alleyassin A, et al. *Fertil Steril.* 2006;85:1661-1666.

These Iranian investigators randomized treatment of 108 patients with unruptured ectopic pregnancy to either a single dose protocol or a multiple dose protocol. The single dose regimen was successful in 48/54 cases (88.9%), while 92.6% (50/54) patients responded to the multiple-dose regimen. The 6 failures in the single-dose protocol all responded to a second course of treatment. In the multi-dose group, 2 required surgery while the other 2 responded to a second course of therapy. Fifteen patients in the single-dose and 20 patients in the multi-dose group had side effects (dermatitis, pruritis, abdominal pain, stomatitis, diarrhea, and elevated liver enzymes).

COMMENTARY

The two protocols used are very familiar to this feeble old mind. I was fortunate enough to have participated with Dr. Thomas Stovall and others in the development of the early multi-dose and single-dose methotrexate protocols.

In the multi-dose protocol used in this study, the patient received 1 mg/kg methotrexate on days 1, 3, 5 and 7 with leucovorin 0.1 mg/kg on days 2, 4, 6, and 8. These injections were continued until the hCG levels decreased 15% in 48 hours or 4 doses of methotrexate had been given. In the single-dose regimen, which was developed after the multi-dose protocol, the patient received methotrexate 50 mg/m2. If measurement of hCG on days 4 and 7 did not show a decrease of 15%, a second course of

therapy was given.

This is by no means the last word on the medical treatment of ectopic pregnancy, but it goes a long way to answer some of the questions. Advantages of the single-dose regimen are obvious: less medicine, fewer injections, less laboratory testing, and less surveillance. If the outcomes are similar, why not use the simpler treatment protocol? This is the first randomized study, but it appears to support the other case series.

The astute reader should recognize that the medical treatment of ectopic pregnancy may not be for every practice. For example, if you cannot reliably diagnose an unruptured ectopic pregnancy without surgery, medical treatment is an illogical option. You might as well treat the ectopic surgically while you're already in there making the diagnosis. Certainly, ruptured ectopic pregnancies that result in a patient being hemodynamically unstable should be treated surgically, not medically. Also, the patient needs to be reliable enough to follow up with you as prescribed. Otherwise, you don't have the opportunity to follow through with the needed treatments and laboratory tests.

Should you treat an ectopic medically if you're not comfortable doing so? I think the answer to that is the same as anything else in the practice of medicine, ie, you can become comfortable if you gain experience under controlled circumstances. For many years, we would field questions over the phone from people who wanted to be reassured that what they were doing was correct. We co-managed patients with clinicians in town. We tried to share as much of our experience as possible. As a result, today, medical treatment for the unruptured ectopic pregnancy is considered mainstream.

So the teaching point of the article is that the 2 regimen are comparable based on the best type of study design, randomized. The unspoken teaching point is that medical treatment of the unruptured ectopic pregnancy is a service that can be incorporated into a women's health practice. ■

Reference

1. Alleyassin A, et al. Comparison of success rates in the medical management of ectopic pregnancy with single-dose and multiple-dose administration of methotrexate: a prospective, randomized clinical trail. *Fertil Steril.* 2006;85:1661-1666.

Phenotypic Differences between Male Physicians, Surgeons, and Film Stars: Comparative Study

ABSTRACT & COMMENTARY

by John C. Hobbins, MD

Professor and Chief of Obstetrics, University of Colorado Health Sciences Center, Denver.

Dr. Hobbins reports no financial relationship to this field of study.

Synopsis: *A paper just emerged in the research section of the* British Medical Journal *that gives new meaning to scientific investigation. The authors noticed early in their training that the taller, better looking students tended to go into surgery, so these Spanish investigators set out to put their observations literally to the test.*

Source: Trilla A, et al. Phenotypic differences between male physicians, surgeons, and film stars: comparative study, *BMJ.* 2006;333:1291-1293.

The investigators enticed 14 male surgeons and 16 male physicians (internal medicine and sub-specialists) to submit recent photographs of themselves to the investigators and to indicate how tall they were. In addition, photographs of 4 actors playing doctors were used as controls. They were George Clooney (E.R.), Patrick Dempsey (Grey's Anatomy), Harrison Ford (The Fugitive) and Hugh Laurie (House). Then, 8 women (5 nurses and 3 doctors) were chosen to review the photographs and to independently judge each according to a 1 to 7 "good-looking score" (7 being outstandingly handsome and 1 being ugly). Standard t tests were used for statistical analysis.

The results bore out the authors' hunch. The surgeons were, on average, better looking than the physicians (4.39 versus 3.65; $p = 0.010$) and were taller (179 cm versus 172 cm; $p = 0.01$). The controls had an average good-looking score of 5.96. A spin-off finding was that surgeons tended to have more hair.

In the Discussion Section, some very cogent points were made. Surgeons practice what the authors called "confidence based medicine" (something not quite similar to evidence based medicine), which requires boldness and an ability to tightly control their domain. The authors felt "being taller and better

looking has several evolutionary advantages." Their extra height affords them more opportunity to be "masters and commanders, and gives them a better view of the operating room" (their designated kingdom). Also, their appearance may be enhanced by their environment. For example, there is more oxygen in the operating room, and, because they have a mask on much of the time, their faces are protected from "microtrauma" (a possible anti-aging trick). Many surgeons even wear clogs to add at least two inches to their height.

On the other hand, the authors indicate that physicians tend to have heavy stethoscopes around their necks, which causes them to stoop, thereby making them appear shorter and less attractive. In addition, the mental weight of having to keep up with the voluminous amount of evidence-based literature "grinds them down" and can play havoc on their demeanor and, in turn, their appearance.

COMMENTARY

The major drawback to this study is that surgeons were only pitted against internists—an unfair comparison—and not against OB/GYNs. Also, who said you have to be tall to be called good looking? Last, who is George Clooney? ■

Reference

1. Trilla A, et al. Phenotypic differences between male physicians, surgeons, and film stars: comparative study. *BMJ*. 2006;333:1291-1293.

CME Objectives

The objectives of *OB/GYN Clinical Alert* are:

- To present the latest data regarding diagnosis and treatment of various diseases affecting women, including cancer, sexually transmitted diseases, and osteoporosis;
- To present new data concerning prenatal care and complications, as well as neonatal health; and
- To discuss the pros, cons, and cost-effectiveness of new testing procedures.

CME Questions

3. The following statements are true regarding the use of postmenopausal hormone therapy and the risk of breast cancer except:

a. Most epidemiologic studies report an increased risk of breast cancer associated with postmenopausal hormone therapy.
b. Most studies report an early increase with estrogen-progestin therapy.
c. The Women's Health Initiative disagrees with most of the literature on the issue.
d. The data with long-term users of estrogen only may be influenced by a greater prevalence of breast cancer risk factors in long-term hormone users.

4. The following statements are true regarding the association between postmenopausal hormone therapy and the risk of breast cancer except:

a. A decline in breast cancer prevalence has paralleled a reduction in the use of hormone therapy.
b. The decline in breast cancer is limited to estrogen receptor positive tumors.
c. Hormone therapy has not been associated with an increase in in-situ breast cancer.
d. The decline in breast cancer has been observed throughout the U.S.

Answers: 3(c); 4(b)

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This Month's Issue Focuses on Women's Health

Breast Cancer Rates Have Dropped Since WHI of 2002

Several important papers have been published in the last 2 months, none more important than the realization that breast cancer rates have dropped precipitously since the publication of the Women's Health Initiative (WHI) in 2002. The issue of estrogen-alone (not in combination with a progestin) and the risk of breast cancer is addressed in a new paper, as is the use of herbal supplements to treat postmenopausal vasomotor symptoms in women who have stopped HRT. Finally the duration of treatment of bisphosphonates for osteoporosis gains some clarity with publication of new data from the Fracture Intervention Trial.

The WHI study of combined estrogen and progesterone was halted in 2002 when it was found that women on the drug combination were at increased risk of breast cancer. Prior to the publication of the study, it was estimated that 30% of American women over the age of 50 were taking HRT. Within 6 months of the publication of WHI, half of those women had discontinued HRT. Now preliminary data suggests that breast cancer rates dropped precipitously in 2003 compared to 2002. The decline was most pronounced in women over the age of 50, and the biggest decline was in estrogen-receptor-positive breast cancer. Breast cancer rates had been rising steadily in this country at an average of 1.7% per year until 1998 when the rate began declining at 1% per year. The 7% drop seen in 2003 was the largest single decrease ever seen within a single year. The data was presented at the 29th Annual San Antonio Breast Cancer Symposium by researchers from MD Anderson. In a separate study, researchers from Northern California presented their own data that showed a decrease in hormone use of 68% between 2001 and 2003, and a decrease in breast cancer rates of 10-11%, which was sustained to 2004 (*J Clin Oncology* 2006;24:e49-50). The implication is that the sudden decrease in HRT use is responsible for the decrease rate of breast cancer, a conclusion supported by the dramatic decrease in ER positive cancers in postmenopausal women.

In contrast to the findings of the estrogens/progesterone wing of the Women's Health Initiative, the estrogen-only wing showed no increased risk of breast cancer (*JAMA*. 2004;291:1701-12). This was in contrast to several European studies, including the Million Woman Study, which showed an increased rate of breast cancer with unopposed estrogen (*Lancet*. 2003;362:419-427). Now a new study also suggests that estrogen-only is associated with a slightly increased risk of breast cancer. The study from Finland looked at nearly 85,000 women using oral or transdermal estradiol, 8,000 women using oral estriol (widely used in Europe but uncommonly used in the United States), and 18,000 women using vaginal estrogens for least 6 months were followed from 1994 through 2001. There was no increase risk for breast cancer for estradiol use of less than 5 years. Women who used estradiol for more than 5 years had a relative risk of breast cancer of 1.44 (1.29-1.59). Oral and transdermal estradiol conveyed similar risk. Oral estriol and vaginal estrogens did not increase breast cancer risk. The authors con-

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clude that the use of estradiol for more than 5 years is associated with a increased risk of breast cancer (*Obstet and Gynecol*. 2006;108:1354-1360).

Herbal Supplements to Treat Vasomotor Symptoms

Many women who have stopped HRT have tried herbal supplements to treat vasomotor symptoms. A new study compares the effectiveness of black cohosh, multibotanicals, and soy with HRT and placebo. Researchers from the University of Washington enrolled 351 women who were in menopausal transition or were postmenopausal. They were given black cohosh 160 mg daily, multibotanical with black cohosh 200 mg plus 9 other ingredients, multibotanical plus dietary soy counseling, HRT with conjugated equine estrogen 0.625 mg daily with or without medroxyprogesterone 2.5 mg daily, or placebo. There was no difference in vasomotor symptoms between the herbal interventions and placebo at 3, 6, or 12 months or for the average over-all follow-up time points ($P > 0.05$ for all comparisons), with the exception that symptom intensity was significantly worse with the multibotanical plus soy compared with placebo ($P = 0.016$). Hormone therapy was effective at reducing vasomotor symptoms ($P < 0.001$). The authors conclude that black cohosh alone or as part of a multibotanical regimen was ineffective at treating menopausal vasomotor symptoms (*Ann Int Med*. 2006; 145: 869-879). As pointed out in an accompanying editorial, even though herbal supplements were found to be ineffective, the good news is that women in the placebo group had a 30% reduction in the severity and frequency of vasomotor symptoms during the 12-month follow up, a number that probably reflects the natural history of postmenopausal symptoms (*Ann Int Med*. 2006;145:924-925).

Bisphosphonates to Treat LBD, After 5 Years?

Since WHI, bisphosphonates have become the drugs of choice for many women with low bone density. Treatment with bisphosphonates for 5 years is safe and effective; however, treatment beyond 5 years has been debated with some experts recommending a "drug holiday" after 5 years because of a concern about diminished bone strength and microfractures. A new study suggests that there is no harm in extending treatment beyond 5 years, although there is minimal benefit. In the Fracture Intervention Trial (FIT), 1,099 postmenopausal women who had used alendronate for 5 years were randomized to 5 more years of alendronate 5 mg per day, 10 mg per day, or placebo. Outcomes were hip bone mineral density (BMD) with an exploratory outcome measure of fracture incidence. Compared to women who continued alendronate, those who were switched to placebo at 5 years had declines in BMD at the total hip (-2.4%; 95% CI, -2.9% to -1.8%; $P < 0.001$) and spine (-3.7%; 95% CI, -4.5% to -3.0%; $P < 0.001$). Still, despite discontinuing alendronate, BMD remained at levels above pretreatment levels 10 years earlier. The cumulative risk for non-vertebral fractures was not significantly different between those continuing or discontinuing alendronate (19% vs 18.9%). Those who continued alendronate had significant lower risk of clinically recognized vertebral fractures, however, (5.3% placebo vs 2.4% alendronate) but no significant reduction in morphometric vertebral fractures. Of the women continuing alendronate, 18 underwent bone biopsies and none showed any qualitative abnormalities. The authors conclude that discontinuing alendronate after 5 years results in a moderate decline in BMD, a gradual rise in biochemical markers, but no higher fracture risk other than for clinical vertebral fractures compared to women who continued alendronate. The data also suggests that stopping alendronate at 5 years is safe, although the authors suggest that high-risk women may want to continue beyond 5 years (*JAMA*. 2006;296:2947-2953). Interestingly, no cases of osteonecrosis of the jaw were reported in women who took alendronate for 10 years.

FDA Actions

The FDA has approved a new estradiol gel for the treatment of moderate to severe vasomotor symptoms assisted with menopause. The gel, which is applied daily, supplies the lowest dose of estradiol approved by the FDA for this indication. Estradiol gel will be marketed as "Elestrin" by Kenwood Therapeutics.

The FDA has approved Novartis' combination antihypertensive "Exforge." The drug combines valsartan and amlodipine in one pill that is dosed once daily. It is expected to be marketed by September 2007.

The FDA has approved the first generic ondansetron injection (Zofran) for the prophylaxis of postoperative nausea and vomiting, and nausea and vomiting associated with cancer chemotherapy. The generic is manufactured by Teva pharmaceuticals.

The FDA has also approved generic oxybutynin extended release tablets (Ditropan XL). 'The new generics will be available in 5 mg and 10 mg extended-release tablets made by Mylan, and 50 mg extended-release tablets manufactured by Impax Laboratories. Oxybutynin is indicated for once daily treatment of overactive bladder in patients with urge incontinence, urgency, and frequency.

A generic bupropion extended-release tablet has been approved by the FDA. The generic version of Wellbutrin XL for the treatment of depression will be available in 150 mg and 300 mg tablets. The new generic is manufactured by Anchen Pharmaceuticals. ■