"THE CASE FOR CHEMOPREVENTION AS A TOOL TO AVERT BREAST CANCER"
STEVEN R. GOLDSTEIN, MD (JULY).

How many women must be treated to avert one case?

In his article about chemoprevention of breast cancer, Dr. Goldstein provided relative-risk tables. I think it would also be helpful to see "need to treat" statistics. That is, how many patients need to take one of these medications to prevent one case of breast cancer? This information is never stated, and I think it is very important information to have if you are a woman trying to decide whether to take one of these expensive drugs.

Donald R. Joyner, MD
Great Falls, Mont

›› Dr. Goldstein responds:

The number needed to treat can be high

In the Multiple Outcomes of Raloxifene Evaluation, or MORE trial, which evaluated women who had osteoporosis rather than a high risk of invasive breast cancer, the absolute risk reduction for invasive breast cancer was 3.1 fewer cases for every 1,000 woman-years of raloxifene use.[1] The number needed to treat (NNT) to prevent one case of cancer: 323 women for 1 year.[2]

In the Study of Tamoxifen and Raloxifene (STAR), which evaluated women at high risk of invasive breast cancer, there was no placebo group, and the incidence of invasive breast cancer was similar between the tamoxifen and raloxifene groups.[3]

In the P-1 trial, which compared tamoxifen with placebo, there were 178 cases of invasive breast cancer in the placebo group versus 89 cases in the tamoxifen group (relative risk reduction, 51%).[4] The rate of invasive breast cancer was 6.76 cases for every 1,000 women in the placebo group, compared with 3.43 cases for every 1,000 women in the tamoxifen group. The absolute risk reduction was 3.33%, and the NNT was 300 women for 1 year.[4]

It is useful to compare these figures with data from another area of treatment, such as the use of atorvastatin (Lipitor) to reduce coronary artery disease (CAD). In a trial of men who were at high risk of CAD (i.e., hypertensive patients who had at least three risk factors), the package insert states that Lipitor significantly reduced the rate of fatal CAD (46 events in the placebo group versus 40 events in the Lipitor group) and nonfatal myocardial infarction (108 events in the placebo group versus 60 events in the Lipitor group), with a relative risk reduction of 36% (P=.0005) (based on an incidence of 1.9% for Lipitor versus 3.0% for placebo). This translates to an absolute risk reduction of 1.1%. One needs to treat 90 such patients for 1 year to prevent the first major CAD event.

References

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JULY 2009

"WE MUST TAKE THE LEAD IN THE BATTLE AGAINST BREAST CANCER"
ROBERT L. BARBIERI, MD (EDITORIAL, JULY).

Gail model is not the only breast cancer prediction tool

My practice consists of menopausal patients, all of whom are screened annually to determine their risk of breast cancer. I use a simplified questionnaire that has accuracy similar to that of the Gail model. It is based on data from the Women's Health Initiative (WHI) cohort and uses age, family history of breast cancer in a first-degree relative, and previous breast biopsies to predict estrogen-receptor-positive breast cancer.

Women 55 years of age or older who have either a previous breast biopsy or a family history of breast cancer in a first-degree relative have a 5-year risk of invasive breast cancer of 1.8% or higher.[1] These women would be offered chemoprevention.

Frank Bonura, MD
Smithtown, NY

Reference

1. Chlebowski RT, Anderson GL, Lane DS, et al; Women's Health Initiative Investigators. Predicting risk of breast cancer in postmenopausal women by hormone receptor status. J Natl Cancer Inst. 2007;99:1695–1705.

"Taking the lead" may raise the risk of a lawsuit

I have practiced ObGyn for 40 years and done thousands of Pap tests—a good thing. But breast disease scares me from a liability perspective.

Of course, I perform breast exams and order mammograms on a regular basis, but I am extremely reluctant to emphasize to anyone that I am an expert on breast disease. Why? I don't want to be sued. Just one "fail-

5. Impaired glucose tolerance.

6. Reduced response to metyrapone test.

E. CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term continuous administration of estrogen, with and without progestin, in women with and without a uterus, has shown an increased risk of endometrial cancer, breast cancer, and ovarian cancer. (See **BOXED WARNINGS, WARNINGS** and **PRECAUTIONS.**)

Long-term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis, and liver. (See **BOXED WARNINGS, CONTRAINDICATIONS,** and **WARNINGS** sections.)

In a 24 month oral carcinogenicity study in mice dosed with 10 mg/kg/day drospirenone alone or 1 + 0.01, 3 + 0.03 and 10 + 0.1 mg/kg/day of drospirenone and ethinyl estradiol, 0.24 to 10.3 times the exposure (AUC of drospirenone) of women taking a 1 mg dose, there was an increase in carcinomas of the harderian gland in the group that received the high dose of drospirenone alone. In a similar study in rats given 10 mg/kg/day drospirenone alone or 0.3 + 0.003, 3 + 0.03 and 10 + 0.1 mg/kg/day drospirenone and ethinyl estradiol, 2.3 to 51.2 times the exposure of women taking a 1 mg dose, there was an increased incidence of benign and total (benign and malignant) adrenal gland pheochromocytomas in the group receiving the high dose of drospirenone. Drospirenone was not mutagenic in a number of *in vitro* (Ames, Chinese Hamster Lung gene mutation and chromosomal damage in human lymphocytes) and *in vivo* (mouse micronucleus) genotoxicity tests. Drospirenone increased unscheduled DNA synthesis in rat hepatocytes and formed adducts with rodent liver DNA but not with human liver DNA. (See **WARNINGS** section.)

F. PREGNANCY

ANGELIQ should not be used during pregnancy. (See **CONTRAINDICATIONS.**)

G. NURSING MOTHERS

Estrogen administration to nursing mothers has been shown to decrease the quantity and quality of the milk. Detectable amounts of estrogens have been identified in the milk of mothers receiving this drug. Caution should be exercised when **ANGELIQ** is administered to a nursing woman.

After administration of an oral contraceptive containing drospirenone about 0.02% of the drospirenone dose was excreted into the breast milk of postpartum women within 24 hours. This results in a maximal daily dose of about 3 mcg drospirenone in an infant.

H. PEDIATRIC USE

ANGELIQ is not indicated in children.

I. GERIATRIC USE

There have not been sufficient numbers of geriatric patients involved in clinical studies utilizing **ANGELIQ** to determine whether those over 65 years of age differ from younger subjects in their response to **ANGELIQ**.

In the Women's Health Initiative Memory Study, including 4,532 women 65 years of age and older, followed for an average of 4 years, 82% (n = 3,729) were 65 to 74 while 18% (n = 803) were 75 and over. Most women (80%) had no prior hormone therapy use. Women treated with conjugated estrogens plus medroxyprogesterone acetate were reported to have a two-fold increase in the risk of developing probable dementia. Alzheimer's disease was the most common classification of probable dementia in both the conjugated estrogens plus medroxyprogesterone acetate group and the placebo group. Ninety percent of the cases of probable dementia occurred in the 54% of women who were older than 70. (See **WARNINGS, Dementia.**)

ADVERSE REACTIONS

See BOXED WARNINGS, WARNINGS, AND PRECAUTIONS.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

The following are adverse events reported with **ANGELIQ** occurring in >5% of subjects:

Table 4: Adverse Events Regardless of Drug Relationship Reported at a Frequency of >5% in a 1-year Double-blind Clinical Trial

ADVERSE EVENT	E2 1 MG (N=226) n (%)	ANGELIQ (N=227) n (%)
BODY AS A WHOLE		
Abdominal pain	29 (12.8)	25 (11)
Pain in extremity	15 (6.6)	19 (8.4)
Back pain	11 (4.9)	16 (7)
Flu syndrome	15 (6.6)	16 (7)
Accidental injury	15 (6.6)	13 (5.7)
Abdomen enlarged	17 (7.5)	16 (7)
Surgery	6 (2.7)	12 (5.3)
METABOLIC & NUTRITIONAL DISORDERS		
Peripheral edema	12 (5.3)	4 (1.8)
NERVOUS SYSTEM		
Headache	26 (11.5)	22 (9.7)
RESPIRATORY SYSTEM		
Upper respiratory infection	40 (17.7)	43 (18.9)
Sinusitis	8 (3.5)	12(5.3)
SKIN AND APPENDAGES		
Breast pain	34 (15.0)	43 (18.9)
UROGENITAL		
Vaginal hemorrhage	43 (19.0)	21 (9.3)
Endometrial disorder	22 (9.7)	4 (1.8)
Leukorrhea	14 (6.2)	3 (1.3)

The following additional adverse reactions have been reported with estrogen and or estrogen/progestin therapy:

1. Genitourinary system

Changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow; breakthrough bleeding, spotting, dysmenorrhea, increase in size of uterine leiomyomata, vaginitis, including vaginal candidiasis, change in amount of cervical secretion, changes in cervical ectropion, ovarian cancer, endometrial hyperplasia, endometrial cancer.

2. Breasts

Tenderness, enlargement, pain, nipple discharge, galactorrhea, fibrocystic breast changes, breast cancer.

3. Cardiovascular

Deep and superficial venous thrombosis, pulmonary embolism, thrombophlebitis, myocardial infarction, stroke, increase in blood pressure.

4. Gastrointestinal

Nausea, vomiting, abdominal cramps, bloating, cholestatic jaundice, increased incidence of gall bladder disease, pancreatitis, enlargement of hepatic hemangiomas.

5. Skin

Chloasma or melasma, which may persist when drug is discontinued, erythema multiforme, erythema nodosum, hemorrhagic eruption, loss of scalp hair, hirsutism, pruritus, rash.

6. Eyes

Retinal vascular thrombosis, intolerance to contact lenses.

7. Central nervous system

Headache, migraine, dizziness, mental depression, chorea, nervousness, mood disturbances, irritability, exacerbation of epilepsy, dementia.

8. Miscellaneous

Increase or decrease in weight, reduced carbohydrate tolerance, aggravation of porphyria, edema, arthralgias, leg cramps, changes in libido, anaphylactoid/anaphylactic reactions including urticaria and angioedema, hypocalcemia, exacerbation of asthma, increased triglycerides.

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ure to diagnose" can take all that you own, including your house.

We just had a $24 million judgment against an ObGyn here in Memphis for failure to diagnose breast cancer in a 23-year-old. The doctor failed to order a mammogram for a patient who had a small "lump" that later turned out to be breast cancer.

What is a doctor to do? Mammography is discouraged in women younger than 30 or 35 years. It is highly unlikely that a 23-year-old could have breast cancer—yet, the plaintiff was awarded a multimillion-dollar judgment. The physician in question was a general ObGyn.

Please tell me where the reward lies for heightened vigilance for breast cancer. We are lawyer fodder.

Peter Ballenger
Memphis, Tenn

Training in breast disease is an unmet need in ObGyn

Dr. Barbieri's editorial on breast cancer prevention resonates strongly with me. I have spent the past 20 years of clinical practice at the University of Michigan focused primarily on disease of the breast. During that time, I have trained all of our residents in the clinical management of all aspects of benign breast disease, including surgical management of benign breast disease and surgical *diagnosis* of malignant breast disease.

It has been my observation that the specialty as a whole has not required standardized education of house officers in ObGyn postgraduate training programs. This troubles me because, in the last two white papers on closed claims from the Physician Insurers Association of America, the leading cause of medical malpractice in the United States was delayed or missed diagnosis of breast cancer. Excluding radiologists, more than 50% of defendants in these cases have been ObGyns. This leads me to conclude that:

- women expect their ObGyn to be able to make a timely diagnosis of breast cancer
- we are not meeting our educational responsibilities to ObGyn trainees.

In July 2008, I started a breast fellowship in gynecology at the University of Michigan to enable a junior faculty member from an academic training program to spend a year at the university learning all aspects of breast disease. The aim is that the fellow will return to his or her academic program to become the clinical

Correction

"UPDATE ON MENOPAUSE" ANDREW M. KAUNITZ, MD (MAY 2009)

In the August 2009 installment of Comment & Controversy, a letter from David Priver, MD, was incorrectly edited. The letter should have read as follows:

Oophorectomy in young women may not be so harmful

One headline in the Update on Menopause was misleading. It said: "Bilateral oophorectomy raises young women's risk of cardiovascular death." In the article itself, in much finer print, it was explained that the mortality rate does not rise if the woman is given hormone replacement therapy immediately after oophorectomy and continues to take it until she is at least 45 years old.

The article does not mention the rather severe surgical difficulties that are often encountered when a physician attempts to remove the ovaries after hysterectomy. I'm sure every gynecologic surgeon has had numerous cases in which the ovaries were plastered to the posterior peritoneum, immediately adjacent to the ureters. These cases are technically difficult and dramatically increase the risk of ureteral injury—and subsequent lawsuit. Also relevant is the fact that there is an incidence of ovarian cyst formation of about 20% in the years following hysterectomy, necessitating oophorectomy. It is important that the patient be informed of this possibility during counseling.

The happiest posthysterectomy patients I have cared for are those who undergo concurrent bilateral salpingo-oophorectomy and spend years comfortably taking estrogen.

David Priver, MD, San Diego, Calif

Dr. Kaunitz stands by his original reply to this letter, which requires no alteration in response to this correction.

expert in breast disease, with the explicit goal of practicing and teaching all aspects of breast disease, including surgical diagnosis of both benign and malignant disease.

This program is not designed to train ObGyn faculty in the surgical management of breast *cancer*; I believe that the complexities of this practice still fall into the subspecialist category (e.g., surgical oncology).

Our first fellow performed more than 150 surgical breast procedures and was trained in open excisional biopsy, wire localization biopsy, core biopsy, and fine-needle aspiration. The training is similar to that of the breast surgical oncology fellowship at the University of Michigan, with rotations through surgical oncology, medical oncology, breast imaging, breast pathology, breast genetics, and breast reconstructive surgery. The fellow operates with me and with surgical oncologists on a weekly basis.

Clearly, our patients have expectations of us, and my hope is that fellowships of this sort will begin to address the unmet need.

Mark Pearlman, MD
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in Reproductive Medicine
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›› Dr. Barbieri responds:

Prevention is the best lifesaving strategy

I deeply appreciate the thoughtful comments of Dr. Bonura, Dr. Ballenger, and Dr. Pearlman. As Dr. Bonura notes, there are at least eight models in use for the prediction of breast cancer. The "simple model" reported by the WHI investigators should be easier to use in general practice because it requires only the patient's age, number of first-degree relatives with breast cancer, and number of previous breast biopsies. Dr. Bonura's practice of assessing the risk of breast cancer in his patients is a "best practice," and I encourage all ObGyns to follow his lead.

I agree with Dr. Ballenger that the current professional liability environment is scary and threatening to ObGyns. Although I fear litigation, I try to avoid having it alter my medical practice.

Dr. Pearlman and his colleagues, through their ObGyn fellowship training program in breast disease, are taking the national lead in preparing the next generation of ObGyns to be experts in breast care. I admire their leadership on this important clinical issue.

The battle against breast cancer is not likely to be "won" by waiting for women to get breast cancer and then hoping surgical, medical, and radiation oncologists can cure all patients. A plan that emphasizes prevention is more likely to be successful. ObGyns play a critically important role in the prevention of breast cancer.

See what your colleagues reported about breast cancer risk assessment and chemoprevention in the **Instant Poll** on page 20