

**Kate O'Hanlan, M. D.**  
**Gynecologic Oncology Associates**  
**4370 Alpine Road, Suite 104**  
**Portola Valley, CA 94028-7927**

Phone: (650)-851-6669

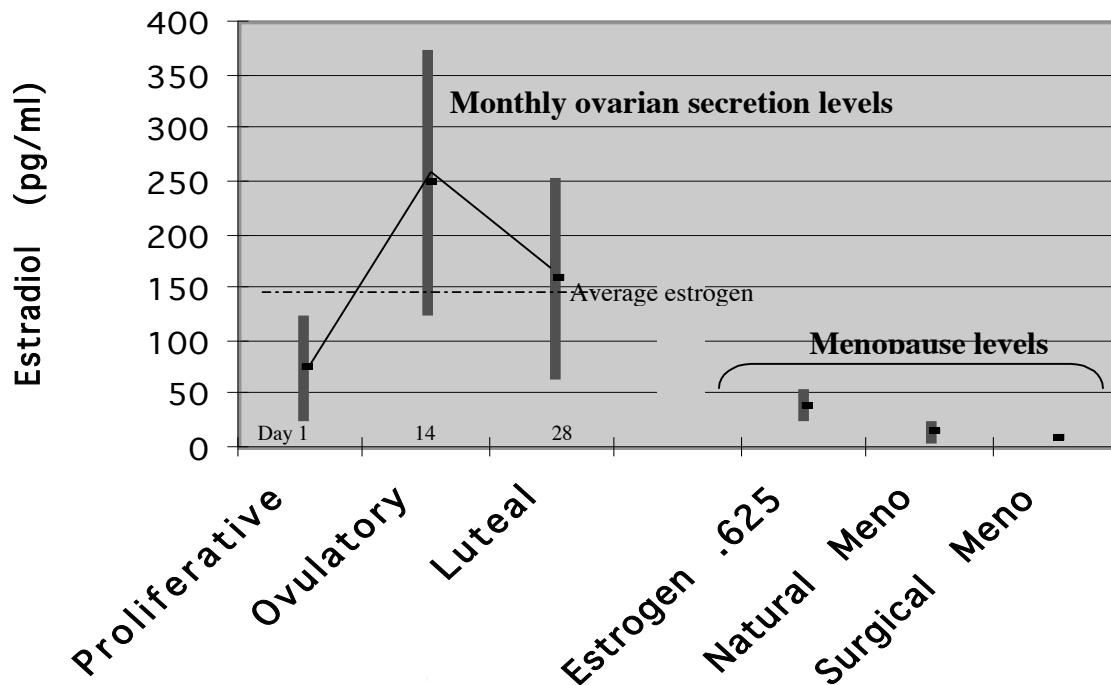
FAX: (650) 851-9747

**Risk of Breast Cancer, Uterine Cancer and ERT use**

Research shows that removal of the uterus and ovaries will halve women's risk of future new and recurrent breast cancer, and prevent uterine, cervical and ovarian cancers. But can these women receive estrogen therapy to prevent the frequently bothersome symptoms of hot flashes, insomnia or loss of focus? The answer is yes, for many reasons.

**First, menopausal estrogen levels are lower than ovarian levels.** The levels of estrogen needed to prevent hot flashes with replacement doses are less than half the levels of estrogen that the active ovaries normally secrete. In the diagram below, monthly average estrogen is 100 to 150pg/ml for pre-menopausal women. Women in menopause have natural estrogen levels of 10-20 pg/ml. If their ovaries are removed, the estrogen levels are closer to 10 pg/ml. Replacement levels of estrogen needed to relieve hot flashes are almost always under 80, and usually 40-60 pg/ml.

**Serum Estradiol throughout life**



**Second, only combination hormone therapy increases breast cancer risk.** The Women's Health Initiative (WHI) Data tells us that the combination of estrogen and progestin used over 5 years increase a woman's risk of breast cancer by about 26%. (Writing group for WHI, JAMA, 2002,

**Third, estrogen does not increase new breast cancer risk.** The WHI study of women who had hysterectomy and took either estrogen alone or placebo showed that use of estrogen alone for over 8 years results in a 26% lower risk of breast cancer in women under age 60. (Anderson et al JAMA, 2004)

Thus, only progesterone is implicated as a promoter of new breast cancer. Estrogen alone is not implicated as a risk for new breast cancer.

**Fourth, oophorectomy before menopause reduces breast cancer risk by half.** Large studies of women who have had their ovaries removed before they entered menopause show that their risk of breast cancer was 50% lower than women who kept their ovaries, whether or not they took hormone therapy. (Schairer et al, JNCI, 1997)

Thus, a lower level of estrogen and absent secretion of ovarian progesterone can reduce breast cancer risk.

**Fifth, estrogen alone does not cause breast cancer recurrence.** A large study of women with breast cancer who took no hormone therapy, estrogen with minimal progestin, or combination estrogen with progestin showed that women using least or no progestin had no increase in recurrence of breast cancer compared with women taking no hormone therapy. Women taking full progestin therapy had a significantly increased risk of breast cancer recurrence. (von Schoultz et al, JNCI, 2005)

Thus, dosing of progestin, but not estrogen, is implicated in breast cancer recurrence.

Two concepts become apparent from the above five large studies:

1. Reducing the ovarian levels of estrogen and removing all progestin can reduce risk of new and recurrent breast cancer. (remove ovaries)
2. Using only estrogen in low doses does not increase new or recurrent breast cancer. (remove uterus, use estrogen for hot flashes)

There are many studies of women with breast cancer during pregnancy and on OCP's (both states with high estrogen and progesterone levels) showing that among these younger women with their naturally higher levels of estrogen and progesterone, there no difference in risk.

Age, sedentary lifestyle, smoking, alcoholism and high BMI are also risk factors for breast cancer. The WHI women had an average age of 63 and BMI of 28.

### Summary:

If the ovaries are before menopause, the benefit would be a near zero risk of ovarian cancer, which is 80% fatal, and a 50% reduced risk of breast cancer recurrence or new primary. The estrogen level will drop, but she will feel perfectly normal as she starts on estrogen pills or patches before she leaves the hospital, and continue the estrogen until about age 51 or so. If a women has no vasomotor symptoms, she needs no estrogen at all.

If the ovaries are left in after hysterectomy, women will go through menopause at an average age of 51 or so and then have a similar drop in estradiol and be facing these same issues then, with a normal (not reduced) risk of breast cancer and ovarian cancer.

(1997). "Breast cancer risk lower in women who undergo oophorectomy." Int J Fertil Womens Med **42**(5): 276-7.

Schairer, C., I. Persson, et al. (1997). "Breast cancer risk associated with gynecologic surgery and indications for such surgery." Int J Cancer **70**(2): 150-4.

Risk of breast cancer was assessed in relationship to gynecologic operations using data from a record-linkage study involving 15,844 women in the Uppsala Health Care Region of Sweden, who underwent surgery between 1965 and 1983. Data abstracted from medical records for the breast cancer cases and a random sample of the cohort allowed examination of risk associated with these operations in regard to menopausal status and indications for the operations. **Among women who were pre-menopausal at the time of operation, a bilateral oophorectomy before the age of 50 years was associated with a 50% reduction in the risk of breast cancer compared with the background population, a reduction in risk evident within 10 years of the operation.** A bilateral oophorectomy after the age of 50 years in pre-menopausal women or after a natural menopause was not associated with any reduction in risk. There were no reductions in risk associated with a unilateral oophorectomy or hysterectomy among women who were pre-menopausal at the time of operation. In fact, hysterectomy alone was associated with a slight increase in breast cancer risk when the operation was due to myomas, abnormal bleeding, and, possibly, severe forms of endometriosis but not to other reasons. Risk did not vary substantially by indications for oophorectomy, including benign ovarian neoplasms and functional ovarian cysts, though endometriosis was associated with a non-significant increase in breast cancer risk.

### **Menopausal hormone therapy after breast cancer: the Stockholm randomized trial.**

von Schoultz, E. and L.E. Rutqvist. 2005. *J Natl Cancer Inst.* 97: 533-535.

In 1997 two independent randomized clinical trials, Hormonal Replacement Therapy After Breast Cancer--Is It Safe? (HABITS; 434 patients) and the Stockholm trial (378 patients), were initiated in Sweden to compare menopausal hormone therapy with no menopausal hormone therapy after diagnosis of early-stage breast cancer. Much of the design of both studies was similar; however, **a goal of the Stockholm protocol, not shared with the HABITS trial, was to minimize the use of progestogen combined**

**with estrogen.** The HABITS trial was prematurely stopped in December 2003, because, at a median follow-up of 2.1 years, the risk for recurrence of breast cancer among patients receiving menopausal hormone therapy was statistically significantly higher (relative hazard [RH] = 3.3, 95% confidence interval [CI] = 1.5 to 7.4) than among those receiving no treatment. **In the Stockholm trial, however, at a median follow-up of 4.1 years, the risk of breast cancer recurrence was not associated with menopausal hormone therapy (RH = 0.82, 95% CI = 0.35 to 1.9).** Statistically significant heterogeneity in the rate of recurrence was observed (P = .02; two-sided likelihood-ratio test) between the two studies, indicating that chance may not be the only explanation. Doses of estrogen and progesterone and treatment regimens for menopausal hormone therapy may be associated with the recurrence of breast cancer.

Chlebowski, R. T. (2002). "**Breast cancer risk reduction: strategies for women at increased risk.**" *Annu Rev Med* **53**: 519-40.

Breast cancer risk reduction now represents an achievable medical objective. Current interventions include selective estrogen receptor modulators (SERMs), prophylactic surgery, and lifestyle change. For SERMs, current evidence supports tamoxifen use for breast cancer risk reduction whereas raloxifene requires further study. **Prophylactic mastectomy and prophylactic oophorectomy, effective in retrospective clinical experiences, should be considered only for women at substantial risk willing to accept the irreversible consequences of these procedures.** Although dietary fat intake is under clinical trial evaluation, lifestyle change, including weight loss, dietary change, and increased physical activity, can be recommended based on other health considerations. Use of any intervention requires careful breast cancer risk assessment, risk-benefit calculations, and informed decision making with full patient participation. Future breast cancer risk assessment may incorporate additional biologic measures of estrogen exposure and/or analyses of collected breast cells. Under active evaluation are novel SERMs, aromatase inhibitors/inactivators, gonadotrophin-releasing hormone agonists, retinoids, statins, and tyrosine kinase and cyclooxygenase-2 inhibitors.

Conto, S. I. and J. S. Myers (2002). "**Risk factors and health promotion in families of patients with breast cancer.**" *Clin J Oncol Nurs* **6**(2): 83-7.

Women with a family history of breast cancer have an increased risk of developing the disease. Women identified as "high risk" for developing breast cancer have been shown to exhibit increased levels of psychological distress and anxiety related to breast cancer. Oncology nurses can address this barrier and others, such as altered risk perception and lack of physician recommendation for screening. Oncology nurses also can identify high-risk families that may be candidates for genetic testing for breast cancer susceptibility, provide comprehensive teaching about breast self-examination (BSE), and clarify misconceptions about early detection. **Primary prevention measures for hereditary breast cancer include prophylactic mastectomy and oophorectomy** and chemopreventative agents. Secondary prevention measures include screening and early detection with mammography, clinical breast examinations, and BSE. Nurses have a responsibility to educate families of patients with breast cancer about risk factors,

primary and secondary preventive measures, genetic testing, and screening recommendations.

Parazzini, F., C. Braga, et al. (1997). "**Hysterectomy, oophorectomy in premenopause, and risk of breast cancer.**" *Obstet Gynecol* **90**(3): 453-6.

**OBJECTIVE:** To analyze the risk of breast cancer in women who underwent pelvic surgery in premenopause using data from two case-control studies conducted between 1983 and 1994 in six Italian centers. **METHODS:** Subjects were 5984 women with histologically confirmed breast cancer diagnosed within the year before interview who were admitted to the major teaching and general hospitals in the areas included in the studies. Controls were 5504 women who resided in the same geographic areas and were admitted for acute conditions to the same network of hospitals in which cases had been identified. Women were not included if they had been admitted for gynecologic, hormonal, or neoplastic disease. **RESULTS:** A total of 719 cases (12%) and 801 controls (15%) underwent pelvic surgery before menopause. **The risk of breast cancer was reduced in women who underwent bilateral oophorectomy with hysterectomy (odds ratio [OR] adjusted for age, calendar year at interview, study, and center, 0.8, 95% confidence interval [CI] 0.7, 0.9) and hysterectomy alone (OR 0.7, 95% CI 0.6, 0.8). The protection tended to increase with time since surgery,** but no relationship emerged when age at menopause was included in the analysis. No clear relationship emerged between time since unilateral oophorectomy with or without hysterectomy or since hysterectomy alone and breast cancer risk. **CONCLUSION:** The risk of breast cancer is lower in women who undergo bilateral oophorectomy before menopause, and the protection increases with time from surgery.

Rhodes, D. J. (2002). "**Identifying and counseling women at increased risk for breast cancer.**" *Mayo Clin Proc* **77**(4): 355-60; quiz 360-1.

Women at increased risk for breast cancer should be identified and counseled about options for risk reduction. Identifying such women is simplified with use of the National Cancer Institute Risk Assessment tool, a computer-based tool that incorporates information on 6 risk factors for estimating an individual's risk of developing breast cancer. However, the tool does not incorporate all known or possible risk factors and may underestimate risk, particularly among women with a complex family history of breast cancer for whom alternative models of risk assessment are more appropriate. **Women found to have an increased risk of breast cancer should be counseled about options for management, including close surveillance, lifestyle modifications, chemoprevention with tamoxifen, enrollment in a breast cancer prevention clinical trial, and prophylactic mastectomy and/or oophorectomy.** In the absence of consensus about which risk level is best suited to which option, decisions about risk reduction depend as much on an individual's priorities and risk aversion as on numerical risk estimates.