



Prevention and Screening of Breast and Cervical Cancer: Advances in Primary Care

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Objectives

- ❖ Pathophysiology
- ❖ Prevention and new developments
- ❖ New treatment modalities

Breast Cancer Update

- ❖ In the United States, breast cancer is the second most common cancer among women, accounting for nearly 1 of every 3 cancers diagnosed.
- ❖ While lung cancer is still the most fatal, and despite the overall decline in breast cancer mortality, approximately 40,000 deaths will be attributed to breast cancer in 2006 alone.

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Breast Cancer Update

- ❖ Regular improvements are made regularly in the diagnosis and treatment of both hormone-positive and hormone-negative disease, posing a challenge to the clinician who must stay current with the most recent advances in both the diagnosis and therapy of breast cancers.

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ACS Breast Cancer Screening Guidelines

- ❖ ACS guidelines for breast cancer screening, which were last updated in 2003, note that average-risk women should have clinical breast examination (CBE) and counseling to raise awareness of breast symptoms, beginning at age 20 years, and regular mammography beginning at age 40 years.

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ACS Breast Cancer Screening Guidelines

- ❖ From ages 20 to 39 years, women should undergo CBE every 3 years, and annually after age 40 years. The ACS no longer recommends that all women conduct regular breast self-examination (BSE), but women should be informed about the potential benefits, limitations, and harms associated with BSE.

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Mammography

- ❖ Despite its use as the tool of choice for breast screening, mammography has significant limitations when used in isolation. Although in general a highly sensitive investigation, sensitivity is much reduced in younger or denser breasts; therefore, mammography is considered inappropriate in patients younger than 35 years. However, many centers are now using mammography in patients aged 30 years and older who are in high-risk groups.

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Mammography

- ❖ The positive predictive value of mammography may be as low as 10%, demonstrating the need for other imaging modalities, such as ultrasonography, to distinguish solid from cystic radiodensities. However, mammography remains the investigation of choice for detecting and classifying microcalcification.
- ❖ Malignant microcalcification is characterized by isolated clusters, punctuate of varying sizes, and a branching or linear pattern.

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Advances in Mammography: CAD

- ❖ Recent advances in mammography include digital mammography, contrast-enhanced mammography, and computer-aided detection (CAD). Digital mammography uses essentially the same mammographic system as conventional mammography, but it is equipped with digital receptors instead of film cassettes.
- ❖ Digital spot view mammography allows faster and more accurate stereotactic biopsy, whereas full-field digital mammography (FFDM) is being promoted as the future modality for the screening and diagnosis of breast cancer.

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Advances in Mammography: CAD

- ❖ CAD uses an image checker computer that analyzes mammographic films that have been scanned and digitized. It then highlights suspicious areas that may be indicative of cancer, thus acting as a pair of second eyes. Studies have shown that for every 100 cancers detected on screening, 22 remain undiagnosed by the radiologist. Use of CAD along with the regular evaluation reduces oversight cases by 99%. CAD is particularly good for dense breasts

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Advances in Mammography: Ultrasound

- ❖ Mammographic features often require further ultrasonographic evaluation, for example to distinguish between solid and cystic lesions or to accurately determine the size of a spiculated lesion.
- ❖ Ultrasonography is becoming ever more sophisticated. Higher resolutions are being achieved, and the introduction of Doppler enables definition of characteristic blood flow patterns. This can aid in separating benign and malignant lesions and distinguishing lymph node metastases from normal or reactive lymph nodes.

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Advances in Mammography: MRI

- ❖ Several recent studies have shown that MRI --- which uses magnetic energy and intravenous material to create detailed images of the breast -- is significantly more sensitive than mammography in detecting breast cancers in high-risk women.

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Advances in Mammography: MRI

- ❖ Researchers of a recent study concluded that combining MRI with mammography would pick up twice as many breast cancers in women at high risk. This advance is especially important for women with mutations on genes BRCA1 or BRCA2. They are typically at greater risk of developing breast cancer in their younger years, when dense breast tissue can make mammography X-rays difficult to interpret.

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Mammography

- ❖ MRI should not replace mammography
- ❖ Mammography was able to detect some cancers that MRI missed. Mammography is also a much better tool than MRI for detecting DCIS
- ❖ Secondly, MRI is not a perfect screening tool, and women at high risk for breast cancer may find that undergoing MRI screening may lead them to have unnecessary additional exams or biopsies.

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Other Diagnostic Testing

- ❖ PET,(positron emission tomography) scanning
 - ❖ a small amount of radioactive sugar is injected into the body. Active cells take up the radioactive sugar, and this helps radiologists identify areas where cells are overactive, which can indicate cancer.
- ❖ Scintimammography-as in a PET scan-
 - ❖ a small amount of radioactive material is injected into the body. Normal breast cells take up little of the radioactive material, while active cells take up more, which can indicate cancer. This can be helpful in determining axillary involvement.

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Other Diagnostic Testing

- ❖ A panel from the Evidence-Based Practice Center in Plymouth Meeting in Pennsylvania identified 81 studies they examined to evaluate the accuracy of MRI, PET, scintimammography, or ultrasound for diagnosing breast cancer in women.

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Other Diagnostic Testing

- ❖ The authors reviewed 81 studies examining MRI, PET, scintimammography, or ultrasound after abnormal mammogram.
- ❖ Following a suspicious mammogram, the sensitivities of PET scanning, MRI, and ultrasound for breast cancer were 82.2%, 92.5%, and 86.1%, respectively. The respective specificities were 78.3%, 72.4%, and 66.4%.

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Other Diagnostic Testing

- ❖ Assuming a woman with an abnormal mammogram had a 20% risk for cancer, the authors note that for every 1,000 women tested with the following modalities, the respective rates of women avoiding unnecessary biopsy and those with a missed cancer would be as follows:
 - ❖ PET scan: 924 and 76
 - ❖ Scintimammogram: 907 and 93
 - ❖ MRI: 962 and 38
 - ❖ Ultrasound: 950 and 50

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Other Diagnostic Testing

- ❖ None of these tests was sufficiently accurate to replace biopsy for women with nonpalpable lesions at average risk for breast cancer.
- ❖ For only palpable lesions, data were insufficient to estimate the accuracy of PET scanning, MRI, ultrasound, and scintimammography.

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Biopsy, Biopsy, Biopsy

- ❖ **Needle biopsy is preferable to open surgical biopsy.**
- ❖ PET scanning, ultrasound, MRI, or scintimammography cannot be recommended in place of invasive testing following an abnormal mammogram suggesting possible cancer, as all of these modalities may miss an unacceptable number of cancer cases.
- ❖ Don't be lured into a false sense of security.

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What about treatment?

- ❖ NEW YORK (Reuters Health) Mar 30, 2006 - A new prospective study has failed to identify a subgroup of patients with ductal carcinoma in situ (DCIS) who benefit from wide excision only without radiation. For decades clinicians have sought to identify a subgroup of patients with DCIS who will benefit from lumpectomy alone, however...

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What about treatment?

- ❖ Dr. Julia S. Wong of the Dana-Farber Cancer Institute in Boston and associates found that the local 5-year recurrence rate for DCIS with wide excision alone was 12%, "high enough that we were compelled by the statistical and ethical bounds of the protocol to cease enrollment short of our accrual goal."

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What about treatment?

- ❖ “The researchers had planned to enroll 200 patients, but stopped at 158 because the rate of local recurrence had met the predetermined termination point. Seven to 63 months after study entry, 13 patients had developed local recurrence, 9 with DCIS and 4 with invasive disease. All were treated successfully.”
- ❖ “Dr. Wong and her team conclude that patients should be informed about the risks of local recurrence with lumpectomy alone, as well as the risks of radiation therapy, so they can make informed choices on treatment.”

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What about treatment?

- ❖ In an editorial accompanying the study, Dr. Lawrence J. Solin of the University of Pennsylvania in Philadelphia points out that radiation with lumpectomy has consistently been shown to halve the risk of local recurrence.
- ❖ At present, Dr. Solin adds, "one must conclude that, after excision, all patients with DCIS (except for the patient with a short life expectancy or substantial comorbid conditions) should be seriously considered for adjuvant treatment with radiation and tamoxifen to minimize the risk of local recurrence."

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What about treatment?

- ❖ In the Dec. 8, 2004 online edition of the *Lancet*, researchers reported results from the Arimidex, Tamoxifen, Alone or in Combination trial, known as ATAC. This study compared 5 years of tamoxifen with 5 years of Arimidex in 9,366 postmenopausal women with early stage disease. Initial results suggested Arimidex outperformed tamoxifen, and these results, after 68 months of follow-up, confirm those findings.

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What about treatment?

- ❖ Arimidex did a much better job than tamoxifen in reducing the number of cancer recurrences during the study. And if the cancer did return, it was after a longer period of time in women who took the aromatase inhibitor than in those who took tamoxifen. Women with hormone-receptor positive tumors, the most common type of breast cancer, had especially good results.

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Aromatase Inhibitors

- ❖ Arimidex also caused fewer side effects than tamoxifen. Women on the drug had fewer cases of endometrial cancer, blood clots, stroke, vaginal bleeding, hot flashes, and vaginal discharge. However, they did experience more joint pain and broken bones. Although those side effects can be serious, the researchers said women on Arimidex can take drugs called bisphosphonates to help strengthen their bones.

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Aromatase Inhibitors

- ❖ Because of these good results, the researchers recommend that Arimidex replace tamoxifen as a first-choice treatment for postmenopausal women with hormone-positive breast cancer. (Aromatase inhibitors have not been tested in younger women.)

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Aromatase Inhibitors

- ❖ As recently as last month, an expert panel from the American Society for Clinical Oncology (ASCO) updated its recommendations on using aromatase inhibitors to prevent breast cancer recurrence. The panel recommended that all postmenopausal women with hormone-receptor positive breast cancer should receive an aromatase inhibitor at some point – either as initial therapy or after 2 to 5 years of treatment with tamoxifen.

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Raloxifene/ Evista

- ❖ Raloxifene, a drug first developed to treat osteoporosis in women. A selective estrogen receptor modulator (SERM), raloxifene binds to estrogen receptors as a mixed estrogen and anti-estrogen effect. It functions as an estrogen sometimes (in bones and on lipid metabolism) and as an anti-estrogen in other target tissues (endometrium and breast).

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Raloxifene/ Evista

- ❖ Results from the MORE (The Multiple Outcomes of Raloxifene Evaluation) study of 7,705 women that were randomized to raloxifene or placebo demonstrated that among postmenopausal women with osteoporosis, the risk of invasive breast cancer was decreased by 76% during three years of treatment with raloxifene.

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Raloxifene/ Evista

- ❖ VIENNA, AUSTRIA -- November 4, 2004 -- **Raloxifene** significantly reduces the risk of invasive **breast cancer** in postmenopausal women -- regardless of whether a woman has previously taken hormone replacement therapy (HRT), a double-blind, placebo-controlled study shows.

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Raloxifene/ Evista

- ❖ **Raloxifene** reduced the risk of developing invasive **breast cancer** by 66%, whether or not the women took HRT. The magnitude of reduction in **breast cancer** incidence associated with **raloxifene** use did not differ between patients who had used estrogen-only HRT or those who had taken combined estrogen-progestin therapy.

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Raloxifene/ Evista

- ❖ Stronger evidence on the safety and efficacy of raloxifene is awaited from the STAR Trial. This trial includes almost 20,000 postmenopausal women in the US who are at increased risk of breast cancer to determine whether raloxifene is as effective in reducing the chance of developing breast cancer as tamoxifen.
- ❖ Final analysis of the trial will begin when a previously determined number of invasive breast cancers has occurred, which is expected in late spring 2006.

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Traditional HRT and Breast Cancer

- ❖ Women who use combination hormone replacement therapy (HRT) with estrogen and progestin face a greater breast cancer risk than those taking estrogen alone, according to a new report (JAMA 2000; 283:485-91, 534-5). The most common estrogen taken was conjugated estrogen, such as Premarin; medroxyprogesterone acetate, or Provera, was the commonly taken progestin.

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Traditional HRT and Breast Cancer

- ❖ **Influence of Estrogen Plus Progestin on Breast Cancer and Mammography in Healthy Postmenopausal Women**
- ❖ Relatively short-term combined estrogen plus progestin use increases incident breast cancers, which are diagnosed at a more advanced stage compared with placebo use, and also substantially increases the percentage of women with abnormal mammograms.

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The Women's Health Initiative Randomized Trial JAMA. 2003;289:3243-3253

Traditional HRT and Breast Cancer

- ❖ “These results suggest estrogen plus progestin may stimulate breast cancer growth and hinder breast cancer diagnosis.” Synthetic progestins seem to have an adverse effect on other tissues as well, and it is my advice to avoid them. They are commonly prescribed as “Provera or Cycrin”

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Traditional HRT and Breast Cancer

- ❖ Cancer Epidemiol 2002 Jul;11(7):593-600.
- ❖ The objective of this study was to investigate the type and duration of postmenopausal therapy and breast cancer risk. The subjects were 5298 postmenopausal women (age range, 50-79 years) with a new diagnosis of invasive breast cancer from statewide tumor registries.
- ❖ For comparison, 5571 controls were randomly selected from population lists. Participants completed a structured telephone interview covering hormone use and breast cancer risk factors. Multivariable regression models were used to estimate relative risks.

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Traditional HRT and Breast Cancer

- ❖ Estrogen-progestin use that was both recent and long term (>5 years in duration) was more strongly associated with breast cancer risk (RR, 1.57; 95% CI, 1.15-2.14) than similar use of estrogen alone. In estrogen-progestin users, risks were similar for sequential and continuous use regimens but perhaps stronger for lobular than ductal breast cancer.

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Traditional HRT and Breast Cancer

- ❖ Use of progestin alone was associated with a doubling of risk (RR, 2.09; 95% CI, 1.07-4.07 for ever use versus nonuse). Estrogen-progestin use, both sequential and continuous, appears to be more strongly associated with risk of breast cancer than use of estrogen alone.

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Traditional HRT and Breast Cancer

- ❖ March 5, 2003
- ❖ Women who take combination hormone replacement therapy for more than four years are at very high risk of breast cancer compared with women who have never used HRT. But estrogen-only HRT is virtually free of breast-cancer risk, a Swedish study suggests.

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Traditional HRT and Breast Cancer

- ❖ The findings, from a study of some 30,000 women age 25-65, appear in the March 15 issue of *Cancer*, the journal of the American Cancer Society. Researchers Håkan L. Olsson, MD, PhD, and colleagues at University Hospital, Lund, Sweden, interviewed the women between 1990 and 1992. They then followed their health status through 2001. Nearly 3,700 of the women said they'd used various forms of HRT

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Traditional HRT and Breast Cancer

- ❖ As did the U.S. Women's Health Initiative (WHI) study, Olsson's team found that HRT containing progestins raised breast-cancer risk. This risk more than quadrupled in women who used continuous progestin/estrogen HRT. It more than tripled in women using progestin-only HRT, and more than doubled in women using sequential progestin/estrogen HRT -- continuous estrogen doses with periodic progestin doses

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Traditional HRT and Breast Cancer

- ❖ "We found that all HRT preparations containing progestins raise the risk for breast cancer -- considerably higher than we thought before," "After four years, combined progestin/estrogen HRT -- whether continuous or sequential -- and progestin-only regimens give women a high risk of breast cancer."
- ❖ In stark contrast, women who received estrogen-only HRT had no added breast-cancer risk.

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Traditional HRT and Breast Cancer

- ❖ July 2001
- ❖ Fear that hormones may increase the risk of cancer recurrence has long discouraged U.S. physicians from recommending estrogen replacement therapy (ERT) to breast cancer survivors, despite its proven advantages for health and quality of life.

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Traditional HRT and Breast Cancer

- ❖ But this policy needs reexamination in light of results from the longest-running study yet done of women who have taken estrogen after breast cancer, said George N. Peters, MD, University of Texas Southwestern Breast Center, Dallas

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Traditional HRT and Breast Cancer

- ❖ Researchers interviewed 607 breast cancer survivors about their experience with ERT. Of these, 67 had used estrogen in some form after being diagnosed with breast cancer. Eleven women whose only exposure had been vaginal creams were excluded from the study. The remaining 56 women, who had used birth control pills, conjugated estrogens, or estradiol patches, were followed prospectively.

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Traditional HRT and Breast Cancer

- ❖ Fifteen-year actuarial disease-free survival within the group that had received ERT was 92.5% , with a single local recurrence at 13.7 years and a single cancer in the contralateral breast at 9.6 years. The women had experienced no regional or distant recurrences or cancer deaths.

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Traditional HRT and Breast Cancer

- ❖ The use of hormone therapy in postmenopausal women with a history of breast cancer is somewhat controversial. The key background issues in this debate are as follows.
- ❖ Many of the current therapies for breast cancer block or invalidate estrogen receptors, so clearly taking estrogen seems somewhat counterproductive, even if it is not the kiss of death we once thought it was.

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Traditional HRT and Breast Cancer

- ❖ After a significant disease free interval, some women may become candidates for estrogen therapy, without significantly increasing their risks of breast cancer recurrence. It is my opinion that progestin should not be used in this add back therapy.
- ❖ But is it really necessary? And are there other important risks to add back estrogen therapy after a disease free interval of perhaps 5 years? Lets look at the symptoms, and risk versus benefit potential.

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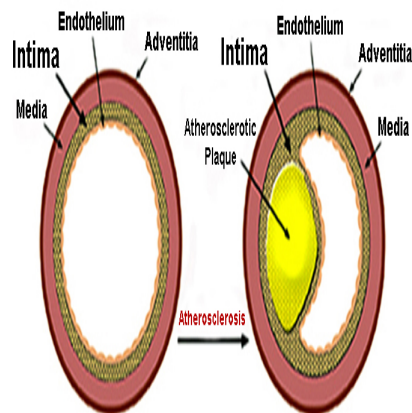
Estrogen Paradox

- ❖ At the 2004 AHA meeting, Dr. Thomas Clarkson described the emerging hypothesis that may explain some of the confusing results regarding estrogen therapy and heart disease risks.
- ❖ Estrogen is a potent up-regulator of matrix metalloproteases. These enzymes are a normal constituent of the endometrium and are important in the menstrual cycle

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Estrogen Paradox

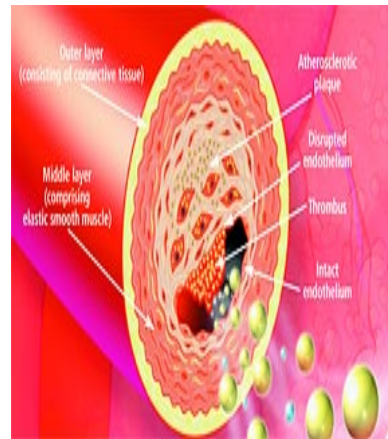
- ❖ Metalloproteases are also found in endothelial lining and the fibrous cap that seals off the necrotic core of an advanced atheroma from the vascular lumen.
- ❖ Most peri-menopausal women enjoy the protective effect throughout their reproductive years and thus have developed little atherosclerotic heart disease.



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Estrogen Paradox

- ❖ If estrogen is added after a plaque is formed, the matrix metalloprotease activity can destabilize the cap allowing necrotic core material to come into contact with the blood stream. This necrotic material is highly thrombogenic, increasing the risk of clot formation in the vascular lumen, and increasing the risks for stroke and heart attack.



Estrogen Paradox

- ❖ Importantly, this information suggests that women who have been menopausal 5-10 or more years without estrogens, may be at increased risk if they re-start estrogens. This is especially important now, as more and more women have decided to “go without” post-menopausal estrogen, and thus may permanently lose a window of cardiovascular protection

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Estrogen Paradox

- ❖ In simple terms, it is pointless to survive breast cancer for 5 years, then... start systemic estrogen and die of a major cardiovascular event precipitated by this mechanism....This also explains the high rate of Cardiovascular incidents in the Estrogen only arm of the WHI, many of these women had been without estrogen for 10 or more years when it was re-started.

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Estrogen Paradox

- ❖ Presented at the ASCO 2005: The Women's Intervention Nutrition Study (WINS), a large-scale, NCI-funded and BCRF-supported clinical trial of over 2,400 women.
- ❖ WINS evaluated the effect of a low-fat diet on breast cancer recurrence and survival.
- ❖ Results showed that eating a low-fat diet reduced the risk of breast cancer recurrence by 20 percent over five years in post-menopausal women compared with women following a standard diet.

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Breast Cancer Pearls

- ❖ Patients are encouraged to be “self aware” of breast changes.
- ❖ Mammography remains important, digital imaging and CAD are resources for the future.
- ❖ MRI is most useful in high risk patients or younger women with dense breasts. It does not replace mammography.
- ❖ PET scans and Scintimammogram hold promise for the future, but do not replace biopsy of suspicious lesions.

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Breast Cancer Pearls

- ❖ Ductal carcinoma in situ needs to be treated by more than just wide local excision.
- ❖ Aromatase inhibitors hold promise in the treatment and prevention of breast cancer and may replace tamoxifen.
- ❖ The STAR trial comparing Raloxifene and Tamoxifen will conclude in 2006, stay tuned for results.

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Breast Cancer Pearls

- ❖ Synthetic Progestins seem in multiple studies to pose risks for breast cancer greater than estrogens.
- ❖ Adding estrogens after a breast cancer free interval of greater than 5 years may predispose to increased risk not of breast cancer but of stroke or heart attack.
- ❖ Low fat diets and avoidance of alcohol may be factors that the patients can control to decrease risk.

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Cervical Cancer

- ❖ Cervical cancer, arising in the lining of the cervix, affects about 13,000 women in the U.S. each year. About 4,000 die. Worldwide, a half million get the disease and 225,000 die.
- ❖ In the 1980s population studies set the pace for the now well-accepted view that cervical cancer is strongly related to the transmission of HPV

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Cervical Cancer

- ❖ Cervical HPV is a group of more than 100 viruses, about 30 of which are said to be linked to cervical cancer. Of these 30 or so, HPV-16 is said to be found in 50 percent of cervical cancers. HPV-18 accounts for another 20 percent.
- ❖ In addition to the population studies that link HPV to cervical cancer, there is research showing that HPV viral DNA can be found integrated in the genetic structure of cervical cancers

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Investigational Vaccine

- ❖ Oct. 6, 2005 - GARDASIL™ (quadrivalent human papillomavirus types 6, 11, 16, 18, recombinant vaccine), an investigational vaccine from Merck & Co., Inc., prevented 100 percent of high-grade cervical pre-cancers and non-invasive cervical cancers (CIN 2/3 and AIS) associated with human papillomavirus (HPV) types 16 and 18 in a new phase III study.

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Investigational Vaccine

- ❖ The analysis compared GARDASIL to placebo in women who were not infected with HPV 16 and 18 at enrollment and who remained free of infection through the completion of the vaccination regimen. Women were followed for an average of two years after enrollment.
- ❖ “These are the first pivotal data to show that vaccination with GARDASIL reduced HPV 16 and 18-related cervical pre-cancer and non-invasive cervical cancer,” said Laura Koutsky, Ph.D., principal investigator, HPV research group, University of Washington, Seattle.

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Investigational Vaccine

- ❖ GARDASIL reduced the risk of developing high-grade pre-cancer and non-invasive cancer (CIN 2/CIN 3, or AIS) associated with HPV types 16 and 18 by 97 percent (n= 5,736); one case was observed in the vaccine group compared to 36 in the placebo group (n= 5,766).
- ❖ There were no discontinuations due to serious vaccine-related adverse events. Adverse events were higher among those who received GARDASIL compared with placebo recipients. The most common vaccine-related adverse event reported was local discomfort at the injection site.

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Investigational Vaccine

- ❖ WHITEHOUSE STATION, N.J., Feb. 7, 2006 - Merck & Co., Inc. announced today that the U.S. Food and Drug Administration (FDA) has accepted the Biologics License Application (BLA) for GARDASIL® (quadrivalent human papillomavirus types 6, 11, 16, 18, recombinant vaccine) and that the investigational cervical cancer vaccine will be given priority review by the agency. A priority designation is intended for products that address unmet medical needs. The FDA has informed Merck that the review goal date is June 8, 2006.

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Investigational Vaccine

Washington Post Monday, October 31, 2005

- ❖ A new vaccine that protects against cervical cancer has set up a clash between health advocates who want to use the shots aggressively to prevent thousands of malignancies and social conservatives who say immunizing teenagers could encourage sexual activity.

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Investigational Vaccine

- ❖ Although the vaccine will not become available until next year at the earliest, activists on both sides have begun maneuvering to influence how widely the immunizations will be employed.
- ❖ In the hopes of heading off a confrontation, officials from the companies developing the shots - - Merck & Co. and GlaxoSmithKline -- have been meeting with advocacy groups to try to assuage their concerns.

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Investigational Vaccine

- ❖ "I would like to see it that if you don't have your HPV vaccine, you can't start high school," said Juan Carlos Felix of the University of Southern California in Los Angeles, who leads the National Cervical Cancer Coalition's medical advisory panel.
- ❖ "Some people have raised the issue of whether this vaccine may be sending an overall message to teenagers that, 'We expect you to be sexually active,' " said Reginald Finger, a doctor trained in public health.

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Investigational Vaccine

- ❖ Gardasil can reduce cervical cancer, but the vaccine won't completely get rid of the disease.
- ❖ Some cervical cancers aren't caused by the types of HPV targeted by the vaccine. Vaccinated women would still need to get Pap tests to check for abnormalities in their cervical cells.
- ❖ The vaccine isn't intended to prevent cervical cancer in women who have previously been infected by HPV. It's not designed to treat cervical cancer or HPV infection.

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Investigational Vaccine

- ❖ Another cervical cancer vaccine, GlaxoSmithKline's Cervarix, is also in the works
- ❖ Cervarix has shown 100% effectiveness against HPV 16 and 18 in phase II studies. Phase III studies of Cervarix are under way.
- ❖ Other cervical cancer researchers are trying to develop additional vaccines.

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Investigational Vaccine

- ❖ One of those vaccines targets an HPV-related protein called L2. That vaccine is made from bacteria, which is "a relatively inexpensive way to make a vaccine
- ❖ Another possible vaccine is being developed by researchers including Tzyy-Chouu Wu, MD, of Johns Hopkins University. It uses DNA to target HPV-related proteins in the hopes that the vaccine might help treat as well as prevent cervical cancer.

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Pearls for PAP Test Result Interpretation and Treatment.

- ❖ ASCUS and AGUS are not the same, AGUS is much more concerning and demands an evaluation of glandular elements including cervical and endometrial glands.
- ❖ ASCUS plus positive for high risk HPV; don't repeat pap, proceed to colposcopy.

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Pearls for PAP Test Result Interpretation and Treatment.

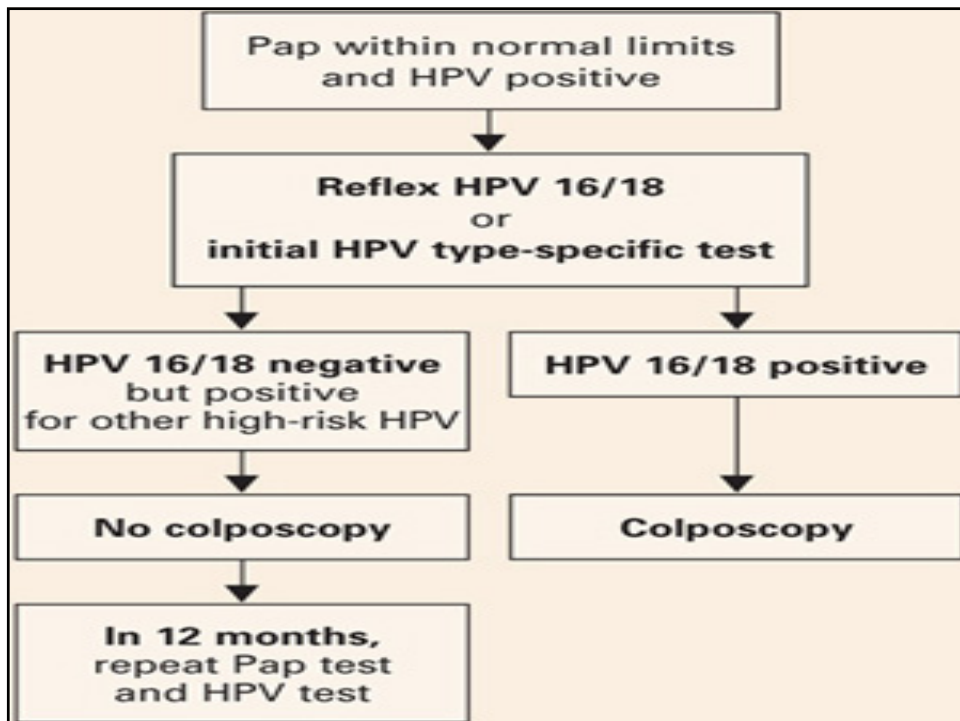
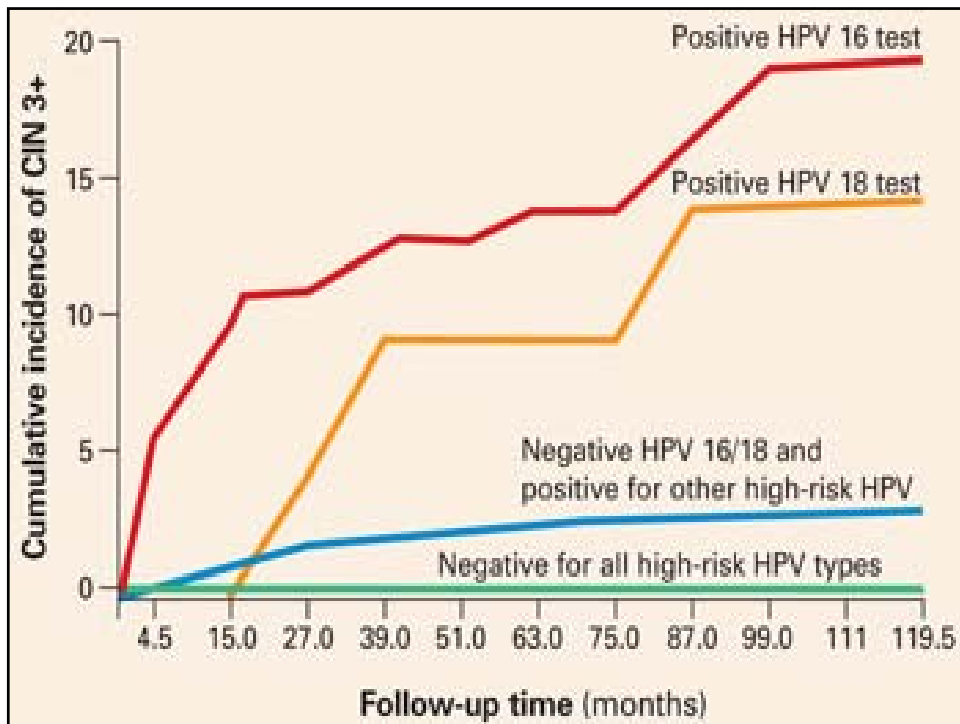
- ❖ Don't overtreat ASCUS or LSIL colposcopic findings, especially in young nulliparous women.
- ❖ 15 to 30 percent of women with LSIL pap will harbor moderate to severe CIN, the remainder will either have no lesion or a mild CIN.
- ❖ Younger women have a higher probability of spontaneous resolution of HPV infection with clearance of the pap and colposcopic findings

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Pearls for PAP Test Result Interpretation and Treatment.

- ❖ Equivocal and mildly irregular Pap tests are the most frequent abnormal cytologic finding, and follow-up is controversial. Options such as repeat serial cytology or referral for immediate colposcopy have significant drawbacks.
- ❖ Testing for high-risk HPV is the preferred approach to follow-up for all women with ASC-US Pap results, as well as adolescents and low-risk postmenopausal women with LSIL Pap results. The HPV test is highly sensitive and specific for underlying moderate to severe CIN, especially in women over 30. HPV testing of liquid-based cytology specimens or HPV co-collection at the time of initial screening is the most cost-effective approach

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Other Recommendations

- ❖ What about the approximately 4% of women aged 30 and older with normal cytology and high-risk HPV?
- ❖ A panel of experts on HPV and cervical screening published “interim guidance” in 2004, recommending that until further data are available, these women should be retested in 6 to 12 months for persistence of HPV or development of abnormal cytology, and referred to colposcopy if still HPV-positive or if Pap results show low-grade squamous intraepithelial lesion (LSIL) or worse, regardless of HPV result

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Treatment Guidelines

- ❖ CIN 2/3 should usually be treated. The only exception is the adolescent with CIN 2, who may be followed with repeat cytology and colposcopy at 4 to 6 months if she is deemed reliable for follow-up, the colposcopy is adequate, and the endocervical sampling is negative.

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Treatment Guidelines

- ❖ An excisional procedure is required for: an unsatisfactory colposcopy in nonpregnant women referred for atypical glandular cells (AGC-H); , or adenocarcinoma in situ (AIS), or repeat atypical glandular cells “not otherwise specified” (AGC-NOS), or HSIL. The only exception is an adolescent with HSIL cytology and a satisfactory and normal colposcopy and biopsy, who may be followed closely.

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Treatment Guidelines

- ❖ Women treated for CIN 2/3 can be monitored after treatment by cytology screening at 6-month intervals 3 or 4 times or by a single HPV test at 6 months, before returning to annual screening. Any repeat abnormal Pap at the threshold of ASC-US or more advanced abnormality or a positive HPV test requires colposcopic evaluation.

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Can patients do anything to influence the course of this disease?

- ❖ Women in the ASCUS LSIL Triage (ALT) study were evaluated prospectively to determine whether systemic levels of folic acid are associated with the occurrence and duration of HPV infections after controlling for other micronutrients (vitamins B12, A, E, C, and total carotene) and for known risk factors for high-risk HPV infections and cervical cancer.

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Can patients do anything to influence the course of this disease?

- ❖ Women with higher folate status were significantly less likely to be repeatedly HPV positive, more likely to become test negative during the 2-year study, and 73% less likely to become newly HPV positive.
- ❖ Recommending oral folate supplements is one of the few things we can offer that can empower our patients with something positive that they can do for themselves.
- ❖ Also, for a variety of reasons, women who smoke are more likely to develop abnormal pap smears and cervical cancers.

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Thank you for your kind attention.



Prevention and Screening of Colorectal Cancer

Doug Schmitz, M.D.
Board Certified Surgeon
Banner Medical Clinic Surgery
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Colorectal Cancer

- ❖ 3rd most frequently diagnosed cancer in men and women
- ❖ 2nd leading cause of cancer death
- ❖ 5.9% of population—lifetime risk

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Colorectal Cancer Screening

- ❖ Particularly effective adenomatous polyps are precursors
- ❖ Localized disease-90% five year survival
- ❖ Only 37% colorectal cancer diagnosed early

86

Colorectal Cancer Screening

- ❖ <40% eligible population screened

87

ACS CRC Screening Recommendations

- ❖ Yearly FOBT or Immunochemical test (FIT)
- ❖ Flex sig every 5 years
- ❖ Yearly FOBT or FIT plus flex sig every 5 years
- ❖ Double contrast BE every 5 years
- ❖ Colonoscopy every 10 years

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New Screening Technologies

- ❖ CT Colonography (virtual colonoscopy)
- ❖ Immunochemical fecal occult blood tests
- ❖ Detection of altered DNA from stool

89

Virtual Colonoscopy

- ❖ Colon cleansing (bowel prep)
- ❖ Colon insufflated to tolerance (rectal tube)
- ❖ Scanned supine and prone
- ❖ 2D and 3D images

90

Virtual Colonoscopy: Advantages

- ❖ Sensitive and specific (polyps > 10mm)
- ❖ Frank lesions (100%)
- ❖ See difficult areas
- ❖ Provide roadmap for colonoscopist

91

Virtual Colonoscopy: Limitations

- ❖ 15% false positive
 1. Retained stool
 2. Diverticular disease
 3. Thick folds
 4. Metal/Motion artifact
 5. Flat adenomas
 6. Cost
 7. Not therapeutic (46% removable lesions)
 8. Learning curve for radiologists

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Virtual Colonoscopy

- ❖ Most published studies-high risk patients
- ❖ Radiologists highly experienced

- ❖ Clinical trials underway comparing colonoscopy with CT colonography in average and high risk populations

93

Colorectal Cancer Screening

- ❖ Immunochemical tests
 1. HemeSelect
 2. FlexsureOBT
 3. InSure
- ❖ Antibodies detect only human hemoglobin
- ❖ Not widely used clinically

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Immunochemical Tests Advantages

- ❖ Specificity – diet, drugs, vitamins, UGI blood
- ❖ Patient compliance- less handling of stool

95

Immunochemical Tests Disadvantages

- ❖ Limited clinical testing
- ❖ Sensitivity limitations (intermittent bleeding)

96

Immunochemical Tests

- ❖ Immunochemical tests are more patient friendly with equal or better sensitivity and specificity.

97

Screening for DNA Mutations

- ❖ DNA is a good marker
- ❖ Stable in the stool
- ❖ EXACT Sciences Corp.-prototype test targets 15 point mutations
- ❖ Appears to be highly sensitive

98

Advantages DNA Screening

- ❖ Neoplasm specific (low false positive)
- ❖ DNA consistently found in stool (one sample)
- ❖ Highly accurate (detects mutations with high degree sensitivity and specificity)
- ❖ Reduced false positives
- ❖ Detection aerodigestive cancers proximal to colon
- ❖ Cost (limit need for colonoscopy)

99

DNA Screening Limitations

- ❖ Lack clinical studies
- ❖ Test refinement
- ❖ Automation
- ❖ Cost (expensive now)
- ❖ Patient acceptance (entire BM to lab)

100

Capsule Video Endoscopy

- ❖ M2A Capsule in conjunction with the Given Diagnostic system
- ❖ Limited to use upper GI system (battery life of 8 hours)
- ❖ 2 pictures per second
- ❖ Slow transit time of colon and larger lumen
- ❖ No evidence to support use in CRC screening

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Surgery for Colon Cancer

- ❖ Complete resection bowel segment with draining lymph nodes
- ❖ 2 cm margin
- ❖ Anal sphincter

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Laparoscopic Techniques

- ❖ Oncologically safe?
- ❖ Multi-center prospective randomized trial ongoing
Quality-of-life component of this trial minimal
short term benefits with LAC

103

Staging

- ❖ TNM
- ❖ AJCC Stage groupings

- ❖ Older Dukes or Modified Astler-Coller
classification schemes not used for treatment
decisions

104

Adjuvant Therapy

- ❖ Stage 0- no
- ❖ Stage I- no
- ❖ Stage II- not for most unless clinical trial
- ❖ Stage III- yes, there are ongoing trials
- ❖ Stage IV or recurrent- depending on site either local resection or palliative chemo/radiation

105

Hepatic Metastasis

- ❖ 50% patients with CRC will have hepatic metastasis- initially or as a result of disease recurrence
- ❖ Based on number and location- Surgical Resection
(negative margin resection 5 year survival 25% to 40%)
- ❖ Unresectable
 - radiofrequency ablation
 - cryosurgery
 - embolization
- ❖ Adjuvant therapy ?

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Questions?

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Prevention and Screening of Colorectal Cancer

Doug Schmitz, M.D.
Board Certified Surgeon
Banner Medical Clinic Surgery
Torrington, WY

Colorectal Cancer

- 3rd most frequently diagnosed cancer in men and women
- 2nd leading cause of cancer death
- 5.9% of population—lifetime risk

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