

Scanning the Literature

by Mona Shalaby, MD, and Susan Vogel, MD

Mammograms in the Forties: One Answer Does Not Fit All

Harris R. Variation of benefits and harms of breast cancer screening with age.

J Natl Cancer Inst Monogr 1997;(22):139-143.

The critical issue in deciding whether to recommend breast cancer screening for women in their forties is to determine whether potential benefits are substantially greater than potential harms. Recent evidence from randomized clinical trials makes it likely that, after 10-12 years of follow-up, there is a real benefit from screening women ages 40-49, on the order of a 15-20% reduction in the relative risk of breast cancer death. This relative risk reduction translates into an absolute risk reduction of 1-2 women whose lives are extended from screening 1,000 women in their forties annually for 10 years (i.e., about one life extended per 5,000 mammograms). The absolute benefit of screening increases with age. Evidence about potential harms is less well established, but it is compelling that there are 15-40 times as many false positive as true positive mammograms (depending on the patient's age), and that at least some of the women

with false positive mammograms have ongoing psychological distress as a result. Some 30% of all women who are screened annually during their forties will have at least one false positive mammogram and this probability likely decreases with advancing age. If the balance between benefits and harms is judged to be a "close call" for women in their forties, a blanket recommendation for all is inappropriate. Instead, each woman in her forties should be helped to understand the pros and cons of screening, to clarify her own values, and to consider with her primary care physician what decision would be best for her.

Comments: On review of this article, and many others about breast cancer screening for women in their 40s, it becomes clear that there is no right answer for all. Reviewing the current data with patients gives them the opportunity to participate in decision making about their own care. That becomes a much healthier approach in such a debated topic.

To Use or Not to Use Estrogen, Alcohol, and Gene Therapy—That Is the Prevention Question

Alberg AJ, Visvanathan K, Helzlsouer KJ. Epidemiology, prevention, and early detection of breast cancer. *Curr Opin Oncol* 1998 Nov;10:492-497.

The evidence that alcohol consumption increases a woman's chances of getting breast cancer is now more persuasive. Higher blood concentrations of organochlorine compounds were not associated with increased risk of breast cancer in recent studies. The relationship of exogenous estrogen use to breast cancer risk is now clarified: current users of both oral contraceptives and hormone replacement therapy experience a slightly elevated risk that dissipates after cessation of use. Alcohol consumption and hormone replacement therapy are both associated with slightly increased breast cancer risk, but the overall health benefits of hormone replacement therapy and low levels of alcohol consumption appear to outweigh the risks in the general population. These circumstances underscore the complex decisions facing women and the need to consider individual risk factor profiles. For the genes *BRCA1* and *BRCA2*, more data are needed to understand the risks associated with specific mutations, optimal implementation of genetic testing, and prevention and early detection strategies for women who have positive test results. Interesting leads in identifying women at increased risk for breast cancer have been generated via the study of genetic polymorphisms. The results of tamoxifen in the Breast Cancer Prevention Trial have made the possibility of chemoprevention for breast cancer a reality. Raloxifene, another antiestrogen, has emerged as a potential chemopreventive agent. Its efficacy in reducing breast cancer risk will be compared with that of tamoxifen in a randomized trial.

Comments: Along with many others covering the topic, this article highlights the questions asked daily by many of our patients. "Do I use it or not?" Estrogen use, low alcohol intake, and *BRCA1* and *BRCA2* gene studies do not fit every patient's profile and risk. It is all about risk versus benefits.

Tamoxifen – What Do Women Need to Know?

Chang JC. A review of breast cancer chemoprevention. *Biomed Pharmacother* 1998;52:133-136.

Breast cancer remains a major cause of mortality and morbidity, and may be amenable to chemoprevention as estrogen stimulation is believed to be responsible for the promotion of this disease. Tamoxifen is the most widely studied compound for chemoprevention and clinical trials involving over 20,000 women world-wide are currently underway. This drug is well-tolerated with low acute toxicity and high compliance, and has a favorable profile in both decreasing serum cholesterol and increasing bone mineral density in postmenopausal women. However, there are fears of its potential carcinogenicity, especially an increased risk of endometrial cancers, which may jeopardize further recruitment and compliance of women in these chemoprevention studies. Meta-analyses of these studies are expected to be conducted in the year 2000 to address the efficacy of tamoxifen in women with an increased familial predisposition and in those with known germline *BRCA* mutations.

Comments: Breast cancer chemoprevention is a hot topic for our patients. Many questions asked by high-risk women as well as average risk patients are about tamoxifen. It appears to be crucial for patients to be informed of both tamoxifen's risk profile and benefits. We need to help our patients to assess their own individual risk and then to apply the pros and cons of tamoxifen to their own circumstances.

Special Populations – Are They Low Priority for Mammograms? Here Are the Facts

Partin MR, Korn JE, Slater JS. Questionable data and preconceptions: reconsidering the value of mammography for American Indian Women. Am J Public Health 1997 Jul;87:1100-1102.

Although the benefits of mammography are well established, many remain skeptical of the value of mammography for American Indian women. This skepticism stems in part from a belief that breast cancer is too rare an event among American Indians to warrant widespread screening. The validity of this assumption for Northern Plains Indians is challenged by a discussion of the limitations of available data on breast cancer in American Indian populations (including lack of generalizability, underestimation, and an over-reliance on relative rather than absolute measures of cancer incidence) and by findings from the Minnesota Breast and Cervical Cancer Control Program, a federally funded program providing free breast and cervical cancer screening to American Indian and other women in Minnesota. In light of this information, the authors recommend that the low priority of mammography for American Indian women be reconsidered.

Comments: The Minnesota Breast Cancer Control Program, like many others, brings to light the importance of ascertaining the validity of the priority criteria of certain practices. One must be very careful in reviewing data that leads to labeling special populations a low priority for screening. Much of that data and its interpretation can be challenged with either careful inspection or other studies.

Fine-Needle Aspiration – What Is the Verdict?

O’Neil S, Castelli M, Gattuso P, Kluskens L, Madsen K, Aranha G. Fine-needle aspiration of 697 palpable breast lesions with histopathologic correlation. Surgery 1997 Oct;122:824-828.

Background: Fine-needle aspiration breast biopsy has been used increasingly as an alternative to excisional biopsy. The purpose of this study is to evaluate the accuracy of fine-needle aspiration with histopathologic confirmation.

Methods: A retrospective study was performed using a computer database over a 5-year period. All women who had had fine-needle aspiration breast biopsy with histopathologic confirmation of the diagnosis were included. Fine-needle aspirations were interpreted as malignant, suspicious, or benign. Histopathologic diagnosis included core-needle biopsy, open excisional biopsy, or mastectomy specimen.

Results: A total of 697 patients fulfilled the criteria. Only 5 (0.7%) of the specimens were inadequate for study. There were 401 total malignant fine-needle aspiration diagnoses, with only 3 false-positive specimens. All three were ductal hyperplasia, one from a previously radiated breast. There were 125 suspicious readings; 84 of these were malignant and 41 were false-suspicious specimens. Most of the false-suspicious lesions were fibrocystic disease. Of the 166 lesions interpreted as benign, there were 13 false-negative specimens. The test had a 97% sensitivity, 78% specificity, 92% positive predictive value, and 92% negative predictive value.

Conclusions: Fine-needle aspiration is a sensitive test that can be useful as an adjunct in the diagnosis of breast cancer. “Malignant” and “benign” interpretations are highly predictive but must be used only in the context of other diagnostic modalities. “Suspicious” lesions require further investigation.

Comments: Will fine needle aspiration decrease the need for many of the excisional and core biopsies in women? This retrospective study indicates it is a sensitive test and has potential. Because of 8% false negatives in benign appearing aspirate specimens, suspicious lesions always require further evaluation.

Alternative Medicine, Somewhere Between Hope and Reality

Rose RC. Vitamin supplementation and breast cancer: is homeostasis a factor? Med Hypotheses 1998; 51:239-242.

Recent observations by several research groups on many thousands of women have yielded the disappointing view that mega-dose vitamin supplementation does not provide significant protection against breast cancer. This is a review of the pertinent literature with a goal of identifying testable hypotheses that might explain the epidemiology and be helpful in designing subsequent evaluations. In one hypothesis presented, the vitamin content of peripheral cells that protect breast endothelium is not markedly affected by supplementation. In the second hypothesis the metabolic status level (redox state) of epithelial cells is more important than the absolute level (reduced plus oxidized) of each anti-oxidant. In either case, extremes in diet fail to alter inherent homeostatic mechanisms.

Comments:

“Do you think it works?” This is the question frequently asked by the patients who bring in a bottle of vitamins, herbs, or nutritional supplements and the best answer for now is pointing out the facts as we know them. Millions of dollars are spent on nutritional supplements and vitamins alike and more studies are needed to justify a stand for or against their use in particular conditions.



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Mammography for Women 75 and Older?

Morrison AS. Efficacy of screening for breast cancer in older women.

J Gerontol 1992; 47(Special Issue):80-84.

The effect of screening on mortality from breast cancer has been evaluated in four intervention (experimental) studies with random assignment, one intervention study with nonrandom assignment, three case-control studies, and one follow-up study. Each of these studies showed a beneficial effect of screening among women who were at least 45, 50, or 55 years old at entry, but there is almost no information available on the value of screening women more than 74 years old. The data are not helpful in choosing a screening interval within the range 12-33 months, or in deciding whether to screen by mammography and palpation combined or by mammography alone. Additional issues in screening very old women are the delay before the effect of screening appears, the high mortality from causes other than breast cancer, and the effect of previous screening.

Comments: Professor Morrison of Brown University reviews nine prominent studies of various designs, beginning with the Health Insurance Plan (HIP) study begun in 1963 (the first to show a mortality benefit from offering screening mammography). These studies reveal a mortality advantage for those offered mammography that begins 5 to 6 years after the first offer of screening. In a woman whose life expectancy is significantly less than 5 years, one might consider recommending clinical breast examination but not mammography.

The Importance of Mammography for Older Women

Glasse L. Breast cancer screening in older women: The consumer perspective.

J Gerontol 1992; 47(Special Issue): 137-141.

Fear of cancer and weak support from physicians make it difficult to encourage women to have regular mammograms. An effective campaign of broad mammography screening should be aimed at both health professionals and women. Essential to this screening is a public policy that establishes public and private insurance coverage. Barriers, including high cost, must be eliminated. Effective organization can succeed in reaching more older women for screening. Rationing breast cancer screening, at a time when the incidence of breast cancer is increasing, violates fundamental beliefs in equality and justice. Proposals to limit or to expand screening require a defensible and supportable rationale. Health professionals should not decide for patients whether they should have a mammogram and what treatment is best. The physician should counsel and assist the patient or the surrogate to decide on an appropriate plan of care.

Comments: Older women hold the advice of their physicians in high regard. Ms. Glasse, President of the Older Women's League, asked the public health and medical communities, and specifically physicians, to take responsibility for creating "the conditions that permit the older female patient to understand and accept the importance of mammography." Since this 1990 conference, breast cancer awareness has increased in the United States, and Medicare has begun payment for mammogram screening in older women, but it is not clear that this has resulted in significantly increased rates of mammography among women over 75.

Mammography for Women 75 and Older? Part 2

Cassel CK. Breast cancer screening in older women: Ethical issues.

J Gerontol 1992; 47(Special Issue): 126 – 130.

No abstract available.

Comments: Among other issues, Dr. Cassel (currently Professor of Geriatrics at Mt. Sinai School of Medicine, President of the American Board of Internal Medicine, and at the time of this article, a fellow at the Center for Advanced Study in the Behavioral Sciences, Pritzker School of Medicine, University of Chicago) tackles the question of mammography screening among significantly demented older patients. She argues that if we are treating hypertension in these women, should we not offer clinical breast examinations and mammographic screening? If we would recommend surgery for a lump detected by clinical examination, should we not perform screening mammography? She argues that advanced breast cancer is “a very disabling and painful disease,” and screening can decrease the chance of dying from advanced breast cancer, even if it confers no overall mortality advantage. Breast cancer “can be a terrible way to die... screening could result in a substantial improvement in quality of life without necessarily demonstrating a reduction in overall death.”

Most large published studies of breast cancer screening by mammography have not included large numbers of those over 75. However, the proportion of false positive mammograms seems to decrease with age, due to both the increased incidence of breast cancer with age as well as the increase in the proportion of breast fat with age, which makes radiological interpretation more reliable. So there is no reason to doubt that mammography can find curable breast cancers earlier, even among those of advanced age.

A common geriatric theme is that there is a remarkable heterogeneity in health status, independence, enjoyment of life, social support, financial status, and personal and cultural values among older women of similar chronological age, and this variation should be considered in making recommendations to individual patients. In addition, it is noted that time constraints and reimbursement for office and nursing home visits make it

difficult to have the ideal discussions with patient and family regarding risks and benefits of breast cancer screening. Even a simple clinical breast examination takes longer in many older women when one considers the time to undress and ascend the examination table, etc.

As a physician specializing in long-term geriatric care, my personal practice for those women in whom I project a non-vegetative life expectancy of 5 years or more is to perform clinical breast examination yearly and to discuss screening mammography when possible.

The preceding reviewed articles are from:

The Journal of Gerontology 1992 Vol. 47 Special Issue

Breast Cancer Screening in Older Women

Recommendations, Supporting Statements, and Background Papers Sponsored by the National Cancer Institute, National Institute on Aging, Health Care Financing Administration, and the University of Massachusetts Medical School

Age Bias in Breast Cancer Treatment Is a Reality

Hebert-Croteau N, Brisson J, Latrielle J, et al. Compliance with consensus recommendations for the treatment of early stage breast carcinoma in elderly women. Cancer 1999; 85:1104-1113.

Background: The goal of this study was to assess variations with age in the management of breast carcinoma and to identify determinants of care received.

Methods: A stratified random sample was selected among women age ≥ 50 newly diagnosed with lymph node negative breast carcinoma in Quebec in 1988, 1991, and 1993. Information was abstracted from medical charts. Predictors of definitive locoregional treatment (total mastectomy with lymph node dissection or breast-conserving surgery with both axillary lymph node dissection and radiation therapy) were identified by multiple logistic regression analysis.

Results: Overall, 1174 patients age ≥ 50 years with breast carcinoma were included. Women ≥ 70 years were much less likely to receive definitive locoregional treatment compared with women ages 50-69 years (48.7% vs 83.5%; $P < 0.0001$). Older women were less likely to undergo surgery with breast preservation (76.7% vs 86.3%; $P < 0.0001$), radiation therapy (54.7% vs 90.5%; $P < 0.0001$), dissection of the axillary lymph nodes (55.6% vs 86.3%; $P < 0.0001$), or chemotherapy (1.2% vs 13.9%; $P < 0.0001$), but not treatment with tamoxifen (66.4% vs 64.7%; $P < 0.41$). Adjusting for comorbidity and other characteristics related to the disease, the hospital, and the attending physician, age remained a strong determinant of the probability of receiving definitive locoregional treatment (odds ratio [OR], 0.14; 95% confidence interval [95% CI], 0.12-0.18 for women age ≥ 70 years vs women ages 50-69 years). The same association was observed when women who did not undergo lymph node dissection but who received systemic adjuvant treatment were considered to have received definitive therapy (OR, 0.13; 95% CI, 0.10-0.17) for women ages ≥ 70 years vs women ages 50-69 years).

Conclusions: Less aggressive patterns of care are provided to elderly breast carcinoma patients, independent of comorbidity. This could explain, at least in part, the sustained breast carcinoma mortality in this population.

Comments: Thirty percent (30%) of invasive breast cancers are diagnosed in women over 70 years of age. In this age group, the mortality rate from breast cancer has not shown the same modest decline in recent years as in younger women.

Elderly cancer patients may not receive optimum treatment for their tumors for reasons that are separate from their health, projected life expectancy, or wishes. Surprisingly, in this study, the differences in treatment were not explained by the number or severity of comorbid conditions, although the functional status of the patients at the time of diagnosis was not recorded. Patients in hospitals admitting less than 100 patients with newly diagnosed early stage breast cancer annually, as well as those in hospitals participating in clinical trials, were more likely to have had definitive local-regional therapy ordered. Physicians in practice more than 30 years (and presumably older?) were twice as likely to prescribe the recommended therapy as their colleagues in practice for less

than 10 years. Since all of the patients were considered "early stage," this study did not need to confront the frequently documented finding that older women, on average, present with a more advanced stage of breast cancer than their younger counterparts. Other than age, differences in treatment given might have been due to:

1. Pronounced differences in functional status among the older patients that were not evident in the hospital chart.
2. The outpatient prescriptions of recommended local-regional therapies, which were not apparent in the hospital charts; however, there is no particular reason why this should have occurred more in the older patients.
3. An increased proportion of older patients who refused further therapies, although those refusals were not documented in the charts. There is evidence from other sources that older women have more fears about radiation, hormonal, and chemotherapies than younger women.

Information from this study is in concordance with studies of other types of cancer that indicate a possible age bias in the treatment of malignancies in older people, which may not be defensible on physiologic grounds. When one considers that an 85-year-old woman has a life expectancy of approximately 7 years, each of us, whether primary care or sub-specialist physician, must be sure that we do not contribute to a decrement in that life expectancy or a fall-off in the quality of life due to a bias based simply on age.

Estrogen Receptor Concentrations in Older Breast Cancer Patients

Ashba J, Traish AM. Estrogen and progesterone receptor concentrations and prevalence of tumor hormonal phenotypes in older breast cancer patients. *Cancer Detect Prev* 1999; 23: 238-244.

We examined the concentrations of estrogen (ER) and progesterone receptors (PR) and the distribution of tumor phenotypes as a function of age in breast cancer patients. ER and PR concentrations were determined in tissue biopsies from 1739 patients with primary breast cancer, using ligand binding assays. Tumors were classified as estrogen receptor positive (ER+) or negative (ER-) and

progesterone receptor positive (PR+) or negative (PR-) based on the presence or absence of receptor binding activity. Tumors were stratified into four phenotypes: ER+PR+; ER+PR-; ER-PR+; and ER-PR-. Significant positive associations were found between ER concentration and age ($p = 0.0001$) and between PR concentration and age ($p = 0.0002$). The median ER concentrations were statistically different by age groups, with the greatest levels in older versus younger patients. The prevalence of ER+PR+ tumor phenotype increased with age. In contrast, the prevalence of ER-PR- and ER-PR+ tumor phenotypes decreased with age. The median PR-to-ER ratio decreased with age ($p = 0.0001$), and this trend was attributed to increased ER concentration with age. The prevalence of ER-PR- and ER-PR+ tumor phenotypes is greater in younger patients suggesting that hormonal regulation of ER gene expression may be responsible for the observed age disparity of tumor phenotypes in breast cancer.

This is one of a small number of studies that included a substantial number of women over the age of 74 (the “older old”) and documented the increased likelihood of positive receptor status in older women. This study also confirmed the increased *concentration* of estrogen receptors in older women, although unfortunately it did not correlate duration of postmenopausal hormone exposure with the concentrations of ER and PR, leaving the following questions for future studies:

1. Do women who use postmenopausal hormones into advanced age have the same increased levels of ER as women who have only low levels of endogenous hormones for many years after menopause?
2. If not, is the effectiveness of adjuvant antiestrogen therapy as effective in long-term hormone users as in those who used them for shorter periods or not at all?

Comments: The continued expression of estrogen receptor (ER) and progesterone receptor (PR) in human breast cancer is associated with disease-free survival. In addition, receptor status is a factor in deciding to prescribe hormonal treatments, principally antiestrogens, for breast cancer. The *presence* of ER and PR both increased linearly with age, but the *concentration* of only ER (not PR) increased linearly with age. Nearly 80% of patients over age 74 had ER+PR+ tumors, while only about 55% of breast cancer patients under age 45 years of age had this favorable profile.

The authors speculate that diminished circulating hormones after menopause allow for up-regulation of the expression of hormonal receptors. If that is the case, one might infer that women who take postmenopausal hormone replacement therapy (HRT) (either estrogen alone or estrogen/progesterone) might have lower concentrations of ER and PR in their breast cancers and possibly have a decreased disease-free survival than matched women who did not take hormones. Unfortunately, the authors did not have data about the administration, type, or duration of HRT in relation to the receptor concentrations.



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