Breast Cancer™ UPDATE

Conversations with Clinical Research Leaders

Bridging the Gap between Research and Patient Care

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Breast Cancer™ UPDATE

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How to use this monograph

This is a CME activity that contains both audio and print components. To receive credit, the participant should listen to the CD or tape, review the monograph and complete the post-test and evaluation form. This monograph contains edited comments, clinical trial schemas, graphics and references, which supplement the audio program and the website, **BreastCancerUpdate.com**, where you will find an easy-to-use interactive version of this monograph with links to relevant full-text articles, abstracts, trial information and other web resources indicated here in **red underlined text**. This regularly updated website also features an extensive breast cancer bibliography, clinical trial links, a "breast cancer web tour" and excerpts from interviews and meetings catalogued by topic.

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Editor's Note

Presenting Options and Making Recommendations

"Over the past 30 years, we have gone from a fairly paternalistic approach to medicine to the other extreme, and many of my colleagues have become so neutral that they do not make a recommendation. The burden of deciding has been removed completely from the physician — who is best qualified to make that choice or recommendation — to the patient, who sometimes is, but most often is not in the best position to make that choice. I understand that patients have autonomy — as they well should — and I think we have the obligation to inform them fully and as best as we can. We need to go beyond that. We need to get to know patients and understand what drives them and help them to make decisions. Obviously our recommendation will reflect our biases and prejudices, but we are better qualified than someone who just had 'oncology 101' during the previous 20-30 minutes."

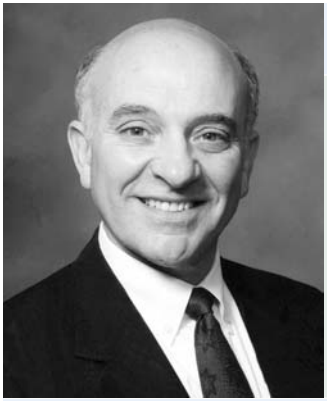
— Gabriel Hortobagyi, MD

This series provides me with the enviable opportunity to chat with some of the great minds in cancer medicine. What I have always found most fascinating about these conversations is learning how these research leaders integrate cutting edge trial results into daily patient care. On the enclosed program, Gabe Hortobagyi is unflinching in his criticism of colleagues who, in his mind, have been slow to react to the ATAC trial data, which on most recent follow-up continue to demonstrate a disease-free survival and toxicity advantage to anastrozole versus tamoxifen.

The theme of research and its implications in clinical practice has always underscored this series. In this edition, Armando Giuliano delineates the border between accepted practice and research as it relates to sentinel node biopsy, Richard Margolese comments on the management of women with DCIS, and Susan Love reviews what we do and do not know about management of women at high risk for breast cancer.

I am interested in your suggestions for future speakers and program topics. Please email me any comments at nlove@med.miami.edu. I look forward to hearing from you soon.

—Neil Love, MD



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Edited comments by Dr Giuliano

ACOSOG-Z0010 trial: Enhanced sentinel node pathology and iliac crest bone marrow aspiration in patients with negative sentinel nodes

ACOSOG-Z0010 is a prospective observational trial designed to determine the clinical significance of sentinel node and bone marrow micrometastases. A number of studies show that bone marrow micrometastases have the same adverse implications as lymph node micrometastases. A patient with negative lymph nodes but positive bone marrow will have a similar outcome as a patient with lymph node metastases.

Interestingly, bone marrow metastasis appears to be an independent prognostic factor, indicating a different metastatic pathway. While lymph node metastases have a lymphatic pathway, bone marrow metastases may have more of a direct systemic pathway.

We may be able to more accurately differentiate high-risk versus low-risk patients by combining lymph node and bone marrow examination. Perhaps patients with both negative bone marrow and a negative lymph node by immunohistochemistry have a very low risk of metastatic disease and don't need adjuvant therapy. Z0010 will tell us so much more about the biology of breast cancer and may cause us to re-examine how we treat especially those patients with node-negative disease.

ACOSOG-Z0011 trial: Axillary dissection versus observation

The ACOSOG-Z0011 trial is a very important trial because we've being doing axillary dissection for over 100 years, and we are still uncertain of its survival benefit. NSABP B-04 is a classic breast cancer study, and even with 26 years of follow-up, there is no survival difference between patients who had imme-

diate dissection and those who did not have axillary dissection unless they had an axillary recurrence.

Z0011 examines the role of axillary dissection in node-positive patients. It's hard to imagine that removing 20 lymph nodes is of value in a node-negative patient, so we are looking only at the node-positive patients. In essence we're doing a "high-tech NSABP B-04."

Patients with H&E metastases are randomized to axillary dissection or no axillary dissection and no axillary radiation. Patients are treated with adjuvant systemic therapy, as indicated. This is a very difficult randomization for physicians and patients to accept. The study has been open for about three years and we've accrued 400 out of our target of 1,800 patients.

PHASE III PROGNOSTIC STUDY OF SENTINEL NODE AND BONE MARROW MICROMETASTASES IN WOMEN WITH STAGE I OR IIA BREAST CANCER Open Protocol

Protocol IDs: ACOSOG-Z0010, GUMC-00152
Projected Accrual: 5,300 patients

Eligibility	Stage I or IIA breast carcinoma diagnosed within 60 days of planned sentinel lymph node dissection

Protocol	Bilateral anterior iliac crest bone marrow aspiration to test for micrometastases → lumpectomy +SLND

Sentinel node + → ACOSOG - Z0011

Patients with no sentinel node identified intraoperatively and patients with sentinel node metastases identified by H & E who choose not to be registered to ACOSOG-Z0011 undergo ALND.

Study Contact:
Armando E Giuliano, Chair. Tel: 310-829-8089
American College of Surgeons Oncology Group

SOURCE: NCI Physician Data Query, February 2003

PHASE III RANDOMIZED STUDY OF AXILLARY LYMPH NODE DISSECTION IN WOMEN WITH STAGE I OR IIA BREAST CANCER WHO HAVE A POSITIVE SENTINEL NODE Open Protocol

Protocol IDs: ACOSOG-Z0011, GUMC-00153
Projected Accrual: 1,900 patients

ARM 1	ALND involving removal of at least level I and II nodes, followed by whole breast radiotherapy (exclusive of a third supraclavicular field) 5 days a week,for a maximum of 7 weeks
ARM 2	Breast radiotherapy only as in Arm 1

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Armando E Giuliano, Chair. Tel: 310-829-8089
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SOURCE: NCI Physician Data Query, February 2003

NSABP B-32 trial of axillary dissection versus no further axillary surgery

NSABP B-32 has a different design than the American College of Surgeons' trials. Patients whose sentinel node is negative are randomized to axillary dissection or no axillary dissection. The study will confirm the accuracy of SLNB and evaluate the clinical recurrence rate and overall survival in a randomized setting. They will also try to determine the prognostic significance of IHC-detected micrometastases. It's an important trial that has accrued approximately 3,500 patients.

Clinical use of endocrine therapy by surgeons

Some surgeons prescribe their own hormonal manipulation, and those physicians will continue to do so as aromatase inhibitors are introduced into practice. Many patients have a fear of tamoxifen. Some women with high-risk breast cancer say, "I don't want to take tamoxifen — it causes cancer." Patients often complain about hot flashes, which affect their quality of life. They also express concerns about endometrial cancer, deep vein thrombosis and even weight gain. Once you start to weigh the risks and rewards there's no question tamoxifen is of tremendous value; however, a drug with fewer side effects would be more tolerable to patients. Anastrozole has fewer side effects and is at least as effective as tamoxifen — it is very easy to use.

Select publications

Branagan G et al. **Detection of micrometastases in lymph nodes from patients with breast cancer.** *Br J Surg* 2002;89(1):86-9. **Abstract**

Carcoforo P et al. **Prognostic and therapeutic impact of sentinel node micrometastasis in patients with invasive breast cancer.** *Tumori.* 2002;88(3):S4-5. **Abstract**

den Bakker MA et al. **Non-sentinel lymph node involvement in patients with breast cancer and sentinel node micrometastasis; too early to abandon axillary clearance.** *J Clin Pathol* 2002;55(12):932-5. **Abstract**

Grube BJ, Giuliano AE. **Observation of the breast cancer patient with a tumor-positive sentinel node: Implications of the ACOSOG Z0011 trial.** *Semin Surg Oncol* 2001;20(3):230-7. **Abstract**

Guenther JM et al. **Axillary dissection is not required for all patients with breast cancer and positive sentinel nodes.** *Arch Surg* 2003;138(1):52-6. **Abstract**

Harlow SP, Krag DN. **Sentinel lymph node--why study it: Implications of the B-32 study.** *Semin Surg Oncol* 2001;20(3):224-9. **Abstract**

Liang WC et al. **Is a completion axillary dissection indicated for micrometastases in the sentinel lymph node?** *Am J Surg* 2001;182(4):365-8. **Abstract**

Mignotte H et al. **Axillary lymph-node dissection for positive sentinel nodes in breast cancer patients.** *Eur J Surg Oncol* 2002;28(6):623-6. **Abstract**

Noguchi M. **Therapeutic relevance of breast cancer micrometastases in sentinel lymph nodes.** *Br J Surg* 2002;89(12):1505-15. **Abstract**

Schwartz GF et al. **Proceedings of the consensus conference on the role of sentinel lymph node biopsy in carcinoma of the breast April 19 to 22, 2001, Philadelphia, Pennsylvania.** *Hum Pathol* 2002;33(6):579-89. **Abstract**

Tjan-Heijnen VC et al. **Micro-metastases in axillary lymph nodes: A reduction of the sentinel lymph node procedure.** *Breast Cancer Res Treat* 2001;70(2):81-8. **Abstract**

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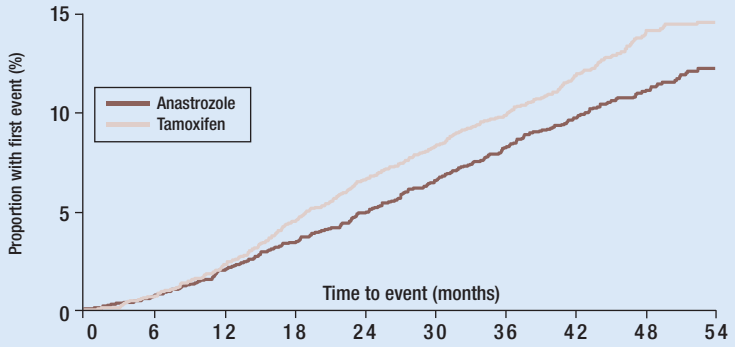
Edited comments by Dr Hortobagyi

Implications of the ATAC trial in clinical practice

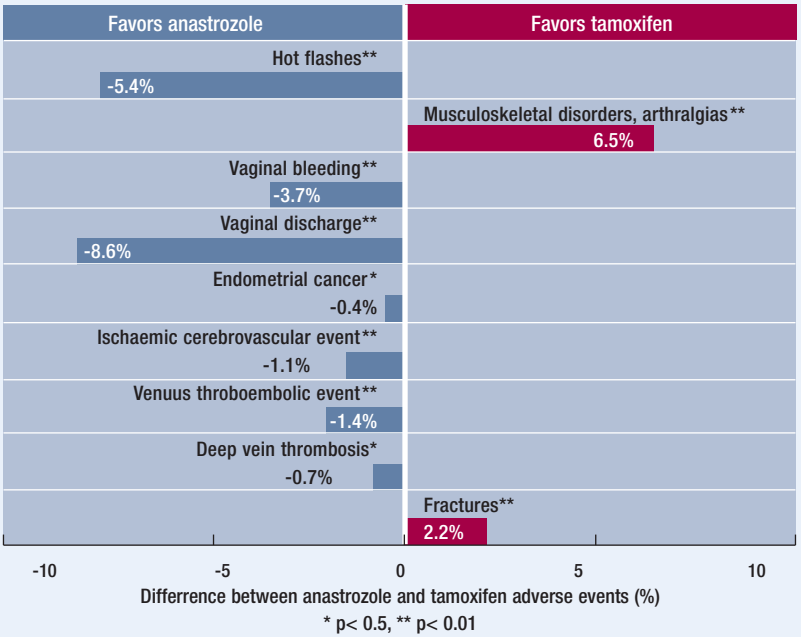
The results of the ATAC trial are quite compelling. Even if you assume for the sake of argument that the curves will come together with further follow-up, the safety profile of anastrozole is still clearly better than tamoxifen. I cannot prevent endometrial cancer short of removing the uterus, but I can prevent or treat osteoporosis and fractures. Since the safety profile of anastrozole is better than tamoxifen and it is therapeutically superior, I have a problem not offering anastrozole to my patients — not as a neutral choice but as a better choice. I do discuss with my patients the enormous amount of clinical experience we have with tamoxifen, but if my sister developed breast cancer today, I would certainly recommend anastrozole as opposed to tamoxifen.

Probability of first event in receptor-positive population



DERIVED FROM: Presentation, A Buzdar, San Antonio Breast Cancer Symposium 2002. Reproduced with permission.

Significant differences in pre-defined adverse events



DERIVED FROM: **Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: First results of the ATAC randomised trial.** *Lancet* 2002;359:2131-39.

Use of other aromatase inhibitors in the adjuvant setting

I do not use the other aromatase inhibitors in the adjuvant setting because there are no data. While we have to extrapolate in a number of situations, I do not see an advantage for the other aromatase inhibitors from the existing data. It is possible that some time in the future someone will show a distinct advantage of one of these other agents, but at this point, the data were generated with anastrozole, so I use anastrozole.

Recommending adjuvant anastrozole based on early trial results

The ASCO technology assessment that does not support the use of adjuvant anastrozole outside a clinical trial is based on fear of the unknown in the face of the single largest clinical trial ever conducted in the adjuvant setting. We have no comparable trial in the history of medical oncology or breast cancer, and there is no other tumor type with so many well-planned clinical trials conducted. We are in a leadership position in oncology, and we can't advocate doing the best trials and then ignore the results of those trials. Every single trial we do brings with it some of the unknown.

We started to move over to tamoxifen well before we had a five-year follow-up. I remember when Michael Baum presented the early data from the NATO trial in 1982. It had less than two years of follow-up, and he was already publicly talking about the advantages of adjuvant tamoxifen — and the NATO trial pales in size and design in comparison to the ATAC trial.

We have very compelling data about anastrozole from the ATAC trial, in terms of its therapeutic and safety profile superiority. I would be doing a disservice to my patients who are candidates for adjuvant anti-aromatase therapy by not presenting the data. I also present tamoxifen as an option, but in the last six months about 60 percent of my postmenopausal patients chose anastrozole rather than tamoxifen. There is no right or wrong decision, but for me, there are compelling data to prefer one versus the other.

Select publications

Use of aromatase inhibitors in the adjuvant setting

Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: First results of the ATAC randomised trial. *Lancet* 2002;359(9324):2131-9. **Abstract**

Pharmacokinetics of anastrozole and tamoxifen alone, and in combination, during adjuvant endocrine therapy for early breast cancer in postmenopausal women: A sub-protocol of the 'Arimidex and tamoxifen alone or in combination' (ATAC) trial. *Br J Cancer* 2001;85(3):317-24. **Abstract**

Baum M. **The ATAC (Arimidex, Tamoxifen, Alone or in Combination) adjuvant breast cancer trial in postmenopausal patients: Factors influencing the success of patient recruitment.** *Eur J Cancer* 2002;38(15):1984. **Abstract**

Baum M. **A vision for the future?** *Br J Cancer* 2001;85 Suppl 2:15-8. **Abstract**

Bianco AR. **ATAC ('Arimidex', Tamoxifen, Alone or in Combination) trial — Anastrozole is superior to tamoxifen as adjuvant treatment in postmenopausal women with early breast cancer.** *Breast Cancer Res Treat* 2002;**Abstract 632**.

Buzdar A. **The ATAC ('Arimidex', Tamoxifen, Alone or in Combination) trial in postmenopausal women with early breast cancer — Updated efficacy results based on a median follow-up of 47 months.** *Breast Cancer Res Treat* 2002;**Abstract 13**.

Buzdar AU. **New generation aromatase inhibitors — From the advanced to the adjuvant setting.** *Breast Cancer Res Treat* 2002;75 Suppl 1:S13-7; discussion S33-5. **Abstract**

Buzdar AU. **Anastrozole (Arimidex) — An aromatase inhibitor for the adjuvant setting?** *Br J Cancer* 2001;85 Suppl 2:6-10. **Abstract**

Goss PE. **Preliminary data from ongoing adjuvant aromatase inhibitor trials.** *Clin Cancer Res* 2001;7(12 Suppl):4397s-4401s; discussion 4411s-4412s. **Abstract**

Jones SE. **Antiaromatase agents: Evolving role in adjuvant therapy.** *Clin Breast Cancer* 2002;3(1):33-42. **Abstract**

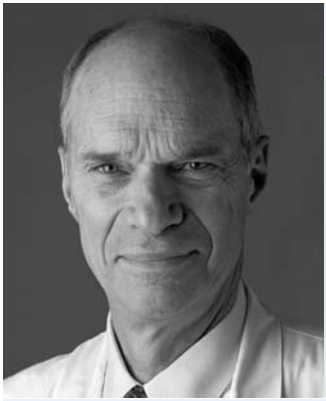
Mokbel K. **The evolving role of aromatase inhibitors in breast cancer.** *Int J Clin Oncol* 2002;7(5):279-83. **Abstract**

Ragaz J. **Adjuvant trials of aromatase inhibitors: Determining the future landscape of adjuvant endocrine therapy.** *J Steroid Biochem Mol Biol* 2001;79(1-5):133-41. **Abstract**

Sainsbury R. **Beneficial side-effect profile of anastrozole compared with tamoxifen confirmed by additional 7 months of exposure data: A safety update from the 'Arimidex', Tamoxifen, Alone or in Combination (ATAC) trial.** *Breast Cancer Res Treat* 2002;**Abstract 633**.

Wellington K, Faulds DM. **Anastrozole in early breast cancer.** *Drugs* 2002;62(17):2485-92. **Abstract**

Winer EP et al. **American Society of Clinical Oncology technology assessment on the use of aromatase inhibitors as adjuvant therapy for women with hormone receptor-positive breast cancer: Status report 2002.** *J Clin Oncol* 2002;20(15):3317-27. **Abstract**



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Prior NSABP clinical trials in patients with DCIS

B-17 was a trial comparing lumpectomy with or without radiation. Local control was improved with radiation; it cut recurrences in half for both invasive and noninvasive cancers. Overall survival was essentially the same for both groups, and the incidence of breast cancer related deaths was exactly as expected, a little over one percent.

The results from B-17 were very reassuring. The study proved that DCIS is a locally controllable disease, and that just like in invasive cancer, radiation therapy helps with local control.

B-17 set the stage for testing the role of adjuvant tamoxifen. So, B-24 was virtually the same protocol in terms of eligibility and characteristics of the patients. In B-24, adding tamoxifen to radiation and lumpectomy improves disease control even more than radiation alone.

NSABP B-35: Anastrozole versus tamoxifen

It is clear that DCIS is a highly curable disease from which almost no one should die. If tamoxifen and radiation therapy can reduce the incidence of future invasive cancer to less than two percent, can we achieve even better results?

On the other hand, there are more promising drugs, such as anastrozole. I think it is worthwhile to test anastrozole and see if the small amount of undesired recurrent cancers can be negated. The question becomes: Will anastrozole be any better than tamoxifen and at what risk?

NASBP B-35 is a large study with 3,000 patients, which will go on for the next five years. It is restricted to postmenopausal patients with DCIS who

have ER-positive tumors. Studies in the advanced and adjuvant settings found that anastrozole was at least as good as tamoxifen and perhaps superior. Also, the toxicity was less worrisome — anastrozole doesn't cause uterine cancer or thromboembolism. The issues with anastrozole are that it can't be used in premenopausal women and that it may cause osteoporosis, which can be a serious cause of mortality in elderly women.

PHASE III RANDOMIZED STUDY OF ANASTROZOLE VERSUS TAMOXIFEN IN POSTMENOPAUSAL WOMEN WITH DUCTAL CARCINOMA *IN SITU* OF THE BREAST UNDERGOING LUMPECTOMY AND RADIOTHERAPY Open Protocol

Protocol IDs: NSABP-B-35, CTSU
Projected Accrual: 3,000 Patients

Eligibility	Postmenopausal women with DCIS treated with lumpectomy, ER-/PR-positive or borderline

ARM 1	Tamoxifen + placebo qd x 5 yrs + XRT
ARM 2	Anastrozole + placebo qd x 5 yrs + XRT

Study Contact:
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National Surgical Adjuvant Breast and Bowel Project
Tel: 514-342-3504

SOURCE: NCI Physician Database Query, February 2003.

Select publications

Ernster VL et al. **Detection of ductal carcinoma in situ in women undergoing screening mammography.** *J Natl Cancer Inst* 2002;94(20):1546-54. Abstract

Fisher ER et al. **Pathologic findings from the National Surgical Adjuvant Breast Project (NSABP) eight-year update of Protocol B-17: Intraductal carcinoma.** *Cancer* 1999;86 (3): 429-38. Abstract

Fisher Bet al. **Tamoxifen in treatment of intraductal breast cancer: National Surgical Adjuvant Breast and Bowel Project B-24 randomised controlled trial.** *Lancet* 1999;353 (9169): 1993-2000. Abstract

Fisher B et al. **Prevention of invasive breast cancer in women with ductal carcinoma in situ: An update of the national surgical adjuvant breast and bowel project experience.** *Semin Oncol* 2001;28 (4): 400-18. Abstract

Hoque A et al. **Her-2/neu gene amplification in ductal carcinoma in situ of the breast.** *Cancer Epidemiol Biomarkers Prev* 2002;11(6):587-90. Abstract

Rodrigues N et al. **Correlation of clinical and pathologic features with outcome in patients with ductal carcinoma in situ of the breast treated with breast-conserving surgery and radiotherapy.** *Int J Radiat Oncol Biol Phys* 2002;54(5):1331-5. Abstract

Silverstein MJ, Lagios MD: **Pathologic findings from the National Surgical Adjuvant Breast Project (NSABP) eight-year update of Protocol B-17.** *Cancer* 2000;88 (1): 242-4. Abstract

Vicini FA, Recht A. **Age at diagnosis and outcome for women with ductal carcinoma-in-situ of the breast: A critical review of the literature.** *J Clin Oncol* 2002;20(11):2736-44. Abstract

Vogel VG et al. **National surgical adjuvant breast and bowel project update: Prevention trials and endocrine therapy of ductal carcinoma in situ.** *Clin Cancer Res* 2003;9(1 Pt 2):495S-501S. Abstract

Warnberg F et al. **Ductal carcinoma in situ of the breast: a new phenotype classification system and its relation to prognosis.** *Breast Cancer Res Treat* 2002;73(3):215-21. Abstract

Wulfkuhle JD et al. **Proteomics of human breast ductal carcinoma in situ.** *Cancer Res* 2002;62(22):6740-9. Abstract

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Edited comments by Dr Love

Anatomy of the breast ductal system

It's amazing but we really don't know the anatomy of the breast ducts. Classically, all the textbooks say there are 15 to 20 ducts in each breast, but that information dates back to Sir Ashley Cooper in 1839. He found there were 15 to 20 straight tubes coming out of the nipple, but he was only able to cannulate five to eight different ducts. Since then others have come up with similar findings. In the 1970s, Otto Sartorius, a surgeon in Santa Barbara, found five to eight ducts. Dr. Teboul, an ultrasonographer in Paris, found that although there were 15 to 20 different ductal systems, there were actually only five to eight holes in the nipple, suggesting some of the ductal systems come together behind the nipple.

I conducted research mapping breast ducts in lactating women and also found six to eight ducts that formed a pattern. There are two or three in the center of the nipple and the others are arranged more peripherally — almost like two concentric circles. We then re-analyzed over 600 of Dr. Sartorius' ductograms and confirmed an inner group of ducts that go straight back from the nipple, and a more peripheral group that extend more radially.

The notion we've had that the ductal system is like the spokes of a wheel and that removing a wedge of breast tissue removes an entire ductal system may not always be right. The ductal system is not flat, it's three-dimensional. To remove a central duct, you may want to core directly back. To excise an entire ductal system, a ductogram before surgery would be beneficial in locating the duct rather than just cutting blindly around calcifications and getting positive margins.

Ductal lavage for patients at high risk for breast cancer

The real role of ductal lavage right now is the assessment of women at high risk for breast cancer. We lavage the fluid-producing ducts because studies looking at nipple aspirate fluid showed these ducts were at higher risk for disease than the nonfluid-producing ducts.

The information gained from ductal lavage assists physicians and high-risk patients in management decisions, such as chemoprevention or prophylactic mastectomy. For example, if you have a patient in her twenties who is considering tamoxifen because her mother died of premenopausal breast cancer, we know that five years of tamoxifen reduces her risk, but during which five years should she take it? One could monitor her with ductal lavage. As opposed to mammography, which is less useful in young women, ductal lavage works great in young women.

A patient with a breast cancer gene has a 50 percent to 80 percent risk of breast cancer, but that's a pretty wide range. If she's considering prophylactic mastectomy, knowing whether she has atypia would be invaluable. The same holds true for women with breast cancer in one breast who are considering a prophylactic mastectomy in the contralateral breast.

In the future ductal lavage may prove useful for menopausal women at high risk for breast cancer who are considering hormone replacement therapy. Instead of waiting to see if they develop cancer, one could perform ductal lavage every six months or annually to see what the cells are doing. It's premature to use it in the general population, because we don't know what to do with the information in women who are not at high risk. For now, it has an important role in risk assessment as we continue to research its potential in other areas.

Aromatase inhibitors for prevention in postmenopausal women

There is some data that shows that estrogen levels are 40 times higher in the breast duct fluid than they are in the blood in postmenopausal women. And the breast itself has aromatase. It may be making its own estrogen. If this is the case in postmenopausal women, that may be why anastrozole may actually be a better drug than tamoxifen for prevention in that group. It probably is not going to have as much of an impact in premenopausal women.

I'm very interested in conducting research to look at whether you can change the hormone levels in the breast duct fluid and whether we can monitor that. If so, that may be another way to determine which patients need prevention. If the hormone levels are very high, then we could put the patient on tamoxifen or aromatase inhibitors.

The mammography debate

One problem is people say things such as, "Mammography can find 80 percent of breast cancers." Absolutely true — but that's not saying it finds 80

percent at an early stage. Then we say, "Mammography can find breast cancer early." Absolutely true — it can, but it doesn't always. And then we say, "Early breast cancer is 95 percent curable." Absolutely true — but people conclude from these statements that mammography can find 80 percent of breast cancers when they're 95 percent curable, and that is not true at all.

In my mind, the data in women over 50 still looks reasonable, and I think annual mammography is worthwhile in this age group. Under 50, I think its benefit is limited because the breasts are denser and the cancers grow faster. These women need to discuss screening with their physicians. And physicians need to tell women that this is the best data we have, and we're never going to have more accurate data because we're never going to do another big randomized study. Mammography is the best screening tool we have at the moment, but it's far from perfect. It would be great if we had something better and, in a way, that's what has driven me to look at the intraductal approach. I'd like to get closer to the Pap smear model where we find atypia, not cancer, and then stop the process so that the patient never develops cancer.

Select publications

Ductal lavage

Domchek SM. **The utility of ductal lavage in breast cancer detection and risk assessment.** *Breast Cancer Res* 2002;4(2):51-3. **Abstract**

Dooley WC et al. **Detection of premalignant and malignant breast cells by ductal lavage.** *Obstet Gynecol* 2001;97(4 Suppl 1):S2. **Abstract**

Dooley WC et al. **Ductal lavage for detection of cellular atypia in women at high risk for breast cancer.** *J Natl Cancer Inst* 2001;93(21):1624-32. **Abstract**

Dooley WC. **Ductal lavage, nipple aspiration, and ductoscopy for breast cancer diagnosis.** *Curr Oncol Rep* 2003;5(1):63-5. **Abstract**

Evron E et al. **Detection of breast cancer cells in ductal lavage fluid by methylation-specific PCR.** *Lancet* 2001;357(9265):1335-6. **Abstract**

Fabian CJ, Kimler BF. **Breast cancer risk prediction: Should nipple aspiration fluid cytology be incorporated into clinical practice?** *J Natl Cancer Inst* 2001;93(23):1762-3. **Abstract**

Khan SA et al. **Ductal lavage and ductoscopy: The opportunities and the limitations.** *Clin Breast Cancer* 2002;3(3):185-91;discussion 192-5. **Abstract**

Morrow M et al. **Evaluation and management of the woman with an abnormal ductal lavage.** *J Am Coll Surg* 2002;194(5):648-56.

Newman LA, Blake C. **Ductal lavage for breast cancer risk assessment.** *Cancer Control* 2002;9(6):473-9. **Abstract**

O'Shaughnessy JA et al **Ductal lavage and the clinical management of women at high risk for breast carcinoma: A commentary.** *Cancer* 2002;94(2):292-8. **Abstract**

Wrensch MR et al. **Breast cancer risk in women with abnormal cytology in nipple aspirates of breast fluid.** *J Natl Cancer Inst* 2001;93(23):1791-8. **Abstract**

Post-test

03-1266-ES-12

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Bridging the Gap between Research and Patient Care

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Signature: _____

Questions *(please circle answer)*:

1. ACOSOG-Z0011 sentinel node trial evaluates the value of axillary dissection in women with negative lymph nodes.
a. True
b. False

2. Anastrozole should only be used in post-menopausal women.
a. True
b. False

3. NSABP B-35 compares tamoxifen to anastrozole in women with ER-positive DCIS.
a. True
b. False

4. Which of the following statements is true about the 47-month updated results of the ATAC trial?
A. The disease-free survival continues to be greater with anastrozole than with tamoxifen
B. There are fewer endometrial cancers with anastrozole
C. The reduction in contralateral breast cancers continues to be greater with anastrozole than with tamoxifen
D. All of the above

5. Which of the following agents is not being investigated in the breast cancer prevention setting?
A. Tamoxifen
B. Anastrozole
C. Raloxifene
D. Docetaxel

6. A number of studies show that bone marrow micrometastases may have the same adverse implications as lymph node micrometastases.
a. True
b. False

7. Which of the following is a toxicity concern regarding the use of adjuvant anastrozole?
A. Deep venous thrombosis
B. Pulmonary embolism
C. Endometrial cancer
D. Fractures

8. The NSABP sentinel node trial evaluates the value of axillary dissection in women with positive sentinel nodes.
a. True
b. False

9. Tamoxifen did not benefit patients with ER-negative DCIS in the NSABP B-24 trial.
a. True
b. False

10. Ductal lavage is a valuable screening tool for the general population.
a. True
b. False

Post-test Answer Key: 1.False, 2.True, 3.True, 4.d, 5.d, 6.True, 7.d, 8.False, 9.True, 10.False

To obtain a certificate of completion and receive credit for this activity, please complete the exam, fill out the evaluation form and mail or fax both to: Postgraduate Institute for Medicine, P. O. Box 260620, Littleton, CO 80163-0620, FAX (303) 790-4876. You may also complete the Post-test and Evaluation online at www.BreastCancerUpdate.com/CME.

Evaluation Form

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Postgraduate Institute for Medicine (PIM) respects and appreciates your opinions. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this evaluation form. Please note, a certificate of completion is issued only upon receipt of your completed evaluation form.

Please answer the following questions by circling the appropriate rating:
5 = *Outstanding* 4 = *Good* 3 = *Satisfactory* 2 = *Fair* 1 = *Poor*

Global Learning Objectives
Upon completion of this activity, participants should be able to:

- Critically evaluate the clinical implications of emerging clinical trial data in the prevention and treatment of noninvasive (DCIS) and invasive breast cancer. 5 4 3 2 1
- Counsel postmenopausal patients with ER-positive tumors about the risks and benefits of aromatase inhibitors in the adjuvant and neoadjuvant setting. 5 4 3 2 1
- Describe the current guidelines of ongoing clinical trials of local and regional therapy for noninvasive and invasive breast cancer. 5 4 3 2 1

Specific Learning Objectives for Issue 1
Upon completion of this activity, participants should be able to:

- Discuss the rationale and design of American College of Surgeons' trials examining the role of sentinel node biopsy and the significance of bone marrow micrometastases. 5 4 3 2 1
- Counsel and make recommendations for postmenopausal patients with ER-positive tumors regarding the use of adjuvant aromatase inhibitors based on updated data from the ATAC trial. 5 4 3 2 1
- Describe current clinical trials of endocrine therapy in the management of ductal carcinoma *in situ*. 5 4 3 2 1
- Counsel patients about their individual risk of developing breast cancer and implications for surveillance and preventive interventions. 5 4 3 2 1

Overall effectiveness of the activity

Objectives were related to overall purpose/goal(s) of activity 5 4 3 2 1
Related to my practice needs 5 4 3 2 1
Will influence how I practice 5 4 3 2 1
Will help me improve patient care 5 4 3 2 1
Stimulated my intellectual curiosity 5 4 3 2 1
Overall quality of material 5 4 3 2 1
Overall, the activity met my expectations 5 4 3 2 1
Avoided commercial bias or influence 5 4 3 2 1

Will the information presented cause you to make any changes in your practice? ___Yes ___No

If Yes, please describe any change(s) you plan to make in your practice as a result of this activity.

_____

What other topics would you like to see addressed in future educational programs?

_____

Degree:

☐ MD ☐ DO ☐ PharmD ☐ RN ☐ NP ☐ PA ☐ BS ☐ Other _____