

NIH State-of-the-Science Conference

Diagnosis and Management of Ductal Carcinoma In Situ (DCIS)

Program and Abstracts

September 22–24, 2009

**William H. Natcher Conference Center
National Institutes of Health
Bethesda, Maryland**

Presented by

National Cancer Institute, NIH
Office of Medical Applications of Research, NIH
The Johns Hopkins University School of Medicine, Educational Provider

Cosponsor

Office of Research on Women's Health, NIH

Partners

Centers for Disease Control and Prevention
Food and Drug Administration

The Agency for Healthcare Research and Quality provided additional conference development support.



U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health



NIH Consensus Development Program

About the Program

The National Institutes of Health (NIH) Consensus Development Program has been organizing major conferences since 1977. The Program generates evidence-based consensus statements addressing controversial issues important to healthcare providers, policymakers, patients, researchers, and the general public. The NIH Consensus Development Program holds an average of three conferences a year. The Program is administered by the Office of Medical Applications of Research within the NIH Office of the Director. Typically, the conferences have one major NIH Institute or Center sponsor, with multiple cosponsoring agencies.

Topic Selection

NIH Consensus Development and State-of-the-Science Conference topics must satisfy the following criteria:

- Broad public health importance. The severity of the problem and the feasibility of interventions are key considerations.
- Controversy or unresolved issues that can be clarified, or a gap between current knowledge and practice that can be narrowed.
- An adequately defined base of scientific information from which to answer conference questions such that the outcome does not depend primarily on subjective judgments of panelists.

Conference Type

Two types of conferences fall under the purview of the NIH Consensus Development Program: State-of-the-Science Conferences and Consensus Development Conferences. Both conference types utilize the same structure and methodology; they differ only in the strength of the evidence surrounding the topic under consideration. When

it appears that there is very strong evidence about a particular medical topic, but that the information is not in widespread clinical practice, a Consensus Development Conference is typically chosen to consolidate, solidify, and broadly disseminate strong evidence-based recommendations for general practice. Conversely, when the available evidence is weak or contradictory, or when a common practice is not supported by high-quality evidence, the State-of-the-Science label is chosen. This highlights what evidence about a topic is available, the directions future research should take, and alerts physicians that certain practices are not supported by good data.

Conference Process

Before the conference, a systematic evidence review on the chosen topic is performed by one of the Agency for Healthcare Research and Quality's Evidence-Based Practice Centers. This report is provided to the panel members approximately 6 weeks prior to the conference, and posted to the Consensus Development Program Web site once the conference begins, to serve as a foundation of high-quality evidence upon which the conference will build.

The conferences are held over 2 1/2 days. The first day and a half of the conference consist of plenary sessions in which invited expert speakers present information, followed by "town hall forums," in which open discussion occurs among the speakers, panelists, and the general public in attendance. The panel then develops its draft statement on the afternoon and evening of the second day, and presents it on the morning of the third day for audience commentary. The panel considers these comments in executive session and may revise their draft accordingly. The conference ends with a press briefing, during which reporters are invited to question the panelists about their findings.

Panelists

Each conference panel comprises 12–16 members who can give balanced, objective, and informed attention to the topic. Panel members:

- Must not be employees of the Department of Health and Human Services.
- Must not hold financial or career (research) interests in the conference topic.
- May be knowledgeable in the general topic under consideration, but must not have published about or have a publicly stated opinion on the topic.
- Represent a variety of perspectives, to include:
 - Practicing and academic health professionals
 - Biostatisticians and epidemiologists
 - Clinical trialists and researchers
 - Public representatives (ethicists, economists, attorneys, etc.)

In addition, the panel as a whole should appropriately reflect racial and ethnic diversity. Panel members are not paid a fee or honorarium for their efforts. They are, however, reimbursed for travel expenses related to their participation in the conference.

Speakers

The conferences typically feature approximately 21 speakers; 3 present the information found in the Evidence-Based Practice Center's systematic review of the literature. The other 18 are experts in the topic at hand, have likely published on the topic, and may have strong opinions or beliefs. Where multiple viewpoints on a topic exist, every effort is made to include speakers who address all sides of the issue.

Conference Statements

The panel's draft report is released online late in the conference's third and final day. The final report is released approximately 6 weeks later. During the intervening period, the panel may edit their statement for clarity and correct any factual errors that might be discovered. No substantive changes to the panel's findings are made during this period.

Each Consensus Development or State-of-the-Science Conference Statement reflects an independent panel's assessment of the medical knowledge available at the time the statement was written; as such, it provides a "snapshot in time" of the state of knowledge on the conference topic. It is not a policy statement of the NIH or the Federal Government.

Dissemination

Consensus Development and State-of-the-Science Conference Statements have robust dissemination:

- A press briefing is held the last day of the conference to assist journalists in preparing news stories on the conference findings.
- The statement is published online at <http://consensus.nih.gov>.
- Print copies are mailed to a wide variety of targeted audiences and are available at no charge through a clearinghouse.

The conference statement is published in a major peer-reviewed journal.

Contact Us

For conference schedules, past statements and evidence reports, please contact us:

NIH Consensus Development Program
Information Center
P.O. Box 2577
Kensington, MD 20891

1-888-NIH-CONSENSUS (888-644-2667)
<http://consensus.nih.gov>



Upcoming Conferences

- NIH State-of-the-Science Conference: **Enhancing Use and Quality of Colorectal Cancer Screening**
February 2–4, 2010
- NIH Consensus Development Conference: **Lactose Intolerance and Health**
February 22–24, 2010
- NIH Consensus Development Conference: **Vaginal Birth After Cesarean: New Insights**
March 8–10, 2010
- NIH State-of-the-Science Conference: **Preventing Alzheimer’s Disease and Cognitive Decline**
April 26–28, 2010
- NIH Consensus Development Conference: **Inhaled Nitric Oxide Therapy for Premature Infants**
October 27–29, 2010

To receive registration notifications and updates about conferences and other program activities, please join the NIH Consensus Development Program Information Network at <http://consensus.nih.gov/alerts.htm>.

Recent Conferences

- NIH State-of-the-Science Conference: **Family History and Improving Health**
August 24–26, 2009
- NIH Consensus Development Conference: **Management of Hepatitis B**
October 20–22, 2008
- NIH Consensus Development Conference: **Hydroxyurea Treatment for Sickle Cell Disease**
February 25–27, 2008
- NIH State-of-the-Science Conference: **Prevention of Fecal and Urinary Incontinence in Adults**
December 10–12, 2007
- NIH State-of-the-Science Conference: **Tobacco Use: Prevention, Cessation and Control**
June 12–14, 2006
- NIH State-of-the-Science Conference: **Multivitamin/Mineral Supplements and Chronic Disease Prevention**
May 15–17, 2006
- NIH State-of-the-Science Conference: **Cesarean Delivery on Maternal Request**
March 27–29, 2006
- NIH State-of-the-Science Conference: **Manifestations and Management of Chronic Insomnia in Adults**
June 13–15, 2005
- NIH State-of-the-Science Conference: **Management of Menopause-Related Symptoms**
March 21–23, 2005
- NIH State-of-the-Science Conference: **Improving End-of-Life Care**
December 6–8, 2004
- NIH State-of-the-Science Conference: **Preventing Violence and Related Health-Risking Social Behaviors in Adolescents**
October 13–15, 2004
- NIH Consensus Development Conference: **Celiac Disease**
June 28–30, 2004
- NIH Consensus Development Conference: **Total Knee Replacement**
December 8–10, 2003

To access previous conference statements, videocasts, evidence reports, and other conference materials, please visit <http://consensus.nih.gov>.

General Information

CME Information

Description

The NIH Consensus Development Program is convening a state-of-the-science conference to assess the available evidence on the diagnosis and management of ductal carcinoma in situ (DCIS). The state-of-the-science statement will be prepared by an independent panel on the basis of a systematic literature review, expert presentations, and audience commentary. Widely distributed to the biomedical community and covered by the news media, the statement will help inform both healthcare providers and the general public, and shape the research agenda for this complex disease.

Who Should Attend

It is important that all key stakeholders be represented, as attendees will have the opportunity to participate in engaging discussions that will influence the panel's statement. This conference is intended for physicians and other health practitioners, healthcare system professionals, health policy specialists, public health experts, researchers, and interested members of the public.

Objectives

At the end of this activity, participants will demonstrate the ability to:

- Recognize the incidence and prevalence of DCIS and its specific pathologic subtypes, including how incidence and prevalence are influenced by mode of detection, population characteristics, and other risk factors.
- Express how the use of MRI or sentinel lymph node biopsy impacts important outcomes in patients diagnosed with DCIS.
- Explain how local control and systemic outcomes vary in DCIS based on tumor and patient characteristics.
- Describe the impact of surgery, radiation, and systemic treatment on outcomes.
- Identify the most critical research questions for the diagnosis and management of DCIS.

Accreditation Statement

This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of The Johns Hopkins University School of Medicine and the National Institutes of Health. The Johns Hopkins University School of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

Credit Designation Statement

The Johns Hopkins University School of Medicine designates this educational activity for a maximum of 13.25 *AMA PRA Category 1 Credits*[™]. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Policy on Speaker and Provider Disclosure

It is the policy of The Johns Hopkins University School of Medicine that the speaker and provider disclose real or apparent conflicts of interest relating to the topics of this educational activity, and also disclose discussions of unlabeled/unapproved uses of drugs or devices during their presentation(s). The Johns Hopkins University School of Medicine Office of Continuing Medical Education has established policies in place that will identify and resolve all conflicts of interest prior to this educational activity. Detailed disclosure will be made in the activity handout materials.

The Johns Hopkins University School of Medicine takes responsibility for the content, quality, and scientific integrity of this CME activity.

Policy on Panel Disclosure

Panel members signed a confirmation that they have no financial or other conflicts of interest pertaining to the topic under consideration.

Videocast

Live and archived videocasts may be accessed at <http://videocast.nih.gov>. Archived videocast will be available approximately 1 week after the conference.

Dining

The dining center in the Natcher Conference Center is located on the main level, one floor above the auditorium. It is open from 6:30 a.m. to 2:30 p.m., serving hot breakfast and lunch, sandwiches and salads, and snack items. An additional cafeteria is available from 7:00 a.m. to 3:30 p.m., in Building 38A, level B1, across the street from the main entrance to the Natcher Conference Center.

Message Service

The telephone number for the message center at the Natcher Conference Center is 301-594-7302.

Online Content

All materials emanating from the NIH Consensus Development Program are available at <http://consensus.nih.gov>.

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Patricia A. Ganz, M.D.

Background

Ductal carcinoma in situ (DCIS) is a condition in which abnormal cells are found in the lining of a breast duct. As “in situ” means “in place,” this means the abnormal cells have not spread outside the duct to other tissues in the breast. Also referred to as intraductal carcinoma and stage zero breast cancer, DCIS is the most common noninvasive tumor of the breast.

DCIS is most often discovered during routine mammograms, presenting as very small specks of calcium known as microcalcifications. However, not all microcalcifications indicate the presence of DCIS and the diagnosis must be confirmed by biopsy. Magnetic Resonance Imaging (MRI) has also been used more recently as a diagnostic tool, but questions about the impact of the test on patient outcomes remain. Since the implementation of screening mammography, the rate of new DCIS cases has increased dramatically.

DCIS currently accounts for approximately 20% of screening-detected breast cancer, but its true prevalence is challenging to measure because nearly all affected individuals are asymptomatic. By most reports, the risk factors associated with the development of DCIS are similar to those for invasive breast cancer: increased age, family history of breast cancer, previous biopsies, history of hormone replacement therapy, and older age at first childbirth. Tamoxifen, a hormonal drug, has demonstrated a reduction in the incidence of DCIS among high-risk women.

Although the natural course of the disease is not well understood, DCIS can become invasive cancer and spread to other tissues. It is also a marker of increased risk for developing cancer elsewhere in the same or opposite breast. However, not all DCIS will progress to invasive disease, and it is thought that DCIS can be present in some individuals without causing problems over a long period of time. Recent research suggests that DCIS is a spectrum of disease and that certain tumor characteristics may be strong or weak risk factors for subsequent invasive breast cancer. Unfortunately, it is currently not clear which lesion types are more likely to become invasive, leading to difficult treatment decisions for patients and providers.

Because of this uncertainty, DCIS patients are typically treated promptly following diagnosis and have a generally good prognosis. Standard DCIS therapies include breast conservation with or without radiation or mastectomy depending on patient and tumor characteristics. Sentinel lymph node biopsy may also be recommended to high-risk patients, since this is the area where cancer spread is often first detected. Hormone therapy may also be used in an effort to prevent DCIS recurrence and to lower the risk of developing estrogen-receptor-positive breast tumors. However, these drugs' potential side effects must be weighed carefully.

Since the natural course of DCIS is not well understood and treatment benefit may depend on specific tumor and patient characteristics, the treatment of DCIS remains controversial. To examine these important issues, the National Cancer Institute and Office of Medical Applications of Research of the National Institutes of Health will convene a State-of-the-Science Conference from September 22–24, 2009. The conference will address the following key questions:

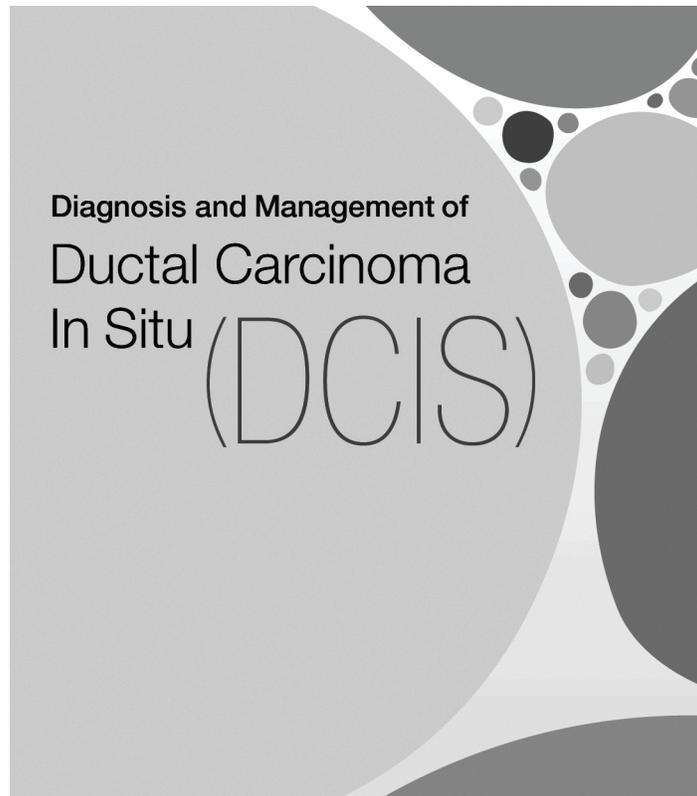
- What are the incidence and prevalence of DCIS and its specific pathologic subtypes, and how are incidence and prevalence influenced by mode of detection, population characteristics, and other risk factors?

- How does the use of MRI or sentinel lymph node biopsy impact important outcomes in patients diagnosed with DCIS?
- How do local control and systemic outcomes vary in DCIS based on tumor and patient characteristics?
- In patients with DCIS, what is the impact of surgery, radiation, and systemic treatment on outcomes?
- What are the most critical research questions for the diagnosis and management of DCIS?

At the conference, invited experts will present information pertinent to these questions, and a systematic literature review prepared under contract with the Agency for Healthcare Research and Quality (AHRQ) will be summarized. Conference attendees will have ample time to ask questions and provide statements during open discussion periods. After weighing the scientific evidence, an unbiased, independent panel will prepare and present a state-of-the-science statement addressing the key conference questions.

About the Artwork

The conference artwork is a stylized representation of microcalcifications, which are tiny abnormal specks of calcium deposits that can be scattered throughout the mammary gland, or occur in clusters. Microcalcifications cannot be felt but are visible on mammography. Depending on their pattern, microcalcifications may be suspicious for ductal carcinoma in situ or cancerous lesions and may indicate a need for further testing. The artwork was designed by Bryan Ewsichek of NIH Medical Arts and is in the public domain. No permission is needed to use the image.



Agenda

Tuesday, September 22, 2009

- 8:30 a.m. Opening Remarks
Peter Greenwald, M.D., Dr.P.H.
Director
Division of Cancer Prevention
National Cancer Institute
National Institutes of Health
- Worta McCaskill-Stevens, M.D., M.S.*
Program Director
Breast Prevention and Minority-Based Community Oncology Program
Community Oncology and Prevention Trials Research Group
Division of Cancer Prevention
National Cancer Institute
National Institutes of Health
- 8:40 a.m. Charge to the Panel
Jennifer Miller Crowell, M.D.
Acting Director
Office of Medical Applications of Research
Office of the Director
National Institutes of Health
- 8:50 a.m. Conference Overview and Panel Activities
Carmen J. Allegra, M.D.
Panel and Conference Chairperson
Chief, Hematology and Oncology
Associate Director for Clinical and Translational Research
Shands Cancer Center
University of Florida
- 9:00 a.m. Terminology, Natural History, and Taxonomy of Ductal Carcinoma in Situ
D. Craig Allred, M.D.
Director, Breast Pathology
Professor, Pathology and Immunology
Washington University School of Medicine

<p>I. What Are the Incidence and Prevalence of DCIS and Its Specific Pathologic Subtypes, and How Are Incidence and Prevalence Influenced by Mode of Detection, Population Characteristics, and Other Risk Factors?</p>
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- 9:20 a.m. Epidemiology of Ductal Carcinoma in Situ
Karla Kerlikowske, M.D., M.S.
Professor of Medicine, Epidemiology, and Biostatistics
University of California at San Francisco School of Medicine

Tuesday, September 22, 2009 (continued)

I. What Are the Incidence and Prevalence of DCIS and Its Specific Pathologic Subtypes, and How Are Incidence and Prevalence Influenced by Mode of Detection, Population Characteristics, and Other Risk Factors? (continued)

- 9:40 a.m. Mode of Detection and Secular Time for Ductal Carcinoma in Situ
Etta D. Pisano, M.D.
Kenan Professor of Radiology and Biomedical Engineering
Vice Dean for Academic Affairs
Director, Biomedical Research Imaging Center
Director, TraCS Institute
University of North Carolina School of Medicine
- 10:00 a.m. Evidence-Based Practice Center Presentation I: The Incidence and Prevalence of Ductal Carcinoma in Situ and the Influence of Mode of Detection, Population Characteristics, and Other Risk Factors
Beth A. Virnig, Ph.D., M.P.H.
Professor
Division of Health Policy and Management
University of Minnesota School of Public Health
- 10:20 a.m. Discussion

II. How Does the Use of MRI or Sentinel Lymph Node Biopsy Impact Important Outcomes in Patients Diagnosed With DCIS?

- 11:00 a.m. Sentinel Lymph Node Biopsy and Management of the Axilla
Thomas B. Julian, M.D., F.A.C.S.
Associate Director, Breast Care Center
West Penn Allegheny Health System
Associate Professor, Human Oncology
Drexel University College of Medicine
Senior Director, Medical Affairs
National Surgical Adjuvant Breast and Bowel Project (NSABP)
- 11:20 a.m. MRI in the Evaluation of Ductal Carcinoma in Situ
Constance D. Lehman, M.D., Ph.D.
Vice Chair and Professor of Radiology
Section Head, Breast Imaging
University of Washington School of Medicine
Director of Medical Imaging
Seattle Cancer Care Alliance

Tuesday, September 22, 2009 (continued)

II. How Does the Use of MRI or Sentinel Lymph Node Biopsy Impact Important Outcomes in Patients Diagnosed With DCIS? (continued)

- 11:40 a.m. Evidence-Based Practice Center Presentation II: The Impact of Magnetic Resonance Imaging and Sentinel Lymph Node Biopsy on Important Outcomes in Patients Diagnosed With Ductal Carcinoma in Situ
Todd M. Tuttle, M.D.
Professor
Department of Surgery
University of Minnesota Medical School
- 12:00 p.m. Discussion
- 12:30 p.m. Lunch
Panel Executive Session

III. How Do Local Control and Systemic Outcomes Vary in DCIS Based on Tumor and Patient Characteristics?

- 1:30 p.m. Local Control of Ductal Carcinoma in Situ Based on Tumor and Patient Characteristics: The Surgeon's Perspective
Lisa A. Newman, M.D., M.P.H., F.A.C.S.
Director, Breast Care Center
Professor of Surgery
University of Michigan Comprehensive Cancer Center
- 1:50 p.m. Local and Systemic Outcomes in Ductal Carcinoma in Situ Based on Tumor and Patient Characteristics: The Pathologist's Perspective
Stuart J. Schnitt, M.D.
Director, Division of Anatomic Pathology
Beth Israel Deaconess Medical Center
Professor of Pathology
Harvard Medical School
- 2:10 p.m. Meta-Analysis of Ductal Carcinoma in Situ Trials: Outcomes From the Early Breast Cancer Trialists' Collaborative Group
Sarah C. Darby, Ph.D.
Professor of Medical Statistics
Clinical Trials Service Unit
University of Oxford
- 2:30 p.m. Local and Systemic Outcomes in Ductal Carcinoma in Situ Based on Tumor and Patient Characteristics: The Radiation Oncologist's Perspective
Nina Bijker, M.D., Ph.D.
Oncologist
Department of Radiation Oncology
Academic Medical Center
University of Amsterdam

Tuesday, September 22, 2009 (continued)

III. How Do Local Control and Systemic Outcomes Vary in DCIS Based on Tumor and Patient Characteristics? (continued)

- 2:50 p.m. Ductal Carcinoma in Situ Outcomes in Breast Cancer Chemoprevention Trials
Victor G. Vogel III, M.D., M.H.S.
National Vice President, Research
American Cancer Society
- 3:10 p.m. Evidence-Based Practice Center Presentation III: Tumor and Patient Characteristics and Associated Outcomes in Ductal Carcinoma in Situ
Tatyana A. Shamliyan, M.D., M.S.
Research Associate
Division of Health Policy and Management
University of Minnesota School of Public Health
- 3:30 p.m. Discussion

IV. In Patients With DCIS, What Is the Impact of Surgery, Radiation, and Systemic Treatment on Outcomes?

- 4:30 p.m. The Impact of Radiation Therapy on Ductal Carcinoma in Situ Outcomes
Lawrence J. Solin, M.D., F.A.C.R., FASTRO
Chairman
Department of Radiation Oncology
Albert Einstein Medical Center
- 4:50 p.m. The Impact of Surgery on Ductal Carcinoma in Situ Outcomes: The Van Nuys Prognostic Index
Melvin J. Silverstein, M.D.
Professor of Surgery
University of Southern California Keck School of Medicine
Director, Hoag Breast Program
Hoag Memorial Hospital Presbyterian
- 5:10 p.m. Discussion
- 5:30 p.m. Adjournment

Wednesday, September 23, 2009

IV. In Patients With DCIS, What Is the Impact of Surgery, Radiation, and Systemic Treatment on Outcomes? (continued)

- 8:30 a.m. The Impact of Surgery on Ductal Carcinoma in Situ Outcomes: The Use of Mastectomy
Eun-Sil (Shelley) Hwang, M.D., M.P.H.
Assistant Professor of Surgery
University of California at San Francisco School of Medicine
- 8:50 a.m. The Impact of Systemic Therapy on Ductal Carcinoma in Situ Outcomes
Sandra M. Swain, M.D.
Medical Director
Washington Cancer Institute
Washington Hospital Center
Professor of Medicine
Georgetown University
- 9:10 a.m. Communications Between Patients and Providers and Informed Decision Making
Joann G. Elmore, M.D., M.P.H.
Professor of Medicine
Adjunct Professor of Epidemiology
University of Washington School of Medicine
Section Head, General Medicine
Harborview Medical Center
- 9:30 a.m. Evidence-Based Practice Center Presentation IV: The Impact of Surgery, Radiation, and Systemic Treatment on Outcomes in Patients With Ductal Carcinoma in Situ
Robert L. Kane, M.D.
Director, Minnesota Evidence-based Practice Center
Professor
Minnesota Chair in Long-term Care and Aging
University of Minnesota School of Public Health
- 9:50 a.m. Discussion

V. What Are the Most Critical Research Questions for the Diagnosis and Management of DCIS?

- 10:50 a.m. Molecular Markers for the Diagnosis and Management of Ductal Carcinoma in Situ
Kornelia Polyak, M.D., Ph.D.
Associate Professor of Medicine
Department of Medical Oncology
Dana-Farber Cancer Institute

Wednesday, September 23, 2009 (continued)

V. What Are the Most Critical Research Questions for the Diagnosis and Management of DCIS? (continued)

11:10 a.m. Imaging for the Diagnosis and Management of Ductal Carcinoma in Situ
Carl J. D'Orsi, M.D., F.A.C.R.
Professor of Radiology, Hematology, and Oncology
Director, Division of Breast Imaging
Emory University Hospital

11:30 a.m. Quality of Life Issues and Outcomes Research in Ductal Carcinoma in Situ
Patricia A. Ganz, M.D.
Professor of Health Services and Medicine
School of Public Health and David Geffen School of Medicine
Director
Division of Cancer Prevention and Control Research
Jonsson Comprehensive Cancer Center
University of California, Los Angeles

11:50 a.m. Discussion

12:20 p.m. Adjournment

Thursday, September 24, 2009

9:00 a.m. Presentation of the Draft State-of-the-Science Statement

9:30 a.m. Public Discussion

11:00 a.m. Adjournment

2:00 p.m. Press Telebriefing

Panel

Panel Chair: Carmen J. Allegra, M.D.
Panel and Conference Chairperson
Chief, Hematology and Oncology
Associate Director for Clinical and
Translational Research
University of Florida
Shands Cancer Center
Gainesville, Florida

Denise R. Aberle, M.D.
Professor of Radiology
Vice Chair of Research, Radiological
Sciences
Section of Thoracic Imaging
University of California, Los Angeles
Los Angeles, California

Pamela Ganschow, M.D.
Director
Breast and Cervical Cancer Screening
Program
John H. Stroger, Jr. Hospital of Cook County
Assistant Professor of Medicine
Rush University Medical Center
Chicago, Illinois

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University of Pennsylvania School of
Medicine
Philadelphia, Pennsylvania

Clara N. Lee, M.D., M.P.P.
Assistant Professor
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Department of Surgery
School of Medicine
University of North Carolina at Chapel Hill
Chapel Hill, North Carolina

**Sandra Millon-Underwood, Ph.D., R.N.,
F.A.A.N.**
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University of Wisconsin at Milwaukee
Milwaukee, Wisconsin

Malcolm C. Pike, Ph.D.
Professor
Preventive Medicine
Keck School of Medicine
University of Southern California
Los Angeles, California

Susan D. Reed, M.D., M.P.H.
Associate Professor
Department of Obstetrics and Gynecology
Adjunct Associate Professor
Department of Epidemiology
Fred Hutchinson Cancer Research Center
Seattle, Washington

Audrey F. Saftlas, Ph.D., M.P.H.
Professor
Department of Epidemiology
College of Public Health
The University of Iowa
Iowa City, Iowa

Susan A. Scarvalone, M.S.W., LCSW-C
Clinical Research Therapist
Prevention and Research Center
The Harry and Jeanette Weinberg Center
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Abstracts

The abstracts are designed to inform the panel and conference participants, as well as to serve as a reference document for any other interested parties. We would like to thank the speakers for preparing and presenting their findings on this important topic.

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Please note that where multiple authors are listed on an abstract, the underline denotes the presenting author.

Terminology, Natural History, and Taxonomy of Ductal Carcinoma in Situ

D. Craig Allred, M.D.

The normal female human breast contains tens of thousands of lobules, which are small grapelike clusters of glands lined by epithelial cells specialized to produce milk.¹ The lobules are interconnected by small ducts which join to form larger ducts which eventually exit through the nipple, transmitting milk to nourish our young. Ductal carcinoma in situ (DCIS) refers to breast epithelial cells that have become “cancerous” but still reside in their normal place in the ducts and lobules. In this setting, cancerous means that there is an abnormal increase in the growth of the epithelial cells, which accumulate within and greatly expand the ducts and lobules. DCIS is a nonlethal type of cancer because it stays in its normal place. However, DCIS is very important because it is the immediate precursor of invasive breast cancers (IBCs), which are potentially lethal.^{2,3}

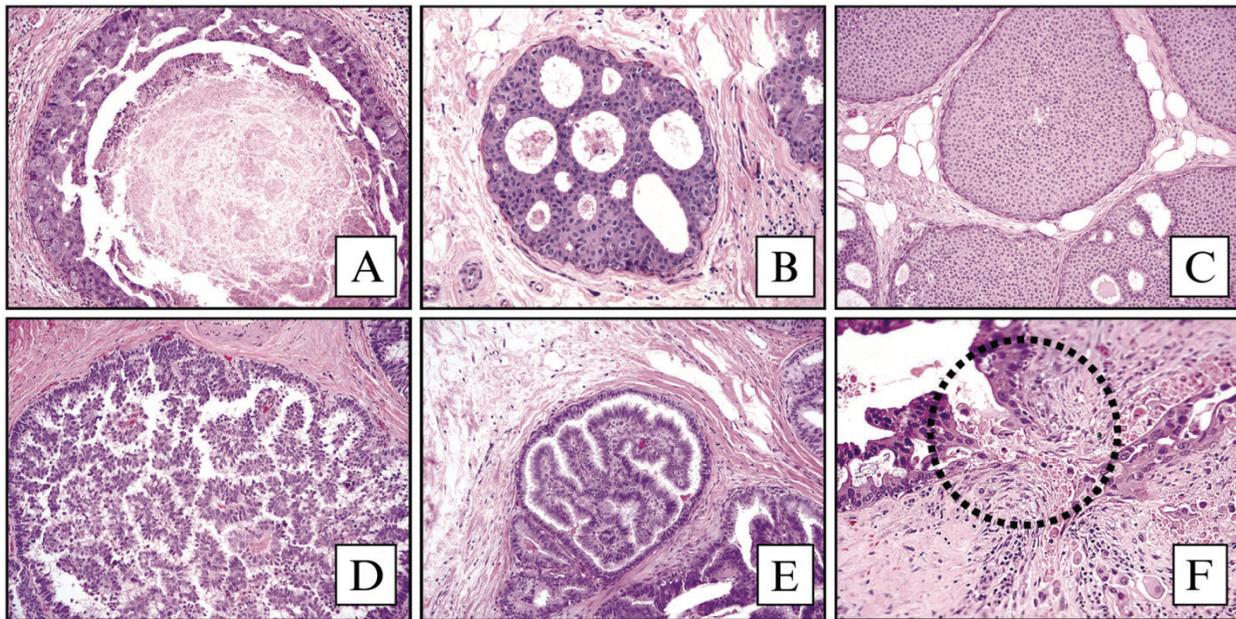
The recognition of DCIS as a specific disease distinct from IBC occurred gradually, primarily during the first half of the 20th century.^{3–9} It was rare during that time, accounting for only 1–2% of newly diagnosed breast cancers, and was usually detected when it formed a large palpable mass.¹⁰ Mastectomy was the standard therapy, and it essentially cured patients.¹⁰

Three developments occurred during the latter half of the 20th century that dramatically changed our awareness and perception of DCIS. First was the general acceptance by the scientific and medical communities that DCIS was indeed the immediate precursor of IBC^{11–17} and, therefore, required effective therapy—ideally something less disfiguring than mastectomy because it is nonlethal. Second was screening mammography, allowing DCIS to be detected early, when it was small and before it had progressed to IBC. Screening greatly increased detection, and DCIS accounts for 20–30% of all newly diagnosed breast cancers in populations with easy access to this technology.^{10,18} Third was the adoption of effective therapies for DCIS that allowed patients to keep their breasts, including lumpectomy, postoperative radiation, and adjuvant endocrine therapy.^{10,19,20} These therapies were previously developed to treat IBC.

Since it was first recognized, clinical and scientific research on DCIS has increased at an accelerating pace, and there is a large body of literature on the subject today. Early achievements included the development of methods of classifying DCIS based on histological features viewed under the microscope. These features included the architectural arrangement or growth pattern of cells, the size and shape of cells and their nuclei, estimates of growth rate based on counting dividing cells referred to as mitotic figures, and the amount of cell necrosis. A commonly encountered type of DCIS in the prescreening era was composed of large cells with a solid growth pattern, irregular shapes, numerous mitotic figures, and abundant necrosis (figure 1A). They were referred to as “comedo” DCIS because the necrotic cell debris oozed from the ducts when the excised tumor was squeezed, resembling comedones (as in acne).⁶ The remaining types of DCIS were referred to by their predominant growth pattern, which included solid, cribriform, papillary, and micropapillary (figure 1B–E). In general, the cells in these tumors were more normal appearing, slower growing, and less necrotic than comedo DCIS, and they were often referred to collectively as “noncomedo” DCIS.⁶ More recent terminology attempted to convey the relative degree that tumor cells resembled normal cells histologically, which is referred to as differentiation. Generally, comedo DCIS are poorly differentiated, and the noncomedo types are well differentiated, or somewhere in between. Numerical grading systems were developed to

reflect differentiation. There were several and the details varied, but most ended by recognizing three grades (I–III), corresponding to well, intermediate, and poorly differentiated DCIS.^{21,22} Grading DCIS was patterned after pre-existing methods developed for IBCs, where a direct relationship between differentiation and clinical aggressiveness had been appreciated for a long time.^{23,24} All of these methods of classifying DCIS are still in use today, often interchangeably, which can be confusing, and which could be improved.

Figure 1. Representative examples of types of DCIS: (A) comedo/high-grade; (B) noncomedo/low-grade cribriform; (C) noncomedo/low-grade solid; (D) noncomedo/low-grade micropapillary; (E) noncomedo/low-grade papillary; (F) tumor cells invading out of DCIS into the surrounding stroma.



The biological features of DCIS have also been studied extensively and, again, the features were usually identified and evaluated in IBCs first.^{11,25–28} Based on all of these studies, there was a gradual appreciation that underlying biological abnormalities were responsible for the microscopic appearance and clinical behavior of tumors. Surprisingly, we learned that the tumor cells of IBC and DCIS are highly similar at the cellular and molecular levels, even though one is invasive and the other is not.^{12,15,26,29–32} Obviously, there must be biological differences between them that are responsible for invasion, but they have been surprisingly difficult to identify so far. Relatively recently, we learned that adjacent stromal cells must cooperate with tumor cells for invasion to occur, and that invasive tumors have many similarities with healing wounds.^{15,33–36} Investigators are currently working hard to determine the cellular and molecular mechanisms of these epithelial-stromal interactions.

It would be very useful to know the natural history of DCIS, including how it develops, whether it will progress to IBC, and when.^{14–16} We know that some DCIS progress in an average lifespan because nearly all IBCs are found intermingled with DCIS, which they almost certainly evolved from.³⁷ We do not know the proportion of DCIS overall that progress to IBC because they are either detected and excised or, unfortunately, not detected at all. However, there are a few small clinical follow-up studies of patients with DCIS that were originally misdiagnosed as benign, suggesting that at least a third, and possibly more, eventually progress to IBC if undetected.^{38–41}

A great deal of indirect but compelling evidence supports the concept that DCIS is the direct precursor of IBC.¹¹ As mentioned, nearly all IBCs are accompanied by DCIS, and foci of histological continuity can be found between them (figure 1F).³⁷ The major risk factors for developing IBC are the same for DCIS.^{10,42} Furthermore, DCIS diagnosed in the past, especially if not completely excised, is a strong risk factor for developing IBC in the future.^{6,43,44} DCIS and IBC share many identical genetic abnormalities, especially when they are in the same breast.^{11,45} Genetically engineered animal models of breast cancer progress from in situ to invasive disease.^{46,47} Progression of noninvasive to invasive cancer occurs in other organs where it is easier to observe, such as skin and cervix, so there is ample biological precedence.

Once detected, current therapy for DCIS is actually quite effective, although there is still a lot of room for improvement.^{10,19,20,48} Better methods of detection, and improved access to them, would be highly beneficial. New methods that precisely identify the boundaries of DCIS would enable surgeons to completely excise them. A deeper understanding of the molecular mechanisms of invasion would lead to new therapeutic strategies to treat or prevent it, as well as new methods to determine the likelihood of progression, so therapy could be individualized.

This symposium will review the state of the art regarding the detection, treatment, and scientific knowledge of DCIS.

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Epidemiology of Ductal Carcinoma in Situ

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The widespread adoption of screening mammography over the past decade has led to an epidemic of diagnoses of ductal carcinoma in situ (DCIS) of the breast. Because it is rarely clinically palpable or symptomatic, DCIS was rarely diagnosed before the advent of modern mammography.¹ Incidence rates for DCIS have risen dramatically since the early 1980s in the United States and elsewhere.^{2–6} Data from the Surveillance Epidemiology and End Results (SEER) program depict about a 500% increase in DCIS from 1983 to 2003, with incidence of DCIS remaining stable since 2003.^{2,7} DCIS now accounts for about 20–25% of all newly diagnosed cases of breast cancer in the United States, and from 17% to 34% of mammography-detected cases.^{8–10} Approximately 1 in every 1,300 mammography examinations performed will lead to a diagnosis of DCIS, and it is estimated that 62,280 cases of DCIS will be diagnosed in 2009.^{8,11} Notably, despite 20 years of detecting DCIS on mammography, a decline in invasive cancer in the United States had not been observed until after the recent, large decline in postmenopausal hormone therapy.¹²

Other than undergoing mammography, older age is one of the strongest risk factors for being diagnosed with DCIS. The rate of DCIS increases with age from 0.6 per 1,000 screening examinations in women aged 40–49 years to 1.3 per 1,000 screening examinations in women aged 70–84 years.^{8,13} Population-based incidence and screening rates of DCIS have been found to be similar among Whites, African-Americans, and Asian/Pacific Islanders.^{14,15} That the rate of DCIS is comparable among women of different ethnicities with a range of invasive cancer rates suggests the incidence of invasive cancer is not directly related to the incidence of DCIS.

Risk factors for DCIS and invasive breast cancer are similar, suggesting a common etiology for both diseases. However, in many instances, the association of a given characteristic is more strongly associated with invasive cancer than DCIS. Family history of a first-degree relative with breast cancer, nulliparity or late age at first birth, history of biopsy, late age at menopause, long-term use of postmenopausal estrogen and a progestin therapy, and elevated body mass index in postmenopausal women not taking hormone therapy increase the risk of DCIS and invasive cancer.^{16–21} High mammographic breast density has also been associated with an increased risk of DCIS and invasive cancer.^{18,19,22} Smoking, increased alcohol consumption, and oral contraceptive use either have not been associated with increased risk of DCIS or results have been conflicting. The prevalence of BRCA1 and BRCA2 mutation carriers among women diagnosed with DCIS is similar to that observed in population-based studies of women diagnosed with invasive breast cancer.^{23,24}

A total of 80 to 85% of DCIS is detected by mammography, and the remaining detected as a lump. The sensitivity of mammography to detect DCIS is high at 86% and varies little with age.⁸ DCIS usually appears on mammography as linear or multiple clusters of fine granular calcifications with a branching-type pattern and can be diagnosed with a core biopsy or needle localization/excisional biopsy. About 95% of DCIS lesions diagnosed on mammography are detected by performing a biopsy of calcifications.²⁵

Given that the natural history of DCIS is unknown—in particular, the natural history of mammographically detected DCIS—the clinical dilemma lies in not being able to distinguish

which lesions will be associated with a subsequent invasive cancer. This results in the vast majority of women with DCIS receiving some surgical treatment. Almost all women who have DCIS detected are currently treated either by mastectomy or lumpectomy with or without radiation, and with or without tamoxifen, with less than 3% receiving no treatment.⁶ The proportion of women undergoing mastectomy for DCIS has declined over time but the absolute numbers of women having mastectomy to treat DCIS has remained the same because of the rising incidence of DCIS over time.²⁶ The proportion of women undergoing lumpectomy alone has remained constant over time, while there has been an increase in the proportion of women receiving lumpectomy and radiation for treatment of DCIS. An increasing rate of contralateral prophylactic mastectomy, from 6.4% in 1998 to 18.4% in 2005, has been reported among women who underwent mastectomy to treat DCIS.²⁷

Mortality from breast cancer is low among women diagnosed with DCIS with all types of treatment. Only 1.0–2.6% of women diagnosed with DCIS will die of invasive breast cancer within 8–10 years of diagnosis.^{28–30} Whether the low risk of death from breast cancer is due to very effective treatments or the fact that the majority of DCIS are relatively benign, or both, is unclear. There are no data that demonstrate detection of DCIS by mammography averts breast cancer deaths. Thus, screening mammography may be benefiting some women whose DCIS would be associated with subsequent invasive cancer, while it is potentially harming other women whose DCIS would never be associated with subsequent invasive cancer, who, for lack of good prognostic indicators, are almost always treated with surgery.

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Mode of Detection and Secular Time for Ductal Carcinoma in Situ

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Paper Overview

In this paper, I will review the published literature on the role of screening mammography in the detection of ductal carcinoma in situ (DCIS). I will review what is known about the detection of DCIS in different demographic groups. Finally, I will describe my views on how the field might be advanced.

Detection of Clinically Occult DCIS Through Screening Mammography

Based on SEER data, incidence rates of carcinoma in situ (CIS), both ductal and lobular, have increased enormously since the widespread adoption of screening mammography, with age-adjusted incidence rates increasing by 660%, from 4.3 to 32.7 per 100,000 woman-years¹ during the years 1973 through 2000. During the same period, the age-specific incidence rate for invasive breast cancer increased only 36%,¹ from 99 to 135 per 100,000 woman-years. The diagnosis of DCIS was the primary driver of this increase in CIS incidence.

A 2002 paper from the National Cancer Institute's Breast Cancer Surveillance Consortium reviewed the cancers diagnosed in a screening population of 540,738 women ages 40 through 84 who underwent 653,833 mammograms. Of the 3,266 cases of breast cancer diagnosed between 1996 and 1997, 591 (18.1%) were DCIS, with the percentage of DCIS decreasing with age, with 28.2% (95% confidence interval [CI] 23.9%–32.5%) for women ages 40–49 years versus 16.0% (95% CI 13.3%–18.7%) for women ages 70–84 years. The rate of DCIS per 1,000 mammograms increased with age, from 0.56 (95% CI 0.41–0.70) for women ages 40–49 years versus 1.07 (95% CI 0.87–1.27) for women ages 70–84 years. Sensitivity for detecting DCIS was higher than for invasive breast cancer—86.0% (95% CI 83.2%–88.8%) versus 75.1% (95% CI 73.5%–76.8%). These authors concluded that 1 in 1,300 screening mammograms leads to the diagnosis of DCIS.²

Perhaps somewhat surprisingly, 14% of the DCIS cases detected in this study (83/591) were among those with negative screening mammograms, but 21 of those 83 (25.3%) were coded as BI-RADS® 3, indicating findings by mammography. Even eliminating those 21, the rate of interval (and presumably symptomatic or detectable on physical examination) DCIS in this large population-based study was 10.5%.² Dershaw et al. have reported a similar rate (14.6%) of symptomatic cases in a report of a single-center series of 51 women with DCIS.³

Rates of detection of DCIS from other large-scale screening mammography programs conducted from the 1970s through the 1990s have varied from 18–25.3%,^{4–10} with one study reporting a DCIS detection rate of 32.8% in noninitial screening rounds.^{8,10} In contrast, the Health Insurance Plan Trial conducted in the 1960s had a DCIS detection rate of 12%.¹¹

Sojourn times or mean duration of preclinical disease has been estimated for DCIS to be 4.8 years through evaluation of the data from the Swedish Two-County Trial,^{12–15} which is shorter than for all other tumor types evaluated. Annual screening mammography has been

associated with smaller tumors, less comedo histology, and lower nuclear grade for DCIS lesions identified.¹⁶

While the U.K. National Health Service Breast Screening Programme (NHSBSP) has placed limits on the target rate of DCIS detection range,¹⁷ and the percentage of mammograms judged to be abnormal at screening is positively and significantly associated with the frequency of DCIS cases diagnosed,¹⁸ there is evidence from the U.K. NHSBSP that screening units with the highest DCIS detection rates (>1.3/1,000) detected over 20% more small invasive cancers than did units with DCIS detection rates within the recommended guidelines.¹⁹

Not much has been published about the variability of the detection of DCIS in assorted demographic groups. Surveillance Epidemiology and End Results (SEER) data reveals that age-adjusted incidence rates for DCIS in Hispanics were 50% lower than for non-Hispanic Whites between 1973 and 1994, and American Indians had the lowest rate overall. Starting in 1985, rates for all groups increased steadily, averaging 17% per year overall (from 2.9 to 11.8 per 100,000 women).²⁰ This increase corresponded to more widespread adoption of screening mammography. A report of the DCIS detection rate using New Mexico Tumor registry described DCIS incidence rates between 1973 and 1994 and showed nonsignificant differences in DCIS rates between non-Hispanic Whites (11%), Hispanic Whites (9%), and American Indians (6%) in that state.²¹ 1994 SEER data reveal that DCIS comprised 14.0% of the breast cancers diagnosed in White women and 13.8% of those diagnosed in African-American women, with 18.2% versus 19.7% reported in 1998.^{22,23}

More recent data from the National Breast and Cervical Cancer Early Detection Program (from July 1991 through March 1998) reveal an overall DCIS detection rate of 0.9 per 1,000 mammograms (95% CI 0.8–1.0), with no significant differences between different ethnic and racial groups (Whites, 1.0 [95% CI 0.8–1.1]; African-Americans, 0.7 [95% CI 0.4–0.9]; American Indians/Alaskan Natives, 0.6 [95% CI 0.3–0.9]; and Hispanics, 0.8 [95% CI 0.5–1.0]).²⁴

Future Research Directions

As has been recommended by the Institute of Medicine in their 2004 report, *Saving Women's Lives: Strategies for Improving Breast Cancer Detection and Diagnosis*,²⁵ a very important goal for improved breast cancer detection is to develop and test individualized screening strategies that allow women at high risk to undergo more vigilant surveillance for breast cancer, and possibly to reduce screening frequency in women at low risk. In order for screening strategies to be evidence-based, it is quite important for clinical trials to be conducted, with attention both to the frequency of screening events and the type of technologies used. These should be focused primarily on high-risk women.

Such trials have been conducted under the auspices of the American College of Radiology Imaging Network,^{25–27} but more research is needed. Work must be continued with attention to newer imaging technologies, such as tomosynthesis,²⁸ breast computed tomography,^{29,30} breast positron emission mammography,³¹ breast-specific gamma imaging,^{32,33} and others still in earlier phases of development.^{34–38}

In addition, we should develop new mechanisms for distinguishing between breast cancer subtypes, both invasive and DCIS, that are at higher risk for becoming invasive and metastatic tumors. This work will most likely involve the application of imaging technologies, including the development of new contrast agents (molecular and otherwise) that can label the biomarkers

(e.g., p53 mutations, erbB2, or other more specific markers of triple negative and basal breast cancer) that increase the risk for lethal outcomes.

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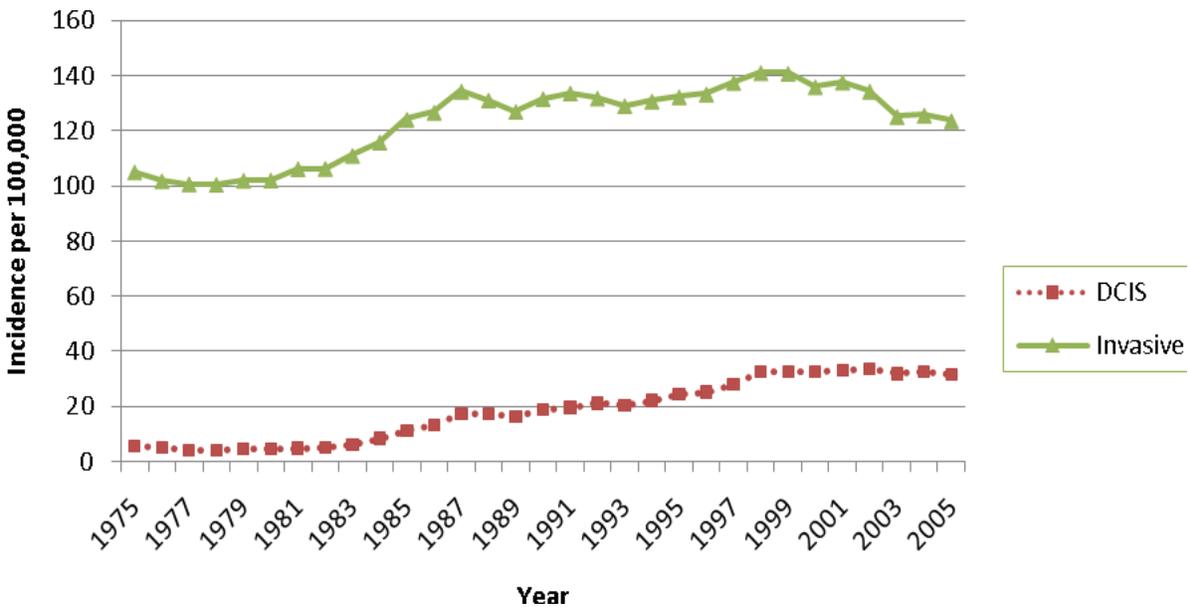
Evidence-Based Practice Center Presentation I: The Incidence and Prevalence of Ductal Carcinoma in Situ and the Influence of Mode of Detection, Population Characteristics, and Other Risk Factors

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We identified 63 publications from population-based studies that reported the incidence of ductal carcinoma in situ (DCIS). We identified 29 studies that examined risk factors for DCIS. Eight population-based mammography trials evaluated the effect of mammography on DCIS and invasive breast cancer incidence.

Regardless of source, the incidence of DCIS has increased dramatically since the early 1970s. The National Cancer Institute (NCI) report: *SEER Cancer Statistics Review, 1975–2004*, estimated the incidence of DCIS in 2004 to be 32.5 per 100,000 women. While considerably higher than the 5.8 per 100,000 rate reported in 1975, the rate is lower than for invasive breast cancer incidence, estimated to be 124.3 per 100,000 in 2004 (figure 1).

Figure 1. Trends in the Incidence of DCIS and Invasive Cancer (1975–2005)



Risk Factors for DCIS

Age. The incidence of DCIS, like invasive breast cancer, is strongly related to age. DCIS is extremely uncommon prior to ages 35–39 (2.5 per 100,000 for women aged 30–34). The incidence rises steadily to a peak of 96.7 per 100,000 at ages 65–69 and then declines, slowly until age 79 and steeply after age 79. In contrast, invasive breast cancer peaks at ages 75–79, with incidence of 453.1 per 100,000 women.

Race. The age-adjusted incidence of DCIS was the highest among Caucasian women, followed by African-Americans and Asian-Pacific Islanders. Hispanic women had the lowest age-adjusted incidence of DCIS.

Menarche and menopause. No study found a statistically significant association between age at menarche and DCIS incidence. Age at menopause is challenging to examine in the context of DCIS because the risk of DCIS increases with age, particularly around the age of menopause (ages 45–60). Thus, it can be challenging to separate the effects of aging with the hormonal changes associated with menopause.

Hormone replacement therapy (HRT). The increased risk of invasive breast cancer associated with HRT is well established. The Women's Health Initiative, a large randomized trial of HRT and breast cancer risk, found no increased risk of DCIS associated with HRT.^{1,2} The large Million Women Study cohort failed to comment on any increase in DCIS associated with HRT use. There was no consistent association between HRT and DCIS in five observational studies.

Age at first birth and parity. Several studies found a significant increase in the risk of DCIS among those who had their first child between 20 and 29 years of age (pooled RR, 1.43) and more than 30 years of age (pooled RR, 1.46) compared to women who were less than 20 years of age at first live birth. Several studies reported a decreased risk of DCIS associated with more children relative to no children or only one child.

Breast density. Studies consistently found that women with higher breast density had increased risk of DCIS relative to those with lower breast density. For example, a nested case control study found increased odds of DCIS among women with higher than 50% versus lower than 10% mean breast density (OR, 2.86).³

Body composition. There is no consistent association between body composition, as measured by body mass index (BMI), and DCIS incidence. An association between increased BMI and increased DCIS incidence has been reported in some age, menopausal status, and HRT subgroups.

Family history. Several studies reported that women with a family history of breast cancer or a first-degree relative with breast cancer had similarly increased odds of DCIS compared to women without a positive family history (pooled OR, 1.97).

Benign breast conditions. Previous breast surgery was not associated with increased odds of DCIS. Three population-based studies reported increased odds of DCIS in women with previous breast biopsies compared with women with no history of breast biopsy (pooled OR, 2.7). Women previously diagnosed with benign breast disease had increased odds of DCIS by 88% (OR, 1.88).

Effect of Screening Mammography

The strongest evidence of the incidence in DCIS due to use of screening mammography comes from eight population-based trials of mammography screening. These trials were initiated between 1963 and 1982: the Health Insurance Plan study,⁴ the Malmö study,⁵ the Swedish Two-County trial,⁶ the Edinburgh trial,⁷ the Stockholm trial,⁸ the Canadian National Breast Screening Trials 1 and 2,^{9,10} and the Gothenburg Breast Screening Trial.¹¹ The trials consistently reported that less than 20% of screen-detected breast cancers were DCIS. All but the National

Breast Cancer Screening Trials found mammography to result in significant reductions in breast cancer mortality (table 1).

Table 1. Population-Based Screening Trials

Trial/Year	Screened/ Control	DCIS (#/Cumulative Rate per 1,000)		Invasive Cancer (#/Cumulative Rate per 1,000)	
		Screened	Control	Screened	Control
Malmo Study ¹⁵	21,088/21,195	240/0.28	178/0.21	2,400/2.8	2,232/2.6
Two-County Trial ¹⁶	77,080/55,985	123/1.60	46/0.82	1,303/16.9	996/17.8
Stockholm Trial ⁸	40,318/19,943	43/0.091	14/0.058	385/0.814	2,03/0.848
Canadian National Breast Screening Trial 1 ¹⁰	25,214/25,126	71/2.92	29/1.19	592/	552
Canadian National Breast Screening Trial 2 ⁹	19,711/19,694	71/38.3	16/8.6	622	610
Gothenburg Breast Screening Trial ¹¹	21,904/30,318	38/NR	40/NR	271/NR	415/NR

NR = not reported

The conclusions from the randomized trials are supported by a number of population-based studies from the United States and around the world. Namely, while mammography results in increased detection of DCIS, the number of invasive cancers always outnumbers DCIS cases. While DCIS increased 200% since 1987 and mammography use increased by almost 250%, the increase in mammography use was seen considerably sooner than the increase in DCIS.

The Breast Cancer Surveillance Consortium and the National Breast and Cervical Cancer Early Detection Program report the incidence of screen-detected DCIS (0.78 per 10,000 screened) to be greater than the incidence of nonscreen-detected DCIS (0.13 per 10,000 nonscreened). There have been greater increases over time in the DCIS incidence per 100,000 population than per 1,000 screened.

Both screening and population-based studies point to increased DCIS detection rates on baseline screen and decreased rates on follow-up screens. The studies suggest that the greatest increase in DCIS incidence will be observed when a population undergoes initial screening, and that the increases in incidence based on this initial screen will overestimate population impact for a population undergoing routine screening.

Chemoprevention of DCIS

While several trials have been used to assess the value of tamoxifen or raloxifene for preventing DCIS, the trials, in reality, were designed to assess the value of the agents for preventing breast cancer, with DCIS as a secondary outcome. The National Surgical Adjuvant Breast and Bowel Project P-1 study¹² examined the protective effect of tamoxifen among high-risk women. The study found statistically significant reductions in both DCIS and invasive breast cancer associated with tamoxifen use. The International Breast Cancer Intervention Study also found a 69% reduction in the incidence of DCIS at 50 months. The Royal Marsden breast cancer prevention trial¹³ did not find a significant protective effect of tamoxifen on DCIS incidence at

13 years of follow-up. The Study of Tamoxifen and Raloxifene (STAR) trial compared tamoxifen and raloxifene and found that women in the tamoxifen group had half the incidence of in situ breast cancer (lobular carcinoma in situ or DCIS) than women in the raloxifene group (57 versus 81 total in situ cancers). However, the study also found both treatments decreased the risk of invasive cancer by half. The Continuing Outcomes Relevant to Evista (CORE) and Multiple Outcomes of Raloxifene Evaluation (MORE) randomized double-blind trials examined the impact of raloxifene on preventing invasive breast cancer among postmenopausal women with osteoporosis.¹⁴ The CORE study found significantly reduced incidence of invasive breast cancer associated with raloxifene (HR, 0.50) but a nonsignificant increase in the incidence of DCIS among the treated women (HR, 1.78).

Conclusion

There is ample evidence that the incidence of DCIS is increasing, and that the increase is largely due to increased use of screening mammography. Several population-based trials along with other population-based registries also support the conclusion that mammography is more effective at identifying invasive breast cancer than DCIS. We were unable to find any study reporting on both DCIS and invasive breast cancer that detected more DCIS than invasive breast cancer. Thus, while the increase in DCIS is likely due to screening, the benefits of screening as a means of detecting invasive breast cancer outweigh the increased detection of DCIS.

There is remarkable similarity in risk factors between DCIS and invasive breast cancer with two notable exceptions. First, the age patterns of DCIS and invasive breast cancer are somewhat different. DCIS peaks at a younger age than does invasive cancer. Second, there is no evidence that HRT is associated with increases in DCIS incidence as it is with invasive breast cancer. Other risk factors including breast density, family history, and history of benign breast disease are similar between invasive cancer and DCIS.

Trials of tamoxifen and raloxifene for breast cancer prevention point to both drugs being effective for preventing invasive breast cancer but tamoxifen being more effective for preventing DCIS. Understanding this effect and how best to prevent all forms of breast cancer deserves further attention.

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Sentinel Lymph Node Biopsy and Management of the Axilla

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Noninvasive carcinoma of the breast or ductal carcinoma in situ (DCIS) comprises 20% of all breast cancers diagnosed by mammography today.¹ Defined as proliferating malignant ductal cells limited to the ducts without invasion through the basement membrane, DCIS is a local disease. As such, there is no regional involvement. Historically, DCIS was a disease detected by physical examination and treated with mastectomy and axillary dissection. With increased use of screening mammography DCIS tumors were detected earlier, at a smaller size, nonpalpable, and associated with a lower rate of nodal involvement. With the low incidence of axillary involvement and the morbidity of axillary dissection, the routine use of axillary dissection for DCIS was abandoned.^{2,3} However, if nondiagnosed invasion exists within the DCIS or if invasive cancer is present in the conservatively treated breast, axillary nodal involvement can occur. Upstaging following a core needle biopsy can occur in up to 20% of cases when compared to the final pathology,⁴ with only 1.4% of the cases having nodal involvement.⁵ In a review of NSABP DCIS Protocols B-17 (lumpectomy +/- whole breast irradiation [WBI]) and B-24 (lumpectomy plus WBI +/- tamoxifen), the risk of axillary recurrences in patients was less than 1%.⁶ A similar finding of very low axillary recurrence in long-term follow-up of DCIS patients treated with lumpectomy and WBI was reported by the City of Hope Cancer Center.⁷ This extremely low rate of recurrence is less than the positive axillary metastasis rate associated with undiagnosed invasive cancer within the presence of DCIS.^{8,9,10,11} Thus, the routine use of sentinel node biopsy (SNB) in patients with pure DCIS is not indicated, since there is no survival data of any magnitude in patients treated by SNB who have an axillary recurrence.

Multiple investigators have stressed the need for SNB in patients with high-risk DCIS as defined by the presence of comedo necrosis, high-grade or large-size.^{12,13,14} The rationale for this view is based on the upstaging of DCIS to microinvasive or invasive disease from core biopsy to final pathology review of the resected tissue, reports of which range from 10–38%.^{15,16,17,18,19,20} These investigators prefer the use of SNB as a diagnostic tool to rule out invasive disease, not wishing to return for a second operative procedure. This is also a fallback mechanism for a less-than-thorough analysis of the resected specimen for invasive cancer.

Conversely, other investigators have not seen the utility of subjecting patients to additional surgical intervention unless invasive disease is confirmed either on core-needle biopsy or on final surgical pathology.^{21,22,23} This approach would also appear to be more cost-effective. More importantly, positive SNB in this population of patients has not been associated with the high risk of local or distant recurrence.^{6,7,23,24}

Although SNB is less morbid than axillary dissection and thus enhances its use, the morbidity is not an absolute zero. In both single institutional studies as well as prospective trials, the sequelae of lymphedema, paresthesias, decreased limb use, persistent pain, and seroma have been reported.^{25,26,27,28,29,30} Therefore, patients should only undergo SNB when the diagnosis of invasive or microinvasive disease is established either on core-needle biopsy, on final surgical pathology, or in selected cases of high-risk or large tumors.

Detailed sentinel node analysis with the use of hematoxylin and eosin stains, as well as immunohistology (IHC), has generated controversy related to outcomes related to micrometastases and nanometastases in patients with invasive breast cancer. In similar fashion,

IHC analysis for DCIS has resulted in the detection of cells that are of questionable prognostic significance. These small clusters of cells may be more related to displacement from biopsy than to the actual tumor biology of dissemination.^{31,32} The significance to outcome of these cells remains nebulous.²⁴ Thus, the need to fanatically pursue these nodes becomes less necessary and costly.

The final scenario for SNB in patients with DCIS is related to those patients undergoing mastectomy for extensive or a large amount of DCIS. In a series of patients undergoing mastectomy for DCIS, upstaging to invasive cancer was 33%.³³ SNB has been reported to have a high identification rate (>96%) in patients undergoing mastectomy for invasive cancer.^{34,35} SNB after mastectomy, although feasible, is less than efficacious.³⁶ Dominguez et al. reported an 11% positive SNB rate in patients undergoing mastectomy for DCIS.³⁷ Since SNB following mastectomy is not uniformly effective, and due to an apparent increased risk for invasive cancer in patients undergoing mastectomy for DCIS, SNB is a very reasonable procedure to carry out at the time of mastectomy.

The current American Society of Clinical Oncology guidelines for sentinel lymph node biopsy in early-stage breast cancer recommend SNB for patients undergoing mastectomy for DCIS due to the technical difficulty of performing SNB after mastectomy, but the routine use of SNB in patients having breast-conserving therapy is not recommended. In circumstances where there is high-risk DCIS or large tumors, SNB is recommended on a case-by-case basis.³⁸ The 2001 Sentinel Lymph Node Biopsy Consensus Conference recommendations were similar. However, a clearer statement for using SNB in patients with DCIS and any type of invasion as opposed to not using SNB in patients with DCIS and no invasion was made.³⁹

In summary, at the present time, based on currently available data, the routine use of SNB in all patients with pure DCIS is not warranted. For patients with proven invasive or microinvasive disease with DCIS, SNB is supported. In patients undergoing mastectomy for DCIS, SNB is recommended at the time of mastectomy. A case-by-case decision should be made for the use of SNB in patients who have high-risk DCIS or large tumors.

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MRI in the Evaluation of Ductal Carcinoma in Situ

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The role of MRI in the evaluation of ductal carcinoma in situ (DCIS) has focused on two specific clinical applications. The first is the performance of magnetic resonance imaging (MRI) in the evaluation of extent of disease in patients with a diagnosis of DCIS prior to therapeutic planning. The second application is early detection of DCIS in breast cancer screening programs. These studies have focused on patients at high risk for breast cancer in whom both mammography and MRI are recommended for screening.

The intention of the studies to date was to clarify the potential of MRI in select patient populations to reduce the morbidity of breast cancer treatment by 1) allowing more targeted and accurate surgical approaches to removing DCIS, with fewer surgeries required to achieve negative margins, and 2) supporting earlier detection of breast cancer in high-risk patients by detecting cancer at a preinvasive stage. In addition, some have hypothesized that MRI may allow more sensitive detection of the DCIS lesions more likely to progress to invasive disease, while allowing less aggressive treatment approaches to those DCIS lesions highly unlikely to progress to invasive disease.

Historically, MRI was considered a poor imaging tool to assess DCIS. In fact, numerous investigators claimed that while MRI had high sensitivity in the detection of invasive cancer, it was a poor imaging tool to identify DCIS. Many urged caution in relying on MRI to evaluate DCIS, claiming that mammography, by detecting calcifications associated with DCIS, was the preferred imaging method for DCIS detection and that MRI was not sensitive in detecting DCIS.¹⁻⁴ Based on the literature available at the time, the American College of Radiology's Breast MRI Practice Guidelines specifically excluded the detection of DCIS as an indication for an MRI examination.⁵ MRI high-risk screening trials provided added support to this limitation of MRI by reporting DCIS cases identified by mammography but occult to MRI.⁶⁻⁹

At the same time, investigators shifted attention from MRI acquisition techniques of lower spatial resolution (with thicker slice acquisitions) and higher temporal resolution (with rapid acquisition of images) to techniques of higher spatial resolution. Using these higher spatial resolution techniques, investigators reported improved detection of DCIS with MRI. In 2004, Berg et al. reported MRI was the preferred method of detecting DCIS in patients with known breast cancer.¹⁰ In her study, all patients with a diagnosis of cancer, whether invasive or in situ, were evaluated with mammography, ultrasound, and MRI to assess the extent of disease prior to treatment planning. As expected, MRI significantly improved the assessment of invasive lobular carcinoma compared to mammography and ultrasound. What was more surprising at the time was the finding that MRI was far superior to either mammography and/or ultrasound in the assessment of the extent of disease of DCIS. MRI sensitivity for accurate assessment of DCIS extent was 89% compared to only 55% and 47% for mammography and ultrasound, respectively.

In 2007, Kuhl et al. published a large study of patients with pure DCIS, showing the sensitivity of MRI far surpassed that of mammography in the detection of DCIS.¹¹ In that study of 7,319 women who underwent both MRI and mammography, pure DCIS was diagnosed in 167 patients. The sensitivity of MRI was 92% for DCIS compared to only 56% by mammography. Of interest, MRI sensitivity was particularly strong in women with high-grade

DCIS. In patients with high-grade or comedo-type DCIS, the sensitivity of MRI was 98%, compared to only 52% for mammography. The majority (87%) of cases of DCIS not identified by MRI were low-grade DCIS. Age, menopausal status, personal or family history of breast cancer or of benign breast disease, and breast density did not differ in women with MRI-only-diagnosed DCIS compared to those with mammography-diagnosed DCIS.

Investigators found that the classic patterns of invasive carcinoma on MRI were not present in the majority of cases of DCIS, and techniques focused on high spatial resolution with thin slices seemed to produce improved results in the detection and diagnosis of DCIS compared to techniques emphasizing high temporal resolution. Patterns of contrast enhancement over time, central to the effectiveness of high temporal-resolution imaging, did not appear to distinguish DCIS lesions from normal tissue. In a large multicenter study by the International Breast MRI Consortium (Mitch Schnall, Principal Investigator), the specific feature of a washout pattern identified only 20% of the cases of DCIS. The sensitivity increased to 60% when plateau enhancement was also included.¹² Other investigators confirmed these findings and clarified that DCIS relies on morphological features more heavily than on kinetic features and typically presents as nonmasslike enhancement with delayed peak enhancement profiles.^{13–15}

In summary, the ability of MRI to detect the presence and extent of DCIS unequivocally significantly exceeds that of mammography or ultrasound and is associated with acceptable specificity. This improved sensitivity is particularly robust for high-grade DCIS lesions. How this improved diagnostic accuracy will impact outcomes in patients at risk for and with breast cancer warrants careful investigation.

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Evidence-Based Practice Center Presentation II: The Impact of Magnetic Resonance Imaging and Sentinel Lymph Node Biopsy on Important Outcomes in Patients Diagnosed With Ductal Carcinoma in Situ

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Magnetic Resonance Imaging

We analyzed 57 studies that reported the outcomes of breast magnetic resonance imaging (MRI) among patients with established ductal carcinoma in situ (DCIS). We excluded studies that did not differentiate between DCIS and invasive cancer and studies when a later publication from the same institution included patients from an earlier study. We were unable to find any study that directly compared survival, recurrence, or quality of life for women receiving postdiagnostic MRI to no MRI.

MRI for detecting multicentric disease. Several studies reported that MRI had higher sensitivity for detecting multicentric disease than mammography. The sensitivity of MRI is estimated to range from 42% to 94% while the sensitivity of mammography was always lower, ranging from 26% to 40% (table 1).¹

Table 1. Sensitivity and Specificity of Breast MRI for Detecting Multicentric Disease

Study	Number of Subjects	Sensitivity of MRI (Specificity)	Sensitivity of Mammogram (Specificity)
Hwang, 2003 ⁶	51	94% (89%)	38% (91%)
Menell, 2005 ¹¹	32	80% (NR)	40% (NR)
Santamaria, 2008 ¹	86	42% (NR)	26% (NR)

NR = not reported

MRI for estimating tumor size. The results of studies comparing mammography with MRI have not been consistent. In a study of 167 patients with DCIS, Kuhl et al. reported that MRI was not better than mammography in determining size.² In another study of 24 patients with DCIS, Uematsu et al. reported that MRI was more accurate than mammography in determining extent of DCIS.³ Several studies have evaluated the underestimation and overestimation rates of MRI in determining DCIS size relative to pathological exam (table 2). Definitions of error were not consistent between studies, and some studies did not explicitly define what they considered to be an error. Several studies compared the accuracy of MRI and mammography with histological examination for determining tumor size. Given the growth pattern of DCIS, limitations inherent in tissue processing make histologically based tumor measurement difficult, as 3-dimensional extent of disease is reconstructed using 2-dimensional pathology slides. Thus, pathological examination can overestimate or underestimate tumor sizes, depending on the plane of section. Some authors have argued that MRI measurements may be more accurate than those in the pathology laboratory.⁴

Table 2. Overestimation and Underestimation of DCIS Size by MRI Compared With Mammography

Author Country	N	Definition of Error	MRI		Mammography	
			Over Estimation (%)	Under Estimation (%)	Over Estimation (%)	Under Estimation (%)
Shiraishi, 2003 ¹² Japan	30	+/- 10 mm	0	30	43.3	43.3
Onesti, 2008 ¹³ United States	16	+/- 5 mm	50	0	ND	ND
Santamaria, 2008 ¹ Spain	86	Not defined	9.3	31	7.0%	18.6%
Esserman, 2006 ¹⁴ United States	45	100%/-50%	23	9	ND	ND
Schouten van der Velden, 2006 ¹⁵ Netherlands	54	+/- 5mm	38	24	26%	47%
Overall (95% CI)			22.1	21.9		

N = number of patients with DCIS
 ND = not determined or not reported

MRI for detecting contralateral breast cancer. We found four studies that reported the use of MRI to detect contralateral breast cancer in patients with DCIS (table 3). In the largest study that included 196 patients, Lehman et al. reported that MRI detected occult contralateral breast cancer in five patients (2.6%); the sensitivity for detecting contralateral breast cancer was 71%.⁵ Importantly, in this study, MRI findings prompted biopsies of the contralateral breast in 18 patients; only five (28%) were positive. No studies compared the performance of MRI to mammography for detecting contralateral breast cancer.

Table 3. Proportion of Patients With MRI-Detected Contralateral Breast Cancer

Author Country	N	MRI-Detected CLBC# (%)	Mammogram Detected CLBC (%)
Hollingsworth, 2006 ¹⁶ United States	85	4.7	ND
Liberman, 2003 ¹⁷ United States	36	5.6	ND
Pediconi, 2005 ¹⁸ Italy	11	27	ND
Lehman, 2007 ⁵ United States	196	2.6	NA
Overall (95% CI)		6.4 (2.3;16.4)	

N = Number of patients with DCIS

CLBC = Contralateral breast cancer

ND = not determined or not reported

NA = not applicable because these were all patients who had negative contralateral mammograms

MRI for identifying invasive disease. We found only one study that evaluated the ability of MRI to identify invasive disease among patients originally diagnosed with DCIS.⁶ Among 17 patients with DCIS originally diagnosed by core needle biopsy, Hwang et al. reported three patients had invasive breast cancer after definitive surgery; MRI correctly predicted invasive breast cancer in all three patients (sensitivity = 100%).⁶ Hwang estimated the specificity of MRI for detecting invasive breast cancer was 86%. After excisional biopsy, the sensitivity of MRI for detecting invasive breast cancer was 75% and the specificity was 85%. Among all patients, the positive predictive value of MRI for detecting invasive breast cancer was only 43%.

Treatment utilization. Nineteen articles reported treatment utilization after diagnostic MRI. Several studies reported change in treatment decisions based on MRI. While studies are small, all consistently point to changes in treatment after MRI. These changes are due to differential ability for MRI to detect multicentric and contralateral disease and accurately estimate tumor size.

Sentinel Lymph Node Biopsy

We identified 51 studies that reported experience with sentinel lymph node biopsy (SLNB) in women with DCIS. Few studies evaluating SLNB for DCIS include consecutive patients, but rather, most report the outcomes of highly selected patients. Thus, in some cases the mastectomy rate is considerably higher than would be expected. We were unable to find any study that directly compared important patient outcomes (survival, recurrence, and quality of life) after SLNB compared with no SLNB.

Since some patients with an original core needle biopsy of DCIS will have invasive breast cancer identified in the excision or mastectomy specimen, we evaluated the incidence of SLN metastases separately for patients with an original and final diagnosis of DCIS. The incidence of SLN metastases was greater for patients with an original diagnosis of DCIS (9.8%) compared with those with a final diagnosis of DCIS (5.0%). For example, in a study of patients initially diagnosed with DCIS by core needle biopsy, Moran et al. reported that 8.6% of patients had SLN metastases.⁷ However, in this series all patients with SLN metastases had a final diagnosis

of invasive breast cancer after excision or mastectomy; thus, no women with a final diagnosis of DCIS had SLN metastases (table 4).

Table 4. Incidence of Sentinel Lymph Node Metastases Among Patients With an Original Diagnosis of DCIS*

Author	Country	SLN Metastases
Maffuz, 2006 ¹⁹	Mexico	12.5% (3; 24)
Polom, 2009 ²⁰	Poland	5.5% (10; 183)
Yi, 2008 ²¹	United States	6.4% (40; 624)
Liu, 2003 ²²	Taiwan	9.1% (3; 33)
Mittendorf, 2005 ²³	United States	22% (9; 41)
Camp, 2005 ²⁴	United States	16.3% (7; 43)
Fraile, 2006 ²⁵	Spain	7% (10; 142)
Tan, 2007 ²⁶	Canada	13% (7; 54)
Moran, 2007 ⁷	Ireland	8.6% (3; 35)
Van la Parra, 2008 ²⁷	Netherlands	9.8% (5; 51)
Dominguez, 2008 ²⁸	United States	11.3% (20; 177)
Sakr, 2006 ²⁹	France	6.4% (9; 140)
Meijnen, 2007 ³⁰	Netherlands	17.2% (5; 29)
Overall (95% CI) pooled with random effects model		9.8% (7.6; 12.7)**

* May include DCIS and DCISM

** Significant heterogeneity

The incidence of pN1 SLN metastases was 0.9% in patients with DCIS; 2.3% in patients with ductal carcinoma in situ with microinvasion (DCISM); and 0.6 in the samples that combined DCIS and DCISM. The incidence of pN1(mic) SLN metastases was 1.5% in patients with DCIS; 3.4% in patients with DCISM; and 2.6% in the samples that combined DCIS and DCISM.

Since about 15% of patients with DCIS identified on core needle biopsy are diagnosed with invasive breast cancer after excision or mastectomy,⁸ the feasibility and accuracy of SLNB after excision is relevant to decisions regarding surgical management of DCIS. Most studies demonstrate that SLNB is feasible after excision. Results from studies evaluating the accuracy of SLNB after excision are not consistent. While some report SLNB false negative rates to be similar after core needle biopsy (7.9%) and excisional biopsy (8.3%),⁹ an analysis from the National Surgical Adjuvant Breast and Bowel Project (NSABP) Trial B-32 (Krag et al.) reported that the SLNB false negative rate was significantly increased after excisional biopsy compared with core needle biopsy or fine needle aspiration (needle biopsy, 8.1%; excisional biopsy, 15.3%; $p = .0082$).¹⁰

Conclusions

The consistent finding that a measurable percentage of women with DCIS on biopsy will be diagnosed with invasive cancer based on full excision suggests that surgical excision of DCIS may be needed to fully evaluate cases for invasive cancer. The findings that some women with

confirmed DCIS will have positive SLNB raises questions about whether this seemingly inconsistent finding reflects underdiagnosis of invasive cancer, overdiagnosis of positive SLN, or a need to reexamine the presumed association between tumors and nodal involvement. Little data links use of SLNB or positive SLNB findings with clinical outcomes or treatment changes.

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Local Control of Ductal Carcinoma in Situ Based on Tumor and Patient Characteristics: The Surgeon's Perspective

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Since ductal carcinoma in situ (DCIS) is largely a disease whose manifestations are confined to in-breast pathology, management strategies focus on various combinations of local therapy: mastectomy, lumpectomy, and breast irradiation. Clinical trials comparing these strategies are summarized in table 1.

Local Therapy

Mastectomy is the oldest treatment for DCIS and is preferred in the following clinical scenarios:

- (i) patients with diffuse, suspicious-appearing microcalcifications in the breast;
- (ii) inability to obtain margin control by lumpectomy and/or reexcision(s);
- (iii) patients with a contraindication to chest wall irradiation (XRT) or who lack access to an XRT; and
- (iv) suboptimal tumor-to-breast-size ratio, where a margin-negative lumpectomy will yield an unacceptable cosmetic result (as defined by the patient).

Mastectomy and lumpectomy have never been directly compared in a prospective, randomized trial designed for DCIS patients. However, comparable survival has been confirmed by indirect comparisons from retrospective studies, and from DCIS patients that were incidentally included in the National Surgical Adjuvant Breast Project (NSABP) B-06 Trial.¹ The B-06 trial was designed to evaluate the outcome of approximately 1,800 Stage I and II breast cancer patients randomized to treatment by breast conservation therapy (with versus without breast irradiation) or by mastectomy. A centralized pathology review subsequently identified 78 cases of DCIS that were randomized as well,¹ and equally divided between the three-study arm. As shown in table 1, the overall survival for all three arms was similar (approximately 96% at 6 years) but the addition of breast irradiation to lumpectomy decreased local recurrence (LR) from 43% to 7%.

Several retrospective studies²⁻¹⁵ have reported outcomes from DCIS managed by lumpectomy, with or without breast irradiation, and mastectomy. As expected, lumpectomy alone resulted in consistently higher rates of LR (range, 8–34%) in comparison to patients treated by lumpectomy and breast radiation (range, 0–17%). Risk factors for LR varied between studies, with involved margin status, young age at diagnosis, and high-grade tumors with comedo necrosis being the most commonly cited predictors. Although inadequate margin control was frequently implicated in risk for developing LR, there was notable variation between studies regarding the optimal extent of a negative margin. Furthermore, as noted in a meta-analysis of breast conservation studies for DCIS by Boyages et al,¹⁵ studies published prior to 1998 often neglected to include margin status in their analyses. In the more recent studies, a negative margin was variously defined as a minimum of one, two, or three millimeters of microscopically normal tissue at the inked lumpectomy borders. Regardless of the definition, within studies the risk of LR was usually lower for subsets where margin control was achieved.

Another consistent finding between studies of lumpectomy for DCIS is that approximately half of all local recurrences are invasive lesions. This finding suggests that the decision to be treated by breast preservation involves a different category of risk that is assumed by the DCIS patient compared to the patient undergoing lumpectomy for invasive cancer. Tamoxifen may be added to the therapeutic regimen to further reduce the risk of new and/or recurrent breast events in patients with estrogen-receptor-positive DCIS, after a thorough discussion of potential adverse side effects. The NSABP B-17 trial reported that tamoxifen reduced the risk of invasive recurrences after lumpectomy and radiation.

Because of the expense, inconvenience, and potential adverse effects of XRT, its routine use following lumpectomy for “low-risk” DCIS has been questioned. The obvious candidates would be small-volume, low-grade DCIS with widely negative margins on lumpectomy. Some groups have developed grading systems that stratify DCIS patients based on the risk of developing LR. The most popular of these is the Van Nuys Prognostic Index, developed by Silverstein et al.¹⁶ and based on the detailed pathology analyses and follow-up of several hundred DCIS patients.

Several groups have implemented studies designed to evaluate the long-term results of treating highly selected subsets of DCIS patients by lumpectomy alone. One such study, conducted by the Dana-Farber/Harvard Cancer Center, utilized DCIS grade 1 or 2, size up to 2.5 centimeter (cm), and final margins of at least 1 cm as eligibility criteria. After accrual of 157 patients (out of an accrual goal of 200), the early closure of this study was recently reported¹⁷ because of an excessive LR rate. At a median follow-up of 40 months, 13 patients experienced an LR (9 were invasive recurrences), corresponding to a 5-year rate of 12.5% and a per annum rate of 2.5% per patient-year.

Regional Therapy

Past studies of mastectomy performed for DCIS revealed axillary metastases in approximately 2% of DCIS cases. It is commonly assumed that these are related to a focus of invasive disease in the breast that was overlooked on pathologic tissue sampling. This low risk of detecting nodal disease and the wish to minimize risk of lymphedema prompted most surgeons to abandon the routine practice of performing an axillary lymph node dissection in DCIS patients. For those patients requiring a mastectomy because of diffuse DCIS, the need for axillary staging becomes more relevant because of the associated increased risk of coexisting microinvasion. In these cases, the standard approach is to perform lymphatic mapping and sentinel lymph node biopsy.

Management Approach for the Individual Patient

The majority of DCIS patients today present with a nonpalpable abnormality detected mammographically, such as microcalcification. The initial management approach should include diagnostic imaging, such as compression/magnification views, to gain a better appreciation for the extent of disease. Breast ultrasound may be useful for asymmetric densities. Whenever possible a percutaneous, image-guided, core-needle biopsy should be the initial diagnostic intervention. Stereotactic biopsies are highly accurate for mammographically detected microcalcifications, and ultrasound may be useful to guide the biopsy of an asymmetric mass density. Fine-needle-aspiration biopsies have a high risk of sampling error, and are unlikely to yield adequate tissue for full histopathologic and molecular characterization of the biopsied lesion. Multiple cores should be extracted (10–15 for microcalcifications), and these should be imaged mammographically to confirm the presence of microcalcifications. Some clusters of microcalcifications are quite small, and may be completely resected with cores, especially if

vacuum-assisted devices are employed. In this setting, a radiopaque clip should be inserted to facilitate subsequent wire-localization lumpectomy for those lesions proven to be cancerous.

When percutaneous core-needle biopsies are unavailable, or if the patient cannot tolerate the positioning necessary for the stereotactic approach, then an open biopsy with image-guided wire localization will be required. Specimen mammography should always be performed to document inclusion of the targeted area, and the specimen should be oriented by the surgeon for pathologic analysis.

For all biopsy material revealing a diagnosis of DCIS (regardless of biopsy method), scrutiny should focus on ruling out microinvasion, and on describing the nuclear grade and the histopathologic pattern. In cases of borderline epithelial lesions, e-cadherin staining may be useful to distinguish DCIS from lobular carcinoma in situ, where expression of this cellular-adhesion molecule is lost.

Once the diagnosis of DCIS has been confirmed, the next management decision is in regard to local therapy. Patients with localized disease should be considered excellent candidates for breast preservation. A postlumpectomy mammogram should always be obtained for cases of DCIS associated with microcalcifications. Patients can usually tolerate this procedure by 2–3 weeks postop. Regardless of the margin status for the previous surgical procedure, any residual, suspicious-appearing microcalcifications should be targeted in a subsequent reexcision. The skin incision for a cancer-related lumpectomy should be curvilinear, and should be placed directly over the area of diseased tissue. Although circumareolar incisions are cosmetically appealing, they should be avoided when the cancerous lesion is peripherally located. A long dissection tunnel from the skin to the site of disease risks exposing normal tissue to cancerous cells. Furthermore, if a reexcision is required for margin control, the long tract increases the volume of tissue that would need to be resected. It is also useful to leave metallic clips at the base and along the walls of the lumpectomy cavity. The radiation oncologist can target this area for a final boost dose, and as the lumpectomy cavity scars down, these clips will be useful for follow-up mammographic imaging.

Once margin control has been achieved, and the postlumpectomy mammogram has been cleared, the option of breast XRT should be offered to all DCIS patients. Irradiation decreases the likelihood of LR in all categories of this disease, and there is no subset of DCIS patients identified to date that has a sufficiently low risk of recurrence that lumpectomy alone would be the standard of care. Follow-up mammography is typically performed 6 months after completion of breast XRT, but the ultimate goal is to return the patient to an annual mammography schedule once a new baseline image has been established.

Patients presenting with widespread, suspicious-appearing microcalcifications are poor lumpectomy candidates, and should be advised to undergo mastectomy for definitive control of disease. Plastic surgery referrals can be arranged for consideration of breast reconstruction options. If the mammogram reveals diffuse microcalcifications approaching the anterior/skin surface, and immediate breast reconstruction is planned, then the skin-sparing technique should be applied cautiously, if at all. This will minimize the chances of pathology revealing DCIS at the anterior margin, in which case postmastectomy irradiation should be considered.

Likelihood of finding microinvasion in the specimen increases in direct proportion to the extent of involved breast tissue. Patients requiring mastectomy because of extensive DCIS are therefore by definition at substantially high risk for harboring invasive foci, and it is therefore prudent to plan for axillary staging and sentinel lymph node biopsy in conjunction with the mastectomy.

Table 1. Results of Prospective, Randomized Clinical Trials Evaluating Treatment for DCIS

Study	NSABP B-06 ^{*1}	EORTC ^{18,19}	NSABP B-17 ^{20,21}	NSABP B-24 ²²	UK/AZ ²³
Eligibility Requirements	<ul style="list-style-type: none"> Designed to evaluate the safety of breast conservation for invasive breast cancer Inked margin tumor-free 	<ul style="list-style-type: none"> Designed to evaluate lumpectomy with versus without breast XRT Mammographically detected DCIS ≤5 cm No margin specification 	<ul style="list-style-type: none"> Designed to evaluate lumpectomy with versus XRT DCIS detected by mammogram or physical exam Inked margin tumor-free 	<ul style="list-style-type: none"> Designed to evaluate the added benefit of tamoxifen as adjuvant therapy for DCIS patients treated with lumpectomy and breast XRT DCIS detected by mammogram or physical exam Inked margin tumor-free 	<ul style="list-style-type: none"> Designed to assess the effectiveness of adjuvant tamoxifen and/or XRT after lumpectomy DCIS respectable by lumpectomy Inked margin tumor-free
Average Follow-Up (Months)	83	65	90	74	53
Randomization Arms	Lump + XRT Lump	Lump + XRT Lump	Lump + XRT Lump	Lump + XRT Lump + Tam	Lump + Tam Lump + XRT Lump + Tam + XRT
# Patients	21	426	411	902	544
# Local Recurrences (%)	9 (42.8%)	83 (19.5%)	47 (11.4%)	87 (9.6%)	119 (22%)
# Invasive Local Recurrences (%)	5/9 (45%)	37/83 (44%)	17/47 (36%)	40/87 (46%)	39/119 (33%)
Overall Survival (All Causes)	96%	97%	96%	97%	NR
Risk Factors for Local Recurrence	<ul style="list-style-type: none"> Lack of XRT following lumpectomy Comedonecrosis 	<ul style="list-style-type: none"> Lack of XRT Age ≤40 years Symptomatic DCIS Involved margins Solid/ciriform/comedo patterns 	<ul style="list-style-type: none"> Lack of XRT Calcifications on mammogram 	<ul style="list-style-type: none"> Lack of tamoxifen Age <50 years Involved margins Comedonecrosis Symptomatic DCIS 	<ul style="list-style-type: none"> Lack of XRT

*76 cases randomized in NSABP B-06 found to be pure DCIS on retrospective pathology review

NSABP = National Surgical Adjuvant Breast and Bowel Project

EORTC = European Organisation for Research and Treatment of Cancer

UK/ANZ = United Kingdom, Australia, and New Zealand

Lump = lumpectomy

XRT = breast irradiation

Tam = tamoxifen

F/U = follow-up

Symptomatic DCIS = palpable mass; nipple discharge

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Local and Systemic Outcomes in Ductal Carcinoma in Situ Based on Tumor and Patient Characteristics: The Pathologist's Perspective

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A variety of clinical features, treatment factors, and tumor characteristics have been reported to be associated with local recurrence and/or progression to invasive breast cancer following breast-conserving therapy for ductal carcinoma in situ (DCIS) (i.e., excision with or without radiation therapy). The major clinical features associated with increased local recurrence are symptomatic presentation and young patient age at diagnosis, although the definition of “young” has not been uniform across studies.¹⁻⁵

With regard to treatment factors, the results of three prospective, randomized clinical trials have demonstrated that the use of radiation therapy following breast-conserving surgery is associated with about a 50% reduction in the risk of local recurrence^{2,6,7} and that the addition of tamoxifen further reduces this local recurrence risk among patients treated with excision and radiation therapy.⁸

Retrospective studies have identified various pathologic characteristics associated with local recurrence of DCIS or progression to invasive breast cancer following breast-conserving therapy. Results from these studies are difficult to compare due to differences in patient selection, extent of surgery, details of radiation therapy (where applicable), histologic classification, and length of follow-up. Features that have been most consistently reported to be associated with a higher risk of local recurrence or progression to invasive breast cancer include high nuclear grade, the presence of comedo necrosis, larger tumor size, and involved margins of excision.⁹⁻¹¹ However, the relative importance of these factors is poorly understood and has varied among these studies.¹² The status of the margins of excision is arguably the most important of these factors. For example, in one large, retrospective study, neither size, nuclear grade, nor comedo necrosis were significant prognostic factors for local recurrence if the lesion was excised with margins of 10 mm or more.¹³ These factors may, however, be of importance with smaller margin widths.¹³ How wide a margin is wide enough remains a matter of debate and likely depends upon whether or not radiation therapy will be used in conjunction with breast-conserving surgery. In a recent meta-analysis of over 4,600 patients, Dunne et al. found that a margin width of 2 mm appears to be as adequate as a margin width of 5 mm or more when patients with DCIS are treated with radiation therapy following breast-conserving surgery.¹⁴

The need to consider length of follow-up in evaluating the potential prognostic importance of histologic features is emphasized by the results of the study of Solin and colleagues.¹⁵ In that study, patients whose DCIS showed the combination of comedo architecture and grade 3 nuclei had a significantly higher 5-year local recurrence rate after breast-conserving surgery and radiation therapy than patients whose DCIS did not show this combination of features (11% versus 2%, respectively; $p=0.009$). However, at 10 years, this difference was no longer statistically significant (18% versus 15%, respectively; $p=0.15$). Early results from the prospective, nonrandomized Eastern Cooperative Oncology Group E5194 Trial, which indicate that the ipsilateral breast tumor recurrence rate at 5 years is higher for high-grade DCIS (13.7%) than for low- or intermediate-grade DCIS (6.8%) treated with excision with at least a 3 mm margin, should be viewed with this observation in mind.¹⁶

Silverstein et al. have suggested that the histologic type of DCIS, the size of the lesion, the width of the margins, and patient age can be combined into a prognostic index to predict the likelihood of local recurrence after breast-conserving therapy and to select treatment options; i.e., excision alone, excision plus radiation therapy, or mastectomy.^{17,18} Although all of the factors included in the University of Southern California/Van Nuys Prognostic Index are important considerations in the selection of treatment options for patients with DCIS, their relative importance and the interactions among them are not well understood.¹²

Data from the pathologic analysis of patients enrolled in three prospective, randomized clinical trials of breast-conserving therapy for DCIS have also indicated that certain pathologic features appear to be associated with an increased risk of local recurrence. In the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-17 Trial, nuclear grade, comedo necrosis, margin status, and histologic type were significant prognostic variables for local recurrence in univariate analysis.⁶ However, in multivariate analysis the presence of comedo necrosis and margin status were the only independent pathologic features associated with local recurrence.⁶ Comedo necrosis was also found to be independently associated with local recurrence in the NSABP B-24 trial.¹⁹ In the most recent analysis of data from the European Organisation for Research and Treatment of Cancer (EORTC) 10853 Trial, the presence of intermediate or high nuclear grade, solid and cribriform architectural patterns, and involved margins were significantly associated with local recurrence in both univariate and multivariate analyses.²

The identification of biological markers that predict the outcome of patients with DCIS is an area of active investigation.^{10,17,20,21} However, the level of expression of many biomarkers that have been studied in DCIS is highly correlated with grade (e.g., estrogen receptor with low-grade lesions; human epidermal growth factor receptor 2 (HER2), p53, and high Ki67 proliferation rate with high-grade lesions), and there is a pressing need to identify biomarkers that predict local recurrence and progression to invasive breast cancer independent of standard prognostic markers such as grade and margin status. A recent, small, case-control study suggested that an abrogated cellular stress response, characterized by high expression of both p16 and Ki67 or high expression of both cytochrome oxidase subunit 2 (COX2) and Ki67, identified a subset of high-grade DCIS lesions that progressed to invasive breast cancers, but this observation requires further investigation.²² Currently, the only biomarker used in clinical practice to help manage patients with DCIS is estrogen receptor status. In an analysis of data from the NSABP-B-24 trial, designed to evaluate the role of tamoxifen in the treatment of patients with DCIS treated with breast-conserving surgery and radiation therapy, the use of tamoxifen was associated with a significantly reduced risk of local-recurrence-only patients whose DCIS was estrogen-receptor-positive.²³ Therefore, testing DCIS for estrogen receptor is now routine practice.

Analysis of genetic alterations, gene expression signatures, and proteomic profiles, as well as study of the microenvironment associated with DCIS, are other important avenues of research that may provide new insights into DCIS recurrence and progression, which may ultimately lead to novel treatment and prevention strategies.^{24,25}

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Meta-Analysis of Ductal Carcinoma in Situ Trials: Outcomes From the Early Breast Cancer Trialists' Collaborative Group

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The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) was set up in 1984–85 to coordinate five yearly meta-analyses of centrally collated individual patient data from women in all randomized trials of the treatment of early breast cancer. In the present cycle, which considers trials that began by 2000, trials of women with ductal carcinoma in situ of the breast have been included for the first time. Five trials of the effect of radiotherapy in women who had been given breast-conserving surgery were eligible. Individual patient data from four trials, including approximately 4,000 randomized women, were available and have been centrally collated. The results of a meta-analysis of these data will be presented.

Local and Systemic Outcomes in Ductal Carcinoma in Situ Based on Tumor and Patient Characteristics: The Radiation Oncologist's Perspective

Nina Bijker, M.D., Ph.D.

Four randomized controlled trials have shown the benefit of radiotherapy after breast conserving surgery for DCIS.¹⁻⁴ Radiotherapy reduces the risk of local recurrence by about 50%, with a similar relative reduction of the recurrence risk in all clinical and pathological subgroups analyzed.⁵ Age and margin status are the most important factors related to the risk of local recurrence. The impact of young age on the outcome of treatment of DCIS has been studied by several groups.^{2,6-9} Potential factors responsible for the increased risk of local recurrence after breast-conserving therapy (BCT) for DCIS in young women are adverse prognostic pathologic features that seem to occur more frequently in young women and treatment-related factors like a smaller excision volume.¹⁰ However, to date, data are limited and sometimes inconsistent.¹⁰ At present, young age per se should not be a contraindication for BCT, especially because it is unknown whether such patients have a superior long-term prognosis if treated by mastectomy. Local recurrences following both skin-sparing and simple mastectomy after DCIS are reported, and seem to occur especially in younger women.^{11,12}

Numerous studies have shown an increased risk of local recurrence when DCIS was excised with doubtful or involved margins.^{2,6,7,13,14} Various thresholds have been reported as a safe margin status, from ≥ 1 cm to $\geq 1, 2, 3,$ or 5 mm. Single institutional studies have suggested that radiotherapy can safely be omitted when margins are ≥ 1 cm;¹⁵ however, prospective studies have not confirmed this.¹⁶ On the other hand, when margins are involved, the risk of recurrence is high, even after radiotherapy (up to 25% at 10 years).² Currently, it remains unknown which is an optimal minimal margin width for BCT.

In all randomized trials, the dose delivered was 50 Gy without a boost being prescribed. In invasive breast cancer, it has been shown that a boost can further reduce the risk of local recurrence.¹⁷ To date, no randomized trial has been performed investigating the value of the boost in DCIS, but retrospective studies support the evidence of a dose-effect relationship in DCIS, especially in younger women.¹⁸ An international Phase III study is forthcoming investigating the value of the boost in women with DCIS.

Most studies have not found a relationship of the risk of local recurrence with the differentiation type of the tumor, but a poorly differentiated DCIS is associated with a more aggressive clinically recurrent tumor, with a higher risk of distant metastases after invasive local recurrence.^{2,7} This is in agreement with the observation that the differentiation type of the DCIS is related to the grade of the invasive (recurrent) tumor.¹⁹ Therefore, for women with poorly differentiated DCIS who are at high risk of local recurrence, like young women or those with lesions that cannot be excised with tumor-free margins, the risk of eventually dying from metastasized disease after an invasive local recurrence could become unacceptably high.

Although radiotherapy reduces the risk of local recurrence in all clinical and histological subgroups, there is a continuous search for groups in which the absolute risk of local recurrence is so low that radiotherapy could be safely omitted. In a subgroup analysis of the European Organisation for Research and Treatment of Cancer Trial, the only patients with an

exceptionally low risk of recurrence were those with a well-differentiated DCIS and a clinging or micropapillary growth pattern.² However, a prospective study would be needed to confirm this.

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Ductal Carcinoma in Situ Outcomes in Breast Cancer Chemoprevention Trials

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In the Multiple Outcomes Studies of Raloxifene Evaluation and Continuing Outcomes Relevant to Evista (CORE) studies of raloxifene for the prevention of osteoporosis, raloxifene did not reduce the risk of noninvasive breast cancer, although the number of events in those studies was very small.¹⁻³ The CORE results through 8 years of follow-up showed that raloxifene continued to offer a significant reduction in invasive disease, despite a lesser impact on noninvasive disease. To compare the relative effects and safety of raloxifene and tamoxifen on the risk of developing breast cancer and other disease outcomes, the National Surgical Adjuvant Breast and Bowel Project conducted the Study of Tamoxifen and Raloxifene (STAR), a prospective, double-blind, randomized clinical trial.⁴⁻⁶ It began July 1, 1999, in nearly 200 clinical centers throughout North America, with final analysis initiated after a prespecified 327 cases of invasive breast cancer were diagnosed. There were 19,747 postmenopausal women (mean age 58.5 years) with increased 5-year breast cancer risk (mean risk, $4.03 \pm 2.17\%$) assessed by the Gail model.⁷⁻⁸ Participants were eligible for enrollment if they had a history of lobular carcinoma in situ (LCIS), but subjects with prior DCIS were excluded. Women were randomly assigned to receive either oral tamoxifen (20 mg/d) or raloxifene (60 mg/d) over 5 years. Initial data were reported based on a cutoff date of December 31, 2005, in June 2006. The mean duration of treatment at the time of the initial report was 3.1 ± 1.7 years for the tamoxifen group and 3.2 ± 1.6 years for the raloxifene group. During the course of the study, 605 women in the tamoxifen group and 532 in the raloxifene group were lost to follow-up.

The predetermined main outcome measures were incidence of invasive breast cancer, uterine cancer, noninvasive breast cancer, bone fractures, and thromboembolic events. At the time of the initial report, there were 163 cases of invasive breast cancer in women assigned to tamoxifen and 168 in those assigned to raloxifene (incidence, 4.30 per 1000 vs. 4.41 per 1000 (RR = 1.02, 95% CI, 0.82–1.28). In contrast to the findings for invasive breast cancer, there were fewer noninvasive breast cancers in the tamoxifen group than in the raloxifene group, although this difference did not reach statistical significance at the initial report.^{4,9} There were 57 incident cases of noninvasive breast cancer among the women who took tamoxifen and 80 among the women who took raloxifene (annual incidence, 1.51 vs. 2.11 per 1000; RR = 1.40; 95% CI = 0.98–2.00). Cumulative incidence through 6 years was 8.1 per 1000 in the tamoxifen group and 11.6 in the raloxifene group ($p = 0.052$). About 36% of the cases were LCIS, and 54% were ductal carcinoma in situ (DCIS), with the balance being mixed types. The pattern of fewer cases among the tamoxifen group was evident for both LCIS and DCIS. When patients with LCIS at baseline were eliminated, there were 28 women with a diagnosis of in situ cancer in the tamoxifen group versus 49 in the raloxifene-treated patients. When both LCIS at baseline or DCIS diagnosed in the first year of participation were eliminated, the difference for in situ cancer was 18 cases in the tamoxifen group and 34 in the raloxifene group.

Participants have now been followed through August 31, 2008, for validated disease outcomes. Details for these participants in the STAR trial are shown in table 1. The number of events and the annual rate for in situ breast cancer are shown in table 2. With increased follow-up time and an increased total number of in situ events, the differences between the tamoxifen and raloxifene groups has decreased from those shown in the initial report (figure 1). Data on the

incidence of in situ breast cancer events from other chemoprevention trials will also be shown, and the implications for the biology of in situ breast cancer will be reviewed.¹⁰⁻¹²

Table 1. Participant Characteristics at Time of Randomization for Women Included in the Current Analyses

Participant Characteristic	Tamoxifen		Raloxifene	
	No.	%	No.	%
Age (years)				
<49	884	9.1	878	9.0
50–59	4,856	49.9	4,854	49.8
60–69	3,137	32.2	3,174	32.5
>70	859	8.8	847	8.7
Race/Ethnicity				
Caucasian	9,105	93.5	9,114	93.4
African-American	233	2.4	243	2.5
Hispanic	192	2.0	193	2.0
Other	206	2.1	203	2.1
No. 1° relatives with breast cancer				
0	2,838	29.1	2,791	28.6
1	5,046	51.8	5,134	52.6
2	1,532	15.7	1,561	16.0
>3	320	3.3	267	2.7
History of lobular carcinoma in situ				
No	8,844	90.8	8,864	90.9
Yes	892	9.2	889	9.1
History of breast atypical hyperplasia				
No	7,545	77.5	7,512	77.0
Yes	2,191	22.5	2,241	23.0
5 -year predicted breast cancer risk (%)				
<2.00	1,055	10.8	1,102	11.3
2.01–3.00	2,993	30.7	2,892	29.7
3.01–5.00	3,042	31.2	3,086	31.6
>5.01	2,646	27.2	2,673	27.4
Total	9,736		9,753	

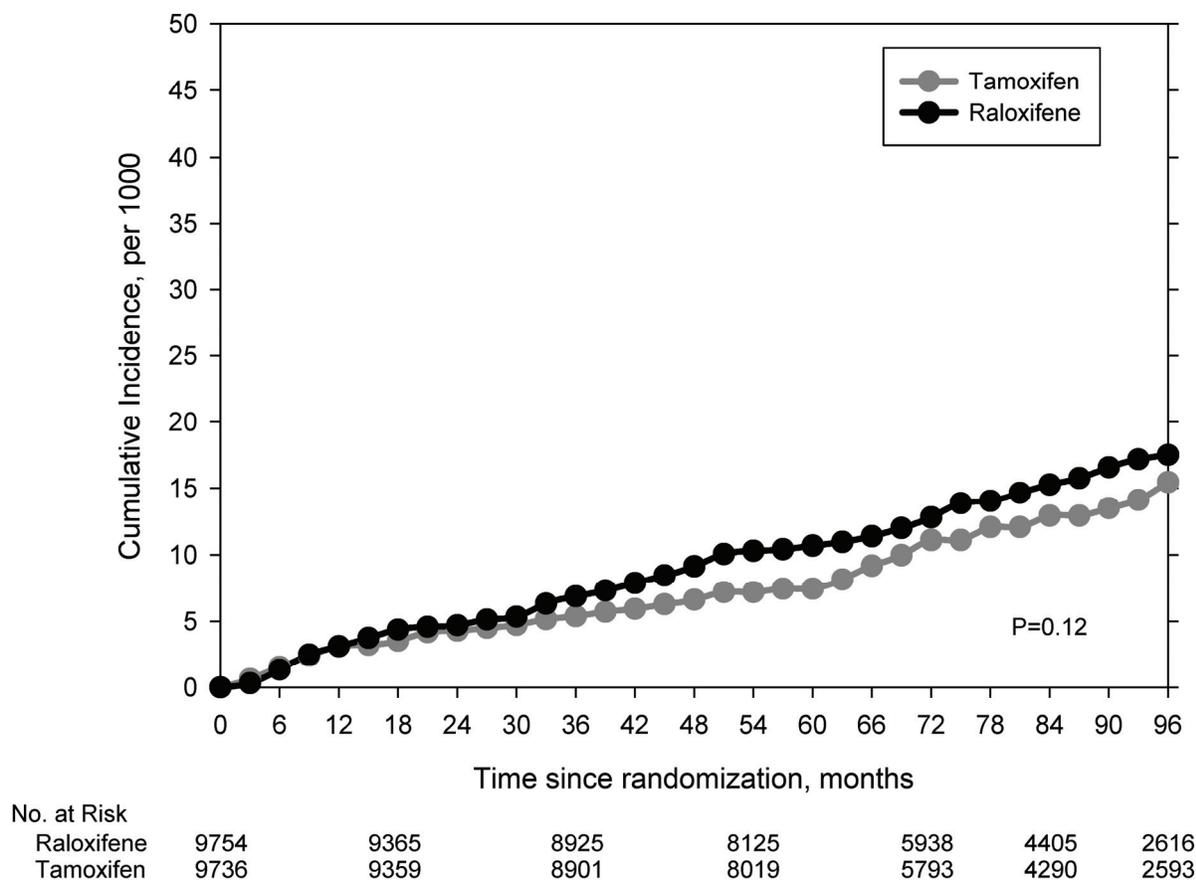
Table 2. Average Annual Rates of in Situ Breast Cancer by Treatment Group and Participant Characteristics at Baseline

Type of In situ Disease	Number of Events		Rate per 1000		Difference*	Risk Ratio (RR)†	RR 95% CI
	Tamoxifen	Raloxifene	Tamoxifen	Raloxifene			
DCIS	66	77	1.17	1.35	-0.18	1.16	0.82 to 1.64
LCIS	32	35	0.57	0.62	-0.05	1.09	0.65 to 1.81
Mixed	8	17	0.14	0.30	-0.16	2.11	0.86 to 5.65
Total	106	129	1.88	2.27	-0.39	1.21	0.93 to 1.58

*Rate in the tamoxifen group minus rate in the raloxifene group

†Risk ratio for women in the raloxifene group compared to women in the tamoxifen group

Figure 1. Cumulative Incidence of Noninvasive Breast Cancer



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Evidence-Based Practice Center Presentation III: Tumor and Patient Characteristics and Associated Outcomes in Ductal Carcinoma in Situ

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We searched several databases to find 133 original prospective trials and observational studies published in English that examined the association between women or tumor factors and patient outcomes, reported main effect of the predictors adjusting for treatments, reported how predictors modified the effects of the treatments, or reported patient outcomes in subgroups with different predictors.

Age

Younger age at diagnosis is a consistent adverse prognostic factor for ductal carcinoma in situ (DCIS) outcomes (table 1). Women over age 40 or 50 consistently had a lower risk of DCIS or invasive recurrence than younger women, with many studies reporting a relative risk of around 0.5. It is less clear whether the age-related disadvantage is attenuated when comparing middle-aged and older women. All-cause mortality, however, is consistently lower in younger women than older women. Consistent with the increased risk of recurrence in younger women, three studies found premenopausal women to face higher risk of recurrence than postmenopausal women.

Race

Surveillance Epidemiology and End Results (SEER)-based studies report higher all-cause mortality and breast cancer mortality among African-American women than White women diagnosed with DCIS. The studies that adjusted for clinical prognostic variables, including tumor size, grade, or necrosis, found no differences in ipsilateral cancer in race subgroups. Two SEER-based papers that adjusted for age, year, tumor registry, and treatment, but not tumor characteristics, reported worse rates of ipsilateral cancer and advanced invasive cancer among African-American women compared to Whites with DCIS. These findings point to differences in tumor characteristics such as size, grade, and necrosis as important explanatory factors for the observed poorer outcomes among African-American versus White women. Advanced cancer was more common in Asian women when compared to Whites.

High mammographic density was associated with greater rates of ipsilateral and contralateral cancer recurrence. Few studies examined the association between reproductive history and DCIS outcomes and they did not find a significant association with age at menarche, oral contraceptive use, or hormone replacement therapy. Parity and age at first birth were not associated with worse DCIS or invasive carcinoma recurrence. All studies found a positive family history to be associated with worse outcomes, though not all effects were statistically significant. Inconsistent evidence suggested that women with one or more comorbidities were more likely to experience a local DCIS or invasive cancer recurrence than women with no comorbidities.

Women diagnosed with DCIS after screening mammography had become a common occurrence (1984–1989) compared to those diagnosed in 1978–1983, and had a 40% reduction in the adjusted relative risk of breast cancer death. The 10-year breast cancer standardized mortality rate in women with DCIS declined from 3.4 (95% confidence interval, 2.4–4.5) before screening mammography was common to 1.9 (95% confidence interval, 1.5–2.3) after wide implementation of breast cancer screening. However, the rates of local recurrence and contralateral breast cancer remained unchanged over this same period.

Positive surgical margins are consistently associated with increased DCIS and invasive breast cancer recurrence in observational studies and randomized controlled clinical trials. There was, however, considerable variability across studies in terms of how margins were defined or classified. For example, some studies classified margins as “free” or “involved,” while others used more precise measures such as <1 millimeter (mm). An analysis of adjusted relative risk suggests risk of local recurrence is reduced with larger widths of negative margins. Margins of 10 mm or more were associated with the largest reduction (98%) in the risk of local recurrence, while no differences were seen using a cutoff of 2 mm or 4 mm.

Tumor size was positively associated with higher rates of local DCIS and invasive recurrence, though many of the estimates were not statistically significant. Estimates generally classified tumors <20 mm as “small,” though some defined small as <5 mm. There was no consistent finding of an association between tumor size and contralateral DCIS, contralateral DCIS or invasive carcinoma, or contralateral invasive carcinoma.

Grade

While labeled somewhat inconsistently, tumors assigned a higher pathological or nuclear grade (grade 3) have a consistently higher probability of local DCIS or invasive recurrence than those at intermediate or low grade (grades 2 or 1). Comparisons of intermediate (2) versus low (1) grade were much less consistent. Overall, the studies suggest that the difference between grades 2 and 1 may be less important than the difference between grade 3 and grades 2 and 1.

Architecture

The most commonly measured architectural feature of DCIS is comedo necrosis. Noncomedo DCIS includes cribriform, micropapillary, and solid types. Comedo necrosis is consistently and strongly associated with increased risk of local DCIS or invasive cancer, with hazard ratios generally above 2.0 and as high as 9.3. No study reported a significant association between comedo and noncomedo DCIS and all-cause mortality, breast cancer mortality, contralateral invasive carcinoma, or all events. Comparisons between other architectural groups are rarely reported and are somewhat inconsistent with higher risk of DCIS or invasive recurrence for women with solid, cribriform, or papillary tumors.

Necrosis

Inconsistent evidence suggests a positive association between necrosis and worse outcomes; this association is more evident for local invasive carcinoma. The association between necrosis and local DCIS or invasive cancer recurrence differed depending on the treatments women had. The association was not significant after mastectomy or skin-sparing mastectomy, and was inconsistent in direction and significance after lumpectomy plus radiation and in studies that combined all treatment together in analysis. Women after lumpectomy had an increased risk of

local DCIS or invasive recurrence by 115.8% (pooled RR, 2.158, 95% confidence interval, 1.263–3.687, I^2 25%).

Van Nuys Index

The Van Nuys Index is scored from 4–12 based on four different predictors of local breast recurrence: tumor size, width of negative margin, pathologic classification, and patient age. Each individual predictor is scored from 1–3. The index measures postsurgical risk of events (since surgical margins comprise one-quarter of the score). The studies applied the exact Van Nuys criteria (9 points total for grade, size, and margin), on an expanded 12-point University of Southern California/Van Nuys Prognostic Index that includes age. Some studies included age, grade, and tumor size but not surgical margins or modified cutoffs for nuclear grade (low=1, intermediate=2, high=3) and margin (>1 mm score=2, ≤1 mm score=3). Women at the highest risk category of Van Nuys index (10–12) had 224% greater odds of mortality and greater rates of ipsilateral cancer than women in the 4 to 6 risk category.

Estrogen and Progesterone Receptor Status

Studies of estrogen receptor (ER) status and DCIS outcomes are generally limited to small studies of approximately 100 cases each. Generally, all are consistent in their findings that positive ER status is associated with reduced likelihood of local DCIS or invasive recurrence, although few of the associations are statistically significant.

The studies investigating the association between progesterone receptor (PR) status and patient outcomes showed a tendency toward less local DCIS or invasive cancer recurrence in PR-positive women.

Her2Neu

The relationship between human epidermal growth factor receptor-2 (Her2) positivity and DCIS recurrence was only studied in relatively small studies of 129 patients or less. Consistently, investigators have found women with Her2-positive DCIS were at higher risk of recurrence. Her3 and Her4 have only been evaluated in a single study.

Calcification

In multiple reports from the same institution using a moderate-sized cohort (132–148 subjects), lack of calcification was strongly associated with DCIS or invasive carcinoma recurrence. The studies did not classify calcifications based on their form, such as fine/granule, etc.

Summary

In general, few of the risk factors for DCIS or breast cancer incidence are also associated with outcomes following DCIS diagnosis. However, the majority of important prognostic factors for DCIS outcomes are also prognostic factors for invasive breast cancer outcomes. Beyond factors that are routinely measured by cancer registries, many of the factors reviewed in this report rely on the findings of small, single-cohort case series from academic centers. Thus, there is a need for larger population-based studies of the relationship between tumor markers and patient characteristics on outcomes after DCIS diagnosis.

Table 1. Summary of the Evidence: Association Between Women and Tumor Characteristics and Patient Outcomes

Risk Factor	Number of Publications	Number of Patients	Estimates of Risk	Evidence
Age	5RCT; 51	173,937	Women younger than 40 years had worse outcomes.	Moderate
Race	12	123,853	African-American women had higher mortality and advanced cancer.	Low
Menopause	8	3,718	Premenopausal women had worse outcomes than postmenopausal women.	Low
Menarche age	1	709	NS	Low
Marital status	2	1,812	Single or unmarried women had worse outcomes.	Low
Education	1	709	NS	Low
Hormone replacement therapy (HRT)	4	1,899	NS	Low
Oral contraceptives	1	709	NS	Low
Age at first birth	1	709	NS	Low
Parity	1	709	NS	Low
Family history	12	4,595	Women with family history had worse outcomes.	Low
Alcohol intake	1	709	NS	Low
Body Mass Index; Weight	2; 1	1,745; 198	Obese women may have worse outcomes.	Low
Comorbidity	2	4,512	Women with one or more comorbidities had worse outcomes.	Low
Breast density	2	6,466	Women with higher density had worse outcomes.	Low
Microinvasion	1 RCT; 4	1,065	NS	Low
Tumor size	2 RCTs; 39	1,095; 53,344	Women with larger tumors may have worse ipsilateral cancer.	Low
Architecture: Columnar cell change; comedo; cribriform, micropapillary, and solid types Necrosis	3 RCTs 25	2,869 47,346	There was consistent evidence that women with comedo necrosis DCIS had worse outcomes. Solid, cribriform, or papillary DCIS were associated with worse outcomes.	High Low
Calcification	6	808	The lack of calcification was strongly associated with DCIS or invasive carcinoma recurrence.	Low
Antiapoptotic Bcl-2 gene expression		216	NS	Low
Expression of p21 cyclin-dependent kinase inhibitor	4	435	NS	Low

Risk Factor	Number of Publications	Number of Patients	Estimates of Risk	Evidence
Estrogen receptors (ERs)	8	1,421	Inconsistent negative effect ER. Women with HER2-positive status tended having worse ipsilateral cancer. HER4-positive women with expression had lower risk of recurrent cancer.	Low
Progesterone receptors	6	1,447		
Human epidermal growth factor receptor 2 (HER2)	5	660		
Tumor grade	2 RCTs; 20	1,401; 45,765	There was consistent evidence that women with high-grade DCIS had worse ipsilateral cancer.	High
Tumor suppressor protein 53	4	435	NS	Low
Methods of detection	2 RCTs; 23	2,579; 8,878	Women with clinical symptoms had worse outcomes.	Moderate
Year of diagnosis Time since diagnosis	1;2	7,072; 25,476	Women diagnosed with DCIS after screening mammography became common had a lower standardized-to-the-general-population, 10-year breast-cancer-mortality ratio. Incidence of contralateral DCIS immediately after diagnosis of the primary DCIS dramatically increased due to active surveillance.	Low
Total volume Volume of excision	1; 3	148; 1,309	Women with less excision volume (≤ 60 cm ³) had worse outcomes.	Low
Positive surgical margins	3 RCTs; 11	2,362	Women with positive margins had worse outcomes. Involved, close, and unknown margins were associated with worse outcomes. Women with negative margins of 10 mm or more had better outcomes.	High
Number of slides with DCIS	1	148	Women with a greater number of slides with DCIS in the specimen had worse outcomes.	Low
Composed risk estimation	1 RCT; 13	775; 20,736	Women at a higher-risk category using Van Nuys Index had worse outcomes.	Moderate

NS = not significant

RCT = randomized controlled clinical trial

The Impact of Radiation Therapy on Ductal Carcinoma in Situ Outcomes

Lawrence J. Solin, M.D., F.A.C.R., FASTRO

Ductal carcinoma in situ (DCIS; intraductal carcinoma) is most commonly detected as suspicious microcalcifications on routine screening mammography. Patients with such asymptomatic mammographic findings are frequently interested in breast conservation treatment, either with or without definitive radiation. For the patient with newly diagnosed DCIS, the options for the local treatment of the breast are (a) lumpectomy (excision) plus radiation treatment; (b) lumpectomy alone without radiation treatment; or (c) mastectomy. As most patients are interested in breast conservation, the major treatment decision for most patients is whether or not to add radiation after lumpectomy. The need for mastectomy on the basis of extensive DCIS disease, found either radiologically as diffuse microcalcifications or pathologically, is relatively infrequent.

The rationale for radiation after lumpectomy for DCIS is straightforward. Four prospective randomized clinical trials have compared lumpectomy to lumpectomy plus radiation treatment.¹⁻⁷ Table 1 summarizes data from these four randomized trials. In all four randomized trials, the addition of radiation after lumpectomy reduced the risk of local recurrence by approximately 50%, both for overall local recurrence and for the subset of invasive local recurrence. Ten-year outcome data have been published from at least three of these randomized clinical trials.²⁻⁶ Tamoxifen does not substitute for radiation after lumpectomy.^{2,3,7-9}

All four prospective randomized trials had sample sizes on the order of approximately 800–1,000 patients. The primary study endpoint in all four randomized trials was local recurrence, not survival. Thus, the absence of a survival benefit from the addition of radiation treatment cannot be considered as statistically valid evidence to support the omission of radiation treatment after lumpectomy. Extrapolation of the data from the overview of randomized clinical trials of radiation treatment after lumpectomy (albeit from primary invasive breast carcinoma)¹⁰ demonstrates that only a very large randomized clinical trial or meta-analysis would have sufficient statistical power to determine whether there is a survival benefit from adding radiation after lumpectomy in the setting of DCIS. The statistical reliability of survival analysis is further limited because typically only half of all local recurrences show an invasive component after treatment for a primary DCIS.

Long-term results from 1,003 patients in a collaborative multi-institutional study have been published with 10-year and 15-year outcome data.^{11,12} All patients were treated with lumpectomy and radiation. Adjuvant tamoxifen was not used because these patients were treated in the era prior to the routine use of adjuvant tamoxifen. The data from this study demonstrated a 15-year overall survival of 89% and a cause-specific survival of 98%. Thus, more patients died from causes not related to breast cancer than from causes related to breast cancer. Final pathology margins from the primary tumor excision and patient age were both demonstrated to be significant factors for local recurrence, with negative margins and older patient age each associated with a lower risk of local recurrence.

Notwithstanding the substantial improvement in local recurrence associated with adding radiation treatment after lumpectomy, efforts continue to attempt to identify a subset of patients with favorable DCIS who are at sufficiently low risk of local recurrence that the risk/benefit ratio

of omitting radiation treatment is reasonable. Surveillance, Epidemiology, and End Results (SEER) data demonstrate that a substantial fraction of patients in the United States are treated with excision alone, without radiation treatment.¹³ Patients at sufficiently low risk to avoid radiation treatment after lumpectomy have not been reproducibly and reliably identified in prospective clinical trials.¹⁴ Although retrospective institutional studies have suggested the possibility of omitting radiation treatment after lumpectomy in favorable subsets of patients, such retrospective studies of lumpectomy alone (without radiation treatment) are hypothesis generating, not hypothesis testing. The minimum negative margin width needed from the lumpectomy specimen is likely smaller when radiation is added (e.g., > 2 mm) compared to when radiation is omitted (e.g., >10 mm).^{14,15}

In the early 1990s, Eastern Cooperative Oncology Group (ECOG) designed a prospective registration study (E5194) for the treatment of selected patients with DCIS using local excision alone (with the omission of radiation treatment).¹⁶ The protocol was amended in 2000 to allow the option to take adjuvant tamoxifen. The two arms of the study were (a) low- or intermediate-grade DCIS, 2.5 cm in size or less; or (b) high-grade DCIS, 1.0 cm in size or less. The median lesion size was 6 mm and 5 mm in the two arms, respectively.

With median follow-up of 6.2 years for patients in the low- or intermediate-grade arm of the ECOG E5194 study, the 5-year rate of ipsilateral local recurrence was 6.1% and the 7-year rate was 10.5%. With a median follow-up of 6.7 years for patients in the high-grade arm, the 5-year rate of local recurrence was 15.3% and the 7-year rate was 18.0%. These data suggest that patients with high-grade DCIS are not suitable for treatment with excision alone (without radiation). For patients with low- or intermediate-grade DCIS, additional follow-up will be needed to determine the long-term results.

In a prospective single-arm study, Wong et al. reported 158 patients treated with local excision alone (with neither radiation nor tamoxifen).¹⁷ A minimum negative margin width of 1.0 cm or no tumor on reexcision was required. The 5-year rate of local recurrence was 12%. This rate of local recurrence exceeded the predetermined stopping threshold for local recurrence and, therefore, the study was closed early to accrual.

In summary, prospective and retrospective studies have demonstrated that there are excellent long-term outcomes at 10 and 15 years after breast conservation treatment with radiation. Adding radiation after lumpectomy reduces the rate of local recurrence by about half in randomized clinical trials. Low-risk patients eligible for treatment with lumpectomy alone (without radiation) have not been reproducibly and reliably identified in prospective clinical trials with long-term outcomes.

Table 1. Summary of Randomized Trials of Radiation After Lumpectomy for DCIS

Study	No. of Patients	Follow-up	Outcome	Ipsilateral Local Recurrence			P Value
				Without RT	With RT	Decrease With RT	
NSABP B-17 Wapnir et al. ³	813	> 12 years median	Cumulative incidence at 12 years	32.9%	15.8%	52%	<.05
EORTC 10853 Bijker et al. ⁴	1,010	10.5 years median	Actuarial at 10 years	26%	15%	42%	<.0001
Swedish Trial Holmberg et al. ⁶	1,046	8 years mean	Cumulative incidence at 12 years	32%*	16%*	50%	<.05
UK/ANZ Trial Houghton et al. ⁷	1,030	4.4 years median	Crude incidence	13.6%	5.6%	59%	<.0001

*Estimated from curves

Abbreviations:

DCIS = ductal carcinoma in situ

RT = radiation treatment

NSABP = National Surgical Adjuvant Breast and Bowel Project

EORTC = European Organisation for Research and Treatment of Cancer

UK/ANZ = United Kingdom, Australia, and New Zealand

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The Impact of Surgery on Ductal Carcinoma in Situ Outcomes: The Van Nuys Prognostic Index

Melvin J. Silverstein, M.D.

Background

The University of Southern California/Van Nuys Prognostic Index (USC/VNPI) is a numerical algorithm designed to help with the decision-making process regarding postexcisional radiotherapy for patients with ductal carcinoma in situ (DCIS) of the breast. The USC/VNPI is based on multiple prognostic factors known to be important in predicting local recurrence. These include tumor size, margin width, nuclear grade, comedo necrosis, and patient age. Scores range from 4 (best prognosis) to 12 (worst prognosis). The original description of the index was published in 1996 and contained 333 breast conservation patients.¹ Treatment recommendations were made for groups of patients; for example:

Those who scored 4–6: excision alone;

Those who scored 7–9: excision plus radiation therapy; and

Those who scored 10–12: mastectomy.

Method

The USC/Van Nuys/Hoag database, through April 2009, contained 947 patients with pure DCIS treated with breast conservation and followed for a median of 89 months. There were analyzed by individual USC/VNPI scores (rather than by group) and by treatment using the Kaplan-Meier method. New recommendations for treatment were made using a 20% local recurrence rate as the maximum allowable. Data exists using 10%, 15%, 25%, or 30% as the maximum allowable recurrence rate.

Results

The table shows the individual USC/VNPI score, some with margin restrictions, and the treatment necessary to achieve local recurrence rates of 20% or less at 12 years. Approximately one-half of the local recurrences are invasive.

USC/VNPI	Treatment	12-Year Recurrence Probability
4, 5, or 6	Excision Alone	≤ 6%
7, margins ≥ 3 mm	Excision Alone	16%
7, margins < 3 mm	Excision + Radiation	14%
8, margins ≥ 3 mm	Excision + Radiation	15%
8, margins < 3 mm	Mastectomy	1%
9, margins ≥ 5 mm	Excision + Radiation	19%
9, margins < 5 mm	Mastectomy	1%
10, 11, or 12	Mastectomy	4%

Conclusion

With almost 3 times as many patients and longer follow-up, the USC/VNPI can be more finely tuned to aid in the treatment decision-making process. As the acceptable threshold for local recurrence changes up or down, the recommendations also change.

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The Impact of Surgery on Ductal Carcinoma in Situ Outcomes: The Use of Mastectomy

Eun-Sil (Shelley) Hwang, M.D., M.P.H.

Genomic and phenotypic similarities between ductal carcinoma in situ (DCIS) and invasive breast cancer support that DCIS is likely a nonobligate precursor of invasive ductal cancer. Because it remains difficult to predict which individuals with DCIS will develop invasive cancer without excision, surgery has long been the mainstay of “treatment” for women diagnosed with DCIS. Presently in the United States, 97% of patients with DCIS undergo surgical excision, one-third of which will involve mastectomy.^{1,2} The most recent National Comprehensive Cancer Network Practice Guidelines in Oncology (v.1.2009) do not clearly stipulate which women require mastectomy for DCIS but, commonly, patients with extensive and/or multifocal disease involving more than one quadrant, those with potential contraindications to breast radiation, and women with a strong preference for mastectomy over breast conservation are considered appropriate candidates for this procedure.

Clinical outcome following mastectomy for DCIS is excellent, with both clinical trial and population-based studies consistently reporting a 1–2% rate of local recurrence with long-term follow-up compared to approximately 10%–15% following breast conservation and radiation.³⁻⁶ Nevertheless, the increased local recurrence risk with breast conservation has not been shown to impact breast cancer-specific survival when compared to patients undergoing mastectomy for DCIS, with both groups enjoying up to a 99% long-term breast-cancer-specific survival rate.^{3,7}

Various surgical approaches are currently used and include simple mastectomy (excision of breast tissue and overlying skin), skin-sparing mastectomy (removal of breast with preservation of the skin envelope), and, most recently, nipple-preserving procedures. None of these approaches appear to confer increased risk of local recurrence, provided that conscientious attention is given to performing a complete excision of all apparent breast tissue.^{8,9} Local recurrences following mastectomy for DCIS are rare and most often present as an invasive focus on the chest wall detected by palpation,⁹ However, isolated nodal recurrences and distant recurrences have also been encountered.

No large studies of local recurrences after mastectomy for DCIS have been performed. A small review of 10 chest-wall recurrences in this setting have suggested that young age and multifocality are associated with increased risk of locoregional failure.¹⁰ One recent study reported on a series of 80 patients who had undergone mastectomy for DCIS and had margins of <10 mm¹¹. At a median follow-up of 61 months, 6 patients (7.5%) had a local recurrence. In this study, recurrences were associated with high grade and margins of ≤2 mm. Young age (defined as <60 years) was again identified as a risk factor for recurrence. However, even in “high risk” patients, postmastectomy radiation for DCIS is uncommon. Treatment for isolated locoregional recurrence is effective, and the majority of patients treated with local excision and radiation remain disease-free at long-term follow-up.¹⁰

The use of sentinel lymph node biopsy (SLNB) in patients with DCIS is controversial, although many advocate for its use in the setting of mastectomy, after which subsequent sentinel node biopsy may be technically difficult. The 10–20% upstaging of DCIS to stage I or II breast cancer supports SLNB in women undergoing mastectomy for DCIS, as it obviates the need for a

second surgery even if invasive cancer is identified upon excision.¹² Women with DCIS and a positive sentinel lymph node are at risk for distant disease¹³.

Data derived from the Surveillance, Epidemiology, and End Results (SEER) Program shows that, following a diagnosis of DCIS, the risk of contralateral breast events is 4.5/1,000 person-years, compared to 5.4/1,000 person-years for the ipsilateral breast.¹⁴ Although historically few women underwent prophylactic mastectomy for DCIS, there has been a recent surge in the prevalence of contralateral prophylactic mastectomy (CPM). Between 1998 to 2005, the CPM rate in women with DCIS increased from 2.1% to 5.2%.¹⁵ Factors contributing to this increase most certainly include the inaccurate perception many women with DCIS harbor regarding their future risk of invasive cancer.¹⁶ This underscores the importance of improving ways to more accurately communicate the risk associated with treatment and follow-up in patients diagnosed with DCIS.

Conclusion

Although mastectomy is an invasive procedure, it remains the gold standard for long-term locoregional control in DCIS. Mastectomy is the recommended surgical option for women with extensive or multicentric disease. Improved surgical techniques, including better outcomes from breast reconstruction, may contribute to selection of this procedure even in women with limited DCIS and in the setting of contralateral prophylactic mastectomy. As we gain greater insight into factors leading to increased risk of invasive cancer in DCIS, efforts must also be focused on understanding how women make treatment decisions about DCIS in order to maximize the benefit and minimize the morbidity resulting from this procedure.

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The Impact of Systemic Therapy on Ductal Carcinoma in Situ Outcomes

Sandra M. Swain, M.D.

In this review, systemic treatment of ductal carcinoma in situ (DCIS) will be discussed. In women with DCIS, following breast surgery and radiation, tamoxifen is indicated to reduce the risk of invasive breast cancer as approved by the Food and Drug Administration.¹ The caveat is that individual risks and benefits should be assessed to guide decision making.

In the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-24 Trial, 1,804 women with DCIS were randomly assigned to 5 years of tamoxifen or placebo after lumpectomy and radiation therapy. Tumor involvement of surgical margins was allowed, and positive estrogen receptor (ER) status was not a prerequisite for treatment.² At the 15-year follow-up, the most recent update of B-24 findings shows that the incidence of invasive breast cancer is still significantly lower in the group of patients receiving tamoxifen as compared to those receiving placebo (12.8% versus 17.5%, $p=0.001$) (J. P. Constantino, personal e-mail communication, June 12, 2009). A significant reduction specifically in the incidence of invasive ipsilateral breast tumors was seen for patients receiving tamoxifen in addition to radiation therapy ($p=0.024$). Noninvasive ipsilateral tumors were not significantly reduced ($p=0.33$). The reduction in the incidence of contralateral breast tumors (invasive or noninvasive) was significant ($p=0.003$). All breast cancer events combined, including invasive and noninvasive breast tumors of the ipsilateral or contralateral breast and recurrence at regional or distant sites, were reduced from an incidence of 28.7% at 15 years for patients receiving radiation and placebo to 22.0% for patients receiving tamoxifen after radiation therapy ($p=0.0002$). There were 122 deaths among patients receiving radiation only and 106 deaths among patients receiving tamoxifen. Fifteen-year survival percentages were 82.9% for patients receiving radiation only and 85.6% for patients additionally receiving tamoxifen.

A retrospective analysis of NSABP B-24³ based on ER status showed that the use of tamoxifen reduced the risk of invasive breast cancer recurrence in ER-positive cases (relative risk .41, $p=0.0002$).

In the adjuvant trial from the United Kingdom/Australia/New Zealand,⁴ 1,701 patients with DCIS were randomized between tamoxifen and/or radiation therapy, in a 2 x 2 factorial design. A total of 142 DCIS recurrences occurred, 7% occurring in the tamoxifen group and 11% occurring in the patients not taking tamoxifen. This represented a reduction in the overall event rate of DCIS (HR 0.68, $p=0.03$). This reduction in DCIS recurrence was largely accounted for by a reduction in ipsilateral DCIS recurrence of 26%. Tamoxifen did not produce a significant reduction in the overall event rate or the rate of invasive breast cancer events. Updated results will be presented at the San Antonio Breast Cancer Symposium in December 2009.

The inconsistency in results of NSABP B-24 and the UK/ANZ trial may be partly explained by differences in the distribution of ages in the trials. UK/ANZ had a smaller proportion of patients younger than 50 when compared to NSABP B-24 (9.5% and 33.5%, respectively). Tamoxifen therapy may be more beneficial in the population younger than 50 years. Statistical analysis of NSABP B-24 patients at 5 years showed that tamoxifen therapy resulted in a 38% reduction in ipsilateral events in patients younger than 50. When compared with the 22% reduction in

ipsilateral events that tamoxifen produced in women 50 years and older, it may account for the more impressive results of the NSABP B-24 trial.²

Another selective estrogen receptor modulator, raloxifene, was evaluated in the NSABP P-2 Breast Cancer Prevention Trial. Raloxifene was as effective as tamoxifen in reducing the risk of invasive breast cancer, but was less effective than tamoxifen in reducing the risk of DCIS.⁵

The adverse effects of tamoxifen, such as increased risk of thromboembolic events, endometrial carcinoma, and menopausal symptoms might not be acceptable to otherwise healthy women. Yen et al.⁶ evaluated the impact of NSABP B-24 results on tamoxifen use in patients with DCIS, and reported that the overall acceptance was 54%. Also, 21% of patients discontinued tamoxifen due to unacceptable side effects or complications.

Aromatase inhibitors reduce the risk of contralateral breast cancer by 50% when compared with tamoxifen in adjuvant breast cancer trials.⁷⁻⁹ The NSABP B-35 Trial and the International Breast Cancer Intervention Study-II (IBIS-II)¹⁰ are currently evaluating the role of anastrozole as adjuvant therapy in patients with DCIS. In NSABP B-35, postmenopausal women with ER-positive and/or progesterone receptor-positive DCIS were treated with lumpectomy and randomized to radiotherapy followed by anastrozole and placebo or tamoxifen and placebo. The study completed the planned accrual of 3,000 patients.¹¹ In a similar design, IBIS-II is evaluating the same drugs, but the radiation therapy is offered at the discretion of the attending physician. IBIS-II is still recruiting patients to reach the planned accrual of 4,000 patients.

The use of exemestane in postmenopausal patients at high risk of developing breast cancer is currently in evaluation in the NCIC-CTG MAP-3 Study,¹² which plans to recruit 4,560 women. Patients with prior diagnosis of DCIS treated with mastectomy, but not with tamoxifen, are eligible for this trial. The primary endpoint is to compare the incidence of invasive breast cancer between women randomized to exemestane for 5 years or placebo for 5 years.

Compared with invasive ductal cancer, DCIS more often overexpresses human epidermal growth factor receptor 2 (HER2)/neu.¹³ NSABP B-43¹⁴ is a Phase III trial of adjuvant trastuzumab for patients with HER2-positive DCIS and negative margins after breast-conserving surgery. Patients will be randomly assigned to receive 6 weeks of whole-breast irradiation with or without concurrent trastuzumab for two cycles. The planned accrual is 2,000 patients, with the primary endpoint of ipsilateral breast cancer event (invasive or noninvasive).

Trastuzumab may also be an effective neoadjuvant therapy for DCIS. The M.D. Anderson Cancer Center is close to completing a trial offering neoadjuvant trastuzumab for HER2-positive DCIS,¹⁵ where a single dose of trastuzumab is given 2 weeks before surgery. The objective is to determine the effect of trastuzumab on the proliferation and apoptotic rates of these lesions. Investigators at the Baylor College of Medicine have begun a multicenter trial supported by the National Cancer Institute of neoadjuvant lapatinib in three different doses (750 mg, 1,000 mg, and 1,500 mg) compared with placebo for patients with either HER2-positive or epidermal growth factor receptor-positive DCIS.¹⁶

Moderate to high levels of cyclooxygenase-2 (COX-2) expression have been detected in invasive breast cancer (43%), in DCIS (63%),¹⁷ and in breast cancers overexpressing HER2.¹⁸ A double-blind randomized study of celecoxib versus placebo in newly diagnosed breast cancer patients was completed in 2008.¹⁹ Final results are not yet available.

Another randomized Phase I trial is studying the effects of sulindac, thought to act on enzymes COX-1 and COX-2, in breast cancer prevention. High-risk women, including those with a history of DCIS, are randomly assigned to sulindac once daily or twice daily for 6 weeks.²⁰

Fenretinide, a synthetic derivative of all-trans retinoic acid, showed activity in inhibiting mammary carcinogenesis in an animal model.²¹ An Italian study randomizing 2,972 women with surgically removed stage I breast cancer or DCIS (only 35 cases) to either fenretinide or no treatment, did not find benefit in the use of adjuvant fenretinide. However, a subgroup analysis detected a possible benefit in premenopausal women (contralateral breast cancer: HR+ 0.66, p=0.045; ipsilateral breast cancer: HR=0.65, p=0.045).²²

Possible interactions between retinoid- and estrogen-induced signaling have been demonstrated.²³⁻²⁵ In this scenario, a combination of an estrogen antagonist and a retinoid could be effective. A pilot study²⁶ evaluated the tolerability of fenretinide combined with tamoxifen in a group of women at high risk for breast cancer. The treatment demonstrated acceptable toxicity. A randomized phase II trial²⁷ is ongoing to evaluate the effectiveness of fenretinide and tamoxifen given before surgery in women with either stage T1 breast cancer or DCIS.

In order to investigate neoadjuvant therapy in DCIS, Esserman et al.^{28,29} initiated a pilot study of tamoxifen or letrozole in hormone-positive DCIS. Hormonal therapy is offered during the 3 months before surgery. Response is evaluated through mammography, magnetic resonance imaging, and biomarkers.³⁰

The use of tamoxifen as systemic therapy for DCIS has demonstrated efficacy in reducing invasive and noninvasive breast cancers. The effect of targeted agents in DCIS is currently under evaluation. The same patterns have emerged that were previously observed in adjuvant and neoadjuvant therapy for invasive breast cancer. It is critical, however, to establish a more accurate classification of DCIS. Adequate selection of patients increases efficacy of treatments. Expression profiling of DCIS can help either in the selection of lesions more likely to progress to invasive disease or in identification of specific targets responsive to treatment.

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Communications Between Patients and Providers and Informed Decision Making

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Women with ductal carcinoma in situ (DCIS) have to make decisions about treatment and future screening. Among the questions they may ask are “What is DCIS?”, “What are the risks and benefits of treatment?”, and “What is my risk of dying from breast cancer?” Full and understandable information is therefore a requirement, not an option. However, with DCIS, as with many areas of medicine, a high level of uncertainty remains. As physicians, our ability to explain uncertainty is limited, and when numbers are involved, our ability to communicate numeric information is often inadequate.¹⁻³

Fear of cancer may hamper communication about DCIS. A heightened sense of risk has been noted in studies of women, even before a diagnosis of DCIS. One survey found that women in their 40s overestimated their risk of a breast cancer diagnosis within the next 10 years by a factor of 6, and their risk of dying of breast cancer by a factor of 20.⁵ Among women with DCIS, uncertainty regarding the relationship of DCIS to invasive cancer often leads to anxiety.^{6,7} A diagnosis of DCIS typically leads to treatment resembling that of early-stage breast cancer.⁸ Even after this treatment, women with DCIS perceive their breast cancer risk to be elevated.⁶

The challenge of understanding cancer risk and numeric information is not unique to patients; clinicians are similarly challenged.^{1,9} For example, 93% of radiologists who provide breast cancer screening overestimated a 70-year-old woman’s 5-year risk of breast cancer, and fully 96% overestimated a 41-year-old woman’s 5-year risk.⁹

The way risk information is presented, including the choice of words and framing, can affect how the information is interpreted by patients. When communicating risks, providers need to consider how they frame the discussion, as expressing logically equivalent information in different forms is important. Positive framing emphasizes healthy outcomes and the absence of disease, while negative framing emphasizes the presence of disease. Clearly, a positive frame usually seems like a preferable outcome to most patients. In addition, much of the communication about cancer risk deals with relative risks, which sound more threatening than absolute risks.¹ Because so many people have trouble grasping the difference between the two, providers need to exercise special care when they talk to patients.

A growing body of research shows that both patients and providers benefit when patients are well informed and play a significant role in deciding how to manage their health conditions.¹⁶ To make informed decisions, however, women must know the risks, benefits, and side effects associated with each diagnosis and treatment option.

Information to aid informed decision making can be communicated verbally, numerically, or visually.¹⁰⁻¹² Numeric information is often provided to patients using risk prediction models that estimate a woman’s 5-year and lifetime risk of an invasive breast cancer diagnosis. DCIS is associated with the risk that the lesion might progress to invasive cancer, as well as with the risk of developing invasive cancer elsewhere in the same or opposite breast. Unfortunately, most risk prediction models perform well at the population level but fall short at the level of the individual.¹⁵ Many “low-risk” women develop invasive breast cancer, while many “high-risk”

women do not. Visual displays seem to aid understanding of risk perception,^{2,3,10,11,13,14} although more research in the area of decision support tools is needed.

Although we have high-tech medical programs and decades of research on cancer, our ability to communicate with patients regarding DCIS is far from optimal. Not only do we need to develop better risk prediction methods; we must also learn how to communicate the uncertainty in our knowledge base, as well as the risks and benefits associated with specific treatment options, in ways that make sense to our patients. High-quality health care demands no less.

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Evidence-Based Practice Center Presentation IV: The Impact of Surgery, Radiation, and Systemic Treatment on Outcomes in Patients With Ductal Carcinoma in Situ

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Five randomized trials addressed the value of radiation therapy or tamoxifen for treatment of ductal carcinoma in situ (DCIS). In addition to information from randomized trials, 133 publications of 64 observational studies (i.e., nonrandomized studies) addressed the impact of treatment on DCIS outcomes (appendix tables F26–F33, full evidence report). The most consistently measured outcomes were ipsilateral DCIS, ipsilateral invasive cancer, combined ipsilateral DCIS and invasive cancer, contralateral DCIS, contralateral invasive cancer, combined contralateral DCIS and invasive cancer, breast cancer mortality, all-cause mortality, chemotherapy use, local recurrence, regional recurrence, distant recurrence, and other outcomes.

For the purposes of this report, we consider breast conserving surgery (BCS), lumpectomy, and wide local excision to be analogous terms.

Breast Conserving Surgery With Versus Without Radiation

In randomized trials, whole-breast radiation therapy (RT) following BCS is associated with a reduction of local DCIS or invasive carcinoma recurrence but has no impact on breast cancer mortality or total mortality. The studies consistently found whole-breast RT to be associated with a reduced incidence of local DCIS recurrence and local invasive carcinoma. While statistically significant, the number of events prevented per 1,000 treated women is typically less than 10%.

Two studies found that while RT had a similar effect on recurrence between those with positive and negative surgical margins, the adverse prognostic effect of positive margins remained after RT. Despite similar effectiveness of RT regardless of tumor size, RT did not completely eliminate the increased risk associated with larger versus smaller tumors.

Multiple observational studies report lower rates of local DCIS or invasive cancer for women undergoing BCS plus RT over BCS alone, though not all report statistically significant patterns. Observational data show a lack of mortality benefit associated with BCS plus RT compared to BCS alone, while a single study did find women receiving RT had lower all-cause mortality.

Although available research comprises low levels of evidence, there is no evidence that BCS plus RT is more or less effective than BCS without RT in the presence or absence of adverse prognostic factors. This lack of differential effect can be seen for the most important prognostic factors, including grade, tumor size, involved margins, and comedo necrosis.

Mastectomy

While not studied in a randomized fashion, several observational studies comparing outcomes between mastectomy and BCS or BCS plus RT found women undergoing mastectomy were less likely than women undergoing lumpectomy or lumpectomy plus RT to experience local

DCIS or invasive recurrence. Women undergoing BCS alone were also more likely to experience a local recurrence. We found no study showing a mortality reduction associated with mastectomy over BCS with or without RT. Low statistical power may account for this apparent lack of benefit. Since the breast cancer mortality after DCIS diagnosis is so low, it is possible that few studies have included sufficient numbers of cases to support identification of a mortality benefit. Selection bias may also contribute to the apparent lack of benefit for mastectomy in observational studies. Clinically larger, multicentric, and more problematic tumors are more likely to be treated with mastectomy than BCS. These tumors are also more likely to recur and are more often associated with breast cancer mortality. Thus, equal mortality despite differences in severity may be masking a clinically superior treatment.

Although available research comprises low levels of evidence, there is no evidence that mastectomy is more or less effective than BCS plus radiation in the presence or absence of adverse prognostic factors. This lack of differential effect can be seen for the most important prognostic factors, including grade, tumor size, involved margins, and comedo necrosis.

Tamoxifen

Tamoxifen use reduced the risk of recurrent DCIS or invasive carcinoma. Tamoxifen was associated with a 50% reduction in contralateral disease and of breast cancer mortality but had no impact on all-cause mortality. Adverse events associated with tamoxifen are consistent with its profile in other settings. There was an increase in hot flashes, fluid retention, and vaginal discharge associated with chemotherapy. Combined treatment (lumpectomy, RT, and tamoxifen) compared to lumpectomy and tamoxifen alone reduced the rates of all cancer events by 29%. There was no differential impact of tamoxifen for women with or without adverse pathological characteristics except for a nonsignificant indication that tamoxifen was less effective for women without comedo necrosis or with smaller tumors.

The only observational study of tamoxifen use after DCIS that included comparisons with nonusers found that women with DCIS who received tamoxifen had the same hazard of local DCIS or invasive cancer as women who did not receive tamoxifen.

Ongoing studies such as the National Surgical Adjuvant Breast and Bowel Project (NSABP)-37 are examining the comparative effectiveness of tamoxifen and aromatase inhibitors and the use of trastuzumab for human epidermal growth factor receptor-2 (Her2)-positive women.

Accelerated Partial Breast Irradiation

An emerging controversy is whether accelerated partial breast irradiation (APBI) therapy is as effective as whole-breast radiation therapy. Observational studies reporting results of APBI for DCIS are limited to the MammoSite® technology, and do not include control groups. The ongoing NSABP-39 trial randomizes women to whole or APBI therapy. For that trial, three partial breast techniques are treated as equivalent: multicatheter brachytherapy, MammoSite® balloon catheter, and 3-D conformational external beam radiation. Other ongoing trials are comparing whole breast to specific types of APBI.

Summary

Randomized trials provide consistent evidence that DCIS treated with BCS plus RT compared to BCS alone results in reduced total local recurrence by 53% and local invasive breast cancer recurrence by 46%, with no differences in overall and breast cancer mortality, all or invasive

contralateral breast cancer, or total distant or local regional node recurrence. Observational studies point to somewhat inconsistent effects regarding the benefit of BCS with RT relative to BCS alone. The observational studies, however, are frequently underpowered, subject to selection bias (that is, patients are not randomly allocated to RT or not) and inconsistent in their control of known confounding factors.

While not studied in a randomized fashion, studies point to equivalent outcomes between BCS plus RT and mastectomy, while BCS alone tends to be inferior to mastectomy.

Subset analyses, while generally representing a lower level of evidence (e.g., they are not always multivariate adjusted), do not point to differential effectiveness of surgery or RT in the presence of adverse prognostic factors. This lack of differential effect suggests that treatment alone may not eliminate the adverse prognosis, but also suggests that for patients with adverse prognostic features, treatment may be particularly important.

Evidence of the effectiveness of tamoxifen for treating DCIS is based on a very small number of randomized and observational studies but is quite promising. Ongoing studies evaluating the value of hormonal therapies and herceptin for use with DCIS will help clarify the benefit of these therapies, particularly if assessment of estrogen and progesterone receptor status and Her2 positivity in the general population increases.

Synthesizing across studies, we found no effects of surgery, RT, or chemotherapy on overall mortality or breast cancer mortality. Only one observational study reported significant reduction in crude odds of breast cancer mortality after adjuvant RT (lumpectomy plus RT, or lumpectomy plus RT plus tamoxifen, versus lumpectomy alone or lumpectomy plus tamoxifen). All cancer events were reduced after combined treatment (lumpectomy plus RT plus chemotherapy) when compared to dual therapy (lumpectomy plus RT or lumpectomy plus tamoxifen). However, given the low level of mortality associated with DCIS and the long treatment horizon, it is likely that even the largest of these studies is underpowered to identify a mortality benefit. A similar conclusion was reached with invasive breast cancer, where mortality is much more common. Yet, until all studies were pooled using meta-analysis, no mortality effect was observed when comparing BCS plus RT to BCS alone.

The overall evidence of treatment effectiveness is consistent with treatment effectiveness for invasive breast cancer. This insight should facilitate transfer of knowledge about treatment effectiveness from invasive breast cancer to DCIS.

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Molecular Markers for the Diagnosis and Management of Ductal Carcinoma in Situ

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Breast tumors evolve via sequential progression through defined clinical and pathologic stages, starting with epithelial hyperproliferation, progressing to in situ, invasive, and metastatic carcinomas.¹ Ductal carcinoma in situ (DCIS) is thought to be the true precursor of invasive ductal carcinoma (IDC), based on molecular-based clonality studies, its increased incidence in women with high risk of invasive breast cancer, its frequent coexistence with invasive lesions, and its high rate of recurrence as an invasive tumor at its original site.² Despite an enormous amount of research, we are still unable to predict which DCIS will progress to IDC or, more importantly, to prevent this progression altogether. There are many reasons for this failure, including, foremost, the overall complexity of the problem, the failure of research to embrace this complexity, and the lack of faithful models of human DCIS to support comprehensive studies.

Numerous studies have been conducted with the aim of identifying molecular markers in DCIS that would predict the risk of invasive progression.^{4,17,30–41} These studies have confirmed that DCIS is just as heterogeneous as IDC, and the same major tumor subtypes (e.g., luminal A/B, HER2+, and basal-like) can be observed and tumors in different subtypes have distinct molecular and biological properties and responses to treatment. Numerous candidate markers, including COX2, S100A7, CD10, have also been identified that have some prognostic value. However, none of these studies have identified molecular markers that uniformly differentiated DCIS from IDC or that would consistently predict risk of invasive progression. Thus, despite all these studies, molecular markers besides hormone receptors and HER2 are still not routinely used in the clinic, since their predictive value has not proven to be better than that of the current grading and classification schemes. However, none of these biomarkers were developed based on a comprehensive screen of DCIS tumors with known clinical outcomes. Thus, further research is needed in this area.

Experimental models of human tumors allow the functional testing of genes implicated in breast cancer and the evaluation of novel cancer-preventative and -therapeutic interventions. Although no single model is ideal, a good model of DCIS would have to resemble the histology and natural history of human DCIS. Carcinogen-induced mammary gland tumors in rats reproduce certain aspects of human DCIS, such as ovarian hormone dependence and gradual progression to invasive disease.³ However, the carcinogen used for the initiation of these tumors may have caused numerous genetic changes that are not easy to identify, making this model unattractive for molecular studies addressing the role of specific genes in mammary tumorigenesis. The same limitation applies to the use of DCIS xenografts formed by subcutaneous injection of pieces of human DCIS tumors into nude mice.⁴ The MCF10AT human breast cell line is one of the most well-characterized human models of breast tumor progression.^{5,6} These cells were derived from the immortalized MCF-10A cells via transformation with T24 mutant c-Ha-ras.^{5,6} Interestingly, the MCF10AT cells appear to contain multipotent (or bipotential) breast stem cells, since both luminal epithelial and myoepithelial cells can be derived from these cells in vivo.⁷ Recently, a derivative of the MCF10AT premalignant human-cell-line model, MCF10DCIS.com, was established, which reproducibly forms comedo DCIS-like lesions that spontaneously progress to invasive tumors.^{5,6} This model has been used for multiple studies in different laboratories and appears to be useful for the analysis of breast tumor progression.^{8–11} However,

due to the origin of MCF10AT cells, it is likely to represent basal-like breast cancer. Thus, additional models for other breast tumor subtypes are needed.

The normal mammary epithelium is composed of multiple cell types, including bipotential stem cells, lineage-committed progenitors, and differentiated luminal epithelial and myoepithelial cells. Luminal epithelial and myoepithelial cells are differentiated using cell-type-specific markers, many of which have been fortuitously identified only following immunohistochemical analysis of breast tissues.^{12–14} In recent years, several genomewide unbiased studies were performed using different cell purification and profiling approaches to better characterize normal luminal epithelial or myoepithelial cells and to identify additional genes specific for a particular cell lineage.^{15–18}

The major diagnostic criteria that pathologists use to differentiate in situ from invasive carcinomas is the presence or absence of an intact myoepithelial cell layer and basement membrane, usually confirmed by performing immunohistochemical analyses.¹⁹ However, little is known as to what leads to the progressive loss of the myoepithelial cells in DCIS and progression to invasion. Myoepithelial cells have been referred to as natural tumor suppressors due to their inhibitory effect on various neoplastic phenotypes, including tumor cell growth, invasion, and angiogenesis.^{20–23} Myoepithelial cells also synthesize the basement membrane of the ducts and alveoli and form a structural barrier between the luminal epithelial cells and the surrounding stroma, thus physically preventing tumor cell invasion. The tumor suppressor phenotype was identified based on the ability of myoepithelial cells to inhibit the growth and invasion of breast cancer cells in coculture assays in vitro and inhibit tumor growth in xenograft assays.^{22–25} Comprehensive molecular profiling of isolated cell types from normal and DCIS breast tissue determined that gene expression and epigenetic changes occur in each cell type, whereas clonally selected genetic alterations are limited to tumor epithelial cells.^{10,26–29} The potential contribution of microenvironmental alterations in tumorigenesis, specifically in DCIS to IDC transition, was tested using a MCF10ADCIS.com cell-line-based xenograft model of human DCIS.^{8,10}

In summary, new and more comprehensive strategies are necessary to understand the progression of DCIS to IDC. “Comprehensive” is key, since it is clear that identifying the critical events in tumor progression will require an inclusive evaluation of cellular, epigenetic, and genetic alterations in tumor epithelium and the stromal microenvironment simultaneously; new mathematical strategies to interpret the results in a prognostically meaningful manner; and relevant models to support mechanistic as well as preclinical studies.

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Imaging for the Diagnosis and Management of Ductal Carcinoma in Situ

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Ductal carcinoma in situ (DCIS) is a distinct lesion of the breast that has the potential to become invasive cancer. Prior to the widespread use of screening mammography, DCIS accounted for less than 5% of breast cancers.¹ Currently, this diagnosis is rendered in about 30% of cases. We realize that some of the cases diagnosed as DCIS will not progress to invasive disease and this has been offered as a risk of screening mammography. This argument would be valid if we had a means, prior to any interventional procedure, to determine which of these in situ malignancies will progress to invasive disease. We do not. As a matter of fact, this is not possible with a high degree of certainty today, even after tissue is obtained and the diagnosis of DCIS is established pathologically. Certainly, studies aimed at which cancers may progress and those which may not should be one of the most active areas for research, both at a detection and pathology level. What we do know is that the diagnosis of DCIS by pathologic means increased with routine use of mammography; the mortality from breast cancer as verified by many worldwide screening trials has decreased by at least 30% and is due almost entirely to mammography; and, finally, we cannot assign a nonaggressive pattern to DCIS with any significance at the detection or diagnostic phase. Thus, it becomes quite clear that until we possess the ability to assign different levels of concern for findings suggestive of DCIS, at the detection phase we must continue searching and verifying the presence of in situ disease to help preserve the dramatic decrease in breast cancer mortality we see today.

Breast imaging for detection of DCIS, as well as invasive disease, is advancing with the introduction of several new and exciting technologies. The initial phase of detection was and, in many instances, is still on a morphologic basis. The identification of certain findings related to the subgross anatomy is the hallmark of early morphologic features suggesting DCIS. The terminal ductal lobular unit (TDLU) is the basic subgross unit of breast anatomy. DCIS is most frequently detected by certain forms and distribution of calcifications in the breast that relate to the TDLU.² With the increasing use of MRI in the breast, we have now added a level of information beyond morphology. By allowing us to judge increased vessel density and "leakiness" of contrast agents, both of which are associated with the abnormal neovascularity of malignancy, we have added physiology to our morphologic considerations. Finally, with the advent of advanced breast-specific technology, the use of nuclear medicine applications for breast imaging has also emerged. This introduces yet another layer of information. The uptake of the glucose analog fludeoxyglucose provides a metabolic basis for tumor detection. There is a great research need to continue efforts in morphologic, physiologic, and metabolic indicators of malignancy with emphasis on combining these technologies into one system.

Morphology

As stated previously, the initial phase of detection related to DCIS involved knowledge of the anatomy of the TDLU and the types of calcifications occurring in the ductal portion of the TDLU. There are three distinct forms of calcifications and their distributions which significantly raise the potential for DCIS. The specific forms of calcifications are amorphous, pleomorphic, and fine linear. The suspicious distributions are linear and/or segmental. The amorphous forms are small (2–300 microns) and hazy. Their association with malignancy, especially DCIS, is as high as 20%.³ Pleomorphic calcifications are more conspicuous than the amorphous forms, are also

irregular in shape, and are the same size range as amorphous calcifications. A linear calcification morphology can be associated with DCIS in up to 80% of cases. The linear and segmental distributions of calcifications are surrogate markers for disease distributed in the duct or ducts of TDLUs. This distribution is equally as important as the forms of calcifications and may be associated with malignancy from 60–80% of the time.⁴

New technologies have recently been investigated to help enhance detection of malignancy. Stereotactic digital mammography (SDM), visualization of the breast in depth, has demonstrated a reduction in false positive detections of 45% with a concomitant increase in true positives of 23% (to be published). Further research is under way to determine if similar results with SDM can be obtained at a reduced dose to the breast. Another area of research is the use of breast tomosynthesis. This consists of obtaining 10–12 images of the breast at different angles with 1/10–1/12 of the dose per image. Once this information is obtained, an almost 3-D data set can be formulated and redemonstrated to the interpreter in many different ways. One method is to view multiple slices on high-resolution monitors, markedly decreasing noise and overlapping tissue superimposition to increase the detection of early breast cancer. Preliminary studies regarding image quality for tomosynthesis demonstrated equal or superior ratings 90% of the time compared to standard mammography. However, resolution of microcalcifications are still somewhat problematic, and more research is required.⁵ More recently and potentially more useful is the development of dedicated breast computed tomography (CT). This is identical in principle to body CT but is specifically designed for the breast. It provides true isotropic 3-D information that can be formatted in any manner without loss of spatial or contrast resolution. Since the KvP is higher than what is used in routine standard 2-D digital mammography, the dose to the breast is similar. On subjective ratings, breast CT was found to be significantly higher for breast mass detection but, again, calcifications were an issue.⁶ The potential of these new technologies promise better detection of early disease with reduced false positives. These improved methods of detection, combined with research to improve characterization of calcifications, may allow us to determine the invasive potential of DCIS before intervention occurs.

Physiology

We know from body CT experience that imaging of large breast cancers may be enhanced after iodine contrast is injected. However, the full-body technique markedly decreases both contrast and spatial resolution of the breast. The contrast resolution of standard mammography does not provide the ability for us to detect areas of enhancement with iodine. However, if one can subtract a precontrast from a postcontrast image utilizing a 2-D digital mammographic technique, the result will be an iodine-only image comparable to the subtraction images of MRIs. An article by Lewin in 2003⁷ demonstrated the feasibility of this technique with dramatic results. Of even greater interest and significance is the combination of this technique with tomosynthesis and dedicated breast CT, permitting exquisite spatial and contrast resolution with physiologic information. More research is critically needed in this area.

Metabolic

Finally, the introduction of dedicated positron emission tomography (PET) breast scanning with improved spatial resolution compared to nondedicated whole-body units is providing dramatic new insights into the detection of DCIS and the efficacy of chemotherapy. Work is being proposed to combine PET and CT together in one unit, with the extremely exciting prospect of combining morphologic, physiologic, and metabolic information within a single unit.

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Quality of Life Issues and Outcomes Research in Ductal Carcinoma in Situ

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Thirty years ago, ductal carcinoma in situ (DCIS) was a rarely diagnosed entity, usually identified in a slowly growing palpable breast mass. The increasing use of mammography in the 1980s transformed this clinically diagnosed entity into one that is most frequently found as occult disease on a screening mammogram, often in an unsuspecting, asymptomatic woman. Over the course of the past three decades we have come to realize that DCIS lies along the spectrum of intraductal neoplasia of the breast, ranging from atypical ductal hyperplasia (ADH) to invasive breast cancer.¹ Moving back the age of mammographic screening to women in their 40s has played a large role in early detection of noninvasive disease and precipitating the rapid rise in the incidence of DCIS.² It is not unusual to see the entire spectrum of intraductal neoplasia identified in a single pathologic specimen obtained from a woman who is found to have new microcalcifications on a screening mammogram. Indeed, some women who have their first screening mammogram in the fourth or fifth decade of life are confronted with a diagnosis of DCIS. What are the psychosocial and quality-of-life (QOL) implications for this common new disease entity, largely diagnosed at the time of mammographic screening? What do we know about the impact of a DCIS diagnosis on women's lives and what type of research must we conduct in the future? What research questions about the outcomes of DCIS diagnosis and treatment need to be addressed?

Despite the large number of women diagnosed with DCIS each year, and the rapid increase in incidence in the past two decades, little is known about the psychosocial impact of this diagnosis. Early reports in the late 1990s and early 21st century were often personal accounts or small qualitative studies that noted women's confusion and dissatisfaction with the treatment and prognostic information that they received.^{3,4} In addition, women were often confused about why, if DCIS is a noninvasive cancer, they needed mastectomy (standard of care for DCIS before trials of breast-conserving therapy was evaluated) when women with invasive cancer were receiving breast conservation therapy. Misinformation about risk of distant recurrence was common, although psychological distress with standard assessment measures was low (see table 1).

In a recent study of an inception cohort of DCIS patients diagnosed between 2000 and 2004,⁵ the authors found that about 10% of patients had substantial anxiety shortly after diagnosis, without significant depression, and with normal scores on a standardized measure of physical and emotional functioning. However, these women demonstrated severe misperceptions about their risk of invasive disease and spread of the DCIS to other parts of their body. Over an 18-month follow-up period, there was little change in these inaccurate risk perceptions and there was a strong relationship between distress (anxiety and intrusive thoughts) and the misperceptions. These authors note that the heterogeneity of DCIS (i.e., small/minimal low-risk lesions versus very large and/or high-grade tumors), along with the variability in treatment plans (i.e., extent of surgery, use of radiation or endocrine therapy), exacerbates the confusion and misinformation that women experience. From this work and earlier publications, the literature supports the need for development of more effective communication tools for patients with DCIS, focusing on the nature of the disease and its risk for dissemination and for individualized treatment options and prognosis.

There are several other studies that have used standardized measures of psychological distress and QOL to compare women with DCIS to women with invasive breast cancer. Most are cross-sectional, with assessments occurring several years after diagnosis, and usually compare women with DCIS to women with invasive breast cancer rather than healthy women (see table 1). Given the frequency of a DCIS diagnosis among women today, there are important limitations to the existing literature on psychosocial and QOL outcomes.

Table 1. Studies of Psychosocial and Quality-of-Life Outcomes in Patients with DCIS

Author/Year	Patient Characteristics	Measures	Outcomes	Comments
Amichetti (1999) ⁶	DCIS (n=83) 6 Italian institutions	Local questionnaire	“Good quality of life” Some anxiety & tension Good body image	*All breast conservation *54.5 months since diagnosis
Bluman (2001) ⁴	DCIS (n=76) Recruited from Duke tumor registry	Knowledge Satisfaction Perceived risk CES-D R-IES	Misperception of risk of recurrence Low depressive symptoms	*1.9 years since diagnosis *68% mastectomy
Rakovitch (2003) ⁷	DCIS (n=64) T1,T2, N0 (n=164) Tertiary Canadian center; consecutive patients 1998–1999	Describe diagnosis Risk of recurrence Symptom assessment	DCIS more accurate at description No significant difference in risk perception Similar rate of psychological distress	*All treated with partial mastectomy *Assessed within 4 months of diagnosis
Casso (2004) ⁸	Stage 0 (n=28) Stage I–IV (n=188) Group Health Seattle, WA	SF-36 CARES-SF CES-D	DCIS sample better on all measures	*40–49 years at diagnosis *5- to 10-year survivors, all stages
Janz (2005) ⁹	Stage 0 (n=555) Stage I (n=462) Stage II (n=239) Detroit and Los Angeles SEER Registry	EORTC QLQ-30 EORTC QLQ-BR23	Physical and role function better in stage 0 (DCIS) (univariate) No difference in QOL by stage in multivariate model	*DCIS as the reference *Interview completed mean 7.2 months after diagnosis

Author/Year	Patient Characteristics	Measures	Outcomes	Comments
Nekhlyudov (2006) ¹⁰	DCIS (n=510) Women without cancer (n=114,728) Nurses' Health Study, prospective cohort	SF-36	Small but statistically significantly greater declines in role—physical, vitality, and social functioning Social functioning and mental health most affected in first 6 months after diagnosis	*Clinical significance uncertain
Van Gestel (2007) ¹¹	DCIS (n=33) Stage I (n=91) Recruited from tumor registry	SF-36 Perceived disease impact Risk of recurrence	DCIS-Slightly better scores on pain & mental health Similar perceived disease impact No difference in risk perceptions	*Mastectomy more common in DCIS *2–3 years' postdiagnosis
Janz (2007) ¹²	Stage 0 (n=598) Stage I (n=482) Stage II (n=253) Detroit and Los Angeles SEER Registry	EORTC QLQ-30 EORTC QLQ-BR23	Fatigue, pain, treatment side effects, breast symptoms, arm symptoms did not differ; only sleep disturbance greater problem for invasive	*DCIS as the reference *Interview completed mean 7.2 months after diagnosis
Partridge (2008) ⁵	DCIS (n=487) Inception cohort followed over 18 months	Risk perceptions SF-36 HADS R-IES	10% anxiety 2% depression SF-36 scores normal range Inaccurate perceptions of recurrence risk Anxiety predicts misperceptions	*Enrolled within 3 months of diagnosis *Mastectomy in 34%

CES-D = Center for Epidemiologic Studies Depression (Scale)

R-IES = Revised Impact of Events Scale

SF-36 = Medical Outcomes Study 36-Item Short-Form Health Survey (Health Institute; New England Medical Center; Boston, MA)

CARES-SF = Cancer Rehabilitation Evaluation System Short Form

SEER = Surveillance, Epidemiology, and End Results

EORTC QLQ = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire

HADS = Hospital Anxiety and Depression Scale

As noted earlier, DCIS development lies on the continuum from ADH to invasive breast cancer and, as such, it may be more relevant to compare the psychosocial and QOL impact of a DCIS diagnosis to the health status of women who are either at high risk for breast cancer based on a preneoplastic biopsy or other risk factors using the Gail Risk Model, or to healthy women at usual risk for breast cancer. To address this question, we have examined baseline, pretreatment QOL data available from the National Surgical Adjuvant Breast and Bowel Project (NSABP) Study of Tamoxifen and Raloxifene (STAR) Trial and unpublished data from the NSABP B-35 trial (a comparison of adjuvant tamoxifen versus anastrozole in postmenopausal women with DCIS) to determine whether or not there are QOL differences between these two groups of women, who are both at high risk for invasive breast cancer. The women entered in these two trials were all postmenopausal and completed the same self-report QOL questionnaires prior to starting endocrine therapy. Women in the STAR trial had to have either lobular carcinoma in situ or a calculated 5-year Gail Risk score of 1.67% or greater.^{13,14} Patients in the B-35 trial were required to have lumpectomy as treatment for their DCIS and were scheduled to have whole breast irradiation. They completed their QOL questionnaires an average of 43 days after surgery at the time of randomization. Data are available from 1,869 women who were in the STAR QOL study¹⁴ and 1,275 who were enrolled in the B-35 QOL trial, and are shown in table 2.

Table 2. Comparison of QOL Mean Scores for STAR and B-35 participants

Scale	STAR	B-35	p-value
SF-12 Physical*	49.3	47.1	<.0001
SF-12 Mental*	53.5	50.7	<.0001
MOS Vitality†	65	58	<.0001
Symptom checklist summary score#	12.7	14.5	<.0001

* Medical Outcomes Study (MOS) SF-12 component summary scores; 50 represents the population mean and each 10 points represents a standard deviation change in score.

† Medical Outcomes Study Vitality scale measures energy and fatigue; a higher score represents greater energy.

A 20-item symptom checklist was used, and this represents a summary score for the total number of items and their severity; a higher score indicates more symptoms and/or greater severity.

The women in the STAR trial were slightly younger (mean age = 58 versus 61, $p < .0001$) with significantly fewer nonwhite participants (7% versus 12%, $p < .0001$). Women with DCIS who participated in B-35 reported worse physical and mental function, less energy, and more severe symptoms than healthy high-risk women who participated in STAR. The major difference in type of symptom reported was musculoskeletal aches and pains (data not shown), most likely reflecting the impact of recent breast cancer surgery for this group. Depressive symptoms were also more common among the B-35 participants, as well as significantly greater severity of problems with all aspects of sexual functioning on the MOS Sexual Functioning Scale (all $ps < .0001$). As the prospective results of the B-35 trial become available, we will be able to track the longitudinal impact of adjuvant endocrine therapy in this DCIS patient population over time, and compare them to the participants in the STAR trial.

In conclusion, DCIS is a very heterogeneous condition, and it is clear that there has been insufficient attention to the study of the impact of this diagnosis on women's lives and their perceptions of future cancer risk. The U.K. Breast Cancer Campaign performed a gap analysis

that emphasized many of the deficiencies in our knowledge of the psychosocial aspects of breast cancer.¹⁵ DCIS is particularly challenging in this regard, as it lies on the continuum between precancerous changes in the breast and invasive cancer. Women who have a small focus of DCIS in a small biopsy specimen that is largely made up of ADH are entirely different from women whose entire breast is replaced by extensive high-grade DCIS. From the limited literature available, we know that women have serious misperceptions about what DCIS is and its risk for recurrence. There is an important need to provide accurate and useful information for women about the risks and benefits of various treatments for DCIS, as well the likely QOL and health outcomes associated with various treatments. More research is necessary, specifically comparing women with DCIS to women without a cancer diagnosis, to facilitate communication about the added burden of various treatments (e.g., surgery, radiation, endocrine therapy), so that well-informed decisions can be made about treatments between patients and their providers. In addition, misperceptions about DCIS and risk of recurrence may influence adherence to preventive interventions and behaviors, as well as needed continued surveillance with screening mammography.

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