

Why the Term of Low Grade Ductal Carcinoma In Situ Should be Changed to Borderline Breast Disease: Diagnostic Issues and Clinical Implications

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UF Health Jacksonville

The Plan

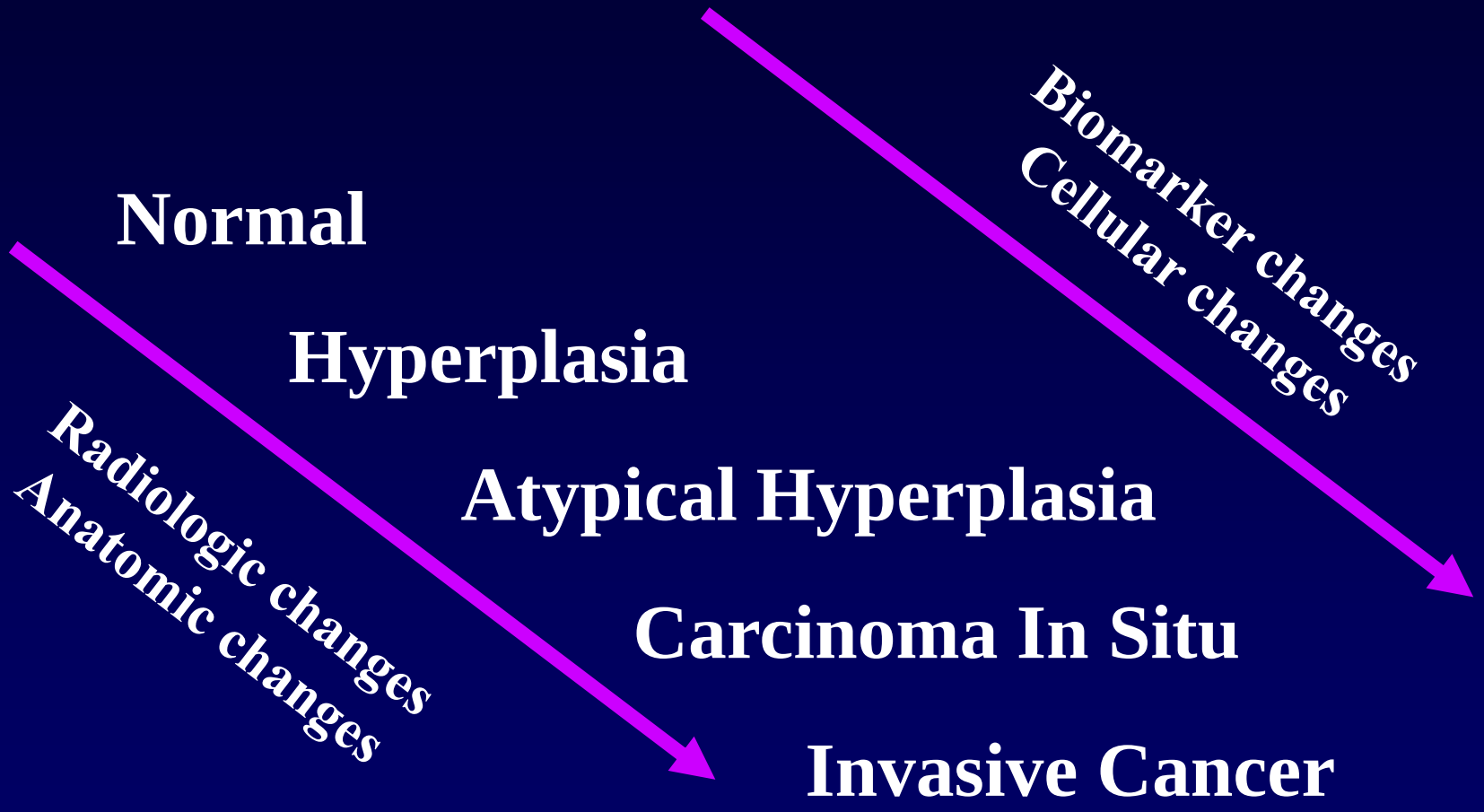
- Summarize the current challenges associated with the diagnosis of low grade ductal carcinoma in situ versus atypical ductal hyperplasia
- Define a rationale to abandon the term of low grade ductal carcinoma in situ and use the term borderline breast disease
- Discuss different strategies for clinical management and long term follow up of patients diagnosed with borderline breast disease

Why the Emphasis on Low Grade Ductal Carcinoma In Situ?

Low Grade Ductal Carcinoma In Situ

- **Common: screening mammography has resulted in increased number of image detected biopsies and the diagnosis of this disease**
- **The distinction from atypical ductal hyperplasia has remained a diagnostic challenge**
- **There are more chances of over diagnosis and overtreatment**
  - **More expense**
  - **More patients anxiety**

Neoplastic Progression



IntraEpithelial Neoplasia

Non-Proliferative



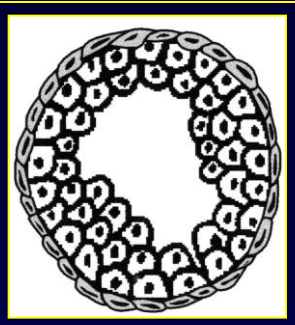
ER 10-30%

Ki-67 ≤ 1%

Proliferation and apoptosis balanced

RR≡1

Hyperplasia

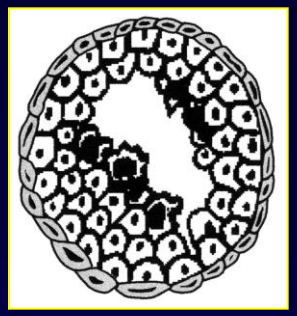


ER 60%

Ki-67 ~ 3%

RR=2

Atypia

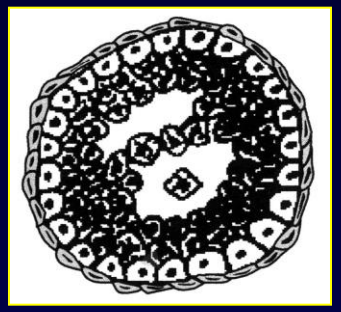


ER 90%

Ki-67 ~ 5%

RR=5

In Situ



ER 50%

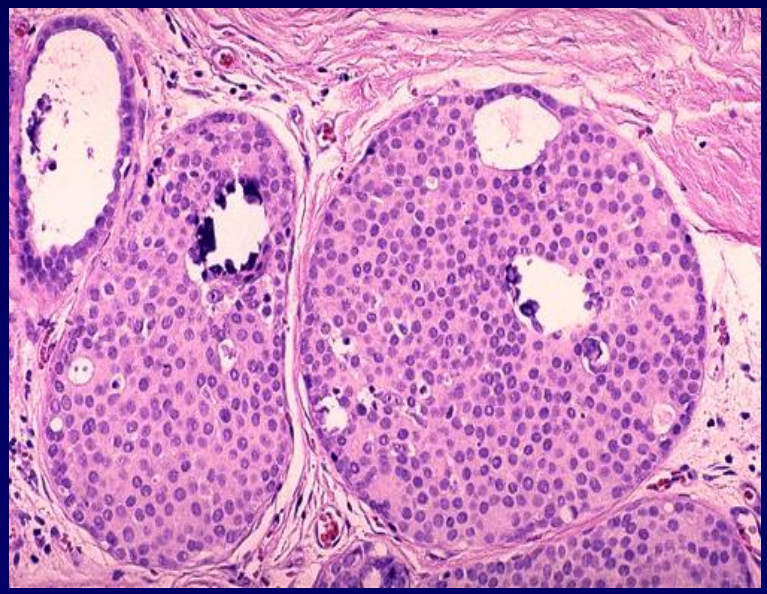
Ki-67 >10%

RR=10-20

Proliferation and apoptosis imbalanced

Ductal Carcinoma In Situ

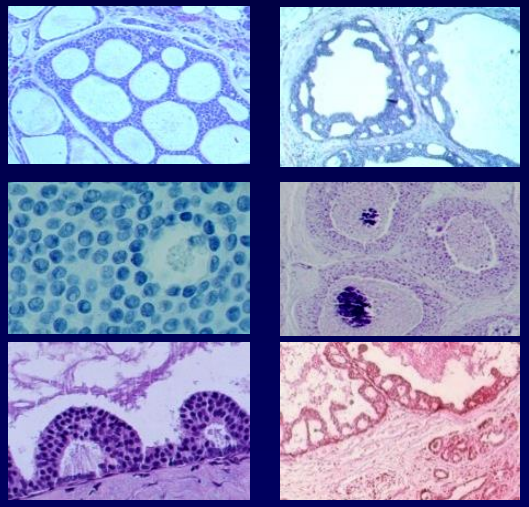
"DCIS is a heterogeneous disease characterized by neoplastic proliferation of ductal epithelial cells with no evidence of stromal invasion"



Ductal Carcinoma In Situ

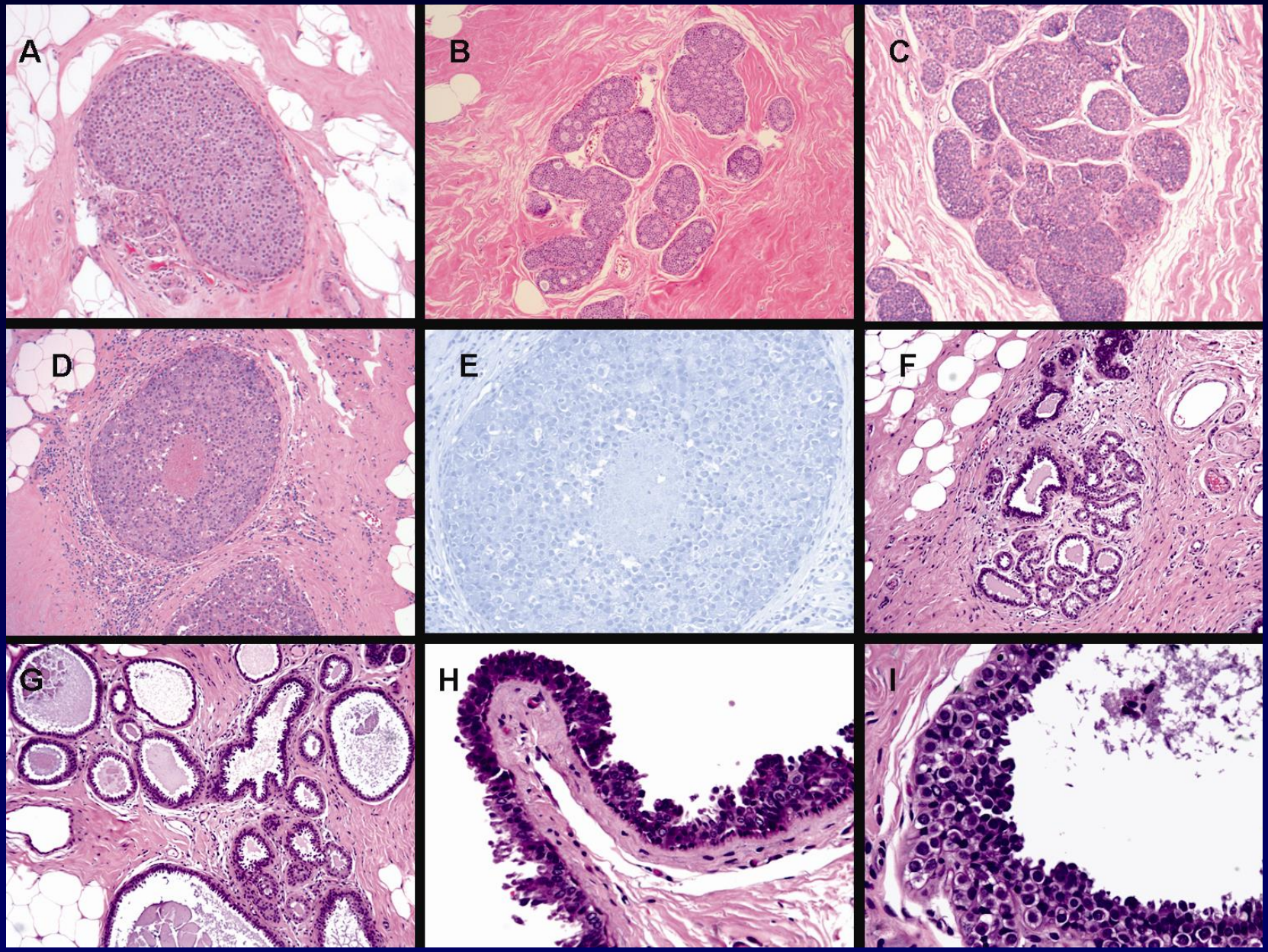
Determinants of tumor behavior

- Morphologic features
  - Nuclear grade
  - Presence or absence of necrosis
  - Growth patterns
- Multicentricity/multifocality



Molecular Biology of DCIS

- High grade lesions are often associated with unfavorable biological markers
- Genetic alterations and loss of heterozygosity at various chromosomal loci differ according to DCIS pattern and grade
- Low grade lesions are associated with the "Low Nuclear Grade Breast Neoplasia Family"



Masood S, Rosa M. Borderline breast lesions: diagnostic challenges and clinical implications. AdvAnat Patl 18(3):190-198, 2011.

Columnar Cell Change

- Columnar Cell Lesions (CCL)
- Columnar Alteration with Prominent Apocrine Snouts and Secretions (CAPSS)
- Atypical Cystic Lobule
- Clinging Carcinoma
- Flat Epithelial Atypia

Columnar Cell Lesions/Flat Epithelial Atypia: Outcome Studies

- Eusebi et al 1994
- Long-term follow up of over 19 years of 25 cases: No evidence of subsequent cancer
- Bijker et al, 2001
- 5.4 year follow up of 50 cases with atypia:
  No evidence of subsequent cancer event

Columnar Cell Lesions/Flat Epithelial Atypia: Indirect Evidence for Precursor Status

- Association with known atypia, LCIS, DCIS, low grade and tubular carcinoma
- Loss of heterozygosity comparable to adjacent known atypia
- Common biomarkers and oncogenes: ER/PR, Cyclin D, Bc1-2

Flat Epithelial Atypia

Author	Evidence for Follow Up Surgical Excision
Guerra-Wallace MM, et al 2004	13%
Kunju LP, et al 2007	21%
Ingegnoli A, et al 2009	20%

Ductal Carcinoma In Situ

Precursor Lesion

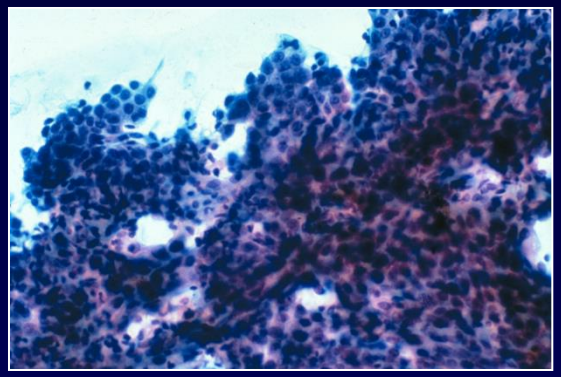
- May be a direct precursor to invasive cancer
- They are slow in progression and if develop an invasive cancer they are often low grade in nature
- Risk of invasion is limited to ipsilateral breast and generally same quadrant and site

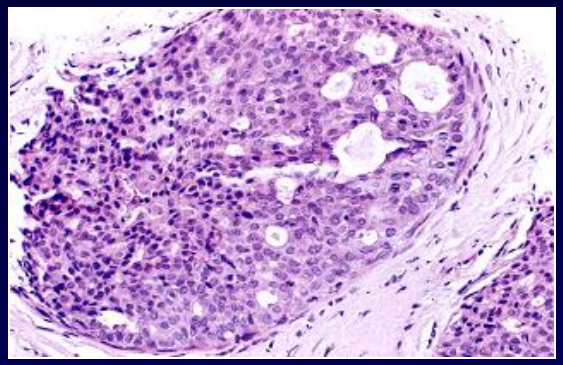
Atypical Ductal Hyperplasia

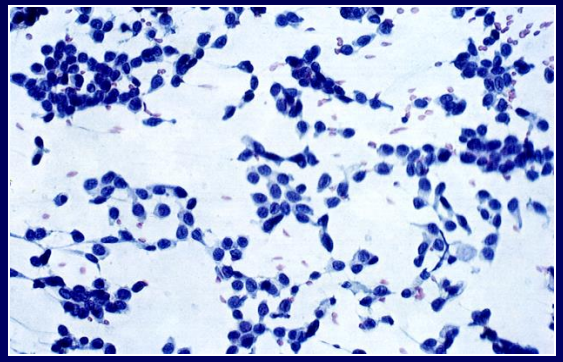
Morphologic Risk Factor

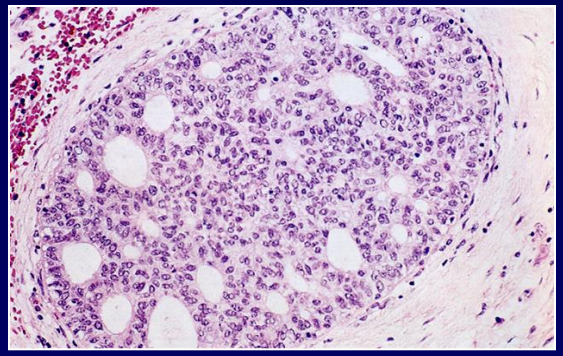
- Indicates increased risk to both breasts
- It is not a precursor for invasive breast cancer
- Difficult to distinguish from low grade ductal carcinoma in situ

ADH Versus DCIS







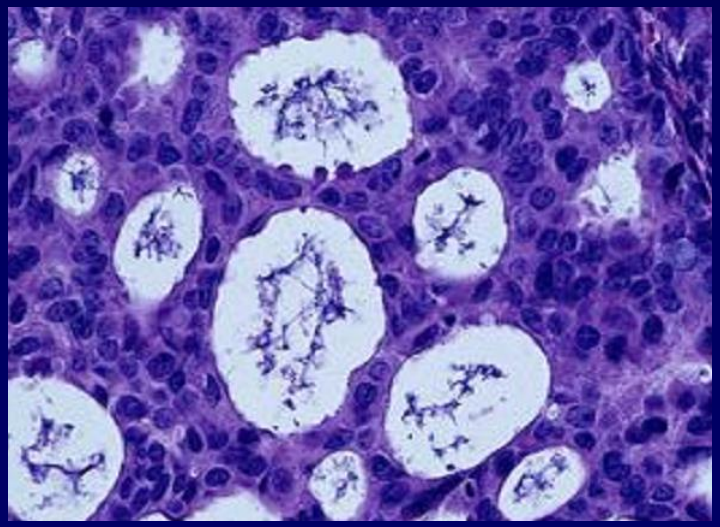


“An Entity Which Has Some but Not All The Features of Low Nuclear Grade Ductal Carcinoma In Situ”

Borderline Breast Lesions

Morphologic criteria for low grade DCIS (Page and Anderson 1987)

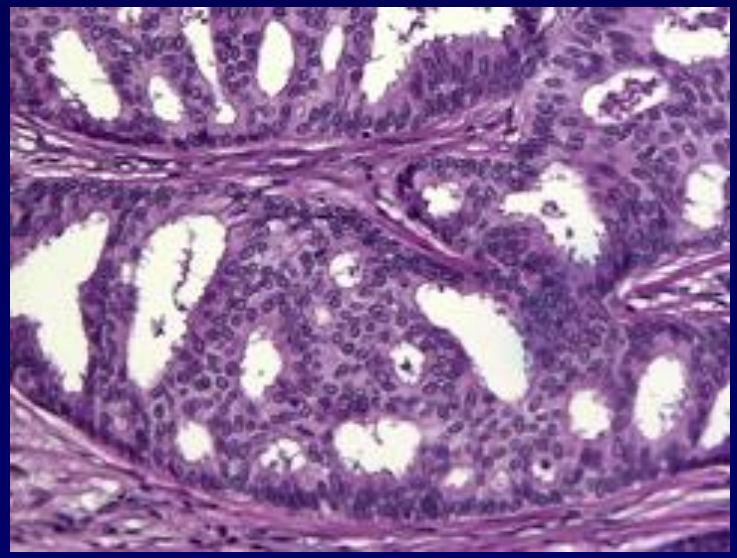
- Two ductal spaces completely effaced in a single terminal ductal lobular unit
- Monomorphous population
- Non-polarized epithelium
- Cribriform bridges without attenuation
- Uniform lacunar spaces



Borderline Breast Lesions

Morphologic criteria for low grade DCIS (Tavassoli and Norris 1990)

- Minimum involvement of two duct spaces
- Sums of diameters of duct spaces must be ≥ 2mm



Interobserver Variability

Hyperplasia versus low grade ductal carcinoma in situ

No Standardized Criteria: 10 Cases, 5 Pathologists

Number of Pathologists in exact agreement/ Percent of Cases:

- 5 of 5 agreed in 0% of cases
- 4 of 5 agreed in 20% of cases
- 3 of 5 agreed in 50% of cases

Rosai J, *Am J Surg Pathol* 15:209-221, 1991.

Interobserver Variability

Hyperplasia versus low grade ductal carcinoma in situ

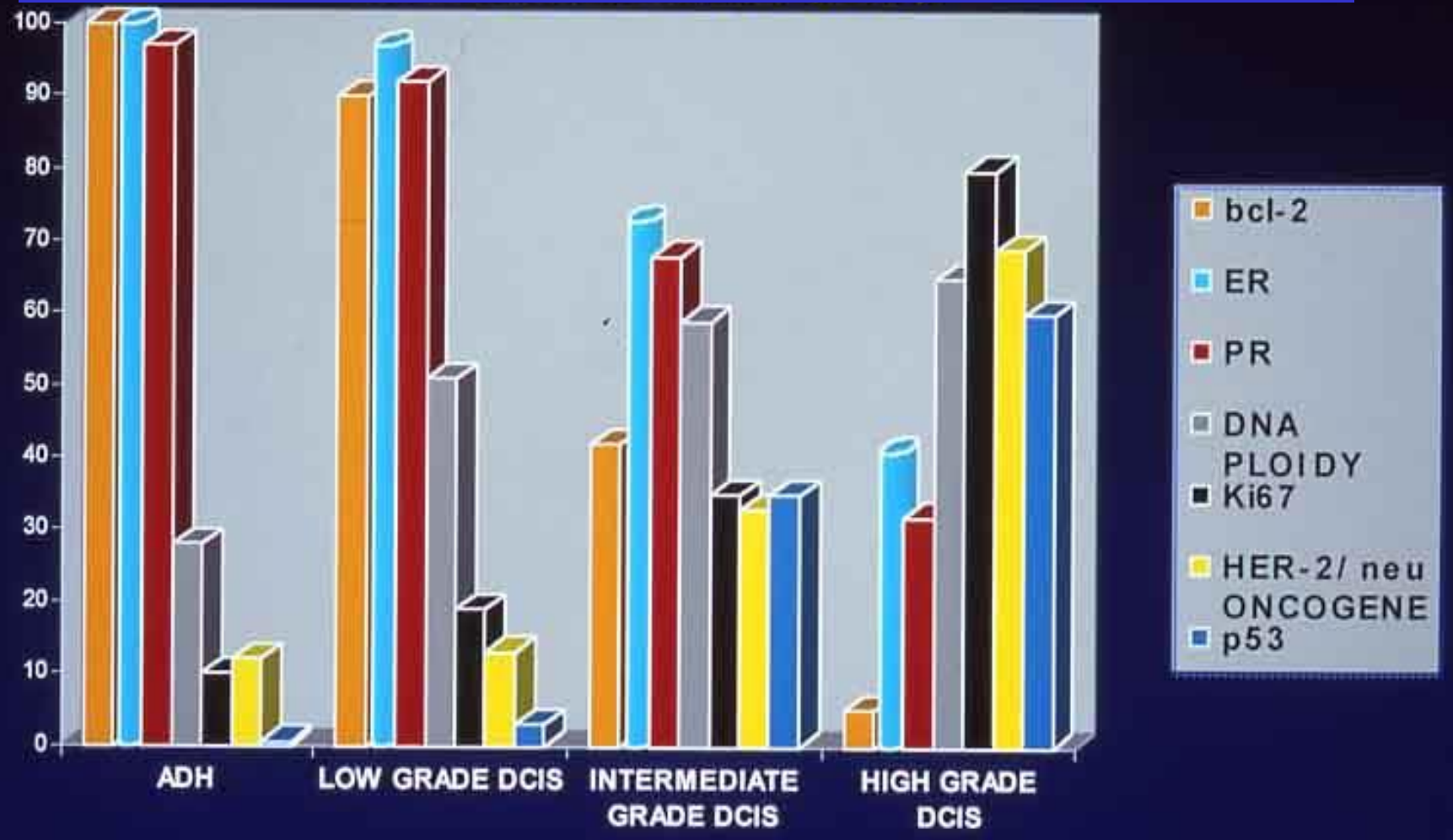
Standardized Criteria: 24 Cases, 6 Pathologists

Number of Pathologists in exact agreement/ Percent of Cases

- **6 of 6 agreed in 58% of cases**
- **5 of 6 agreed in 71 % of cases**
- **4 of 6 agreed in 92% of cases**

Schnitt SJ, et al. *Am J Surg Pathol* 16:1133-1143, 1992.

PATTERN OF EXPRESSION OF VARIOUS BIOMARKERS IN ATYPICAL DUCTAL HYPERPLASIA (ADH) AND DUCTAL CARCINOMA IN SITU (DCIS)



The Issue

“Is it possible that ADH and low grade DCIS are in reality represent the spectrum of the same entity?”

Suggested Terminologies

- "Intraepithelial Mammary Neoplasia"
- "Ductal Intraepithelial Neoplasia"
- "Low Nuclear Grade Breast Neoplasia Family"

Borderline Breast Lesions

ADH vs. DCIS

- **There is no consensus presently on the criteria that should be adopted and how they should be applied for the distinction between atypical hyperplasia, and carcinoma *in situ***

Rosen P: Rosen Breast Pathology: Third Edition. 264-284, 2008.

Borderline Breast Lesions

ADH vs. DCIS

- **Morphological criteria for the diagnosis of "atypia", implying increased breast cancer risk, and *in situ* carcinoma may be improved when it is possible to relate proliferative lesions to specific genetic or biochemical markers**

Rosen P: Rosen Breast Pathology: Third Edition. 264-284, 2008.

Atypical Ductal Hyperplasia vs. Low Grade Ductal Carcinoma In Situ

Diagnostic Challenge

- FNA biopsy
- Core needle biopsy
- Surgical biopsy



The story of a patient

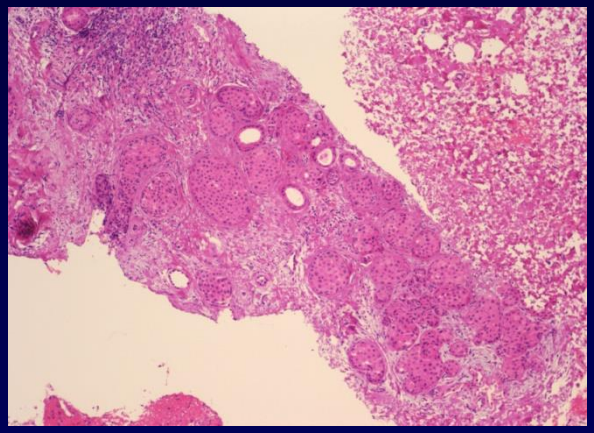


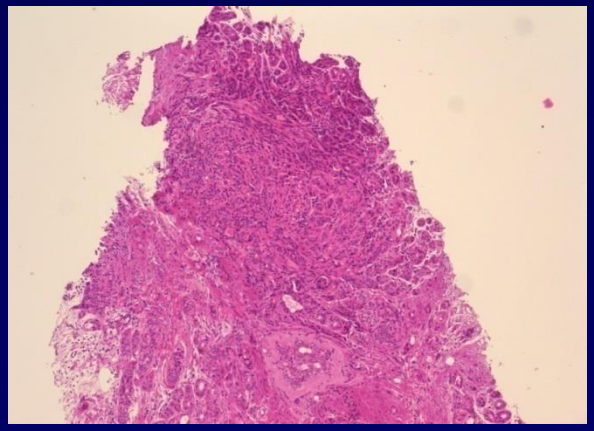
The Story

- A self-referred newly diagnosed breast cancer patient was scheduled to undergo mastectomy and lymph node dissection
- The patient was 32 years old with no risk factors and discovered the mass when showering
- The breast mass was sampled by core needle biopsy and was diagnosed as an invasive cancer
- A palpable lymph node was found and was assumed to represent a lymph node metastasis
- The patient was advised to have mastectomy and axillary dissection followed by chemotherapy

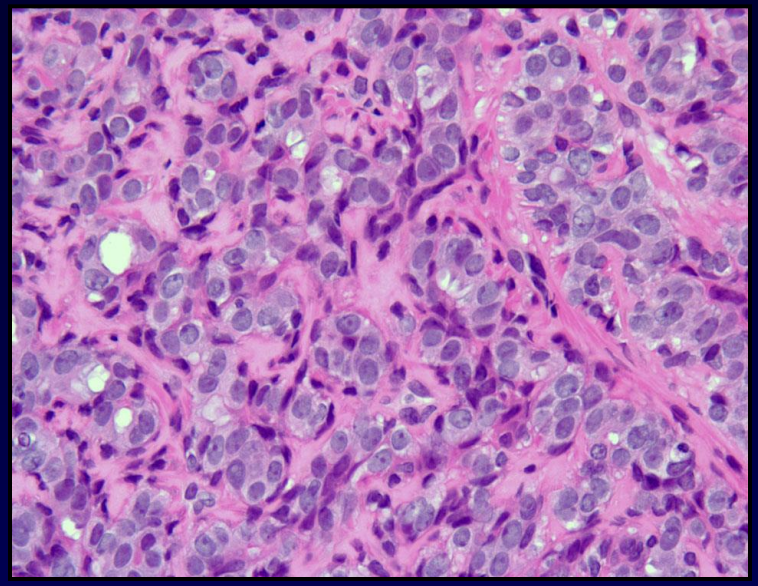
Biopsy Original Diagnosis

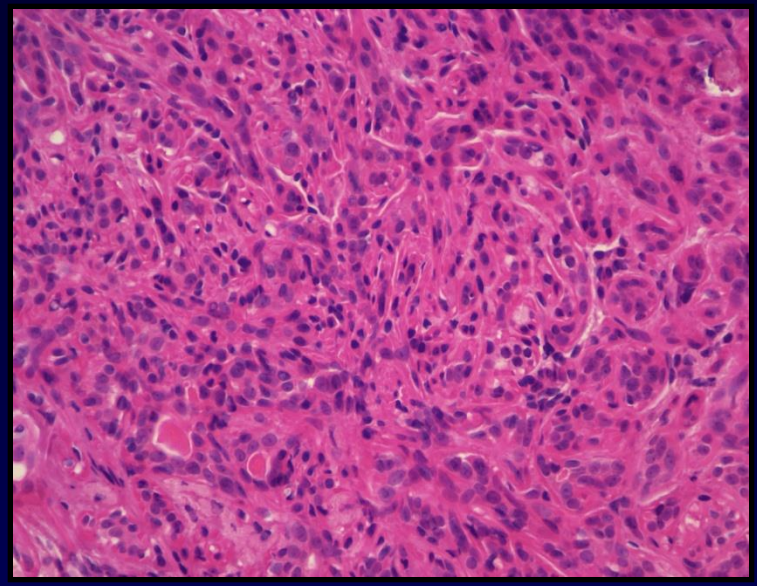
- Invasive moderately differentiated ductal carcinoma.
- Low grade ductal carcinoma in situ.

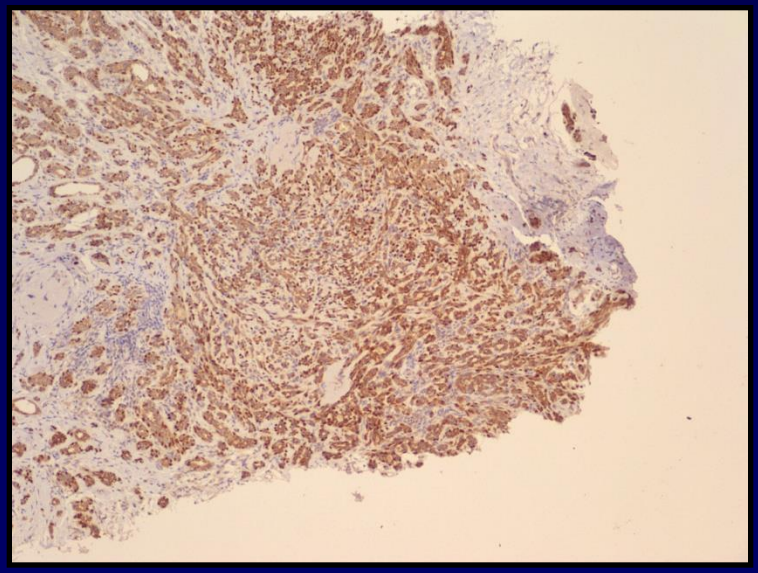


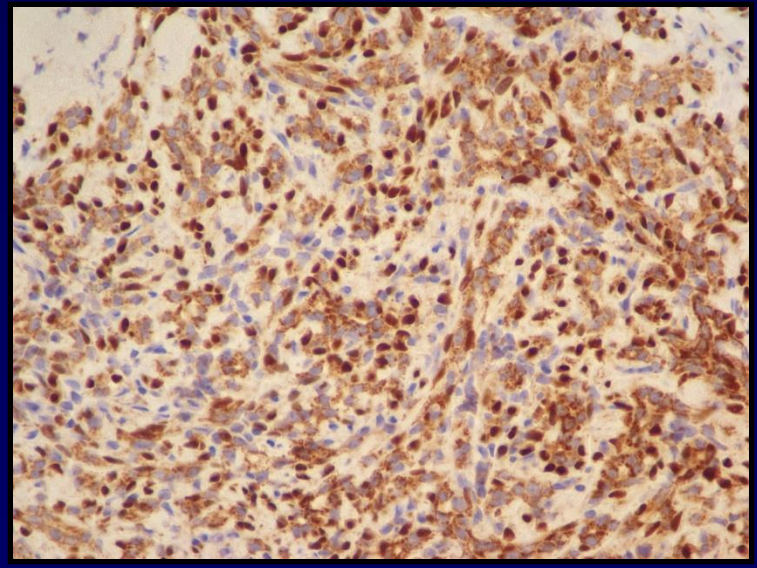


Review of the biopsy at our institution



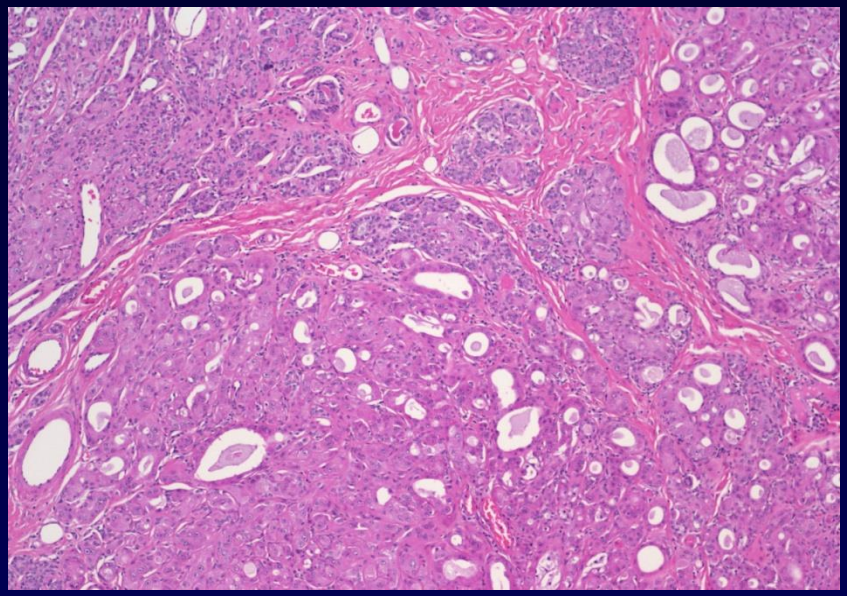


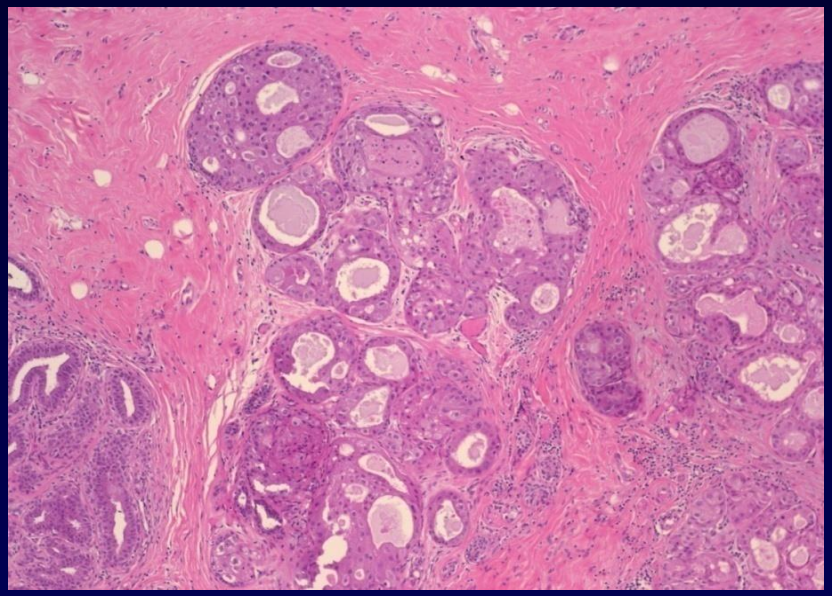


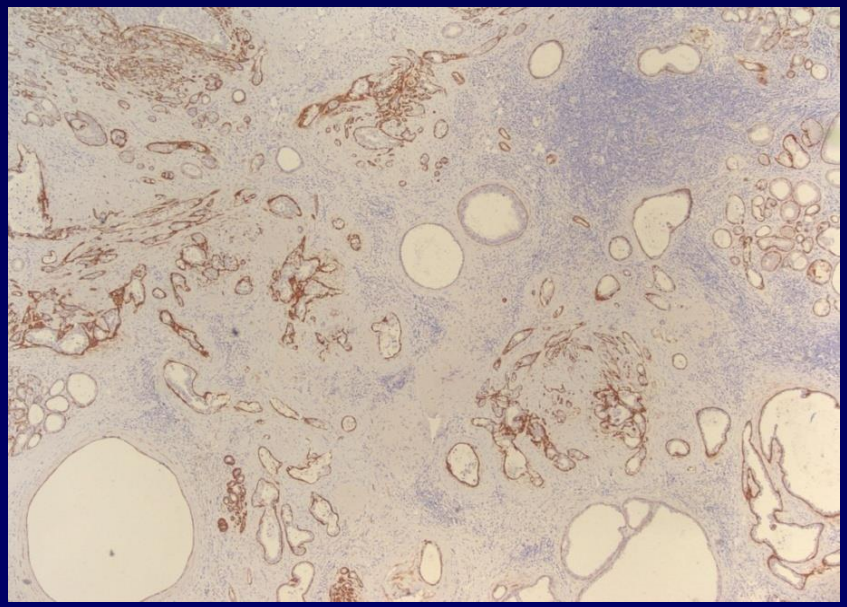


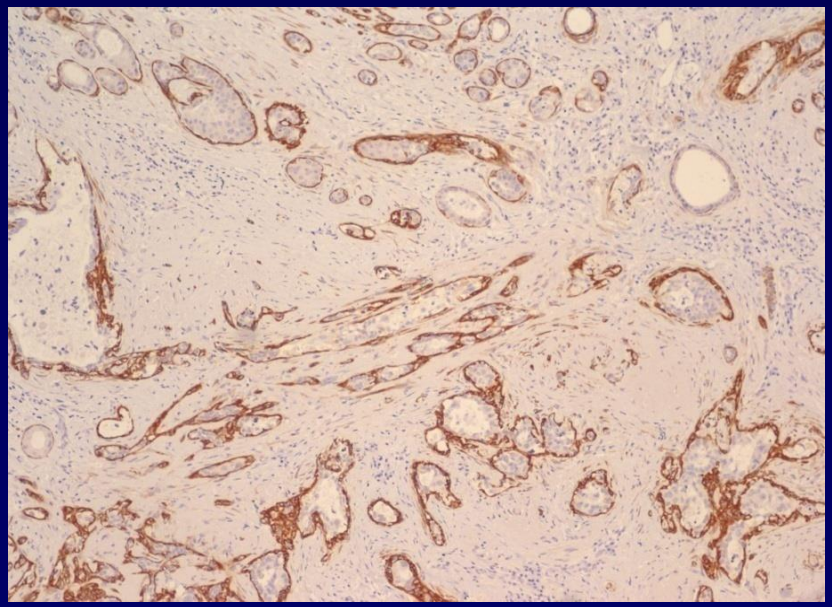
Calponin

Follow-up Excisional Biopsy









Consultant Reviews

- **Diagnosis #1: Atypical apocrine adenosis with sclerosis and associated florid sclerosing adenosis**
- **Diagnosis #2: Low grade apocrine ductal carcinoma in situ, with focal sclerosis, periductal and radial, involving multiples cores**


Hug Me

Prone to Error: Earliest Steps To Find Cancer



"All the News That's Fit to Print"

The New York Times

Late Edition

VOL. CLIX ... No. 55,107 NEW YORK, TUESDAY, JULY 20, 2010 $2.00

Prone to Error: Earliest Steps To Find Cancer

From Tiniest Samples to Needless Surgery

By STEPHEN H. SIGA

Monica Long had expected a routine appointment. So how she was sitting in her ob-gyn's office, and he was delivering ungodly disturbing news.

Nearly a year earlier, in 2007, a pathologist at a small hospital in Chebeyan, Mich., had found the earliest stage of breast cancer from a biopsy. Extensive surgery followed, leaving Ms. Long's right breast missing a golf-ball-size chunk.

Now she was being told the pathologist had made a mistake. Her new doctor was certain she would feel the diseased cells if they had carcinoma in situ, as D.C.I.S. is called, at least some of it. — the surgery, the radiation, the drugs and, worst of all, the fear.

"Psychologically, it's horrible," Ms. Long said. "I never should have had to go through what I did."

Like most women, Ms. Long had assumed the breast biopsy as the gold standard, an infallible way to identify cancer. "I thought if you got cut out and sliced," said Ms. Long, who is a yoga-and-Pilates teacher.

At a turns out, diagnosing the earliest stage of breast cancer can be surprisingly difficult, prone to both outright error and overzealous disagreements over whether a cluster of cells is benign or malignant, according to an accumulating body of research cited in The New York Times.

Advances in technology have saved other lives, pathologists say, but the push to detect ever smaller growths has also led to a few grains of salt. Determining the difference between some benign changes and early-stage breast cancer is a particularly challenging area of pathology, involving a distilled moments and interviews with doctors and patients.

Beginning D.C.I.S. "is a 10-year history of confusion, different rates of opinion and underwriting," said Dr. Rachel Mosteni, the head of pathology at the University of Florida College of Medicine in Jacksonville. "There are studies that show that diagnosing these borderline breast lesions occasionally comes down to the flipped a coin."

There is an increasing recognition of the problems, and the bal-

Continued on Page A12

Participants in a study on curbing H.I.V. infections listened as test results were announced Monday in Vulindlela, South Africa.

2 AFRICAN STUDIES GIVE WOMEN HOPE IN FIGHTING H.I.V.

FOCUS ON PREVENTION

Payments Promising — Vaginal Gel May Be Years From Public

By CELIA W. DUGGER

VULINDLELA, South Africa With an AIDS vaccine still out of reach, two significant new studies have found different ways to sharply cut H.I.V. infections among women and teenagers, who make up a majority of the newly infected in sub-Saharan Africa.

After two decades in which researchers searched fruitlessly for an effective vaginal microbicide to block H.I.V., South African researchers working in two AIDS-devastated communities of South Africa, one rural and one urban, say they have finally found something that shows real promise.

Women who used a vaginal microbicidal gel containing an antiretroviral medication widely used to treat AIDS, sensitive were 39 percent less likely, overall, to contract H.I.V. than those who used a placebo. Those who used the gel most regularly reduced their chances of infection by 54 percent, according to research findings in a study of 889 women by CAPRISA, a Durban-based AIDS research center.

Separate trials are needed to confirm the results, and it will most likely be years before the product is publicly available, but if produced on a large scale the gel would cost less than 10 cents per application, the researchers' project scientist.

Because the trial was related to only a small area and just two numbers about in the previous infections, AIDS treatment and public health officials around to see whether trial get similar results before they endorse the drugs. Some are raising and public education to help that would be needed to make billions of dozens of the gel, as well as the applicators, which may be expensive, and there is to persuade women to use them over generations of past reluctance to adopt them.

Dr. Bruce Walker, a Harvard Medical School researcher who was not involved in the study, said a chaste program when researchers provided their findings to a small group of scientists and activists in Durban.

"This is the first time that there's been a test that women can use to protect themselves from becoming infected," he said. "It's a game-changer."

In Vienna, where the meeting of the International AIDS Society just opened, leaders of the global fight against AIDS said they found the results of the studies inside trial very impressive. The study was published online on Monday by Science magazine.

"This is very encouraging."

Continued on Page A6

Senate Is Set To Extend Aid To the Jobless

By CARL HULSE

WASHINGTON — Senate Democrats are poised to break a party unity stalemate on Tuesday and vote to extend unemployment benefits for millions of Americans who have been without work for six months or more, but the fight seems sure to intensify playing out as a defining issue in the midterm elections.

The day before a crucial procedural vote to provide added unemployment assistance, Senate Democratic leaders and the White House, President Obama appeared in the State Dining on Monday with three moderate Democrats in Senate Republicans for blocking the extension and now by insisting, over Democratic objections, that the $34 billion extra of the benefits not be added to the deficit.

"The same people who didn't have any problem spending hundreds of billions of dollars on tax breaks for the wealthiest Americans are now saying we shouldn't offer relief to middle-class Americans," Mr. Obama said.

Democrats have been one vote

Continued on Page A15

Iraq's Conflict, Reflected in a Family Tragedy

By TIM ARANGO

SAMARRA, Iraq — When the American soldiers left, Ahmed Ahmed, a farmer in Iraq's northern Diyala Province, imagined a new life for his family. Instead it was the harsh end of a story. In seven hard years, nothing went as planned.

He spoke good English and had served in America. He got a job, his family says, with the United States military. Less last month, he found an upland at the hands of his 32-year-old son, who had turned into an insurgent who sought money and purpose in fighting the Americans.

"I don't say everything is here," the son, Ahmed, said in an interview a few short hours before he was killed by American soldiers. "I don't say everything is here," the son, Ahmed, said in an interview a few short hours before he was killed by American soldiers.

Abdul Ahmed, held by the police in Samarra, Iraq, northeast in killing his father, Hamid Ahmed.

Continued on Page A10

A City Outsources Everything. California's Sky Doesn't Fall.

By DAVID STREITFELD

SEATTLE, Calif. — You must, not once, but three times in the last two weeks, Andrew Quezada says, he was stopped and questioned by law enforcement here.

Mr. Quezada, a high school student who does volunteer work for the city, pronounced himself frightened.

The walking sting at night carrying an oversized bag," he said, describing two of the incidents. "I took suspicion. They showed the sheriff's department a photograph."

Clash an another Mayoral initiative who appeared at the city's annual experiment in municipal governing. City officials say the results first of Mayoral's employees and subsidized their jobs.

While many communities are horribly, unsurprising, many are cuts, Mayoral says is a big first city in the nation in the current downturn to take an as to outsource.

The school crossing guards were let go. Parking enforcement was outsourced, too. City Hall workers dismissed, some maintenance workers made redundant. The police safety duties of the Fence Department were handed over to the Los Angeles County Sheriff's Department.

At first, people at this point, long-troubled and heavily Democratic city southeast of Los Angeles loosed his assembly.

Some citizens were afraid they would be assaulted as they walked down the streets. Parents worried the police would be shot and their children would have no where to watch. play. Landlords and their owners had begun suggesting their evictions depended services they would no longer be obliged to pay rent.

The apocalypse never arrived. In fact, it seems this city was not bad at being a city that outsource-

Continued on Page A9

To Get an Internship at City Hall, It's Not Always What You Know

By DAVID M. CHEN and RACHEL BARKLEY

They are the children and relatives of hardhat mayors, like Lloyd C. Bramhall, the chief executive of Coleman Tactic. Peter G. Peterson, co-founder of the Blackstone Group, and Laurence A. Tisch, who was a hotel mogul and chief executive of CBS.

They enjoyed a comfortable childhood and, as it turns out, a second summer job. They all landed internships at New York's City Hall under Mayor Michael R. Bloomberg, according to a list obtained by The New York Times. Long excluded and heavily Democratic, the Bloomberg administration has opened its doors to the children of the elite to a degree not seen in the eight years.

"It was either that or going to summer camp," Sarah Dartmell said as an interview. Now at Yale, she recently enjoyed her stint in the mayor's office of management, which oversees operations. "I truthfully couldn't tell you how I got the internship," he said. "I'm sure it be working with a bunch of 30- to 40-year-olds, and you didn't have a sense that you were in an internship program."

The mayor's office is not eager to share information about who got the internships and took them. Only after a request through the Freedom of Information Act request and repeated follow-up messages Ava Lavatto, a city spokeswoman, explained that the internships provided to relatives of insiders was a tiny fraction of the almost 1,200 that have traveled since Mr. Bloomberg took office.

He said a vast majority of the positions were reserved through city hall's online applications or school programs. The children of at least two employees of the

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NATIONAL A12-17

Evolution of a Neighborhood

Another Spill Tactic, in Case

NEW YORK A21-23

Recheck for State Tests

INTERNATIONAL A4-10

A Rough-Speaking Warrior

BUSINESS DAY B1-10

Big Profit at Delta Air Lines

ARTS C1-8

A Madoff Play, Minus Wizard

SCIENCE TIMES D1-7

A Pump, but No Thump

SPORTS D1-EDITION B1-10

Cycling's Unwritten Rules

EDITORIAL, OP-ED A22-23

David Brooks

A UPLOPE

Assessing Godard's 'Contempt'

New York Times Article

The New York Times
Well
Tara Parker-Pope on Health

JULY 19, 2010, 9:01 PM

Doubt About Pathology Opinions for Early Breast Cancer

By TARA PARKER-POPE

Advances in imaging technology mean that more and more breast cancers are being detected at the earliest stages — sometimes when the rogue cells are as tiny as a few grains of salt. But now there are new questions about whether many pathologists are able to render reliable opinions on such tiny lesions, according to an extensive New York Times examination of breast cancer cases.

Stephanie Saul of The Times reports that pathology errors put women at risk for unnecessary and disfiguring surgery and potentially harmful radiation treatment.

New York Times Article

Discerning the difference between some benign lesions and early stage breast cancer is a particularly challenging area of pathology, according to medical records and interviews with doctors and patients. Diagnosing D.C.I.S. "is a 30-year history of confusion, differences of opinion and under and over treatment," said Dr. Shahla Masood, the head of pathology at the University of Florida College of Medicine-Jacksonville. "There are studies that show that diagnosing these borderline breast lesions occasionally comes down to the flip of a coin."

To learn more, read the full report, "Cancer Errors May Increase With Early Test," then please join Ms. Saul for a discussion below.

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The Story of the Patient

The Question

- Whose fault is it?
- Are we overdiagnosing breast cancer?



“The Current Challenges Associated with the Practice of Breast Pathology”

Current Issues In Breast Pathology

- Diversity in tissue handling, processing and reporting
- Insufficient evidence-based correlation between morphology and patient outcome
- Significant interobserver variability in diagnosis and test results
- Communication barriers among physicians involved in breast care

Current Issues In Breast Pathology

- There are no uniform guidelines to measure the rate of diagnostic errors
- Fear of disclosure and medicolegal issues limits the reporting of diagnostic errors
- There are many look-alikes in breast pathology that can mimic cancer

Current Issues in Breast Pathology

- Breast pathology is considered as a component of general surgical pathology
- Breast pathology fellowships are not accredited by ACGME
- Referral of pathology samples to commercial laboratories impairs communication

Suggestions

- To acknowledge the challenges associated with the current practice of breast pathology
- To design studies that can appropriately analyze the problems and quantitate their impact on therapy, patient outcome and health economy

Suggestions

- Establishment of quality assurance programs
  - Internal quality measures
    - Consensus slide conference
    - Mandatory second review of cancer cases
    - Mandatory adherence to established guidelines
- Second opinion
  - The review of outside pathology slides and reports by a local pathologist before the initiation of cancer therapy
- Involvement in external quality assurance programs

Borderline Breast Lesions

The Suggestions

- Abandon the term of “Low Grade Ductal Carcinoma In Situ”
- Use the term of “Borderline Breast Disease”
- Completely remove the entire lesion
- Offer risk assessment/risk reduction options

The Models to Follow

- Offer the options of “wait and watch” for borderline lesions/low grade DCIS similar to low grade prostate cancer

Masood S. Focusing on breast cancer overdiagnosis and overtreatment: the promise of molecular medicine. *The Breast Journal* 2013;19(2):127-129.

The Impact

- Reduced anxiety to the patient and her family
- Minimizing unnecessary expense
- Restoring patient trust



“ADH vs. Low Grade DCIS”



The Urgent Need

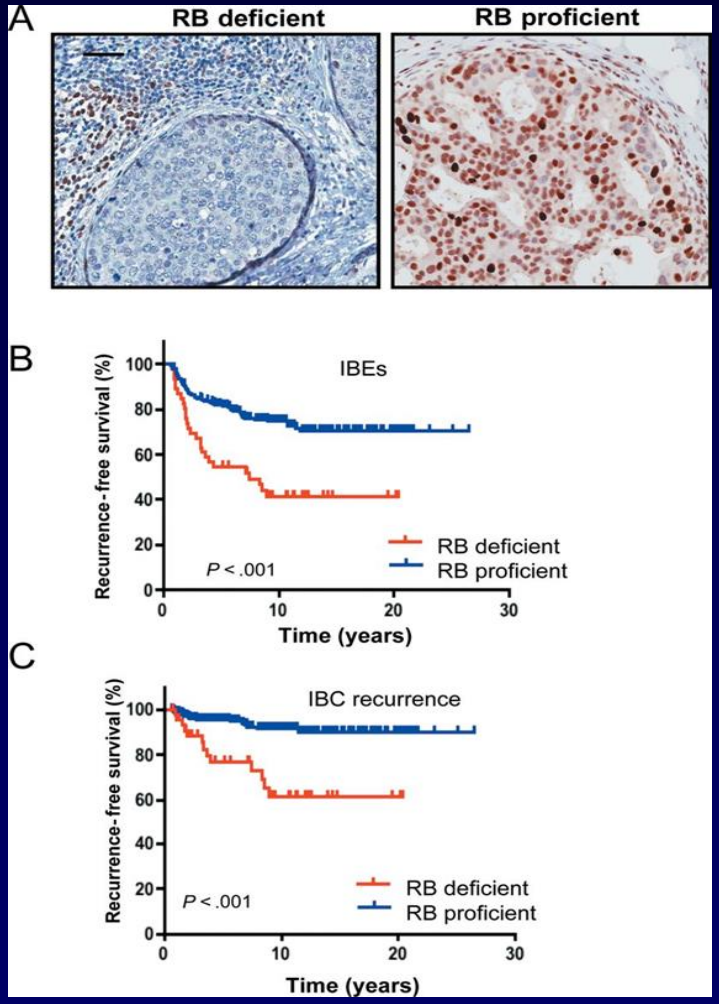
- Better define the morphologic and biologic characteristics of spectrum of high risk proliferative and precursors breast lesions
- Change the concept, terminology, and the pattern of practice

Masood S. Focusing on breast cancer overdiagnosis and overtreatment: the promise of molecular medicine. *The Breast Journal* 2013;19(2):127-129.

Loss of Tumor Suppressor Genes Linked to DCIS Breast Cancer Progression

Knudsen E S et al. Retinoblastoma and phosphate and tensin homolog tumor suppressors: impact on ductal carcinoma in situ progression. JNCI J Natl Cancer Inst 2012;104:1825-1836

Retinoblastoma (RB) status is associated with ductal carcinoma in situ (DCIS) recurrence and invasive progression.



Knudsen E S et al. JNCI J Natl Cancer Inst 2012;104:1825-1836

The Significance?

- Over 1.1 million women are diagnosed with breast cancer each year across the globe
- Estimated diagnostic errors in breast pathology may be about 2%
- It appears that a significant number of women will receive under/over treatment

The Message

Raising the Bar:

A plea for standardization and improved quality of breast pathology

Masood S: The Breast Journal 12(5):409-412, 2006.


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