Are We Overtreating DCIS?

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Our understanding of “cancer” has evolved over time:
Treatment for invasive cancer is evolving, screening must evolve as well

CANCER IS A COLLECTION OF HETEROGEOUS DISEASES
cancer
noun
1. Pathology
   a. a malignant and invasive growth or tumor, especially one originating in epithelium, tending to recur after excision and to metastasize to other sites.

   b. any disease characterized by such growths.

2. any evil condition or thing that spreads destructively; blight.
PATIENTS ASSUME THAT CANCER, LEFT UNTREATED, WILL KILL YOU

Physicians too
Normal Cell → Atypical Cell → Carcinoma In Situ → Stage 1 Cancer → Stage 2-3 Cancer → Metastasis → Cancer death

Old Paradigm (inexorable progression)

Early Detection Will Reduce Mortality
Late Stage Death
Early Stage
High Grade CIS
Atypia/CIS
Atypia/CIS
Normal Cell

INDOLENT
SLOWLY PROGRESSIVE
RAPIDLY PROGRESSIVE

Early Stage
Late Stage
Death

Early Stage
Late Stage
Death

Early Stage
• Workshop convened around overdiagnosis
• Subgroup to compile recommendations to NCI
  – Signal the physician, patient community
  – Generate a shift in philosophy to enable improvements to screening, prevention, and treatment
  – Explanation for previous approach and motivation to change
    • contentious debate → exploration of new concepts
    • amnesty for previous beliefs
Recommendations Working Group

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- Ian M Thompson, UTHSC, San Antonio
- Brian Reid, M.D., Ph.D., Fred Hutchinson CRC
- Peter Nelson, M.D., Fred Hutchinson CRC
- David F. Ransohoff, M.D., UNC, Chapel Hill
- H. Gilbert Welch, M.D., M.P.H., Dartmouth
- Shelley Hwang, M.D., Duke University
- Donald A. Berry, Ph.D., UT MD Anderson Ca Ctr
- Kenneth W. Kinzler, Ph.D., Johns Hopkins University
- William C Black M.D., Dartmouth
- Howard Parnes, NCI
- Mina Bissell, LBL Berkeley
- Sudhir Srivastava, NCI, EDRN
WE NEED TO RECOGNIZE THAT

OVERDIAGNOSIS OCCURS AND IS COMMON
OVERDIAGNOSIS IS MORE COMMON WITH SCREENING

Preponderance of Evidence Shows that
For Both Breast and Prostate
Incidence Rates Have Risen and Remain Higher

BREAST

PROSTATE
Chance Increases with Screening

- **Lung**: 70% present late stage; survival 70% and 40% for stage 1,2
  - NLS Trial: LDCT showed 20% decrease in lung ca death
    - Incidence of stage 1 CA >> reduction in stage 2-4 cancers
  - Screening of general population increases incidence without changing mortality
  - Autopsy and screening: overdiagnosis 20-25%

- **Thyroid**
  - In office screening of thyroid nodules has become routine
  - SEER data: incidence has tripled, death rate constant
    |
    | 1975 | 2009 |
    |------|------|
    | Incidence | 4.9 | 14.3 |
    | Death rate | 0.56 | 0.52 |
Non-invasive Cancer

• Barrett’s Esophagus
  – Condition that is more common with gastric reflux
  – Considered high risk for esophageal cancer
  – Barrett’s patients are screened routinely with bx

• Longitudinal studies
  – The vast majority of Barrett’s pts will never develop esophageal Ca
  – Barrett’s is a homeostatic adaptation to reflux
  – Endoscopic screening is no longer recommended
  – Practice of screening continues
WHAT IS THE PROBLEM WITH DIAGNOSING ALL OF THESE CANCERS?
TREATMENTS HAVE CONSEQUENCES

There is a toll physically, emotionally, financially
## Recommendations to the NCI

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<tbody>
<tr>
<td>1</td>
<td>Embrace the development of new terminology to replace the word “cancer” where appropriate; use companion diagnostics to support this process</td>
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<td>2</td>
<td>Create observational registries for IDLE conditions with low or uncertain risk of progression to cancer</td>
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<td>3</td>
<td>Mitigate over-diagnosis by testing strategies that lower the chance of detecting unimportant lesions</td>
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<td>4</td>
<td>Embrace new concepts for how to approach cancer progression and prevention</td>
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Recommendation #2

EMBRACE THE DEVELOPMENT OF NEW TERMINOLOGY TO REPLACE THE WORD “CANCER” WHERE APPROPRIATE
Establish a New Naming Convention

• Call for a naming convention without the word cancer in the label
  • Indolent lesions (invasive cancers)
  • Precancerous

• Example: Urothelial tumors
  • In 1998, the classification from 1973 was revised
    • Papillomas, Grade 1 carcinoma → PUNLMP (papillary urothelial neoplasia of low malignant potential)
      “remove the word carcinoma- why call it carcinoma grade 1 if it almost never is associated with invasion and the risk of disease recurrence and progression are both very low?” Dr. Reuter
DCIS Has Increased 500% Since the Advent of Mammographic Screening . . .

Figure 2. SEER9 Age-adjusted incidence rate of breast cancer by stage (1973-2005)

DCIS rates are again rising in 2007 2nd to digital screening?

*DeSantis 2011 Cancer Epi Biomarkers*
In comparison…

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Breast</td>
<td>20%</td>
<td>+18%</td>
</tr>
<tr>
<td>Colon</td>
<td>32%</td>
<td>-17%</td>
</tr>
<tr>
<td>Cervix</td>
<td>55%</td>
<td>-52%</td>
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</table>
IT IS UNLIKELY THAT THE MAJORİTY OF DCİS DETECTED IS DESTINED FOR SIGNİFİCANT CANCERS
Recommendation #2

CREATE OBSERVATIONAL REGISTRIES WHERE THERE IS UNCERTAIN RISK OF PROGRESSION TO “METASTATIC” CANCER
DCIS is an excellent example
No emergency to operate

- Generate and participate in trials that change our treatment approach and learn more about natural history
  - Low/intermediate lesions: Neoadjuvant Hormone therapy
    - CALGB 40903 (Hwang): 6 months AI, MRI monitoring, preoperatively
    - Follow-on trials need to be developed
  - Hormone negative lesions: Develop and participate in trials that encourage a “prevention” approach
    - Window trials-short term exposure
Incorporate Disease Dynamics into Pathology Paradigm

Observation could become an integral part of diagnosis

- Imaging abnormalities, precancerous lesions

Recognize that the underlying biology determines timing of progression

- Some lesions are evolve slowly, some more quickly

Classification could be reassessed after a window of observation or treatment

- Observation under therapeutic pressure (e.g. 40903)
Time Can Be Used as the Discriminator of Who Needs Surgical intervention

- For those whose DCIS recede or disappear, perhaps no further surgical therapy is needed.
- For those whose DCIS do not change, close followup may be appropriate.
- For those whose DCIS progress, they are declaring the need for more aggressive intervention.

Example of integrating disease dynamics to change classification and treatment.

DCIS is NOT an emergency, nor a life threatening cancer. We MUST enable an approach that allows us to learn and better inform patients.
If we continue on the same clinical path, we cannot hope to see change

IF WE STUDY AN ALTERNATIVE APPROACH, WE MAY BE SURPRISED AT WHAT WE LEARN
Remarkable Variation in Approach to Management of “Risk”

• Within Breast Cancer
  – BRCA1 patient: 85% risk for invasive breast cancer
    • Surveillance, prophylactic mastectomy
  – DCIS patient: 10-20% risk for invasive breast cancer
    • Surgical excision, radiation, mastectomy

• Active Surveillance Across Cancer Types
  – For Invasive Prostate Cancer
  – Not even for breast premalignant lesions (DCIS)
A QUANTITATIVE MULTIGENE RT-PCR ASSAY FOR PREDICTING RECURRENCE RISK AFTER SURGICAL EXCISION ALONE WITHOUT IRRADIATION FOR DUCTAL CARCINOMA IN SITU (DCIS): A PROSPECTIVE VALIDATION STUDY OF THE DCIS SCORE FROM ECOG E5194


Eastern Cooperative Oncology Group (ECOG)
North Central Cancer Treatment Group (NCCTG)
Genomic Health, Inc (GHI)

2011 San Antonio Breast Cancer Symposium
DCIS SCORE: 10-YEAR IPSILATERAL BREAST EVENTS (IBE) BY RISK GROUP

**ANY IBE**

<table>
<thead>
<tr>
<th>DCIS Score Group</th>
<th>N</th>
<th>10 Year Risk (95% CI)</th>
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<tbody>
<tr>
<td>High</td>
<td>36</td>
<td>27.3% (15.2%, 45.9%)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>45</td>
<td>24.5% (13.8%, 41.1%)</td>
</tr>
<tr>
<td>Low</td>
<td>246</td>
<td>12.0% ( 8.1%, 17.6%)</td>
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Log rank P = 0.02

**INVASIVE IBE**

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<tr>
<td>High</td>
<td>36</td>
<td>19.1% (9.0%, 37.7%)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>45</td>
<td>8.5% (2.0%, 25.3%)</td>
</tr>
<tr>
<td>Low</td>
<td>246</td>
<td>5.1% (2.8%, 9.5%)</td>
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Log rank P = 0.01

Average Lifetime Risk: 12%

Gail Risk 2.5

Atypia and Chemoprevention

- Retrospective review evaluated 2460 patients diagnosed with atypia from 1999 and beyond from Mass General (Hughes et al)
- Atypia included Borderline DCIS, ADH, ALH, LCIS
- Final data set looked at outcomes of 1938 pts
  - 466 patients treated
    - Tamoxifen, Raloxifene, and/or Exemestane
    - Any duration of time
  - 1472 patients not treated

Probability of Cancer After Atypia Diagnosis With and Without Chemoprevention

n=466 w chemoprevention
n=1472 without chemoprevention

<table>
<thead>
<tr>
<th>Invasive Cancer Risk</th>
<th>10 year ipsilateral</th>
<th>5 year ipsilateral</th>
<th>Lifetime (either breast)</th>
<th>Offered/preferred*</th>
</tr>
</thead>
<tbody>
<tr>
<td>LCIS</td>
<td></td>
<td></td>
<td></td>
<td>Active surveillance</td>
</tr>
<tr>
<td>Atypia</td>
<td></td>
<td></td>
<td></td>
<td>Active surveillance</td>
</tr>
<tr>
<td>DCIS Score 10</td>
<td>5.0%</td>
<td>2.5%**</td>
<td>10-20%</td>
<td>Lumpectomy</td>
</tr>
<tr>
<td>DCIS Score 30</td>
<td>7.0%</td>
<td>3.5%**</td>
<td>10-20%</td>
<td>Lumpectomy +XRT* +/− Tamoxifen</td>
</tr>
<tr>
<td>DCIS Score 65</td>
<td>15%</td>
<td>7.**</td>
<td>15-30%</td>
<td>Mastectomy</td>
</tr>
<tr>
<td>BRCA 1/2</td>
<td></td>
<td>5-7%</td>
<td>50-85%</td>
<td>Active Surveillance/screening Prophylactic mastectomy and/or oophorectomy Tamoxifen (BRCA2)</td>
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The Evidence Supports Overdiagnosis and Overtreatment of DCIS

*Facts do not cease to exist because they are ignored*

Aldous Huxley

*Don’t look so hard for it, especially in women who are older*

*Don’t call it cancer*

*Try doing less- and learn from it (participate in trials, registries)*

*Allow time to provide information on disease dynamics*
Recommendation #4

MITIGATE OVER DIAGNOSIS BY TESTING STRATEGIES THAT LOWER THE CHANCE OF DETECTING UNIMPORTANT LESIONS
What is the magnitude of the problem in screening?

• The focus of screening shifted
  – Invasive cancers → DCIS → Any calcifications
  – 500,000-1 million biopsies a year in the US

• No established benefit to the shift
  – Should we be afraid to let “calcifications” go?
  – Is someone’s life threatened by not knowing?

• Aggregate cost of screening
  – 65% of population (age 40+ annually): $7.8 billion
  – 85% of population (age 40+ annually): $9.9 billion
  – 85% of population (USPSTF biennially): $3.8 billion
    • Biopsy rates are half (Kerlikowski Annals Int Med 2011)
    • No significant increase in the rates of locally advanced cancers

*It is time to step up as a community and call for a change*
Embracing Learning and Change Going Forward

Look less hard when screening:

• Many biopsies are performed for calcifications with a low risk of being low grade DCIS-
  – Most often benign, incidental DCIS
  – Should these be a target for screening?
  – Urgency to diagnose?

• Targeting more appropriate lesions for detection will reduce the number of biopsies
  • Target >50% risk DCIS or >10% Invasive Ca
Flowers, Esserman SABCS 2011

1 cancer
3mm IDC grade 1

If biopsy performed on all BI-RADS 4 Lesions
Actual CDEP Results
Scenario #1
Inv Ca RE ≥ 10%
DCIS RE ≥ 10%
Scenario #2
Inv Ca RE ≥ 10%
DCIS RE ≥ 50%
Scenario #3
Inv Ca RE ≥ 10%

Biopsy Rate
% of Invasive Cancers Recommended for 6 mo. F/U
Cancer-to-Biopsy Yield
ATHENA Reader Study

• 750 images from the 5 UC medical centers
• Goal:
  – validate ability of radiologists to classify risk for either DCIS or invasive cancer
  – Test of different thresholds for intervention
• Progress
  – 10 radiologists read 250 cases each
  – Preliminary results show that radiologists can calibrate on invasive cancer risk, even DCIS
Ways to Find Less DCIS

• Raise Thresholds for biopsy

• Recommend every other year screening
  – Reduces biopsy rates substantially without significantly increasing late stage presentation

• Future: risk based screening
  – Tailor screening frequency to risk/ models
    • Family history, gene mutations and variations, breast density, exposures
Recommendation #4

EMBRACE NEW CONCEPTS FOR HOW TO APPROACH CANCER PROGRESSION AND PREVENTION
Biology Determines The Type of Progression

- Indolent Lesion
- Normal Cell
- Slowly Progressive
- Rapidly Progressive

Factors:
- DNA Damage / Failure to Repair
- Hereditary Risk
- Exposures
- Microenvironment
- Tumor Biology
What Can Clinicians Do Today?

• Be judicious about what you biopsy mammograms and MRIs-
• Reassure your patients that DCIS is not an emergency
• Reassure your patients that DCIS is a Ductal Lesion, NOT cancer
• Recognize that the evidence does not show that early intervention impacts mortality or ultimate treatment
  – Consider the type of disease that is most likely to arise
  – Use emerging biomarkers to help you change your approach
  – Limit radiation for those lesions that are large (>2.5 cm); HR negative and or Her2+ or with high 21 Gene RS
  – Consider prevention or observation for low risk lesions (track results)
• Send patients to participate in studies like CALGB 90304
The Evidence Supports Overdiagnosis and Overtreatment of DCIS

Don’t look so hard for it, especially in women who are older

Don’t call it cancer: Call it a Ductal Lesion

Try doing less- and learn from it (participate in trials, registries)

Allow time to provide information on disease trajectory

Consider a prevention approach