Breast Cancer Screening: Benefits and Harms
What Should the Future Hold?

Laura Esserman MD MBA
Director, UCSF Carol Franc Buck Breast Care Center
Professor of Surgery and Radiology
University of California San Francisco

What Do We Need to Understand in Order to Enable Change and Improvement?

- Does indolent disease exist?
  - Is early detection always the best option?
- Who benefits most? Least?
- What should we tell patients?
- How can we harness all that we have learned in the last 20 years to create a better approach?
  - Personalized screening

Old Paradigm: *inexorable progression*

New Paradigm: *variable progression*

**“Cancer”**
*Dictionary.com Definition*

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

March 2012

- Workshop convened around overdiagnosis
- Subgroup to compile recommendations to NCI
  - Signal the physician community
  - Signal the patient community
  - Generate shift in philosophy, enable improvement
  - Explain previous approach and motivate change
    - contentious debate \rightarrow exploration of new concepts
- Findings summarized
  - JAMA 2013
  - Lancet Oncology May 2014

Recommendations to the NCI

1. Recognize that over-diagnosis occurs and is common

2. Embrace the development of new terminology to replace the word “cancer” where appropriate; use companion diagnostics to support this process

3. Create observational registries for IDLE conditions with low or uncertain risk of progression to cancer

4. Mitigate over-diagnosis by testing strategies that lower the chance of detecting unimportant lesions

5. Embrace new concepts for how to approach cancer progression and prevention

Recommendations Working Group

- Laura J. Esserman, UCSF
- 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 M.D. NCI
- Mina Bissell LBL Berkeley
- Sudhir Srivastava NCI, EDRN

Esserman et al  Lancet Oncology May 2014

Recommendation #1

RECOGNIZE THAT OVERDIAGNOSIS OCCURS AND IS COMMON

Recommendation #1

OVERDIAGNOSIS IS MORE COMMON WITH SCREENING
OVERDIAGNOSIS REPRESENTS OUR ABILITY TO DETECT THE ENTIRE SPECTRUM OF CANCERS THAT ARISE

For Both Breast and Prostate
Incidence Rates Have Risen and Remain Higher

Chance Increases with Screening

- Lung:
  - Screening of general population increases incidence without changing mortality: Focus on HIGHEST RISK pts
  - 20% decrease in lung CA death
  - Incidence of stage 1 CA >> reduction in stage 2-4 cancers
  - Nodules <1cm on CT: 1.5% chance of cancer
- 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
  - Common with gastric reflux
  - Considered high risk for esophageal cancer
  - Barrett’s patients are screened with biopsy

- Longitudinal studies
  - The vast majority will never develop Ca
  - Barrett’s is an adaptation to reflux

And yet, endoscopic screening continues . . .

an IDLE condition?
A TUMOR WITH LITTLE POTENTIAL FOR METASTASIS AND NONE FOR DEATH

IDLE CONDITIONS are part of the spectrum of breast cancer biology
WHAT IS THE MAGNITUDE?
Effect of screening on the detection of good and poor prognosis breast cancers

Laura Esserman, Yiwey Shieh, Laura Van’t Veer
Dan Moore, Emiel JT Rutgers, Michael Knauer, Valesca Retel, Stella Mook, Sabine Linn, Flora E van Leeuwen, Annuska Glas
Early Detection Research Network, UCSF Dean’s Summer Research Fellowship

Study Design

- Large database of 862 patients with known 70-gene prognosis signature outcomes from previous European trials. Selected node-negative cases only.
- Cohort 2: Screening era: pts diagnosed 2004-6 in 17 community-based hospitals (RASTER) in the Netherlands, where screening uptake is approx 80%.
- Subset of screen-detected cancers
- Analyzed 2 age groups separately:
  - Age 49-60: screened in cohort 2 but not cohort 1 (TEST)
  - <40 years: not screened in either cohort (CONTROL)

Findings

- As age increases, the proportion (both cohorts) of grade 1 tumors increases
  - MammaPrint low (good risk) tumors increase
  - Hormone receptor positive tumors increase
- Distribution of good/poor risk tumors
  - Does not shift in women under the age of 40
    - 25-30% good risk
  - Substantially shifts in women aged 49-60
    - Cohort 1: 40% good risk (no screening)
    - Cohort 2: 58% good risk (“screening”)
      - 67% good risk in screen detected cancers

Defining “IDLE” Tumors

70 gene Prognosis Signature: “Ultra-low Threshold”

- 70 significant prognosis genes
- Ultralow threshold
- Good signature: white +
- Poor signature: brown -

van’t Veer et al., Nature 2002

Canadian RCT: 25 years of followup

Women 40-69, conducted during the Tamoxifen Era

No difference in rate of death from breast cancer at 10, 15, and 25 years

- 1 in 424 women were diagnosed with and treated for cancers that would never come to clinical attention

Miller et al BMJ Feb 2014

30% of Screen Detected Are Categorized as “Ultralow Risk” Cancers

Women aged 49-60

- What could this mean?
  - Excision alone would be sufficient
  - The right Companion Diagnostics can change treatment

- Ultralow
- Low (non-Ultralow)
- High

Esserman, Shieh, van’t Veer Breast Cancer Research and Treatment 2011
IDLE tumors

- Excess of 106 cancers/
- Estimate: 1/424 women screened
- 22% of all cancers
- 50% of non-palpable cancers
  - Identical finding to ultralow risk designation

Finding cancer at the earliest possible point may not be optimal under all conditions

IF WE CANNOT RECOGNIZE AND TREAT ACCORDINGLY

Weighing Benefits and Harms meta-analysis and review

A Systematic Assessment of Benefits and Risks to Guide Breast Cancer Screening Decisions
Pace, L; Keating, N JAMA 2014

DCIS Has Increased 500% Since the Advent of Mammographic Screening...

If the majority of lesions will not be consequential, at a minimum, for low grade disease, we should not radiate

FIRST DO NO HARM

Who benefits least?

WHO BENEFITS MOST?

New Paradigm: Tumor progression and benefit from screening variable

Screening should reflect our new understanding of breast cancer biology

WHAT CAN BE DONE?
Recommendations to the NCI
1. Recognize that over-diagnosis occurs and is common
2. Embrace the development of new terminology to replace the word “cancer” where appropriate; use companion diagnostics to support this process
3. Create observational registries for IDLE conditions with low or uncertain risk of progression to cancer
4. Mitigate over-diagnosis by testing strategies that lower the chance of detecting unimportant lesions
5. Embrace new concepts for how to approach cancer progression and prevention

What Can Be Done?
- Recognize that non-palpable mammographically detected breast cancers have a high chance of being IDLE
  - AVOID OVERTREATMENT
- Invest in better biomarkers of extremely low metastatic potential
- Don’t overscreen and don’t overbiopsy
  - Minimize detection of IDLE conditions
  - Don’t make low grade DCIS a target of early detection

Encourage Your Patients to Participate in observation trials for DCIS
- DCIS is NOT an emergency
- Consider observation
- Consider a trial
  - CALGB; Preoperative Letrozole x 6 months
  - EORTC trial in development
  - ATHENA registry to open June 2014

Rethink Prevention Models

<table>
<thead>
<tr>
<th>Screening</th>
<th>Test Result</th>
<th>Patient</th>
<th>Physician</th>
</tr>
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<tbody>
<tr>
<td>Yes</td>
<td>Positive</td>
<td>“Caught in time”</td>
<td>Appreciation from patient</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>Grateful; reassured</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>Not screened</td>
<td>Missed opportunity for early diagnosis</td>
<td>Possible anger from patient; MD malpractice concern</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Outcome</th>
<th>Patient</th>
<th>Physician</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>Cured</td>
<td>Grateful</td>
<td>Appreciation from patient</td>
</tr>
<tr>
<td></td>
<td>Not Cured</td>
<td>“Everything was done”</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>Not cured</td>
<td>“Could more have been done?”</td>
<td>“Should more have been done? WILL be sued?”</td>
</tr>
</tbody>
</table>
The Randomized Screening Trials

- Initiated 30-40 years ago . . .
- Prior to the our understanding of breast cancer subtypes
  - ER, PR, HER2
  - Mammaprint, Oncotype, Intrinsic Subtypes
  - Indolent disease and overdiagnosis
- Prior to our understanding of hereditary risk
  - BRCA, BROCA, SNPs
- Prior to the use of modern breast imaging tools
- Prior to understanding breast density as a risk factor

More Light
Less Heat

The last decade . . .

- Tumor Heterogeneity
  - Ultra low risk to ultra high risk
- Development of prognostic and predictive multigene assays
- Ability to tailor therapy
  - Who benefits from chemotherapy
  - Who benefits from hormone therapy
  - Who benefits from radiation therapy

What Does that Tell Us?

- Women get different types of cancer
  - We no longer treat everyone the same
  - Everyone is not at risk for the same cancer
  - Everyone should not be screened the same way
  - Everyone identified at high risk is not going to benefit equally from the same preventive agents
- Time for a paradigm shift . . .
Implementing Risk-Based Cancer Screening Using an Adaptive Learning Engine

An ATHENA Initiative

Cancer Screening Today
Impacts everybody

BREAST CANCER
- Costs $8-10 billion/yr in U.S. alone
- Little change in 30 years
- Unintended consequences:
  - False positives (75% of biopsies ➞ benign)
  - Overdiagnosis and Overtreatment
- Mired in controversy
- Ripe for disruption
- Stuck in “one size fits all” mentality

“One Size Does NOT Fit All”

Cancer Screening
What it Can Be

- Personalized
- Based on advances
  - Risk-assessment
  - Biology
- Much more cost effective
- Integrated with prevention
- Evidence-based, adaptive, evidence-generating
- More effective at finding “relevant” cancers

USPSTF Screening Guidelines:
*Scientific Evidence, Huge Economic Impact*
Not Adopted in Practice

ASSIGN: Age to Start, Frequency
PROFILE: Tumors at Diagnosis ➞ LEARN
ADAPT: Refine risk, screening assignments

EVERY WOMAN: ANNUAL SCREENING Ages 40-85
Opportunities in our evolving policy and technology landscape

- Supreme Court Decision June 2013
  - Cannot patent the genome
  - Enables emerging technologies to compete and for the market to drive down price
- Next Generation Risk Assessment
  - Risk: BRCA, BROCA, SNPs at high volume - inexpensive
  - Tumor profiling
  - 2D/3D mammography, MRI, breast density
- Affordable Care Act
  - Everyone is covered, no pre-existing conditions
  - Enables the provision of information that would have previously rendered a person “uninsurable”

Genetic “Architecture” of Breast Cancer

- Next Generation Technology
  - BRCA, BROCA at high volume - inexpensive
- Emerging evidence on SNPs
  - Can identify population with low (<6%) lifetime risk
  - Can identify population at higher risk for both HR+ and HR- disease

Opportunities Enabled by Changing Technology and Emerging Data

- Next Generation Technology
  - BRCA, BROCA at high volume - inexpensive
- Emerging evidence on SNPs
  - Can identify population with low (<6%) lifetime risk
  - Can identify population at higher risk for both HR+ and HR- disease

Trial Design: Preference Based Adaptive Learning in Personalized Screening Arm

Risk Based Screening (RBS)
Program Overview

Risk Based Screening: Huge Economic Value
The Athena Breast Health Network is proposing a personalized screening trial. The architecture was built to implement a personalized approach:
- Engine for patient reported outcomes
- Health Questionnaire System on Salesforce
- Automated risk assessment and prevention counseling
- Integrated biospecimen collection
- Standardization across sites: radiology, pathology, treatment

Participating women: 56,000 today → 150,000 by 2016

Risk Based Screening Can Be More Than just an improved screening strategy!

Risk Based Screening
- LEARN who gets what kind of cancer
- CONTINUOUS IMPROVEMENT
- ADAPT/TAILOR
  - Prevention
  - Biopsy
  - Treatment
  - Screening

Profiling of Tumors
- Who is at Risk for What Kind of Cancer: CED→ Tailoring Treatment Based on Biology
  - DCIS
    - Oncotype DCIS
  - Invasive cancer
    - IHC4: ER, PR, Ki-67, Her2
      - Harmonization project across the UC's
      - Expression Profiling
        - Mammaprint Ultralow risk, low risk, high risk
        - Luminal A,B, Her2, Basal

Where Are We in Our Process?
- Building workflow design plan, risk models, communication plan
- Convening partners: Stakeholder Meeting June 2014
  - NCQA (National Committee for Quality Assurance)
  - Salesforce (consumer data collection and integration tools)
  - Scientific Granting Agencies
  - Blue Shield (coverage with evidence development)
  - Genetic Profiling Providers: options for comprehensive testing
- Usher in a disruptive AND replicable model:
  - Adaptive learning in practice → Affordable Effective Healthcare

More Light
Less Heat
UNDERSTANDING THE EVIDENCE . . .
THE POWER TO CATALYZE CHANGE