OVER-DIAGNOSIS OF BREAST CANCER

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OVERVIEW

- Introduction
- Screening Practices and Recommendations
- Treatment of Breast Cancer
- Over-diagnosis of breast cancer
- Next steps?

IMPACT

- 1 in 8 women diagnosed with breast cancer (12%)
- 2.8 million breast cancer survivors
- 2014 estimates from the ACS
  - 232,670 new cancers
    - 62,570 will be in situ
  - 40,000 will die from breast cancer
- 2nd leading cause of cancer death
  - 1 in 36 women

SCREENING PRACTICES

- Various screening modalities make it all more confusing
  - Digital mammogram
  - Tomosynthesis
  - MRI
  - Screening US
- Variable depending on the organization making the recommendation
- Confusion for patients and physicians

CURRENT GUIDELINES

Group	Recommendation
• American Cancer Society	• Yearly starting at 40
• American College of Surgeons	• Supports ACS
• USTF	• Biennial between 50-74 yo

Average Sensitivity-80% (variability based on age, density, etc) Thus a 20% false negative mammography rate

CURRENT TREATMENT RECOMMENDATIONS - SYSTEMIC

- Duration from 6 months to 5 (10) years
  - The longer the therapy the better
- Recommendations are dependent on various factors
  - Estrogen receptors / Progesterone receptors
  - Her-2/neu (0-3+)
  - Stage
  - Age and comorbid conditions
  - Genetic profile of the tumor (Oncotype, Mammoprint, etc)

CURRENT TREATMENT RECOMMENDATIONS - SYSTEMIC

- Chemotherapy
  - Usually Adriamycin based
  - 4-8 cycles depending on regime
- Anti-hormonal therapy (ER/PR)
  - ER/PR positive tumors only
  - SERM vs. AI
    - SERM only possibility for pre-menopausal women (Tamoxifen)
    - AI for pre or postmenopausal women with invasive cancers only
- Biologic agents (Her-2)
  - Invasive cancers only
  - Duration of one year

CURRENT TREATMENT RECOMMENDATIONS – SURGICAL

Primary Tumor

- Breast Conservation v. Mastectomy
  - Stage (ie no T4)
  - Tumor/breast ratio
  - Patient preference
  - Will they get XRT?
  - Cosmesis

Nodal Evaluation

- No SLN / SLN / ALND
  - DCIS v. Invasive cancers
  - Overall pt comorbidities
  - Known axillary disease?
- SLN
  - Invasive cancers
  - DCIS only if getting a mastectomy or discordant path
- ALND
  - Known disease in axilla that is bulky
  - Positive frozen SLN on mastectomy

CURRENT TREATMENT RECOMMENDATIONS - RADIATION

- Indications
  - Post Lumpectomy
    - Almost always – should be though of hand and hand
    - May avoid in the very elderly, significant pulmonary disease, severe co-morbidities
  - Post Mastectomy
    - Tumors ≥ 5cm (T3) or inflammatory BCA/chest wall invasion (T4)
    - ≥ 4 nodes positive (N2) – moving target with great indication for 1-3 nodes

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- Whole Breast
  - Standard
    - About 6 weeks
  - Hypofraction (Canadian)
    - About 2.5-3 weeks
- Partial Breast
  - Mammosite
  - External beam
- Intra-operative
  - Coming soon to the OR
  - One time dose lasting 25-45 minutes
    - Done before closing

OVER-DIAGNOSIS

- Defined as the diagnosis of a neoplasm that never would have clinical significance
  - Could be DCIS in the healthy?
  - Could be invasive in those with poor health and limited survival due to co-morbid conditions?
- Trick is how to tell and how often it really occurs……

ASSESSING FOR OVER-DIAGNOSIS

- Ideally we would compare two populations that only differed by screening v. no screening
  - Does not exist
  - Estimated range in literature 0-54%
- Autopsy studies
- Population based studies

AUTOPSY STUDIES

Study	N	Invasive (%)	In situ (%)	Age 40-70
VA, 1973	70	1.4	4.3	n/a
CA, 1975	67	0	4.5	10 % (DCIS)
Denmark, 1984	77	1.3	14.3	n/a
CA, 1985	101	0	8.9	13 % (DCIS)
Australia, 1985	207	1.4	12.1	n/a
NM, 1987	221	1.8	0	7% (IBC)
Denmark, 1987	109	0.9	14.7	39% (DCIS)

Median Prevalence: IBC 1.3%; Median DCIS 8.9%

Modified from Welch, et al Annals of Internal Medicine Vol 127:11; p 1023-1028

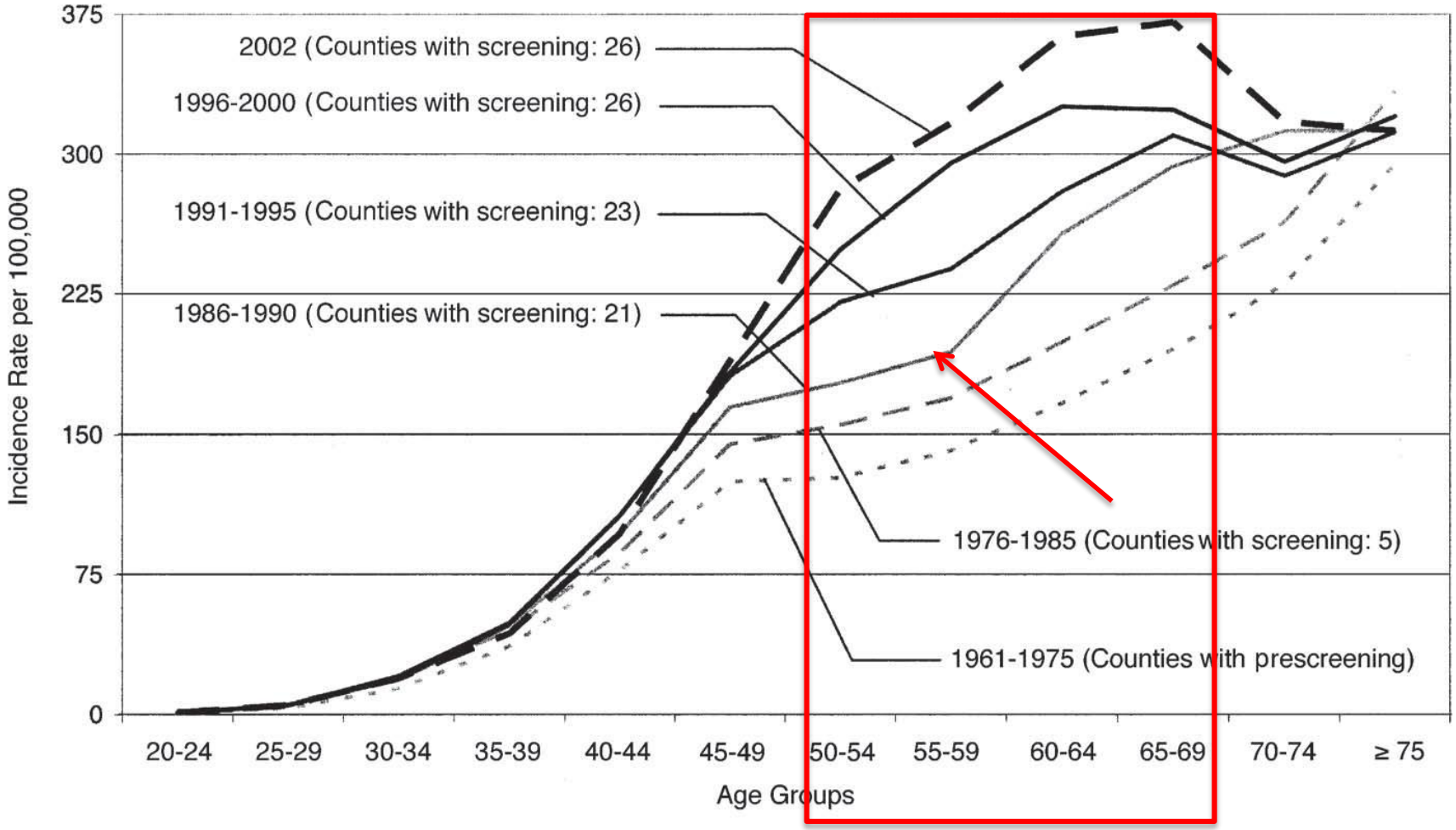
POPULATION-BASED STUDIES

- Prospective evaluation of incidence
- What we should see
  - Initial spike in cancer followed by a fall of incidence to below initiation levels
  - Cumulative incidence should be the same between screened and non-screened
- What we do see is not that!
  - Initial spike without a return to pre-screen incidence

POPULATION-BASED STUDIES – SWEDISH STUDY

- 1985 beginning of screening program
  - Intervals of 18-27 months
- Prevalence period and stabilized period
- In all age groups, there was the expected spike in diagnosis
  - However, 70-74yo returned to expected incidence
    - Lead time?

SWEDISH STUDY

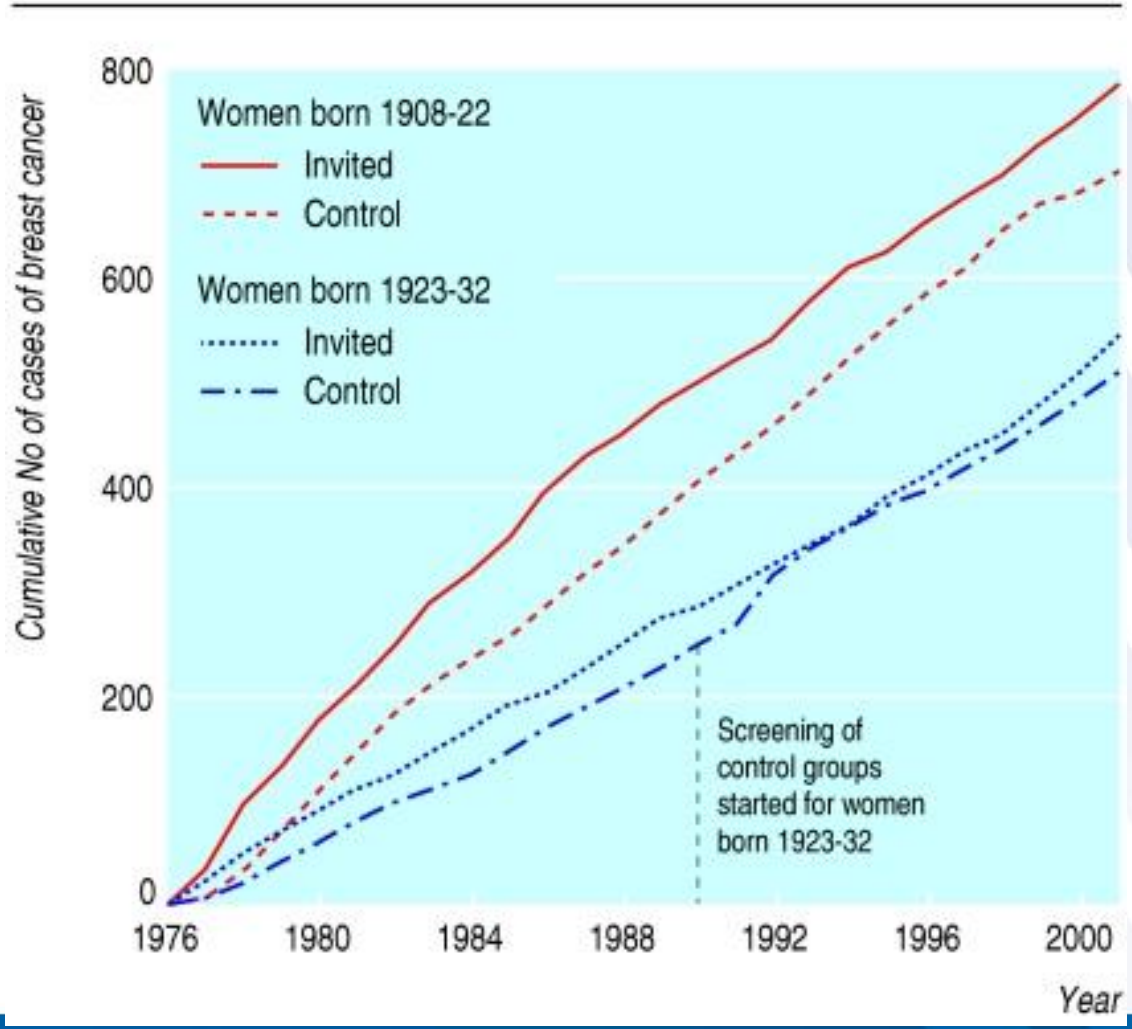


Journal of Clinical Oncology, Vol 22, No 22 (November 15), 2004: pp 4652-4655

POPULATION-BASED STUDIES - MALMO

- 10 year duration (1976)
- Women age 55-69 randomly assigned to invitation to screen (21,088) versus no invitation (21,195)
- Women age 45-54 eventually invited to screen
- 15 years after trial ended, 10% increase in incidence of breast cancer (7% for invasive only)

MALMO



BMJ. 2006 March 25; 332(7543): 689–692.

COCHRAN REVIEW, 2013

- RCT of mammographic screening with no mammographic screening
- 8 trials with 600,000 women age 39-74
- 3 trials with no reduction in mortality (good randomization)
- 4 trials with 25% risk reduction (suboptimal randomization)
- Overall RR is 0.81
- For every 2,000 treated – 1 woman will avoid dying of BCA and 10 women will be treated unnecessarily

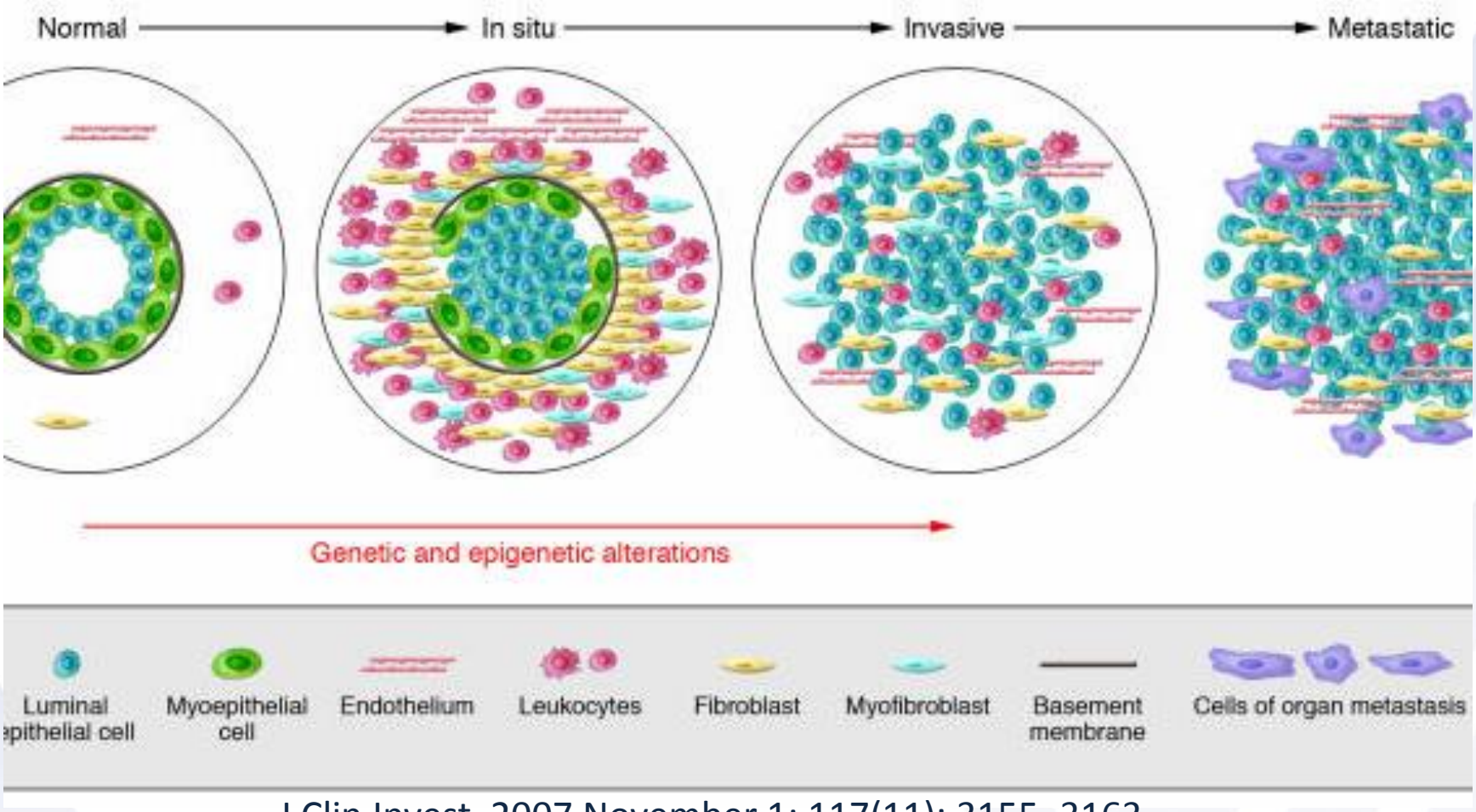
- How do we interpret?
- How do we talk to patients?

- Target DCIS?
- Target pathologist’s diagnostic criteria

DUCTAL CARCINOMA IN SITU (DCIS)

- About 20-25% of new cancer diagnosis
- Proliferation of abnormal epithelial cells within the confines of the basement membrane of the duct without stromal invasion
- Stage 0 breast cancer
  - 98-99% survival

PROGRESSION



J Clin Invest. 2007 November 1; 117(11): 3155–3163

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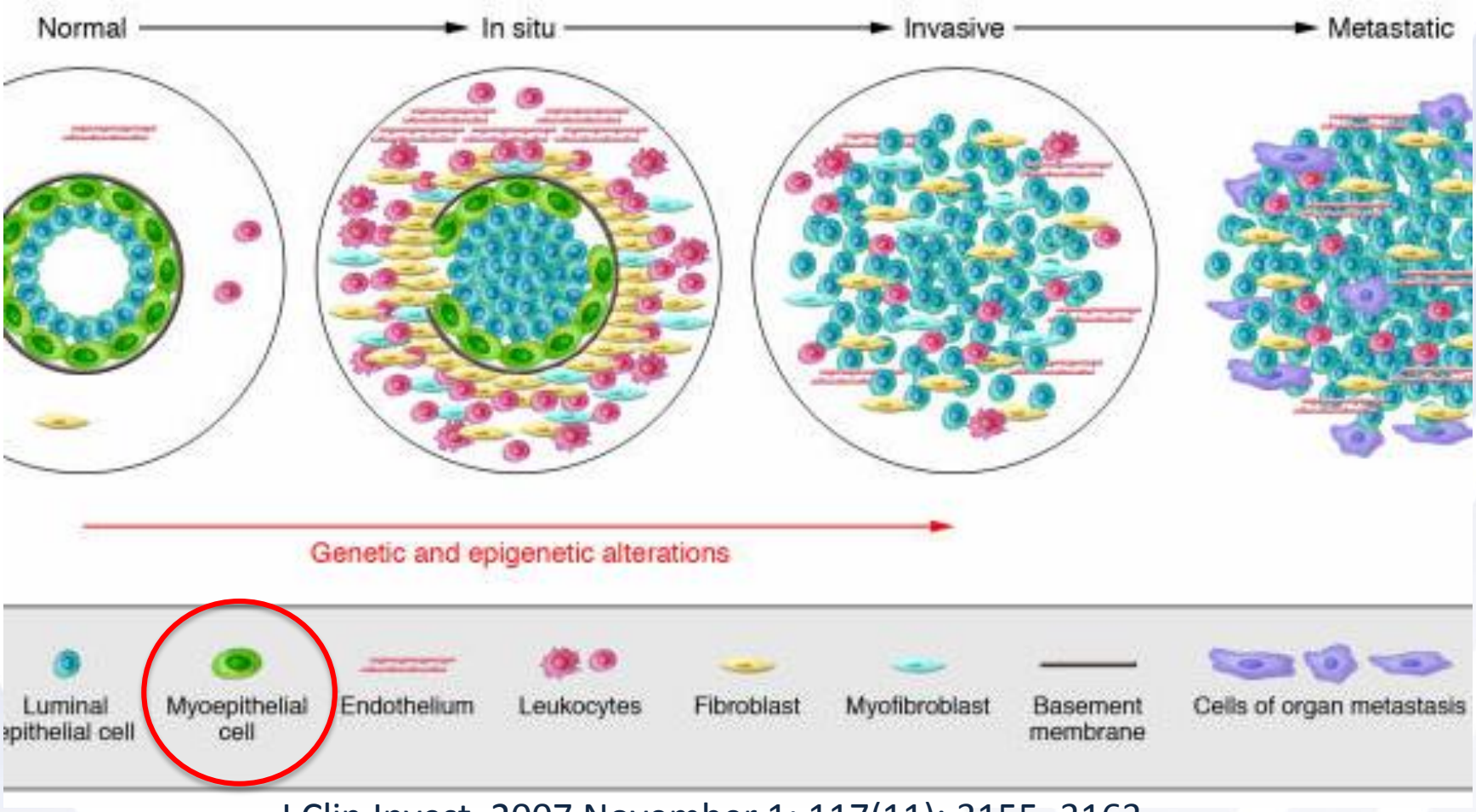

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MYOEPITHELIAL CELLS

- Myoepithelial cells important in progression from non-invasive to invasive
  - Changes in coding of secreted proteins that include basement membrane components
- Decreased CD10 (myoepithelial-cell specific marker) associated with lower Disease Free Survival (DFS)

MOLECULAR MARKERS IN DCIS

Protein – coding genes

- COX-2 and Ki67
  - High expression correlates with high risk of recurrence of invasive and non-invasive
- Rb pathway abnormalities
  - Contribute to invasive?
- ERBB2 and 14-3-3ʒ
  - Contribute to invasive by promoting transition from epithelial to mesenchymal cells

microRNA

- miR-21
  - Targets PTEN, PDCD4, TMI
  - Increase with tumor progression
- miR-145
  - Increase in DCIS compared to ADH

INTRA-TUMOR HETEROGENEITY

- DCIS heterogeneity – positive for p53 and thus mutation in TP53 (Allred, et al)
- Heterogeneity seen in cell lines with expression of CD44 and CD 24 (Park et al)
  - Basal-like tumors high diversity
  - Luminal and Her2 low diversity
  - Intra-tumoral diversity a predictor of invasive progression like in Barrett's esophagus?

MOLECULAR DIVERSITY IN DCIS AND EARLY INVASIVE CANCER

- Gene expression patterns
  - 31 pure DCIS; 36 pure IC; 42 mixed; 6 controls
  - 22% luminal A; 28% luminal B; 15% Her2; 18% basal-like
- Subset of DCIS with gene expressions more similar to invasive cancers than DCIS
  - ER/PR negative; high proliferation; high-grade; Her2 positive (7)
- High levels of EMT-related genes
  - CXCL1, SNAI1, S100A7, MMP1

Muggerud, et al

BIOMARKERS?

- P16/cyclooxygenase 2 (COX-2)/Ki-67
  - 2x increase risk of invasive recurrence
- ER-/Her2+/Ki67+
  - Increase risk of noninvasive recurrence
- Her2
  - May be associated with a higher risk of recurrence but not invasive recurrence

ST GALLEN CLASSIFICATION?

- 458 women with DCIS
- ER/PR positive if greater than 1%; Ki67 high if greater than 14%
- No one had endocrine or chemo post-op
  - Luminal A 186 pts
  - Luminal B (Her2-) 33 pts
  - Luminal B (Her2+) 74 pts
  - Her2+/ER – 61 pts
  - Triple Negative 27 pts
- No statistically significant difference between subtypes for local, regional or distant recurrences

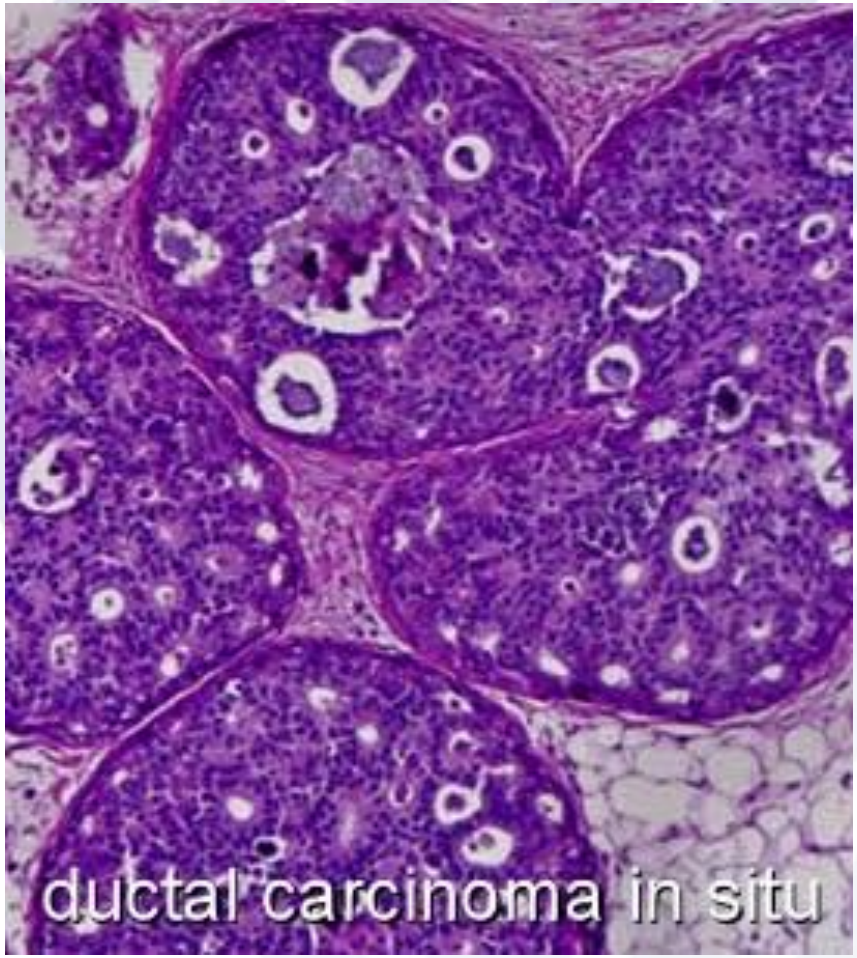
Zhou et al BMC Cancer 2013, 13:512

- AT THIS POINT IN TIME, THERE IS NO CLEAR-CUT WAY TO DISTINGUISH WHICH DCIS WILL BECOME CLINICALLY SIGNIFICANT AND WHICH WILL NOT

DO WE TARGET OVER-SCREENING ANOTHER WAY?

- Pathologic diagnosis
- When should we stop screening mammograms?

PATHOLOGY



PATHOLOGY

- The fine line between ADH and DCIS
- Do we change the nomenclature?
- Do we use Oncotype or some other molecular study?
  - Ideally would help distinguish high risk and low risk DCIS
  - Test DCIS only then you discount the environment which may be equally as important
    - Myoepithelial cell changes, etc

WHEN TO STOP SCREENING MAMMOGRAPHY?

- What are the recommendations?
- How do you tell a patient in a kind way?

MAMMOGRAPHY IN THE ELDERLY

- Randomized trials did not include women older than 74
- Observational studies indicate extending it past 74 for women who are expected to live longer than 10 years
- Modeling studies
  - 2 fewer BC deaths/1000 with biennial screening in 70s
  - 200 false positives/1000
  - 13 over-diagnosis/1000

EXAMPLE

- 74 yo woman
- Co-morbidities:
  - HTN
  - Afib
  - GERD
  - Severe obesity BMI 46
  - Asthma
  - OSA
  - SOB with any exertion
  - h/o “enlarged heart”

- Screening mammogram?
- What is her life expectancy?
- How do you tell her not to screen?

- Bx DCIS – OR for lumpectomy

CONCLUSION

- We likely over-diagnose
- Particularly true with the implementation of screening mammography programs
  - Increase in DCIS diagnosis has not resulted in a decrease in the number of invasive cancers
- May also be because of the persistence of screening mammography in patients whose life expectancy is shortened secondary to co-morbid conditions
- Limited understanding on the progression to clinically significant disease as in DCIS

CONCLUSION

- There are markers that show promise but are not conclusive
- Can not use current grade or classification system to predict those that go on to invasive cancers
- Until we can predict, will need to continue to treat as if clinically significant

THANK YOU