

ANCO's 2011 San Antonio Breast Cancer Symposium Highlights

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Michael Alvarado, M.D. Disclosure

- Advisory Board Member
 - Genomic Health DCIS Study Group

Selected Topics

- Contralateral Breast Cancer Risk BRCA
- Atypical Lesions and Future Risk
- Molecular Assay and DCIS Recurrence

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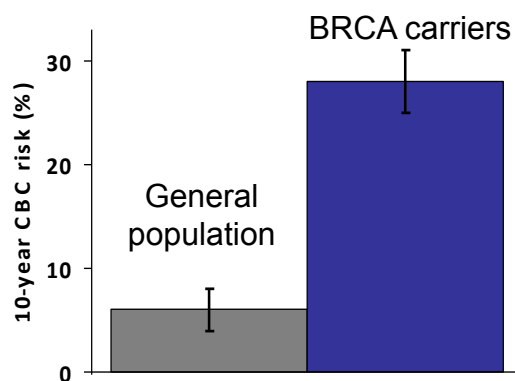
Risk of contralateral breast cancer in BRCA1/2 carriers compared to non-BRCA1/2 carriers in a consecutive patient series

Alexandra J van den Broek, Marjanka K Schmidt,
Rob AEM Tollenaar, Laura J van 't Veer and Flora E van Leeuwen

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Contralateral breast cancer (CBC) risk



1 Adami et al. Cancer 1985;55(3):643-7
2 Harvey et al. Natl Cancer Inst Monogr 1985;68:99-112
3 Liebens et al Eur J Cancer 2006

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CBC risk in BRCA carriers: Gaps in knowledge

- CBC risk estimates in a large unselected population
- Interaction with non-genetic modifiers

It is important to provide precise risk estimates of CBC and identify factors which predict the risk of CBC in this group of high risk women

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Study population: BOSOM

Breast cancer Outcome Study Of Mutation carriers

- Consecutive patient series
- Invasive breast cancer, n = 7495
- Diagnosed < 50 years
- 1970 - 2003
- 10 different hospitals throughout The Netherlands
- Clinico-pathological data: Medical files, Medical Registries and the Netherlands Cancer Registry
- n = 5065 with germline DNA
- Median follow-up time: 9.2 years

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BRCA mutation analysis

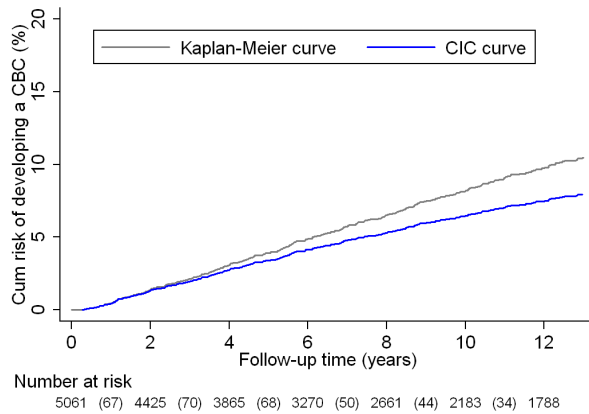
- Germline DNA: isolated from FFPE tissue blocks
- BRCA1/2 mutations: Allelic discrimination or Fragment length analyses, sequencing was used to confirm the mutations
- % of known pathogenic BRCA1/2 mutations in The Netherlands captured with our methods:

BRCA1	BRCA2	Overall
78%	51%	70%

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Cumulative risks of CBC

Cumulative incidence curve accounting for competing risks



- KM- curve / Cox regression models over-estimate the risk
- CIC- curves are modeled by Fine and Gray method
- All models adjusted for age at diagnosis

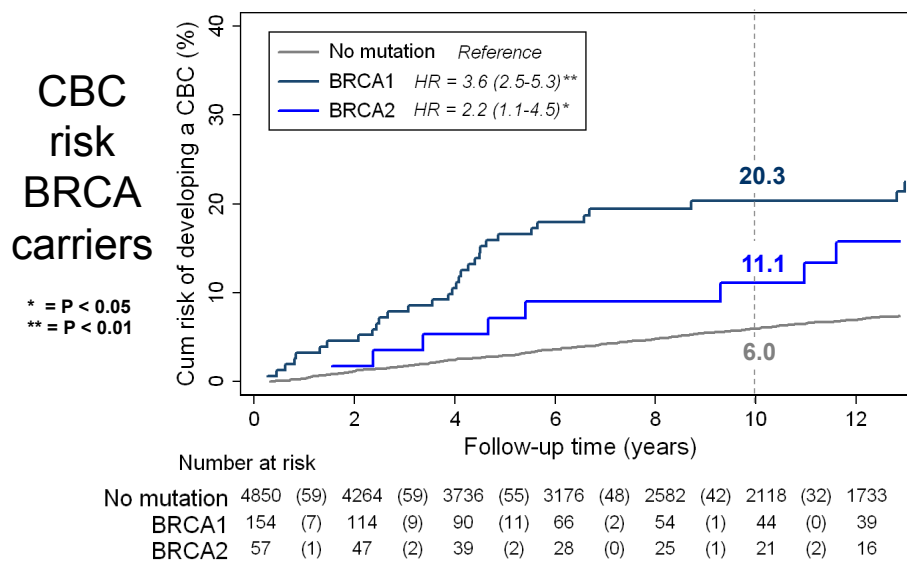
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BRCA mutation prevalence

BOSOM cohort

BRCA mutation status	N	%
No mutation	4850	95.8
BRCA1	154	3.04
BRCA2	57	1.13

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Non-genetic modifiers which predict the risk of CBC in carriers

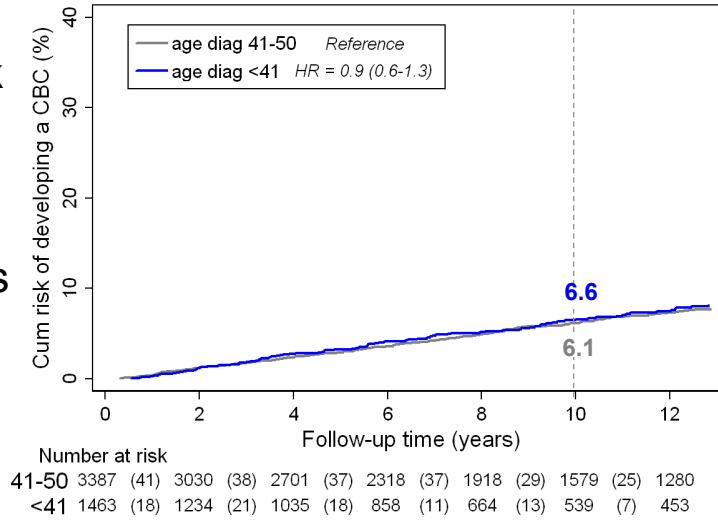
Is it possible to define subgroups based on characteristics of the first BC?

- Age at diagnosis
(<41 vs 41-50)
- Triple negative (TN) status
(ER- & PR- & HER2- vs ER+ and/or PR+ and/or HER2+)

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**CBC risk
non-
carriers:
age at
diagnosis**

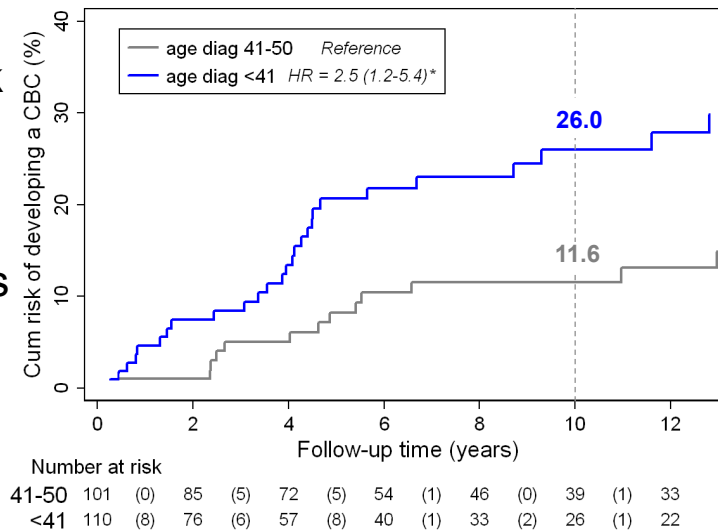
P = ns



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**CBC risk
BRCA
carriers:
age at
diagnosis**

* = P < 0.05



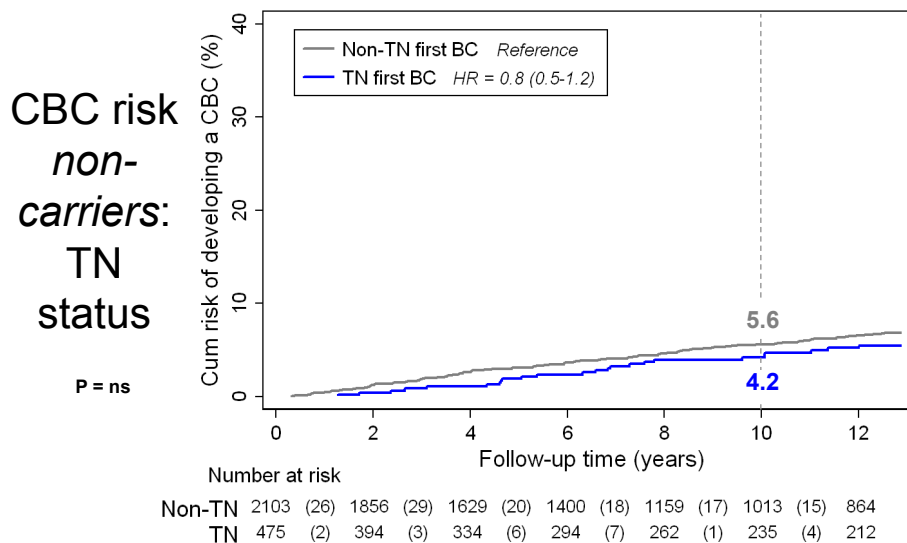
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Non-genetic modifiers which predict the risk of CBC in carriers

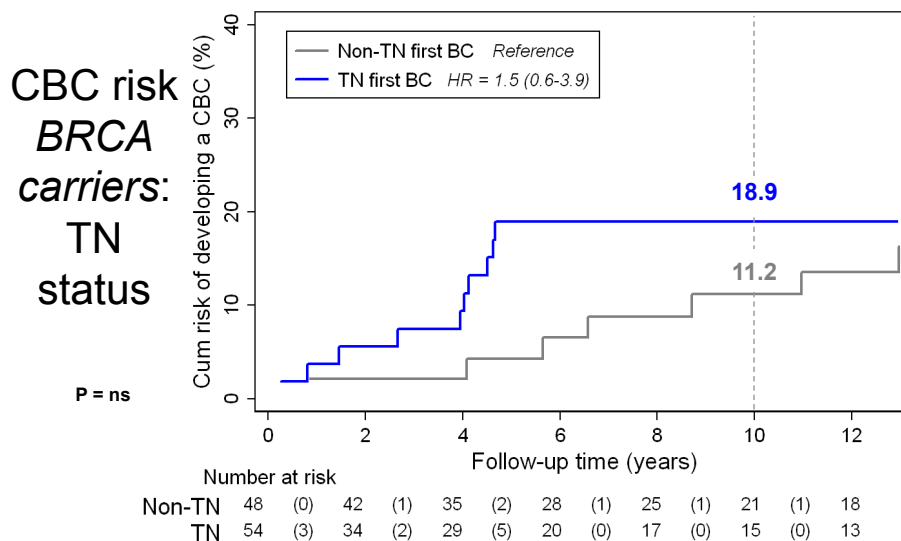
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- Age at diagnosis (<41 vs 41-50)
- Triple negative (TN) status (ER- & PR- & HER2- vs ER+ and/or PR+ and/or HER2+)

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CBC risk in subgroups: *non-carriers*

Age diagnosis first BC	Receptor status first BC	Total N	# CBCs	Cum 10-year risk	95% CI
Non-carriers					
41-50	Non-TN	1499	95	5.8	4.7-7.1
<41	Non-TN	604	35	5	3.4-7.1
41-50	TN	308	19	5	2.9-7.9
<41	TN	167	5	2.6	0.9-6.1
BRCA mutation carriers					
41-50	Non-TN	32	3	3.5	0.3-15.1
<41	Non-TN	16	4	26	8.0-44.8
41-50	TN	20	3	15	3.7-33.5
<41	TN	34	7	21.2	9.4-36.2

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CBC risk in subgroups: *BRCA* carriers

Age diagnosis first BC	Receptor status first BC	Total N	# CBCs	Cum 10-year risk	95% CI
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<41	TN	34	7	21.2	9.4-36.2

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CBC risk dependant on therapy first BC?

Chemo- / hormonal therapy	Total N	# CBCs	Cum 10-year risk	95% CI	Total N	# CBCs	Cum 10-year risk	95% CI
Non-carriers				Carriers				
No	2069	152	6.7	5.7-7.9	78	18	20	11.9-30
Yes	2091*	105	5	4.0-6.1	102**	17	17	10.2-25

* Of which 632 (22 CBC) were treated with hormonal therapy

** Of which 11 (1 CBC) were treated with hormonal therapy

- Adjustment for therapy (chemo and/or hormonal) given for the first BC did not materially change the previous results

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Conclusions BRCA carriers

10-year cumulative risk for CBC

- Non-carriers: 6%
- BRCA1 carriers: 20%
- BRCA2 carriers: 11%

Subgroups of BRCA carriers:

Low risk subgroup	<i>Patients with a non-TN first BC diagnosed between ages 41-50</i>	3.5 %
Higher risk subgroups	<i>Patients with a TN first BC diagnosed between ages 41-50</i>	15 %
	<i>Patients with a first BC diagnosed under age 41</i>	26 %

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Discussion / Future research

- Other adjustments did not change the results:
 - Year of diagnosis of the first BC
 - Therapy given for the first BC (Chemo- / hormonal therapy)
- Similar results as for TN-status are seen for ER-status
- Similar risk estimates seen in BRCA1 mutation carriers alone

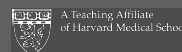
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Clinical relevance

- Improving personalized surveillance after BC
- Improving personalized treatment choices
- Contribution to the understanding of the etiology of BC

If confirmed in other studies, age criteria and receptor-status of the first breast tumor may be included in guidelines for prophylactic measures and screening in the follow-up of BRCA1/2 mutation carriers

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Clarifying the Risk of Breast Cancer in Women with Atypical Breast Lesions

SB Coopey, E Mazzola, JM Buckley, J Sharko, AK Belli, EMH Kim, F Polufriagino, G Parmigiani, JE Garber, BL Smith, MA Gadd, MC Specht, AJ Guidi, CA Roche, KS Hughes

Division of Surgical Oncology, Massachusetts General Hospital, Boston, MA; Department of Biostatistics & Computational Biology, Dana-Farber Cancer Institute, Boston, MA; Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA; Department of Pathology, Newton-Wellesley Hospital, Newton, MA



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Certain pathologic diagnoses significantly increase breast cancer risk

- Atypical ductal hyperplasia (ADH)
- Atypical lobular hyperplasia (ALH)
- Lobular carcinoma in situ (LCIS)
- Borderline DCIS/Severe ADH

Objectives

Clarify level of risk by diagnosis

Evaluate the efficacy of chemoprevention

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Methods

- **All electronically available pathology 1987-2010**
 - Mass General, Brigham & Women's, Newton Wellesley
- **Natural Language Processing** (Clearforest, Waltham, MA)
 - Atypia diagnoses verified by human reader
- **All women diagnosed with ADH, ALH, LCIS, or Borderline DCIS**
 - No prior or concurrent breast cancer
 - Intact breasts
- **Trumping order for maximum diagnosis**
 - Borderline DCIS > LCIS > ALH > ADH
- **Use of chemoprevention agents identified by chart review**
 - Yes, No, Unknown
- **Effect of chemoprevention analyzed from 1999 forward**

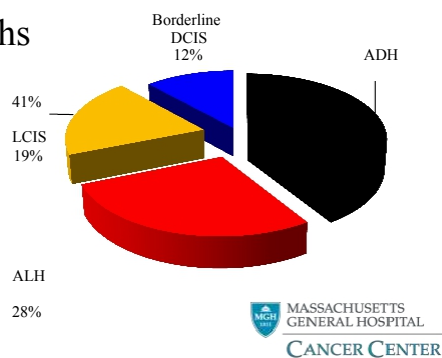
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Results

- **76,333 breast pathology reports**
 - 42,950 individuals
- **2942 women with atypical breast lesions**
 - Mean Age Dx: 53 years (range: 19-93)
 - Mean FU all: 66 months



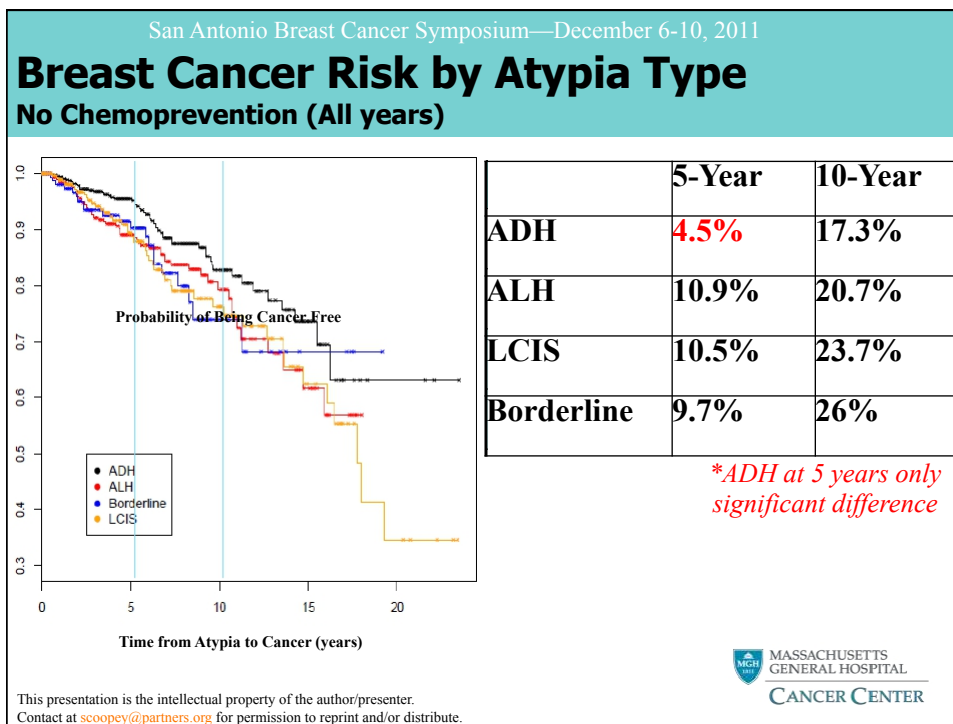
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Estimated 5 and 10-Year Breast Cancer Risks Based on Atypia Type

Atypia Type	5-Year Cancer Risk	10-Year Cancer Risk
ADH (n=1199)	4.8%	14.8%
Borderline (n=345)	7.1%	14.5%
ALH (n=828)	9.4%	20.2%
LCIS (n=570)	8.7%	16.3%

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Laterality of Cancer No Chemoprevention (All years)

Number of Cancers	Ipsilateral Cancer	Contralateral Cancer	Bilateral Cancer	Side Unknown
Borderline (n=21)	47.6%	42.8%	4.8%	4.8%
LCIS (n=45)	55.6%	37.8%	4.4%	2.2%
ADH (n=57)	59.6%	38.6%	1.8%	0%
ALH (n=61)	60.7%	37.7%	0%	1.6%

Significantly more ipsilateral cancers for all atypia types combined (p<0.005)

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Invasive vs. DCIS

No Chemoprevention (All years)

Number of Cancers	Invasive Cancer	Non-Invasive Cancer
ADH (n=57)	47.4%	52.6%
Borderline (n=21)	57.1%	42.9%
ALH (n=61)	68.9%	31.1%
LCIS (n=45)	71.1%	28.9%

- *invasive vs non-invasive cancer*
 - **ADH and Borderline:** *No significant difference*
 - **ALH and LCIS:** *p<0.001*



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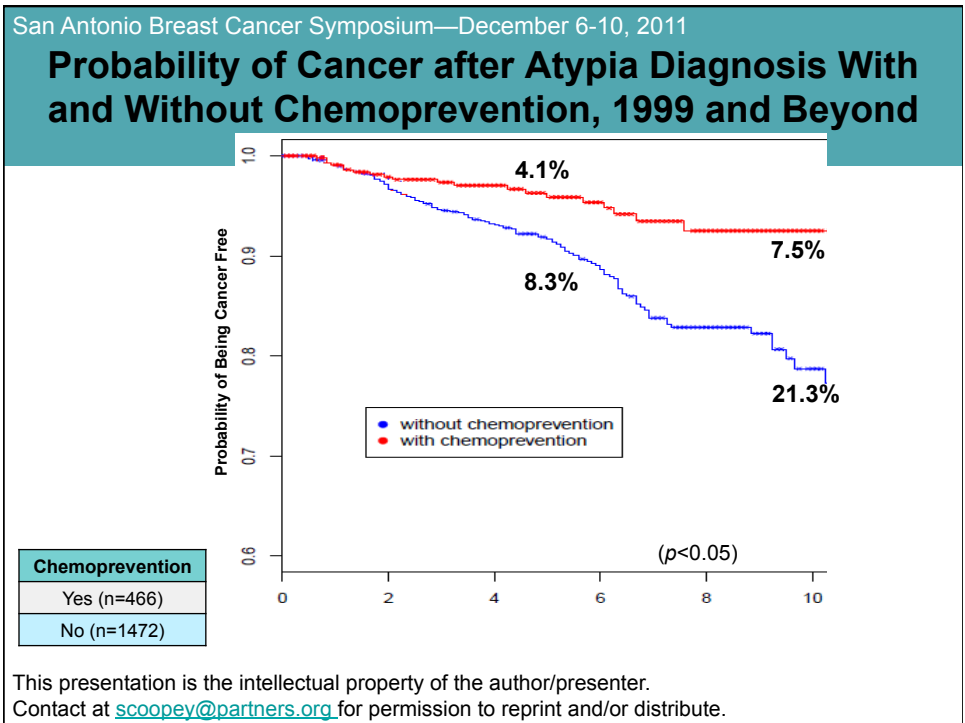
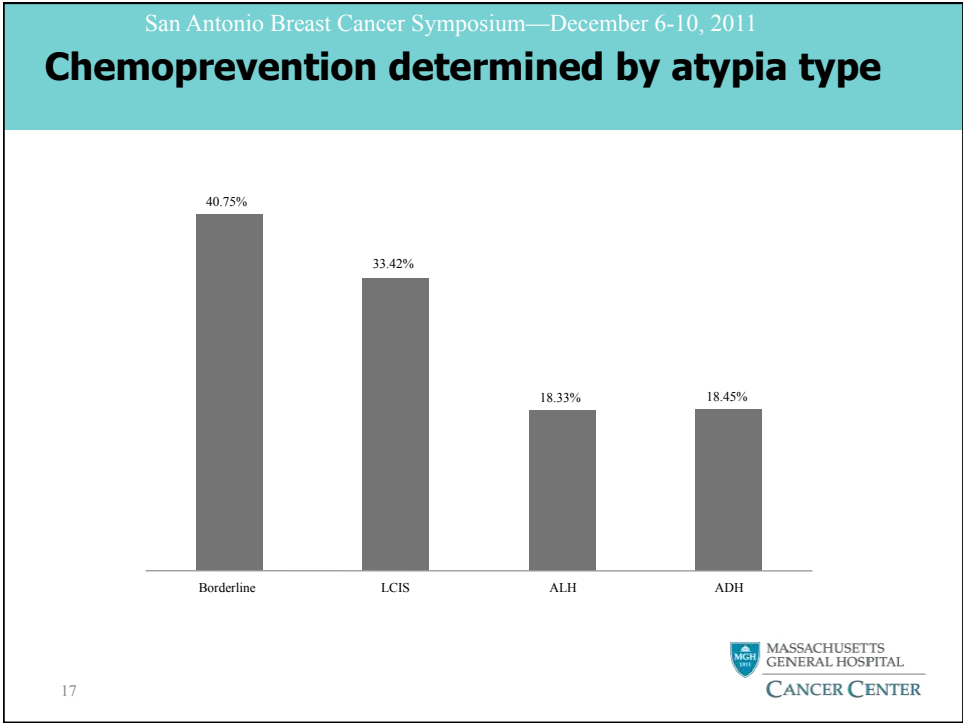
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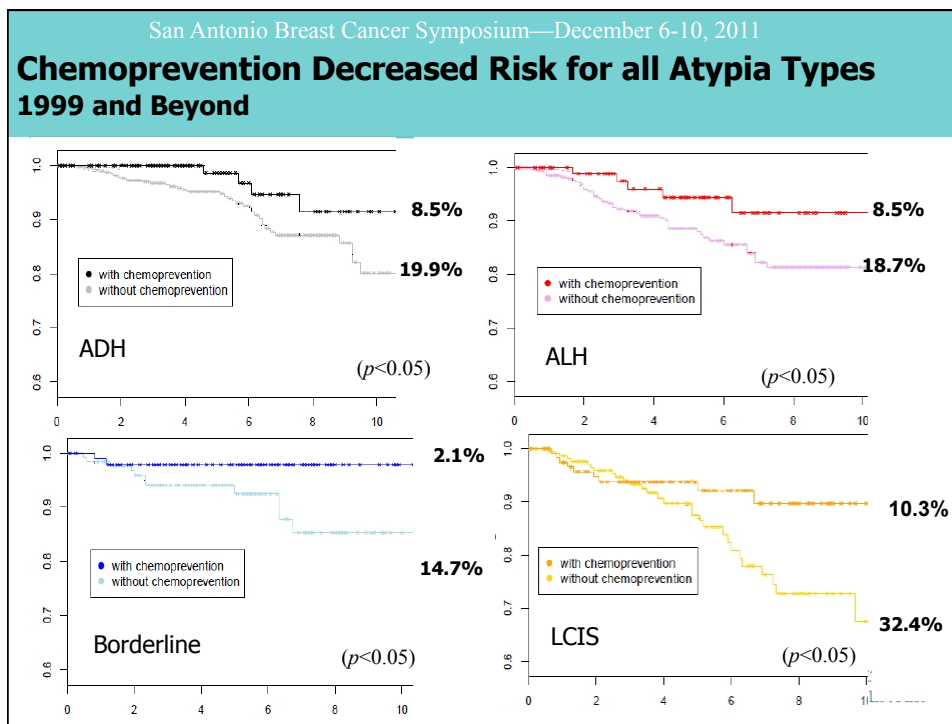
Results: Chemoprevention

- **2460 patients 1999 and beyond**
 - 466 (18.9%) treated
 - » Tamoxifen, raloxifene, and/or exemestane
 - » Any duration
 - 1472 (59.8%) patients not treated
- 522 (21.2%) patients with data unavailable



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Conclusions

- ADH, ALH, LCIS, and Borderline DCIS increase a woman's risk of breast cancer to a similar amount
- Chemoprevention for all atypia types significantly reduces breast cancer risk at 5 and 10 years
- Increased use of chemoprevention for patients with atypia will significantly decrease cancer risk

This data will be used to create a better model of breast cancer risk prediction based on atypia type and use of chemoprevention

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**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**

**Solin LJ, Gray R, Baehner FL, Butler S, Badve
S, Yoshizawa C, Shak S, Hughes L, Sledge G,
Davidson N, Perez EA, Ingle J, Sparano J,
Wood W**

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

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DUCTAL CARCINOMA IN SITU: BACKGROUND

45,000 new cases in 2010 in U.S. (estimated)

**Most patients (~ 60-70%) eligible for breast conservation surgery
(lumpectomy)**

- Radiation and tamoxifen reduce risk

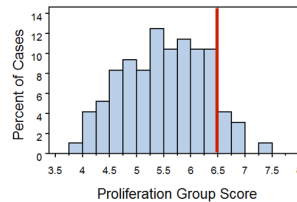
**Reliable methods to select treatment with surgery alone have not
been established using clinical and pathologic factors**

**NIH State-of-the-Science recommendation:
“Develop and validate risk stratification models....”
Allegra, JNCI, 2010**

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NEW DCIS SCORE: DEVELOPMENT

- A genomic-based score to predict local recurrence, regardless of adjuvant tamoxifen, was desired
- Based on prior studies, a DCIS Score algorithm was developed
 - Selected a subset of genes from *Oncotype DX* Recurrence Score that were prognostic in tamoxifen treated and untreated patients
 - No thresholding for proliferation gene group for DCIS Score
 - Different from Recurrence Score (thresholded at score 6.5)
 - Proliferation lower in DCIS (92% < 6.5) compared to invasive disease

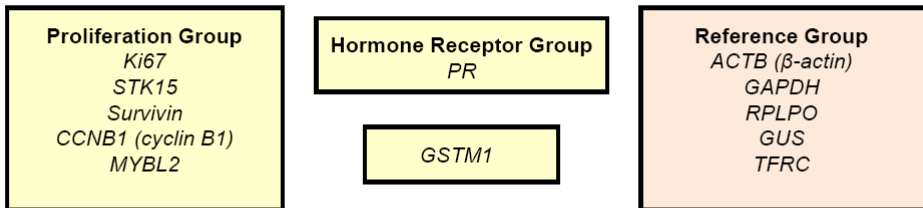


GHI data on file

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DCIS SCORE



DCIS Score (0 – 100) evaluated 2 ways:

- Continuous variable
- 3 prespecified risk groups:
 - Low < 39
 - Intermediate 39 – 54
 - High ≥ 55

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ECOG E5194 (PARENT STUDY)

Prospective multicenter study 1997-2000 (n = 670)

Cohort 1: Low/intermediate grade, size \leq 2.5 cm

Cohort 2: High grade, size \leq 1 cm

Study treatment

- Surgical excision
- Minimum 3 mm negative margin width
- No radiation
- Tamoxifen option beginning May 2000

Reported outcomes at 5 and 7 years (Hughes, JCO, 2009)

- Currently 10-year outcomes

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PRESPECIFIED STUDY OBJECTIVES

Primary:

To determine whether there is a significant association between the DCIS Score and the risk of an ipsilateral breast event (IBE)

Secondary:

To determine whether the DCIS Score provides value beyond standard clinical and pathologic factors

Conditional (if DCIS Score validated):

To evaluate the Recurrence Score as a predictor of risk of an ipsilateral breast event (IBE)

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METHODS FOR DCIS SCORE VALIDATION STUDY

- **Prospective-retrospective study design**
Prespecified: Study objectives, population, laboratory assays, endpoints, statistical methods
- **Oncotype DX assay performed (n = 327; 49%)**
Standardized methods for 21 gene assay
Central pathology review
Calculated: DCIS Score and Recurrence Score
- **Study endpoint: Ipsilateral breast events (IBE)**
1° Endpoint: Any IBE (DCIS or invasive carcinoma)
2° Endpoints: Invasive IBE
DCIS IBE

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PATIENT AND TUMOR CHARACTERISTICS

<u>Characteristic*</u>	<u>Number</u>
Patient age	61 years (Median)
Postmenopausal	248 (76%)
Tumor size	7 mm (Median)
Tumor size \leq 10 mm	260 (80%)
Negative margins \geq 5 mm	214 (65%)
Tamoxifen use	96 (29%)
ER positive (RT-PCR)	318 (97%)
Study cohort: Cohort 1	273 (83%)
Cohort 2	54 (17%)

*Similar to parent trial for all variables except for tumor size

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PRIMARY ANALYSES OF THE RISK FOR AN IPSILATERAL BREAST EVENT (IBE)

	Hazard Ratio* (95% CI)	P value
Primary Analysis		
DCIS Score	2.34 (1.15, 4.59)	0.02
Tamoxifen use	0.56 (0.24, 1.15)	0.12
Conditional Analysis		
Recurrence Score	0.70 (0.15, 2.65)	0.62

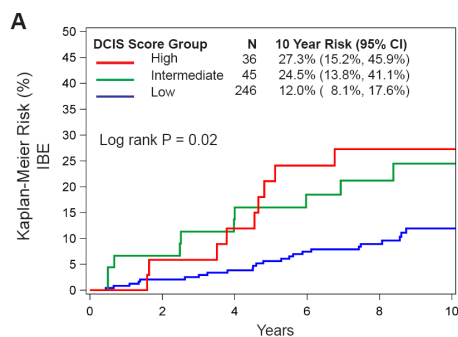
*Hazard ratio is for a 50 point difference

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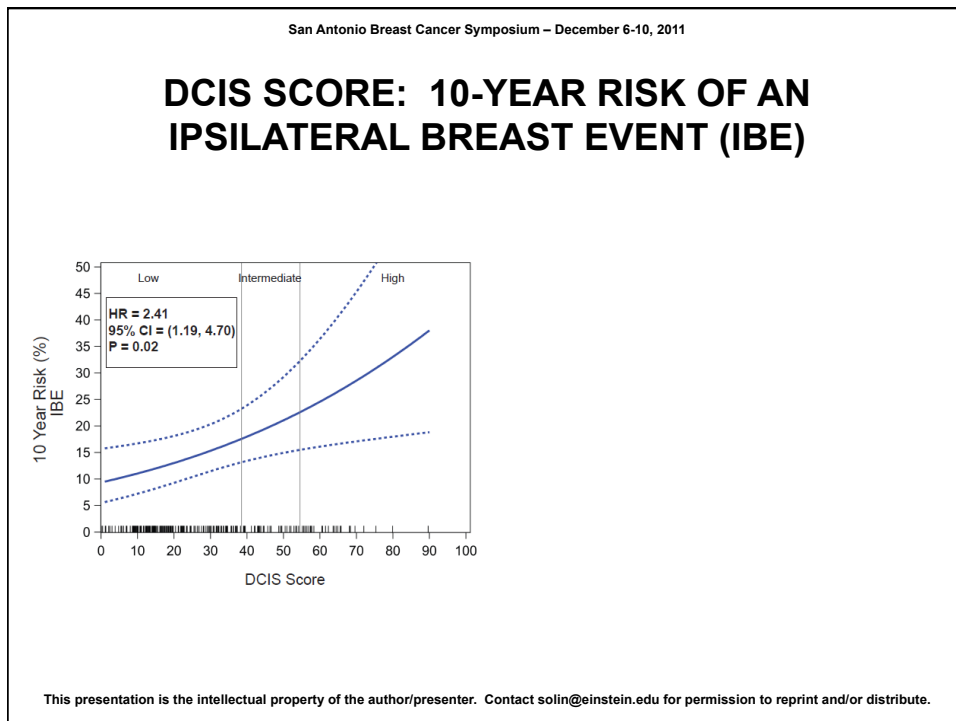
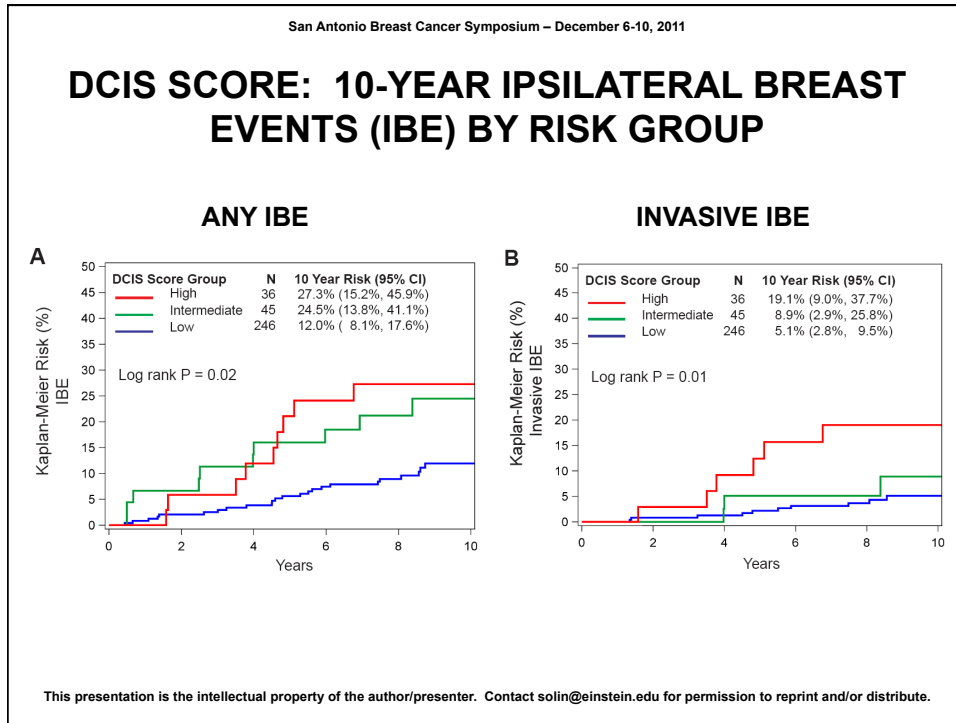
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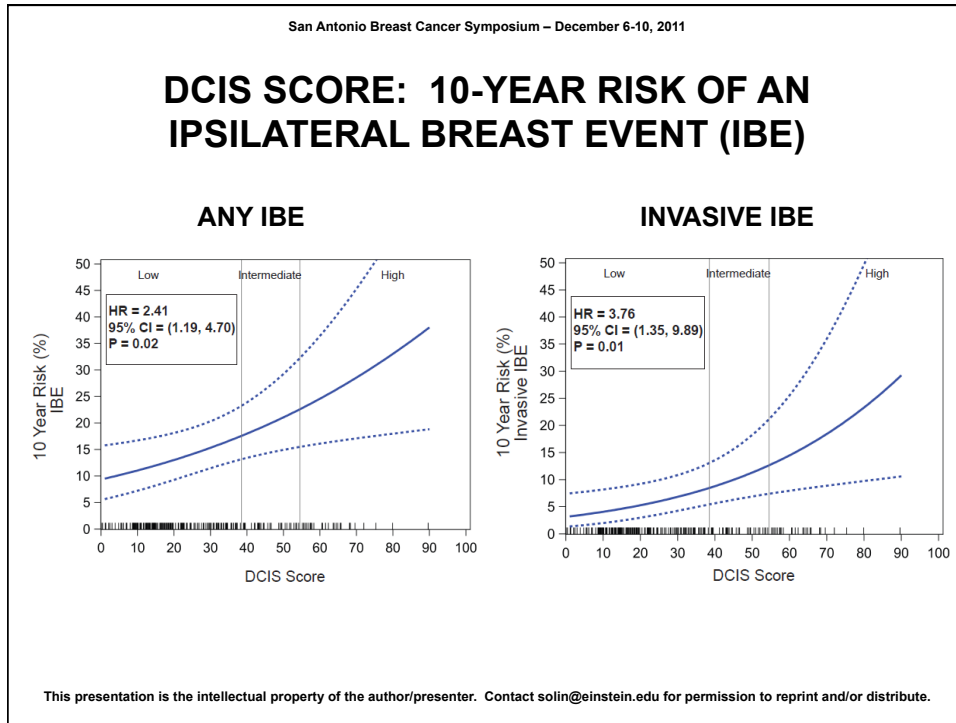
DCIS SCORE: 10-YEAR IPSILATERAL BREAST EVENTS (IBE) BY RISK GROUP

ANY IBE



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MULTIVARIABLE MODELS OF RISK FOR IBE

	Hazard Ratio (95% CI)	P value
Excluding the DCIS Score		
Tumor size	1.54 (1.14, 2.02)	0.01
Postmenopausal	0.49 (0.27, 0.90)	0.02
Including the DCIS Score		
DCIS Score	2.41 (1.15, 4.89)	0.02
Tumor size	1.52 (1.11, 2.01)	0.01
Postmenopausal	0.49 (0.27, 0.90)	0.02

For study cohort, surgical margins, grade, comedo necrosis, and DCIS pattern, all $p > .46$. For tamoxifen, $p = .09$.

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SUMMARY: DCIS SCORE

- 1. Present study validates the DCIS Score as a predictor of an ipsilateral breast event (IBE) and invasive IBE**
- 2. DCIS Score quantifies 10-year risk of IBE**
 - Continuous variable or 3 risk groups**
- 3. DCIS Score provides independent information on IBE risk beyond clinical and pathologic variables**
 - Including tamoxifen, grade, and negative margin width**
 - Identifies underlying tumor biology**
- 4. DCIS Score provides a new clinical tool to guide treatment selection for patients with newly diagnosed DCIS**

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Poster Discussion

SABCS 2011

Vacuum assisted biopsies of Ductal Carcinoma in situ and concordance with post-operative histology: implications for the Low risk DCIS Trial

Soni Soumian, Sue Down, Fozia Roked, Shalini Chaudhri, Adele Francis

Background

The enormous increase in the diagnosis of Ductal carcinoma in situ (DCIS) by the NHS Breast screening has not led to an expected decrease in the incidence of invasive breast cancer. It is not clear if all grades of DCIS progress inevitably to invasive cancer if left untreated. There is recognition that DCIS is over-treated, as if left alone may not cause harm during the woman's lifetime. In the absence of new clinical trial data, surgery still remains the universal treatment.

Recently a randomized trial called the Low risk DCIS Trial has been proposed which intends to specifically compare the current treatment of low grade DCIS to surgery with active monitoring using annual mammography. In order to effectively implement this, concordance between diagnostic biopsy and excision histology is vital and therefore vacuum assisted minimotome biopsy (VAB) and a central pathology review of diagnostic biopsy specimens prior to randomization will be mandatory.

Therefore, in this study, we assessed the concordance between diagnostic biopsies performed by VAB technique and the post operative histology for DCIS in our institution.

Low Risk DCIS Trial Pathway

Results

Results

> In the **Low grade group**, the concordance with final histology was 74% (17/23). In this group, the diagnosis was upgraded to intermediate grade in 17% (4/23) and invasive carcinoma in 9% (2/23).

> Further analysis of the results in the Low grade group that upgraded to invasive cancer (2/23) revealed that one of the patients had a ultrasound diagnosed mass (7 mm macrocalcification within the mass) which would exclude the patient from the Low risk DCIS trial.

> The other patient on final histology had a 1.3 mm lobular carcinoma (low microcalcification on mammogram) within the DCIS.

Materials & Methods

Retrospective data of all diagnostic breast biopsies specifically using the VAB technique with the primary diagnosis of DCIS from year 2001 to 2010 in our institution was collected. Both screening and symptomatic patients were included.

Concordance between diagnostic histology and post operative excision histology was assessed for high, intermediate and low grade DCIS. Demographic details and potential factors influencing concordance including number of cores taken and lesion size were also collected for analysis.

Inclusion Criteria

- Low risk DCIS - Vacuum assisted with histology confirmed by Central pathology review
- Asymptomatic

Exclusion Criteria

- Suspicious mass
- Mass lesion on Mammography
- Mass lesion on Ultrasonography

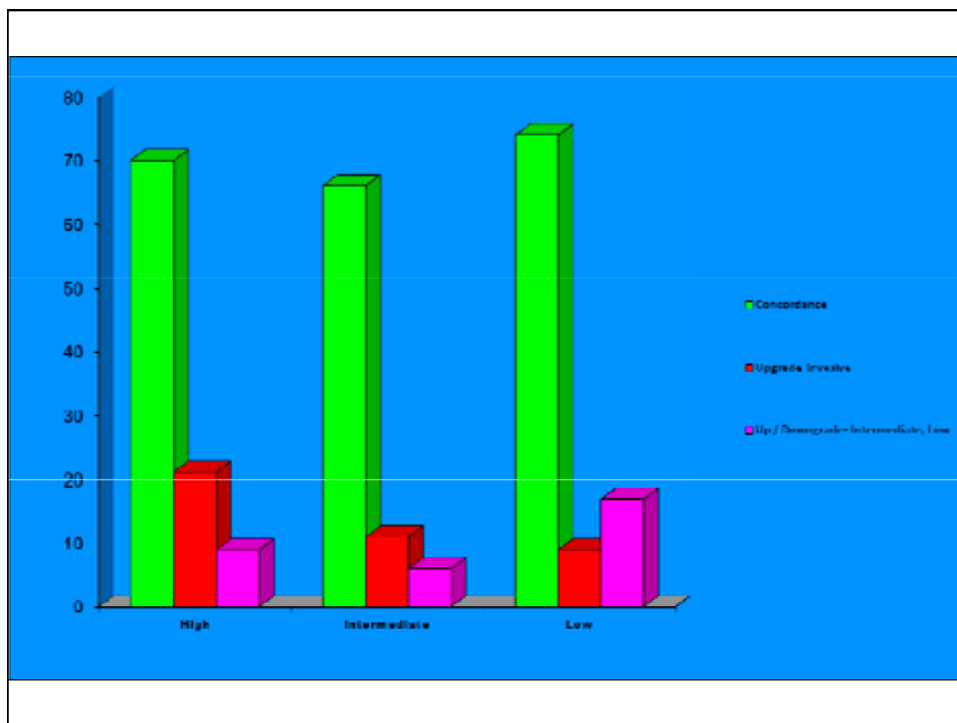
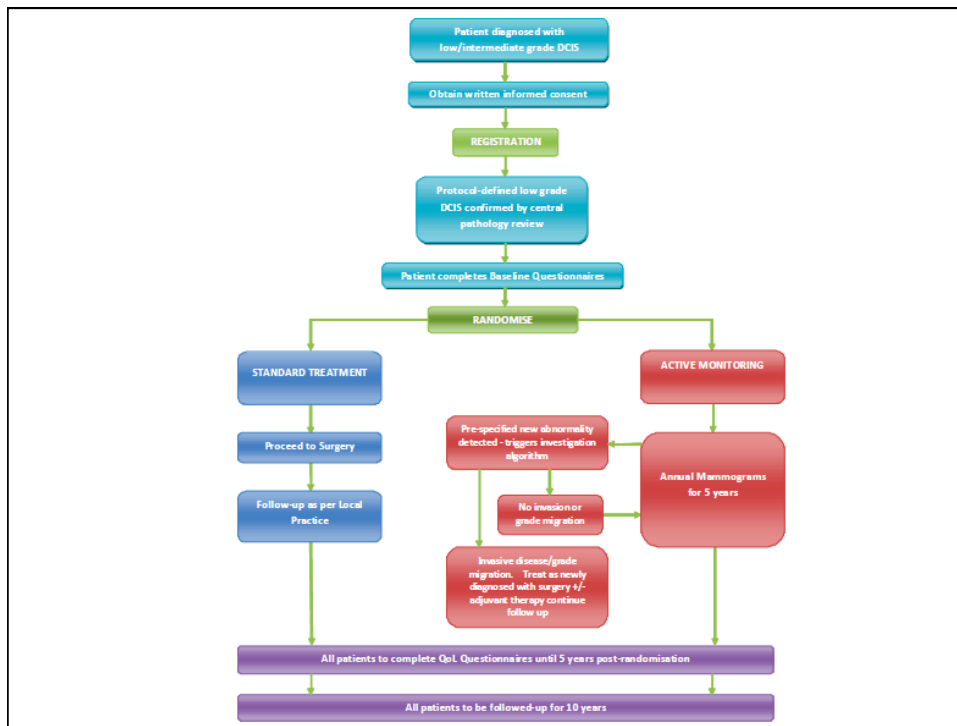
Conclusions

> Concordance was the highest in the low grade DCIS group in this series and to our knowledge the first to be reported using specifically large volume biopsies done using VAB techniques.

> These results and concordance audit data from other centres in the UK, will be used to trial pathologists to write protocols for the Low risk DCIS trial.

Determine Concordance Core Biopsy and Excision

- UK Trial to evaluate “active monitoring of Low Grade DCIS
- Retrospective analysis of consecutive Core Biopsy for DCIS compared to surgical excision



Thank you