

# Meeting the Research Challenges: Update on Current Population-Level DCIS Research

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Ductal Carcinoma In Situ: Strategies for Integrating Tumor Biology and  
Population Sciences

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# Outline

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- Population-level studies and the research challenge
- Summary of current population-level research
- Preliminary findings of a population-level DCIS biomarker study
- Strategies for moving forward

# How can Current Population-Level Studies help meet the Research Challenge?

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- Secular trends in incidence, treatment and mortality
- Characteristics of DCIS tumors in general population (eg, HER2 status)
- Etiology of DCIS and different DCIS subgroups
- Prognostic value of patient and clinical factors, pathologic features, and standard tumor markers
- Development of prognostic index (combination of factors)
- Populations for discovery and validation of new markers

# Recent/Ongoing Population Studies on DCIS

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Type	Number	Main Factors of Interest
<u>Observational</u>		
Descriptive	>20	Incidence, treatment , mortality, pathologic features (subtype, size)
Quality of Life	8	Psychosocial, behavioral, sexual, physical
Risk factors for DCIS	8	Reproductive factors, family hx, lifestyle pesticides, medications, BRCA1/2
DCIS outcome/prognosis		
Treatment/clinical	>20	Mastectomy, excision + XRT, excision alone, margins, size, grade, necrosis, age
Risk factor	7	Reproductive factors, family hx, lifestyle mammographic density, BRCA1/2, pathologic features, tumor markers
<u>Randomized clinical trials</u>		
Phase III trials	9	Exc +/- XRT, Exc and XRT +/- Tam, Exc and XRT +Tam or AI, WBI vs PBI

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# Relatively few studies of DCIS –Why?

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- Up until the mid-1980s, rarely diagnosed, and even now relatively small numbers.
- Breast cancer researchers interested primarily in risk factors for invasive cancer; same for outcome studies.
- High risk of local recurrence, but low risk of breast cancer mortality.
- Few new treatments to evaluate.
- Small tumors, so minimal tissue for marker studies.

# Recent Descriptive Studies of Incidence and Treatment

Study	Population	Ages	No. Cases	Dx Years	Description
Baxter, 2004	US-SEER	18+	25,206	1992-1999	Trends in DCIS treatment
Katz, 2005	LA County Detroit	All	659	2002	Patterns and correlates of treatment for DCIS
Kricker, 2004	New South Wales	All	2109	1995-2000	Patient and pathology characteristics of DCIS pts
Li, 2006	US - SEER	All	37,692	1988-2002	Rates of Inv Cancer after DCIS and LCIS
Rakovitch, 2007	Ontario Breast Screening Program	All	727	1991-2000	Treatment patterns for DCIS
Sumner, 2007	Florida Cancer Data	All	23,810	1981-2001	Incidence and treatment patterns

# Quality of Life Studies

Study	Population	No. Cases	Dx Years	Quality Question
Claus, 2006	SEER Connecticut	696	1994-1998	QOL in DCIS pts at 5 years after diagnosis compared to controls
Kaplan	California	300	2000-2002	Treatment decisions and QOL among Latinas with DCIS
Nekhlyudov 2006	NHS I/II	510	1992-2000	Changes in QOL after DCIS
van Gestel, 2006	Netherlands Hospitals	47	2002-2003	QOL in patients with DCIS vs node-negative invasive breast ca
Winer	Dana Farber others	450	2003-2005	QOL in DCIS pts, psychosocial outcomes and health behaviors

# Recent/Ongoing Studies of Risk Factors for DCIS

Study	Population	Ages	No. Cases/ controls	Dx Years	Risk Factors	Bio specimens
Bernstein/ Press 2004, 2006	SEER, LA County	35-64	567/614	1995- 1998	Reproductive factors, lifestyle	Some blocks
Bernstein	California Teachers Study	All	660/ 117,000	1996- 2003	Reproductive factors, lifestyle, etc	No
BCSC	Breast Cancer Surveillance	All	Cohort > 800,000	1996- present	Reproductive factors, lifestyle, etc	?
Brody, 2004	Cape Cod	< 64	224/1006	1988- 1995	Lifestyle, reproductive pesticides	?
Claus, 2001	SEER Connecticut	20-79	875/999	1994- 1998	Reproductive, family hx, lifestyle	Blocks
Millikan	Carolina Breast Study (White and Black women)	< 64	300/300	1995- 2000	Reproductive, family hx, pesticides, medications, BRCA 1/2	Blood Blocks
Newcomb/ Trentham- Dietz, 2000	WI, MA, NH	20-74	1655 /8041	1996- 1999	Reproductive, family hx, diet, alcohol	Buccal Blocks

## Recent/Ongoing DCIS Outcome Studies: Treatment and clinical factors

Study	Population	Ages	No. pts	Dx Year	Treatment	Clinical Factors	Bio Specimens
Cutuli, 2001	9 French Cancer Cntr	21-87	1223	1985-1996	Mastectomy BCS+ XRT BCS alone	Standard path	No
Rakovitch	Ontario Cancer Reg	20-97	8000	1994-2003	All treatments	Age, path features	slides
Solin, 2005	US, Canada Europe	26-86	1003	1967-1990	BCS+ XRT	Age, margins, size, grade, family hx	?
Silverstein, 2007	Van Nuys USC Norris	20-89	1289	1971-2000	Mastectomy BCS+ XRT BCS alone	Age, grade, size, margins, necrosis	?
Vargas, 2005	Beaumont Cancer Inst	All	405	1981-1999	Mastectomy BCS+ XRT BCS alone	Standard path	?
Wong, 2006	Dana Farber/ Harvard	35-81	158	1994-2002	Wide excision alone (1+ cm)	Standard path	?
Hughes, 2006	E5194 trial (1- arm)	18+	711	1997-2002	Screening after exc alone	Standard path	Blocks=341 Slides=137

# Recent/Ongoing DCIS Outcome Studies: Risk Factors

Study	Population	Ages	No. Cases	Dx Years	Prognostic Factors	Bio specimens
Claus	SEER Connecticut	20-84	1200	1994-1998	Reproductive, family hx, IHC markers, BRCA 1/2	Blocks Buccal
Habel/Porter, 1998	Western Washington	20-74	709	1980-1992	Reproductive, family hx, lifestyle, IHC	Slides =341 IHC=245
Habel, 2004	NSABP B17	<84	504	1990-1997	Mammographic density	No
Habel	Kaiser NC	<84	900	1990-1997	Mammographic features reproductive, family hx	No
Habel	3 HMOs (includes Kaiser NC)	<84	3100	1990-2001	Reproductive, family hx, IHC, gene expression	Blocks on cases and controls
Kerlikowske, 2003	SF Bay Area SEER	30+	1460	1983-1996	Reproductive, family hx, IHC	Blocks
Newcomb/Trentham-Dietz	Wisconsin Tumor Reg	20-74	2500	1996-2005	Reproductive, lifestyle, family hx, IHC	Buccal blocks

# Phase III Randomized Clinical Trials

Study	Population	No. Cases	Treatment	Pub'd Results	Bio Specimens
NSABP B-17	US	818	Exc +/- XRT	yes	Blocks
NSABP B-24	US	1804	Exc and XRT +/- Tam	yes	Blocks
EORTC 10853	Europe	1010	Exc +/- XRT	yes	Blocks
UK DCIS	UK	1701	Exc +/- XRT +/- Tam	yes	?
SweDCIS	Sweden	1046	Exc +/- XRT	yes	?
RTOG 9804	US	1990	Exc +/- Tam vs XRT +/- Tam	pending	Blood Blocks
NSABP B-35	US	3000	Exc and XRT + Tam or AI	pending	Blocks
IBIS-II DCIS	UK	4000	Exc + Tam or AI	pending	Blocks
NSABP B-39	US	?	WBI vs. PBI	pending	Blocks

# Overview of Current Studies

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- Studies are examining a variety of questions related to risk of disease, treatment and outcomes.
- Source populations and designs vary.
- Some are retrospective, others prospective.
- Relatively small number of studies with both clinical data and biospecimens.

# Preliminary Findings from a DCIS BioMarker Study

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Title: Clinical and Pathologic Predictors of Recurrence after DCIS

PI: Laurel Habel

Funding: NCI (through the Cancer Research Network)

## Aims

1. Examine risk of recurrence and:
  - patient and clinical factors
  - histopathologic features of the index DCIS
  - tumor markers (IHC and gene expression)
2. Develop a prognostic index that uses a combination of factors.

# Collaborators

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Kaiser Permanente Northern California (KPNC)

Balaram Puligandla (KP Pathologist)

Charles Quesenberry (Biostatistician)

Harold Wadley (KP Mammographer)

Kaiser Permanente Southern California (KPSC)

Reina Haque

Ann Geiger

Harvard Pilgrim Health Center (HPHC)

Larissa Nekhlyudov

Suzanne Fletcher

Beth Israel Deaconess Medical Center (BIDMC)

Stuart Schnitt

Laura Collins

PhenoPath (IHC Markers)

Lynn Goldstein

Genomic Health, Inc (Gene Expression)

Steve Shak

# Study Design

## *DCIS cohort*

- KPNC, KPSC, HPHC
- Aged 20-84 years
- New primary DCIS 1990-2001
- Breast-conserving surgery
- N=3,700 potentially eligible DCIS patients
- Medical record review to identify recurrences and obtain data on patient and clinical factors

## *Recurrences (cases)*

- N=340
- Obtain pathology reports, slides, and blocks on index DCIS

## *Non-recurrences (controls)*

- 2 per case
- Matched on HMO, age, year of initial diagnosis, and follow-up time
- Obtain pathology reports, slides, and blocks on index DCIS

## *Pathology*

### *Slide review (BIDMC)*

- Histopathologic features
- DCIS classification systems

### *Tumor marker studies*

- Immunohistochemistry  
ER, PgR, HER-2-neu,  
p53, ki-67, COX-2, VEGF
- Gene expression profiling

## Selected characteristics of final cohort

Characteristic	Total Cohort	Percent	No. with Recurrence	Percent
<b>Diagnosis Year</b>				
1990-93	628	20.4%	110	32.1%
1994-97	1,023	33.3%	164	47.8%
1998-01	1,421	46.3%	69	20.1%
<b>Race</b>				
White	2,100	68.4%	231	67.3%
Asian	366	11.9%	29	8.5%
Black	297	9.7%	52	15.2%
Hispanic	263	8.6%	30	8.7%
Other	9	0.3%	0	0.0%
<b>Age</b>				
< 50	781	25.4%	105	30.6%
50-59	876	28.5%	98	28.6%
60-69	826	26.9%	92	26.8%
70+	589	19.2%	48	14.0%
<b>Treatment</b>				
Surgery only	1,302	42.4%	230	67.1%
XRT (No Tam)	1,269	41.3%	100	29.2%
Tam (No XRT)	133	4.3%	2	0.6%
XRT+Tam	339	11.0%	5	1.5%
Unknown	29	0.9%	6	1.7%
	<b>3,072</b>	<b>100.0%</b>	<b>343</b>	<b>100.0%</b>

# Number and Types of Events

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Type of recurrence	Number	Percent
Ipsilateral DCIS	176	51.3%
Ipsilateral Invasive	126	36.7%
Regional	26	7.6%
Distant	15	4.4%
Total	343	

Type of Contralateral	Number	Percent
DCIS	52	38.5%
Invasive	83	61.5%
Total	135	

# Preliminary Findings

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## **Patient factors and prognosis**

- Age, race, BMI, etc

## **Mammographic features and prognosis (KPNC only)**

- Microcalcifications
- Mammographic density

## **Pathologic features and prognosis**

- Histopathology
- DCIS classification system
- IHC markers (ER, PR, HER-2, p53, ki-67, Cox-2, VEGF)

# Patient and clinical factors

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- Recurrence higher in younger women, those with symptomatic DCIS, and black women.
- Risk slightly higher in pre-menopausal women and those with a history of benign breast disease.
- Recurrence not associated with BMI or family history.

# Mammographic Findings

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- Scattered calcifications approximately doubles the risk of a recurrence (similar to NSABP B-17 findings).
- Risk is elevated among patients with highly dense breasts, but increase may be largely for contralateral cancer.

# Pathology

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- Risk increased for comedo necrosis, larger tumors and status of margins, but not nuclear grade.
- Risk higher for tumors with poor cell polarity or stromal inflammation.
- Risk higher among patients with ER- and PR- tumors and possibly p53+ tumors; women with ER/PR-, HER+ also appeared to be at increased risk of recurrence.

# Overall Summary of Preliminary Findings

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- No single factor is strongly prognostic.
- A few are modestly or weakly prognostic.

# Next Steps

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## Gene expression studies

- Examine Oncotype DX, as well as discovery of new genes

## Develop prognostic index

- Combine clinical, path features and markers

## Validate index in other populations

## Collaborations with Breast SPOREs

- Dana Farber Cancer Center
- Johns Hopkins

# Some Lessons Learned

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- Retrospective tumor retrieval rates vary substantially -- from <50% to >90% across our 3 participating sites.
- Lower retrieval rates of slides and blocks on patients who have a recurrence.
- Not all DCIS is really DCIS – central review important.
- Expert breast pathologists are very busy and reviews of 100s of patients (and 1000s of slides) take time.

# Some Lessons Learned

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- Most DCIS tumors small and many patients have only one block with tumor (exhaustion of tumor is a concern).
- Must prioritize marker studies and be careful about possible bias due to over-representation of larger tumors.
- A big study is never big enough.

# How do we Move Forward to Meet the Challenge?

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- Incorporate biomarkers into new studies.
- Combine populations to increase sample sizes.
- Establish set of key variables (and definitions) to collect on all DCIS patients.
- Develop prognostic index that combines clinical factors and markers into a single score.

# How do we Move Forward to Meet the Challenge?

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- Conduct retrospective studies for long-term outcomes.
- Conduct prospective studies of better pathology assessment and newer therapies.
- Validate promising markers and risk scores in multiple independent populations.
- Bring together population scientists, clinical scientists, and basic scientists.