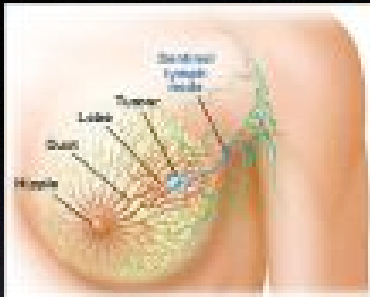


Estimating the effects of the BRCA mutation on breast cancer risk:

frailty selection, competing risks and paired event times

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Breast Cancer

- Second leading cancer death in US women
- Diagnoses: 200,000/yr Deaths: 40,000/yr
- 14% risk by age of ninety
sometimes said to be 1/7 lifetime chance
- Spectrum of disease
- Heritable component clearly demonstrated

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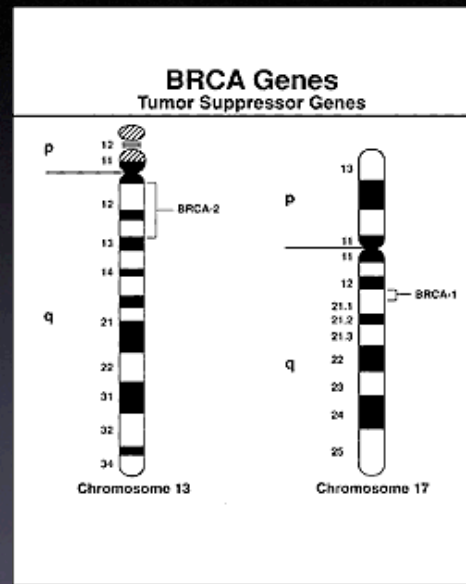
BRCA I and II Genes

Predispose to high risk of breast & ovarian cancer

Responsible for 5-10% of cancers

More than 700 known mutations

Lifetime risk of cancer unclear
early estimates: 85%



almost certainly too high

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BRCA penetrance studies

- Typical approach: identify a series of probands (cancer cases and controls)
- Genotype family members
- Examine risk of breast cancer in family members
- Clever but problematic!

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Frailty Selection

- Suppose families vary in unmeasured risk factors for breast cancer (cf, a frailty)
- Selection by case probands gives overestimate of risk of cancer in relatives
- The relative risk of cancer in BRCA +/- subjects also appears to be off
- The culprit: frailty selection

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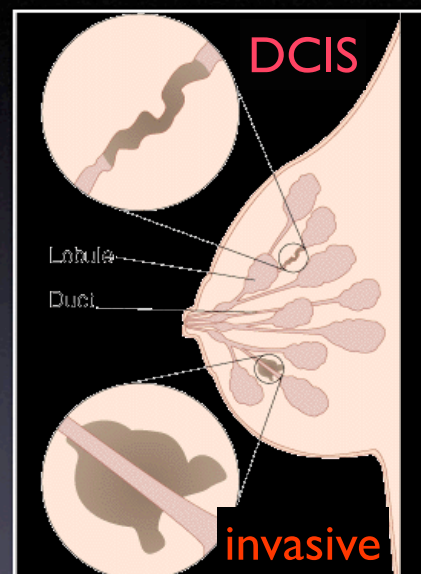
Ductal Carcinoma in Situ

Cancer has not invaded the breast tissue

May or may not progressive to invasive cancer

Detected by mammography

Unclear if DCIS elevated in women with BRCA mutations



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BRCA penetrance study

- Hwang and colleagues.....
- Recruit a series of subjects at high risk for cancer (based on family history): n=398
- Test for BRCA: 128+ (32%) 270- (68%)
- Examine their risk of for future breast cancer: invasive and DCIS
- *Does BRCA elevate risk of DCIS?*

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Aspects of the Study

- Events recorded in age (e.g. DCIS in 47 yo)
- Unclear how long subjects in study (e.g., age at enrollment)
- Possible personal history of events
- Part of a long-term follow-up protocol

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Outcomes in the Study

- Possible events (in left or right breast)
 - DCIS
 - Invasive Cancer
- Mastectomy: greatly reduces risk
- Oophorectomy: greatly reduces risk
- Tamoxifen: greatly reduces risk
- Death (rare in this study)

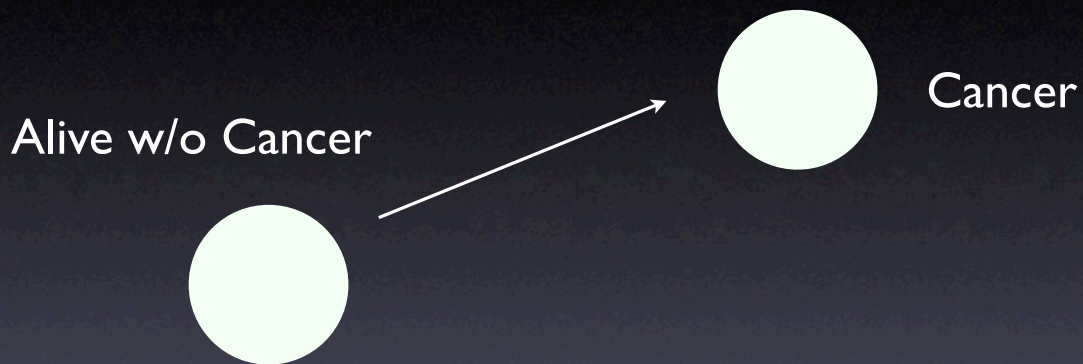
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Structure of Events

- DCIS in two breast: parallel events
- Invasive in two breast: parallel events
- Mastectomy: affects risk in single breast
- Oophorectomy: affects risk in both breasts
- Death: affects risk in both breasts

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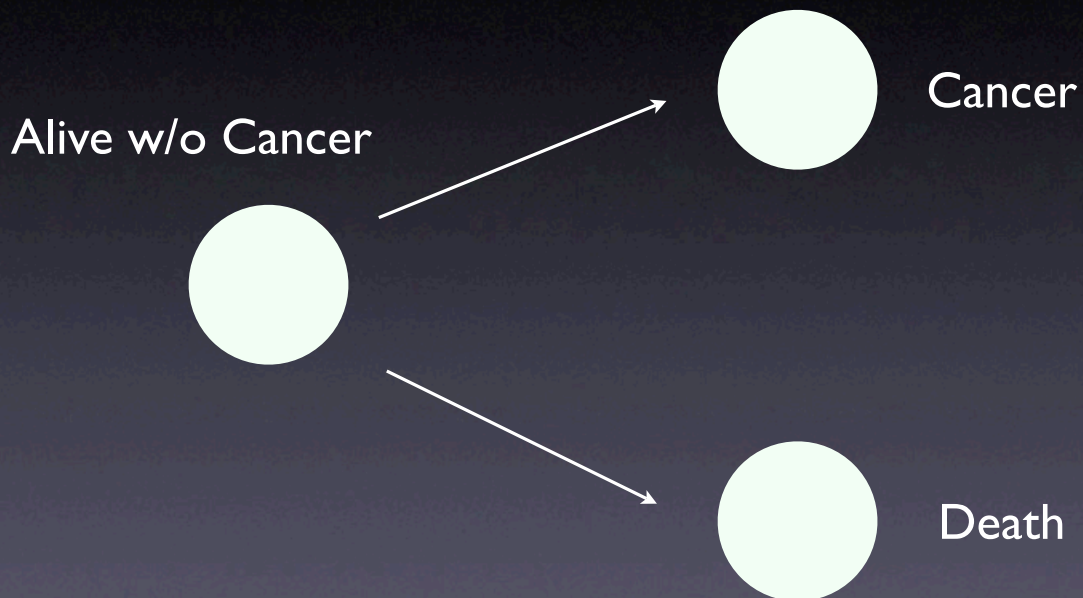
Competing Risks



Interesting Data

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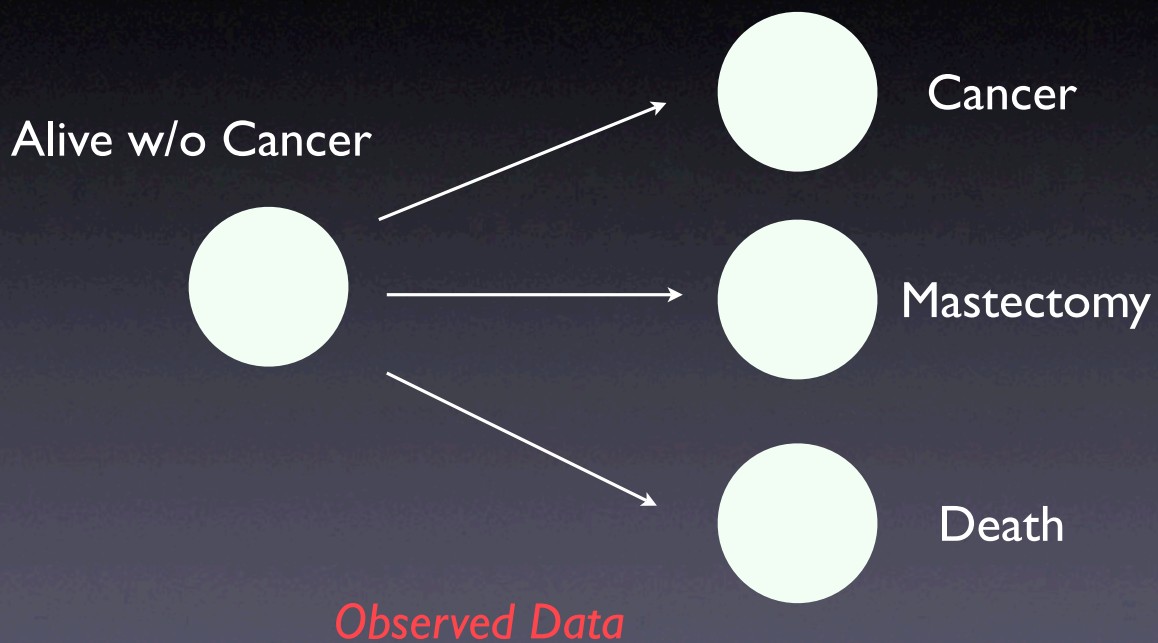
Competing Risks



Possible Data

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Competing Risks



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Competing Risks

- Particular type of multiple events data
- Multiple possible events (e.g., cancer/death)
- Occurrence of 1 event prevents obs of other
- Either because of biology (death) or because patients are or can not followed further

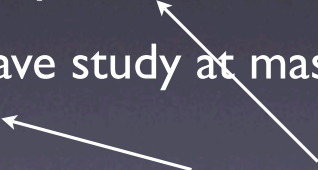
14

Cause-Specific Hazard

Hazard for competing risks data

- Rate of transition from cancer-free to cancer
- Only those alive and cancer free contribute to denominator
- Death: leave study at death time
- Mastectomy: leave study at mastectomy

This is like “censoring” data



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Death v. Mastectomy

- Important difference: death is biologically inherent
- Mastectomy is not: we'd like to know what would've happened if no mastectomy
- Issue: have to assume that cancer risk is represented by those breasts w/o mastectomy
- Independent type censoring assumption

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DCIS v. Invasive

- DCIS can occur in either breast: paired event
- Invasive cancer also paired
- Model the two events separately

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DCIS Data

*Weak
Concordance*

Left Breast

*148 DCIS
events*

		Left Breast	
		No	Yes
Right Breast	No	268	55
	Yes	57	18

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Invasive Data

*Weak
Concordance*

Left Breast

*164 invasive
events*

Right
Breast

	No	Yes
No	250	65
Yes	67	16

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Invasive v. DCIS Data

*Stronger
Concordance*

Invasive

Left

Right

DCIS

	No	Yes
No	300	23
Yes	15	60

	No	Yes
No	301	24
Yes	16	57

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Invasive Data

Strong
Concordance

Any Invasive

		Any Invasive	
		No	Yes
Any DCIS	No	230	38
	Yes	20	110

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DCIS: First event

- Age at first DCIS in either breast
 $\min(T_{\text{left}}, T_{\text{right}})$
- Person is the unit of analysis
no cluster: 1 event per person
- Can be thought of as DCIS-free time
- Discards the second event
second events: 18/148 DCIS events

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Cox Model

Cox regression -- Breslow method for ties

```
No. of subjects =          398          Number of obs =          398
No. of failures =          127
Time at risk    =          17902
Log likelihood   = -659.85083          LR chi2(1)    =          3.23
                                          Prob > chi2   =          0.0722
```

_t	Haz. Ratio	Std. Err.	z	P> z	[95% Conf. Interval]
obrca	1.446994	.2896662	1.85	0.065	.9773928 2.142221

obrca = BRCA1 positive or BRCA 2 positive

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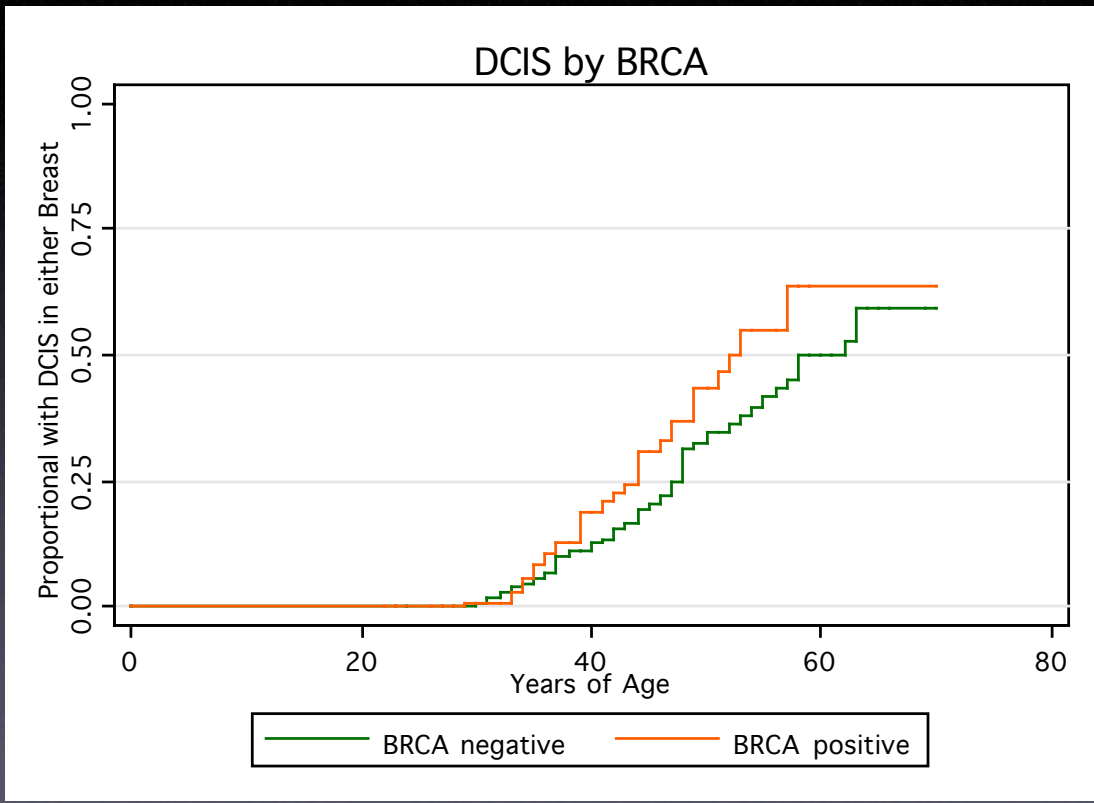
Cox for first Invasive

Cox regression -- Breslow method for ties

```
No. of subjects =          398          Number of obs =          398
No. of failures =          143
Time at risk    =          17906
Log likelihood   = -734.41153          LR chi2(1)    =          6.11
                                          Prob > chi2   =          0.0134
```

_t	Haz. Ratio	Std. Err.	z	P> z	[95% Conf. Interval]
obrca	1.602686	.2965992	2.55	0.011	1.115121 2.30343

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Not Using All Events

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Dan's Idea

- Use clustered data approach
- Model the rate of DCIS in breast selected at random
- Breast is unit of analysis
- Uses all DCIS events

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Marginal Cox for DCIS

Cox regression -- Breslow method for ties

```
No. of subjects      =          796      Number of obs      =          796
No. of failures      =          148
Time at risk        =          36343
Log pseudolikelihood = -870.22694      Wald chi2(2)       =          5.20
                                          Prob > chi2        =          0.0743
```

(Std. Err. adjusted for 398 clusters in id)

```
-----+-----
      _t |      Haz. Ratio   Robust      z   P>|z|   [95% Conf. Interval]
-----+-----
      brca1 |    1.625297   .4083341   1.93   0.053   .9932988   2.659413
      brca2 |    1.510552   .3978326   1.57   0.117   .9014789   2.531138
-----+-----
```

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Marginal Cox for DCIS

Cox regression -- Breslow method for ties

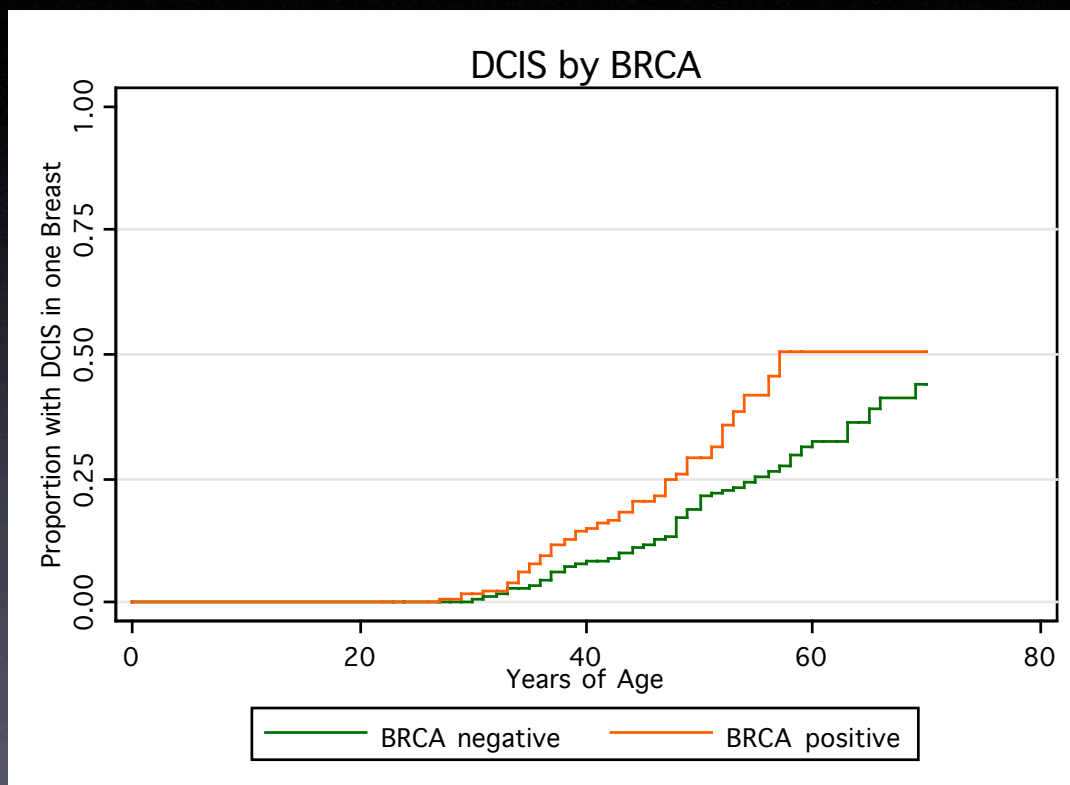
```
No. of subjects      =          796      Number of obs      =          796
No. of failures      =          148
Time at risk         =          36343
Log pseudolikelihood = -870.23009      Wald chi2(1)       =           5.15
                                          Prob > chi2        =           0.0232
```

(Std. Err. adjusted for 398 clusters in id)

_t	Haz. Ratio	Robust Std. Err.	z	P> z	[95% Conf. Interval]	
obrca	1.573656	.3142728	2.27	0.023	1.063941	2.327567

Significant!

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Another Possibility

- A multiple events framework
number of DCIS events
- Model rate of DCIS events (not hazard)
- Proportional rate model
- Also a proportional means model
mean number of events prop at any time
- Uses all DCIS events

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Data Set-Up

id	dtime	dstatus	dmax	obrca
2495	44	1	52	0
1673	41	1	43	1
1673	43	1	43	1
1697	33	1	37	1
1697	37	1	37	1
110	62	0	62	0

can be
hard to
define!

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Proportional Rates for DCIS

Cox regression -- Breslow method for ties

```
No. of subjects      =          398      Number of obs      =          416
No. of failures      =          148
Time at risk        = 17974.02099
Log pseudolikelihood = -760.12567      Wald chi2(2)       =          5.24
                                          Prob > chi2        =          0.0729
```

(Std. Err. adjusted for 398 clusters in id)

_t	Haz. Ratio	Robust Std. Err.	z	P> z	[95% Conf. Interval]	
brca1	1.619039	.4078232	1.91	0.056	.9882037	2.652579
brca2	1.544735	.4193717	1.60	0.109	.9073315	2.629917

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Proportional Rates for DCIS

Cox regression -- Breslow method for ties

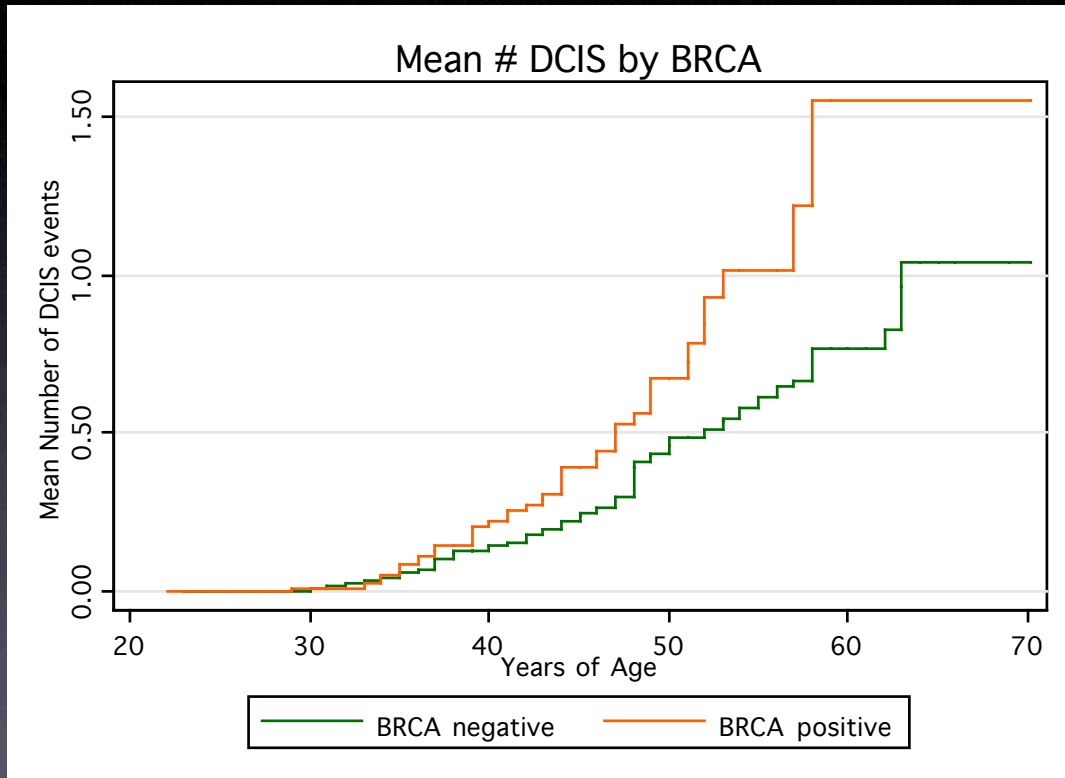
```
No. of subjects      =          398      Number of obs      =          416
No. of failures      =          148
Time at risk        = 17974.02099
Log pseudolikelihood = -760.11025      Wald chi2(1)       =          5.21
                                          Prob > chi2        =          0.0225
```

(Std. Err. adjusted for 398 clusters in id)

_t	Haz. Ratio	Robust Std. Err.	z	P> z	[95% Conf. Interval]	
obrca	1.587871	.3217275	2.28	0.022	1.067452	2.362011

Significant!

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Proportional Rates for Invasive Cancer

Cox regression -- Breslow method for ties

```

No. of subjects      =          398          Number of obs      =          544
No. of failures      =           164
Time at risk         = 17999.02099
Log pseudolikelihood = -837.8059
Wald chi2(1)         =           8.93
Prob > chi2          =           0.0028

```

(Std. Err. adjusted for 398 clusters in id)

_____+_____		Robust				
_t	Haz. Ratio	Std. Err.	z	P> z	[95% Conf. Interval]	
obrca	1.760767	.3333293	2.99	0.003	1.214959	2.551774

Not hugely different than DCIS

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Mediation

- How much of effect of BRCA on invasive cancer passes thru DCIS?
- Can fit proportional rates to invasive with and without hx of DCIS as covariate
- Attenuation of coefficient can measure “mediation”

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Some issues

- Addressing mediation in data set
- Robustness to competing risk assumptions *who underwent mastectomy, etc.?*
- Handling censoring better in multiple events framework
- Work in DCIS grade to analysis
- Understand second DCIS events better!

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This Data

- Rare combination
 - Illustration of multiple events issues: pairing, competing risks, multiple outcomes
 - Compelling clinical question