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Familial aggregation of age of onset for breast cancer risk

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Introduction

Breast cancer ages of onset may be correlated for sisters. Such correlation would have implications for screening and support the importance of genetic and early life exposures.

Aim

Assess whether the hazard for breast cancer increases near the age at which a sister had formerly been diagnosed with breast cancer.

Sample

48,630 women ages 35-74 from the Sister Study who had not been diagnosed with breast cancer at enrollment (2003-2009) who had a full sister diagnosed with breast cancer at a known age of onset.

Methods

Model: We used Cox models to estimate hazard ratios on an age-time scale:

$$\lambda(t) = \lambda_0(t) \cdot exp(\beta_1 Z_{ij}(t) + \beta \boldsymbol{x})$$

Exposure: 'Closeness covariate'
Closeness to age(s) of breast cancer diagnosis in sisters was modeled using a time-dependent covariate. The Gaussian shape allows for increased (or decreased) breast cancer hazard ratios as the participant attains the proband age at breast cancer diagnosis. We stratified analyses by proband early-onset status (<50 years).

$$Z_{ij}(t) = exp\left(\frac{-(t - \overline{T}_i)^2}{2\sigma^2}\right)$$

Methods, cont...

- t time scale (chronological age)
- $\overline{T}_i$ average age at diagnosis of sisters diagnosed prior to participant's enrollment
- σ^2 scaling factor
- i, j i^{th} person in j^{th} family.
- $\boldsymbol{x}$ Other covariates including: age at menarche, age at first birth, time-dependent menopause status, BMI, BMI and menopause product term. These covariates could be predictors of familial clustering.

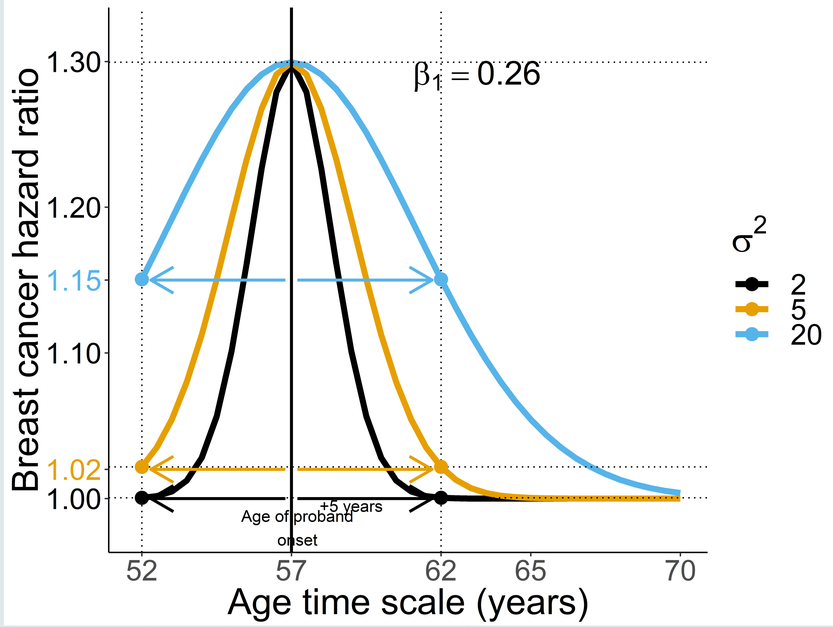

Figure 1. Sample hazard ratio values for closeness covariate over time (age) scale by different scaling factors

Characteristics of participants

Variable[a]	proband>=50	proband<50	Total
n	20856	27774	48630
Age, menarche	12.6 (1.5)	12.7 (1.5)	12.7 (1.5)
BMI	27.8 (6.1)	27.6 (6.3)	27.7 (6.2)
Participant baseline age	60.3 (7.5)	52.3 (8.4)	55.8 (8.9)
Proband age at diagnosis	57.2 (5.9)	42.4 (5.8)	48.7 (9.4)
Age at first birth, %			
Nulliparous	16.4	19.8	18.4
(0,20]	21.4	16.4	18.6
(20,24]	29.0	22.4	25.2
(24,29]	21.6	24.2	23.1
(29,55]	11.5	17.2	14.8
Proband age of onset %			
<40		30.4	17.3
40-49		69.6	39.8
50-59	71.2		30.5
60-69	24.8		10.6
>70 years	4.0		1.7

[a] All age variables are in year units and continuous variables are characterized by mean (SD).

Closeness breast cancer HR (95% CI)

	Unadjusted	Adjusted[a]
Full sample		
$exp(-0.5(t - \bar{T})^2/5)$ †	1.17 (0.99, 1.38)	1.17 (0.99, 1.39)
Young-onset proband, $\bar{T} < 50$		
$exp(-0.5(t - \bar{T})^2/2)$ †	1.04 (0.72, 1.50)	1.04 (0.72, 1.50)
Older-onset proband, $\bar{T} \geq 50$		
$exp(-0.5(t - \bar{T})^2/20)$ †	1.29 (1.08, 1.55)	1.30 (1.09, 1.56)

[a] Adjusted for age at menarche, age at first birth, body mass index (BMI), time-dependent menopause status and the product term between BMI and menopause.
[b] Estimate for full sample is from a Cox model stratified by proband early-onset status.
† t is the time scale in participant chronological age and $\bar{T}$ is average age at onset for probands.

Interpretation: Among those with an older-onset proband, there is a 30% larger relative hazard at the proband age of diagnosis relative to the ages farthest away from the proband age of diagnosis.

Model fit

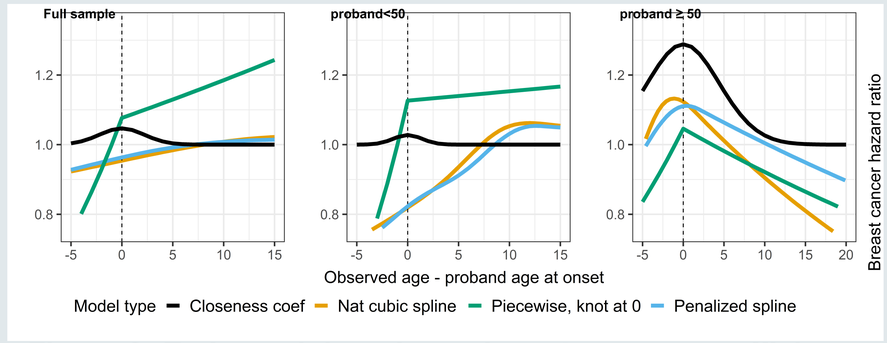

Figure 2. Estimated time-dependent closeness coefficients

⇒ Time-dependent splines confirm the shape of the closeness coefficient for participants with an older-onset sister.

Summary

In the largest study of its kind, we found support for familial clustering of breast cancer age of onset for women who did not have a sister with young-onset disease. Determining risk over time relative to an affected sister's age of onset has potential implications both for personalized screening and for understanding etiology.

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