Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

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eTable 1. Hazard Ratios and 95% CIs Measuring the Time-Dependent Effect of Risk-Reducing Salpingo-Oophorectomy (RRSO) on BC Risks Based on Different TVC Models in BRCA1 and BRCA2 Families From the BCFR

TVC model[&]	Time since RRSO (in years)										LRT[†]
	1	2	3	4	5	6	7	8	9	10	(p-value)
BRCA1 carriers - Competing risks model											
CO	0.14	0.39	0.55	0.61	0.63	0.63	0.64	0.64	0.64	0.64	15.23
	(0.04, 0.56)	(0.11, 0.76)	(0.2, 0.84)	(0.29, 0.91)	(0.34, 0.93)	(0.38, 0.94)	(0.39, 0.96)	(0.39, 0.99)	(0.39, 0.99)	(0.4, 1.02)	(0.002)
ED	0.12	0.39	0.66	0.83	0.92	0.96	0.98	0.99	1	1	11.12
	(0.02, 1.21)	(0.11, 1.12)	(0.24, 1.06)	(0.39, 1.03)	(0.56, 1.02)	(0.68, 1.01)	(0.78, 1)	(0.85, 1)	(0.9, 1)	(0.93, 1)	(0.004)
PE	0.57	0.57	0.57	0.57	0.57	0.57	0.57	0.57	0.57	0.57	9.04
	(0.38, 0.84)	(0.38, 0.84)	(0.38, 0.84)	(0.38, 0.84)	(0.38, 0.84)	(0.38, 0.84)	(0.38, 0.84)	(0.38, 0.84)	(0.38, 0.84)	(0.38, 0.84)	(0.003)
BRCA1 carriers - No competing risks model											
CO	0.23	0.53	0.65	0.69	0.7	0.7	0.7	0.7	0.7	0.7	9.28
	(0.07, 0.65)	(0.26, 0.94)	(0.39, 1.12)	(0.42, 1.17)	(0.43, 1.18)	(0.43, 1.19)	(0.43, 1.19)	(0.43, 1.19)	(0.43, 1.19)	(0.43, 1.19)	(0.026)
ED	0.46	0.82	0.95	0.99	1	1	1	1	1	1	6.46
	(0.25, 0.83)	(0.64, 0.95)	(0.86, 0.99)	(0.95, 1)	(0.98, 1)	(0.99, 1)	(1, 1)	(1, 1)	(1, 1)	(1, 1)	(0.040)
PE	0.63	0.63	0.63	0.63	0.63	0.63	0.63	0.63	0.63	0.63	5.86
	(0.39, 1.02)	(0.39, 1.02)	(0.39, 1.02)	(0.39, 1.02)	(0.39, 1.02)	(0.39, 1.02)	(0.39, 1.02)	(0.39, 1.02)	(0.39, 1.02)	(0.39, 1.02)	(0.016)
BRCA2 carriers - Competing risks model											
CO	0.06	0.3	0.55	0.68	0.73	0.75	0.76	0.77	0.77	0.77	13.77
	(0.02, 0.28)	(0.09, 0.7)	(0.22, 0.91)	(0.36, 1.03)	(0.43, 1.09)	(0.46, 1.14)	(0.46, 1.16)	(0.47, 1.19)	(0.47, 1.23)	(0.47, 1.23)	(0.003)
ED	0.05	0.26	0.56	0.77	0.89	0.95	0.98	0.99	1	1	12.86
	(0.01, 0.41)	(0.09, 0.91)	(0.22, 0.99)	(0.37, 1)	(0.51, 1)	(0.63, 1)	(0.72, 1)	(0.8, 1)	(0.85, 1)	(0.89, 1)	(0.002)
PE	0.62	0.62	0.62	0.62	0.62	0.62	0.62	0.62	0.62	0.62	5.65
	(0.41, 0.94)	(0.41, 0.94)	(0.41, 0.94)	(0.41, 0.94)	(0.41, 0.94)	(0.41, 0.94)	(0.41, 0.94)	(0.41, 0.94)	(0.41, 0.94)	(0.41, 0.94)	(0.018)
BRCA2 carriers - No competing risks model											
CO	0.3	0.46	0.55	0.59	0.61	0.62	0.62	0.62	0.63	0.63	11.50
	(0.1, 0.64)	(0.2, 0.81)	(0.3, 0.91)	(0.34, 0.96)	(0.36, 1)	(0.37, 1.03)	(0.37, 1.05)	(0.37, 1.05)	(0.37, 1.06)	(0.37, 1.06)	(0.009)
ED	0.04	0.27	0.57	0.79	0.91	0.96	0.98	0.99	1	1	10.84
	(0.01, 2.36)	(0.1, 1.9)	(0.25, 1.57)	(0.43, 1.37)	(0.59, 1.27)	(0.72, 1.19)	(0.8, 1.12)	(0.87, 1.09)	(0.92, 1.06)	(0.94, 1.04)	(0.004)
PE	0.65	0.65	0.65	0.65	0.65	0.65	0.65	0.65	0.65	0.65	3.82
	(0.41, 1.01)	(0.41, 1.01)	(0.41, 1.01)	(0.41, 1.01)	(0.41, 1.01)	(0.41, 1.01)	(0.41, 1.01)	(0.41, 1.01)	(0.41, 1.01)	(0.41, 1.01)	(0.051)

[&]Best TVC model for ***BRCA1*** and ***BRCA2*** families is indicated in bold; CO=Cox and Oakes, ED=exponential decay, PE=permanent exposure

[†]Likelihood ratio test statistics comparing to the null model with no RRSO effect.

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eTable 2. Hazard Ratios and 95% CIs Measuring the Time-Dependent Effect of Risk-Reducing Salpingo-Oophorectomy (RRSO) on BC Risks Based on the Best TVC Model With or Without Competing Risks and Without Adjustment for MS History in BRCA1 and BRCA2 Families From the BCFR

TVC model[&]	Time since RRSO (in years)										LRT[†]
	1	2	3	4	5	6	7	8	9	10	(p-value)
	BRCA1 carriers - Competing risks model without adjustment for MS										
PE	0.55	0.55	0.55	0.55	0.55	0.55	0.55	0.55	0.55	0.55	5.77
	(0.36, 0.84)	(0.36, 0.84)	(0.36, 0.84)	(0.36, 0.84)	(0.36, 0.84)	(0.36, 0.84)	(0.36, 0.84)	(0.36, 0.84)	(0.36, 0.84)	(0.36, 0.84)	(0.016)
	BRCA1 carriers - No competing risks model without adjustment for MS										
PE	0.67	0.67	0.67	0.67	0.67	0.67	0.67	0.67	0.67	0.67	3.44
	(0.42, 1.05)	(0.42, 1.05)	(0.42, 1.05)	(0.42, 1.05)	(0.42, 1.05)	(0.42, 1.05)	(0.42, 1.05)	(0.42, 1.05)	(0.42, 1.05)	(0.42, 1.05)	(0.064)
	BRCA1 carriers - Competing risks model without adjustment for MS										
CO	0.28	0.45	0.56	0.62	0.65	0.67	0.68	0.68	0.68	0.68	9.69
	(0.09, 0.58)	(0.19, 0.73)	(0.3, 0.86)	(0.37, 0.94)	(0.4, 0.99)	(0.41, 1.02)	(0.42, 1.04)	(0.42, 1.05)	(0.42, 1.05)	(0.42, 1.06)	(0.021)
	BRCA1 carriers - No competing risks model without adjustment for MS										
CO	0.24	0.51	0.67	0.74	0.76	0.77	0.78	0.78	0.78	0.78	6.56
	(0.05, 0.69)	(0.12, 0.92)	(0.23, 1.06)	(0.34, 1.14)	(0.42, 1.2)	(0.45, 1.22)	(0.46, 1.23)	(0.47, 1.24)	(0.48, 1.24)	(0.48, 1.24)	(0.087)
	BRCA2 carriers - Competing risks model without adjustment for MS										
PE	0.72	0.72	0.72	0.72	0.72	0.72	0.72	0.72	0.72	0.72	2.80
	(0.47, 1.10)	(0.47, 1.10)	(0.47, 1.10)	(0.47, 1.10)	(0.47, 1.10)	(0.47, 1.10)	(0.47, 1.10)	(0.47, 1.10)	(0.47, 1.10)	(0.47, 1.10)	(0.095)
	BRCA2 carriers - No competing risks model without adjustment for MS										
PE	0.79	0.79	0.79	0.79	0.79	0.79	0.79	0.79	0.79	0.79	1.16
	(0.52, 1.21)	(0.52, 1.21)	(0.52, 1.21)	(0.52, 1.21)	(0.52, 1.21)	(0.52, 1.21)	(0.52, 1.21)	(0.52, 1.21)	(0.52, 1.21)	(0.52, 1.21)	(0.281)
	BRCA2 carriers - Competing risks model without adjustment for MS										
ED	0.16	0.39	0.62	0.78	0.88	0.94	0.97	0.98	0.99	1	9.00
	(0.06, 0.42)	(0.15, 0.8)	(0.27, 0.94)	(0.39, 0.98)	(0.51, 1)	(0.62, 1)	(0.71, 1)	(0.78, 1)	(0.84, 1)	(0.88, 1)	(0.011)
	BRCA2 carriers - No competing risks model without adjustment for MS										
ED	0.34	0.51	0.66	0.78	0.86	0.91	0.94	0.96	0.98	0.99	5.72
	(0.16, 0.66)	(0.26, 0.85)	(0.36, 0.93)	(0.46, 0.97)	(0.55, 0.99)	(0.62, 1)	(0.69, 1)	(0.75, 1)	(0.79, 1)	(0.83, 1)	(0.057)

[&]Best TVC model for ***BRCA1*** and ***BRCA2*** families is indicated in bold; CO=Cox and Oakes, ED=exponential decay, PE=permanent exposure

[†]Likelihood ratio test statistics comparing to the null model with no RRSO effect.

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eTable 3. Hazard Ratios and 95% CIs Mmeasuring the Time-Dependent Effect of Risk-Reducing Salpingo-Oophorectomy (RRSO) on BC Risks Based on a Piece-Wise TVC Model With or Without Competing Risks and With or Without Adjustment for Mammography Screening (MS) in BRCA1 and BRCA2 Families From the BCFR

	BRCA1 mutation carriers			
	Competing risks		**No competing risks**	
Time since RRSO	with MS adjustment	without MS adjustment	with MS adjustment	without MS adjustment
< 2 years	0.10 (0.00, 2.60)	0.26 (0.06, 1.15)	0.15 (0.01, 2.86)	0.37 (0.09, 1.50)
2 −5 years	0.35 (0.11, 1.13)	0.27 (0.06, 1.27)	0.59 (0.24, 1.46)	0.52 (0.18, 1.46)
> 5 years	0.59 (0.35, 0.97)	0.66 (0.41, 1.08)	0.77 (0.46, 1.31)	0.78 (0.46, 1.31)
LRT[†] (p-value)	7.62 (0.054)	7.29 (0.063)	1.08 (0.783)	4.98 (0.174)

	BRCA2 mutation carriers			
	Competing risks		**No competing risks**	
Time since RRSO	with MS adjustment	without MS adjustment	with MS adjustment	without MS adjustment
< 2 years	0.07 (0.05, 0.11)	0.24 (0.18, 0.31)	0.12 (0.08, 0.19)	0.08 (0.06, 0.11)
2 −5 years	0.62 (0.27, 1.42)	0.48 (0.13, 1.77)	0.95 (0.49, 1.83)	0.89 (0.37, 2.14)
> 5 years	0.74 (0.43, 1.27)	0.95 (0.58, 1.56)	0.86 (0.50, 1.47)	0.96 (0.56, 1.65)
LRT[†] (p-value)	9.90 (0.019)	4.37 (0.224)	9.87 (0.020)	8.59 (0.035)

[&]Piece-wise TVC model assumes RRSO effect on BC is constant within the intervals: < 2 years, 2 − 5 years and > 5 years

[†]Likelihood ratio test statistics comparing to the null model with no RRSO effect.

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eMethods

1. Model

Our methodology is based on a survival analysis approach that was developed specifically to model the occurrence of competing events (i.e., invasive primary BC, invasive primary OC or death from causes other than BC or OC), where the risk of each competing event can depend on time-independent (e.g., gender, mutation status) and time-varying covariates (RRSO) [18].

The motivation for using the competing risks framework is that the (cause-specific) hazard for BC at time t is expressed conditionally on surviving all events up to time t including BC, OC and death (due to other causes than BC and OC) (see eq. 1, below). It is particularly advantageous to assess a clinical intervention that is specific to one of the competing events, i.e., the association of RRSO with BC in our case. As an alternative approach, treating OC as a censoring variable for BC would have more serious consequences, since OC cannot be considered as a random censoring event for BC (Putter et al., Statistics in Medicine, 26: 2389-2430, 2007). In genetic studies, the estimation of the probability for an individual affected with a specific cancer (e.g., breast/ovarian cancer) to carry a specific gene mutation can also be affected by competing risks if, for example, mutation carriers have different probabilities of surviving all causes of cancers compared to noncarriers (Katki et al., Statistics in Medicine, 27: 4532-48, 2008). Accounting for computing risks ensured therefore that the imputation of missing mutation status is not biased. Finally, the competing risks framework allows us also to account for RRSO as a censoring event for OC, as we mentioned in the Method section.

The follow-up time was defined using age as time scale starting from age 16, and followed up until a first event (BC, OC, or death) or last observed time. RRM was considered a

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censoring event for BC and RRSO a censoring event for OC.

2. Time varying covariates

We modeled RRSO as 3 separate TVC functional forms: permanent exposure (PE) model [19] in which the effect stays constant since time of the treatment exposure, exponential decay (ED) model where the TVC effect decays over time with a given rate parameter [19], and the Cox and Oakes (CO) model that is very similar to the ED model but adds a parameter that measures the converged effect of TVC [20,21]. The CO model hazard function decreases until a certain level and then plateaus after that. While the main TVC considered is RRSO, we also added MS events to models as separate TVCs (up to 3 MS events) as MS may confound the assessment of the association between RRSO and BC risk. We therefore applied 12 models (3 TVC forms, competing risks or not, inclusion of MS or not) to evaluate the association of RRSO with BC risk as described in Table 1 below.

Table 1: The 12 time-varying covariate (TVC) models used for evaluating risk-reducing salpingo-oophorectomy (RRSO) effect on breast cancer in the Breast Cancer Family Registry

TVC model	**Functional form for RRSO effect†**	**Competing risks**	**Adjustment for MS events**
PE	Constant over time	Yes/No	Yes/No
ED	Decays exponentially over time	Yes/No	Yes/No
CO	Decays exponentially over time until reaching a fixed **threshold**	Yes/No	Yes/No

†Measured by the hazard ratio (HR).
PE = Permanent exposure; ED = exponential decay; CO = Cox and Oakes.
MS = Mammographic screening.

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The competing risks model with TVCs that we used assumes that the cause-specific hazard, λ_{ijf}, for family member *i* in family *f* and event *j*, *j*=1,2,3 follows the following regression model [18]:

$$\lambda_{ijf}(t|X_{if}(t), z_{jf}) = \lambda_{0j}(t) z_{jf} exp(\beta_2 G_{ijf} + m_j(X_{if}(t))), \quad (1)$$

where $\lambda_{0j}(t)$ corresponds to the baseline hazard function for event *j*, $X_{if}(t)$ represents the history of RRSO or mammographic screening (MS) up to time *t* for individual *i* in family *f*, $m_j(X_{if}(t))$ is the effect of the time-varying covariate (TVC), i.e., RRSO or MS, related to event *j* and z_{jf} a shared frailty term for family *f* specific to event *j* (i.e., all relatives from the same family 'share' the same frailty value), G_{ijf} is the carrier status (1 for carrier and 0 for non-carrier) for either *BRCA1* or *BRCA2* pathogenic variant and β_2 its associated regression coefficient. Note that RRSO and MS events were only allowed to have an effect on BC, that is for *j* = 1.

The effect of the TVC, $m(X_{if}(t))$, is described in three different structures: assuming either a PE, ED, or CO model. The function $m_j(X_{if}(t)) = 0$ if $t < t_8$ (PE, ED, CO) and β_j (PE), or $\beta_j exp\{-\eta_j(t - t_8)\}$ (ED) or $\beta exp\{-\eta_j(t - t_8)\} + \eta_{0j}$ (CO), if $t \geq t_8$, where t_8 is the time to a RRSO or a MS event.

The time-dependent association of the TVC on BC can be assessed by its effect on the hazard function assessed by the hazard ratio (HR) given by $\exp(m_j(X_{if}(t)))$ or on BC cumulative incidence (i.e., penetrance function), which are both defined as cause-specific functions [18]. We previously showed that Akaike's Information Criterion (AIC) is the most appropiate criteria to choose the best TVC model [18].

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We provide the time-dependent effect within a specific interval by the average HR, which is obtained by exponentiating the TVC effect $m_{\$}(X_{"\#}(t))$ averaged over the interval. The 95% confidence intervals (CIs) for the TVC effects and penetrance functions are based on 1000 simulated sets of the parameters generated from the multivariate normal distribution, with the parameter estimates and their robust variance matrix obtained from the model.

3. Selection of TVC model for RRSO effect on BC risk over time

Based on AIC, the best TVC model to fit the RRSO effect over time was CO for *BRCA1* families (AIC=19080.8) and ED model for *BRCA2* families (AIC=13518.0) taking into account competing risks with MS adjustment. This means that for women with *BRCA1* mutations, the effect of RRSO on BC risk diminishes over time until reaching a threshold, i.e., an HR of 0.64 (95% CI 0.38-0.97) (Table 2, Appendix Tables 1 & 2), while for *BRCA2* families, there is no threshold and the HR reaches unity about 5-6 years post-RRSO (Table 2, Appendix Tables 1 & 2). Including MS history (up to 3 screenings) improves substantially the fit of the model for both *BRCA1* and *BRCA2* families, and thus MS cannot be ignored when assessing the RRSO effect. Finally, there is evidence for residual familial correlation (P<0.001, one-sided mixture chi-square test) in both *BRCA1* and *BRCA2* families, as estimated by the parameter of the frailty distribution.

4. Sensitivity to RRSO modeling assumptions

Our best TVC models assume a parametric form (exponential decay) for the variation of RRSO effect over time. To assess this assumption, we fitted a more general piece-wise TVC for RRSO (Appendix table 3), where the hazard ratio was constant within intervals, but did

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not follow any particular functional form. We considered three time intervals: ≤2 years, 2-5 years and > 5 years. The HR estimates from this model are close to the best TVC models for both *BRCA1* and *BRCA2* mutation carriers and confirm that the exponential decay for RRSO effect over time is a reasonable assumption.

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