Title Page

‘Factors influencing uptake and timing of risk reducing salpingo-oophorectomy in women at risk of familial ovarian cancer: a competing risk time to event analysis.’

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Running Title

Risk reducing salpingo-oophorectomy: timing and uptake

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Abstract

Factors influencing uptake and timing of risk reducing salpingo-oophorectomy in women at risk of familial ovarian cancer: a competing risk time to event analysis.

Objective

To evaluate factors affecting uptake of risk-reducing salpingo-oophorectomy(RRSO) over time in women at high-risk of familial ovarian cancer.

Design

Prospective observational cohort

Setting

Tertiary high-risk familial gynaecological cancer clinic

Population/Sample

New clinic attendees between March-2004 and November-2009, fulfilling high-risk criteria for the UK Familial Ovarian Cancer Screening Study.

Methods

Risk management options discussed included RRSO and ovarian surveillance. Outcomes data were analysed from a bespoke database. The competing risk method was used to model the cumulative incidence function(CIF) of RRSO over time, and Sub-Hazard ratio(SHR) to assess the strength of association of variables of interest with RRSO. Gray's test was used to evaluate the difference in CIF between two groups and multivariable competing risk regression analysis to model the cumulative probabilities of co-variates on the CIF.

Results

Of 1133 eligible women 265(21.4%) opted for RRSO and 868(69.9%) for screening. Women undergoing RRSO were older (49years,IQR-12.2) than those preferring

screening (43.4years,IQR-11.9)($p<0.0005$). The cumulative probability(CIF) for RRSO at 5years was 0.55(CI0.45,0.64) for BRCA1/2 carriers and 0.22(CI0.19,0.26) for women of unknown mutation status($p<0.0001$); 0.42(95%CI0.36,0.47) for postmenopausal women($p<0.0001$); 0.29(95%CI0.25,0.33) for parity ≥ 1($p=0.009$) and 0.47(95%CI 0.39,0.55) for a personal history of breast cancer($p<0.0001$). Variables of significance from the regression analysis were: a BRCA1/2 mutation(SHR 2.31(CI 1.7, 3.14)), postmenopausal status(SHR2.16(CI 1.62,2.87)) and a personal history of breast cancer(SHR1.5(CI 1.09,2.06)).

Conclusions

Decision making is a complex process and women opt for surgery many years after initial risk assessment. BRCA carriers, postmenopausal women and women who had breast cancer are significantly more likely to opt for preventative surgery.

Key Words

BRCA, Risk Reducing Salpingo-oophorectomy, RRSO, ovarian cancer, tubal cancer, unknown mutation status, competing risk

Introduction

Mutations in the BRCA1/2 genes contribute to most of the known ovarian cancer risk in women at increased risk for familial ovarian cancer, with a number of moderate to low penetrance variants accounting for the residual familial risk. Women carrying a BRCA1 or BRCA2 mutation have up to a 49-65% risk of developing breast cancer and a 18-40% risk of developing ovarian cancer till 70 years age.[1, 2] Higher penetrance estimates have been reported in series of high-risk families with multiple cancer cases ascertained through genetic clinics.[3-6]

Risk reducing salpingo-oophorectomy (RRSO) has been shown to be the most effective option for preventing tubal/ ovarian cancer, with a hazard ratio (HR) of 0.21 (95%CI 0.12, 0.39)[7] having been reported on meta-analysis in known BRCA carriers. Oophorectomy has also been found to half the risk of subsequent breast cancer in premenopausal women who have not undergone prophylactic mastectomy.[7] Screening for ovarian cancer in this population is still of unproven benefit and is currently recommended only within the context of a research study. The advantage of reduction in ovarian cancer risk with RRSO must be weighed against the as yet unproven benefit of screening in this population, anxiety associated with false positive surveillance results as well as the potential surgical risks[8-10] and residual risk of primary peritoneal cancer.[11] Despite the lack of evidence of benefit, many women opt for screening and RRSO uptake rates have been found to vary considerably within centres as well as between countries.[12, 13]

In addition in premenopausal women, RRSO also leads to the onset of premature menopause and the loss of subsequent fertility. Premature menopause has been

associated with a higher risk of cardiovascular disease,[14-16] potential cognitive impairment and Parkinsonism,[17-19] osteoporosis, vasomotor symptoms, and detrimental impact on quality of life.[20, 21] A potential mortality impact[22] has also been described. Risks seem to be higher for women who undergo the procedure under the age of 45 and do not take hormone replacement therapy (HRT).[21, 22] Thus, the timing of surgery is of significant importance and the choices high-risk women make may change over time. However, only three of the previous reports evaluating uptake of preventative surgery in BRCA carriers report a time to event analysis.[23-25] A study of 306 Dutch BRCA1/BRCA2 carriers found a 75% RRSO uptake rate over a 10 year period.[24] A study from Chicago, found a 70% uptake over a 7 year period in 88 BRCA1/BRCA2 carriers.[25] A Manchester based study of 212 BRCA1/2 carriers reported higher uptake in BRCA1 (52%) compared to BRCA2 carriers (28%) over a 7 year period.[23] The median time to surgery in these studies varied from 12.5 to 34 months.

Here we undertake a time to event analysis to report on the factors affecting uptake of RRSO in high-risk women attending a tertiary multidisciplinary gynaecological familial cancer clinic. The uniqueness of our cohort includes the presence of a large number of women from high-risk families for whom genetic testing is unavailable in the UK due to the absence of a live affected relative. Moreover, for the first time in such an analysis we use a competing risk method which reduces potential bias related to censoring associated with Kaplan Meier[26] and standard Cox[27] models in earlier reported time to event analyses.

Materials and Methods

The familial gynaecological cancer clinic at UCLH is a tertiary level clinic for managing women at 'high-risk' for familial gynaecological cancer. Women were identified from the clinic's bespoke database as high-risk on the basis of the inclusion criteria (family history / mutation status) for the United Kingdom Familial Ovarian Cancer Screening Study (UKFOCSS) (Supplemental table-1).[9, 28] BRCA gene testing within the UK National Health Service (NHS) is primarily available to cancer affected individuals from high-risk families (≥20% carrier probability) or individuals from a family with a confirmed BRCA mutation. Thus a number of high-risk women in the UK are unable to access gene testing and are of unknown mutation status (UMS).

Women are managed within the context of a multi-disciplinary team, which includes gynaecological oncologists, a radiologist, a clinical geneticist, a clinical psychologist, a clinical nurse specialist, minimal access gynaecologists and a pathologist.[9] All women attending the clinic undergo a pedigree-based clinical risk assessment and receive comprehensive advice on the advantages and disadvantages of RRSO and ovarian cancer screening as well as reproductive and life style issues. The primary recommendation for high-risk women is RRSO after the age of 40, if her family is completed. Premenopausal women undergoing surgery are generally advised short term HRT till the age of 50 years. Screening for ovarian cancer is available in the context of a national trial, UKFOCSS for those >35 years age.

Prior to RRSO, all high-risk women undergo a pre-operative CA125 and transvaginal ultrasound scan (TVS). Surgery involves removal of both tubes and ovaries (or all

147 remaining adnexae in women who had undergone previous partial removal),
148 peritoneal washings for cytological examination and endometrial sampling.
149
150 Prospectively collected demographic, clinical and pathology data were stored in a
151 bespoke database and used for the current analysis. Where necessary, hospital case
152 notes as well as pathology records were reviewed. The database was searched for
153 high-risk women from breast and/or ovarian cancer families who had their first clinic
154 visit between April-2004 and November-2009. Women who had amenorrhoea for 12
155 months (excluding those with a medical or physiological explanation such as, Mirena
156 IUS, hormonal therapy or breast feeding) were considered to be postmenopausal.
157 Statistical Analysis:
158 The effect of individual variables on RRSO was initially evaluated using univariate
159 analysis. The Mann-Whitney non-parametric test was used to compare age
160 distributions between groups after reviewing histograms. Chi-Square with Yates'
161 continuity correction and Fisher's exact test were used to calculate the difference
162 between proportions. Two sided p values are reported for all statistical tests.
163
164 Competing Risk Analysis:
165 In a competing risks setting, the main disadvantage of standard survival analysis
166 methods relates to censoring. Popular methods, such as the Kaplan-Meier estimator or
167 the Cox proportional hazards model assume that censoring is non-informative and
168 independent.[26, 27] Patients who withdraw or are lost to follow-up during the study are
169 classified as censored and are assumed to have the same risk of RRSO (event of
170 interest) as others who are alive and have not undergone RRSO at the end of the
171 study. However, women who undergo a competing risk event such as death from

unrelated causes during the study are also treated as censored within a Kaplan-Meier analysis. But, as they are deceased they are no longer at risk of RRSO. Some women who are undergoing screening will have to undergo surgery due to a screen detected abnormality. This would not be true 'prophylactic surgery'. Thus there may be a number of reasons (competing risks) as a result of which women cannot subsequently opt for RRSO. Using the traditional Kaplan-Meier product-limit method in such situations gives a false/ over-inflated picture of the cumulative incidence of the event of interest (RRSO). Hence, in the presence of competing risks, instead of the traditional Kaplan-Meier method[26] we have used a competing risk / actuarial cumulative incidence analysis used that considers cause-specific hazard functions (i.e for each competing risk separately).[29]

In this analysis, we have used a competing risk method to model the cumulative incidence function (CIF) of RRSO over time. The cumulative incidence function gives the cumulative probability of occurrence of a particular event type in the presence of other (=competing) events and is a function of both the survival function and cause-specific hazard function at time *t*. Withdrawals due to death; bilateral salpingo-oophorectomy resulting from a screen detected abnormality; and negative genetic test for a known predisposing mutation in the family were treated as competing risks. Individuals were censored at the point of all other reasons for withdrawal or at last follow-up (study end).

The impact of individual variables on the cumulative incidence function was calculated for RRSO and competing risk events. In addition to CIF plots for different factor levels, the significance was assessed univariately using Gray's test for

subhazard distributions. This is similar to the familiar log-rank test, except that in the latter test a subject with a competing event would exit the 'at risk' set whereas in Gray's test the subject remains 'at risk' forever.[30, 31]

It is expected that many of the identified covariates will be correlated, and provide similar information. We chose to identify those factors that have a uniquely strong relationship with time to RRSO. A competing risks version of the Cox proportional model allows a regression of multiple variables on time to RRSO. In this model, the exponentiated coefficients are known as the subhazard ratios (SHR), and were used to assess the strength of association for a variable with the primary event's subhazard distribution, which is directly related to the CIF. As with the standard Cox model, the assumption of proportional subhazards means the effect of the SHRs work multiplicatively on the baseline subhazard. Selection of variables was via a forward stepwise regression with inclusion set at p=0.05 and exclusion at p=0.1.This analysis was undertaken using Stata 11.0. and the 'cmprsk' package written for R. Two sided p values are reported for all statistical tests.

Results

Between April 2004 and November 2009, 1241 high-risk women from breast and/or ovarian cancer families attended clinic (initial visit) and underwent risk assessment and counselling. Of these, 108 (8.7%) were <35 years and deferred decision making. Of the remaining 1133 women by November 2009, 265 (21.4%) underwent RRSO and 868 (69.9%) opted for screening within UKFOCSS. Of the women being screened, 105 (12.1%) withdrew during the study period. Of these 43 (4.95%) underwent surgery for a screen detected abnormality, 27 (3.1%) tested negative for a

known familial BRCA mutation, 9 (1%) moved residence, 10 (1.1%) changed their mind and 16 (1.8%) gave no reason for withdrawal. Detailed characteristics of the cohort are described in Table-1.

Of the 1133 women, 157 were BRCA1 carriers, 130 were BRCA2 carriers, and 3 carried both a BRCA1 and BRCA2 mutation. 843 women had unknown mutation status, of whom 43% were from breast cancer only, 83% from breast and ovarian cancer and 95% from ovarian cancer only families. Women undergoing RRSO were older (median age 49, IQR 12.2years) than those opting for screening (median age 43.4, IQR 11.9 years) ($p<0.0005$). The median time to RRSO was 36.53 (IQR 17.65, 52.64) months. Initial univariate analysis showed that women who carried a BRCA1/2 mutation, were post-menopausal, had a personal history of breast cancer, and were from breast cancer only families were more likely to opt for RRSO over screening (Table-1).

On competing risk analysis the overall cumulative probability of undergoing prophylactic surgery in the entire cohort over 60 months was 0.29 (95%CI 0.26, 0.32). The cumulative probability for undergoing RRSO at 5 years was 0.55 (95%CI 0.45,0.64) for BRCA1/2 carriers and 0.22 (95%CI 0.19,0.26) for women of UMS. Gray's test showed this difference between BRCA carriers and UMS women to be highly significant ($p<0.0001$) for RRSO but not for competing risk events ($p=0.111$) (Table-2, Fig-1). Similarly the CIF for RRSO was significantly different between pre- and post-menopausal groups, women with and without a personal history of breast cancer, those with and without a history of ovarian cancer <50 years in the family, nulliparous women and those with parity≥1, as well as between women from breast

cancer only families and those from breast and ovarian/ ovarian only families (Table-3). Menopausal status (p=0.251), a personal history of breast cancer (p=0.327), history of early onset ovarian cancer in the family (p=0.698), parity (p=0.396) and a family history of breast cancer (p=0.191) did not have any significant affect on competing risk events (Fig 2a, 2b, 2c, 2d and 2e respectively). We also found the CIF to be significantly different for RRSO between age groups of 30-40 years, 40-50 years, 50-60 years, 60-70 years and 70-80 years ($p<0.0001$, Fig 2f), but not for the competing risk events (p=0.553).

A competing risk regression assuming proportional subhazards was undertaken to identify the key covariates from Table-1 which remained significant for RRSO (Table-4). In the final model, the sub hazard ratios (SHR) were 2.31 (95%CI 1.7, 3.14) for BRCA1/2 carriers, 2.16 (95%CI 1.62, 2.87) for postmenopausal women, and 1.5 (95%CI 1.09, 2.06) for those with a personal history of breast cancer. The SHR of 1.43 (95%CI 0.99, 2.06) for parity≥1 neared statistical significance (p=0.056) and remained part of the final equation (Table-4). All SHRs were greater than one, indicating that an increase (or presence) in this factor increased the subhazard and hence the CIF for RRSO.

Discussion

Our study highlights that counselling and decision making for women at high risk of familial ovarian cancer is a complex process and women continue to opt for surgery many years after their initial risk assessment. It re-emphasises the previously reported dynamic nature of decision making which changes over time.[23-25] BRCA carriers,

postmenopausal women and those who have had breast cancer are significantly more likely to opt for risk reducing surgery.

The cumulative probability of undergoing prophylactic surgery in our cohort was 0.29 (95%CI 0.26, 0.32). This is less than most reports in the literature, where varying RRSO uptake rates ranging from 15% to 78% have been reported, but the majority are over 48%.[12] However, the bulk of all these reports include BRCA carriers in the main and are limited by not accounting for time in the analysis. The RRSO rates reported in previous time to event analysis vary from 45% to 75%.[23-25] A significant factor accounting for our lower uptake is the larger proportion of women of unknown mutation status (CIF of 22.2% at 60 months) in our cohort. This low level of uptake in untested women has been reported in one previous small series,[32] and is in keeping with previous reports of a positive BRCA genetic test result being a predictor of RRSO uptake.[32, 33] The CIF for RRSO of 54.5% at 60 months found in BRCA1/2 carriers in our cohort is consistent with one previous time to event analysis[23] but lower than other reports in the literature.[24, 25, 34] In addition to restricted access to genetic testing in the UK these differences may also be due to heterogeneity of populations, individual preferences or other psychosocial factors. The ability to opt for a national ovarian cancer screening study at our centre may also have contributed to these results.

The strengths of our study include its large size, a mixed cohort of women with known BRCA mutations and unknown mutation status, longitudinal nature of follow-up, prospectively collected data and use of the competing risk method for analysis. To the best of our knowledge ours is the largest series with high-risk women who were

296 unable to, or chose not to undergo genetic testing for BRCA1/2 mutations. Our study
297 is different from previous time to event analysis[24, 25] as it helps to highlight the
298 differences in genetic testing practices in the UK and elsewhere in the world. Our data
299 that BRCA carriers are 2.3 times more likely to opt for preventative surgery suggests
300 that uptake of prophylactic oophorectomy may vary with level of proven ovarian
301 cancer risk. Such a finding of risk-linked uptake of preventative surgery has
302 previously been reported for prophylactic mastectomy.[23] One time to event analysis[23]
303 reported an increased RRSO rate in BRCA1 carriers who are known to have a higher
304 risk compared to BRCA2 carriers.[23, 35] However, consistent with the Dutch study,[24]
305 and most other analyses we did not find a significant difference in RRSO rates
306 between BRCA1 and BRCA2 carriers (p=0.54). Increasing access to genetic testing in
307 the UK with resultant confirmation of risk may lead to higher RRSO uptake rates with
308 the potential to reduce ovarian/tubal cancer incidence in high-risk women.
309
310 Our study is one of the few to explore time as a factor in the uptake of preventative
311 surgery. Another advantage of our study is the use of competing risk methodology. 60
312 (57%) of the 105 withdrawals in our study were due to a competing risk event. These
313 women could not have subsequently undergone RRSO. Within a routine Kaplan-
314 Meier analysis these cases would be considered at similar risk of subsequent events as
315 other subjects with continued follow-up. In fact most other studies do not report
316 details of reasons for salpingo-oophorectomy. Competing risks have not been reported
317 in three previous time-to-event analyses of preventative surgery for BRCA carriers.[23-
318 [25] It is possible this bias may have contributed to the higher rates of prophylactic
319 salpingo-oophorectomy reported in those series.
320

We found that women continue to opt for RRSO many months / years after their initial decision. A significant proportion of BRCA carriers underwent surgery >12-24 months after their initial counselling appointment following results of genetic testing (Table-2). This is in contrast with most previous reports suggesting that BRCA carriers undergo surgery within a year after learning their genetic test result[36-38] but consistent with three recent time to event analysis[24, 25] indicating that BRCA carriers continue to opt for surgery many years later. Our data indicate that this finding also holds true for women with unknown mutation status, with only half of those women opting for surgery doing so within 12 months of their initial consultation (Table-2). The overall median time to RRSO in our study was greater than the Chicago study[25] but similar to a Dutch study.[24]

Consistent with findings of others,[25, 32, 36, 39] including two previous time to event analysis,[24, 25] we found that increasing age (Fig 2f) and having children (Fig 2d) were factors associated with RRSO uptake. The median age of women opting for RRSO in our study is slightly older than most other reports in the literature, including the Dutch and Chicago study.[24, 25] The Manchester study[23] like ours found a significant difference in RRSO uptake across age groups. However, they reported higher uptake rates with time in younger women, while we found an increasing RRSO uptake with increasing age (Fig 2f). Postmenopausal women in our study were 2.16 times more likely to opt for RRSO. Although menopause was not reported as an independent risk factor in previous time to event analyses it has been found to be of importance in other studies.[34] Pre-menopausal women are more likely to be younger, nulliparous, have concerns regarding detrimental effects of the menopause and hence, delay surgery.[23, 25]

346 Our finding of a personal history of breast cancer being associated with increased
347 RRSO uptake was not reported in earlier time to event analyses[23-25] but has been
348 described by other series.[13, 21, 38, 40, 41] However, in contrast with some other reports we
349 did not find that having a first degree relative with ovarian cancer[35, 42] or a family
350 history of early onset breast cancer were significant predictors of RRSO. The finding
351 that a history of early onset ovarian cancer (<50 years) in the family was inversely
352 associated with uptake of preventive surgery on univariate analysis is likely to be a
353 confounding effect or chance finding as it was not maintained following multivariable
354 competing risk regression analysis. Although the Chicago study reported a family
355 history of ovarian cancer to be a significantly associated with RRSO uptake, this was
356 not observed in our study or the other time to event analyses.[23, 24] We did not find
357 Jewish ethnicity to be a factor affecting uptake of risk reducing surgery in our cohort.
358 A lower surgical uptake has been reported in some minority populations such as
359 African-American populations.[25]
360
361 Multivariable regression analysis (Table-4) indicated that the main factors affecting
362 decision making were having a BRCA gene mutation, being postmenopausal, a
363 personal history of breast cancer and having children. The fact that these factors did
364 not have any significant effect on competing risk events (Fig 1, 2a, 2b, 2c, 2d) is
365 reassuring as it suggests that competing risk events in the cohort occurred
366 independently of co-variates of significance. Although Gray's test showed a
367 significant difference in RRSO uptake across age groups, age was not part of the final
368 model, as the effect of this variable was probably accounted for by menopausal status
369 in the equation. It is interesting to note that the SHR for postmenopausal status was
370 similar to that for carrying a BRCA carrier status indicating that the magnitude/

contribution of these factors towards decision making was similar in high-risk women. Limitations of our analysis are that we lacked data on factors such as psychosocial factors, perceived risk, cancer worry and fear of surgery, which have been shown to affect uptake of preventative surgery.[34, 43, 44] In addition it was not possible to assess whether decision making varied depending on the individual clinician (from the familial clinic team) seen at each consultation.

The study has important implications for counselling/ management and for planning/ commissioning of services of women at high-risk of familial ovarian/tubal cancer, particularly in the UK and other countries with restricted access to genetic testing. It adds to the knowledge base related to factors influencing RRSO in high-risk women and the amount of time that this decision-making process can take. It also highlights the large number of high-risk families with no living cancer affected relatives who could benefit from expanded genetic testing to further clarify their cancer risks as well as access to risk management options.

Conclusion

A large number of high-risk women find bilateral salpingo-oophorectomy to be an acceptable option for reducing their risk of ovarian and tubal cancer. Decision making is a complex and dynamic process which changes over time. Women continue to opt for surgery many years after their initial counselling and risk assessment. Clinicians should pursue follow-up opportunities with their high-risk patients as many will delay decision making. A number of different factors affect uptake of risk reducing surgery in these women. RRSO uptake is risk dependent with lower uptake rates in high risk women who are unaware of their mutation status. A number of women delay surgery

until they have completed their families or reached the menopause. Known BRCA carriers and women who have had breast cancer are more likely to opt for preventative surgery. Recognition and appreciation of these matters can assist in planning and commissioning of services for high-risk women. Relaxation of BRCA testing criteria in the UK may lead to greater access to genetic testing, detection of more carriers and increased RRSO uptake. Risk management options need to be individualised for each woman and it is important for clinicians to be aware of these issues when counselling women at increased risk.

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Disclosure of interests

IJ has consultancy arrangements with Becton Dickinson, who have an interest in tumour markers and ovarian cancer. IJ and UM have a financial interest in Abcodia, Ltd., a company formed to develop academic and commercial development of biomarkers for screening and risk prediction. IJ is a member of the board of Abcodia Ltd and Women's Health Specialists Ltd. ANR has received honoraria from Fujirebio Diagnostics for giving lectures and attending meetings on the use of biomarkers in ovarian cancer management, but none were directly related to this work. ES received honoraria from Ethicon for provision of training to healthcare professionals; this was not related to this work. The other authors declare no conflict of interest.

Contribution to authorship

RM, AA and MJ were involved in initial data collection. RM, UM, IJ were involved in analysis, drafting and writing of the paper. MB and RM performed the statistical analysis and contributed to writing the statistical sections of the manuscript. ANR, LS, ES, AA, AS, DO, SG, MJ, CB, EB contributed to writing of the manuscript. UM,

IJ, RM, ANR, CB, LS, SG, ES, EB, AS, DO were responsible for the clinical care of the patients. The final draft was prepared by RM, UM, IJ and approved by the others.

Details of ethics approval

The project was referred to the Chair of the Research Ethics committee (National Hospital for Neurology and Neurosurgery & institute of Neurology Joint REC, reference number 07L 173). Under the Research Governance Framework the project was deemed to be a clinical audit, and permission for data analysis and submission for publication was given.

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TABLES LIST

Table-1: Baseline characteristics of the cohort

FDR- First degree relative, FH- Family History, HBC- High-risk breast cancer only family, HBOC- high-risk breast and ovarian cancer family, HOC- High-risk ovarian cancer only family, IQR- Inter-quartile range, RRSO- Risk reducing salpingo-oophorectomy, UMS- Unknown mutation status, yrs- years

Table-2: Cumulative RRSO Probability (CIF) by BRCA1/2 status over time

CIF- Cumulative Incidence Function, CI- confidence interval, RRSO- Risk reducing salpingo-oophorectomy , UMS- Unknown mutation status,

Table-3: Cumulative RRSO Probability (CIF) at 5 years

CIF- Cumulative Incidence Function, CI- confidence interval, FH- family history, h/o- history of, RRSO- Risk reducing salpingo-oophorectomy

Table-4: Competing Risk Multivariable Regression Analysis
CI- confidence interval, SHR- Sub-Hazard Ratio, Std. Err- standard error, Self Breast Cancer- personal history of breast cancer.

Figure-1: Cumulative Incidence Function (CIF) for RRSO and competing risk by BRCA1/2 status

BRCA yes- BRCA1/BRCA2 carriers

BRCA No- Unknown mutation status

Surgery- RRSO (Risk Reducing Salpingo-oophorectomy)

Figure 2: Cumulative Incidence Function (CIF) for RRSO and competing risk

Figure 2a: CIF for RRSO and competing risk by menopausal status

Figure 2b: CIF for RRSO and competing risk by personal history of breast cancer

Figure 2c: CIF for RRSO and competing risk by family history of ovarian cancer <50 years

Figure 2d: CIF for RRSO and competing risk by Parity

Figure 2e: CIF for RRSO and competing risk by high risk breast cancer family

Figure 2f: CIF for RRSO and competing risk by Age groups 30-40 years, 40-50 years, 50-60 years, 60-70 years and 70-80 years

Surgery- RRSO (Risk Reducing Salpingo-oophorectomy)

PM- post-menopausal

Yrs- years

Parity1+: Parity ≥1

Parity0= Nulliparous: Baseline CIF

Table-1: Baseline characteristics of the cohort

	RRSO (n= 265)	Screening (n= 868)	p value
Median age (IQR)	**49 (12.2)**	**43.4 (11.9)**	**<0.0005 ¥**
BRCA 1,2 Carriers	**111 (41.9%)**	**179 (20.6%)**	**<0.0005 #**
BRCA1	**63 (23.8%)**	**97 (11.2 %)**	**<0.0005 #**
BRCA2	**48 (16.7%)**	**85 (7.7%)**	**<0.0005 #**
BRCA1+2	**0**	**3**	**1 ***
UMS	**154 (58.1%)**	**689 (79.4%)**	**<0.0005 #**
Post-menopausal	**138 (52.1%)**	**251`(28.9%)**	**<0.0005 #**
Parity ≥1	**189/225 (84%)**	**624/818 (76.3%)**	**0.013 #**
Jewish Ancestry	**54/254 (18%)**	**203/847 (19.5%)**	**0.371 #**
FAMILY HISTORY			
HBC	**76/259 (29.3%)**	**195/847 (23%)**	**0.038 #**
HBOC	**150/259 (57.9%)**	**517/847 (61%)**	**0.369 #**
HOC	**31/259 (12%)**	**133/846 (15.7%)**	**0.162 ***
FDR Breast cancer	**138/258 (53.5%)**	**443/846 (52.4%)**	**0.752 #**
FDR Ovarian cancer	**125/258 (48.4%)**	**455/845 (53.8%)**	**0.129 #**
FH of Ovarian cancer <50yrs	**64/257 (24.9%)**	**271/846 (32%)**	**0.029 #**
FH of Breast cancer <45yrs	**148/257 (57.6%)**	**466/845 (55.1%)**	**0.491 #**
Self breast cancer	**97/258 (37.6%)**	**157/845 (18.6%)**	**<0.0005 #**

FDR- First degree relative, FH- Family History, HBC- High-risk breast cancer only family, HBOC- high-risk breast and ovarian cancer family, HOC- High-risk ovarian cancer only family, IQR- Inter-quartile range, RRSO- Risk reducing salpingo-oophorectomy, UMS- Unknown mutation status, yrs- years

Chi Square, * Fisher's exact test, ¥ Mann Whitney Test

Using a Bonferroni correction for multiple testing the above p values should be compared with a critical value of $\alpha = 0.003$

Table-2: Cumulative RRSO Probability (CIF) by BRCA1/2 status over time

Months	12	24	36	48	60	Gray's Test
BRCA1/2 CIF	0.299	0.381	0.429	0.482	0.545	RRSO incidence BRCA1/2 vs. UMS: p<0.0001
95% CI	(0.243, 0.355)	(0.319, 0.443)	(0.362, 0.496)	(0.406, 0.557)	(0.449, 0.641)	
UMS CIF	0.114	0.173	0.192	0.204	0.222	Competing Risk incidence BRCA1/2 vs. UMS: p= 0.111
95% CI	(0.092, 0.136)	(0.146, 0.200)	(0.163, 0.221)	(0.174, 0.234)	(0.189, 0.256)	

CIF- Cumulative Incidence Function, CI- confidence interval, RRSO- Risk reducing salpingo-oophorectomy , UMS- Unknown mutation status,

Table-3: Cumulative RRSO Probability (CIF) at 5 years

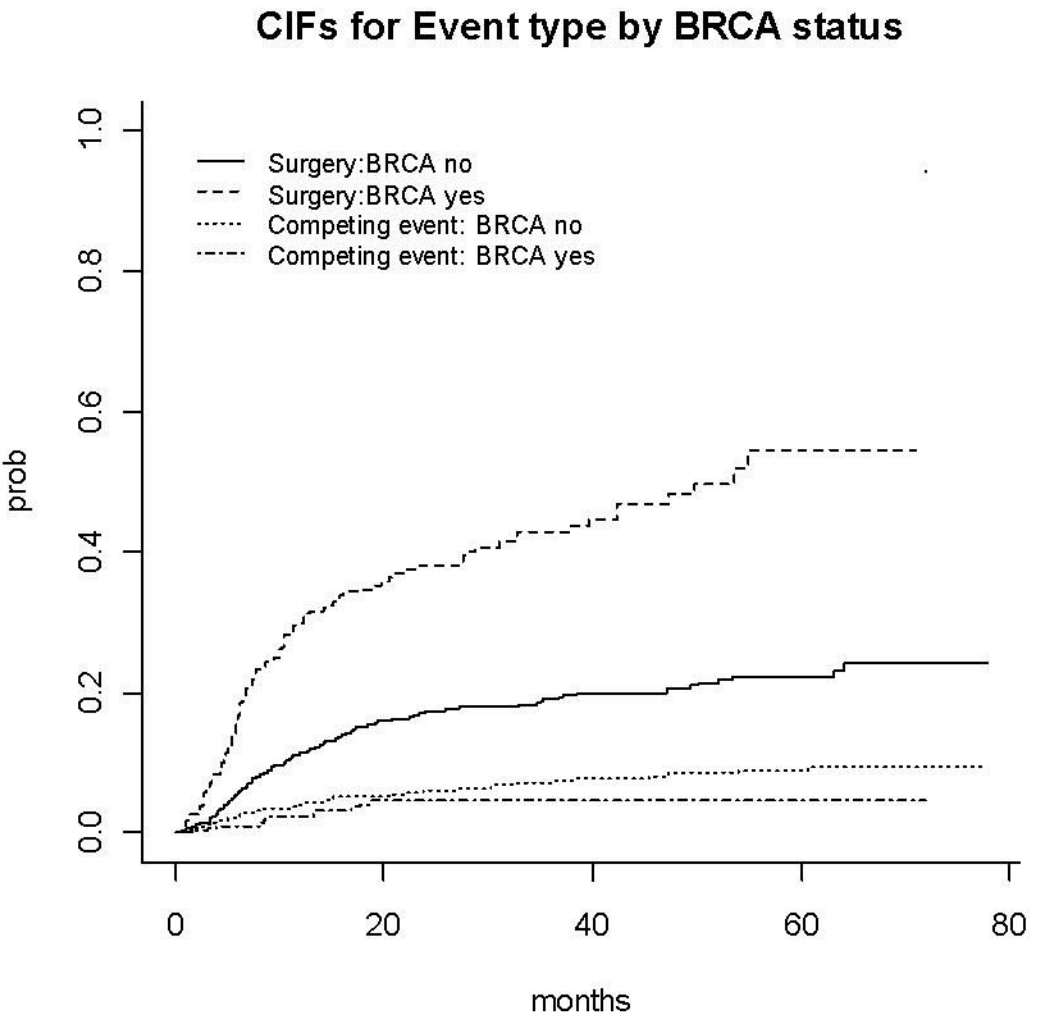
Variable	Cumulative RRSO Probability	95% CI	Gray's Test	Figure
Premenopausal	0.23	0.19, 0.27	p<0.0001	2a
Postmenopausal	0.42	0.36, 0.47		
Personal h/o breast cancer	0.47	0.39, 0.55	p<0.0001	2b
No personal h/o breast cancer	0.24	0.21, 0.28		
FH of early onset ovarian cancer	0.23	0.18, 0.28	p=0.006	2c
No FH of early onset ovarian cancer	0.32	0.28, 0.37		
Nulliparous	0.20	0.14, 0.27	p=0.009	2d
Parity≥1	0.29	0.25, 0.33		
FH: breast cancer only family	0.35	0.43, 0.28	p=0.006	2e
FH: breast and ovarian/ovarian cancer only families	0.27	0.24, 0.31		

CIF- Cumulative Incidence Function, CI- confidence interval, FH- family history, h/o- history of, RRSO- Risk reducing salpingo-oophorectomy

Table-4: Competing Risk Multivariable Regression Analysis for RRSO

Co-variate	SHR	Std. Err.	z	P>z	[95% CI]	
Parity ≥1	1.428	0.266221	1.91	0.056	0.990813	2.05776
Postmenopausal	2.158	0.314172	5.28	<0.0001	1.621955	2.870272
BRCA1/2	2.314	0.361977	5.36	<0.0001	1.70296	3.14422
Self Breast Cancer	1.501	0.243502	2.5	0.012	1.0921	2.062774

CI- confidence interval, SHR- Sub-Hazard Ratio, Std. Err- standard error, Self Breast Cancer- personal history of breast cancer.


CIFs for Event type by BRCA status
Surgery:BRCA no
Surgery:BRCA yes
Competing event: BRCA no
Competing event: BRCA yes
prob
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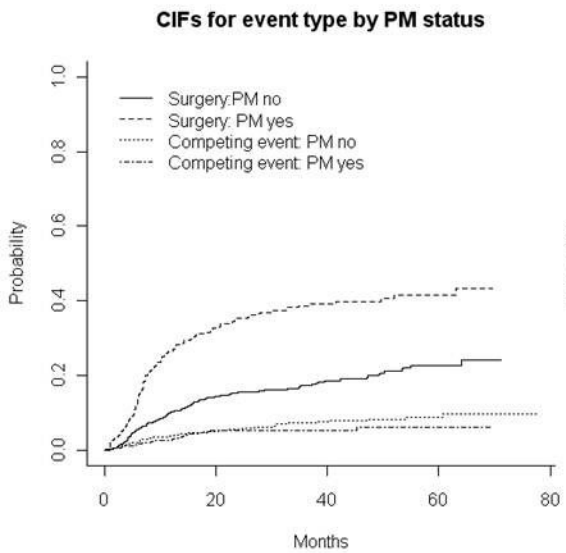
0.2
0.4
0.6
0.8
1.0
0
20
40
60
80
months

Figure 2a



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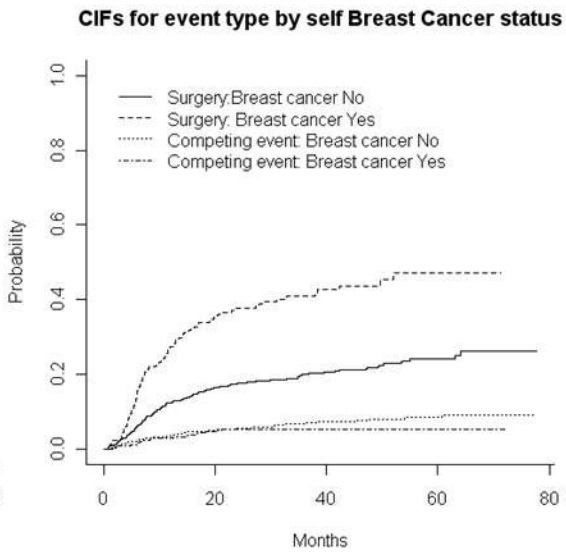

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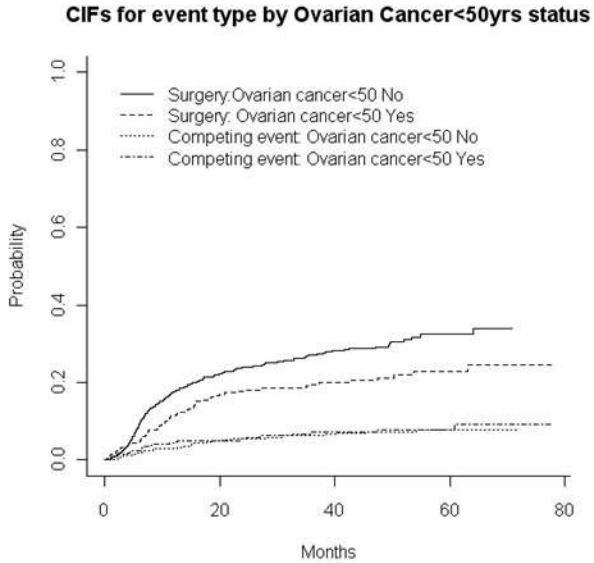

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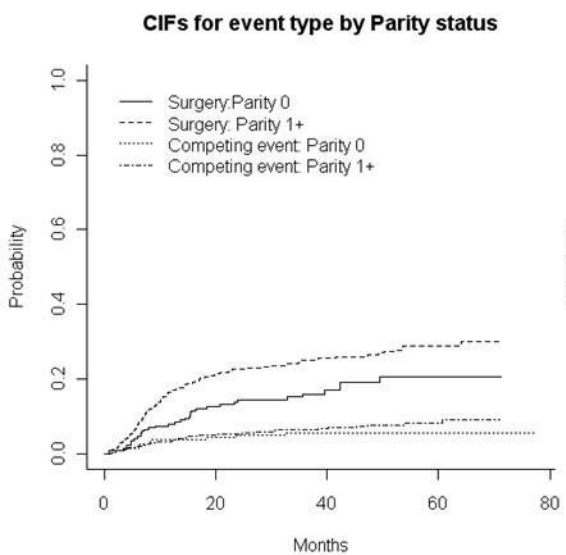

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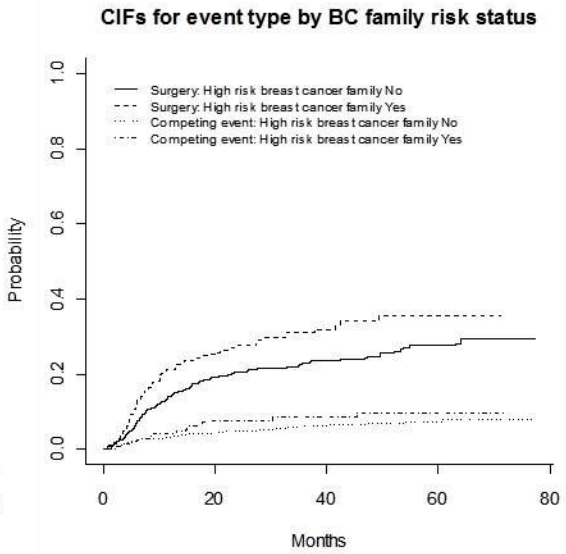

Figure 2f