JAMA. Author manuscript; available in PMC 2010 October 01.

Published in final edited form as:
JAMA. 2010 September 1; 304(9): 967–975. doi:10.1001/jama.2010.1237.

Association of Risk-Reducing Surgery in *BRCA1* or *BRCA2* Mutation Carriers with Cancer Risk and Mortality

Susan M. Domchek[1,2], **Tara M. Friebel**[3], **Christian F. Singer**[4], **D. Gareth Evans**[5], **Henry T. Lynch**[6], **Claudine Isaacs**[7], **Judy E. Garber**[8], **Susan L. Neuhausen**[9], **Ellen Matloff**[10], **Rosalind Eeles**[11], **Gabriella Pichert**[12], **Laura Van t'veer**[13], **Nadine Tung**[14], **Jeffrey N. Weitzel**[15], **Fergus J. Couch**[16], **Wendy S. Rubinstein**[17], **Patricia A. Ganz**[18], **Mary B. Daly**[19], **Olufunmilayo I. Olopade**[20], **Gail Tomlinson**[21], **Joellen Schildkraut**[22], **Joanne L. Blum**[23], and **Timothy R. Rebbeck**[1,3]

[1]Abramson Cancer Center, The University of Pennsylvania School of Medicine, Philadelphia, PA [2]Department of Medicine, The University of Pennsylvania School of Medicine, Philadelphia, PA [3]Center for Clinical Epidemiology and Biostatistics, The University of Pennsylvania School of Medicine, Philadelphia, PA [4]Division of Special Gynecology, Medical University of Vienna, Austria [5]Department of Clinical Genetics, St. Mary's Hospital, Manchester, UK [6]Creighton University, Omaha, NE [7]Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC [8]Dana Farber Cancer Institute, Boston, MA [9]Epidemiology Division, UC Irvine School of Medicine, Irvine, CA [10]Yale University, New Haven, CT [11] The Institute of Cancer Research & Royal Marsden NHS Foundation Trust, London & Sutton [12]Guys and St. Thomas Foundation Trust, London, UK [13]Netherlands Cancer Institute, Amsterdam, Netherlands [14]Beth Israel Deaconess Medical Center, Boston, MA [15]City of Hope National Medical Center, Duarte, CA [16]Mayo Clinic College of Medicine, Rochester, MN [17]NorthShore University HealthSystem, Evanston, IL and The university of Chicago, Chicago, IL [18]Jonsson Comprehensive Cancer Center at the University of California, Los Angeles, CA [19]Fox Chase Cancer Center, Philadelphia, PA [20]University of Chicago Medical Center, Chicago, IL [21]University of Texas, Southwestern Medical Center, Dallas, TX [22]Duke University Medical Center, Durham, NC [23]Baylor-Charles A. Sammons Cancer Center, Dallas, TX.

Abstract

Corresponding Author: Timothy R. Rebbeck, Ph.D. Department of Biostatistics and Epidemiology, University of Pennsylvania School of Medicine, 217 Blockley Hall, 423 Guardian Drive, Philadelphia, PA 19104-6021, Tel: 215-898-1793, Fax: 215-573-1050, rebbeck@mail.med.upenn.edu.

The PROSE Consortium includes the following centers and individuals, with the number of participants contributed to the present study provided in parentheses: University of Vienna, Austria (n=360; Christian Singer); Beth Israel, Boston, MA (n=119; Nadine Tung); Baylor-Charles A. Sammons Cancer Center (n=13, Joanne L. Blum, Becky Althaus, Gabrielle Ethington, Estelle Brothers); City of Hope, Duarte, CA (n=98, Jeffrey Weitzel); Creighton University, Omaha, NE (n=348; Carrie Snyder, Henry T. Lynch, Patrice Watson); Dana-Farber Cancer Institute, Boston, MA (311; Katherine Corso, Kathryn Stoeckert, Judy E. Garber); Duke University, Durham, NC (n=19, Joellen Schildkraut); NorthShore University HealthSystem, Evanston, IL (n=88; Wendy S. Rubinstein, Christina Selkirk, Scott M. Weissman); Fox Chase Cancer Center, Philadelphia, PA (n=71; Mary B. Daly); Guy's Hospital and St. Thomas Foundation Trust, London, UK (n=123, Gabriella Pichert, Caroline Langman, Leena da Silva); Georgetown University, Washington, DC (n=315, Camille Jasper, Claudine Isaacs); University of California, Los Angeles (n=79, Patricia A. Ganz, Joyce L. Seldon); Mayo Clinic College of Medicine, Rochester, MN (n=96, Fergus Couch); Netherlands Cancer Institute, Amsterdam, Netherlands (n=121, Marc van Beurden, Laura van 't Veer); The Institute of Cancer Research & Royal Marsden NHS Foundation Trust, London & Sutton (n=128, Rosalind Eeles, Elizabeth Bancroft, Elizabeth Page, Lucia D'Mello, Susan Shanley, Audrey Ardern-Jones, Elena Castro, Anita Mitra, Kelly Kohut, Jennifer Wiggins, The Carrier Clinic Collaborators); St. Mary's Hospital, Manchester, UK (n=353, Gareth Evans, Andrew Shenton); University of Texas-Southwestern, Dallas (n=63, Gail Tomlinson); University of Chicago, Chicago, IL (n=65, Shelly Cummings, Olufunmilayo Olopade); University of Pennsylvania, Philadelphia, PA (n=465, Susan Domchek, Tara M Friebel, Timothy Rebbeck, Jill Stopfer, Jacquelyn Powers, Katherine Nathanson); University of Utah, Salt Lake City, UT and University of California, Irvine (n=270, Susan Neuhausen, Linda Steele); Women's College Hospital, Toronto, CA (n=108, Steven A. Narod); Yale University, New Haven, CT (n=179, Ellen T. Matloff, Karina L. Brierly).

Europe PMC Funders Author Manuscripts

Context—Risk-reducing mastectomy (RRM) and salpingo-oophorectomy (RRSO) are widely used by carriers of *BRCA1* or *BRCA2* mutations to reduce their risks of breast and ovarian cancer.

Objectives—To estimate risk and mortality reduction stratified by mutation and prior cancer status.

Design—A prospective multi-center cohort study was used to assess the relationship of RRM and RRSO on cancer outcomes.

Setting—Twenty-two clinical and research genetics centers in Europe and North America.

Participants—2,482 women identified 1974-2008 and followed until the end of 2009 who tested positive for *BRCA1* or *BRCA2* mutations.

Interventions—257 (10%) underwent RRM and 993 (40%) underwent RRSO.

Main outcomes measures—Breast and ovarian cancer risk; cancer-specific and overall mortality.

Results—No breast cancers were diagnosed in women with RRM compared to 7% of women without RRM. In women who underwent RRSO, 1.1% were subsequently diagnosed with ovarian cancer, 11.4% were subsequently diagnosed with breast cancer, and 3% subsequently died from any cause, compared with 5.8% ovarian cancer, 19.2% breast cancer, and 10% overall mortality in women who did not undergo RRSO. RRSO was associated with a lower risk of ovarian cancer in those with (Hazard Ratio (HR) 0.31, 95% CI 0.12-0.82) and without a prior breast cancer (HR 0.15, 0.04-0.63), and a lower risk of first breast cancer in both *BRCA1* (HR 0.63, 0.41-0.96) and *BRCA2* (HR 0.36, 0.16-0.82) mutation carriers. RRSO was associated with a reduction in all-cause (HR 0.40, 0.26-0.61), breast cancer-specific (HR 0.44, 0.26-0.76), and ovarian cancer-specific (HR 0.25, 0.08-0.75) mortality.

Conclusions—Among a cohort of women with *BRCA1* and *BRCA2* mutations, the use of RRM was associated with a lower risk of breast cancer, and RRSO was associated with a lower risk of ovarian cancer, first breast cancer, and overall, breast-, and ovarian-cancer specific mortality.

Introduction

Women who have inherited mutations in the *BRCA1* or *BRCA2* (*BRCA1/2*) genes have substantially elevated risks of breast cancer (BC) and ovarian cancer (OC), with a lifetime BC risk of 56%–84% [1-3]. The estimated OC risks range from 36%-63% for *BRCA1* and 10%-27% for *BRCA2* mutation carriers [3-6]. Mutation carriers have cancer risk management options that include risk-reducing salpingo-oophorectomy (RRSO), risk-reducing mastectomy (RRM), screening, and chemoprevention. Due to the lack of effective screening for OC, RRSO is strongly recommended once child-bearing is complete.

RRSO has been demonstrated to decrease the risk of both BC and OC in *BRCA1/2* mutation carriers [7-16]. However, risk and mortality reduction estimates for women with and without a prior history of BC may differ and be of clinical relevance. Likewise, data are emerging that suggest *BRCA1* mutation carriers may experience differential benefits from interventions such as RRSO compared to *BRCA2* mutation carriers[15, 17]. We examine here a large cohort of *BRCA1/2* mutation carriers followed prospectively. We report cancer risk reduction estimates following RRSO and RRM in a number of scenarios incorporating mutation type (*BRCA1* vs. *BRCA2*), cancer history (prior history of BC vs. none), and use of HT.

Europe PMC Funders Author Manuscripts

Methods

Participants

Women with inherited, disease-associated *BRCA1/2* mutations were identified from 22 centers in the PROSE consortium (see Acknowledgements). Participants were ascertained between 1974 and 2008 (Median: 1999). The PROSE protocol is as previously described[12]. All participants underwent an informed consent process for participation in research. This protocol was approved by each institution's IRB. Study participants were enrolled as a cohort with time of follow up starting from patient ascertainment into the research program. Genetic testing was performed per institutional guidelines and all patients received post-testing counseling to review medical management options. Women who declined RRSO or PM were offered increased surveillance at all centers according to established guidelines. At US sites, this consisted of annual mammogram and annual MRI for those with breast tissue, and every 6-12 month transvaginal ultrasound and CA125 for those with ovaries in place (www.nccn.com). In the UK, women were offered yearly mammograms, as well as yearly MRI until age 50 (www.nice.org.uk). Ovarian cancer screening consisted of TVUS and CA125 every 4 months (www.instituteforwomenshealth.ucl.ac.uk/academic_research/gynaecologicalcancer/gcrc/ukfocss). Participants were eligible for the study if they had no ovarian cancer diagnosis and no RRSO at the time of ascertainment and had a minimum of 6 months of follow-up; they were excluded if they had a cancer diagnosis within the first six months of follow-up to avoid including cancers that would have been minimally influenced by RRSO or RRM. Participants were followed until the end of 2009 (Median date of follow up: 2005). The median follow up for women was 3.65 years (Range: 0.52-27.4 years) among those who underwent surgery, and 4.29 years (range; 0.5-27.9 years) in controls who did not undergo surgery.

4255 known *BRCA1/2* mutation carriers in the PROSE study were considered for inclusion: 12 were excluded because they had both *BRCA1* & *BRCA2* mutations, 525 because they underwent RRSO before ascertainment date, 363 because they were diagnosed with ovarian cancer before ascertainment date, 738 because we had less than 6 months of follow-up, and 135 because they were incident cases. Participants who had undergone RRM prior to ascertainment were excluded from all breast cancer incidence analyses. BC included invasive cancers and ductal carcinoma *in-situ*.

Risk-Reducing Mastectomy (RRM)

Unaffected women (without RRM) were followed prospectively from the time of ascertainment. Exposed women with RRM after ascertainment were followed from the age of their RRM. Our primary outcome was BC. If no BC occurred, women were censored at the date of OC, death, or date of last contact.

Risk-Reducing Salpingo-Oophorectomy (RRSO)

Women who underwent RRSO after ascertainment were considered “exposed”. If they did not undergo RRSO, they were considered “unexposed”. Exposed women were followed from age of RRSO and unexposed women were followed from age of ascertainment. The outcomes of interest were: 1) OC, 2) BC, 3) second primary BC in those with a prior BC, and 4) mortality.

For OC endpoints, women were followed until OC or censoring at death or date of last contact. Women were excluded if they were diagnosed with an occult OC at RRSO. When missing data were encountered, the individual was dropped from the analysis that involved the missing data point, but the individual was included in other analyses where complete data were available; in fact, because many of the data items were required for enrollment,

Europe PMC Funders Author Manuscripts

missing data was only applicable to ovarian cancer endpoints, with missing OCP data. For BC endpoints, women were excluded if they underwent RRM prior to ascertainment. Women who had RRM after ascertainment but before RRSO were considered unexposed and were censored at RRM. Women were followed until BC or were censored at OC, RRM, death, or last contact. For analysis of second primary BC, the aforementioned censoring criteria were applied, and women were also censored at the time of a contralateral mastectomy (CM). A second BC was defined as any contralateral BC or an ipsilateral BC more than five years after the first.

For the mortality analysis, the inclusion and follow-up methods were similar to the RRSO analyses described above. However, women were censored at the date of last contact, with the primary outcome being death.

Statistical Analysis

The effect of RRSO/RRM on cancer incidence and mortality was analyzed by Cox proportional hazards models. A robust variance-covariance estimation method was used to correct for non-independence of observations among participants from the same family or within centers [18]. Adjustment for year of birth was undertaken in all analyses using Cox regression. Oral contraceptive use was adjusted for when OC was the outcome. Adjustment for center of ascertainment was undertaken by stratifying analyses by center to avoid imposing linear constraints in the model. Surgical participants were followed from age of RRSO or RRM. Non-surgical participants were followed from age of ascertainment. All analyses were undertaken using STATA8 (College Station, TX). All statistical tests were based on two-sided hypotheses, and inferences of statistical significance were made at the p=0.05 level.

Results

RRM and BC Risk (Table 1)

RRM was associated with a decreased risk of breast cancer in *BRCA1/2* mutation carriers: No BC events were seen in women who underwent RRM during 3 years of prospective follow-up. In contrast, 7% of women without RRM over a similar follow up period were diagnosed with BC. *BRCA1BRCA2*

RRSO and OC Risk (Table 2)

RRSO was associated with a decreased risk of OC. Among those with no prior breast cancer, the risk reduction estimate in all *BRCA1* mutation carriers was Hazard ratio (HR)=0.31 (95% CI: 0.12-0.82). No OC events were seen in *BRCA2* mutation carriers without prior breast cancer who underwent RRSO during 6 years of prospective follow-up. In contrast, 3% of women without RRSO over a similar follow up period were diagnosed with OC*BRCA2* Among women with a prior diagnosis of BC, the risk reduction in *BRCA1* mutation carriers was HR=0.15 (95%CI: 0.07-0.33), while no post -RRSO OC were diagnosed in *BRCA2* mutation carriers.

RRSO and BC Risk (Table 3)

RRSO was associated with a decreased risk of BC in both *BRCA1* (HR=0.63, 95%CI: 0.41-0.96) and *BRCA2* (HR: 0.36, 95%CI: 0.16-0.82) mutation carriers with no prior diagnosis of BC. There was evidence for an age effect with a reduction in BC risk among *BRCA1* mutation carriers who had their RRSO before age 50 (HR=0.51 95%CI: 0.32-0.82), but no suggestion of BC risk reduction in women who underwent RRSO after age 50 (HR=1.36; 95%CI: 0.26-7.05); a test of interaction was significant with p=0.027 (HR: 0.62, 95%CI 0.41-.95). In *BRCA1* and *BRCA2* mutation carriers with a prior diagnosis of BC,

there was no evidence for reduction in risk of a second primary BC diagnosis*BRCA1BRCA2. BRCA1BRCA2BRCA1BRCA2*

Effect of RRSO on Mortality (Table 4)

RRSO was associated with significantly lower all-cause mortality in those with no prior cancer (HR=0.45, 95%CI: 0.21-0.95) and those with prior BC (HR=0.30, 95%CI: 0.17-0.53; Table 4a).*BRCA1BRCA2*When analyzed by mutation status, RRSO was associated with a significantly lower all-cause mortality in *BRCA1* mutation carriers overall [0.38 (0.24-0.62)]. With fewer participants and fewer events, all-cause mortality in *BRCA2* mutation carriers was not statistically significant [0.52 (0.22-1.23)].

RRSO was associated with a lower BC-specific mortality (HR=0.44, 95% CI: 0.26-0.76) (Table 4b) and OC-specific mortality (HR=0.24, 95% CI: 0.08-0.73) (Table 4c). In *BRCA1* mutation carriers, RRSO was associated with improved BC- (HR=0.38, 95%CI: 0.2-0.72; Table 4b) and OC-specific mortality (HR=0.25, 95%CI: 0.08-0.75; Table 4c). There were no OC deaths following RRSO in *BRCA2* mutation carriers, nor were there any BC deaths in *BRCA2* mutation carriers who underwent RRSO prior to cancer diagnosis. In an exploratory analysis, overall survival was associated with RRSO in those <50 (HR 0.41, 0.25-0.67) and in those ≥50 (HR 0.37, 0.15-0.94); however, a test of interaction was not significant suggesting no difference in overall mortality benefit between these two groups. There have been eight deaths after RRSO in those without cancer prior to RRSO: two deaths from BC, three from post-RRSO primary peritoneal cancer, one from leukemia, one from stomach cancer, and one non-cancer related (Supplementary Table 2). Although 151 (34%) of those with no prior cancer also underwent RRM, neither of the two who died from BC had undergone RRM. In those patients with BC prior to RRSO, 23 died including 19 BC deaths and one OC death.

Discussion

The clinical management of cancer risk in *BRCA1* and *BRCA2* mutation carriers is complex and is best informed by accurate knowledge of the outcomes of interventions. Most prior studies that have investigated the effect of RRSO or RRM on BC risk either did not examine effects by mutation status [7], [9], [12] or by prior cancer diagnosis [14], [19]. There may be little added benefit of RRSO on BC risk if women have chemotherapy-induced menopause, or if they are already receiving hormonal therapy. We hypothesize that both of these factors are important in determining precise estimates of risk reduction. Our results confirm that RRM is associated with a significant reduction in BC risk. In addition, RRSO is associated with a significant decrease in OC risk in both *BRCA1* and *BRCA2* mutation carriers, and in those with and without a prior BC. There is a significant reduction in BC risk following RRSO in both *BRCA1 and BRCA2* mutation carriers with no prior cancer. Overall mortality was improved in women undergoing RRSO.

RRM is a highly effective strategy for BC risk reduction [20], [21]. In our prospective analysis, *no* BC were observed after RRM. The observation of no prospectively identified BC cases may be due to biases in prior retrospective studies, or improved surgical techniques in recent prospective analyses.

RRSO is highly effective in reducing ovarian and fallopian tube cancers in both *BRCA1* and *BRCA2* mutation carriers and in those with and without a prior BC. Precise estimates of risk reduction following RRSO are needed to balance the increasingly recognized health risks caused by premature menopause[22]-[26]. We observed no primary peritoneal cancers following RRSO in *BRCA2* mutation carriers, although such cancers have been reported [10]. In *BRCA1* mutation carriers, RRSO was associated with a 70% reduction in risk of OC in

those without a prior BC and 85% in those with a prior BC. Whether these numbers are truly different, reflect censoring from death due to BC, or a protective effect following BC treatment is unknown.

RRSO was associated with a significantly decreased risk of BC in those with no prior BC with both *BRCA1* (37% reduction) and *BRCA2* mutations (64% reduction). In mutation carriers with a prior BC, RRSO had no effect on second primary BC risk. In women with sporadic BC, the benefit of RRSO when added to standard adjuvant treatment is uncertain and is the subject of multiple ongoing clinical trials. Chemotherapy often leads to cessation of menses, so any effect of ovarian ablation from RRSO may be achieved in some women by chemotherapy. In premenopausal women with estrogen receptor (ER) positive tumors, hormonal therapy in addition to chemotherapy significantly improves disease-free survival[27], [28]. Our data are in contrast to prior reports demonstrating benefit of oophorectomy in preventing contralateral BC[29], [30]. Differences in adjuvant therapy use could explain these discrepancies; however, a limitation of our study is the absence of detailed treatment information. It is important to note that OC risk is independent of menopause; menopause either naturally occurring or chemotherapy-induced is not known to decrease the risk of OC. Regardless of the effect of oophorectomy on second BC, oophorectomy is essential to reduce the risk of OC, which can be a significant cause of morbidity and mortality in women with early stage breast cancer [29].

Our data suggest that RRSO may be associated with a lower BC risk in *BRCA2* mutation carriers than in *BRCA1* mutation carriers (64% vs. 37%). Kauff et al [15] observed a statistically significant BC risk reduction following RRSO in *BRCA2* but not *BRCA1* mutation carriers. The potentially larger risk reduction associated with RRSO in *BRCA2* compared with *BRCA1* mutation carriers is of interest given the high proportion of ER positive breast tumors in *BRCA2* mutation carriers compared with *BRCA1* mutation carriers[31]. Additional research is required to address this issue.

We are still unable to provide definitive data with respect to the timing of RRSO on the efficacy of BC risk reduction as the numbers in each subgroup remain small with a limited number of events. Eisen et al. [14] reported that the BC risk reduction with RRSO was greater in *BRCA1/2* mutation carriers who underwent surgery before age 50 than in women who underwent surgery after age 50. The results of the present analyses are consistent with this finding for unaffected women who undergo RRSO before or after age 50.

The importance of understanding the optimal age at RRSO is underscored by several reports[32] in the general population that suggest that oophorectomy in women under age 45 is associated with increased mortality, particularly if HT is not used [26] Although these data are not directly applicable to *BRCA1/2* mutations who have markedly increased risks of breast and ovarian cancer and therefore a different risk/benefit profile, issues of timing and the safety of HRT are important. The Women's Health Initiative in postmenopausal women did not demonstrate a cardiovascular benefit overall from HT [33], but younger women going through natural menopause may derive such benefit [33], [34]. It is possible that *BRCA1/2* mutation carriers undergoing abrupt surgical menopause to reduce OC risk and receive HT may derive health benefits. Two prior studies have examined HT in *BRCA1/2* mutation carriers. Rebbeck et al.[35] examined 462 patients and reported no increased BC risk with post-RRSO HT use. Eisen et al.[14] examined HT in women with and without RRSO and observed no increased risk associated with HT. Further work is needed regarding this important issue.*BRCA1BRCA1BRCA2BRCA1/2*

We observed an association of RRSO with a significant reduction in all-cause, BC-specific, and OC-specific mortality. We previously reported that RRSO was associated with a 90%

reduction in BC–specific mortality, a 95% reduction in gynecologic cancer–specific mortality, and a 76% reduction in overall mortality[12]. Our present estimates are consistent with those reports. The apparent lesser effect on mortality in *BRCA2* vs. *BRCA1* mutation carriers may be due to the lower risk of OC in *BRCA2* mutation carriers as well as the more aggressive biological features of *BRCA1*-associated BC, however, more data is needed to adequately address this important question.

We recognize a number of limitations of the study. We designed our study to maximize follow up time and statistical power. However, this choice could have compromised our results in a number of ways. Our study design was powered to detect effects of RRSO and RRM stratified on *BRCA1/2* as well as the other groups defined in the tables. The observation of statistically significant p-values in many strata provides evidence that we had sufficient power for our pre-planned hypotheses. A few strata-specific analyses did not achieve statistical significance, suggesting that we did not have sufficient power to detect some smaller than anticipated effects. Therefore, analyses in some substrata may require additional study after accrual of much larger sample sizes.

Ideally, the evaluation of risk reducing surgery on cancer risk and mortality reduction would involve a randomized trial design. However, it is accepted in the field that a randomized approach would neither be acceptable nor ethical. As a result, this field of research is limited to undertaking observational studies that have methodological limitations. An observational design requires that statistical methods be used to correct for factors that may influence relative risk estimates. We have attempted to correct for a number of limitations of the observational study design by using the recommended analysis approaches of Klaren [36] and Hartmann [37]. However, additional analytical corrections could be considered in future analyses, including the effect of competing risks, or the consideration of time-dependency of RRSO/RRM and other covariates. As a result of these limitations, our results cannot be definitively inferred to be causal in nature.

An additional limitation of an observational study design is the need to determine appropriate follow-up periods for participants. Once choice is whether to follow individuals from the time of ascertainment vs. the time from genetic testing. All individuals in our cohort underwent genetic testing, however some individuals were ascertained prior to their genetic testing; the median ascertainment year was 1999 and median genetic test disclosure date 2001. To address the implications of this choice, we performed an exploratory analysis examining overall mortality using the time of genetic testing (rather than ascertainment) as the starting point, with all other criteria met as in the methods section. With this approach, we see a significant mortality benefit: RRSO was associated with a decreased risk of overall mortality in the entire group (HR=0.36; 0.20-0.62), in *BRCA1* mutation carriers (HR 0.42; 0.22-0.81), and in *BRCA2* mutation carriers (HR 0.10, 0.01-0.77). However, due to smaller number we lose power to address other questions and therefore have continued to use our initial, preplanned analysis as the primary analysis.

Although all women who chose to forego RRSO were counseled to undergo intensive screening, we do not have detailed information on compliance of these recommendations at all centers. However, there are no data that ovarian cancer screening is effective in reducing the risk of developing ovarian cancer, or in dying from ovarian cancer[38]. Therefore, we feel that it is unlikely that compliance would significantly alter our results related to ovarian cancer endpoints of incidence and mortality. Intensive breast cancer surveillance does not reduce the risk of developing breast cancer, but aims to improve early detection. Due to our lack of detailed information on breast MRI compliance, we cannot conclude that RRSO improved breast cancer specific mortality compared to optimal screening; however, we do see that women who choose RRSO are associated with better outcomes in terms of breast

cancer risk, ovarian cancer risk, and ovarian cancer specific- survival, none of which would be anticipated to be affected by compliance to intensive breast screening. We also see an association between RRSO and breast-cancer specific and overall survival, when compared to women who have not chosen RRSO. *BRCA1BRCA2BRCA1BRCA2*

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This paper is dedicated to the late Andrew Shenton, who contributed significantly to this research.

This study was supported by grants from the Public Health Service (R01-CA83855 and R01-CA102776 to TRR), the University of Pennsylvania Cancer Center (to TRR), the Cancer Genetics Network (HHSN21620074400C to SMD and CI), the Marjorie Cohen Research Fund (to SMD) the Dana-Farber/Harvard Cancer Center SPORE in BC P50 CA-089393 (to JEG), the Department of Defense (DAMD-17-96-I-6088 to AKG; DAMD-17-94-J-4340 and DAMD-17-97-I-7112 to HTL; DAMD-17-03-1-0619 to SMD), P30-CA51008-15 (to Georgetown University), The Utah Cancer registry (funded by Public Health Service Grant NO1-CN-6700) and the Utah State Department of Health, the Nebraska State Cancer and Smoking-Related Diseases Research Program (LB595 to HTL), P30-CA-16042 (to PAG), Cancer Research UK Grant Number C5047/A7357 (to RE), and NCI P30 CA51008-12 (to CI). OIO is Doris Duke Distinguished Clinical Scientist. RE acknowledges The Support of the NIHR to The Biomedical Research Centre at The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust. None of these funding agencies had involvement in the study design; collection, analysis, or interpretation of data; in the writing of the report; nor in the decision to submit the paper for publication.

References

1. King MC, Marks JH, Mandell JB. Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. Science. Oct 24; 2003 302(5645):643–646. [PubMed: 14576434]
2. Struewing JP, Hartge P, Wacholder S, et al. The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews. N Engl J Med. May 15; 1997 336(20):1401–1408. [PubMed: 9145676]
3. Chen S, Parmigiani G. Meta-analysis of BRCA1 and BRCA2 penetrance. J Clin Oncol. Apr 10; 2007 25(11):1329–1333. [PubMed: 17416853]
4. Ford D, Easton DF, Stratton M, et al. Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. The Breast Cancer Linkage Consortium. American Journal of Human Genetics. 1998; 62(3):676–689. [PubMed: 9497246]
5. Prevalence and penetrance of BRCA1 and BRCA2 mutations in a population-based series of breast cancer cases. Anglian Breast Cancer Study Group. Br J Cancer. Nov; 2000 83(10):1301–1308. [PubMed: 11044354]
6. Satagopan JM, Boyd J, Kauff ND, et al. Ovarian cancer risk in Ashkenazi Jewish carriers of BRCA1 and BRCA2 mutations. Clinical Cancer Research. 2002; 8(12):3776–3781. [PubMed: 12473589]
7. Rebbeck TR, Lynch HT, Neuhausen SL, et al. Prophylactic oophorectomy in carriers of BRCA1 or BRCA2 mutations. N Engl J Med. May 23; 2002 346(21):1616–1622. [PubMed: 12023993]
8. Rebbeck TR, Levin AM, Eisen A, et al. Breast cancer risk after bilateral prophylactic oophorectomy in BRCA1 mutation carriers. J Natl Cancer Inst. Sep 1; 1999 91(17):1475–1479. [PubMed: 10469748]
9. Kauff ND, Satagopan JM, Robson ME, et al. Risk-reducing salpingo-oophorectomy in women with a BRCA1 or BRCA2 mutation. N Engl J Med. May 23; 2002 346(21):1609–1615. [PubMed: 12023992]
10. Finch A, Beiner M, Lubinski J, et al. Salpingo-oophorectomy and the risk of ovarian, fallopian tube, and peritoneal cancers in women with a BRCA1 or BRCA2 Mutation. JAMA. Jul 12; 2006 296(2):185–192. [PubMed: 16835424]

11. Kramer JL, Velazquez IA, Chen BE, Rosenberg PS, Struewing JP, Greene MH. Prophylactic oophorectomy reduces breast cancer penetrance during prospective, long-term follow-up of BRCA1 mutation carriers. J Clin Oncol. Dec 1; 2005 23(34):8629–8635. [PubMed: 16314625]
12. Domchek SM, Friebel TM, Neuhausen SL, et al. Mortality after bilateral salpingo-oophorectomy in BRCA1 and BRCA2 mutation carriers: a prospective cohort study. Lancet Oncol. Mar; 2006 7(3):223–229. [PubMed: 16510331]
13. Chang-Claude J, Andrieu N, Rookus M, et al. Age at menarche and menopause and breast cancer risk in the International BRCA1/2 Carrier Cohort Study. Cancer Epidemiol Biomarkers Prev. Apr; 2007 16(4):740–746. [PubMed: 17416765]
14. Eisen A, Lubinski J, Klijn J, et al. Breast cancer risk following bilateral oophorectomy in BRCA1 and BRCA2 mutation carriers: an international case-control study. J Clin Oncol. Oct 20; 2005 23(30):7491–7496. [PubMed: 16234515]
15. Kauff N, Domchek S, Friebel T, et al. Risk-Reducing Salpingo-Oophorectomy for the Prevention of BRCA1 and BRCA2 Associated Breast and Gynecologic Cancer: A Multi-Center, Prospective Study. Journal of Clinical Oncology. 2008; 26(8):1331–1337. [PubMed: 18268356]
16. Rutter JL, Wacholder S, Chetrit A, et al. Gynecologic surgeries and risk of ovarian cancer in women with BRCA1 and BRCA2 Ashkenazi founder mutations: an Israeli population-based case-control study. J Natl Cancer Inst. Jul 16; 2003 95(14):1072–1078. [PubMed: 12865453]
17. Shah P, Rosen M, Stopfer J, et al. Prospective study of breast MRI in BRCA1 and BRCA2 mutation carriers: effect of mutation status on cancer incidence. Breast Cancer Res Treat. Jul 17.2009
18. Lin DY, W L. Robust Inferences for the Cox Proportional Hazards Model. JASA. 1989; 84:1074–1078.
19. Kauff ND, Barakat RR. Risk-reducing salpingo-oophorectomy in patients with germline mutations in BRCA1 or BRCA2. J Clin Oncol. Jul 10; 2007 25(20):2921–2927. [PubMed: 17617523]
20. Meijers-Heijboer H, van Geel B, van Putten WL, et al. Breast cancer after prophylactic bilateral mastectomy in women with a BRCA1 or BRCA2 mutation. New England Journal of Medicine. 2001; 345(3):159–164. [see comment]. [PubMed: 11463009]
21. Rebbeck TR, Friebel T, Lynch HT, et al. Bilateral prophylactic mastectomy reduces breast cancer risk in BRCA1 and BRCA2 mutation carriers: the PROSE Study Group. J Clin Oncol. Mar 15; 2004 22(6):1055–1062. [PubMed: 14981104]
22. Parker WH, Jacoby V, Shoupe D, Rocca W. Effect of bilateral oophorectomy on women's long-term health. Womens Health (Lond Engl). Sep; 2009 5(5):565–576. [PubMed: 19702455]
23. Parker WH, Manson JE. Oophorectomy and cardiovascular mortality: is there a link? Menopause. Jan-Feb;2009 16(1):1–2. [PubMed: 18971791]
24. Rocca WA, Bower JH, Maraganore DM, et al. Increased risk of cognitive impairment or dementia in women who underwent oophorectomy before menopause. Neurology. Sep 11; 2007 69(11): 1074–1083. [PubMed: 17761551]
25. Rocca WA, Bower JH, Maraganore DM, et al. Increased risk of parkinsonism in women who underwent oophorectomy before menopause. Neurology. Jan 15; 2008 70(3):200–209. [PubMed: 17761549]
26. Parker WH, Broder MS, Chang E, et al. Ovarian conservation at the time of hysterectomy and long-term health outcomes in the nurses' health study. Obstet Gynecol. May; 2009 113(5):1027–1037. [PubMed: 19384117]
27. Fisher B, Jeong JH, Bryant J, et al. Treatment of lymph-node-negative, oestrogen-receptor-positive breast cancer: long-term findings from National Surgical Adjuvant Breast and Bowel Project randomised clinical trials. Lancet. Sep 4-10; 2004 364(9437):858–868. [PubMed: 15351193]
28. Davidson NE, O'Neill AM, Vukov AM, et al. Chemoendocrine therapy for premenopausal women with axillary lymph node-positive, steroid hormone receptor-positive breast cancer: results from INT 0101 (E5188). J Clin Oncol. Sep 1; 2005 23(25):5973–5982. [PubMed: 16087950]
29. Metcalfe K, Lynch HT, Ghadirian P, et al. Contralateral breast cancer in BRCA1 and BRCA2 mutation carriers. J Clin Oncol. Jun 15; 2004 22(12):2328–2335. [PubMed: 15197194]

30. Pierce LJ, Levin AM, Rebbeck TR, et al. Ten-year multi-institutional results of breast-conserving surgery and radiotherapy in BRCA1/2-associated stage I/II breast cancer. J Clin Oncol. Jun 1; 2006 24(16):2437–2443. [PubMed: 16636335]

31. Lakhani SR, Van De Vijver MJ, Jacquemier J, et al. The pathology of familial breast cancer: predictive value of immunohistochemical markers estrogen receptor, progesterone receptor, HER-2, and p53 in patients with mutations in BRCA1 and BRCA2. Journal of Clinical Oncology. 2002; 20(9):2310–2318. [PubMed: 11981002]

32. Rocca WA, Grossardt BR, de Andrade M, Malkasian GD, Melton LJ 3rd. Survival patterns after oophorectomy in premenopausal women: a population-based cohort study. Lancet Oncol. Oct; 2006 7(10):821–828. [PubMed: 17012044]

33. Rossouw JE, Prentice RL, Manson JE, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. JAMA. Apr 4; 2007 297(13):1465–1477. [PubMed: 17405972]

34. Manson JE, Allison MA, Rossouw JE, et al. Estrogen therapy and coronary-artery calcification. N Engl J Med. Jun 21; 2007 356(25):2591–2602. [PubMed: 17582069]

35. Rebbeck TR, Friebel T, Wagner T, et al. Effect of short-term hormone replacement therapy on breast cancer risk reduction after bilateral prophylactic oophorectomy in BRCA1 and BRCA2 mutation carriers: the PROSE Study Group. J Clin Oncol. Nov 1; 2005 23(31):7804–7810. [PubMed: 16219936]

36. Klaren HM, van't Veer LJ, van Leeuwen FE, Rookus MA. Potential for bias in studies on efficacy of prophylactic surgery for BRCA1 and BRCA2 mutation. Journal of the National Cancer Institute. 2003; 95(13):941–947. [see comment]. [PubMed: 12837830]

37. Hartmann LC, Degnim A, Schaid DJ. Prophylactic mastectomy for BRCA1/2 carriers: progress and more questions. J Clin Oncol. Mar 15; 2004 22(6):981–983. [PubMed: 14981099]

38. Evans DG, Baildam AD, Anderson E, et al. Risk reducing mastectomy: outcomes in 10 European centres. J Med Genet. Apr; 2009 46(4):254–258. [PubMed: 18996907]

Europe PMC Funders Author Manuscripts

Europe PMC Funders Author Manuscripts

Table 1

Risk-Reducing Mastectomy (RRM) and Risk of First Breast Cancer (BC)*

		Prior or concurrent RRSO			No prior or concurrent RRSO	
	ALL	***BRCA1***	***BRCA2***	**ALL**	***BRCA1***	***BRCA2***
Total Participants	959	617	342	660	415	245
Total RRM (“Exposed”)	172	116	56	75	43	32
Post-RRM BC	0	0	0	0	0	0
Total non-RRM (“Controls”)	787	501	286	585	372	213
Controls with BC	64 (8%)	44 (9%)	20 (7%)	34 (6%)	19 (5%)	15 (7%)
Mean Age at RRM	40.7 (22.4-64.6)	40.1 (24.8-62.5)	42.0 (22.4-64.6)	37.9 (22.4-64.6)	36.7 (24.8-52.1)	39.4 (22.4-64.6)
Mean Age Start of Follow-Up	40.5 (18.3-87.8)	39.5 (18.3-87.8)	42.2 (18.9-79.7)	37.6 (18.3-87.8)	36.7 (18.3-87.8)	39.1 (18.9-79.7)
Mean Yrs Follow-up to BC (Range)	3.1 (0.5-9.3)	3.3 (0.5-9.3)	2.6 (0.6-6.8)	3.1 (0.6-8.71)	3.6 (0.6-8.7)	2.5 (0.6-6.8)
Mean Yrs Follow-up to Censor (Range)	3.5 (0.5-13.0)	3.7 (0.5-13.0)	3.0 (0.5-11.5)	2.7 (0.5-13.0)	2.7 (0.5-13.0)	2.5 (0.5-11.5)
Occult BC ***	4	3	1	3	2	1
HR **** (95% CI); N	No cancer events	No cancer events	No cancer events	No cancer events	No cancer events	No cancer events

*No breast cancer prior to ascertainment or RRSO, participants censored at OC, death or date of last contact.

**Adjusted for year of birth and stratified by center;

***Found incidentally at the time of prophylactic mastectomy and excluded from analysis;

****No Cancer Events in those with RRM. HR cannot be estimated

Europe PMC Funders Author Manuscripts

JAMA. Author manuscript; available in PMC 2010 October 01.

Table 2

Risk-Reducing Oophorectomy (RRSO) and Ovarian Cancer (OC) Risk *

	No breast cancer prior**			Breast cancer prior***		
	Total	***BRCA1***	***BRCA2***	**Total**	***BRCA1***	***BRCA2***
Total Participants	1557	1003	554	1060	684	376
RRSO (“Exposed”)	465	342	123	474	339	135
N (%) Post-RRSO Primary Peritoneal Cancer	6 (2%)	6 (2%)	0	4 (1%)	4 (1%)	0
No RRSO (“Controls”)	1092	661	431	586	345	241
N (%) Controls with OC	63 (6%)	49(7%)	14 (3%)	35 (6%)	27(8%)	8 (3%)
Mean Age at RRSO (Yrs)	43.2 (20.5-79.0)	42.1 (20.5-79.0)	46.2 (32.9-68.5)	47.7 (29.7-75.2)	44.1 (29.7-75.2)	49.1 (30.4-72.9)
Mean Start Age (Yrs, for Controls)	36.7 (18.1-90.4)	35.4 (18.2-90.4)	38.6 (32.9-68.5)	45.4 (21.9-86.2)	44.2 (21.9-86.2)	47.0 (26.1-77.7)
Mean FU to OC (Yrs)	6.2 (0.8-17.8)	6.2 (0.8-17.8)	6.0 (0.8-17.8)	4.2 (0.5-13.4)	4.4 (0.5-13.4)	3.3 (0.7-5.8)
Mean Follow-up to Censoring (Yrs)	5.7 (0.5-27.9)	5.6 (0.5-27.7)	5.8 (0.5-26.9)	4.4 (0.5-24.6)	4.5 (0.5-24.6)	4.1 (0.5-15.4)
Occult Ov Ca^	9	7	2	13	10	3
HR**** (95% CI);N	0.28 (0.12-0.69); 1367	0.31 (0.12-0.82); 880	No cancer events; 487^^	0.14 (0.04-0.59); 857	0.15 (0.04-0.63); 563	No cancer events; 294

* Participants censored at death, or last contact.

** No breast cancer prior to RRSO, or in the controls prior to the start of follow up.

*** Breast cancer allowed prior to RRSO or start of follow up.

**** Adjusted for year of birth, oral contraceptive use; and stratified by center;

^ Found incidentally at the time of RRSO and excluded from analysis;

^^ Adjustment was made for OCP use; those with missing data were excluded from the analysis.

Europe PMC Funders Author Manuscripts

Table 3

Risk-Reducing Oophorectomy (RRSO) and Breast Cancer (BC) Risk*

	No Prior Breast Cancer **			Prior Breast Cancer ***		
	Total	***BRCA1***	***BRCA2***	**Total**	***BRCA1***	***BRCA2***
Total Participants	1,370	869	501	647	397	250
RRSO (“Exposed”)	336	236	100	208	138	70
N (%) Post-RRSO BC	39	32 (14%)	7 (7%)	23	19 (14%)	4 (6%)
No RRSO (“Controls”)	1,034	633	401	439	259	180
N (%) Controls with BC	223	129 (20%)	94 (23%)	60	46 (18%)	14 (8%)
Mean Age at RRSO (Yrs)	43.8 (20.5-79.0)	42.7 (20.5-79.0)	46.6 (35.4-68.5)	48.5 (29.8-74.8)	48.2 (29.8-74.8)	49.1 (34.0-69.5)
Mean Start Age (Yrs, for Controls)	36.2 (18.1-90.4)	35.0 (18.2-90.4)	38.1 (18.1-82.7)	44.8 (21.9-86.2)	43.3 (21.9-86.2)	47.1 (27.1-77.7)
Mean Follow-up to BC (Yrs)	4.7 (0.5-21.0)	4.7 (0.5-21.0)	4.8 (0.5-20.6)	4.4 (0.5-16.1)	4.5 (0.5-16.1)	4.0 (0.7-11.7)
Mean Follow-up to Censoring (Yrs)	4.7 (0.5-27.8)	4.7 (0.5-27.7)	4.7 (0.5-27.8)	3.8 (0.5-18.4)	3.7 (0.5-18.4)	3.9 (0.5-15.4)
HR **** (95% CI)	0.54 (0.37-0.79)	0.63 (0.41-0.96)	0.36 (0.16-0.82)	1.00 (0.56-1.77)	1.01 (0.54-1.89)	1.11 (0.31-3.98)

* Participants censored at OC, RRM, death, or last contact.

** No breast cancer prior to RRSO, or in the controls prior to the start of follow up.

*** Breast cancer allowed prior to RRSO or start of follow up

**** Adjusted for year of birth and stratified by center.

Europe PMC Funders Author Manuscripts

JAMA. Author manuscript; available in PMC 2010 October 01.

Table 4a

Risk-Reducing Oophorectomy (RRSO) and All Cause Mortality*

	All eligible women			No breast cancer prior**			Breast cancer prior***		
	All	***BRCA1***	***BRCA2***	**All**	***BRCA1***	***BRCA2***	**All**	***BRCA1***	***BRCA2***
Total Participants	2,482	1587	895	1,458	935	523	1,027	654	373
RRSO(Exposed)	993	706	287	447	327	120	451	317	134
N (%) Post-RRSO deaths	31 (3%)	25 (4%)	6 (2%)	8 (2%)	8 (2%)	0	19 (4%)	14 (4%)	5 (4%)
No RRSO (Controls)	1,489	881	608	1,011	608	403	576	337	239
N (%) Controls deaths	146 (10%)	93 (11%)	53 (9%)	60 (6%)	43 (7%)	17 (4%)	92 (16%)	54 (16%)	38 (16%)
Mean Age at RRSO (Yrs)	45.4 (20.5-79.0)	44.5 (20.5-79.0)	47.6 (30.4-72.9)	43.2 (20.5-79.0)	42.1 (20.5-79.0)	46.4 (33.0-68.5)	47.6 (29.7-75.2)	47.0 (29.7-75.2)	49.1 (30.4-72.9)
Mean Start Age (Yrs, Controls)	39.8 (18.1-90.4)	38.5 (18.2-90.4)	41.6 (18.1-82.7)	36.3 (18.1-90.4)	35.1 (18.2-90.4)	38.2 (18.1-82.7)	45.3 (21.9-86.2)	44.2 (21.9-86.2)	46.9 (26.1-77.7)
Mean FU-up to death (Yrs)	6.0 (0.5-23.5)	5.9 (0.6-22.3)	6.2 (0.5-23.5)	9.0 (0.96-23.5)	8.5 (1.0-22.3)	10.3 (2.8-23.5)	4.6 (0.5-20.3)	4.3 (0.6-20.3)	5.1 (0.5-13.3)
Mean FU to Censoring (Yrs)	5.0 (0.5-27.9)	5.0 (0.5-27.7)	4.9 (0.5-27.9)	5.8 (0.5-27.9)	5.7 (0.5-27.7)	5.9 (0.5-27.9)	4.5 (0.5-24.6)	4.8 (0.5-24.6)	4.1 (0.5-15.4)
HR**** (95% CI)	0.40 (0.26-0.61)	0.38 (0.24-0.62)	0.52 (0.22-1.23)	0.45 (0.21-0.95)	0.52 (0.24-1.14)	No Deaths	0.30 (0.17-0.52)	0.26 (0.13-0.52)	0.45 (0.17-1.16)
<50 HR (95% CI)	0.41 (0.25-0.67)	0.40 (0.24-0.68)	0.16 (0.02-1.30)	0.70 (0.31-1.57)	0.50 (0.21-1.20)	No Deaths	0.28 (0.14-0.55)	0.30 (0.14-0.64)	0.19 (0.02-1.59)
>=50 HR (95% CI)	0.37 (0.15-0.94)	0.22 (0.06-0.85)	0.47 (0.12-1.80)	0.28 (0.03-2.42)	0.93 (0.11-8.12)	No Deaths	0.37 (0.13-1.03)	0.12 (0.02-0.73)	0.46 (0.10-2.13)

* Participants censored at the date of last contact.

** No breast cancer prior to RRSO, or in the controls prior to the start of follow up.

*** Breast cancer allowed prior to RRSO or start of follow up

**** Adjusted for year of birth and stratified by center;

Europe PMC Funders Author Manuscripts

JAMA. Author manuscript; available in PMC 2010 October 01.

Table 4b

Risk-Reducing Oophorectomy (RRSO) and Breast Cancer-Specific Mortality *

	All eligible women			No breast cancer prior **			Breast cancer prior ***		
	All	***BRCA1***	***BRCA2***	**All**	***BRCA1***	***BRCA2***	**All**	***BRCA1***	***BRCA2***
Total Participants	2,407	1536	871	1,414	902	512	995	636	359
RRSO (“Exposed”)	983	697	286	441	321	120	448	314	134
N (%) Post-RRSO deaths	21 (2%)	16 (2%)	5 (2%)	2 (0.5%)	2 (1%)	0	16 (4%)	11 (4%)	5 (4%)
No RRSO (“Controls”)	1,424	839	585	973	581	392	547	322	225
N (%) Controls deaths	81 (6%)	51 (6%)	30 (5%)	22 (2%)	16 (3%)	6 (2%)	63 (12%)	39 (12%)	34 (11%)
Mean Age at RRSO (Yrs)	45.3 (20.5-75.2)	44.4 (20.5-75.2)	47.5 (30.4-72.9)	43.2 (20.5-73.9)	42.0 (20.5-73.9)	46.4 (32.9-68.5)	47.6 (29.7-75.2)	47.0 (29.7-75.2)	49.1 (30.4-72.9)
Mean Start Age (Yrs, for Controls)	39.3 (18.1-87.6)	38.0 (18.2-87.6)	41.2 (18.1-82.7)	35.8 (18.1-87.6)	34.5 (18.2-87.6)	37.8 (18.1-82.7)	45.1 (21.9-86.2)	2.9 (0.6-10.2)	4.7 (0.5-13.3)
Mean FU to death (Yrs)	4.6 (0.5-21.4)	4.1 (0.6-21.4)	5.4 (0.5-27.9)	8.6 (1.6-21.4)	8.5 (1.6-21.4)	8.8 (2.8-18.3)	3.6 (0.5-13.3)	2.9 (0.6-10.2)	4.7 (0.5-13.3)
Mean FU to Censoring (Yrs)	5.0 (0.5-27.9)	5.0 (0.5-27.7)	4.9 (0.5-27.9)	5.8 (0.5-27.9)	5.7 (0.5-27.7)	5.9 (0.5-27.9)	4.5 (0.5-24.6)	4.8 (0.5-24.6)	4.1 (0.5-15.4)
HR **** (95% CI);	0.44 (0.26-0.76)	0.38 (0.20-0.72)	0.82 (0.30-2.20)	0.27 (0.05-1.33)	0.30 (0.06-1.53)	No Deaths	0.35 (0.19-0.67)	0.27 (0.12-0.58)	0.87 (0.32-2.37)

* Participants censored at the date of last contact.

** No breast cancer prior to RRSO, or in the controls prior to the start of follow up.

*** Breast cancer allowed prior to RRSO or start of follow up.

**** Adjusted for year of birth and stratified by center;

Europe PMC Funders Author Manuscripts

JAMA. Author manuscript; available in PMC 2010 October 01.

Table 4c

Risk-Reducing Oophorectomy (RRSO) and Ovarian Cancer-Specific Mortality*

	All eligible women			No breast cancer prior**			Breast cancer prior***		
	All	***BRCA1***	***BRCA2***	**All**	***BRCA1***	***BRCA2***	**All**	***BRCA1***	***BRCA2***
Total Participants	2,343	1502	841	1,417	907	510	928	597	331
RRSO (“Exposed”)	966	685	281	442	322	120	433	304	129
N (%) Post-RRSO deaths	4 (0.4%)	4 (1%)	0	3 (1%)	3 (1%)	0	1 (0.2%)	1 (0.3%)	0
No RRSO (“Controls”)	1,377	817	560	975	585	390	495	293	202
N (%) Controls deaths	34 (3%)	29 (4%)	5 (1%)	24 (3%)	20	4	11 (2%)	10	1
Mean Age at RRSO (Yrs)	45.3 (20.5-75.2)	44.4 (20.5-75.2)	47.4 (30.4-72.9)	43.2 (20.5-73.9)	42.0 (20.5-73.9)	46.4 (32.9-68.5)	47.6 (29.7-75.2)	47.0 (29.7-75.2)	48.9 (30.4-72.9)
Mean Start Age (Yrs, for Controls)	39.5 (18.1-87.9)	38.2 (18.2-87.9)	41.3 (18.1-82.7)	36.1 (18.1-87.9)	34.8 (18.2-87.9)	38.0 (18.1-82.7)	45.6 (21.9-86.2)	44.4 (21.9-86.2)	47.3 (26.1-77.7)
Mean Follow-up to death (Yrs)	8.4 (1.4-22.3)	8.7 (1.4-22.3)	6.9 (5.2-9.0)	8.8 (1.4-22.3)	9.1 (1.4-22.3)	7.0 (5.2-9.0)	7.6 (2.8-18.7)	7.6 (2.8-18.7)	6.6 (6.6)
Mean Follow-up to Censoring (Yrs)	5.0 (0.5-27.8)	5.0 (0.5-27.7)	4.9 (0.5-27.9)	5.8 (0.5-27.9)	5.7 (0.5-27.7)	5.9 (0.5-57.9)	4.5 (0.5-24.6)	4.8 (0.5-24.6)	4.1 (0.5-15.4)
HR**** (95% CI); N Total	0.21 (0.06-0.80)	0.22 (0.06-0.83)	No Deaths	0.39 (0.12-1.29)	0.46 (0.08-2.72)	No Deaths	0.10 (0.01-1.42)	0.09 (0.01-1.44)	No Deaths

* Participants censored at the date of last contact.

** No breast cancer prior to RRSO, or in the controls prior to the start of follow up.

*** Breast cancer allowed prior to RRSO or start of follow up

**** Adjusted for year of birth and stratified by center