JNCI Cancer Spectrum (2020) 4(4): pkaa029

doi: 10.1093/jncics/pkaa029
Article

Penetrance of Breast and Ovarian Cancer in Women Who Carry a *BRCA1/2* Mutation and Do Not Use Risk-Reducing Salpingo-Oophorectomy: An Updated Meta-Analysis

Jinbo Chen, PhD,[1,*] Eunchan Bae , MS,[2,3] Lingjiao Zhang , MS,[1] Kevin Hughes , MD,[4] Giovanni Parmigiani , PhD,[2,3] Danielle Braun , PhD,[2,3] Timothy R. Rebbeck , PhD[5,*]

[1]Department of Biostatistics, Epidemiology and Informatics, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA; [2]Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, MA, USA; [3]Department of Data Sciences, Dana Farber Cancer Institute, Boston, MA, USA; [4]Massachusetts General Hospital, Boston, MA, USA; and [5]Dana FarberCancer Institute and Harvard T.H. Chan School of Public Health, Boston, MA, USA

*Correspondence to: Jinbo Chen, PhD, Department of Biostatistics, Epidemiology and Informatics, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA (e-mail: jinboche@pennmedicine.upenn.edu) and Timothy R. Rebbeck, PhD, Dana Farber Cancer Institute and Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA (e-mail: timothy_rebbeck@dfci.harvard.edu).

Abstract

Background: Use of risk-reducing Salpingo-oophorectomy (RRSO) substantially reduces the risk of ovarian and breast cancer for women who carry a *BRCA1/2* mutation. It is important to adjust for RRSO use in the estimation of *BRCA1/2* penetrance of breast and ovarian cancer. **Methods:** We searched PubMed for penetrance estimates of breast and ovarian cancer from studies that genotyped individual patients and explicitly adjusted for RRSO use by censoring follow-up at the age of RRSO. We meta-analyzed penetrance estimates from 7 identified studies. We implemented the resulting penetrance estimates in a Mendelian risk prediction model as iplemented in the software package BRCAPRO, which we applied to estimate carrier probabilities in 2 *BRCA* cohorts. **Results:** Penetrance estimates by age 70 years for breast cancer were 64.6% (95% confidence interval [CI] = 59.5% to 69.4%) for BRCA1 mutation carriers and 61.0% (95% CI = 48.1% to 72.5%) for BRCA2 mutation carriers, and for ovarian cancer they were 48.3% (95% CI = 38.8% to 57.9%) and 20.0% (95% CI = 13.3% to 29.0%), respectively. When integrated into BRCAPRO, our estimates led to good calibration and different estimates of carrier probabilities for some individuals when evaluating the models in 2 cohorts. **Conclusions:** The report updates penetrance estimates for BRCA1/2-associated cancer. We report higher estimates than previously reported, which did not adjust for RRSO. Differential use of RRSO may partially explain heterogeneity in the currently available penetrance estimates. For some individuals, using our estimates in BRCAPRO may result in changes in estimated carrier probabilities, which warrants validation in future studies.

Counseling women who carry *BRCA1/2* mutations about clinical management of their breast and ovarian cancer risk has critically relied on penetrance estimates. Lifetime risk of breast cancer has been estimated to be 30%-85% for *BRCA1/2* mutation carriers, and for ovarian cancer it has been estimated to be 20%-40% for *BRCA1* mutation carriers and 10%-20% for *BRCA2* mutation carriers (1). The variation in available estimates makes it a challenge for clinicians to decide which one to use. An integrated set of estimates obtained via meta-analysis is currently available[1] that summarized 10 studies that genotyped individual patients and explicitly accounted for ascertainment in statistical analyses. This meta-analysis also concluded that the inter-study variability cannot be explained by mutation type, study designs, statistical methods of estimation, and patient ethnicity. It is important to understand and identify sources of heterogeneity and to provide more homogeneous estimates.

Risk-reducing Salpingo-oophorectomy (RRSO) modifies cancer risk for women who carry *BRCA1/2* mutations (2). RRSO use may decrease the risk of ovarian cancer by more than 85% and breast cancer risk by more than 50%, although the efficacy of RRSO in BRCA1 mutation carriers has been disputed. The rate of RRSO by age 50 years was estimated to be 86% in *BRCA1* and 71% in *BRCA2* mutation carriers (3). Many studies reporting penetrance did not adjust for RRSO, and ages and rates of RRSO may vary across studies. We conjectured that differential use of RRSO may be an important source of heterogeneity in available penetrance estimates.

Received: October 29, 2019; **Revised:** February 5, 2020; **Accepted:** April 7, 2020

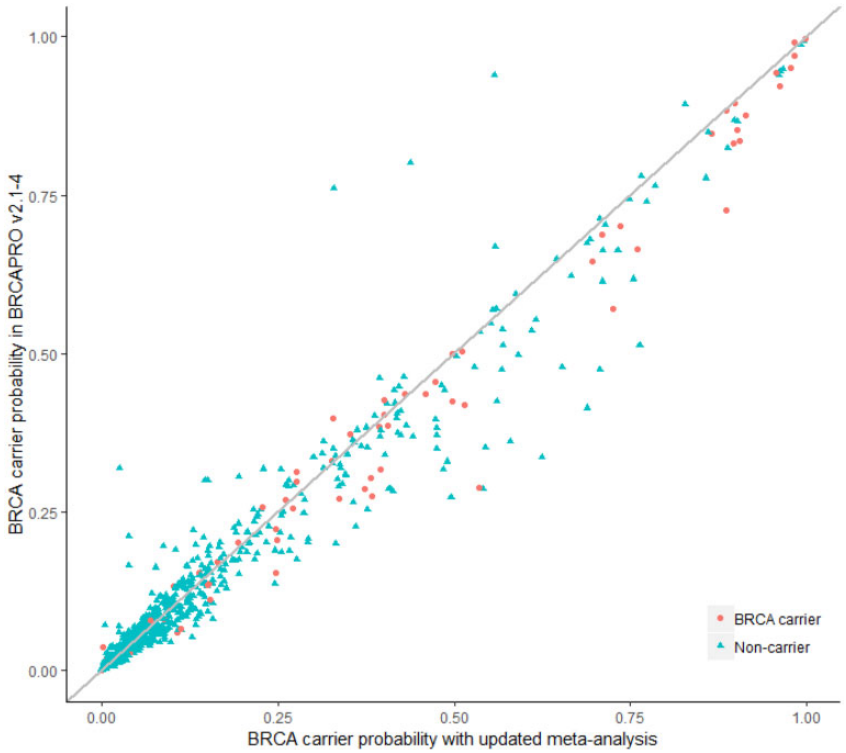

Figure 1. Newton-Wellesley Hospital carrier estimates.

Therefore, in our current analysis, we aimed to obtain RRSO-adjusted penetrance estimates.

Direct validation of our penetrance estimates would require a representative cohort of carrier women who opt not to have RRSO and are followed for sufficiently long periods to accumulate a sufficient number of ovarian and breast cancer events. One important application of penetrance estimates is to predict the probability that a woman carries a *BRCA1* or *BRCA2* mutation. We therefore evaluated our estimates by applying them to predict carrier probabilities and assess how well our estimates performed on real data. We used BRCAPRO, a widely used Mendelian risk prediction model for such estimation, which utilizes a woman's family history and general population-based estimates of penetrance and prevalence. We evaluated predicted carrier probabilities in 2 cohorts from Newton-Wellesley Hospital (NWH) (4) and Cancer Genetics Network (CGN) (5) using the latest version of BRCAPRO available at the time of the study (v2.1-5).

Methods

Meta-Analysis of Available Estimates

We performed a PubMed search using the same criteria as Chen and Parmigiani (1), searching the "title" for "risk" or "penetrance," "breast cancer" or "ovarian cancer," and "*BRCA1*" or "*BRCA2*." We identified the studies that estimated penetrance based directly on genotype data for individual patients and accounted for RRSO use by censoring follow-up time at age of RRSO use. Studies that did not report censoring women's follow-up at time of RRSO use were excluded.

To summarize all eligible penetrance estimates meta-analytically, we assumed that the age-specific penetrance of ovarian and breast cancer in *BRCA1/2* mutation carriers follows a beta distribution to enforce that penetrance estimates are necessarily constrained in the range of 0 to 1. This choice was made to be consistent with the earlier BRCAPRO models (1). We solved for the distribution parameters based on the mean and standard error estimates reported in each study. We then applied the DerSimonian and Laird random effects approachto combine the mean and standard error estimates, which appropriately accommodates for the heterogeneity in individual estimates.

The NWH and CGN Cohorts

The NWH cohort (4) consists of 1345 probands referred for genetic counseling at NWH with a median age of 53 years. Most of the probands were recruited through risk assessment at a breast imaging visit. A total of 684 probands (50.9%) had unilateral breast cancer and 66 (4.9%) had ovarian cancer. The CGN cohort (5) consists of 2038 probands (median age: 50 years) recruited from 8 high-risk genetic counseling clinics: Huntsman Cancer Institute, University of Texas Southwestern Medical Center, MD Anderson Cancer Center, Baylor College of Medicine, Johns Hopkins University, Duke University, University of Pennsylvania, and Georgetown University. Probands from high-risk clinics were referred because of a family history of breast or ovarian cancer. A total 1169 (57.4%) probands had unilateral breast cancer and 166 (8.1%) had ovarian cancer. The detailed characteristics of both the NWH and CGN cohorts are summarized in the Supplementary Methods (available online).

Statistical Measures for Quantifying Accuracy for Predicting Carrier Probabilities

We evaluated accuracy of BRCAPRO with the existing penetrances and our new penetrance estimates for predicting carrier

Table 1. Seven eligible studies identified through PubMed search

Study	Population	Ascertainment	No. of families	No. of carriers[a]	Estimation		
					Ovarian cancer	Breast cancer	Statistical method
Scott et al., 2003 (8)[b]	kConFab, Australian	High-risk families with mutations	53	28 + 23	No	Yes (Figure 1)	Modified segregation analysis
King et al., 2003 (9)	New York hospital Ashkenazi Jewish with breast cancer	Population-based patients	1008	42 + 25 + 37[b] in patients, 212 in relatives	Yes (Table 2,Figure 1B)	Yes (Table 2,Figure 1A)	Kaplan-Meier
Evans et al., 2008 (10)	Overlapping regions of Manchester and Birmingham, mid-north England	High-risk families with mutations	385	839 + 603	Yes (Table 3, Figure 2)	No[c]	Kaplan-Meier
Evans et al., 2014 (11)	Women with family member identified as mutation carrier in Manchester area, northwest England	Population-based prospective cohort study	333	254 + 238	No	Yes (Table 2, Figure 1)	Kaplan-Meier
Kuchenbaecker et al., 2017 (7)	IBCCS, BCFR, kConFab	Population-based prospective cohort study	Ovarian: 1214 Breast: 821	Ovarian: 770 + 736 Breast: 501 + 485	Yes (Figure 1)	Yes	Kaplan- Meier
Gabai-Kapara et al., 2012 (12)	Ashkenazi Jewish from Israel	Population-based prospective cohort study	172		Yes (Table 1, Figure 2C)	Yes (Table 1, Figure 2B)	Kaplan-Meier
Satagopan et al., 2002 (13)	Ashkenazi Jewish ovarian cancer patients from multiple hospitals	Population-based case-control study	436	76 + 27 + 44[d]	Yes (Table 4)	No	Odds ratio, mutation prevalence in controls, and incidence rates of OC in population

[a]Number of BRCA1 carriers + number of BRCA2 carriers. BCFR = Breast Cancer Family Registry; IBCCS = International BRCA1/2 Carrier Cohort Study; kConFab = Kathleen Cuningham Foundation Consortium for research into Familial Breast cancer.

[b]Reference numbers in this column correspond to those in the main text.

[c]Penetrance estimates were provided for breast cancer, but we used the estimates from their later study in 2014 (18).

[d]Three mutations were tested: 185delAG + 5382insC + 6174delT.

Table 2. Estimated breast and ovarian cancer penetrance and 95% CI by age interval starting at age 20 years for breast cancer and age 30 years for ovarian cancer for female BRCA1 or BRCA2 mutation carriers[a]

		End age (years)					
Gene	Cancer	30	40	50	60	70	80
BRCA1	Breast	0.029 (0.018 to 0.047)	0.192 (0.143 to 0.253)	0.395 (0.349 to 0.442)	0.525 (0.462 to 0.568)	0.646 (0.595 to 0.694)	0.692 (0.588 to 0.781)
	Ovarian	—	0.025 (0.019 to 0.034)	0.131 (0.078 to 0.212)	0.304 (0.212 to 0.415)	0.483 (0.388 to 0.579)	0.544 (0.44 to 0.645)
BRCA2	Breast	0.025 (0.008 to 0.072)	0.135 (0.093 to 0.191)	0.315 (0.244 to 0.395)	0.475 (0.390 to 0.562)	0.610 (0.481 to 0.725)	0.669 (0.506 to 0.799)
	Ovarian	—	0.013 (0.001 to 0.099)	0.037 (0.022 to 0.061)	0.106 (0.068 to 0.161)	0.200 (0.133 to 0.290)	0.305 (0.186 to 0.457)

[a]CI = confidence interval.

Table 3. Performances of predicting mutation carrier probability for each penetrance estimate with 95% CI, evaluated by net reclassification improvement, calibration, discrimination, and accuracy

	Newton-Wellesley Hospital		Cancer Genetics Network	
Mutation	Updated penetrance	Chen and Parmigiani (1)	Updated penetrance	Chen and Parmigiani (1)
Net Reclassification Index				
BRCA	0.234 (0.18, 0.29)		0.136 (0.10, 0.17)	
BRCA1	0.405 (0.25, 0.45)		0.247 (0.20, 0.29)	
BRCA2	0.105 (0.04, 0.16)		0.04 (−0.01, 0.08)	
Observed or expected				
BRCA	1.00 (0.82, 1.15)	1.04 (0.85, 1.2)	0.97 (0.89, 1.07)	1.01 (0.94, 1.11)
BRCA1	0.89 (0.65, 1.11)	0.82 (0.61, 1.05)	1.1 (0.99, 1.22)	1.06 (0.96, 1.18)
BRCA2	1.14 (0.88, 1.41)	1.34 (1.02, 1.65)	0.81 (0.68, 0.95)	0.96 (0.8, 1.12)
AUC				
BRCA	0.65 (0.59, 0.71)	0.64 (0.59, 0.7)	0.77 (0.74, 0.8)	0.77 (0.74, 0.8)
BRCA1	0.75 (0.67, 0.83)	0.74 (0.67, 0.82)	0.79 (0.76, 0.82)	0.79 (0.76, 0.82)
BRCA2	0.58 (0.51, 0.64)	0.57 (0.51, 0.64)	0.71 (0.66, 0.76)	0.71 (0.66, 0.76)
Brier Score				
BRCA	0.096 (0.083, 0.109)	0.095 (0.081, 0.109)	0.149 (0.137, 0.161)	0.146 (0.135, 0.158)
BRCA1	0.037 (0.029, 0.046)	0.039 (0.031, 0.049)	0.105 (0.097, 0.115)	0.105 (0.097, 0.116)
BRCA2	0.061 (0.049, 0.073)	0.059 (0.046, 0.07)	0.065 (0.056, 0.073)	0.061 (0.053, 0.071)

[a]AUC = area under the curve.

probabilities using 3 measures: first, net reclassification improvement, based on the proportions of correctly and incorrectly reclassified patients compared with an old model (6); second, calibration, as measured by the ratio of the observed number of carriers to the expected number of carriers; and third, discrimination, as measured by the area under the receiver operator characteristic curve to distinguish between those who have inherited a BRCA1/2 mutation (carriers) and those who have not (noncarriers) (iv) Mean squared error (MSE) of prediction for BRCA1/2 carrier probabilities compared with a binary label of carrier status for either gene. BRCAPRO v2.1-5 requires annual age-specific penetrance estimates from age 1 to 94 years for mutation carriers and noncarriers. Because our meta-analysis results in 10-year interval estimates up to age 80 years, we interpolated the estimated penetrance of breast cancer in the age interval 20-80 years and ovarian cancer in the age interval 30-80 years. Also, we extrapolated the estimated penetrance of breast cancer and ovarian cancer outside of estimated ranges. Interpolation and extrapolation procedures are summarized in the Supplementary Methods (available online). Annual age-specific penetrance estimates are presented in Supplementary Figure 1 (available online).

Results

Meta-Analysis

Among the studies (7–13) that provided penetrance estimates for ovarian cancer, only 1 study (13) provided an estimate for ovarian cancer by age 30 years, which was 1% for *BRCA1* and 0.2% for *BRCA2* mutation carriers. Three studies (9, 13, 14) provided penetrance estimates for ovarian cancer by age 40 in *BRCA2* mutation carriers, which were 2%, 1.3%, and 0.7%, respectively. Therefore, we focused on estimation of risk beyond age 30 years for ovarian cancer. Two studies, Evans et al. (10) and Evans et al. (11) had overlapping study patients, where the latter provided updated estimates of breast cancer penetrance. Therefore, we included the Evans et al. (11) study in the estimation of the breast cancer penetrance and the Evans et al. (10) study in the estimation of ovarian cancer penetrance. That is,

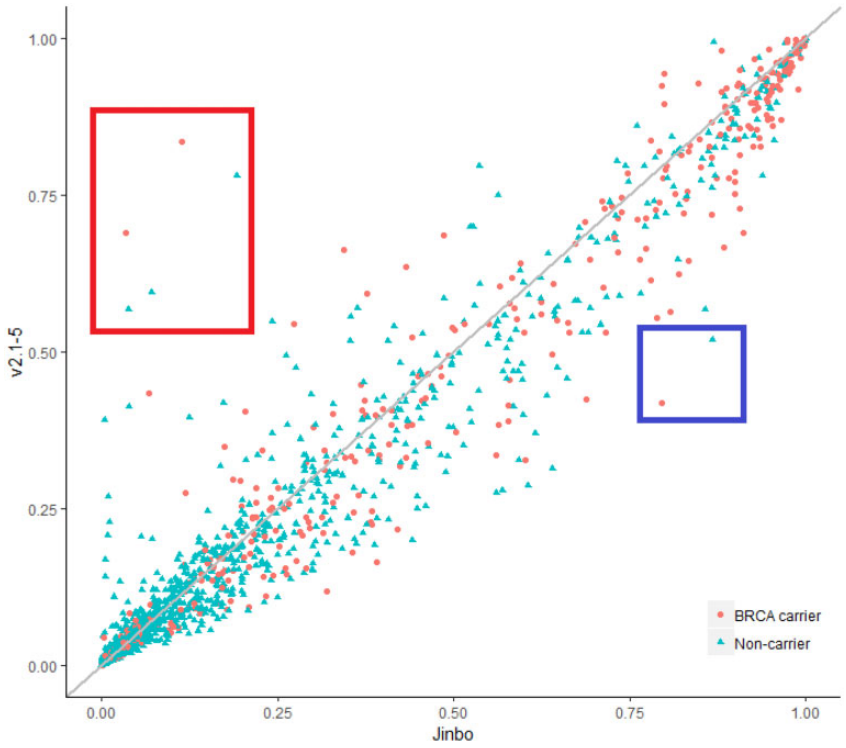

Figure 2. Cancer Genetics Network carrier estimates.

the 2 studies were not included in the same analysis simultaneously.

Penetrance estimates by age 70 years for breast cancer were 64.6% (95% confidence interval [CI] = 59.5% to 69.4%) for BRCA1 mutation carriers and 61.0% (95% CI = 48.1% to 72.5%) for BRCA2 mutation carriers, and for ovarian cancer they were 48.3% (95% CI = 38.8% to 57.9%) and 20.0% (95% CI = 13.3% to 29.0%). Compared with estimates that did not fully account for RRSO, our estimated penetrance of breast cancer in the age interval 20-70 years was higher than prior estimates for *BRCA1* and *BRCA2* mutation carriers by 8.2% and 14.2%, respectively (Table 2). For ovarian cancer, our estimates in the age interval 30-70 years increased over prior estimates by 14.5% and 6.7% for *BRCA1* and *BRCA2* mutation carriers, respectively (Table 2). Age-specific annual penetrance estimates generated by this procedure and penetrance estimates in Chen and Parmigiani (1) are presented in Supplementary Figure 1 (available online). Our penetrance estimates of breast cancer were generally higher, and those of ovarian cancer shifted to the left. The age peak for ovarian cancer risk for *BRCA1* carriers was 55-60 years and later for *BRCA2* carriers.

Estimation of Carrier Probabilities in NWH and CGN Cohorts

Table 3 summarizes results for comparing BRCAPRO estimates of carrier probabilities in the NWH and CGN cohorts using our current penetrance estimates vs those using Chen and Parmigiani (1). Our new penetrance estimates led to improved net reclassification for individuals carrying either BRCA1 or BRCA2 mutation, a BRCA1 mutation alone, and a BRCA2 mutation alone. The 3 other measures (area under the curve, O/E, MSE) for the 2 sets of estimates were largely similar, although O/E was closer to the target value of 1 based on our new penetrance estimates. Our new penetrance estimates also led to slightly higher MSE—0.096 (95%CI= 0.083 to 0.109) in NWH and 0.149 (95%CI: 0.137, 0.161) in CGN—compared with 0.095 (95%CI: 0.081, 0.109) and 0.146 (95%CI: 0.135, 0.158) using Chen and Parmigiani (1), but the confidence intervals overlapped.

The predicted carrier probabilities for some probands become lower when our penetrance estimates were used (Supplementary Figure 4, available online). On further examination, these probands all had a family member diagnosed with ovarian cancer before age 40 years. Because our new ovarian penetrance estimates were lower before age 40 years (Supplementary Figure 1, available online), this was not surprising. Probands with higher predicted carrier probabilities using our new penetrance estimates all had a family member who was diagnosed with breast cancer either before age 40 years or after age 60 years. This is because our new penetrance estimates for breast cancer were higher in these 2 age intervals (Supplementary Figure 1, available online).

Discussion

We provided new breast and ovarian cancers penetrance estimates for *BRCA1* and *BRCA2* mutation carriers in women who have not undergone RRSO. Compared with estimates that did not fully account for RRSO use (1), our estimated penetrance of breast cancer in the age interval 30-70 years was marginally higher, and ovarian cancer penetrance estimates were lower for ages 0-30 years (1). It was not straightforward to perform a formal test to assess whether our estimates were statistically different from existing ones, because 3 studies included in our analysis were also included in the previous meta-analysis. Despite the small number of studies, we performed additional meta-analyses separately for the 3 studies

that included only Ashkenazi Jews (9, 12, 13) and the remaining 4 studies (7, 8, 10, 11). The 2 sets of results were largely similar (Supplementary Table 2). We showed that a new version of BRCAPRO, a well-validated model for predicting probabilities of carrying BRCA mutations, that incorporates our new penetrance estimates still performs well. The differences in penetrance estimates compared with Chen and Parmigiani (1) appeared to have an impact on the point estimates of carrier probabilities with BRCAPRO in various subsets of individuals in NWH and CGN cohorts (Supplementary Figure 2, available online).

Our results highlight the importance of estimating penetrance of breast and ovarian cancer for *BRCA1/2* mutation carriers stratified on risk modifier statuses. Besides RRSO, other risk modifiers, such as oral contraceptive use, breast feeding, smoking (15), and genetic factors, have been identified. Variability in penetrance estimates across risk modifier subgroups is expected to partially explain the heterogeneity in existing penetrance estimates. More importantly, the refined estimates that incorporate risk modifier information are expected to be essential for individualized clinical counseling of women who carry *BRCA1/2* mutations.

The carrier probability estimation with BRCAPRO in NWH and CGN cohorts may not adequately reflect the differences resulting from using our current penetrance estimates vs those of Chen and Parmigiani (1), because only invasive breast cancer but not ductal carcinoma in situ (DCIS) were recorded in both cohorts. Unfortunately, not all studies included in our meta-analysis reported whether they ascertained only invasive breast cancer or both invasive breast cancer and DCIS breast cancer. The 1 study that did ascertain only invasive breast cancer (12) reported higher penetrance estimates than other studies that ascertained both invasive and DCIS breast cancer. We assumed that penetrance for developing either invasive or DCIS breast cancer is the same as that for developing only invasive breast cancer in *BRCA1/2* carriers.

We provide new penetrance estimates of breast and ovarian cancer for women who carry *BRCA1/2* mutations and have not undergone RRSO. Our estimates are higher than those reported in a previous meta-analysis that did not account for RRSO. For some individuals, using our estimates in BRCAPRO may result in changes in estimated carrier probabilities, which warrants validation in future studies.

Funding

This work was supported by Public Health Service (grant number R01-CA164305 to LZ and JC), N01PC74400-6-0-1, and the National Institutes of Health (4P30CA0006516-51 to GP and TRR).

Notes

Role of the funders: The funders had no role in the design of the study; the collection, analysis, and interpretation of the data; the writing of the manuscript; and the decision to submit the manuscript for publication. JC and TRR are independent of any commercial funder, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Conflicts of interest: JC declares she has no conflict of interest. EB declares he has not conflict of interest. LZ declares she has no conflict of interest. KH declares he has no conflict of interest. GP declares he has no conflict of interest. DB declares she has no conflict of interest. TRR declares he has no conflict of interest.

Acknowledgments: JC and TRR are independent of any commercial funder, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Chen S, Parmigiani G. Meta-analysis of BRCA1 and BRCA2 penetrance. *J Clin Oncol*. 2007;25(11):1329–1333.
2. Rebbeck TR, Lynch HT, Neuhausen SL, et al. Prophylactic oophorectomy in carriers of BRCA1 or BRCA2 mutations. *N Engl J Med*. 2002;346(21):1616–1622.
3. Domchek SM, Friebel TM, Singer CF, et al. Association of risk-reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality. *JAMA*. 2010;304(9):967–975.
4. Biswas S, Atienza P, Chipman J, et al. A two-stage approach to genetic risk assessment in primary care. *Breast Cancer Res Treat*. 2016;155(2):375–383.
5. Parmigiani G, Chen S, Iversen ES, et al. Validity of models for predicting BRCA1 and BRCA2 mutations. *Ann Intern Med*. 2007;147(7):441–450.
6. Pencina MJ, D' Agostino RB, D' Agostino RB, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Stat Med*. 2008;27(2):157–172.
7. Kuchenbaecker KB, Hopper JL, Barnes DR, et al. Risks of breast, ovarian, and contralateral breast cancer for BRCA1 and BRCA2 mutation carriers. *JAMA*. 2017;317(23):2402–2416.
8. Scott CL, Jenkins MA, Southey MC, et al. Average age-specific cumulative risk of breast cancer according to type and site of germline mutations in BRCA1 and BRCA2 estimated from multiple-case breast cancer families attending Australian family cancer clinics. *Hum Genet*. 2003;112(5-6):542–551.
9. King MC, Marks JH, Mandell JB. Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. *Science*. 2003;302(5645):643–646.
10. Evans DG, Shenton A, Woodward E, Lalloo F, Howell A, Maher ER. Penetrance estimates for BRCA1 and BRCA2 based on genetic testing in a Clinical Cancer Genetics service setting: risks of breast/ovarian cancer quoted should reflect the cancer burden in the family. *BMC Cancer*. 2008;8(1):155.
11. Evans DG, Harkness E, Lalloo F, Howell A. Long-term prospective clinical follow-up after BRCA1/2 presymptomatic testing: BRCA2 risks higher than in adjusted retrospective studies. *J Med Genet*. 2014;51(9):573–580.
12. Gabai-Kapara E, Lahad A, Kaufman B, et al. Population-based screening for breast and ovarian cancer risk due to BRCA1 and BRCA2. *Proc Natl Acad Sci USA*. 2014;111(39):14205–14210.
13. Satagopan JM, Boyd J, Kauff ND, et al. Ovarian cancer risk in Ashkenazi Jewish carriers of BRCA1 and BRCA2 mutations. *Clin Cancer Res*. 2002;8(12):3776–3781.
14. Mavaddat N, Peock S, Frost D, et al. Cancer risks for BRCA1 and BRCA2 mutation carriers: results from prospective analysis of EMBRACE. *J Natl Cancer Inst*. 2013;105(11):812–822.
15. Friebel TM, Domchek SM, Rebbeck TR. Modifiers of cancer risk in BRCA1 and BRCA2 mutation carriers: systematic review and meta-analysis. *J Natl Cancer Inst*. 2014;106(6):dju091.