ORIGINAL REPORT

Meta-Analysis of *BRCA1* and *BRCA2* Penetrance

Sining Chen and Giovanni Parmigiani

A B S T R A C T

Purpose
Genetic counseling is now routinely offered to individuals at high risk of carrying a *BRCA1* or
BRCA2 mutation. Risk prediction provided by the counselor requires reliable estimates of the
mutation penetrance. Such penetrance has been investigated by studies worldwide. The reported
estimates vary. To facilitate clinical management and counseling of the at-risk population, we
address this issue through a meta-analysis.

Methods
We conducted a literature search on PubMed and selected studies that had nonoverlapping
patient data, contained genotyping information, used statistical methods that account for the
ascertainment, and reported risks in a useable format. We subsequently combined the published
estimates using the DerSimonian and Laird random effects modeling approach.

Results
Ten studies were eligible under the selection criteria. Between-study heterogeneity was
observed. Study population, mutation type, design, and estimation methods did not seem to
be systematic sources of heterogeneity. Meta-analytic mean cumulative cancer risks for
mutation carriers at age 70 years were as follows: breast cancer risk of 57% (95% CI, 47% to
66%) for *BRCA1* and 49% (95% CI, 40% to 57%) for *BRCA2* mutation carriers; and ovarian
cancer risk of 40% (95% CI, 35% to 46%) for *BRCA1* and 18% (95% CI, 13% to 23%) for
BRCA2 mutation carriers. We also report the prospective risks of developing cancer for currently
asymptomatic carriers.

Conclusion
This article provides a set of risk estimates for *BRCA1* and *BRCA2* mutation carriers that can be
used by counselors and clinicians who are interested in advising patients based on a comprehen-
sive set of studies rather than one specific study.

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INTRODUCTION

Genetic counseling is now routinely offered to
individuals at high risk of carrying a *BRCA1*
(MIM 113705) or *BRCA2* (MIM 600185) muta-
tion. At-risk individuals receive advice and make
decisions about genetic testing, screening, and
prevention strategies such as chemoprevention
and prophylactic surgeries. To personalize man-
agement strategies according to risk level, risk
assessment is first given to the counselee, often
through the use of a risk prediction model.[1-4]
Such a model predicts the risk of carrying a dele-
terious mutation and the risk of developing breast
or ovarian cancer based on prespecified pen-
etrance. In this article, penetrance refers to the
risk of developing breast and ovarian cancers
among *BRCA1* and *BRCA2* mutation carriers.
Thus, a reliable estimate of penetrance is crucial
for counseling and decision making.

Different penetrance leads to different risk as-
sessments. This is currently problematic for risk
counseling. There has been controversy over the ex-
tent of the variation and the reasons for it. To pro-
vide a basis for more evidence-based counseling and
decision making, we investigate potential sources of
variation and then integrate the penetrance esti-
mates into a consensus set of penetrance.

METHODS

We addressed this issue via a meta-analysis. We per-
formed a PubMed search for combinations of the
following words in the title of the article: ("risk" OR
"penetrance") AND ("breast cancer" OR "ovarian
cancer") AND ("BRCA1" OR "BRCA2"). We then
restricted attention to the studies that satisfied all of
the following criteria: study was based on genotyping
information; if the study was not population-based,
the statistical analysis corrected for ascertainment;
study reported age-specific breast and ovarian cancer

risks for mutation carriers with CIs; and study patients did not overlap with patients in other included studies. Motivated by the extent of heterogeneity observed in the eligible studies, we combined the published estimates using the DerSimonian and Laird random effects modeling approach.[5]

RESULTS

Ten studies met our search criteria. Studies that provided risk-related information but failed to satisfy the criteria are listed in Appendix Table A1 (online only), with reasons for exclusion. In Table 1, we give a synopsis of the included studies, briefly describing study population, design, mutation testing information, and risk estimation methods.

Heterogeneity was observed among the reported risks (Fig 1). Visual pairwise comparisons of CIs include many that overlap as well as some that do not. To quantify this study-to-study variation, we performed tests of heterogeneity[5] for all age-specific risks, after logit transformation. With two cancer sites, two genes, and six age intervals, a total of 24 tests were performed. For ovarian cancer, nine of the 12 P values ranged from .11 to .92. The other three P values were .02, .04, and < .001; all occurred at age 30 years or younger, where the risk estimates are low and unstable. Therefore, we conclude that there is not enough evidence for heterogeneous ovarian cancer risks. Breast cancer risks are more heterogeneous. For BRCA1 carriers, all P values ranged from .001 to .045. For BRCA2 carriers, the P values were .23 and .22 at ages 20 and 30 years and between .02 and .05 at later ages.

Next, we searched for systematic sources of heterogeneity from various aspects of study characteristics. Systematic differences could arise from the mutation type, the study population, or the design/analysis strategy. Regarding mutation type, Hopper et al[7] was the only

Study	Population	Ascertainment	No. of Families	No. of Carriers*	Genotyping Method	Estimation Approach	Necessary Condition for Unbiasedness
Ford et al[6] and Easton et al[7]	BCLC	Four or more patients	237	64 + 36	Markers flanking BRCA1/2	Maximum LOD score, equivalent to retrospective likelihood	No additional familial aggregation other than BRCA1/2
Struewing et al[8]	AJs in Washington, DC area	Population-based volunteers	4,873	61 + 59	ASO and allele-specific PCR	Used empirical risk to first-degree relatives to deduce carrier risk	The incidence rate among the volunteers was the same as in the general AJ population
Hopper et al[9]	Australian Cancer Registry	Population-based early-onset patients	388	9 + 9	PTT	(1) Repeated sampling; (2) joint likelihood of family history conditioning on the index patient and on her being a carrier	The predefined protein truncation mutations have the same penetrance as all mutations pooled
Satagopan et al[10]	New York + Canada hospital-based AJ breast cancer patients	Population-based patients	782	45 + 12 + 23†	PCR or ASO	Used patients from Struewing et al as a control group to estimate age-specific relative risk	The control group is representative of the general population in terms of mutation prevalence
Satagopan et al[11]	AJ ovarian cancer patients from multiple hospitals	Population-based patients	436	76 + 27 + 44†	PCR or ASO	Used patients from Struewing et al as a control group to estimate age-specific relative risk	The control group is representative of the general population in terms of mutation prevalence
Scott et al[12]	kConFab, Australian	High-risk families with mutations	53	28 + 23	PTT or CCM or HA or DGGE, all with sequencing	Modified segregation analysis, similar to Ford et al	No additional familial aggregation other than BRCA1/2
Antoniou et al[13]	European + North America (Israel) + Australia + Hong Kong	Population-based patients	8,139	289 + 221	Various	Joint likelihood of family history conditioning on the index patient and on her being a carrier	No effect from size-biased sampling; or, risks to carrier patient cases and their relatives are not higher than carrier non–patient cases
King et al[14]	New York hospital-based AJ breast cancer patients	Population-based patients	1,008	42 + 25 + 37† in patients, 212 in relatives	Sequencing	Genotyped all relatives of found patient carriers and used Kaplan-Meier analysis	No effect from size-biased sampling; or, risks to carrier patient cases and their relatives are not higher than carrier non–patient cases
Marroni et al[15]	From five Italian cancer genetic clinics	High-risk families	568	46 + 39	PTT-SSCP alone, with sequencing or with FAMA	Retrospective likelihood: joint likelihood of genotyping result conditioning on family history	No additional familial aggregation other than BRCA1/2
Chen et al[16]	AJ and non-AJ families from the US Cancer Genetics Network	High-risk families	1,948	296 + 130	Various	Retrospective likelihood	No additional familial aggregation other than BRCA1/2

Table 1. Characteristics of Eligible Studies

Abbreviations: BCLC, Breast Cancer Linkage Consortium; AJ, Ashkenazi Jew; LOD, logarithm of the odds; ASO, allele-specific oligonucleotide; PCR, polymerase chain reaction; PTT, protein truncation test; kConFab, Kathleen Cuningham Foundation Consortium for Research into Familial Breast Cancer; CCM, chemical cleavage mismatch; HA, heteroduplex analysis; DGGE, denaturing gradient gel electrophoresis; SSCP, single strand conformational polymorphism; FAMA, fluorescence-assisted mutational analysis.
*In the form of No. of BRCA1 carriers + No. of BRCA2 carriers, unless otherwise noted.
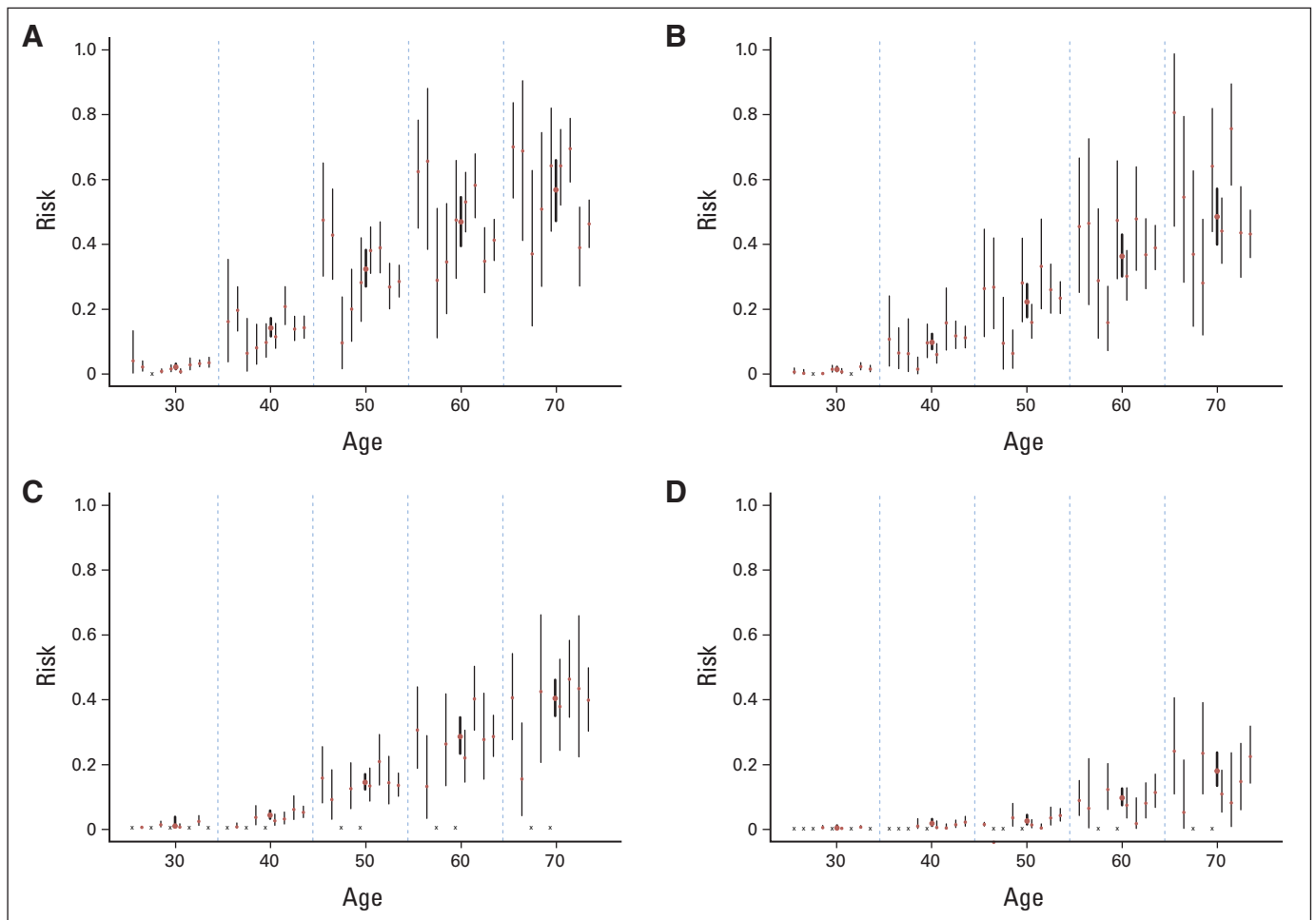†For AJs where only the three founder mutations were tested, #185delAG + #5382insC + #6174delT.

Fig 1. (A) Breast cancer risk for *BRCA1* carriers, (B) breast cancer for *BRCA2* carriers, (C) ovarian cancer for *BRCA1* carriers, and (D) ovarian cancer for *BRCA2* carriers. The cumulative risk estimates from published studies (thin vertical bars) and the meta-analytic mean (thick vertical bars, height represents 95% CIs). Within each 10-year age interval, the published studies are arranged in the following order (left to right): Ford et al[6] and Easton et al,[7] Struewing et al,[8] Hopper et al,[9] Satagopan et al,[10,11] Scott et al,[12] Antoniou et al,[13] King et al,[14] Marroni et al,[15] and Chen et al.[16] An "x" represents not available.

study that exclusively looked at protein-truncating mutations. All other studies included carriers of a mixed pool of mutation types. If penetrance was mutation specific, we would wish to learn about the penetrance(s) associated with each distinct type of mutation(s). However, it is not presently feasible to separate the effects of mutations from these studies. Instead, a reachable goal is to learn about the average risk among a group of carriers with a representative mix of mutations in a population. Because Hopper et al[9] looked only at protein-truncating mutations, which are reported to confer lower risks than other types of mutations, we conducted our meta-analysis of this risk both including and excluding this study. The issue of study populations is similar to that of mutation type in that different populations (by ethnicity, eg, Ashkenazi Jew *v* not, or geographic locations) may segregate different mutations or share different risk factors. Currently, there are studies containing more than one subpopulation; however, they provide limited evidence of population-specific variation in penetrance, either by geographical region or by ethnicity.[13,16,17] Regarding design and analysis, as shown in Table 1, each study used an analysis method that addressed ascertainment mechanism in its design. Although it has been conjectured that the designs and analyses used in the studies may result in biases,[8,9,13,18] which could generate

the observed heterogeneity, some of the empirical evidence also suggests the contrary. For example, the Breast Cancer Linkage Consortium studied families with higher logarithm of the odds scores and also demonstrated that the penetrance estimates are equally high when families with low logarithm of the odds scores are included. Meanwhile, King et al[14] used case series data and arrived at similar estimates. Scott et al,[12] Marroni et al,[15] and Chen et al[16] used a similar design and analysis as Ford et al[6] and reported lower penetrance. In summary, as the number of studies grows, there is no clear systematic trend attributable to the design and analysis.

Motivated by the lack of systematic heterogeneity among current penetrance estimates, we summarized them with a random effects model using the DerSimonian and Laird approach.[5] The resulting consensus estimates are weighted averages of the risks reported by all studies, whereas their SEs take into account both within-study SEs and study-to-study heterogeneity. This approach relies on an assumption of normality of the random effects, which is reasonable because there is no pronounced asymmetry and no study is an obvious outlier.

On the basis of our analysis, we report the mean and standard deviation of the meta-analytic penetrance by 10-year age intervals, as shown in Figure 1. In a separate analysis, we excluded the Hopper et al[9]

study. However, the difference was minimal (< 0.1 percentage point at all age intervals).

For comparison, we also obtained the estimate of the penetrance assuming no interstudy variation. The resulting cumulative risks by age 70 years are as follows: breast cancer risk of 55% (95% CI, 50% to 59%) for *BRCA1* and 47% (95% CI, 42% to 51%) for *BRCA2* mutation carriers; and ovarian cancer risk of 39% (95% CI, 34% to 45%) for *BRCA1* and 17% (95% CI, 13% to 21%) for *BRCA2* mutation carriers. Compared with the random effects model, the point estimates are within 2 percentage points of each other. However, the CIs for breast cancer risks become much narrower by ignoring existing heterogeneity, whereas those for the ovarian cancer risks remain similar.

Penetrance curves based on these results have been incorporated in the genetic counseling and risk prediction software BayesMendel,[3] which includes the *BRCA* mutation prediction tool BRCAPRO,[19] and will be incorporated in the next version of CancerGene.[20] Note that penetrance by definition is the net risk in the absence of any competing risks. We also derived the future risks of developing cancer for currently asymptomatic carriers after taking into account deaths as the competing cause (death hazard was obtained from Surveillance, Epidemiology, and End Results 13 Incidence and Mortality, 2000-2002; http://seer.cancer.gov/canques/mortality.html). We report those risks in Table 2. An at-risk individual can directly read her prospective risks from this table, depending on her current age, and use them to make clinical decisions such as those regarding prophylactic surgeries.

DISCUSSION

In this article, we integrated information on available studies on the risk of breast and ovarian cancer for *BRCA1* and *BRCA2* mutation carriers (penetrance), with the goal of assisting clinicians and counselors in understanding and combining the information provided by the numerous studies that have investigated this question.

A graphical summary of penetrance estimates (Fig 1) and statistical tests show that study-specific estimates are somewhat heterogeneous. However, after taking into account the estimates' uncertainties, each study has CIs overlapping with several others, and there are no pronounced outliers. This suggests that the heterogeneity among studies is a surmountable obstacle.

A critical question in presence of heterogeneity is the identification of its sources. In this article, we systematically examined penetrance estimates across all studies, along with characteristics that are likely to be potential sources, including study population, mutation detection strategy, and design/analysis approach. A systematic comparison of groups of studies by potential heterogeneity source is informative about whether any of the characteristics can explain the variation. However, none of the potential sources considered was able to systematically explain the observed variation across studies. Because of the inherent complexity of gene characterization studies, there may be study characteristics that we have not been able to examine.

Table 2. Predicted Mean Cancer Risk to Currently Unaffected *BRCA1*/2 Mutation Carriers

Current Age	Risk (%) of Developing Cancer by Age									
	30 Years		40 Years		50 Years		60 Years		70 Years	
	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI
Breast cancer: *BRCA1*										
20 years	1.8	1.4 to 2.2	12	9.5 to 14	29	24 to 35	44	37 to 52	54	46 to 63
30 years	—		10	8.2 to 13	28	23 to 34	44	36 to 52	54	45 to 63
40 years	—		—		20	16 to 25	38	31 to 45	49	41 to 58
50 years	—		—		—		22	18 to 27	37	30 to 44
60 years	—		—		—		—		19	15 to 24
Breast cancer: *BRCA2*										
20 years	1	0.78 to 1.4	7.5	5.8 to 9.8	21	17 to 26	35	28 to 42	45	38 to 53
30 years	—		6.6	5.1 to 8.6	20	16 to 26	35	28 to 42	45	38 to 53
40 years	—		—		15	12 to 19	30	24 to 36	42	34 to 49
50 years	—		—		—		18	15 to 22	32	26 to 38
60 years	—		—		—		—		17	14 to 20
Ovarian cancer: *BRCA1*										
20 years	1	0.68 to 1.8	3.2	2.3 to 5.1	9.5	7.3 to 13	23	18 to 28	39	34 to 44
30 years	—		2.2	1.6 to 3.4	8.7	6.7 to 12	22	18 to 27	39	34 to 43
40 years	—		—		6.7	5.2 to 8.9	20	17 to 24	38	33 to 41
50 years	—		—		—		15	12 to 17	34	29 to 36
60 years	—		—		—		—		22	20 to 23
Ovarian cancer: *BRCA2*										
20 years	0.19	0.09 to 0.47	0.7	0.37 to 1.5	2.6	1.5 to 4.5	7.5	5.1 to 11	16	12 to 20
30 years	—		0.52	0.28 to 1	2.4	1.5 to 4.2	7.4	5.1 to 11	16	12 to 20
40 years	—		—		1.9	1.2 to 3.2	7	4.8 to 10	16	12 to 20
50 years	—		—		—		5.2	3.7 to 7.2	14	11 to 17
60 years	—		—		—		—		9.8	7.8 to 11

NOTE. The CI is provided for the mean risk, not the risk itself.

However, it seems unlikely that there exists one simple answer to the nature of heterogeneity.

In current clinical practice, two scenarios are possible. In the first, the clinician is able to identify a single study that matches the relevant patient population for his or her practice. In the second, which is perhaps more common, there is no clear criterion for deciding which study is most appropriate for a particular patient. In this case, given current knowledge, a meta-analysis that acknowledges heterogeneity is the most evidence-based and, arguably, ethically sound approach to risk counseling. This does not conflict with the concept that risk counseling should be made as individualized as possible by taking into account well-understood risk modifiers.

AUTHOR CONTRIBUTIONS

Conception and design: Sining Chen, Giovanni Parmigiani
Data analysis and interpretation: Sining Chen
Manuscript writing: Sining Chen, Giovanni Parmigiani
Final approval of manuscript: Sining Chen, Giovanni Parmigiani

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Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).