Bias correction methods explain much of the variation seen in breast cancer risks of BRCA1/2 mutation carriers

Janet R. Vos, et al

Supplementary table 1 Overview of full or partial clinical studies with breast cancer CLTR estimations by age 70 in *BRCA1/2* mutation carriers

Study	Year	Ascertainment	Analysis	Bias correction method	Censoring, at age of	BC by age 70 CLTR (95% CI)		BC/OC by age 70 CLTR (95% CI)	
						BRCA1	*BRCA2*	*BRCA1*	*BRCA2*
Dorum et al [6]	1999	Family cancer clinic series and consecutive ovarian-cancer series from Sweden and Norway, families harboring *BRCA1* founder mutation 1135insA or 1675delA	Kaplan-Meier analysis	Including all female mutation carriers (demonstrated, affected or obligate), excluding index cases	Death or last contact (RRM N=0)	± 52 & 57	NA	NA	NA
				Including all female mutation carriers (demonstrated, affected or obligate), excluding index cases	RRSO, death or last contact	NA	NA	90 (SE: 3)	NA
				Including all female mutation carriers (demonstrated, affected or obligate) and their untested unaffected sisters, excluding index cases		NA	NA	70 (SE: 4)	NA
				Including all female mutation carriers (demonstrated, affected or obligate) and a proportion of their untested unaffected sisters, excluding index cases		NA	NA	76 (SE: 7)	NA
Einbeigi et al [14]	2001	*BRCA1* founder mutation 3171insA Family cancer clinic, Sweden	Kaplan-Meier analysis	Including all female mutation carriers (proven or obligate) and affected sister, excluding index cases	RRSO, death or last contact (RRM N=0)	NA	NA	93 (80-99)	NA
				Including all female mutation carriers (demonstrated, affected or obligate) and all sisters, excluding index cases		NA	NA	59 (46-73)	NA
Brose et al [19]	2002	Consecutive cohort of *BRCA1* mutation carriers, counseled at a family cancer clinic, USA (BCLC)	Life-table method	Including all female mutation carriers (proven, obligate and presumed)	Death or last contact	73 (68-78)	NA	NA	NA
Heimdal et al [21]	2003	Family cancer clinic series and consecutive breast and ovarian cancer series, Norway, families harboring founder mutation 816delGT, 1135insA, 1675delA or 3347delAG	Kaplan-Meier analysis	Including all female mutation carriers (demonstrated, affected or obligate), excluding index cases	RRM, OC, death or last contact	58 (51-66)	NA	NA	NA
				Including all female mutation carriers (demonstrated, affected or obligate), excluding index cases	Death, last contact or 110 yrs	NA	NA	84 (SE: 2)	NA
				Including all female mutation carriers (demonstrated, affected or obligate) and their untested unaffected FDRs, excluding index cases		NA	NA	62 (SE: 2)	NA
				Including all female mutation carriers (demonstrated, affected or obligate) and a proportion of their untested unaffected FDRs, excluding index cases		NA	NA	70 (SE: -)	NA
Scott et al [24]	2003	High-risk families and known *BRCA* families, Australia (kConFab)	Modified segregation analysis (MLE: joint likelihood)	Maximized the conditional likelihood of all phenotypic and genotypic information in the family given the breast cancer status and age at diagnosis or else age interview of all family members, and genetic information of the index case	RRM, RRSO, death, last contact or 85 yrs	48 (22-82)	74 (50-93)	NA	NA
Southey et al [25]	2003	Family cancer clinic series, *BRCA1* families with putative splice site mutation IVS6-2delA, Australia (kConFab)	Modified segregation analysis (MLE: joint likelihood)	Maximized the conditional likelihood of all phenotypic and genotypic information in the family given the breast cancer status of all family members	Death or last contact	49 (13-96)	NA	NA	NA
Marroni et al [26]	2004	Family cancer clinic series including high-risk families both positive and negative for *BRCA1/2* mutations, Italy	MCMC	Retrospective likelihood conditioned on all phenotypic data	-	39 (27-52)	44 (29-58)	NA	NA

Kroiss et al [28]	2005	Consecutive cohort of female *BRCA1/2* mutation carriers counseled at the family cancer clinic, Austria	Kaplan-Meier analysis	-	RRM, RRSO, death or last contact	85 (75-97)	NA	NA	NA
Tesoriero et al [29]	2005	High-risk families and known *BRCA* families, *BRCA1/2* families with splice site variants, Australia and New Zealand (kConFab)	Modified segregation analysis	Joint likelihood conditioned on all phenotypic data in the family and the genotypic information of the index carrier	RRM, RRSO, death, last contact or 85 yrs	64 (28-96)	79 (48-98)	NA	NA
Antoniou et al [30]	2006	High-risk French-Canadian breast and/or ovarian cancer families	Modified segregation analysis	Joint likelihood conditioned on all phenotypic data in the family and the genotypic information of the index carrier	OC, death, last contact or 70 yrs	72 (0-93)	75 (0-97)	NA	NA
					Death, last contact or 70 yrs	NA	NA	83 (34-96)	89 (34-98)
Chen et al [31]	2006	Population-based and clinic-based high-risk families	MCMC	Mendelian retrospective likelihood conditioned on all phenotypic data	-	46 (39-54)	43 (36-51)		NA
Vogl et al [37]	2007	High-risk family *BRCA1* mutation 4056C>T, USA	Kaplan-Meier analysis	Including all proven female mutation carriers, excluding ascertainment cases	Death or last contact (RRM N=0)	53 (35-75)	NA	NA	NA
			Segregation analysis	Retrospective likelihood conditioned on all phenotypic data		39 (29-49)	NA	NA	NA
			Segregation analysis	Conditional likelihood (MLOD) on all affected individuals		30 (17-47)	NA	NA	NA
Evans et al [40]	2008	Family cancer clinics, England	Kaplan-Meier analysis	Including proven and obligate female mutation carriers, and a proportion of FDRs	RRM, OC, RRSO, death or last contact	68 (65-71)	75 (72-78)	NA	NA
				Including unaffected carriers and FDRs at time of family ascertainment		30-79yr: annual incidence of 2%		NA	NA
Milne et al [41]	2008	Family cancer clinic, Spain	Modified segregation analysis	Joint likelihood conditioned on all phenotypic data in the family and the genotypic information of the index carrier	RRM, other cancers, RRSO, death, last contact or age 70	52 (26-69)	47 (29-60)	NA	NA
Cardenosa et al [44]	2010	Family cancer clinic, Spain	Kaplan-Meier analysis	-	Last contact	NA	NA	78 (71-85)	
Beristain et al [50]	2010	Family cancer clinic, Spain	Kaplan-Meier analysis	Including index cases	OC, RRSO, death or last contact (RRM N=0)	64 (39-78)	69 (40-84)	NA	NA
				Excluding index cases		36 (5-57)	38 (12-56)	NA	
Van der Kolk et al [51]	2010	Family cancer clinic, Northern-Netherlands	Kaplan-Meier analysis	Including index cases	RRM, RRSO<50 yrs, death or last contact	71 (67-82)	88 (82-93)	NA	NA
				Excluding index cases		60 (55-66)	78 (69-88)	NA	NA
Tea et al[53]	2014	Family Cancer Clinic, Austria	Kaplan-Meier analysis	Including index cases, excluding obligate carriers	RRM,RRSO, death or last contact	NA	88 (81-95)	NA	NA
Brohet et al [54]	2014	Family cancer clinic series, the Netherlands	Modified segregation analysis	Joint likelihood conditioned on all phenotypic data in the family and the genotypic information of the index carrier	RRM, OC, RRSO, death, last contact, last DNA-test family member or 70 yrs	45 (36-52)	27 (14-38)	NA	NA
Vos et al [52]	2014	Family cancer clinics, the Netherlands	Kaplan-Meier analysis	Including index cases	RRM, OC, RRSO, death or last contact	72 (66-78) 76 (71-79)	78 (69-85) 72 (64-78)	NA	NA
				Excluding index cases		58 (50-66) 68 (62-73)	64 (50-75) 61 (50-69)	NA	NA

BC, breast cancer; FDRs, first-degree relatives; MCMC, Markov Chain Monte Carlo; MLE, maximum likelihood estimate; MLOD, maximum logarithm of the odds; OC, ovarian cancer; RRM, risk-reducing mastectomy; RRSO, risk-reducing salpingo-oophorectomy; NA, not applicable.

Supplementary Figure 1 Flow diagram of the literature search