Title: *BRCA1*- and *BRCA2*-Associated Hereditary Breast and Ovarian Cancer *GeneReview* – Probability Models for *BRCA1* and *BRCA2* Pathogenic Variants
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Probability Models for *BRCA1* and *BRCA2* Pathogenic Variants

Each probability model has its unique attributes determined by the methods, sample size, and population used to create it. These models include those using logistic regression, genetic risk models using Bayesian analysis (BRCAPRO and Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm [BOADICEA]), as well as empiric data such as the Myriad prevalence tables.

The validity of several of the models has been compared in different studies, and the data show that these models perform reasonably well in typical breast-ovarian cancer families seen in cancer genetics clinics [Antoniou et al 2008]. Most models do not include other *BRCA1*- or *BRCA2*-related cancers (e.g., pancreatic cancer, prostate cancer). Interventions that decrease the likelihood that an individual will develop cancer (such as oophorectomy and mastectomy) may influence the ability to estimate the probability of a *BRCA1* or *BRCA2* pathogenic variant [Katki 2007]. Furthermore, one study has shown that the models are sensitive to the amount of family history information available and do not perform as well with a limited family structure, defined as having fewer than two first- or second-degree female relatives surviving beyond the age of 45 years in either lineage [Weitzel et al 2007].

The performance of the models can vary in specific ethnic groups as well [Oros et al 2006, Vogel et al 2007, Kurian et al 2008, Kurian et al 2009]. The addition of breast tumor markers including estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 has been shown to improve the performance of BRCAPRO and BOADICEA [Tai et al 2008, Mavaddat et al 2010, Biswas et al 2012].

As more individuals have undergone *BRCA1* and *BRCA2* molecular genetic testing, risk assessment models have improved. Nevertheless, there is an art to risk assessment and thus, probability models cannot replace clinical judgment. Also, it is important to note that there are factors that could limit the ability to provide an accurate risk assessment (i.e., small family size, few female relatives, and/or risk-reducing surgeries).

Table. Characteristics of Common Models for Estimating the Likelihood of a *BRCA1* or *BRCA2* Pathogenic Variant

	Myriad Prevalence Tables [1]	BRCAPRO [2]	BOADICEA [3]	Tyrer-Cuzick [4]

Method	Empiric data from Myriad Genetics based on personal & family history reported on requisition forms	Statistical model, assumes AD inheritance	Statistical model, assumes polygenic risk	Statistical model, assumes AD inheritance
Features of model	Proband may or may not have breast or ovarian cancer	Proband may or may not have breast or ovarian cancer	Proband may or may not have breast or ovarian cancer	Proband must be unaffected
	Considers age of breast cancer diagnosis as <50 yrs, >50 yrs	Considers exact age at breast & ovarian cancer diagnosis	Considers exact age at breast & ovarian cancer diagnosis	Also incl reproductive factors & body mass index to estimate breast cancer risk
	Considers breast cancer in ≥1 affected relative only if diagnosed <50 yrs	Considers prior genetic testing in family (i.e., *BRCA1 & BRCA*2 pathogenic variant-negative relatives)	Includes all FDR & SDR relatives w/& w/o cancer	
	Considers ovarian cancer in ≥1 relative at any age	Considers oophorectomy status	Incl AJ ancestry	
	Incl AJ ancestry	Incl all FDR & SDR w/& w/o cancer		
	Very easy to use	Incl AJ ancestry		
Limitations	Simplified/limited consideration of family structure	Requires computer software & time-consuming data entry	Requires computer software & time-consuming data entry	Designed for individuals unaffected w/breast cancer
		Incorporates only FDR & SDR; may need to change proband to best capture risk & account for disease in paternal lineage		
		May overestimate risk in bilateral breast cancer [5]		
	Early age of breast cancer onset	May perform better in White populations than in	Incorporates only FDR & SDR; may need to change	

		minority populations [6]	proband to best capture risk	
		May underestimate risk of *BRCA* pathogenic variant in high-grade serous ovarian cancers but overestimate risk for other histologies [7]		

From National Cancer Institute Genetics of Breast and Gynecologic Cancers (PDQ®)
AD = autosomal dominant; AJ = Ashkenazi Jewish; BOADICEA = breast and ovarian analysis of disease incidence and carrier estimation algorithm; FDR = first-degree relatives; SDR = second-degree relatives
1. Frank et al [1998]
2. Parmigiani et al [1998], Katki [2007]
3. Parmigiani et al [1998], Antoniou et al [2004]
4. Tyrer et al [2004]
5. Ready et al [2009]
6. Huo et al [2009], Kurian et al [2009]
7. Daniels et al [2014]

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