Letter

Incorporating tumor immunohistochemical markers in *BRCA1* and *BRCA2* carrier prediction

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The pathology of a patient's breast carcinoma can be highly indicative of *BRCA1* mutation status. Compared to sporadic and *BRCA2* deficient breast carcinomas, *BRCA1* deficient carcinomas tend to be estrogen receptor (ER) negative, progesterone receptor (PR) negative, HER2 negative, cytokeratin (CK)5/6 positive, and CK14 positive [1,2]. BRCAPRO is an accurate, widely used risk prediction model that estimates the probability that an individual carries a deleterious germline mutation in *BRCA1* or *BRCA2* based upon their personal and/or family history of breast and ovarian cancer. Recently, when BRCAPRO carrier probabilities were updated using a patient's pathological sub-type, in a two-step process, risk estimation was improved [3]. Here we describe how we have substantially improved BRCAPRO by directly integrating marker information into the estimation of carrier probabilities and cancer risk.

The theory underlying BRCAPRO is described elsewhere [4,5]. Briefly, the model transforms information on mutation frequency, disease penetrance, and Mendelian transmission patterns into gene carrier probabilities through application of Bayes' rule. For unaffected individuals the model predicts cancer risk from a weighted average of the penetrance for mutation carriers and non-carriers, with the estimated carrier probabilities as weights. The derived conditional probability of the marker status given carrier status used in our calculations were obtained from published data [1,2] and are presented in Table 1. These conditional probabilities are derived from a single study and from a highly selected group of high-risk breast cancer families and thus should be interpreted with some care. The following assumptions were made about the use of markers in combination. First, for ER negative tumors, carrier probabilities were updated using CK5/6 and CK14 status, if available. PR status does not influence carrier predictions if ER status is included because of a strong correlation between ER and PR. Second, Her-2 neu status was not used because it was not predictive of marker status after accounting for ER [1]. Third, marker information was assumed not to be associated with *BRCA2* mutation status, because *BRCA2* and sporadic tumors have similar marker profiles. Updating *BRCA1* probability can have a residual impact on the *BRCA2* carrier probability.

Our updated software package is freely available from [6,7]. A clinical example of a 54 year old female counselee with breast cancer at 45 whose mother had breast cancer at age 63 and no other family history, under various marker scenarios, is presented in Table 2. Without marker data, the counselee's carrier probabilities for *BRCA1* and *BRCA2* are 2.2% and 2.3%, respectively. These probabilities are 5.5% if

Table 1

Conditional probability of marker status given carrier status

Marker status				Marker status given carrier status	
ER	CK14	CK5/6	PR	*BRCA1*	Non-*BRCA1*
+	.	.	.	0.1	0.65
–	+	+	.	0.438	0.016
–	+	–	.	0.124	0.048
–	–	+	.	0.134	0.024
–	–	–	.	0.209	0.24
.	.	.	+	0.21	0.63

Estimates obtained from Lakhani and colleagues [1]. Plus signs (+) denote positive; hyphens (–) denote negative; periods (.) denote missing.

CK = cytokeratin; ER = estrogen receptor; PR = progesterone receptor.

Table 2

Example of clinical application: *BRCA1* and *BRCA2* carrier probabilities (%) under selected marker profile scenarios

Cancer history								Estimated carrier probabilities (%)	
Counselee: 54 year old with breast cancer at 45				Mother: breast cancer at 63					
ER	CK14	CK5/6	PR	ER	CK14	CK5/6	PR	*BRCA1*	*BRCA2*
.	.	.	.	.	.	.	.	2.2	2.3
–	.	.	.	.	.	.	.	5.5	2.3
+	.	.	.	.	.	.	.	0.35	2.4
.	.	.	-	.	.	.	.	4.6	2.3
.	.	.	+	.	.	.	.	0.75	2.4
–	+	+	.	.	.	.	.	38	1.5
–	.	.	.	-	.	.	.	11	2.1
–	.	.	.	+	.	.	.	2.1	2.3
–	+	+	.	–	+	+	.	36	1.5
–	+	–	.	–	+	–	+	2.1	2.3

No other family history is available. Plus signs (+) denote positive; hyphens (–) denote negative; periods (.) denote missing.

her tumor is ER negative or 0.35% if ER positive. Changes in carrier probability generally correspond to markedly different clinical recommendations regarding genetic testing and cancer prevention. Including this information greatly impacts BRCAPRO carrier probabilities and improves distinction between *BRCA1* and non-*BRCA1* breast tumors.

Competing interests

The authors declare that they have no competing interests.

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