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Original Article

A preliminary validation of a family history assessment form to select women at risk for breast or ovarian cancer for referral to a genetics center

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The medical community and general population have become aware that genetic testing is available to look for *BRCA1* and *BRCA2* mutations. However, criteria for who should be referred for genetic counseling and possible subsequent testing have yet to be determined, and many genetics centers have been overwhelmed by the demand for service. We set out to develop a family history assessment tool (FHAT) that could be used by physicians to select individuals for genetic counseling. Arbitrarily, we chose individuals who would have an approximate doubling of their lifetime risk for breast or ovarian cancer. The FHAT was then applied to 184 unrelated families, with an index patient who had breast or ovarian cancer and who had accepted the offer of *BRCA1*/*BRCA2* testing. Data were compiled to compare the number of individuals who would have been referred for genetic counseling and the number of mutation-positive individuals who would have been screened out from counseling using FHAT, the tables from Claus, and the BRCAPRO system. In this population, FHAT was effective in minimizing both the number of referrals and the likelihood of missing women who were later found to be mutation-positive.

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Key words: *BRCA* mutations – breast cancer – family history – ovarian cancer – risk assessment

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As physicians and the general population become more aware of genetic testing for hereditary breast and ovarian cancers, there is significant pressure to refer women to genetics departments because of a perceived increased risk for breast and/or ovarian cancer. The Gail model (1) has been used in a number of chemoprevention trials and is perhaps the best known among the several methods currently in use for breast cancer risk assessment. The model uses several factors of personal and family history to assess risk, and is available on a number of easy to use computer programs. However, limitations include its data set that consists of women undergoing yearly mammograms and the failure to include a history of ovarian cancer or to consider the age of onset of breast cancer in the relatives. Also, it is not known whether the personal history factors it uses play any role in hereditary cancer (2). The tables provided by Claus et al. (3) were designed for use with women who have a positive family history and they do take into account the age of onset of breast cancer in the relatives and do provide a cumulative risk. However, the data are limited to 2 affected family members with breast cancer, so the method does not assess the entire pedigree and it does not include ovarian cancer, male breast cancer, or bilateral breast cancer. The model is predicted to underestimate the risk to potential *BRCA1* or *BRCA2* gene carriers and to overestimate the risk to non-carriers (2). Frank et al. (4) and Couch et al. (5) have each derived models that predict the probability of a mutation being present in a family, but neither method includes the impact that unaffected family members may have on the overall estimation of risk. The BRCAPRO model (Dept. of Biostatistics, Johns Hopkins School of Public Health) incorporates age-specific, positive and negative family history

information for breast and ovarian cancer from both sides of the family (8). A Bayesian approach is used and, in theory, this should provide a precise risk estimate, but current knowledge of the prevalence and penetrance of the *BRCA1* and *BRCA2* mutations may be problematic. Use of any method requires some knowledge and understanding, and in the case of BRCAPRO, some facility with a computer. None of these methods readily lends itself to a general family practice setting as a way to select patients for referral. In the absence of clear and validated guidelines for how to refer appropriately, women whose risks are not greatly elevated are included in referrals to genetics departments, which can become quickly overwhelmed. Recently, the UK Cancer Family Study Group (6) published their guidelines for primary care physicians as to when they should reassure women considered to be at low risk, when they should institute early surveillance, and when they should refer to genetics. The Claus model was used to produce a table that physicians can use to assess a woman's risk. A risk of less than three times that of the population was considered as low. No data were provided as to the validity of the approach, although the limitations of different methods of risk assessment and the need for prospective studies were discussed.

We set out to develop a simple family history assessment tool (FHAT) that could be used by referring physicians to determine which women should be referred for genetic counseling. Based upon a local consensus, we set a doubling of the general population lifetime risk for breast (0.11) or ovarian (0.016) (7) cancer as our target cut-off for referral. We thought that at this level of risk women and their families might derive significant benefit from genetic counseling and that the approach would make most effective use of limited resources.

A FHAT was devised, which a physician could use to record and assess the family history of cancer. Each member of the family who has been diagnosed with breast, ovarian, early (diagnosed before age 50 years) colon, or prostate cancer is scored separately. The individual scores are modified by factors such as age of onset. The total family score determines if an individual should be referred for genetic counseling. The goal was to select those who were at approximately twice the population risk of developing breast or ovarian cancer and not to determine whether the family would meet research criteria for genetic testing, nor to estimate the actual likelihood of their developing cancer, nor to calculate the likelihood of finding a *BRCA1* or *BRCA2* mutation. A cut-off value was deemed to be the most effective way to simplify the use of this FHAT and this value was arbitrarily set at 10 points for simplicity. Two types of comparisons were made in order to validate the approach. First, women who would be either selected or excluded by the tool were compared to how those same individuals would be assessed using a doubling (22%) of the lifetime risk as estimated by the Claus tables (3) and the BRCAPRO program (8). Second, a note was made of the number of *BRCA1/2* mutation-positive patients who would have been selected or excluded by each of the three methods. The FHAT compared favorably with both of these methods, which are in common use for assessing risk.

Materials and methods

Patient ascertainment

Individuals were ascertained through the Ontario Familial Breast Cancer Registry (OFBCR), local physician referrals, and a small local research study that was examining women's attitudes towards *BRCA1/2* testing (9). The OFBCR is a NIH-funded registry of incident cases of breast cancer that occurred in the province of Ontario between 1 January 1996 and 31 December 1998. Pathologically confirmed cases of breast cancer are ascertained through the Ontario Cancer Registry, and all women aged 20–54 years, all men aged 20–79 years, and 35% of women aged 55–69 years are selected. If the listed physician gives permission (90%), the patient is mailed a family history questionnaire and about 70% of these are returned. The propositus is then classified as familial or probably sporadic. All the familial cases and a randomly selected quarter of the sporadic cases are invited to participate more extensively. Referral of those women who agree (90%) is then made to the local genetics center, where the family history is confirmed and expanded. Participation includes collection of family history, lifestyle and diet questionnaires, genetic counseling appointment(s), and the offer of genetic testing of the *BRCA1* and *BRCA2* genes to those individuals at a potentially increased risk of carrying a mutation in *BRCA1* or *BRCA2*, as well as to 15% of the sporadic cases (controls). Also, the OFBCR study offers genetic testing for the three common Ashkenazi Jewish mutations to all such women in Ontario who have a first- or second-degree relative with breast or ovarian cancer. Referrals from local physicians required at least 1 first- and 1 second-degree relative with breast or ovarian cancer in order to be counseled, while the small local study required a first-degree relative diagnosed under the age of 50

with breast cancer (9). Criteria for testing followed those of the OFBCR. Of the study population, 92 were local referrals, 77 were from the OFBCR, and 15 from the local project.

Development of the FHAT

The FHAT was developed without reference to the family histories or *BRCA1* or *BRCA2* results for any of the 184 families that form the basis for this study. The approach involved development of a weighting of the points assigned to the characteristics (age of onset, type of cancer, degree of relationship to the index) of the cancers in affected individuals from a series of 26 hypothetical pedigrees. The pedigrees were developed by one of us (AH) to illustrate a range of familial patterns of age of onset, relationships, and cancer types. The pedigrees were sent to 16 clinical geneticists who were involved in providing cancer genetics services in Canada. The geneticists were asked to select which of the propositi should be referred for genetic counseling regarding their family history of cancer, and which could be managed by an experienced nurse. There was $\geq 75\%$ agreement on 18 of the 26 pedigrees (68.4%), 100% on 6. The 8 pedigrees where there was less consensus were evenly split between those weighting towards *refer* and *not-refer* categories. These opinions, together with estimated risks from Claus tables (3), were then discussed within our clinical group. The weighting of affected individuals was adjusted by trial and error until a score of ≥ 10 was obtained for those pedigrees considered to merit referral, and of < 10 for those not considered to require referral. The cut-off was considered to approximate a doubling of the lifetime risk for breast cancer in the general population. Development of the FHAT predated availability of BRCAPRO (8). Assessments of the risk estimates and calculation of the FHAT score were then completed prospectively by the genetic counselor (CAG). The study included 184 families with an affected woman who was referred for genetic counseling for breast/ovarian cancer and who opted for *BRCA1*/2 testing from August 1996 to November 1999. In order to make the calculations comparable between women, the next youngest unaffected sister of the women diagnosed with breast or ovarian cancer and who was tested for *BRCA1*/2 was used as the propositus. If a woman did not have a younger sister, she was assigned a hypothetical unaffected sister aged 2 years younger than she was at the time of her diagnosis.

Four calculations were done for each woman: 1) the lifetime risk to age 79 years to develop breast cancer based on her family history using Claus tables (3); 2) a Bayesian analysis of her risk to develop breast and ovarian cancer to age 80 years (± 2 years) using BRCAPRO (8); 3) the probability of a *BRCA1* or *BRCA2* gene mutation in the unaffected woman's family using BRCAPRO; 4) the family history assessment (using FHAT).

To use the FHAT, each member of the woman's extended family who had been diagnosed with breast, ovarian, colon, or prostate cancer is given a column on the family FHAT. Points are assigned based on the relationship of the affected individual to the woman being assessed, their age at diagnosis, and the type and number of primary cancers (bilateral, multifocal, breast/ovarian). All affected relatives as far as third-degree are included. Column totals are combined to give a family score (Fig. 1). For example, if a woman's mother was diagnosed with breast cancer (4 points) at age 46 years (2 points) and her maternal aunt was diagnosed with ovarian cancer (3 points) at age 54 years (4 points), the total score for this woman's family would be 13 (Fig. 1). A single individual may receive points from multiple categories. For example, a 45-year-old sister diagnosed with bilateral breast cancer at age 45 years would be scored as 3 points as a sister, 3 points as bilateral, and 2 points for her age for a total of 8 points. If there is a history of breast and/or ovarian cancer on both sides of the family, each side of the family is assessed separately and the side with the higher score is used.

Laboratory methods

All coding regions of the *BRCA1* and *BRCA2* genes were screened using the following approach. The protein truncation test (PTT) was used to screen for mutations in both the *BRCA1* and *BRCA2* genes. Briefly, exons 11 of both *BRCA1* and *BRCA2* were polymerase chain reaction (PCR)-amplified using DNA extracted with the ABI-341 Nucleic Acid Purification System (Applied Biosystems Inc., Foster City, CA). For the remaining exons, cDNA was synthesized utilizing RNA extracted with the RNEasy kit (Qiagen, Mississauga, ON, Canada) and both random hexamer primers and oligo dT primers. The PCR products were then used in an *in vitro* transcription, translation reaction (Promega, Madison, WI, USA) and the resulting proteins were electrophoresed on a 4–15% gradient SDS PAGE gel (Biorad, Mississauga, ON, Canada). Mutations in patients with a PTT-positive result were identified by sequencing utilizing the Thermosequenase II Dye Terminator Cycle Sequencing kit (Amersham, Baie d'Urfé, QC, Canada), followed by electrophoresis with the

Risk Factor		Points	Mo	Au						
Breast & Ovarian	mother	10								
	sibling	7								
	2nd/3rd degree	5								
Breast	mother	4	4							
	sibling	3								
	2nd/3rd degree	2								
	male add to above	2								
Age of onset (Breast)	20-29	6								
	30-39	4								
	40-49	2	2							
	Pre (peri) menopausal *	(2)								
Breast	bilateral/ multifocal tumour	3								
Ovary	mother	7								
	sister	4								
	2nd/3rd degree	3		3						
Age of onset (Ovary)	<40	6		4						
	40-60	4								
	>60	2								
Age of onset (Prostate)	<50	1								
Age of onset (Colon)	<50	1								
Sub-Totals			**6**	**7**						
Family Total		**13**								

Fig. 1. The FHAT used to score a family where the mother was diagnosed with breast cancer at age 46 years and a maternal aunt was diagnosed with ovarian cancer at age 54 years. Total score for this family is 13.

ABI-373A automated sequencer. The *BRCA1* 185delAG mutation was analyzed separately using the method described by Rohlfs et al. (10). It is estimated that this method detects approximately 85% of mutations (11).

Results

The total number of 'points' visible on the graphs (Figs. 2–5) may not appear to correspond to the numbers reported in the text because identical or similar values tend to be superimposed. Sensitivities, specificities, positive and negative predictive values for the different methods are summarized in Table 1.

FHAT versus Claus tables (Fig. 2)

Eighteen women whose FHAT totals were < 10 points had $\geq 22\%$ estimated lifetime risks (average 28.3%) of developing breast cancer as calculated using the Claus tables (left upper quadrant). Mutations were not identified in any of these women. The 8 points on the x-axis represent women for whom a Claus score could not be determined because only ovarian cancer or male breast cancer was present in their families. Twenty-four women had FHAT totals ≥ 10 with Claus risks of $< 22\%$ (average 15.3%, excluding the women directly on the x-axis). Seven of these women (29.2%) had a mutation identified.

FHAT versus breast cancer risk to age 80 years by BRCAPRO (Fig. 3)

All women whose estimated lifetime risk of developing breast cancer was doubled as calculated using BRCAPRO (dashed line at 22%), and had a family history total of ≥ 10 points on the FHAT, would have been offered genetic counseling as a new referral (right upper quadrant). The rate of mutations detected when the BRCAPRO score was $\geq 22\%$ was high (18/35, 51.4%). Using the FHAT, we would have offered genetic counseling to 94% (33/35) of women in whom mutations were identified. One of the 2 women who would have been missed (left lower quadrant) had a sister who was diagnosed with breast cancer at age 46 years and a mother diagnosed with breast cancer at age 70 years (BRCAPRO estimate: 8.9% chance of developing breast cancer by age 80 years). The other had a family history limited to a sister diagnosed with breast cancer at the age of 49 years (BRCAPRO estimate 14.7% by age 80 years). Fifteen of 71 women (21.1%) who had FHAT totals of ≥ 10 and BRCAPRO risk estimates of less than 22% (average 12.5%) had a mutation detected (right lower quadrant).

FHAT versus ovarian cancer risk to age 80 years by BRCAPRO (Fig. 4)

Two women (left upper quadrant) had FHAT totals of < 10 points and had calculated BRCAPRO lifetime risks greater than double that of the general population (3.2%) of developing ovarian can-

Fig. 2. FHAT vs. Claus values. Women falling in either the right upper or left lower quadrants indicate agreement between the methods. Those in the left upper quadrant would be referred using Claus tables, but not the FHAT, while the opposite holds for the right lower quadrant.

Fig. 3. FHAT vs. BRCAPRO breast cancer risk by age 80 years. Women falling in either the right upper or left lower quadrants indicate agreement between the methods. Those in the left upper quadrant would be referred using BRCAPRO, but not the FHAT, while the opposite holds for the right lower quadrant.

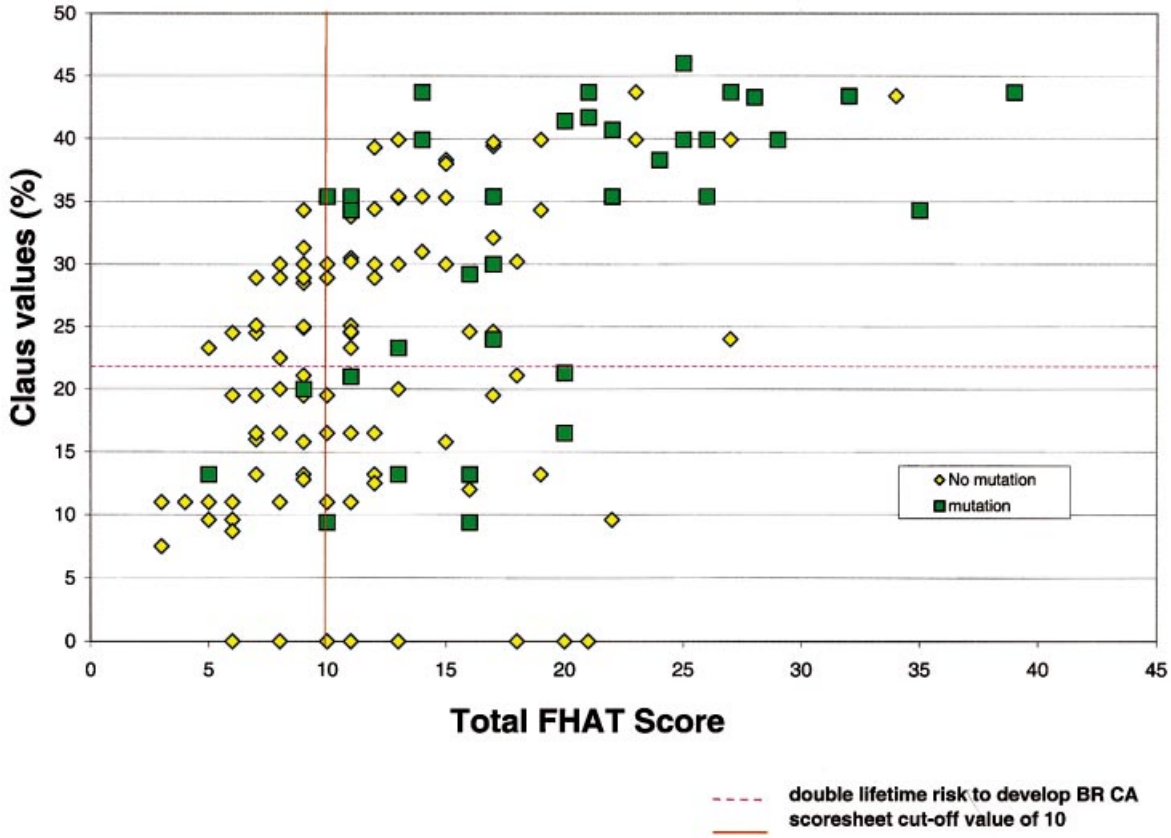

Claus values (%)
Total FHAT Score
No mutation
mutation
double lifetime risk to develop BR CA
scoresheet cut-off value of 10

Fig. 2

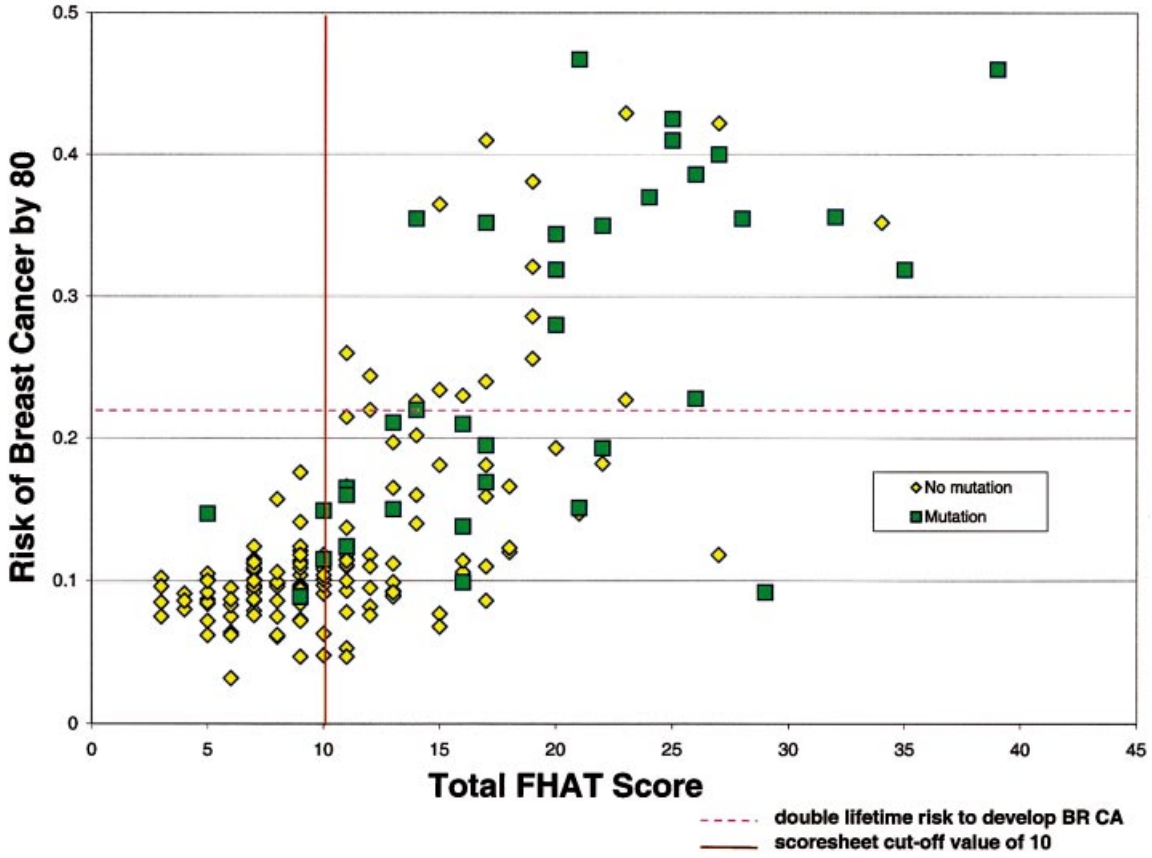

Risk of Breast Cancer by 80
Total FHAT Score
No mutation
Mutation
double lifetime risk to develop BR CA
scoresheet cut-off value of 10

Fig. 3

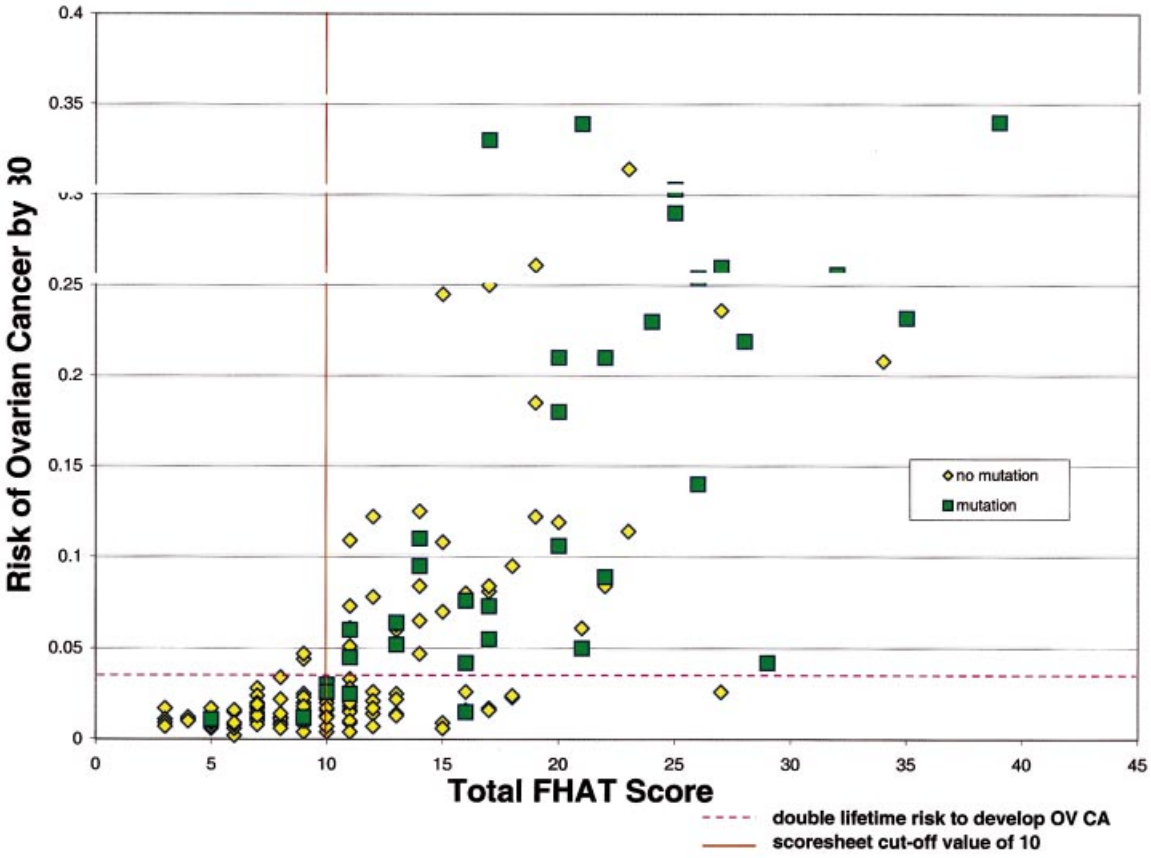

Risk of Ovarian Cancer by 30
Total FHAT Score
no mutation
mutation
double lifetime risk to develop OV CA
scoresheet cut-off value of 10

Fig. 4

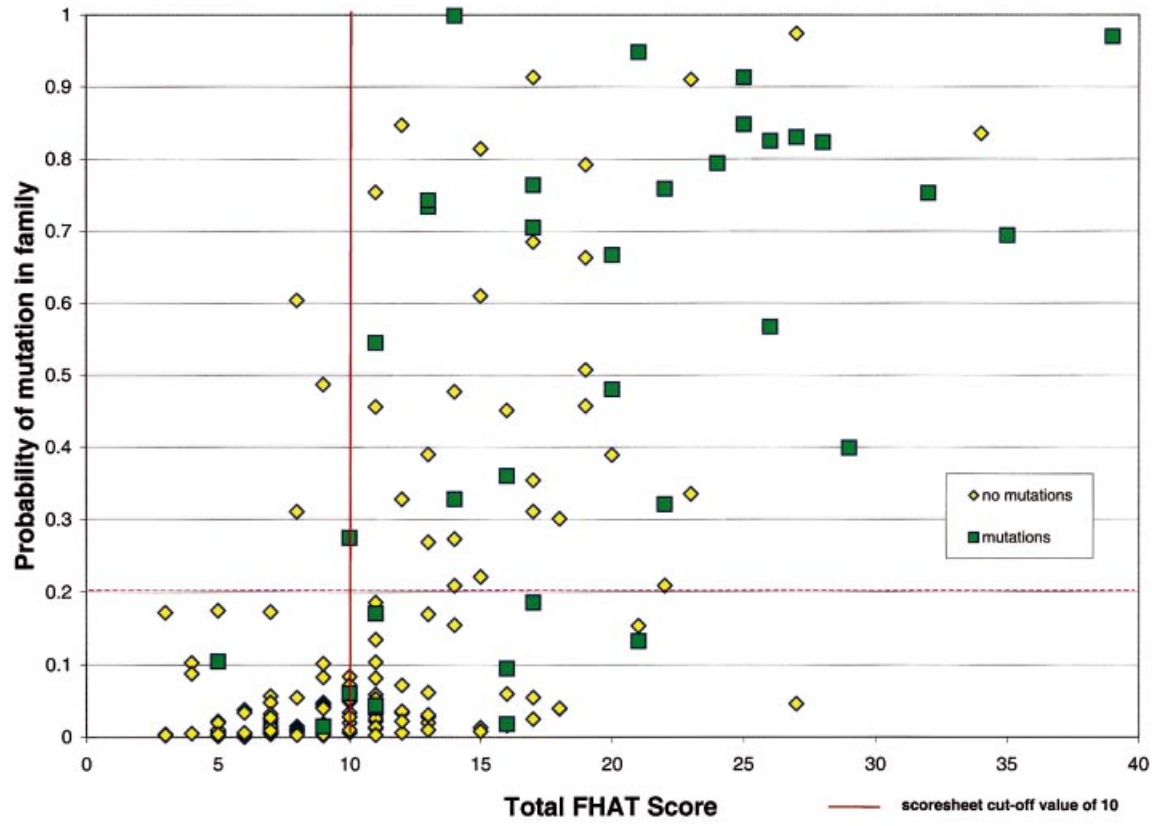

Probability of mutation in family
Total FHAT Score
no mutations
mutations
scoresheet cut-off value of 10

Fig. 5

Table 1. Sensitivity, specificity, and positive and negative predictive values of the different methods applied

	Sensitivity	Specificity	Positive predictive	Negative predictive
Claus	0.74	0.54*	0.28	0.90*
BRCAPRO breast	0.51	0.89	0.51	0.89
BRCAPRO ovary	0.83	0.76	0.45	0.94
BRCAPRO mutation	0.74	0.79	0.46	0.93
FHAT	0.94	0.51	0.31	0.97

* The specificity and negative predictive value of the Claus is slightly exaggerated because the 8 women who had ovarian cancer histories and did not have mutations were counted as negative although no Claus score could be calculated.

cer. One of these women was of Ashkenazi Jewish descent and would have been offered genetic counseling regardless of her FHAT value. The other woman had a sister who was diagnosed with breast cancer in her 20s and had no other family history. In neither case was a mutation identified. Twenty-nine of 61 (47.5%) women with BRCAPRO estimates of $\geq 3.2\%$ and FHAT values ≥ 10 had a mutation identified. Forty-six women with FHAT totals ≥ 10 had BRCAPRO estimates below the doubling lifetime risk cut-off (average 1.7% to age 80 years), and 5 of them (10.9%) were mutation-positive (right lower quadrant, 2 points superimposed). The same 2 cases as discussed in Fig. 3, who were mutation-positive and scored < 10, appear in Fig. 4 (left lower quadrant).

FHAT versus probability of BRCA1/2 mutation in the family by BRCAPRO (Fig. 5)

Three women who would not have been offered genetic counseling based on their total FHAT ($<$ 10) had an estimated $> 20\%$ risk by BRCAPRO to carry a *BRCA1* or *BRCA2* mutation in their families (left upper quadrant). However, these women were all of Ashkenazi Jewish descent; therefore, they all would have been offered genetic counseling regardless of their FHAT total and none had a mutation identified. One of these women was also in the left upper quadrant on Fig. 4. Conversely, there were 50 women estimated to have less than a 20% likelihood to carry a mutation per BRCAPRO who had FHAT values ≥ 10 (average mutation probability of 0.057). Seven (14%) of them had a mutation detected.

Claus values from BRCAPRO compared to standard Claus (data not shown)

The standard Claus tables (3) were used to estimate risk in this study. However, BRCAPRO does provide, as part of its program, a risk based upon the Claus model. We therefore compared the Claus estimates provided with BRCAPRO with those obtained from the tables. Fourteen women who were identified as carrying mutations in *BRCA1* or *BRCA2* had a $< 22\%$ estimated lifetime risk of developing breast cancer according to the Claus value given by BRCAPRO, compared to only 9 mutation carriers falling below 22% using the standard Claus tables. Furthermore, there were 30 individuals whose risk estimates differed by at least a factor of 2, and inspection of the individual pedigrees suggested that in 21/30 (70%) there was paternal family history of breast cancer that did not appear to have been included in the BRCAPRO calculations.

Discussion

We set out to develop a FHAT that would allow an office physician to select, more appropriately, patients concerned about the risk of breast or ovarian cancer for referral to a genetics center. A requirement of any such tool is that it selects or excludes patients in a pattern comparable to the methods of risk assessment in current use, or at least if there are any significant differences, that they do not have an adverse effect upon patient care. Failure to ascertain and refer a patient at risk and who carries a *BRCA1*/2 mutation would be an

Fig. 4. FHAT vs. BRCAPRO ovarian cancer risk to age 80 years. Women falling in either the right upper or left lower quadrants indicate agreement between the methods. Those in the left upper quadrant would be referred using BRCAPRO, but not the FHAT, while the opposite holds for the right lower quadrant.

Fig. 5. FHAT vs. BRCAPRO probability of mutation in family. The graph shows that all but two mutations were detected in women with FHAT scores ≥ 10. BRCAPRO appears to underestimate the likelihood of a mutation for a small proportion of patients.

example of an adverse outcome. If there were a perfect correlation between the apportioning of women into *refer* and *not-refer* categories by the FHAT and either of the other methods, all the data points would fall in the left lower and right upper quadrants of Figs. 2–4. Clearly, that did not occur.

The data in Table 1 show that the FHAT had higher positive and negative predictive values than the Claus tables. In looking more closely at the data, there was agreement for 142/184 (77.2%) of cases. Of the 42 discrepant cases, 18 would have been classed as *refer* with the Claus tables but not by our FHAT. Examination of the individual cases did not reveal a common explanation for the differences, although none of the women had mutations and Claus would be expected to overestimate the risk in a large family where most of the women are unaffected. There were 24 women with Claus estimated risks of $< 22\%$ and FHAT totals of ≥ 10. Their mean Claus risk score was 15.3%, and 7 (29.2%) were found to have mutations. Clearly, the Claus tables underestimate the risk for some families who turn out to have mutations, and this is largely attributable to the fact that the tables do not include data for *BRCA1*/2-associated cancers other than that of the breast and for more than 2 affected relatives. It has been suggested that the use of the Claus model be limited to women at moderate risk, and it is predicted that it will underestimate the likelihood of cancer in *BRCA1*/2 carriers (2). Where the FHAT and the Claus tables agree on *referral*, there was a high probability of detecting a mutation (27/77, 35.1%). The overall rate of detecting a mutation was 31.1% (33/106) for a score ≥ 10, compared to 27.4% (26/95) for a Claus breast cancer risk estimate of $\geq 22\%$. Using the FHAT would result in 11 more patients being counseled and seven more mutations being found.

In contrast to the Claus tables, there were no instances where BRCAPRO gave a lifetime estimate of developing breast cancer of $\geq$ 22% and the FHAT total was < 10. A combined BRCAPRO risk of $\geq 22\%$ and FHAT total of $\geq$ 10 selected a population of women at high risk for mutation (18/35, 51.4%). BRCAPRO does have a significantly higher positive predictive value than the FHAT and would lead to fewer referrals to genetics (Table 1). However, it has a lower negative predictive value and would miss mutation-positive cases ascertained by the FHAT. Specifically, 71 women with BRCAPRO risk estimates of $<$ 22% had a FHAT total of ≥ 10. The average BRCAPRO risk estimate for this group of women was 12.5%, while 15 (21.2%) of them had a mutation detected. Given that our laboratory only expects to detect 80–85% of *BRCA1/2* mutations, and a lifetime penetrance of 80–85%, these data suggest that BRCAPRO has a slight tendency to underestimate the risk of breast cancer in some families. A possible explanation for this finding is that BRCAPRO estimates the penetrance of *BRCA1* mutations from the Breast Cancer Linkage Consortium data of 33 highly penetrant families (12), and *BRCA2* penetrance is derived from two large families with a *BRCA2* gene mutation (13). Therefore, in assuming a high penetrance for families in the general population, BRCAPRO may give too much weight in the Bayesian calculations to unaffected members of the sibship, thus resulting in an underestimation of the risk of breast cancer and the probability of a *BRCA1/2* mutation. A similar result might be obtained if the actual frequency of the *BRCA1/2* mutation in the general population is higher than the estimate used in the program.

The correlation between a BRCAPRO estimate of less than twice the population risk (3.2%) for ovarian cancer and a FHAT total of < 10 risk was also good. The 2 discrepant cases are described under results. For women who are classified as *refer* by both methods, the likelihood of detecting a mutation is high (29/61, 47.5%). Again, BRCAPRO had a higher positive, but lower negative predictive value than the FHAT. Five of the 46 (10.9%) women that would be excluded using the BRCAPRO had a mutation detected, whereas their average calculated risk for ovarian cancer was 1.7%. Even allowing for reduced penetrance of ovarian cancer in gene carriers, it appears likely that BRCAPRO may be underestimating the risks for some families, possibly for the same reasons as were discussed above. This conclusion is supported by the data on the BRCAPRO estimates of the likelihood of detecting a *BRCA1/2* mutation in the family. There are 50 families with a mutation likelihood of less than 0.2 (average 0.057) and a FHAT total of ≥ 10 (Fig. 5). Seven (14%) were found to have a mutation.

The lower left quadrants of Figs. 2–4 include women who are categorized as *non-refer* by both of the methods being compared. In all three figures there are 2 women who tested positive for a mutation, representing 3.4, 2.6, and 2.7% of the respective groups. Short of population screening for *BRCA1/2*, it is clear that any method of selecting women for referral for counseling and/or *BRCA 1/2* testing will miss a proportion of women who are estimated to be at low risk, but turn out to carry mutations. From the perspective of validating the FHAT, it is important that no women who we would have excluded and who turned out to

have a mutation would have been referred by either of the other two methods. Several women who would have been referred using the BRCAPRO risk estimate and were excluded by the FHAT were Ashkenazi Jews who would have been offered genetic testing for the three common mutations. It would be relatively trivial to include this aspect in future versions of FHAT or, perhaps better, to simply exclude such women as a separate category.

The FHAT was devised in 1996 and weighted according to our interpretation of the then-current knowledge. Recent data suggest that there may not be a simple relationship between early age of onset and the likelihood of inherited ovarian cancer. Frank et al. (4) found that age was not a factor in the likelihood of finding *BRCA1* or *BRCA2* mutations in women with ovarian cancer, and Stratton et al. (14) did not find mutations in women with sporadic ovarian cancer diagnosed under the age of 30 years. However, the peak age of onset for ovarian cancer in *BRCA1* carriers is between 40 and 50 years, and Whittemore et al. (15) concluded that ovarian cancer diagnosed before age 40 years may confer a risk as high as 18% for a *BRCA1* mutation. Our population was heavily weighted towards ascertainment by breast cancer and it would be of interest to test, and probably modify, the FHAT on a population ascertained through ovarian cancer. Similarly, on the basis of studies suggesting an increased risk for prostate and colon cancer in *BRCA1* mutation carriers (16), we assigned 1 point to a family history of prostate and colon cancer. This additional scoring did not influence the categorization of any family; indeed, the colon scoring was only used on three occasions, and it may be appropriate and simpler to eliminate this aspect in future use of the FHAT.

In conclusion, in this sample of 184 women at varied risk for breast and ovarian cancer, the FHAT performed well in selecting patients for referral as compared to using standard Claus tables or the Bayesian BRCAPRO method. Both positive and negative predictive values were better than the Claus tables. The BRCAPRO was more effective in reducing the number of referrals to genetics (positive predictive value), but would have missed a number of women selected by the FHAT and found to be mutation-positive. While we estimate that our laboratory approach may fail to detect about 15% of *BRCA1* and *BRCA2* mutations, there is no *a priori* reason to expect such cases to be distributed differently among the families than were those in which the mutation was found. Therefore, such missed cases do not effect our basic conclusions. Our comparisons were made using an estimated doubling of the lifetime risk for breast or ovarian cancer as the cut-off. Clearly this is arbitrary (6) but the impact of using different thresholds can be estimated from the figures we have provided. It must be stressed that the FHAT is in no way an alternative approach to estimating either the risk of developing breast/ovarian cancer or the likelihood of finding a *BRCA1* or *BRCA2* mutation. It is solely intended to provide an objective means for selective referral of patients whose risks must then be further evaluated by verifying the family history and the use of an appropriate risk-assessment model. It is to be expected that current research will soon provide more precise prevalence and penetrance data for specific populations. Incorporation of these data into programs such as BRCAPRO (8) should allow a very accurate estimate of risk for individual women. There are two further important steps that must be taken before one could consider using an approach like the FHAT in the community. First, the form was completed by a genetic counselor with experience in dealing with pedigrees of familial cancer. The form requires redesign to a more *user friendly* form with clear instructions on its use, and must then be field-tested in a controlled family-practice setting. Secondly, while this sample included women with a broad range of risk from very low to very high, it does have a significant bias towards the higher risks, and the FHAT requires testing in a more general population of women, for which it is intended.

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