Familial Cancer (2005) 4: 121–126
DOI: 10.1007/s10689-004-7995-y

Psychological distress in women at risk of hereditary breast/ovarian or HNPCC cancers in the absence of demonstrated mutations

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Received 23 September 2004; accepted in revised form 13 December 2004

Key words: anxiety, depression, familial breast and ovarian cancer, familial colon cancer, psychological distress

Abstract

Aim: To examine psychological distress in women at risk of familial breast–ovarian cancer (FBOC) or hereditary non-polyposis colorectal cancer (HNPCC) with absence of demonstrated mutations in the family (unknown mutation).*Materials and methods*: Two-hundred and fifty three consecutive women at risk of FBOC and 77 at risk of HNPCC and with no present or past history of cancer. They were aware of their risk and had received genetic counseling. Comparisons were made between these two groups, normal controls, and women who were identified to be BRCA1 mutation carriers. The questionnaires Beck Hopelessness Scale (BHS), General Health Questionnaire (GHQ-28), Hospital Anxiety and Depression Scale (HADS) and Impact of Event Scale (IES) were employed to assess psychological distress.*Results*: No significant differences concerning psychological distress were observed between women with FBOC and women with HNPCC. Compared to mutation carriers for BRCA1, the level of anxiety and depression was significantly higher in the FBOC group with absence of demonstrated mutation. Compared to normal controls, the level of anxiety was higher, while the level of depression was lower in the groups with unknown mutation.*Conclusions*: Women in the absence of demonstrated mutations have higher anxiety and depression levels than women with known mutation-carrier status. Access to genetic testing may be of psychologically benefit to women at risk for FBOC or HNPCC.

Introduction

Genetic testing to identify mutations causing familial breast and ovarian cancer (FBOC) and familial non-polyposis colorectal cancer (HNPCC) have become available. However, no mutation is found in many FBOC or HNPCC kindreds, and no predictive testing is available to relatives at risk [1, 2].

Reduction or no change in anxiety, depression, and cancer-related worry has been shown in non-carriers compared to carriers after receiving test results [3–16]. Numbers of relatives with cancer are associated with psychological distress [17].

In contrast, there are fewer reports on psychological distress in families without access to predictive testing. Meiser et al. [4] examined a control group of 53 women who could not have genetic testing and at 12 months post-notification, carriers showed a significant decrease in level of anxiety and depression compared to the women who could not be tested.

The uncertainty of members in families with absence of demonstrated mutations cannot currently be settled by genetic testing. These families have seen cancer as a prevalent cause of death at an early age among close relatives. Family members may feel uncertain about cancer development in their future. No studies are known to us about how these family members are emotionally affected by this state of uncertainty.

The aim of the study was to explore psychological distress in women at risk of FBOC and HNPCC cancers and without access to genetic testing, and to compare them with mutation carriers and with healthy women from the general population.

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Materials and methods

Participants

Patients were referred from doctors or they were self-referred to the Section for Genetic Counselling, Department of Cancer Genetics, The Norwegian Radium Hospital. We did not make contact with any of our patients' relatives – we invited them via the index cases and waited untill they contacted our Section. All referrals had to be in writing, telephone calls were not accepted.

For each patient/family, information on family structure and on all cancer cases, was obtained in writing from all family members approaching the Section for Genetic Counselling. All cancer cases in the families were, whenever possible, confirmed in the medical files of the treating hospital or The Cancer Registry of Norway. For all such confirmations, written informed consent was obtained from the person in question or (if dead) from his/her descendants. All the information was kept in our medical files. We have previously reported high compliance when carrying out health service in this way, and also that family members pass our information to their relatives [18]. Clinical follow-up aimed at early diagnosis and treatment were provided to all who meet our criteria of being at risk of FBOC or HNPCC.

The European recommendations suggested by 11 clinical genetic centers through a Biomed program were employed as criteria for FBOC and for follow-up examinations [19]. We have previously reported the efficacy of these criteria to identify FBOC, and the outcome of follow-up in at-risk women identified this way. Briefly, breast cancer continued to occur in the family, and 84% of such cancers were in excess of chance expectation [20]. We have later demonstrated that about half of those 84% are breast–ovarian kindreds carrying a BRCA mutation, while we do not find mutations in the breast-cancer-only kindreds [21]. For HNPCC, we employed the revised Amsterdam criteria for definition of at-risk persons [22] (Table 1), and we have previously reported that mutations are found in a fraction of the families meeting the criteria [23]. At-risk women were referred for colonoscopy and endometrial ultrasound every second year, as suggested by ICG-HNPCC [22].

Many families at risk had been subjected to extensive mutation testing in a research project and no mutation had been demonstrated. In some families, no living family member with cancer was available for mutation testing. All FBOC families with a woman alive with breast cancer were tested for a mutation, but did not carry any of the frequent Norwegian BRCA mutations [24]. Each woman included had been informed at genetic counseling that a mutation was assumed to cause inherited cancer in the family but could not be demonstrated, and as sisters or daughters of affected relatives they had a 50% chance of having the mutation. In FBOC kindreds, we also included women affected person through a male, having 25% chance it carrying a mutation.

All at-risk FBOC and HNPCC women referred from January 2000 to December 2001 were included in the study. After three months post-counseling, each woman received a letter of invitation including a questionnaire concerning background, general health, psychological distress, and personality traits. The patients provided informed consent by returning a completed questionnaire. A reminder was sent to those who did not respond within four weeks.

Normal controls

The Hospital Anxiety and Depression Scale (HADS) [25] had been rated by all participants of the Health Study of Nord-Trøndelag County, Norway (the HUNT study) [26]. Among the 32,061 women of HUNT who filled in HADS, a random sample of 10,000 women was stratified in age-matched groups. We also had information on civil status, number of children, and level of education as well as data on cancer among relatives.

BRCA1 mutation carriers

We employed the information on 68 unaffected women consecutively demonstrated to be mutation carriers who had completed the same questionnaires, as previously reported [27].

Measures

Demographic characteristics and cancer-related variables
Demographic variables were recorded as were also cancer-related variables such as numbers of affected and deceased relatives, the women's age when parent was affected by or died of cancer, and the family side of the inheritance.

The Hospital Anxiety and Depression Scale (HADS)
HADS [25] measures levels of anxiety and depression by self-report. HADS has seven items on the anxiety

Table 1. Clinical criteria for FBOC [19] and HNPCC [22].

FBOC
• A family history of two or more first degree relatives (or second degree relatives though males) with early onset (< 50 years) breast cancer, and/or • Multiple cases of breast cancers in the same lineage compatible with dominant inheritance in the family, and/or • A combination of early onset breast cancer and ovarian cancer in the family
HNPCC
• There should be at least three relatives with an HNPCC-associated cancer (CRC, cancer of the endometrium, small bowel, ureter, or renal pelvis) • One should be a first-degree relative of the other two • At least two successive generations should be affected • Atleast one should be diagnosed before age 50 • Familial adenomatous polyposis should be excluded in the CRC • Case(s) if any • Tumors should be verified by pathological examination • CRC, colorectal cancer

subscale (HADS-A) and seven items on the depression subscale (HADS-D). Each item is scored from 0 (not present) to 3 (maximally present), and the sum scores on each subscale range from 0 to 21. A sum score of eight or higher on each HADS subscale represents an optimum balance between sensitivity and specificity based on receiver operating characteristics, and was used as cut-off score to identify cases. Caseness indicates possible anxiety or depressive disorder that would give reason for further clinical examination [28, 29].

The General Health Questionnaire (GHQ-28)

GHQ-28 [30] measures psychosocial distress, which is a composite concept consisting of social functioning, somatic symptoms, anxiety/sleep disturbances, and depression. Each item was scored from 0 to 3. We used the 'simple' scoring to identify 'cases' and applied a cut-off ≥6 as threshold for 'caseness' of psychological distress, since our patients were healthy persons.

Beck Hopelessness Scale (BHS)

BHS [31] is a 20-item questionnaire designed to measure the degree of hopelessness with item score from 0 to 1. BHS sum score ranges from 0 to 20, and scores from 9 to 13 indicate moderate hopelessness, while scores of 14 or more imply severe hopelessness.

The impact of Event Scale (IES)

IES [32] is a self-report measure for distress in relation to a stressful life event, which in our study is cancer risk. IES measures psychological distress on two subscales. *Intrusion* refers to intrusively experienced images, thoughts, feelings, and dreams, while *avoidance* covers consciously recognized avoidance of certain feelings, ideas, or situations. The intrusion subscale (IES-I) has seven items, the avoidance subscale (IES-A) eight items. Each item is scored from 0 to 5. Scores from 9 to 19 on each IES subscale are considered as moderate level of distress, and scores of 20 or more as severe distress [32]. The psychometric properties of IES are good in samples with increased risk for hereditary breast cancer [33].

Scoring of the questionnaires

If less than 10% of the items on a subscale were missing, the items were given a sum score computed as the mean of rated items multiplied by total number of questions.

Statistics

SPSS™ version 11.0 was used for data handling and statistical analyses. Descriptive statistics were performed to characterize the sample and the groups. Differences between the groups were analyzed by independent and one-sample *t*-tests or χ^2 tests as appropriate. The modifying effects of demographic- and cancer-related variables on psychological distress were examined by multiple linear regression analyses. All statistical tests were done two-sided, and the significance level was set at $P < 0.05$.

Ethics

The National Data Inspectorate and the Regional Committee of Ethics in Medical Research approved the study. All procedures were carried out according to Norwegian legislation. Family members were offered genetic clinical services free of charge. Insurance companies or other agencies had no access to our patient registers.

Results

Out of 330 invited women at risk of FBOC/HNPCC with absence of demonstrated mutations, 239 (72%) returned the questionnaires. Of these, 176 out of 253 (70%) came from 120 FBOC families, and 63 out of 77 (82%) from 40 HNPCC families (Figure 1).

Demographic data and cancer-related variables

Demographic data and cancer-related variables are detailed in Table 2. Age is known to be associated with a number of psychosocial findings, but multiple linear regression did not show any differences for psychological distress between the groups with respect to age, and no correction for age was included in the subsequent analyses.

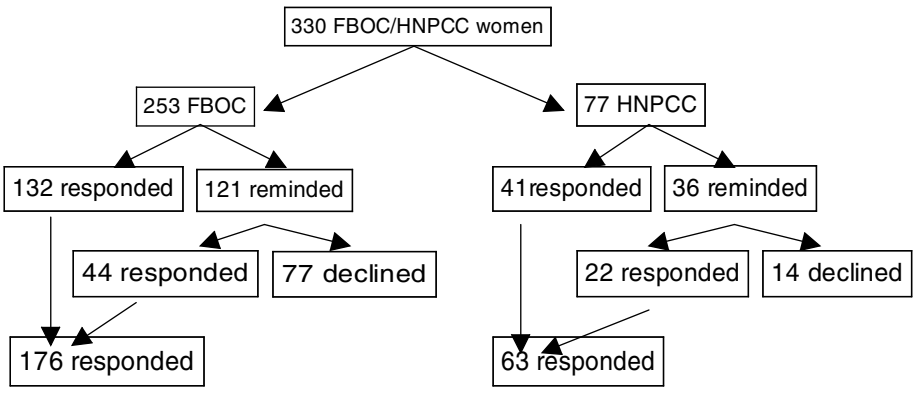

Figure 1. Flow-chart visualizing how 176 FBOC and 63 HNPCC respondents were obtained.

Table 2. Demographic- and cancer-related variables for FBOC, HNPCC, BRCA1 mutation carriers and normal controls.

Characteristic	FBOC	HNPCC	BRCA1 mutation carriers	FBOC/HNPCC	Normal controls
No. of patients	176	63	68	239	10,000
Age, mean (SD)	40.5 (9.7)	44.9 (13.5)*	42.0 (10.6)	41.9 (11.0)	42.5 (10.9)
Children, mean (SD)	2.7 (1.0)	2.7 (1.2)	2.0 (1.2)	2.7 (1.0)	2.3 (1.2)**
Relatives with cancer, mean (SD)	4.3 (2.1)	8.8 (19.4)*		5.7 (10.5)	0.9 (0.4)**
Affected parent	138 (77%)	63 (100%)*	44 (64%)*	201 (84%)	2634 (26%)**
Age of patient when parent became affected, mean (SD)	20.9 (10.0)	26.6 (12.0)*			
Age of patients when parent affected					
Number ≤ 18 years	60 (35%)	20 (31%)			
Number ≥ 19 years	78 (43%)	43 (61%)***			
Deceased parent	81 (46%)	45 (71%)			
Age of patient when parent died, mean (SD)	29.1 (13.3)	32.2 (14.7)			
Age of patients when parent died of cancer					
Number ≤ 18 years	18 (10%)	5 (8%)			
Number ≥ 19 years	63 (36%)	40 (61%)*			
Marital status					
Married/Cohabiting	136 (78%)	47 (78%)	60 (88%)***	183 (78%)	8900 (89%)**
Single/divorced/widowed	40 (22%)	16 (22%)	8 (12%)	56 (22%)	1100 (11%)
Education					
≤ 3 years after high-school	103 (59%)	48 (77%)***	49 (70%)*	151 (63%)	7680 (77%)**
≥4 years after high-school	73 (41%)	15 (23%)***	9 (30%)	88 (37%)	2320 (23%)

*$P < 0.01$ compared to FBOC.
**$P < 0.001$ compared to FBOC/HNPCC.
***$P < 0.05$ compared to FBOC.

Psychological distress

Mean values for scores and prevalence of cases, and results of comparisons between the groups are detailed in Table 3. The significant differences found were: FBOC/HNPCC had higher scores for anxiety, higher prevalence of anxiety cases, but lower scores for depression compared to normal controls. FBOC had higher scores for anxiety, depression and general distress (GHQ-28), and increased prevalence of depression and general distress cases compared to BRCA1 mutation carriers.

Discussion

Women at risk for cancer, but without access to genetic testing, were more anxious but less depressed than population controls, and they had more anxiety,

Table 3. Differences in sum scores of HADS, GHQ-28, BHS and IES.

Measures	FBOC	HNPCC	BRCA1 mutation carriers	FBOC/HNPCC	Normal controls
HADS-D, mean (SD)	2.4 (2.9)	2.3(2.2)	1.7 (2.4)*	2.4 (2.8)**	3.2 (2.9)
Cases HADS-D	7%	3%	3%***	6%	9%
HADS-A, mean (SD)	5.2 (3.8)	5.3 (3.9)	4.2 (3.6)*	5.3 (3.9)†	4.5 (3.5)
Cases HADS-A	24%	27%	24%	25%†	18%
GHQ 28, mean (SD)	3.3 (5.4)	3.6 (5.0)	2.3 (4.0)*		
Cases GHQ 28	23%	24%	12%*		
IES-I, mean (SD)	10.2 (8.7)	10.9 (9.5)	9.8 (7.6)		
Cases IES-I	18%	23%	13%		
IES-A, mean (SD)	8.3 (7.9)	9.2 (9.5)	8.4 (7.6)		
Cases IES-A	13%	9%	7%		
BHS, mean (SD)	3.7 (2.5)	4.0 (2.8)	3.8 (2.6)		
Cases BHS	5%	7%	2%		

*$P < 0.05$ compared with FBOC.
**$P < 0.01$ compared with normal controls.
***$P < 0.01$ compared with FBOC.
†$P < 0.05$ compared with normal controls.
HADS-D: The Hospital Anxiety and Depression Scale – depression subscale.
HADS-A: The Hospital Anxiety and Depression Scale – anxiety subscale.
GHQ-28: The General Health Questionnaire.
IES-I: The Impact of Event Scale – intrusion subscale.
IES-A: The Impact of Event Scale – avoidance subscale.
BHS: Beck Hopelessness Scale.

depression, and general distress than demonstrated mutation carriers. Our interpretation is that being a member of cancer kindred is associated with anxiety, and having access to mutation testing may be beneficial, also when a deleterious mutation is demonstrated.

Our finding supports the previous notion by Meiser et al. [4] who found that women not offered testing showed an increased level of anxiety compared to carriers.

Because anxiety is a response to threat, increased anxiety in women at risk of cancer indicates perception of the threat and can be seen as a natural psychological response. The finding of reduced anxiety in mutation carriers compared to FBOC with undemonstrated mutation may indicate that it is better to know than to be uncertain.

We studied women who had asked for help. Our results may not be used as an argument to seek women at risk for cancer and impose information upon them and advise them to be tested.

It is possible that anxious women come to counseling more frequently than those with depression. This may actually be probable, because anxiety is a healthy response to a threat and may cause action to avoid the danger. Our sample can therefore be biased towards those with a healthy response to the threat. To examine this, we would have to contact those who did not want to come to counseling. Such a study would violate current legislation and imply ethical problems.

Our conclusion is that women in the absence of demonstrated mutations have higher anxiety and depression levels than women with known mutation-carrier status and genetic testing may be psychologically beneficial to women at risk for FBOC and HNPCC.

Acknowledgements

The Norwegian Foundation for Health and Rehabilitation, and the National Council For Mental Health, Norway supported this study with a research grant to Amy Østertun Geirdal. The study was supported by a donation from Edith Kongshem, Oslo.

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