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Research Article

Psychological Impact of Cancer Risk Assessment: Anxiety, Depression and Distress in an Italian Sample

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Abstract

Purpose: Evaluating whether and how anxious and depressive symptoms change from prior to Oncological Genetic Counseling (OGC) to one month following BRCA genetic test result. Short-term psychological impact of genetic test disclosure in an Italian sample was also assessed.

Methods: 106 Italian natives completed Hospital Anxiety and Depression scale (HADs) both before accessing OGC (t1) and one month following their test result (t2). In t2 they also completed the Italian translation of Multidimensional Cancer Risk Assessment (MICRA).

Results: An overall reduction of HADs scores over time in BRCA-carriers was observed. Higher distress median values (MICRA) were found in carriers than non-carriers.

Discussion: In carriers, the simultaneous presence of both a reduction of anxiety/depression and a greater distress should be explained basing on Post-Traumatic-Growth studies in cancer patients. Being a carrier may represent an explanation for cancer disease, and allow patients to access specific risk-reduction programs.

Keywords: Anxiety; Cancer; Depression; Distress; Oncological Genetic Counseling; Post-traumatic Growth

Abbreviations

HAD-A: Hospital Anxiety and Depression - Anxiety subscale; HAD-D: Hospital Anxiety and Depression - Depression Subscale; HADs: Hospital Anxiety and Depression scale; MICRA: Multidimensional Cancer Risk Assessment; OGC: Oncological Genetic counseling; PTG: Post-Traumatic Growth

Introduction

With the identification of two cancer susceptibility genes, BRCA1 [1] and BRCA2 [2], genetic testing is now commonly available in clinical practice. BRCA1/2 mutations are associated with an increased risk for breast, ovarian and pancreatic cancers in females and breast, prostatic and pancreatic cancers in males [3]. Detecting BRCA1/2 carriers is necessary to offer them regular monitoring, preventive measures and to decrease cancer morbidity [4].

Oncological Genetic Counseling (OGC) and DNA-testing are offered both to affected patients (basing on their family history or on the early onset of disease) [5] and to healthy relatives of BRCA1/2 carriers.

International literature research explored the psycho-emotional impact of OGC focusing on psychological distress prior to and after results disclosure [6].

In affected and unaffected BRCA1/BRCA2 carriers changes in psychological distress after genetic testing reflect mixed results: although an increase in short-term distress has been highlighted, research has shown no long-term consequences on psychological well-being [6]. Bennett et al. [7] found short-term increases in anxiety levels that returned to baseline within 12 months; another study [8] detected high distress in women with breast cancer mostly in the year after receiving genetic results. Indeed, cancer diagnoses usually raises cancer-related distress [9] depression, anxiety and adjustment disorder [10,11].

Overall literature data seem to exclude severe anxiety, depression [12] and distress [13,14] issues due to OGC impact in BRCA1/2 carriers. However, some research reported anxiety and depression [15,16], anger and distress [17], cancer-related worry [18], vulnerability and stigma, alterations in self-perception and quality of life [19,20] after BRCA1/2 testing. All these aspects are strictly connected to cancer-related distress.

The identification of emotional, cognitive, and behavioral variables connected to OGC impact is crucial to promote patients' adherence to monitoring programs, increase their empowerment and strengthen their health-decision-making process [21,22]. Therefore, primary aim of the present paper was evaluating whether and how anxious and depressive symptoms could change from prior to one month after genetic counseling and testing.

Second goal was to assess the short-term impact of genetic test disclosure in an Italian sample using for the first time the Multidimensional Impact of Cancer Risk Assessment (MICRA) [23], a self-report tool specifically designed to measure socio-psychological concerns associated with genetic counselling and testing for cancer [24,25]. Third aim was to understand possible associations between anxiety and depression and the short-term impact of OGC.

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Methods

The study enrolled 106 consecutive Caucasian patients who underwent OGC and Testing in IRCCS Istituto Tumori "Giovanni Paolo II". All participants were Italian Natives, both index patients (i.e., oncological patients who initiate a counseling process for their family) and relatives (i.e., relatives of an index patient). Other inclusion criteria were being >18 years old and absence of psychiatric diagnosis that may hinder the questionnaire completions. The total sample analyzed included 106 participants and all participants signed an informed consent.

Patients accessing OGC underwent a psychological assessment and received an in-person pre-test counseling session to evaluate their oncological risk, based on their personal and/or family medical history [26]. Pre-test counseling sessions revealed the indication to perform a BRCA1/2 genetic test for all patients. Blood samples were collected in the Hospital Laboratory. Genetic-testing results were available within 3 months and were discussed during an in-person post-test counseling session.

All participants completed HADs prior to pre-test OGC (t1) and 1 month following their test disclosure (t2). At t2, participants also completed the Italian translation of MICRA. The time for completion was about 30min.

Tools

Data collected included a specifically developed socio-demographic form assessing the following variables: age, gender, civil status, number of children, cancer history, mutational status, being an index/relative. One self-report item was taken to investigate previous psychological suffering since it is a well-known factor of concern for the development of anxious/depressive symptoms following a cancer diagnosis [27,28].

HADs is a renowed emotional distress self-report measure and it is one of the most frequently used in oncological settings as well as in other somatic diseases [29]. It composed of 14 items to which patients answer through a 4-point Likert-scale referring to overt symptoms within the last week. It is consists in two scales - HAD-A for anxiety (7 items) and HAD-D for depression (7 items). Its global score is derived by summing responses for each of the two subscales. Higher scores indicate greater levels of anxiety or depression.

MICRAis a 25-item instrument designed to assess the specific impact of result disclosure after genetic testing. It assesses both negative and positive responses to testing experience [23]. Each item is measured on a 4-point Likert-scale. It is composed by three subscales: Distress, Uncertainty and Positive Experience. Except for Positive Experience, higher scores indicate more genetic test-related distress. Two items dropped out of the subscales: items 13 and 21 must be considered as individual items and are respectively measuring choices for prevention and early detection, and feeling regret since receiving the risk information. The instrument also includes other two subscales: one (2 items) regarding worry about children and one (2 items) regarding coping with current or previous cancer diagnosis. The three subscales and the items named above show acceptable internal consistencies [30]. Although the Italian translation of MICRA is accessible on http://www.facit.org, no scientific literature about the Italian Validation of MICRA is available.

The study has been approved by the Institute Ethical Committee.

Statistical methods

Data were analyzed with R (version 3.6.2). Check for normality assumption (Shapiro-Wilk normality test) and for extreme outliers have been performed with "rstatix" package. Data were preliminarily evaluated to check if the normality assumption was accomplished. Shapiro-Wilk test was significant and thus non-parametric statistics have been used. Moreover, no extreme outlier was identified.

Qqplot for visual inspection have been drown with "ggpubr" package. Aligned Ranks Transformation ANOVA was the test used to analyze HADs score as repeated measures. Wilcoxon test ("rstatix" R package) has been used to compare MICRA scores between groups. Graphs have been depicted through "ggplot2" R package. α Cronbach has been evaluated through "psych" R package.

All results have been considered as significant when p-values<0.05.

Results

The cohort (N=106) was analyzed in two different time points: prior to (t1) and one month after (t2) genetic test disclosure.. Participants are aged between 21 and 78 and have an average age of 50 years old and socio-demographic information is shown in Table 1.

HADs scorings within stratified groups and over time

In the overall cohort a significant reduction in depression and anxiety levels over time was found. HAD-D, HAD-A and HADs are significantly higher (p-value: 0.04; 0.006; 0.004, respectively) in t1 (median values of 4, 6.5 and 11), than in t2 (3, 5.5, 9, respectively). A statistical analysis by groups was performed. None of HAD-A, HAD-D and HADs values was significant when cohort was stratified

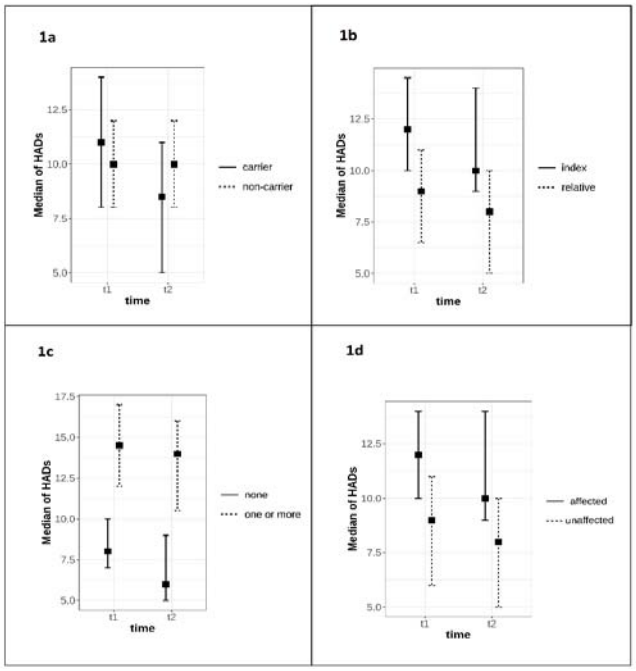

Figure 1: HADs scorings over time stratified by groups. a) Stratification for mutational status (carrier/non carrier); b) Stratification for being an index/relative; c) Stratification for previous psychological suffering; d) Stratification for cancer history (affected/unaffected).

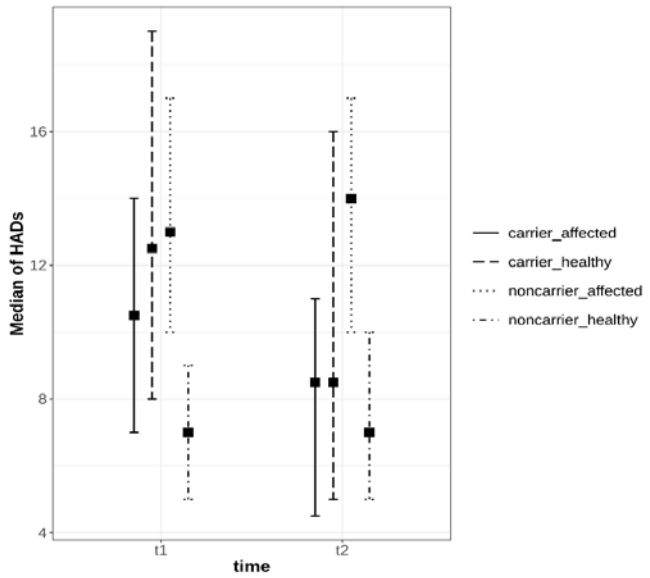

Figure 2: HADs scorings over time stratified for mutational status (carriers/non carriers) and cancer history (unaffected/affected).

for the presence/absence of a BRCA mutation. Interestingly, the reduction in t2 is greater in carriers than in non-carriers (Figure 1a).

Comparing indexes and relatives, statistical significance was detected: HAD-D, HAD-A and HADs values (p-value: 8.12e-05; 0.01; 0.0005, respectively) are higher in indexes (t1: 4.5, 7.5, 12; t2: 7, 5, 10, respectively) than in relatives (t1: 3, 5, 9; t2: 2, 4, 8, respectively) in both time-points (Figure 1b).

Participants who referred a personal history of psychological suffering (no episode *vs.* one or more episodes of serious psychological suffering or breakdown) show significant higher HADs values than others (t1: 14.5, 8 t2: 14, 6 respectively; p-value 7.61e-07) (Figure 1c). A similar result was obtained when considering their cancer-related clinical history (presence/absence of cancer): although HADs scores of both affected and unaffected subjects decrease over time, higher scores in cancer patients are shown both in t1 and t2 (Figure 1d)

The cohort was stratified both for mutational status (BRCA-carriers *vs.* non-carriers) and clinical history (affected *vs.* non-affected). Among unaffected subjects, HADs scores in t2 decrease significantly more in carriers than non-carriers (p-value=0.02). (t1: 7, 5.5, 12.5; t2: 5, 3, 8.5; t1: 4, 3, 7; t2: 4, 2, 7, respectively). Conversely, among affected patients, while carriers HADs scores decrease in t2, non-carriers scores increase (p-value< 0.0001) (Figure 2).

MICRA scorings in t2

The Italian translation of MICRA show good internal consistence (α Cronbach: 0.75).

MICRA results are shown in Table 2. Significant higher median values of distress subscale were observed in BRCA-carriers than non-carriers (p-value <0.0001) and in subjects with a personal history of previous psychological suffering than others (p-value = 0.001). No significant difference was underlined nor among indexes *vs.* relatives, nor among affected *vs.* unaffected participants.

Uncertainty subscale values were significantly higher in subjects

Table 1: Description of the cohort.

Characteristics	N (%)
Sex	
Female	85 (80.1)
Male	21 (19.9)
Age (median, range)	50 (21-78)
Index	54 (51)
Relative	52 (49)
BRCA status	
Carrier	38 (35.8)
Non-carrier	68 (64.2)
Previous Cancer History	
Affected	61 (57.5)
Unaffected	45 (42.5)
Children	
No	19 (18)
Yes	87 (82)
Psychological suffering	
None	59 (55.6)
One or more	47 (44.4)
Unaffected carrier	14 (13.2)
Affected carrier	24 (22.6)
Unaffected non-carrier	31 (29.2)
Affected non-carrier	37 (35)

referring a previous psychological suffering than others (mean 7.98 ± 5.03 *vs.* 6.12 ± 4.57, p-value = 0.03) and its median values were slightly higher in affected subjects than unaffected. No significant difference was found in carriers than non-carriers.

Positive Experience subscale median scores were significantly higher in non-carriers than in carriers (p-value <0.0001). Conversely, lower median scores for both conditions were observed as a statistical trend in cancer patients and in subjects whit a previous psychological suffering than others (p-value= 0.05).

Analyzing Item 13 (understanding choices for prevention and early detection), no meaningful difference was found when participants were stratified nor by genetic risk category, health status, nor previous psychological suffering.

Focusing on Item 21, 101/106 (97.1%) patients reported "never" feeling regret about receiving their risk information. No meaningful differences were found among groups.

The "Worry about children" subscale (Items 22-23) has been completed only by participants having children (87/106, 82%). In this group, cancer patients had higher median scores than healthy ones (mean 5.47± 2.39 *vs.* 4.18± 2.26, p-value = 0.002). Also, patients with a previous history of psychological suffering reported significant higher values than others (mean 5.71 ± 2.44 *vs.* 4.3 ± 2.21, p-value = 0.006).

The "Cope with cancer" subscale (Items 24-25) has been completed only by cancer patients (61/106, 57.5%). No significant difference was found both in carriers *vs.* non-carriers and in subjects

Table 2: Comparison of MICRA subscale score between groups in t2.

	Previous Cancer History		p-value	BRCA status		p-value	Psychological suffering		p-value
	Affected	Healthy		Carrier	Non-carrier		None	One or more	
Distress	4.41 ± 4.12	4.47 ± 5.37	ns*	7.72 ± 4.86	2.58 ± 3.36	<0.0001	2.92 ± 3.08	6.33 ± 5.56	0.001
Positive experience	12 ± 4.81	13.9 ± 3.79	ns*	9.92 ± 3.2	14.4 ± 4.34	<0.0001	13.5 ± 3.79	11.9 ± 5.16	0.05
Uncertainty	7.71 ± 5.43	5.87 ± 3.67	ns*	6.49 ± 4.17	7.2 ± 5.2	ns*	6.12 ± 4.57	7.98 ± 5.03	0.03
Item 13: comprehension of risk reduction programs	4.47 ± 0.88	4.96 ± 0.29	ns*	4.84 ±0.71	4.79 ± 0.7	ns*	4.83 ± 0.67	4.78 ± 0.75	ns*
Item 21: regret	0.05 ± 0.3	0.08 ± 0.46	ns*	0.1 ±0.5	0.04 ± 0.36	ns*	0.05 ± 0.3	0.08 ± 0.46	ns*
Item 22/23: worry about children	5.46 ± 2.41	4.18 ± 2.26	**0.003**	5.1 ± 2.5	4.87 ± 2.38	ns*	4.3 ± 2.21	5.71 ± 2.44	0.006
Item 24/25: cope with cancer	/	/	/	3.42 ± 1.98	2.92 ± 2.14	ns*	3.17 ± 2.04	3 ± 2.11	ns*

ns*: non significant.

Table 3: Multivariate logistic regression performed considering HADs measured at t1 as independent variable and MICRA subscales as dependent variables. Adjustments for mutational status (carrier *vs.* non-carrier), health status (affected *vs.* unaffected), previous psychological suffering and being an index *vs.* relative.

	Distress OR (95% CI)	P-value
HADs*		
Low	Ref	
High	5.4 (1.88- 17.38)	0.002
BRCA Status		
Carrier	Ref	
Non carrier	0.06 (0.0.17-0.2)	9.34e-06
Psychological suffering		
None	Ref	
One or more	2.84 (1.02-8.34)	0.04
	Positive experience OR (95% CI)	**P-value**
Mutation		
Carrier	Ref	
Non carrier	9.27 (3.65-26.25)	8.00e-06
	Uncertainty OR (95% CI)	**P-value**
HADs*		
Low	Ref	
High	2.24 (0.95-5.28)	**0.06**

*HADS data have been dichotomized accordingly to median value.

with previous psychological sufferings *vs.* others.

Multivariate logistic analysis

A multivariate logistic analysis was also carried out considering the following independent variables: being unaffected *vs.* affected, being carrier *vs.* non-carrier, being index *vs.* relative, having a history of psychological suffering *vs.* others and HADs scores. Results of this analysis are shown in Table 3.

Concerning Distress Subscale, other variables being equal, higher HADs scores resulted an independent predictive factor that increases the risk of distress (p-value 0.002). Also, being a carrier resulted a predicting variable: non-carriers have significantly lower risk of obtaining high Distress scores (p-value 9.34e-06).

As regards Positive Experience subscale, mutational status is the only significant predicting variable (p-value 8e-06): non-carriers are more likely to having higher scores for positive experience.

Finally, regarding the Uncertainty Subscale, the only predictive variable was HADs scorings with a statistical trend: as HADs scores increase, the Uncertainty subscale scores also increase (p-value 0.06).

Discussion

Literature data show that a personal history of psychological suffering [31], personal cancer history [32], familial cancer history [33] and mutational status represent factor of concern for the onset of anxiety and depression both prior to and after OGC and testing. Our results are partially consistent with previous researches, exception made for familial cancer history: in our sample indexes show higher anxious/depressive symptoms than relatives both prior to and one month after OGC and testing.

We assume this difference is due to our sample composition: 100% of indexes were cancer patients while a great part of relatives (84.6%) was unaffected. Therefore, since being a cancer patient is a predisposing factor for the onset of anxiety and depression [6,28,32], we hypothesize that psychopathological symptoms of indexes are related to their personal cancer history.

Among affected subjects, carriers showed a meaningful decrease in symptoms over time, while non carriers show higher anxiety and depression levels both prior to OGC and over time. Instead, among unaffected ones, anxious-depressive symptoms remain almost unchanged over time for non-carriers, whereas carriers showed a meaningful decrease in symptoms over time.

We assume this result is related to patients' possibility to access a cancer risk reduction programs [34]: being BRCA carriers, although challenging, may represent patients' opportunity to find a reason for their illness and re-gain control over their lives thus developing a real empowerment. Conversely, non-carrier cancer patients cannot find an explanation for their illness and are not even allowed to access risk-reducing prophylactic surgery (as carriers).

MICRA scorings within stratified group in the three subscales.

International literature data [23-25] show a significant association between MICRA scorings and mutational status.

As far as we know, this is the first study using the Italian version of MICRA. The results obtained in our sample partially confirm previous studies: carriers differ from non-carriers both for Distress (higher in carriers) and Positive experience (higher in non-carriers). However, in the present sample no difference in Uncertainty subscale was found among groups: this is consistent with the hypothesis that

experiencing cancer may be more challenging than the revelation of mutational status [7].

MICRA items dropped out of the three subscales.

Consistently with literature data [25] in our sample only 3 of 104 participants (2.9%) expressed feeling regret about receiving their risk information (item 21), and a 1 of 3 was a non-carrier.

However, although previous research testify that carriers show more children-related worries than non-carriers [24], in our sample participants expressed concern for their children (item 22-23) significantly more if they had cancer or had a previous psychological suffering, but no correlation emerged with mutational status. We assume this difference is due to our sample composition and that cancer experience is more related to uncertainty for the future than OGC.

Also, in accordance with scientific literature, no difference between carriers *vs.* non-carriers was highlighted in understanding risk reduction options nor in cancer-related worries [23]. Thus, participants equally understand their risk-reduction and early-diagnosis options (item 13) regardless their psychopathological and/or cancer-history and mutational status.

Clinical Implications

Physicians should be aware of the paradoxes of genetically-at-risk status. In fact, being a carrier, both emotionally challenges patients and pushes them to transform their health into a project [35]. In their new health-project, patients can improve their healthy lifestyles and choose whether they prefer to access a specific cancer risk reduction surgery-program or a clinical surveillance program.

In carriers, we assume that the simultaneous presence both of a reduction of anxious-depressive symptoms and of a greater distress after test disclosure is due to HADs and MICRA sensitiveness to two different constructs. Actually, HADs is specifically developed to evaluate psychological suffering in non-psychiatric hospitalized patients, (investigating the presence and severity of anxious and depressive symptoms), conversely, MICRA Distress Subscale investigates the psychological consequences of genetic test disclosure, considering its traumatic potential.

We interpret these results in relation to Post-Traumatic Growth (PTG) studies in cancer patients [36,37]. According to the functional descriptive model of Tedeschi and Calhoun, PTG is defined as "positive psychological changes experienced as a result of the struggle with traumatic of highly challenging life circumstances" [38,39]. Literature data [39,40] showed how PTG and emotional distress often coexist in cancer survivors: in the typical complexity of a human being, it is possible the perception of self-improvement coincides high levels of post-traumatic distress.

Study Limitations

This study presents some limitations.

First, the sample size and composition should be better addressed. In fact, since we enrolled consecutive patients receiving OGC, the sample could be unbalanced in terms of gender and percentage of healthy/affected subjects among carriers/non-carriers and index/relatives groups. Thus, as this is not a multi-center study, our sample cannot be considered large enough to be representative of the Italian population.

Second, the one-month-period for follow-up considered in the present study, is sufficient for measuring some psychological changes over time, but not enough to account for a more complex adaptation to carriers' condition. Third, so far, few studies focused on the psychological impact of OGC and testing in relation to PTG theory, which could account for some of the present findings. Therefore, further research is needed.

Conclusions

Results of the present paper indicate that one month after genetic test disclosure Italian BRCA carriers show higher distress than non-carriers. These subjects should be addressed to specific psychological support programs to facilitate their cancer and/or oncological risk information processing and acceptance.

Despite the risk of developing distress, BRCA carriers showed a significant reduction over time of anxious and depressive symptoms. These results must be related to the possibility for carriers both to find an explanation for their illness and to have access to specific clinical risk reduction programs. Another explanation may be related to PTG in cancer patients: as post-traumatic growth proceeds, psychological well-being increases (reduction of anxious-depressive symptoms) together with the distress of facing a challenging event. Short-term distress can be considered as marker of patients' cognitive restructuring when seeking for a meaning in their cancer experience. Literature data show that the time spent after the disease is a significant moderator for distress and the relationship between distress and PTG is reversed over time. At this purpose, further studies on long-term impact of OGC are needed.

Thus, in cancer patients the psychological impact of discovering to be a non-carrier should not be underestimated. It would be appropriate to offer non-carriers an adequate psychological support to help them find a meaning to their illness experience and recover their sense of agency.

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