DOI: 10.1002/pon.5302

PAPER

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How to facilitate psychosocial adjustment in women tested for hereditary breast or ovarian cancer susceptibility? Insights from network analysis

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Funding information

European Union Horizon 2020 research and innovation programme, Grant/Award Number: 634935; Ile-de-France Cancer Pole, Grant/ Award Number: 2015-1-EMERG-14-ICH-1

Abstract

Background: Increasingly complex genetics counseling requires guidance to facilitate counselees' psychosocial adjustment. We explored networks of inter-relationships among coping strategies and specific psychosocial difficulties in women tested for hereditary breast or ovarian cancer.

Methods: Of 752 counselees consecutively approached, 646 (86%) completed questionnaires addressing coping strategies (Brief-COPE) and psychosocial difficulties (PAHC) after the initial genetic consultation (T1), and 460 (61%) of them again after the test result (T2). We applied network analysis comparing partial correlations among these questionnaire scales, according to the type of genetic test - single genetargeted or multigene panel, test result and, before and after testing.

Results: Overall, 98 (21.3%), 259 (56.3%), 59 (12.8%) and 44 (9.6%) women received a pathogenic variant, uninformative negative (panel testing), variant of uncertain significance (VUS) or true negative (targeted testing) result, respectively. In most networks, connections were strongest between avoidance and general negative emotions. Cognitive restructuring was inter-related to lower psychosocial difficulties. Avoidance and familial/social relationship difficulties were strongly related in women receiving a pathogenic variant. Stronger inter-relationships were also noticed between avoidance and worries about personal cancer and concerns about hereditary predisposition in women receiving a VUS result. Differences in the prominence of inter-relationships were observed by type of testing and assessment time.

Conclusions: Network analysis may be fruitful to highlight prominent interrelationships among coping strategies and psychosocial difficulties, in women tested for HBOC susceptibility, offering guidance for counseling.

KEYWORDS

coping strategies, genetic counseling, hereditary breast and ovarian cancer, network analysis, psychosocial difficulties

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1 INTRODUCTION

The discovery of new cancer susceptibility genes has led to the implementation of multigene testing in clinical practice. In the context of the hereditary breast or ovarian cancer (HBOC) syndrome, testing a panel of genes increases the complexity of counselling especially because of the addition of cancer genes at moderate risk and the identification of an increased number of variants of uncertain clinical significance (VUS),¹ both with unclear risk estimates and clinical recommendations (actionability).²

Gene panel testing is generally proposed to index cases, often affected with breast cancer (BC) and who are tested first in the family. In HBOC index case testing, possible results include a pathogenic variant on BRCA1/2 or other high/moderate-risk gene, an uninformative negative (ie, no pathogenic variant identified) or a VUS result. An index case with a pathogenic variant result may then inform her blood relatives that they may have a genetic susceptibility to cancer. They may thus be offered single gene targeted testing, leading to a pathogenic variant or true negative result.

Carriers of a BRCA1 or a BRCA2 pathogenic variant face up to 72% and 69% risk of BC by age 80 years, and 44% and 17% risk of ovarian cancer (OC), respectively.³ When affected with BC, the risk is of 40% (BRCA1) and 26% (BRCA2) of developing a contralateral BC.⁴ Pathogenic variants identified in other genes that may be included in the panel, such as ATM, CHEK2, PALB2, BARD1 or RAD51D, are associated to moderate risk of BC.⁵ Clinical recommendations for BC or OC genetic risk management follow specific guidelines. Women with a pathogenic variant and those with an uninformative negative or VUS result depending on their personal or familial cancer history, may be proposed enhanced screening routines.6

Psychosocial implications of genetic testing vary according to the test result. For example, women who carry a pathogenic variant may experience persistent anxiety, guilt and helplessness in informing relatives, concerns about cancer risk medical management options with different impact on cancer risk reduction and quality of life. Women receiving an uninformative negative or VUS test result may feel uncertain, confused about cancer risk management choice and information to convey to relatives.

In that context, women undergoing genetic testing for HBOC susceptibility experience a stressful situation due to the perceived threat to themselves and their families. A wide range of specific psychosocial difficulties is elicited in relation to the personal or familial cancer vulnerability, management of the hereditary predisposition or communication about cancer risk within the family.7-9 These difficulties may solicit various coping strategies.¹⁰⁻¹²

How individuals cope with stressful events is broadly characterized as increased efforts or giving-up responses.¹³ According to Lazarus and Folkman,¹⁴ coping consists of a process of "constantly changing cognitive and behavioral efforts to manage specific external and/or internal demands that are appraised as taxing or exceeding the resources of the person". Coping responses may thus be thought to vary specifically according to individuals' appraisals interacting with the characteristics of the situation. In the HBOC context, empirical research has shown that coping strategies could differ according to BC risk perception or worry.^{11,15,16} and clinical features, such as the BC diagnosis status^{17,18} or test result.¹⁷

Little research has focused on the role of different coping strategies in relation to the various psychosocial difficulties that arise in cancer genetics.¹² Coping strategies such as avoidance,¹⁷ distraction or helplessness,^{16,19} self-controlling (eg, excessive breast self-examination)¹⁵ or reliance on others¹⁹ have been shown to predict increased worry and psychological distress. Women at high genetic risk of BC do not evidence severe, enduring distress following genetic testing,^{19,20} but they may need further help to minimize their psychosocial difficulties.^{7,19} Psychosocial difficulties may be inter-related to coping strategies in possible feed-back loops. For example, more intense worries may elicit (in)appropriate coping strategies which in turn may cause more (or less) worrying. Identifying these possible vicious/virtuous cycles of mutual relationships may guide counselling as intervention on one element can have an impact on another.

Network analysis (NA) is a useful statistical approach to analyze the inter-relationships among elements of complex psychological phenomena.^{21,22} To our knowledge, this approach recently applied in psychology²³ has never been used in the psychosocial field in cancer genetics. In contrast to statistical approaches such as regression analyses, which explain a specific outcome by a number of independent factors, or psychometric analyses, which reveal latent unobservable variables, NA summarizes complex patterns of associations by computing conjoint inter-relationships among elements of phenomena.²¹ This analysis statistically determines the unique association between two elements, controlling for their associations with all the other elements (ie, conditional dependence relationships). Moreover, NA may also be used to investigate inter-individual variability comparing networks according to the characteristics of the situation.

Hence, the main objective of this study was to estimate networks of inter-relationships among coping strategies and specific psychosocial difficulties in women undergoing testing for HBOC susceptibility. We also descriptively compared these networks according to the type of genetic testing, the test result and, before and after receiving the test result as counselees may have expectations about their possible genetic susceptibility to cancer which may affect their psychological reactions.

2 **METHODS**

This is a prospective multicenter study undertaken within BRIDGES ("Breast Cancer Risk after Diagnostic Gene Sequencing") research program (https://bridges-research.eu) which aims to develop a comprehensive genetic test for BC risk assessment to provide personalized BC risk estimates and help genetic counselors and patients to make informed clinical decisions.

The protocol was approved in France by the Comité consultatif sur le traitement de l'information en matière de recherche dans le domaine

de la santé (CCTIRS: Consultative committee for information management in health research-N°16.314), in Germany by the Ethics Committee of the University Hospital of Cologne (N°16-098) and, in Spain by the Ethics Committee of the Instituto Catalán de Oncología of Bar-

2.1 | Counselees

celona (N°-PR111/16).

From November 2016 to April 2018, women over the age of 18 years, eligible for BC risk testing according to national criteria, unaffected or affected by a non-metastatic BC were recruited at the Cancer genetic unit of Institut Curie (IC, France), Breast cancer clinic of Cologne University Hospital (CUH, Germany) and Cancer genetic unit of Barcelona Institute of Oncology (ICO, Spain). Women with a BC recurrence, a personal history of OC or a major psychiatric disorder were not included. All recruited women provided written informed consent.

Researchers approached the women on the day of the initial cancer genetic counselling visit and, when they agreed to participate they were given questionnaires to fill in at home and return within two weeks (T1). Two months after the test result notification visit, they received another set of questionnaires to be filled in at home and returned within two weeks (T2). A sample size of 500 counselees was targeted in order to compare groups of at least 50 counselees by main genetic test results (ie, positive, negative or VUS).

2.2 | Questionnaires and data collection

Socio-demographic and clinical data were collected from counselees after the initial genetic consultation or from medical records.

2.3 | Psychosocial assessment

Genetic-specific psychosocial difficulties were assessed at T1 and T2 using the 26-item "Psychosocial Aspects of Hereditary Cancer" (PAHC) questionnaire⁹ translated and empirically validated in French, German and Spanish cancer genetics settings.²⁴ It provides scores of increasing difficulties on a 0 to 100 scale for six domains addressing concerns about hereditary predisposition (eg, worrying about the choice of possible preventive options), family/social relationship difficulties (eg, feelings of responsibility toward family members related to genetic testing), general negative emotions (eg, insecure about the future), grief/worries about familial cancer (eg, worry that family member has cancer), worries about personal cancer (eg, worry about chance of getting cancer again), and children-related issues (eg, guilt about passing genetic alteration).

The six-factor PAHC model yielded acceptable confirmatory factor analysis goodness-of-fit indexes ($\chi^2/df = 3.64$, RMSEA = 0.061 [90%CI: 0.057-0.066], CFI = 0.91, TLI = 0.90) and adequate internal consistencies with Cronbach's alpha >.70 found for these scales in the three language versions.²⁴

Coping was measured at T1 and T2 using the Brief-COPE abbreviated inventory of coping responses.²⁵ Available in French-,²⁶ German-²⁷ and Spanish-²⁸ language, this 28-item measure presents fourteen 2-item scales. Following a higher order empirical validation,²⁹ to allow a more parsimonious assessment, these scales were aggregated into five dimensions: (a) avoidance, (b) cognitive restructuring, (c) problem solving, (d) distraction and (e) support seeking. Instructions asked about the counselee's usual strategies to respond to difficult events such as the risk of cancer.

All but two of the five scales and three languages (avoidance: Cronbach's alpha = .57 in Spanish; Distraction: Cronbach's alpha = .58 in French) exceeded Cronbach's alpha .60, which is above the value of .50 regarded as minimally acceptable.

2.4 | Statistical analyses

Statistical analyses were performed with R software (R Core Team, 2017). NAs were carried out with the ggraph statistical package of R software.³⁰

The computation of socio-demographic, clinical and psychosocial univariate and bivariate statistics has been described previously.^{24,31}

Network analyses provide graphs, which consist of two elements: nodes (circles; observed variables corresponding to the Brief-COPE and PAHC domains in orange and blue, respectively) and edges (lines; links or inter-relationships between these variables).^{30,32} The links between variables are estimated using partial correlation coefficients, controlling for all other variables. The thickness of the edge represents the strength of the inter-relationship and is proportional in absolute value to the size of the partial correlation coefficient. The stronger the link between two nodes, the thicker the edge. Positive and negative links are denoted by blue and red edges, respectively. Additional information on NA is provided in Supporting Information S1.

Network comparisons: we compared networks estimated according to the type of genetic testing (ie, single gene-targeted or multigene panel), the test result received (ie, pathogenic variant, uninformative negative, or VUS) and, the assessment time, T1 and T2, for either pathogenic variant or uninformative negative result. The number of cases was insufficient to perform network analyses for the VUS group (N = 59, 12.8%). We investigated whether the basic structures of the networks were similar by calculating the linear correlation between the strength of inter-relationships among variables in a network and those in another network. A high correlation (r > .70) between networks reflects that if the strength of a relationship between two variables is high in a network, this relationship is also strong in the other network.

Note that NA did not include the PAHC children-related domain as items were completed by fewer women (478 or less compared to at least 644 for other PAHC domains) and so an insufficient number of evaluable cases for comparing subgroup networks. In addition, the true negative result sample was too small (N = 44, 9.6%) to allow for estimating networks in women receiving that test result.

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3 | RESULTS

3.1 | Sample characteristics

Socio-demographic and clinical characteristics of the sample are provided in Supporting Information S2. Among 752 counselees consecutively approached, 646 (86%) and 460 (61%) returned the questionnaires at T1 and T2, respectively. Eligible counselees and respondents did not differ on age, parental and BC diagnosis status. At T2, women affected with BC were more frequently respondents (P < .05).

Overall eligible counselees' and respondents' mean (SD) age was 47.8 (11.5) and 47.7 (11.4), respectively.

Counselees undergoing multigene panel differed as expected to those undergoing targeted testing, in that notably they were older (P < .001), were more frequently affected by BC (P < .001), lost a family member more frequently (P < .001).

Among respondents at T2, networks were estimated for 98 (21.3%), 259 (56.3%) and 59 (12.8%) women who received a pathogenic variant, uninformative negative and VUS result, respectively.

3.2 | Psychological characteristics

The mean (SD) levels of genetic-specific psychosocial difficulties (PAHC) and coping strategies (Brief-COPE) by test result and at T1 and T2 are provided in Supporting Information S3. Less than 10% item omission was present in psychosocial assessments.

3.3 | Network description

Figure 1A-C and provided in Supporting Information S4, Figures 2A,B and 3A-D show networks of inter-relationships between coping strategies and psychosocial difficulties in women receiving a pathogenic variant, uninformative negative or VUS result, those undergoing targeted or panel testing, and at T1 and at T2 in women receiving a pathogenic variant or uninformative negative result, respectively.

The conceptual distinction between psychosocial difficulties and coping strategies is reflected in the global graphical structure of all networks, as domains of psychosocial difficulties (represented by nodes in blue) were more closely connected to each other than to domains of coping (represented by nodes in orange) and conversely. These concepts were thus reflecting different clinical entities that could be investigated in their relationships.

Across networks, a striking feature was the centrality of the "emotions" node, connected to other psychosocial difficulties and to specific coping strategies. This node had more and stronger connections with other difficulties and coping strategies than other nodes in the network. This reflects that among all domains of difficulties and coping strategies, general negative emotions were the most important clinical manifestation strongly linked to all other domains.

Concentrating on inter-relationships between coping strategies and difficulties (partial r > .10), the strongest links were observed between avoidance and higher negative emotions in seven over nine networks. Avoidance was also linked to familial/social relationship difficulties in five of the networks. Cognitive restructuring was the only coping strategy related to lower psychosocial difficulties, that is, negative emotions (partial r = -.12 to -0.25), grief/worries about familial cancer (partial r = -.13 and -.14) or worries about personal cancer (partial r = -.12 to-.19). Problem solving, distraction and seeking support were to a lesser extent linked to psychosocial difficulties. Partial correlations coefficients >.10 between coping strategies and psychosocial difficulties in Network Analyses are provided in Supporting Information S5.



FIGURE 1 A-C, Networks of relationships among coping strategies and psychosocial difficulties in women receiving a pathogenic variant, an uninformative negative or a variant of uncertain significance. Linear correlation between networks' coefficients for women having received a pathogenic variant or a negative uninformative result: r = .60; linear correlation between networks' coefficients for women having received a pathogenic variant or a variant of uncertain significance result: r = .59; linear correlation between networks' coefficients for women having received a pathogenic variant or a variant of uncertain significance result: r = .59; linear correlation between networks' coefficients for women having received a negative uninformative or a variant of uncertain significance result: r = .71

3.4 | Network comparison

In the following, examples of differences among networks are presented.

In women offered multigene testing, a relatively strong connection emerged between avoidance and negative emotions (partial r = .21), while in women offered targeted testing, avoidance was strongly linked to familial/social difficulties (partial r = .20).

Avoidance and emotions (partial r = .29) and familial/social difficulties (partial r = .26), were strongly connected in women who received a pathogenic variant. In women who received a VUS result, avoidance was linked to worries about personal cancer (partial r = .19) and concerns about hereditary predisposition (partial r = .15). In women receiving an uninformative result, avoidance was also connected to emotions (partial r = .26) which, to a lesser degree, was also linked to cognitive restructuring (partial r = .17).

When comparing networks over T1 and T2 (Figure 3A-D shown in Supporting Information S4), we noted, for example, in pathogenic variant carriers, a strong connection between avoidance and familial/ social difficulties, absent at T1, revealed at T2 (partial r = .24), while the same strong link in women with uninformative negative test result present at T1 (partial r = .20), was no longer present at T2.

4 | DISCUSSION

In this study, we applied NA among coping strategies and specific psychosocial difficulties in women undergoing genetic testing for HBOC susceptibility and contrasted networks by clinical features to suggest specific counselling needs. Extending previous studies that assessed coping strategies in relation to distress as a specific outcome, ^{15-18,33} NA evidenced unique inter-relationships among various coping strategies and a comprehensive range of psychosocial difficulties relevant to the cancer genetics context.⁹

Among networks drawn in this study, the "negative emotions" node was central. The PAHC questionnaire domain evidenced high correlation to psychological distress²⁴ and so, among nodes which were positively correlated to negative emotions, specific coping strategies may reveal unhelpful.

Avoidance was relatively low in this sample (10-11 on a range of 8-32); however, prominent inter-relationships between avoidance and, negative emotions as well as familial/social difficulties were revealed, highlighting a potential target for counselling when undergoing BC or OC genetic testing. Although a "distraction" coping strategy may be useful while waiting for the genetic test result,³⁴ avoidance has been recognized as an unhelpful strategy in women affected with BC generally¹³ and in those facing HBOC susceptibility specifically.¹⁵⁻¹⁷ In contrast, cognitive restructuring was the only coping strategy that inter-related to lower psychosocial difficulties. This is in line with a decreased long-term distress in relation to coping by fostering reassuring thoughts in women from HBOC syndrome families.¹⁵

Network structures proved similar across clinical features, especially over time. However, depending on the clinical situation, specific variations could be observed. For example, a relative strong link between avoidance and familial/social difficulties was revealed in women undergoing targeted testing. These women often unaffected with BC and surrounded by familial losses due to cancer¹¹ may have difficulty soliciting genetic information and support from relatives already affected with cancer.

In addition, we also evidenced relatively strong connections between avoidance and familial/social difficulties in women who received a pathogenic variant, which suggests that among carriers, those who use avoidance to cope may need further help to address their difficulties in communicating about the genetic cancer predisposition with concerned family members.³⁵

Moreover, links between avoidance and, concerns about hereditary predisposition or worries about personal cancer emerged in women who received a VUS result. The disclosure of an ambiguous test result with a lack of actionability may be difficult to understand, maintain uncertainty and distress³⁶ and require further counselling to interpret the significance of this result in the context of personal or familial cancer history.³⁷

Referring to coping flexibility³⁸ or the ability to modulate the choice of coping strategies according to the situation, Bennett¹² observed that individuals attending cancer genetic counselling generally used cognitive restructuring in response to concerns they could not change, and support seeking to gain information. Similarly, we observed an inter-relationship between cognitive restructuring and negative emotions in women who learn that they did not carry a pathogenic variant whereas this link was not present in these women before obtaining their test result. The information gained from the test result, that is, the absence of an identified pathogenic variant explaining their personal or familial cancer history, also means that the cancer risk estimated by the family pedigree has not been clarified by genetic testing and therefore the medical recommendation remains unchanged. This situation may have prompted an acceptance mode of coping in facing one's personal cancer concerns.

A relatively smaller link between the problem solving strategy and difficulties related to hereditary predisposition was evidenced in women who received a pathogenic variant. This test result may raise concerns about the choice of possible cancer risk management strategies and thus efforts to actively manage the stress associated to the confirmed high cancer risk.

5 | LIMITATIONS AND STRENGTHS

This study is the first to use NA in the psychosocial field in cancer genetics, providing nuanced information on the link between coping strategies and genetic-specific psychosocial difficulties. It includes a relatively large sample with a high initial response rate. However, findings are only valid to women opting for genetic testing and who were mainly affected with BC. We contrasted networks according to the type of genetic test or test result; however differences between these networks may also be explained by factors such as women's age, loss of family members due to BC or OC, or BC diagnosis status that was related to the type of test proposed and subsequently the result obtained. Specifically, in women receiving an uninformative negative

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or VUS result, the link between coping strategies and psychosocial difficulties may reflect psychological reactions due to the diagnosis of BC. A longer delay in the receipt of the test result in women undergoing gene panel compared to a single targeted test may also have affected the comparison between test result networks.

While causal relationships between strongly inter-related variables may be advocated, the direction in the relationships among coping strategies and difficulties may not be ascertained by cross-sectional analyses. Future research could employ time-series designs in order to estimate dynamic networks in which an edge denotes a predictive relation (eg, higher avoidance predicting higher negative emotions).³⁹

6 | CLINICAL IMPLICATIONS

These NA findings suggest further areas for HBOC counselling. In particular, women with a pathogenic variant may need further help to overcome avoidance and their difficulties in contacting family members and making decision about their cancer risk management. Cognitive restructuring should be generally facilitated, especially since it was related to less negative emotions, personal and familial cancer worries.

ACKNOWLEDGMENT

Project funded by the European Union Horizon 2020 research and innovation programme under grant agreement No 634935 (BRIDGES). Partly funded in France through the SiRIC label and Institut Curie integrated cancer research site and a grant from Ile-de-France Cancer Pole N° 2015-1-EMERG-14-ICH-1.

CONFLICT OF INTEREST

Peter Devilee reports grants from EU Horizon2020 during the conduct of the study.

DATA AVAILABILITY STATEMENT

Data availability The study database is hosted at Methodology and Quality of Life in Oncology unit (INSERM UMR 1098), University Hospital of Besançon. It may be available after main publication for BRID-GES research program performed (in 2022).

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Brédart A, Dick J, Cano A, et al. How to facilitate psychosocial adjustment in women tested for hereditary breast or ovarian cancer susceptibility? Insights from network analysis. *Psycho-Oncology*. 2019;1–7. <u>https://</u>doi.org/10.1002/pon.5302