ONCOLOGY

Psychosexual Morbidity in Women With Ovarian Cancer: Evaluation by Germline BRCA Gene Mutational Status

Chloe A. Logue, MBChB, MRes,[a,#] Julia Pugh, BNurs (hons), MSc, PGDip,[a,#] Philip Foden, BSc, MSc,[a] Reem D. Mahmood, MBChB, MRCP,[a,b] Robert D. Morgan, MBBS,[a,b] Claire Mitchell, MBBS, MRCP, PhD,[a,b] Jurjees Hasan, MSc, MD, FRCP,[a,b] Andrew R. Clamp, MA, BMBCh, PhD,[a,b] and Gordon C. Jayson, PhD, FRCP[a,b]

ABSTRACT

Introduction: Up to 75% of women with ovarian cancer experience psychosexual morbidity and approximately 15−20% of women with ovarian cancer have a germline *BRCA1/2* mutation (g*BRCA*m). However, psychosexual morbidity remains unexplored in women with g*BRCA*m ovarian cancer.

Aim: Given their younger age, genetic diagnosis, breast cancer risk, and increased prevalence of surgically-induced menopause, we aim to assess whether women with g*BRCA*m ovarian cancer experience distinct psychosexual morbidity.

Methods: Psychosexual morbidity was investigated in 2 cohorts of women with ovarian cancer: women with g*BRCA*m ovarian cancer vs women with g*BRCA* wildtype (g*BRCA*wt) ovarian cancer. Between August 2019 and March 2020, women with high-grade serous carcinoma of the ovary, Fallopian tube or primary peritoneum were approached in clinic or telephoned and invited to take part. Exclusion criteria included: women with alternative histology; women admitted from clinic; and women who lacked capacity to independently complete the questionnaire. The Female Sexual Function Index (FSFI) and background information were collected at a single time-point per patient. Scores below 26.55 were interpreted to suggest psychosexual dysfunction.

Main Outcome Measure: Responses including total and domain FSFI scores, self-reported psychosexual problems and interest in psychosexual support were compared.

Results: Of 103 women approached, 53% returned questionnaires. In this exploratory analysis, women with g*BRCA*m ovarian cancer were significantly younger (51−60 years vs 61−70 years, g*BRCA*wt, $P = .010$). There was a trend towards increased prevalence of surgical menopause (57% vs 27%, $P = .097$) and breast surgery (53% vs 22%, $P = .132$, g*BRCA*m vs g*BRCA*wt, respectively). Women with g*BRCA*m ovarian cancer scored higher in the FSFI questionnaire, particularly women under 60 years (15.1 vs 2.7, $P = .070$), approaching significance. Women with g*BRCA*m ovarian cancer expressed more interest for face-to-face services ($P = .018$), especially psychosexual therapy (65% vs 30%) and more often felt the service was insufficient, approaching significance (71% vs 44%, g*BRCA*m vs g*BRCA*wt, respectively, $P = .076$).

Conclusion: Women with g*BRCA*m ovarian cancer are younger, express more interest for specialist psychosexual support and potentially different psychosexual problems, warranting further exploration. **Logue C, Pugh J, Foden P, et al., Psychosexual Morbidity in Women With Ovarian Cancer: Evaluation by Germline BRCA Gene Mutational Status. Sex Med 2022;10:100465.**

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[a]The Christie NHS Foundation Trust, Manchester, UK;

[b]Manchester Cancer Research Centre, Division of Cancer Sciences, Faculty of Biology, School of Medical Sciences, Medicine and Health, University of Manchester, Manchester, UK

[#]Denotes joint first authors.

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INTRODUCTION

Ovarian cancer is the sixth commonest cancer affecting women in the United Kingdom (U.K.), with approximately 7,500 women newly diagnosed each year.[1] High-grade serous carcinoma of the ovary typically presents at an advanced stage, increasing the risks of psychosexual morbidity.[2] Abdomino-pelvic debulking may induce a surgical menopause, pain and neuropathy.[3] Body image may change with stomas, ports, scarring and alopecia.[4] Up to 75% of women with ovarian cancer experience psychosexual morbidity.[5] The common symptoms reported include dyspareunia, vaginal dryness, negative changes to sex lives, diminished perceived body image and reduced intimacy with partners.[5] Over half of women with ovarian cancer are at risk of anxiety and over a third are vulnerable to depression.[6,7] We recently identified potential risk factors for psychosexual morbidity in women with ovarian cancer: younger age; premenopausal status at diagnosis; noncurative aim of treatment; extensive surgery; high courses of chemotherapy; cardiovascular comorbidities; anxiety, and depression.[5]

Women with ovarian cancer are living longer with the side effects of treatment; the latest U.K. data shows 5-year survival increased from 42.3% to 46.2% (2006−2011).[1] This was largely attributed to greater access to optimal primary treatment, more use of maintenance therapies and more aggressive treatment of recurrent disease.[1,2] Initiatives such as "Living With and Beyond Cancer" in the U.K., focus on improving symptom management.[8] National guidance stipulates that clinicians should offer information regarding psychosexual morbidity to women with ovarian cancer.[9] Psychosexual morbidity is a priority for women with ovarian cancer yet is rarely documented in clinical notes, suggesting it is not discussed.[10,11] There are several tools that evaluate psychosexual morbidity, which largely focus on patient reported outcome measures.[12,13] Of the questionnaires specifically evaluating psychosexual morbidity, the Female Sexual Function Index (FSFI) is a 19-item self-report measure of sexual function which is validated in women with cancer and assesses 6 domains (desire, arousal, lubrication, orgasm, satisfaction and pain), generating a total possible score of 36 (Appendix B.2.).[14] The FSFI score identifies a risk of psychosexual dysfunction but cannot diagnose it. FSFI does not assess distress which is a fundamental component of a psychosexual dysfunction diagnosis. Psychosexual morbidity arises from different stages of the sexual response cycle which include both physical aspects (vaginal dryness and dyspareunia) and psychological (reduced desire, arousal and orgasm).[15] In this manuscript the term psychosexual morbidity refers to difficulties arising from any stage of the sexual response cycle. The FSFI assesses both the physical and psychological aspects of sexual functioning and is commonly used across the literature.[5]

Women with ovarian cancer and a germline *BRCA1/2* mutation (g*BRCA*m) may be at greater risk of psychosexual morbidity, as they are on average 10 years younger at diagnosis, more likely to have undergone surgical menopause, breast cancer surgery or risk-reducing bilateral mastectomies.[2] Distinct treatment options are available specifically for women with g*BRCA*m ovarian cancer with notably favourable outcomes.[2] Additionally, women with a g*BRCA*m ovarian cancer may experience increased psychological distress after being diagnosed with a genetic mutation, owing to familial consequences. Indirect or subconscious factors may play a role in psychosexual morbidity in such cases and appropriate therapy could help patients recognise unconscious feelings if not already apparent. Despite these potential risk factors and distinguishing features, the psychosexual morbidity of women with g*BRCA*m ovarian cancer remains unexplored. We therefore hypothesised: are women with g*BRCA*m ovarian cancer at greater risk of psychosexual morbidity compared with women with ovarian cancer and wild-type/unknown *BRCA* status (g*BRCA*wt); do their FSFI scores differ; and do they express different priorities and preferences for psychosexual support?

MATERIALS AND METHODS

Approval was granted from the trust NHS Foundation Trust Quality Improvement and Clinical Audit Committee (reference 18/2369) to conduct this single centre, observational audit as part of clinical service improvement.

Between August 2019 and March 2020, women attending gynaecological oncology outpatient clinic were identified from screening clinic lists, approached by the authors and invited to take part in the study, after a discussion about the study with their clinician in a private room with an opportunity to ask questions. The following inclusion criteria applied: high-grade serous carcinoma of the ovary, Fallopian tube or primary peritoneum, with g*BRCA*wt or g*BRCA*m genetic status. Exclusion criteria included: cancer of unknown primary; histology other than high-grade serous; women with somatic mutations; women admitted from clinic that day; women who did not speak English or who were deemed to lack the capacity to independently complete the questionnaire. Women were then also invited by telephone to participate by completing a questionnaire at home, to return to the trust via an annonymised prepaid envelope. The consent process was agreed with the Clinical Audit Committee and implied consent was demonstrated by return of their questionnaire.

The FSFI and a background demographic questionnaire with free text space were provided (Appendix B.1). A background questionnaire was developed by the authors and approved by the Clinical Audit Committee , to capture information deemed clinically relevant by the clinicians including: demographics, treatment history and patient satisfaction with the current service provision for psychosexual morbidity. An invitation letter provided information regarding the study rationale, confidentiality and information handling. Questionnaires were pseudo-anonymised and an onsite password-protected list of the patient's details was maintained,

accessible by the first authors only. Total FSFI scores below the conventional threshold of 26.55 were interpreted to suggest psychosexual dysfunction, with lower scores indicating potentially worse psychosexual morbidity (Appendix B.2).[13,14] The total composite FSFI score does not convey the nature of any specific concerns, so individual subsection domains were also evaluated (Table A.3). Pseudo-anonymised data populated password-protected spreadsheets. Incomplete questionaries were included in subsection analysis whilst complete questionnaires informed total score analysis. Scoring rules were created where women who stated they were sexually inactive omitted certain questions and were scored zero. According to an 80% power calculation assuming pre-published conventional values of a difference in mean FSFI score of 5,[16] and a standard deviation of mean FSFI score of 7,[14] accepting an alpha value of 0.05, the minimum number required in each group to reach statistical significance was calculated to be 32. Unfortunately, this sample size threshold was not quite met as the COVID-19 pandemic hindered later stages of data collection. Initially differences between catergorical data were analysed using Chi-square test and continuous data using Mann Whitney U test (Fisher's exact when nonparametric) but the results are provided for information only regarding the signals observed. As a signal finding study, due to the small sample sizes, it was not possible to perform robust quantitative or qualitative analysis. Tests were carried out using Microsoft Excel (2016), Microsoft Corporation, Washington USA and GraphPad Prism-9.1.0 for Windows, GraphPad Software, San Diego, California USA. In accordance with the journal's guidelines, we will provide our data for the reproducibility of this study upon request.

RESULTS

A total of 103 women were approached to answer the questionnaire; 55 women returned questionnaires (53% response rate; g*BRCA*m n = 26; g*BRCA*wt n = 29). Of the returned FSFI questionnaires, 55% were completed fully (g*BRCA*m [69%]; g*BRCA*wt [41%]), thus the sample size was not met. The exploratory analysis revealed that women with g*BRCA*m ovarian cancer were significantly younger than women with g*BRCA*wt ovarian cancer (median age range 51−60 years vs 61−70 years, $P = .01$, respectively, Mann-Whitney). The data suggest women with g*BRCA*m may score higher on the FSFI questionnaire, suggesting better sexual function; particularly in women under 60 years (15.1 vs 2.7, $P = .07$, Mann-Whitney, Figure 1) but does not reach significance. There is a modest difference in likelihood of sexual inactivity between the 2 groups (53.8% vs 62.1%, g*BRCA*m vs g*BRCA*wt, respectively).

The data suggest women with g*BRCA*m ovarian cancer are more likely to have undergone surgical menopause (57% vs 27%, $P = .09$, Chi-square) and previous breast surgery (53% vs 22%, $P = .13$, Chi-square, Figure 2) but does not achieve significance. Overall, 91% of patients did not recall being

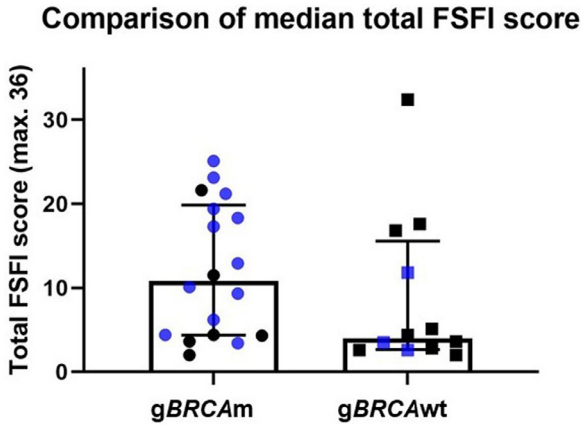

Figure 1. The data suggest women with ovarian cancer and a germline BRCA mutation (gBRCAm) score higher on the FSFI than women with ovarian cancer and wildtype/unknown BRCA gene status (gBRCAwt), approaching significance when comparing women younger than 60 years (blue datapoints; 15.1 vs 2.7, $P = .070$, Mann-Whitney). Women aged 60 years and older (black datapoints) (color version of figure is available online).

asked about psychosexual morbidity, only 6% recalled being offered support and 71% of women with g*BRCA*m ovarian cancer felt that the service did not address their needs (vs 44% of g*BRCA*wt ovarian cancer, $P = .08$, Chi-square). Women with g*BRCA*m ovarian cancer were significantly more interested in specialist face-to-face services (comprising group and psychosexual therapy, $P = .018$, Chi-square), especially psychosexual therapy (65% vs 30%) warranting further exploration. The distribution of psychosexual problems was broadly similar across 2 cohorts. However, signals of other promising differences between the g*BRCA*m and g*BRCA*wt groups emerged, requiring further study to assess significance. Within the FSFI domain subsections, women with g*BRCA*m ovarian cancer appeared to score higher than g*BRCA*wt in arousal (median score 4 vs 0.5, respectively) and satisfaction (median score 6 vs 3.5, respectively) and were less likely to report that psychosexual support was not relevant to them or omit the question, approaching significance ($P = .06$, Chi-square).

The free text sections were completed by over half of women in the study. Women frequently commented on the negative impact of their diagnosis and treatment on their sex lives, body image and intimate relationships. Anecdotally, 1 woman in clinic reported that while she had been feeling low about her quality of life and psychosexual problems, she was offered and completed the questionnaire, which she felt legitimised her problems, prompting her to contact her general practitioner about suitable vaginal lubricants. There was not a qualitative design to this study and the free-text section was insufficient for thematic analysis. However, the free text section was included as part of the service evaluation and provided useful insight, demonstrating that women are willing to share their experiences. The responses

Figure 2. Women with ovarian cancer and a germline BRCA mutation (gBRCAm) appeared to be more likely than women with ovarian cancer with wildtype/unknown BRCA gene status (gBRCAwt) to have undergone surgical menopause (57% vs 27%, *P* = .097, Chi-square) and previous breast surgery (53% vs 22%, *P* = .132, Chi-square) approaching significance.

were not representative of the themes but did provide individual views (Appendix A, Table A.1).

DISCUSSION

Summary of Main Results

Considering the limited sample size, the exploratory analysis performed revealed that women with g*BRCA*m ovarian cancer were significantly younger than women with g*BRCA*wt ovarian cancer. The data suggest women with g*BRCA*m ovarian cancer score higher on the FSFI questionnaire compared to g*BRCA*wt ovarian cancer, suggesting better sexual function; particularly women under 60 years; greater numbers are required. There was a trend towards women with g*BRCA*m more commonly having undergone surgical menopause (likely secondary to their younger age) and previous breast surgery; more data are needed.

Women with g*BRCA*m ovarian cancer were more interested in specialist face-to-face support, especially psychosexual therapy, whereas women with g*BRCA*wt ovarian cancer preferred written information. The signals exhibited in the results suggest women with g*BRCA*m ovarian cancer may experience distinct psychosexual morbidity. This should prompt further study to explore the potential need to tailor support in this cohort.

Results in the Context of Published Literature

Up to 3 quarters of women with ovarian cancer experience some symptoms of psychosexual morbidity.[5] Despite national recommendations, 91% of patients did not recall discussing regarding psychosexual morbidity and only 6% recalled being offered support. Low rates of recalling discussions surrounding psychosexual morbidity could result from the shock of receiving a cancer diagnosis. Clinicians, therefore, need to be mindful about the appropriate timing of discussing psychosexual problems and the frequency of follow up enquiries throughout treatment and maintenance therapies. Additionally, there may be discord regarding what patients consider important compared to clinicians.

Younger age is associated with a higher risk of psychosexual morbidity in women in ovarian cancer.[5] Conversely, our study's data suggest women with g*BRCA*m ovarian cancer, who were significantly younger, report greater arousal and satisfaction and score higher overall in sexual functioning, yet still expressed greater interest in specialist services. It has been demonstrated that the FSFI does not function as well when women have been sexually inactive, but allows for selection of "No sexual activity."[17] Suitable questionnaires in women with ovarian cancer are limited, meaning comparable, informative evaluation of psychosexual morbidity in ovarian cancer clinic remains stunted.

Premenopausal status at time of diagnosis is a potential risk factor for psychosexual morbidity, attributed to the early onset of the menopause, vaginal dryness and vasomotor symptoms.[5] The data suggest that more women with g*BRCA*m ovarian cancer may experience a surgical menopause (57% vs 27%). Furthermore, 71% of women in the g*BRCA*m ovarian cancer cohort reported menopausal symptoms which impacted their sexual wellbeing (vs 65% g*BRCA*wt ovarian cancer); larger samples may confirm this modest difference. Vaginal lubricants and hormone replacement therapies provide simple measures to alleviate these symptoms.[11] However, the psychological sequelae of the diagnosis, treatment and body image changes may persist requiring talking therapies.[18]

Genetic testing for *BRCA* gene mutations in women with ovarian cancer is becoming routine with notable differences to treatment pathways and outcomes.[2] The association of increased psychosexual morbidity after prophylactic mastectomy is recognised.[19,20] These data suggest that women with g*BRCA*m ovarian cancer are more likely to have had breast surgery but further exploration is required. Furthermore, ongoing research investigating psychosexual morbidity in women with breast cancer who carry *BRCA* mutations, and the psychological distress

incurred through the inheritance of a genetic mutation, could shed light on the impact of the genetic diagnosis on women with g*BRCA*m ovarian cancer.[21,22]

Strengths and Weaknesses

This is the first study to explore the impact of *BRCA* mutation status on psychosexual morbidity in women with ovarian cancer. As such, it was a signal study to power future studies, focus the reader on the unmet need, and raise awareness amongst clinicians and research. Women participating in this study were predominantly White and heterosexual, English literate and able to independently complete the questionnaire. The sample size threshold was unfortunately not reached as the covid-19 pandemic hindered data collection. Nearly half of the women contacted did not return questionnaires and many questionnaires were returned incomplete; it was not within the scope of this preliminary study to recontact women to explore this. The data presented in Appendix A include both analyses including and excluding omitted answers, as this may reflect the perceived appropriateness of questions and inform future studies.

Our recent review of psychosexual morbidity in women with ovarian cancer highlights the limitations of patient reported outcome measures for women with ovarian cancer.[5] To avoid overwhelming the participants, a single questionnaire was chosen: the FSFI because it is quick to complete, focuses solely on psychosexual morbidity, generates a comparable score and is validated for women with cancer.[14] Whilst the composite total FSFI score does not convey the nature of specific issues that are of concern, the subsection domains were examined. The FSFI was originally designed to be used in women who had engaged in sex within the 4 prior weeks.[13] However, as 60% of participants had been sexually inactive in the preceding month, the FSFI was unable to accurately quantify psychosexual morbidity. It was not deemed appropriate to ask women about sexual activity before offering a questionnaire to exclude them if they had not had intercourse in the prior 4 weeks. Therefore, the FSFI was limited in its assessment of psychosexual morbidity as a large proportion of women attending clinic are sexually inactive. Therefore, it was not possible to comprehensively quantify psychosexual morbidity across the clinic. Furthermore, sexually inactive women may still experience aspects of psychosexual morbidity.[15]

Implications for Practice and Future Research

Our findings suggest differences in psychosexual morbidity between women with g*BRCA*m ovarian cancer and g*BRCA*wt ovarian cancer which may benefit from discrete approaches to treatment. This signal seeking study intends to prompt clinicians to consider the psychosexual needs of women with ovarian cancer and to provide data upon which further studies can be powered. Involvement of patients in future research is crucial to ensure patient priorities are considered and qualitative approaches may prove more illustrative. Solutions to improve psychosexual morbidity for patients can be low-cost and easy to implement. However, first the issue needs to be identified and documented to direct resources appropriately.

The FSFI score identifies increased risk of psychosexual dysfunction but does not assess distress which is fundamental in diagnosing psychosexual dysfunction. A need remains for the following: more suitable, specific, validated questionnaires which allow for answers from sexually active and inactive women; improved clinician and patient tools; and more training to improve the conversation about psychosexual morbidity. Given the limited sample sizes obtained, further exploration of the differences approaching significance is recommended, alongside more diverse participant populations. Reasonable alternative questionnaires include: The Sexual Activity Questionnaire, as it explores different aspects of psychosexual morbidity,[23] and the Hospital Anxiety and Depression Scale, to explore the relationship between clinical anxiety and depression and psychosexual morbidity.[24]

CONCLUSIONS

Psychosexual morbidity in women with ovarian cancer remains an unmet priority that, if addressed, could significantly improve quality of life. This single-centre exploratory analysis proposes that women with g*BRCA*m ovarian cancer prefer more specialist approaches to psychosexual support and may experience distinct psychosexual morbidity. Women with g*BRCA*m ovarian cancer (especially those under 60 years) appear to score higher on the FSFI questionnaire compared to g*BRCA*wt ovarian cancer, suggesting potentially better psychosexual function. Further work to investigate the signals of differences observed in this study, to streamline questionnaires and to explore more diverse patient demographics is recommended. It is hoped these findings will inform future studies and ultimately improve patient experience.

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Corresponding Author: Dr Chloe Logue, MBChB, MRes, Gastro Respiratory Research, Level B1 Menzies Building, Waikato Hospital, Pembroke Street, 183, Private Bag 3200, Hamilton 3240, New Zealand. Tel: +64 (0) 07 839 8899; E-mail: chloe.logue@waikatodhb.health.nz

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STATEMENT OF AUTHORSHIP

Chloe Logue: Conceptualization, Methodology, Validation and Formal Analysis, Investigation, Writing – Original Draft, Writing – Review & Editing; Julia Pugh: Conceptualization, Methodology, Writing – Original Draft, Writing – Review & Editing; Philip Foden: Methodology, Validation and Formal Analysis, Writing – Review & Editing; Reem D. Mahmood: Investigation, Writing – Review & Editing; Robert Morgan: Methodology, Writing – Review & Editing; Claire Mitchell: Writing – Review & Editing, Supervision; Jurjees Hasan: Writing – Review & Editing, Supervision; Andrew R. Clamp: Writing – Review & Editing, Supervision; Gordon C. Jayson: Conceptualization, Writing – Review & Editing, Supervision.

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SUPPLEMENTARY MATERIALS

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