PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

Title (Provisional)

Korean patients with hereditary cancer: A prospective multicenter cohort study protocol exploring psychosocial and health outcomes

Authors

Kim, Jun-Kyu; Jang, Mi-Ae; Park, Jong Eun; Won, Dongju; Ha, Jung-Sook; Kim, Kyoung-Bo; Park, Boyoung; Kong, Sun-Young

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VERSION 1 - REVIEW

Reviewer	**1**
Name	**Kim, Raymond**
Affiliation	**University Health Network**
Date	**21-Oct-2024**
COI	**I understand and consent to the named publication of this review.**

This study proposes to examine various health impact of genetic variants in people in Korea who have undergone genetic testing. It is well written and straightforward. A few areas of suggested improvement.

1. The authors state that there is a dearth of information in long term impacts of genetic variation. There actually have been a lot of information on quality of life, unmet needs, and mental health on patients with hereditary cancer. However, the authors should highlight there are very few studies done in Korean patients and that most published studies are on white women. The strength of this study is that it is done on Korean people which may bring unique information on quality of life, and mental health.

2. The inclusion criteria should specifically state if gene positive, VUS and gene negative patients are included. I believe all three categories should be included.

Reviewer	**2**
Name	**Perea, Jose**

Affiliation	**Fundacion Jimenez Diaz-UTE**
Date	**06-Dec-2024**
COI	**I understand and consent to the named publication of this review.**

I have read with interest the MS sent by Kim et al. In my opinion, there is not much more things to add. Nevertheless, I think the authors should clarify the panel of genes that are involved in the NGS analysis, and what it is going to be done for those cases with pathogenic germline mutation in other genes different than BRCAs. And the other point it is that I think the authors should compare in the discussion Korean guidelines with other guidelines for BRCAs mutations.

VERSION 1 - AUTHOR RESPONSE

Reviewer 1

This study proposes to examine various health impact of genetic variants in people in Korea who have undergone genetic testing. It is well written and straightforward. A few areas of suggested improvement.

1. The authors state that there is a dearth of information in long term impacts of genetic variation. There actually have been a lot of information on quality of life, unmet needs, and mental health on patients with hereditary cancer. However, the authors should highlight there are very few studies done in Korean patients and that most published studies are on white women. The strength of this study is that it is done on Korean people which may bring unique information on quality of life, and mental health.

Author response: Thank you for your insightful comment and for emphasizing the importance of highlighting the unique contribution of our study. In response to the comment, we have revised the Introduction section to explicitly acknowledge the existing body of research on hereditary cancer patients, which primarily focuses on White women, and to highlight the lack of studies involving Korean population.

In the revised text, we emphasized that studies on Asian populations are relatively rare, and large-scale investigations targeting Koreans are almost non-existent. We have further clarified that this study aims to address this critical gap by analyzing the quality of life, mental health, and medical needs of Korean hereditary cancer patients, thereby contributing unique insights into this underrepresented population. (page 6)

Existing research on hereditary cancer patients has primarily focused on White women, neglecting the diverse racial and cultural contexts of patients worldwide. Studies involving Asian populations are relatively rare, and large-scale investigations targeting Koreans are almost non-existent. Consequently,

there is a critical lack of systematic data on the quality of life, mental health, and medical needs of Korean hereditary cancer patients. This study aims to bridge this gap by establishing a multi-institutional cohort of hereditary cancer patients in Korea to analyze long-term changes in health status, quality of life, and mental health.

2. The inclusion criteria should specifically state if gene positive, VUS and gene negative patients are included. I believe all three categories should be included.

Author response: Thank you for emphasizing the need for additional detail in this section and for the opportunity to clarify the classification of genetic variants in our study. In response, we have revised the Methods section to provide a detailed explanation of how patients were categorized based on genetic testing results and the rationale behind the grouping criteria. (page 10)

Inclusion criteria This study included patients suspected of hereditary cancer who underwent genetic counseling and related genetic testing, regardless of insurance coverage status. Based on the results of genetic testing, patients were categorized into three groups: Pathogenic Variant (PV or Likely PV), Variant of Uncertain Significance (VUS), and Not Detected (Likely Benign or Benign).

According to the American College of Medical Genetics and Genomics (ACMG) guidelines, genetic variants are classified into five categories: Pathogenic, Likely Pathogenic, Uncertain Significance, Likely Benign, and Benign. However, this study categorized patients into three groups—PV, VUS, and ND—to systematically evaluate the clinical and psychological indicators of hereditary cancer patients. This classification established a group of patients with clinically significant variants closely associated with the disease, while also including groups of patients with VUS and those with no detected variants as comparative cohorts. These groups served as valuable control cohorts for future clinical research. By doing so, the study aimed to provide a detailed evaluation of the clinical and psychological characteristics of each group and to better understand the impact of genetic testing results on the health and quality of life of hereditary cancer patients.

Reviewer 2:

1. I have read with interest the MS sent by Kim et al. In my opinion, there is not much more things to add. Nevertheless, I think the authors should clarify the panel of genes that are involved in the NGS analysis, and what it is going to be done for those cases with pathogenic germline mutation in other genes different than BRCAs.

Author response: Thank you for the insightful feedback and the opportunity to clarify how our study addresses cases where pathogenic germline mutations are identified in genes other than BRCA1/2. In response, we have included a detailed list of genes in the NGS panel used in our study as Supplementary Table S1 to provide further clarity.

Clinically management and treatment plans may differ depending on the gene. However, in this study,

individuals who have undergone genetic testing are included in the inclusion criteria. Therefore, the same survey will be conducted for individuals with mutations in genes other than BRCA. By enrolling individuals with various genetic mutations, this study will provide insights into the quality of life, unmet needs, and mental health of individuals with rare mutations.

2. And the other point it is that I think the authors should compare in the discussion Korean guidelines with other guidelines for BRCAs mutations.

Author response: Thank you for your valuable suggestion. We have revised the Discussion section and incorporated TableS2 to include a comparison of Korean guidelines with those from the United States (NCCN) and the United Kingdom (NICE). This revision underscores how Korea's approach to BRCA mutations differs from that of other countries and highlights how each country's guidelines are tailored to their specific regional contexts and healthcare systems. (page 20-21).

Korean guidelines for BRCA mutation carriers include screening recommendations for breast and ovarian cancers in women and breast and prostate cancers in men. Additionally, screening principles for other cancers, such as pancreatic, gastric, and colorectal cancers, have been proposed. However, there is a lack of clear evidence regarding the appropriate timing and methods for screening these cancers, limiting their practical application. In contrast, the guidelines in the United States and the United Kingdom provide more detailed and systematic strategies for managing hereditary cancers. The NCCN guidelines in the United States emphasize regular monitoring and early detection for various cancers, including breast, ovarian, pancreatic cancers, and melanoma, with specific and detailed recommendations tailored to each cancer type. Similarly, the NICE guidelines in the United Kingdom adopt a broader approach, encompassing high-risk individuals with BRCA1/2 or TP53 mutations. These guidelines provide tailored surveillance strategies and recommendations for preventive surgeries based on family history and individual risk factors.

Correction: *Korean patients with hereditary cancer: a prospective multicentre cohort study protocol exploring psychosocial and health outcomes*

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This article has been corrected since it was published online. The funding information has been update from "This work was supported by the Korean Cancer Survivors Healthcare R&D Project through the National Cancer Centre, which is funded by the Ministry of Health and Welfare, Republic of Korea (Grant numbers RS-2023-CC13920 (NCC-23F1850))." to "This work was supported by the Korean Cancer Survivors Healthcare R&D Project through the National Cancer Centre, which is funded by the Ministry of Health and Welfare, Republic of Korea (Grant numbers RS-2023-CC139201(NCC-23F1850))".

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