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Korean patients with hereditary cancer: A prospective multicenter cohort study

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ABSTRACT

Introduction

Although genetic testing for hereditary cancers is increasing, data on health attitudes based on genetic pathogenicity are limited. This cohort study aims to establish three sub-cohorts based on genetic testing results to assess the health impact of genetic variations. This study evaluates changes in participant quality of life, unmet needs, and mental health over time based on their genetic variant status.

Methods and analysis

This prospective cohort study will recruit 1,435 patients with suspected hereditary cancer who have undergone *BRCA1/2* or next-generation sequencing (NGS) testing. The study began in July 2023 and will continue until December 2027. By 2026, participants will be surveyed up to four times annually during their outpatient visits. The survey consists of 342 items across five domains: comorbidities (96), health behaviors (80), quality of life (QoL) (41), unmet needs (75), and mental health (50). Data were collected using 11 validated surveys. In addition, information on the chronic diseases, cancer diagnoses, medical history, and treatment history of participants will be extracted from their electronic medical records to analyze their health status and cancer treatment experiences. Genetic variant data from *BRCA1/2* and NGS will be used to classify participants into three sub-cohorts: pathogenic variants, variants of uncertain significance, and undetectable mutations. A three-generation pedigree that includes details such as the year of cancer diagnosis, age at diagnosis, cancer type, survival status of family members, and age at death will be constructed for each participant. the collected data will be linked to secondary sources such as cancer registries and National Health Insurance Service data to provide a comprehensive analysis of the impact of hereditary cancer on health and survival.

Ethics and dissemination

The study protocol was approved by the Research Ethics Committees of the participating institutions. The study outcomes will be disseminated through conference presentations, peer-reviewed publications, and social media.

Keywords: Genetic testing, Genetic predisposition to disease, Genetic variation, High-throughput

nucleotide sequencing, Health behavior

STRENGTHS AND LIMITATIONS OF THE STUDY

1. The Korean hereditary cancer cohort study is a large-scale multicenter study conducted at five major university hospitals in Korea, targeting 1,435 patients.

2. The study is designed to track participants through annual surveys over five years, analyzing long-term health outcomes, changes in quality of life, and unmet healthcare needs based on genetic variant status. This will help understand the evolving healthcare needs of hereditary cancer patients.

3. Participants are classified into three sub-cohorts based on pathogenic variants(PV), variants of uncertain significance (VUS), and undetectable variants(ND), allowing for a precise analysis of differences in health outcomes according to genetic status.

4. The participating hospitals are concentrated in metropolitan areas, the study does not include patients from rural regions, which may limit the external validity of the results.

5. There may be challenges in achieving statistical significance when analyzing smaller subgroups with rarer genetic mutations or specific conditions.

INTRODUCTION

The diagnosis of hereditary cancers has steadily increased, primarily owing to the introduction of *BRCA1/2* genetic testing and advancements in next-generation sequencing (NGS) [1-4] (Figure 1). Hereditary cancers account for 5–10% of all cancer cases and are mostly inherited in an autosomal-dominant manner [5]. This often results in the sharing of identical genetic variants among family members, which significantly affects familial health management.

Hereditary cancers generally occur at a younger age and pose a higher cancer risk compared to sporadic cancers. Individuals with pathogenic variants (PV) in the *BRCA1* and *BRCA2* genes have a 65–80% and 45–85% risk of developing breast cancer, respectively, and a 37–62% and 11–23% risk of developing ovarian cancer, respectively [6]. However, the genetic variants that cause hereditary cancer are often unidentifiable during genetic testing on individuals suspected of hereditary cancer. Variants of uncertain significance (VUS) are detected in many cases. A VUS is defined as a genetic variant for which the association with the disease has not been clearly established. Current scientific knowledge and available data cannot classify these variants as pathogenic or benign. Additionally, no known mutations or variants have been identified in some cases [7, 8].

Uncertainty and confusion regarding various genetic test results and their management can lead to severe psychological stress in patients with hereditary cancer, including anxiety, depression, and fear of cancer recurrence [9]. In addition, sharing genetic information with family members can cause tensions and conflicts within families. Moreover, the lack of genetic counseling makes it difficult for individuals to make informed decisions regarding health management and preventive measures [10]. Living with the risk of hereditary cancer has long-term effects, including continuous health surveillance, lifestyle adjustments, and the possibility of preventive surgeries, which substantially affect the overall quality of life in patients and family members who share genetic components [11]. In addition, clinical management becomes ambiguous when a personal or family history of hereditary cancer is suspected but an uncertain variant is detected [12]. Given the limited research on uncertain variants, it is necessary

to conduct additional data analyses on these variants [13]. Therefore, it is crucial to prioritize patients with detailed family histories, including pedigrees, and to incorporate a wide range of pathogenic genetic variants when planning clinical studies targeting patients with hereditary cancer [14]. Furthermore, efforts should be made to include cohorts of patients with VUS and those whose test results are inconclusive in establishing valuable control groups and evaluating consistency in result interpretation [15].

Despite the rapid increase in hereditary cancer, the exact number of hereditary cancers is small. Thus, it is essential to establish a multi-institutional cohort to collect substantial data and systematically study the health problems of patients with hereditary cancer and those who are suspected to have hereditary cancer without established causative variants. Previous studies have highlighted the unmet needs of healthcare providers concerning hereditary cancers, including the lack of clinical guidelines, need for reduced testing costs, and necessity for additional testing for undiagnosed hereditary cancers [16]. The provision of tailored healthcare may address unmet healthcare needs, improve health outcomes, and enhance quality of life. Therefore, the present study aimed to identify long-term health impacts of genetic variations. This study further aimed to evaluate changes in quality of life, unmet needs, and mental health according to genetic variant status to promote health improvement and quality of life. This approach will also support the development and validation of personalized healthcare technologies.

METHODS AND ANALYSIS

Study aim

In this study, we established a prospective cohort of Korean patients with hereditary cancer. Three sub-cohorts will be formed based on the genetic test variant results: patients with PV, VUS, and no detectable mutations (ND).

Table 1 Project research question and hypotheses

Questions	Hypotheses

How do the long-term health impacts differ among patients with hereditary cancer characterized by pathogenic variants (PV), variants of uncertain significance (VUS), and undetected (ND) variants?	Patients with PV will experience higher cancer incidence rates and more health complications over the long term than those with VUS and ND variants.
What is the relationship between genetic variant status and changes in quality of life among patients with hereditary cancer over time?	Patients with PV will experience greater stress and anxiety than those with VUS and ND variants, leading to a more considerable decline in quality of life scores over time.
How do unmet healthcare needs and mental health outcomes differ based on genetic variant status in patients with hereditary cancer?	Patients with PV will require more healthcare services and psychological support, and will have higher rates of mental health issues, such as anxiety and depression, than those with VUS and ND variants.

Study design

This study is a prospective multicenter cohort study conducted in five hospitals: National Cancer Center, Samsung Medical Center, Severance Hospital, Hanyang University Guri Hospital, Keimyung University Dongsan Hospital. The research protocols are as follows:

1. **Participant registration**: Researchers at each participating institutions explained the study objective, research procedures and methods, potential risks and discomfort associated with participation, and the right of patients suspected of having hereditary cancer to voluntarily withdraw from the study at any time. Informed consent was obtained from the participants for study participation and the use of human biological materials. Relevant data, including family history, clinical data, genetic test results, and blood samples are collected after enrolling the participants. Blood samples stored in the Department of Laboratory Medicine were collected as specified in the informed consent form. Specifically, residual blood samples of at least 4 mL in EDTA bottles were collected. Next, plasma and buffy coat were separated and stored at -80 °C. These residual blood samples were used to identify the risk factors and prognostic predictors of hereditary cancer.
2. **Survey:** The survey is conducted over a five-year period, with four annual follow-up surveys after the baseline. The survey consists of 342 items across five domains: comorbidities, health behaviors, quality of life, unmet needs, and mental health.

3. **Expected cohort output:** The data collected in this study will provide foundational information for clinical and genetic research on hereditary cancers in Korea. These data will help establish clinical guidelines for patients with hereditary cancer, propose policies for patient management and support, and promote clinical advancements through detailed and practical clinical research on hereditary cancer.

4. **Short-term outcome:** The short-term goals of this study are to evaluate changes in QoL, identify unmet needs, and assess mental health and health behaviors. QoL encompasses the overall patient well-being, including physical, mental, and social health. Unmet needs refer to the demands of patients not currently met by existing healthcare services. Survey tools validated for patients with cancer are used to evaluate how the QoL of the participants changes. Baseline QoL scores and changes will be analyzed at each follow-up.

   Additionally, the study annually tracks changes in participant mental health by evaluating depression, suicidal thoughts, anxiety, fear of cancer recurrence, and disease awareness using standardized survey tools. It also analyzes how knowledge of genetic status affects lifestyle choices and preventive health measures through the annual monitoring of health behaviors. Unmet needs are assessed using comprehensive survey tools designed to capture general and hereditary cancer-specific requirements, helping identify the most common unmet needs among patients.

5. **Long-term outcome:** The long-term objectives of this study are as follows: 1) To track cancer incidence and analyze causes of death. This will involve the monitoring of new cancer cases and systematic analysis of the causes of death through annual follow-ups, including medical records, self-reports, and official death records; 2) We use secondary data linkages to track cancer incidence and analyze the causes of death. This involves utilizing the system of data integration established by authorized institutions to protect personal information and link secondary data sources, such as the cancer registry and National Health Insurance Service data.

This approach aims to obtain more accurate and comprehensive data on cancer incidence and causes of death.

Inclusion criteria

The high risk of cancer among patients with suspected hereditary cancer is attributed to genetic factors, such as family history, age at cancer onset, and the occurrence of specific cancer types in multiple family members [17, 18].

According to the 2012 National Health Insurance (NHI) coverage guidelines in Korea, *BRCA1/2* pathogenic variant testing is recommended for patients with breast cancer and ovarian cancer who meet the following criteria: a family history of breast or ovarian cancer within second-degree relatives, early onset breast cancer (diagnosed at age ≤ 40 years), bilateral breast cancer, concurrent breast and ovarian cancer, male breast cancer, or multiple primary cancers. The NHI coverage guidelines revised in 2020 further recommended *BRCA1/2* pathogenic variant testing for patients with breast cancer with a family history of the disease, ovarian cancer, male breast cancer, metastatic prostate cancer, or pancreatic cancer within third-degree relatives; early-onset breast cancer (diagnosed at age ≤ 40 years); triple-negative breast cancer diagnosed at age ≤ 60 years; bilateral breast cancer; concurrent breast cancer with ovarian or pancreatic cancer; male breast cancer; or epithelial ovarian cancer (including fallopian tube and primary peritoneal cancer), excluding histologically pure mucinous ovarian cancer. Additionally, NGS has been conditionally covered with 50% co-payment since March 2017, and the co-payment rate increased to 80% in December 2023. This study included patients who underwent genetic testing regardless of insurance coverage status, including minors aged 13 years or older who underwent genetic counseling and related genetic testing for suspected hereditary cancer.

Study population estimate

The extent to which patient-centered decision-making is implemented in clinical settings in South Korea remains largely understudied. Consequently, evidence on this topic often relies on international literature. A study conducted at a tertiary university hospital in South Korea reported that 37.4% of orthopedic patients engaged in patient-centered decision making. Additionally, a national survey of the general population indicated that 33.5–44.3% of individuals prefer shared decision-making between patients and healthcare providers [19, 20].

In this study, we hypothesized that the rate of patient-centered decision-making without intervention would be approximately 30%. We further assumed that using a tailored decision-making tool would increase this rate by 10%, increasing it to a total of 40%. A two-proportion test with a significance level (α) of 5% and a power (1-β) of 85% was performed based on these assumptions. The required sample size was calculated to be 405 patients in each group. When the power was set to 80%, the required sample size was 354 patients per group, resulting in a total of 708 patients.

Considering an estimated dropout rate of 20% and the fact that the number of patients with PV was expected to be lower than that of those with VUS or negative variants, the target sample size was adjusted. The final target sample size was set at 1,435 patients to ensure equal enrollment of patients with PV and those with VUS or negative variants. Sample size estimation was conducted to establish a cohort of Korean patients with hereditary cancer.

Data collection items

This study collected clinical, survey, genetic variant, and pedigree data from the participants.

1. **Clinical data**: Clinical data were directly extracted by researchers with access to electronic medical records. These data included histories of chronic diseases (e.g., hypertension, diabetes, and heart disease), cancer diagnosis (year of diagnosis, age at diagnosis, and type and stage of cancer), and surgeries related to cancer treatment (date of surgery, type, and outcome). Treatment history included the current and past types, duration, and outcomes of

anticancer therapies (chemotherapy, radiotherapy, and hormone therapy), including related side effects and complications. The test results include health assessment outcomes, such as general blood tests, cancer marker tests, ECGs, and pulmonary function tests. Imaging data include the results and interpretations of imaging tests conducted during cancer diagnosis and treatment, such as CT, MRI, PET, and ultrasonography. Anthropometric data include patient weight, height, BMI, and other measurements. Obstetric, menstrual, breastfeeding, and hormone use histories are also included for female patients.

2. **Surveys:** The surveys were designed to be completed within 20 minutes to facilitate ease of response for the participants and were structured to be administered as interviewer-administered questionnaires. The survey tools were tailored to different time points: at the time of cancer diagnosis; during treatment (typically four months post-diagnosis); and at 1-, 2-, 3-, and 4-year intervals post-diagnosis. These surveys collect detailed information on lifestyle factors, environmental exposures, and other health-related data.
3. **Genetic variants:** Genetic mutation data were obtained using *BRCA1/2* or NGS panel testing. Based on these results, patients were classified into three sub-cohorts: PV, VUS, and ND.
4. **Family history and pedigree:** Pedigree data were collected by the participants after they were educated on how to construct a pedigree chart encompassing three generations. This includes information on the years of cancer diagnosis, age at diagnosis, and type of cancer among family members, as well as whether the family member is deceased and their age at death. This structured approach ensures comprehensive data collection and analysis suitable for the research objectives.
5. **Biospecimen collection**: Biological samples are collected from the blood of participants in accordance with protocols outlined in the informed consent documentation, with storage facilitated by the Department of Laboratory Medicine. Specifically, we use residual blood samples collected following clinical blood collection. A minimum of 4 mL of residual blood is collected in EDTA tubes. Post-collection, the plasma and buffy coat are separated and

stored in an ultra-low temperature freezer at -80 °C. These residual blood samples will be used to identify risk factors and prognostic predictors associated with hereditary cancer. This approach is integral for improving the accuracy of assessing genetic risk factors and clinical prognoses related to hereditary cancer.

Survey tools and data collection

Data were collected as follows: Baseline surveys are initially conducted with participants following receipt of their genetic test results. Subsequently, annual follow-up surveys will be conducted for four years from the baseline survey date. Surveys were self-administered through questionnaires or telephone interviews. Participants were provided with explanations by well-trained nurses who assisted them in completing the questionnaires or in conducting telephone surveys to record their responses.

In this study, data were collected from participants using 11 different survey tools (Table 2).

Table 2 An overview of survery questionnaire

Area	N of items	Subarea	Survey tool
Comorbidities	96	-	Korea National Health and Nutrition Examination Survey (KNHANES)
Health behavior	80	Obesity and Weight Management	
		Alcohol Consumption	
		Mental Health	
		Smoking/Secondhand Smoke/Smoking Cessation	
		Oral Health	
		Physical Activity	
		Sleep Health	
		Dietary Habits	

Quality of life	41	Quality of Life in Cancer Patients	EORTC-QLQ-C30
		General Quality of Life	EQ-5D-5L
Unmet needs	75	Comprehensive Needs Assessment	CNAT
		Hereditary Cancer Specific Needs Assessment	Development of additional items
Mental health	50	Depression	PHQ-9
		Suicide	MINI
		Anxiety	GAD-7
		Fear of Cancer Recurrence	QOL-CS
		Disease Awareness	BIPQ

1. **Comorbidities:** The current medical diagnostic status of the study participants was recorded using the Korea National Health and Nutrition Examination Survey [21]. Major chronic conditions included hypertension, diabetes, cardiovascular diseases. In addition, the presence of malignant tumors such as gastric cancer, liver cancer, colorectal cancer, and other conditions was noted. Detailed information on comorbidities, including age at diagnosis and current treatment status, was collected to comprehensively assess the health status of participants and to analyze the occurrence and treatment status of comorbidities.

2. **Health behaviors:** The Korea National Health and Nutrition Examination Survey consists of eight detailed items for evaluating health-related behaviors [21, 22]. 1) Obesity and weight management were assessed using self-reported weight changes and weight management methods over the previous year. 2) Alcohol consumption was evaluated by measuring the frequency and quantity of alcohol consumption to assess the health risk factors related to alcohol consumption. 3) General mental health status was assessed using standardized questions. 4) Smoking status, passive smoking exposure, as well as cessation

attempts and intention were evaluated to assess smoking-related health risks. 5) Oral health status was assessed through self-reporting of dental hygiene habits and oral health problems. 6) Physical activity was assessed by measuring the frequency, duration, and intensity of physical activity. 7) Sleep health was assessed by evaluating sleep duration, quality, and disturbances to identify sleep-related issues. 8) Finally, dietary habits were evaluated by assessing the frequency and diversity of food intake. A comprehensive evaluation of individual health habits and lifestyles was conducted through responses to each item used as foundational data for health promotion.

3. **Quality of Life**: The general and cancer-specific QoL were assessed using the EQ-5D-5L questionnaire to measure five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety or depression [23]. Each dimension was evaluated on a 5-point scale scored from 1 (no problem) to 5 (severe problem). The responses were subsequently combined to express a 5-digit number representing health status. This facilitated a comprehensive assessment of general QoL levels. The QoL of patients with cancer was assessed using the EORTC-QLQ-C30, which consists of functional (physical, role, emotional, cognitive, and social functioning), symptom (fatigue, nausea, vomiting, pain, dyspnea, insomnia, loss of appetite, constipation, diarrhea, and financial difficulties), an overall health status, and single-item scales [24]. Each item was evaluated on a Likert scale ranging from 1 (not at all) to 4 (very much), with higher scores indicating better functional status and worse symptom burden.

4. **Unmet needs:** This assessment comprised comprehensive and hereditary cancer-specific needs. Comprehensive needs were assessed using the CNAT to evaluate the following subdomains: information and education, psychological issues, medical staff, physical symptoms, hospital facilities and services, family/interpersonal issues, religious/spiritual issues, and social support [25]. Each item was rated from 0 (not at all needed) to 3

(extremely needed). Specific needs related to hereditary cancer were assessed using the Study for HeredItary questionnaire Development (SHIELD) questionnaire developed by the research team, with a focus on information and education, psychological issues, medical services, and social support [26]. Each item was rated on a scale of 0 (not at all needed) to 3 (extremely needed). Scores for each item were calculated to determine the level of need, with higher scores indicating a greater need.

5. **Mental health:** This evaluation comprises five detailed areas: depression, suicide risk, anxiety, fear of cancer recurrence, and illness perception. The depression domain was assessed using the PHQ-9 to evaluate nine depressive symptoms, with each item scored from 0 (not at all) to 3 (nearly every day). This yielded a total score of 0–27, with higher scores indicating higher levels of depression [27]. Furthermore, suicide risk was assessed using the MINI questionnaire to evaluate the suicide risk levels of respondents based on their thoughts, plans, and attempts. Each item was scored as yes (1 point) or no (0 points) [28]. The anxiety domain was assessed using the GAD-7 questionnaire to evaluate seven anxiety symptoms. Each item was scored from 0 (not at all) to 3 (nearly every day), yielding a total score of 0–21; higher scores indicate higher anxiety levels [29]. Moreover, fear of cancer recurrence was assessed using the QOL-CS questionnaire to measure the concerns of cancer survivors about recurrence from various aspects. Each item was scored from 0 (not at all) to 3 (very much), with higher scores indicating greater fear of cancer recurrence [30]. Illness perception was assessed using the BIPQ to measure the perceptions and attitudes of patients toward the disease. The BIPQ consists of nine items that are each scored on a scale of 0–10, with higher scores indicating stronger negative perceptions of the disease [31]. The scores for each item are summed to calculate the overall illness perception score, with higher scores indicating stronger negative perceptions of the disease.

Study plan

The study commenced in July 2023. Following participant enrollment and discussions among the research team, 11 survey instruments were used to comprehensively collect baseline data in the first year. Subsequent follow-up surveys are scheduled annually, with the scope and items to be determined based on an analysis of the first year's results.

Data management

The data were collected by well-trained nurses who directly interacted with the participants to administer the survey. The nurses provided detailed explanations of the survey questions and content to ensure that the participants responded completely and accurately. Each participant was assigned a unique research identification number to anonymize the data. These identifiers were used to enter data into a de-identified database, thereby protecting personal information and maintaining privacy.

The collected data were reviewed and validated monthly. To enhance the accuracy and completeness, an automated system was employed to identify and correct out-of-range values, missing fields, and input errors, ensuring the integrity of the data. Monthly meetings were held with all researchers to discuss issues arising during data collection and seek solutions, facilitating protocol adherence and continuous improvement.

Access to the database was strictly controlled; the analytical database was encrypted and restricted to essential members of the research team. These procedures were established to maintain high standards of data integrity, privacy, and security while promoting continual protocol compliance and improvement through regular oversight and discussions.

Data linkage

This study initially collected baseline data through annual surveys over the first four years. From the fifth year onwards, we will conduct a long-term follow-up study by linking secondary data sources, including the cancer registry, National Health Insurance Service (NHIS), and mortality data from Statistics Korea. This approach will facilitate a systematic analysis of cancer incidence, secondary cancers, the onset of other diseases, and causes of mortality among participants.

Pseudonymized data were used to ensure the protection of personal information. Data linkage will be performed securely and reliably through a pseudonym information integration system provided by the NHIS, Health Insurance Review and Assessment Service, and Korea Health Industry Development Institute.

The linked data will be utilized for various analyses, including the tracking of cancer incidence, analysis of mortality causes, examination of secondary cancer occurrences, and investigation of comorbid chronic diseases.

Ethics and dissemination

The protocol for this study has been approved by the Institutional Review Boards of each participating institution, which have taken responsibility for supervising all aspects of the study. All participants who agree to take part in the study will sign an informed consent form. The study protocol has been registered with the Clinical Research Information Service (CRIS) in Korea, and the study results will be presented at both national and international conferences. The research data will be linked with related institutions and deposited at the National Cancer Data Center. Personal identifiable information will be encrypted and stored separately from other research data.

DISCUSSION

Most studies on hereditary cancer have been conducted in Western populations, with only small-scale studies focusing on Korean populations [32]. Previous multi-ethnic Asian cohort studies involving 1056 patients with suspected hereditary breast cancer have provided insight into the prevalence of genetic variants across various Asian ethnicities, including Chinese, Malay, Indian, and Middle Eastern populations [33]. These studies highlighted the genetic diversity and risk variations among these groups and demonstrated the feasibility and effectiveness of guideline-based panel testing in Asians with suspected hereditary breast cancer. *BRCA1/2* and multi-gene panel tests have been covered by health insurance since 2018 in Japan [34]. However, there remains a need for medical staff and patient education to improve access to genetic testing and counseling. Risk-reducing mastectomy and bilateral salpingo-oophorectomy are performed at rates of 19.3% and 24.1%, respectively in Japan, with many institutions considering their introduction. These studies emphasize the specific needs for and genetic diversity in the management of hereditary cancers across various Asian populations. Furthermore, they demonstrate the need for tailored genetic testing panels, comprehensive risk assessments, and development of region-specific guidelines for effective management and prevention strategies.

Research on Korean populations is insufficient compared to Western studies, and Korea lacks integrated management of patients with hereditary cancer [35]. Some variability has been observed in the risk assessment for secondary cancers, preventive surgeries, and screening recommendations across medical institutions. Additionally, there is a need for comprehensive studies on genetic testing and management of families.

Our study aims to establish a cohort of patients with hereditary cancer in Korea by collecting substantial data to address the unmet healthcare needs of these patients. This will enable tailored medical interventions and support services that consider the genetic, environmental, and cultural characteristics of the Korean population.

This study has some limitations. First, the participating hospitals are concentrated in metropolitan areas. This limits the collection of data from patients with hereditary cancer who reside in rural areas. This restriction reduces the external validity of the study and increases the risk of overlooking important information related to characteristics of hereditary cancers in patients residing in rural areas. Second, the accuracy of the survey data has limitations. Respondents may not accurately report their health status or may rely on memory when answering questions about comorbidities or family histories, leading to a recall bias that can undermine the reliability of the study results. Therefore, it is essential to use objective data sources, such as electronic medical records, and to collect data through multiple verification processes to enhance data reliability.

This study aims to elucidate the practical issues and challenges faced by Koreans during the diagnosis and treatment of hereditary cancer. We formed three cohorts: patients with PV, VUS, and negative variants. We aim to identify the specific needs of each variant group and propose a comprehensive care plan. This approach will support genetic counseling and testing accessibility, communication with healthcare providers, psychological support, and decision-making regarding treatment and preventive measures.

Our study will contribute to a better understanding of the genetic and environmental factors involved in hereditary cancers. The collection of survey data from participants will provide insights into their health behaviors, QoL, and unmet needs, and elucidate differences among the cohorts. We will also collect genomic data and biospecimens to secure samples for future research and develop a variant risk assessment model using pathogenic variant prediction. This will further reveal the factors influencing the onset and progression of hereditary cancers and facilitate the development of personalized treatment and prevention strategies.

Finally, establishing a cohort of Korean patients with hereditary cancer will lead to further research in the field of hereditary cancer in Korea. This will consequently address the specific medical needs of this population. Moreover, our findings will highlight the importance of equitable healthcare access and

support for the development of medical and health policies aimed at ensuring a healthy life for all individuals.

Author contributions

JKK drafted the manuscript. MAJ, JEP, DJW, JSH, KBK, BYP, and SYK contributed to the study design and conception, as well as the overall study planning. JKK, BYP, and SYK critically revised the manuscript and prepared the final version. All authors contributed to the revision of the manuscript and approved the final version for submission.

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Competing interests

None declared.

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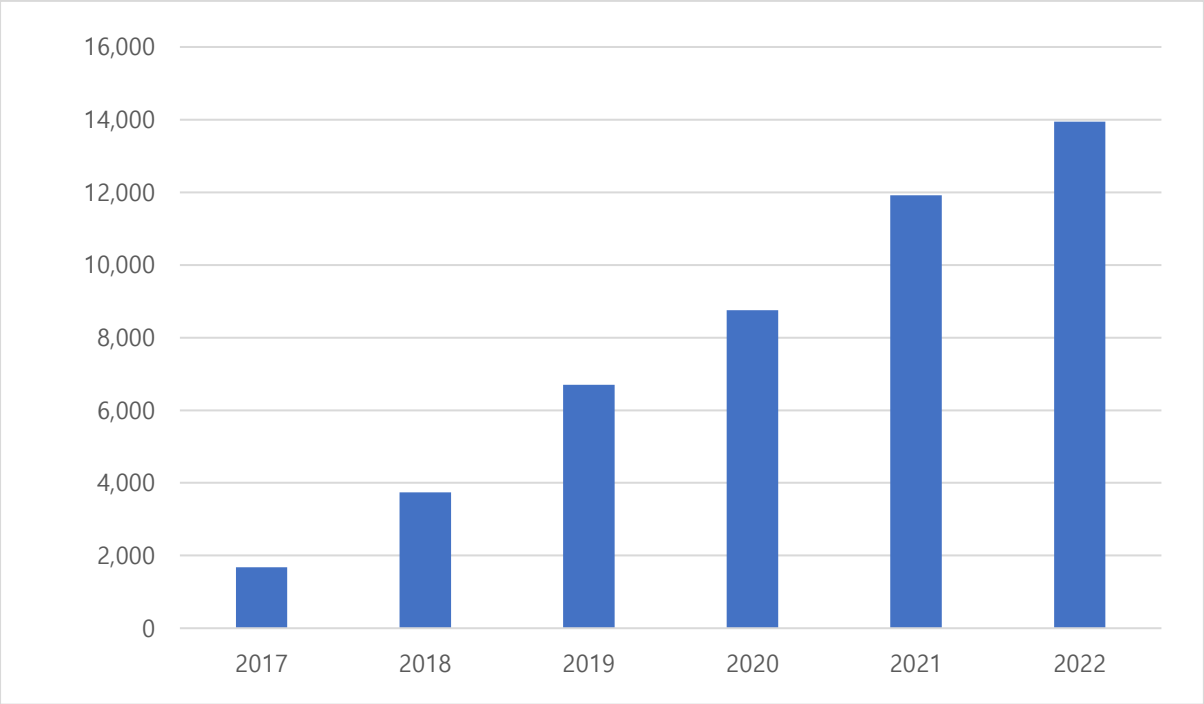
FIGURE LEGENDS

Figure 1. **Trends in hereditary cancer diagnostic testing in Korea from 2017 to 2022.** The data for this figure were sourced from the Health Insurance Review and Assessment Service Big Data Open Portal. It illustrates the increase in the number of next-generation sequencing-based genetic panel tests conducted annually to diagnose hereditary diseases in Korea.

Figure 2. Establishing a protocol logic for the hereditary cancer cohort.



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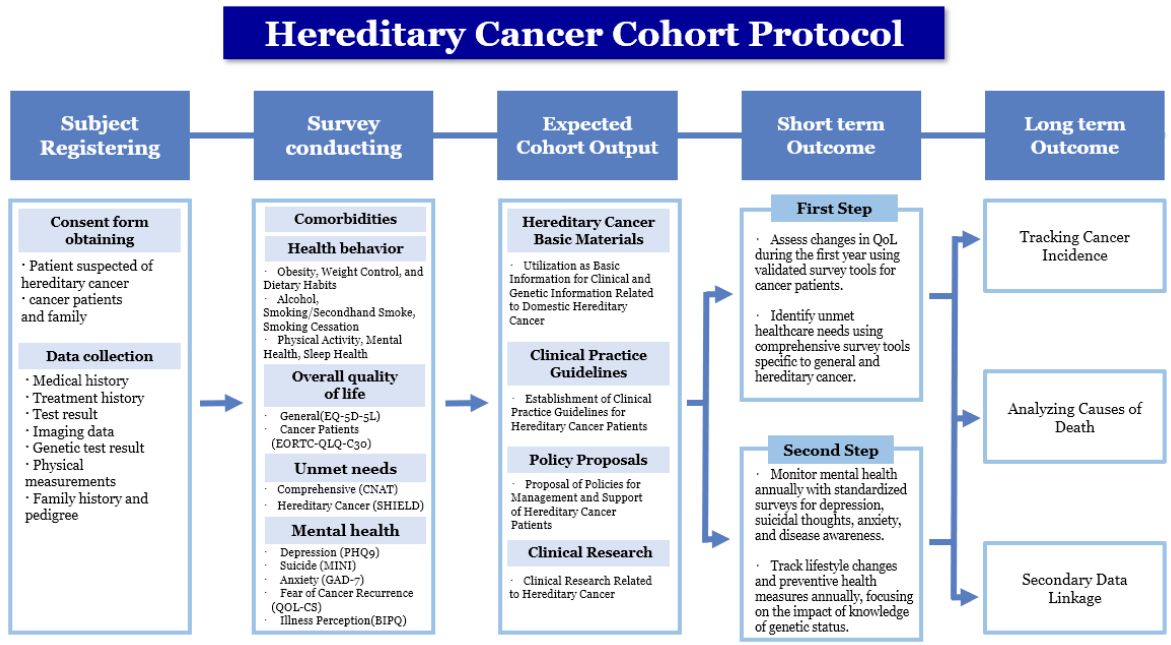

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Korean patients with hereditary cancer: A prospective multicenter cohort study protocol exploring psychosocial and health outcomes

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

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ABSTRACT

Introduction

Although genetic testing for hereditary cancers is increasing, data on health attitudes based on genetic pathogenicity are limited. This cohort study aims to establish three sub-cohorts based on genetic testing results to assess the health impact of genetic variations. This study evaluates changes in participant quality of life, unmet needs, and mental health over time based on their genetic variant status.

Methods and analysis

This prospective cohort study will recruit 1,435 patients with suspected hereditary cancer who have undergone *BRCA1/2* or next-generation sequencing (NGS) testing. The study began in July 2023 and will continue until December 2027. By 2026, participants will be surveyed up to four times annually during their outpatient visits. The survey consists of 342 items across five domains: comorbidities (96), health behaviors (80), quality of life (QoL) (41), unmet needs (75), and mental health (50). Data were collected using 11 validated surveys. In addition, information on the chronic diseases, cancer diagnoses, medical history, and treatment history of participants will be extracted from their electronic medical records to analyze their health status and cancer treatment experiences. Genetic variant data from *BRCA1/2* and NGS will be used to classify participants into three sub-cohorts: pathogenic variants, variants of uncertain significance, and undetectable mutations. A three-generation pedigree that includes details such as the year of cancer diagnosis, age at diagnosis, cancer type, survival status of family members, and age at death will be constructed for each participant. the collected data will be linked to secondary sources such as cancer registries and National Health Insurance Service data to provide a comprehensive analysis of the impact of hereditary cancer on health and survival.

Ethics and dissemination

The study protocol was approved by all the Ethics Committees: the National Cancer Center IRB (NCC2023-0179), the Samsung Medical Center IRB (SMC2023-09-057), the Yonsei University Health System, Severance Hospital IRB (4-2023-0627), the Hanyang University Guri Hospital IRB (GURI2023-08-021), and the Keimyung University IRB (DSMC IRB 2024-05-048). The study

outcomes will be disseminated through conference presentations, peer-reviewed publications, and social media.

Trial registration number KCT0009460

Keywords: Genetic testing, Genetic predisposition to disease, Genetic variation, High-throughput nucleotide sequencing, Health behavior

STRENGTHS AND LIMITATIONS OF THE STUDY

1. The Korean hereditary cancer cohort study is a large-scale multicenter study conducted at five major university hospitals in Korea, targeting 1,435 patients.

2. The study is designed to track participants through annual surveys over five years, analyzing long-term health outcomes, changes in quality of life, and unmet healthcare needs based on genetic variant status. This will help understand the evolving healthcare needs of hereditary cancer patients.

3. Participants are classified into three sub-cohorts based on pathogenic variants(PV), variants of uncertain significance (VUS), and undetectable variants(ND), allowing for a precise analysis of differences in health outcomes according to genetic status.

4. The participating hospitals are concentrated in metropolitan areas, the study does not include patients from rural regions, which may limit the external validity of the results.

5. There may be challenges in achieving statistical significance when analyzing smaller subgroups with rarer genetic mutations or specific conditions.

INTRODUCTION

The diagnosis of hereditary cancers has steadily increased, primarily owing to the introduction of *BRCA1/2* genetic testing and advancements in next-generation sequencing (NGS) [1-3] (Figure 1). Hereditary cancers account for 5–10% of all cancer cases and are mostly inherited in an autosomal-dominant manner [4]. This often results in the sharing of identical genetic variants among family members, which significantly affects familial health management.

Hereditary cancers generally occur at a younger age and pose a higher cancer risk compared to sporadic cancers. Individuals with pathogenic variants (PV) in the *BRCA1* and *BRCA2* genes have a 65–80% and 45–85% risk of developing breast cancer, respectively, and a 37–62% and 11–23% risk of developing ovarian cancer, respectively [5]. However, the genetic variants that cause hereditary cancer are often unidentifiable during genetic testing on individuals suspected of hereditary cancer. Variants of uncertain significance (VUS) are detected in many cases. A VUS is defined as a genetic variant for which the association with the disease has not been clearly established. Current scientific knowledge and available data cannot classify these variants as pathogenic or benign. Additionally, no known mutations or variants have been identified in some cases [6, 7].

Uncertainty and confusion regarding various genetic test results and their management can lead to severe psychological stress in patients with hereditary cancer, including anxiety, depression, and fear of cancer recurrence [8]. In addition, sharing genetic information with family members can cause tensions and conflicts within families. Moreover, the lack of genetic counseling makes it difficult for individuals to make informed decisions regarding health management and preventive measures [9]. Living with the risk of hereditary cancer has long-term effects, including continuous health surveillance, lifestyle adjustments, and the possibility of preventive surgeries, which substantially affect the overall quality of life in patients and family members who share genetic components [10]. In addition, clinical management becomes ambiguous when a personal or family history of hereditary cancer is suspected but an uncertain variant is detected [11]. Given the limited research on uncertain variants, it is necessary

to conduct additional data analyses on these variants [12]. To enhance clinical studies targeting hereditary cancer, it is essential to prioritize patients with detailed family histories, including pedigrees, and to incorporate a broad range of pathogenic genetic variants [13]. Establishing cohorts that include patients with VUS or inconclusive test results can provide valuable control groups and aid in the consistent interpretation of genetic findings [14].

Existing research on hereditary cancer patients has primarily focused on White women, neglecting the diverse racial and cultural contexts of patients worldwide [15-17]. Studies involving Asian populations are relatively rare, and large-scale investigations targeting Koreans are almost non-existent [18, 19]. 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.

Despite the rapid increase in hereditary cancer, the exact number of hereditary cancers is small. Thus, it is essential to establish a multi-institutional cohort to collect substantial data and systematically study the health problems of patients with hereditary cancer and those who are suspected to have hereditary cancer without established causative variants. Previous studies have highlighted the unmet needs of healthcare providers concerning hereditary cancers, including the lack of clinical guidelines, need for reduced testing costs, and necessity for additional testing for undiagnosed hereditary cancers [20]. The provision of tailored healthcare may address unmet healthcare needs, improve health outcomes, and enhance quality of life. Therefore, the present study aimed to identify long-term health impacts of genetic variations. This study further aimed to evaluate changes in quality of life, unmet needs, and mental health according to genetic variant status to promote health improvement and quality of life. This approach will also support the development and validation of personalized healthcare technologies.

METHODS AND ANALYSIS

Study aim

In this study, we established a prospective cohort of Korean patients with hereditary cancer (Table 1). Three sub-cohorts will be formed based on the genetic test variant results: patients with PV, VUS, and no detectable mutations (ND).

Table 1 Project research question and hypotheses

Questions	Hypotheses
How do the long-term health impacts differ among patients with hereditary cancer characterized by pathogenic variants (PV), variants of uncertain significance (VUS), and undetected (ND) variants?	Patients with PV will experience higher cancer incidence rates and more health complications over the long term than those with VUS and ND variants.
What is the relationship between genetic variant status and changes in quality of life among patients with hereditary cancer over time?	Patients with PV will experience greater stress and anxiety than those with VUS and ND variants, leading to a more considerable decline in quality of life scores over time.
How do unmet healthcare needs and mental health outcomes differ based on genetic variant status in patients with hereditary cancer?	Patients with PV will require more healthcare services and psychological support, and will have higher rates of mental health issues, such as anxiety and depression, than those with VUS and ND variants.

Study design

This study is a prospective multicenter cohort study conducted in five hospitals: National Cancer Center, Samsung Medical Center, Severance Hospital, Hanyang University Guri Hospital, Keimyung University Dongsan Hospital. The research protocols are as follows (Figure 2):

1. **Participant registration**: Researchers at each participating institutions explained the study objective, research procedures and methods, potential risks and discomfort associated with participation, and the right of patients suspected of having hereditary cancer to voluntarily withdraw from the study at any time. Informed consent was obtained from the participants for study participation and the use of human biological materials. Relevant data, including family history, clinical data, genetic test results, and blood samples are collected after enrolling the participants. Blood samples stored in the Department of Laboratory Medicine were collected

as specified in the informed consent form. Specifically, residual blood samples of at least 4 mL in EDTA bottles were collected. Next, plasma and buffy coat were separated and stored at -80 °C. These residual blood samples were used to identify the risk factors and prognostic predictors of hereditary cancer.

2. **Survey:** The survey is conducted over a five-year period, with four annual follow-up surveys after the baseline. The survey consists of 342 items across five domains: comorbidities, health behaviors, quality of life, unmet needs, and mental health.
3. **Expected cohort output:** The data collected in this study will provide foundational information for clinical and genetic research on hereditary cancers in Korea. These data will help establish clinical guidelines for patients with hereditary cancer, propose policies for patient management and support, and promote clinical advancements through detailed and practical clinical research on hereditary cancer.
4. **Short-term outcome:** The short-term goals of this study are to evaluate changes in QoL, identify unmet needs, and assess mental health and health behaviors. QoL encompasses the overall patient well-being, including physical, mental, and social health. Unmet needs refer to the demands of patients not currently met by existing healthcare services. Survey tools validated for patients with cancer are used to evaluate how the QoL of the participants changes. Baseline QoL scores and changes will be analyzed at each follow-up.

   Additionally, the study annually tracks changes in participant mental health by evaluating depression, suicidal thoughts, anxiety, fear of cancer recurrence, and disease awareness using standardized survey tools. It also analyzes how knowledge of genetic status affects lifestyle choices and preventive health measures through the annual monitoring of health behaviors. Unmet needs are assessed using comprehensive survey tools designed to capture general and hereditary cancer-specific requirements, helping identify the most common unmet needs among patients.

5. **Long-term outcome:** The long-term objectives of this study are as follows: 1) To track cancer incidence and analyze causes of death. This will involve the monitoring of new cancer cases and systematic analysis of the causes of death through annual follow-ups, including medical records, self-reports, and official death records; 2) We use secondary data linkages to track cancer incidence and analyze the causes of death. This involves utilizing the system of data integration established by authorized institutions to protect personal information and link secondary data sources, such as the cancer registry and National Health Insurance Service data. This approach aims to obtain more accurate and comprehensive data on cancer incidence and causes of death.

Inclusion criteria

The high risk of cancer among patients with suspected hereditary cancer is attributed to genetic factors, such as family history, age at cancer onset, and the occurrence of specific cancer types in multiple family members [21, 22].

According to the 2012 National Health Insurance (NHI) coverage guidelines in Korea, *BRCA1/2* pathogenic variant testing is recommended for patients with breast cancer and ovarian cancer who meet the following criteria: a family history of breast or ovarian cancer within second-degree relatives, early onset breast cancer (diagnosed at age ≤ 40 years), bilateral breast cancer, concurrent breast and ovarian cancer, male breast cancer, or multiple primary cancers. The NHI coverage guidelines revised in 2020 further recommended *BRCA1/2* pathogenic variant testing for patients with breast cancer with a family history of the disease, ovarian cancer, male breast cancer, metastatic prostate cancer, or pancreatic cancer within third-degree relatives; early-onset breast cancer (diagnosed at age ≤ 40 years); triple-negative breast cancer diagnosed at age ≤ 60 years; bilateral breast cancer; concurrent breast cancer with ovarian or pancreatic cancer; male breast cancer; or epithelial ovarian cancer (including fallopian tube and primary peritoneal cancer), excluding histologically pure mucinous ovarian cancer.

Additionally, NGS has been conditionally covered with 50% co-payment since March 2017, and the co-payment rate increased to 80% in December 2023.

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 [23]. 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.

Study population estimate

The extent to which patient-centered decision-making is implemented in clinical settings in South Korea remains largely understudied. Consequently, evidence on this topic often relies on international literature. A study conducted at a tertiary university hospital in South Korea reported that 37.4% of orthopedic patients engaged in patient-centered decision making. Additionally, a national survey of the general population indicated that 33.5–44.3% of individuals prefer shared decision-making between patients and healthcare providers [24].

In this study, we hypothesized that the rate of patient-centered decision-making without intervention would be approximately 30%. We further assumed that using a tailored decision-making tool would increase this rate by 10%, increasing it to a total of 40%. A two-proportion test with a significance level (α) of 5% and a power (1-β) of 85% was performed based on these assumptions. The required sample size was calculated to be 405 patients in each group. When the power was set to 80%, the required sample size was 354 patients per group, resulting in a total of 708 patients.

Considering an estimated dropout rate of 20% and the fact that the number of patients with PV was expected to be lower than that of those with VUS or negative variants, the target sample size was adjusted. The final target sample size was set at 1,435 patients to ensure equal enrollment of patients with PV and those with VUS or negative variants. Sample size estimation was conducted to establish a cohort of Korean patients with hereditary cancer.

Data collection items

This study collected clinical, survey, genetic variant, and pedigree data from the participants.

1. **Clinical data**: Clinical data were directly extracted by researchers with access to electronic medical records. These data included histories of chronic diseases (e.g., hypertension, diabetes, and heart disease), cancer diagnosis (year of diagnosis, age at diagnosis, and type and stage of cancer), and surgeries related to cancer treatment (date of surgery, type, and outcome). Treatment history included the current and past types, duration, and outcomes of anticancer therapies (chemotherapy, radiotherapy, and hormone therapy), including related side effects and complications. The test results include health assessment outcomes, such as general blood tests, cancer marker tests, ECGs, and pulmonary function tests. Imaging data include the results and interpretations of imaging tests conducted during cancer diagnosis and treatment, such as CT, MRI, PET, and ultrasonography. Anthropometric data include patient

weight, height, BMI, and other measurements. Obstetric, menstrual, breastfeeding, and hormone use histories are also included for female patients.

2. **Surveys:** The surveys were designed to be completed within 20 minutes to facilitate ease of response for the participants and were structured to be administered as interviewer-administered questionnaires. The survey tools were tailored to different time points: at the time of cancer diagnosis; during treatment (typically four months post-diagnosis); and at 1-, 2-, 3-, and 4-year intervals post-diagnosis. These surveys collect detailed information on lifestyle factors, environmental exposures, and other health-related data.
3. **Genetic variants:** Genetic mutation data were obtained using *BRCA1/2* or NGS panel testing (S1 table). Based on these results, patients were classified into three sub-cohorts: PV, VUS, and ND.
4. **Family history and pedigree:** Pedigree data were collected by the participants after they were educated on how to construct a pedigree chart encompassing three generations. This includes information on the years of cancer diagnosis, age at diagnosis, and type of cancer among family members, as well as whether the family member is deceased and their age at death. This structured approach ensures comprehensive data collection and analysis suitable for the research objectives.
5. **Biospecimen collection**: Biological samples are collected from the blood of participants in accordance with protocols outlined in the informed consent documentation, with storage facilitated by the Department of Laboratory Medicine. Specifically, we use residual blood samples collected following clinical blood collection. A minimum of 4 mL of residual blood is collected in EDTA tubes. Post-collection, the plasma and buffy coat are separated and stored in an ultra-low temperature freezer at -80 °C. These residual blood samples will be used to identify risk factors and prognostic predictors associated with hereditary cancer. This approach is integral for improving the accuracy of assessing genetic risk factors and clinical prognoses related to hereditary cancer.

Survey tools and data collection

Data were collected as follows: Baseline surveys are initially conducted with participants following receipt of their genetic test results. Subsequently, annual follow-up surveys will be conducted for four years from the baseline survey date. Surveys were self-administered through questionnaires or telephone interviews. Participants were provided with explanations by well-trained nurses who assisted them in completing the questionnaires or in conducting telephone surveys to record their responses.

In this study, data were collected from participants using 11 different survey tools (Table 2).

Table 2 An overview of survey questionnaire

Area	N of items	Subarea	Survey tool
Comorbidities	96	-	Korea National Health and Nutrition Examination Survey (KNHANES)
Health behavior	80	Obesity and Weight Management	
		Alcohol Consumption	
		Mental Health	
		Smoking/Secondhand Smoke/Smoking Cessation	
		Oral Health	
		Physical Activity	
		Sleep Health	
		Dietary Habits	
Quality of life	41	Quality of Life in Cancer Patients	EORTC-QLQ-C30
		General Quality of Life	EQ-5D-5L
Unmet needs	75	Comprehensive Needs Assessment	CNAT
		Hereditary Cancer Specific Needs Assessment	Development of additional items
Mental health	50	Depression	PHQ-9

	Suicide	MINI
	Anxiety	GAD-7
	Fear of Cancer Recurrence	QOL-CS
	Disease Awareness	BIPQ

1. **Comorbidities:** The current medical diagnostic status of the study participants was recorded using the Korea National Health and Nutrition Examination Survey [25]. Major chronic conditions included hypertension, diabetes, cardiovascular diseases. In addition, the presence of malignant tumors such as gastric cancer, liver cancer, colorectal cancer, and other conditions was noted. Detailed information on comorbidities, including age at diagnosis and current treatment status, was collected to comprehensively assess the health status of participants and to analyze the occurrence and treatment status of comorbidities.

2. **Health behaviors:** The Korea National Health and Nutrition Examination Survey consists of eight detailed items for evaluating health-related behaviors [25, 26]. 1) Obesity and weight management were assessed using self-reported weight changes and weight management methods over the previous year. 2) Alcohol consumption was evaluated by measuring the frequency and quantity of alcohol consumption to assess the health risk factors related to alcohol consumption. 3) General mental health status was assessed using standardized questions. 4) Smoking status, passive smoking exposure, as well as cessation attempts and intention were evaluated to assess smoking-related health risks. 5) Oral health status was assessed through self-reporting of dental hygiene habits and oral health problems. 6) Physical activity was assessed by measuring the frequency, duration, and intensity of physical activity. 7) Sleep health was assessed by evaluating sleep duration, quality, and disturbances to identify sleep-related issues. 8) Finally, dietary habits were evaluated by assessing the frequency and diversity of food intake. A comprehensive

evaluation of individual health habits and lifestyles was conducted through responses to each item used as foundational data for health promotion.

3. **Quality of Life**: The general and cancer-specific QoL were assessed using the EQ-5D-5L questionnaire to measure five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety or depression [27]. Each dimension was evaluated on a 5-point scale scored from 1 (no problem) to 5 (severe problem). The responses were subsequently combined to express a 5-digit number representing health status. This facilitated a comprehensive assessment of general QoL levels. The QoL of patients with cancer was assessed using the EORTC-QLQ-C30, which consists of functional (physical, role, emotional, cognitive, and social functioning), symptom (fatigue, nausea, vomiting, pain, dyspnea, insomnia, loss of appetite, constipation, diarrhea, and financial difficulties), an overall health status, and single-item scales [28]. Each item was evaluated on a Likert scale ranging from 1 (not at all) to 4 (very much), with higher scores indicating better functional status and worse symptom burden.

4. **Unmet needs:** This assessment comprised comprehensive and hereditary cancer-specific needs. Comprehensive needs were assessed using the CNAT to evaluate the following subdomains: information and education, psychological issues, medical staff, physical symptoms, hospital facilities and services, family/interpersonal issues, religious/spiritual issues, and social support [29]. Each item was rated from 0 (not at all needed) to 3 (extremely needed). Specific needs related to hereditary cancer were assessed using the Study for HeredItary questionnaire Development (SHIELD) questionnaire developed by the research team, with a focus on information and education, psychological issues, medical services, and social support [30]. Each item was rated on a scale of 0 (not at all needed) to 3 (extremely needed). Scores for each item were calculated to determine the level of need, with higher scores indicating a greater need.

5. **Mental health:** This evaluation comprises five detailed areas: depression, suicide risk, anxiety, fear of cancer recurrence, and illness perception. The depression domain was assessed using the PHQ-9 to evaluate nine depressive symptoms, with each item scored from 0 (not at all) to 3 (nearly every day). This yielded a total score of 0–27, with higher scores indicating higher levels of depression [31]. Furthermore, suicide risk was assessed using the MINI questionnaire to evaluate the suicide risk levels of respondents based on their thoughts, plans, and attempts. Each item was scored as yes (1 point) or no (0 points) [32]. The anxiety domain was assessed using the GAD-7 questionnaire to evaluate seven anxiety symptoms. Each item was scored from 0 (not at all) to 3 (nearly every day), yielding a total score of 0–21; higher scores indicate higher anxiety levels [33]. Moreover, fear of cancer recurrence was assessed using the QOL-CS questionnaire to measure the concerns of cancer survivors about recurrence from various aspects. Each item was scored from 0 (not at all) to 3 (very much), with higher scores indicating greater fear of cancer recurrence [34]. Illness perception was assessed using the BIPQ to measure the perceptions and attitudes of patients toward the disease. The BIPQ consists of nine items that are each scored on a scale of 0–10, with higher scores indicating stronger negative perceptions of the disease [35]. The scores for each item are summed to calculate the overall illness perception score, with higher scores indicating stronger negative perceptions of the disease.

Study plan

The study commenced in July 2023. Following participant enrollment and discussions among the research team, 11 survey instruments were used to comprehensively collect baseline data in the first year. Subsequent follow-up surveys are scheduled annually, with the scope and items to be determined based on an analysis of the first year's results.

Data management

The data were collected by well-trained nurses who directly interacted with the participants to administer the survey. The nurses provided detailed explanations of the survey questions and content to ensure that the participants responded completely and accurately. Each participant was assigned a unique research identification number to anonymize the data. These identifiers were used to enter data into a de-identified database, thereby protecting personal information and maintaining privacy.

The collected data were reviewed and validated monthly. To enhance the accuracy and completeness, an automated system was employed to identify and correct out-of-range values, missing fields, and input errors, ensuring the integrity of the data. Monthly meetings were held with all researchers to discuss issues arising during data collection and seek solutions, facilitating protocol adherence and continuous improvement.

Access to the database was strictly controlled; the analytical database was encrypted and restricted to essential members of the research team. These procedures were established to maintain high standards of data integrity, privacy, and security while promoting continual protocol compliance and improvement through regular oversight and discussions.

Data linkage

This study initially collected baseline data through annual surveys over the first four years. From the fifth year onwards, we will conduct a long-term follow-up study by linking secondary data sources, including the cancer registry, National Health Insurance Service (NHIS), and mortality data from Statistics Korea. This approach will facilitate a systematic analysis of cancer incidence, secondary cancers, the onset of other diseases, and causes of mortality among participants.

Pseudonymized data were used to ensure the protection of personal information. Data linkage will be performed securely and reliably through a pseudonym information integration system provided by the

NHIS, Health Insurance Review and Assessment Service, and Korea Health Industry Development Institute.

The linked data will be utilized for various analyses, including the tracking of cancer incidence, analysis of mortality causes, examination of secondary cancer occurrences, and investigation of comorbid chronic diseases.

Patient and public involvement

Our study aims to integrate the needs of hereditary cancer patients into the research process and effectively disseminate research findings to them. By collaborating with patient representatives, we seek to actively incorporate the perspectives of both patients and the general public, ensuring that the study is designed and conducted in alignment with their real-world needs and interests.

In this study, we will collect survey data on the health behaviors, quality of life, unmet medical needs, and mental health of hereditary cancer patients. Based on this data and feedback from patient representatives, we aim to identify additional research questions that reflect patient experiences and perspectives. This approach will help ensure that the study addresses the actual needs of patients and generates meaningful and practical results.We plan to invite groups of hereditary cancer patients to share the study findings and evaluate how they interpret and perceive the results. This process will allow us to refine the findings and present them in a way that is easily understandable to a broader audience.

We will further collaborate with patient representatives to develop strategies for effectively disseminating research output, ensuring that the plain language summary is clear and accessible to all.

Ethics and dissemination

The study protocol has been approved by the Ethics Committees of the participating institutions: the National Cancer Center Institutional Review Board(IRB) (NCC2023-0179), the Samsung Medical Center IRB (SMC2023-09-057), the Yonsei University Health System, Severance Hospital IRB (4-2023-0627), the Hanyang University Guri Hospital IRB (GURI2023-08-021), and the Keimyung University IRB (DSMC IRB 2024-05-048). Each IRB is responsible for overseeing all aspects of the study to ensure compliance with ethical standards. All participants who agree to take part in the study will sign an informed consent form. The study protocol has been registered with the Clinical Research Information Service (CRIS) in Korea under the registration number KCT0009460, and the study results will be presented at both national and international conferences. The research data will be linked with related institutions and deposited at the National Cancer Data Center. Personal identifiable information will be encrypted and stored separately from other research data.

DISCUSSION

Most studies on hereditary cancer have been conducted in Western populations, with only small-scale studies focusing on Korean populations [36]. Previous multi-ethnic Asian cohort studies involving 1056 patients with suspected hereditary breast cancer have provided insight into the prevalence of genetic variants across various Asian ethnicities, including Chinese, Malay, Indian, and Middle Eastern populations [37]. These studies highlighted the genetic diversity and risk variations among these groups and demonstrated the feasibility and effectiveness of guideline-based panel testing in Asians with suspected hereditary breast cancer. *BRCA1/2* and multi-gene panel tests have been covered by health insurance since 2018 in Japan [38]. However, there remains a need for medical staff and patient education to improve access to genetic testing and counseling. Risk-reducing mastectomy and bilateral salpingo-oophorectomy are performed at rates of 19.3% and 24.1%, respectively in Japan, with many institutions considering their introduction. These studies emphasize the specific needs for and genetic diversity in the management of hereditary cancers across various Asian populations. Furthermore, they demonstrate the need for tailored genetic testing panels, comprehensive risk assessments, and development of region-specific guidelines for effective management and prevention strategies.

Research on Korean populations is insufficient compared to Western studies, and Korea lacks integrated management of patients with hereditary cancer [39]. Some variability has been observed in the risk assessment for secondary cancers, preventive surgeries, and screening recommendations across medical institutions. Additionally, there is a need for comprehensive studies on genetic testing and management of families.

Korean guidelines for *BRCA* mutation carriers include screening recommendations for breast and ovarian cancers in women and breast and prostate cancers in men [40]. 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 [41]. 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 (S2 Table) [42].

Our study aims to establish a cohort of patients with hereditary cancer in Korea by collecting substantial data to address the unmet healthcare needs of these patients. This will enable tailored medical interventions and support services that consider the genetic, environmental, and cultural characteristics of the Korean population.

This study has some limitations. First, the participating hospitals are concentrated in metropolitan areas. This limits the collection of data from patients with hereditary cancer who reside in rural areas. This restriction reduces the external validity of the study and increases the risk of overlooking important information related to characteristics of hereditary cancers in patients residing in rural areas. Second, the accuracy of the survey data has limitations. Respondents may not accurately report their health status or may rely on memory when answering questions about comorbidities or family histories, leading to a recall bias that can undermine the reliability of the study results. Therefore, it is essential to use objective data sources, such as electronic medical records, and to collect data through multiple verification processes to enhance data reliability.

This study aims to elucidate the practical issues and challenges faced by Koreans during the diagnosis and treatment of hereditary cancer. We formed three cohorts: patients with PV, VUS, and negative variants. We aim to identify the specific needs of each variant group and propose a comprehensive care plan. This approach will support genetic counseling and testing accessibility, communication with

healthcare providers, psychological support, and decision-making regarding treatment and preventive measures.

Our study will contribute to a better understanding of the genetic and environmental factors involved in hereditary cancers. The collection of survey data from participants will provide insights into their health behaviors, QoL, and unmet needs, and elucidate differences among the cohorts. We will also collect genomic data and biospecimens to secure samples for future research and develop a variant risk assessment model using pathogenic variant prediction. This will further reveal the factors influencing the onset and progression of hereditary cancers and facilitate the development of personalized treatment and prevention strategies.

Finally, establishing a cohort of Korean patients with hereditary cancer will lead to further research in the field of hereditary cancer in Korea. This will consequently address the specific medical needs of this population. Moreover, our findings will highlight the importance of equitable healthcare access and support for the development of medical and health policies aimed at ensuring a healthy life for all individuals.

Author contributions

JKK drafted the manuscript. MAJ, JEP, DJW, JSH, KBK, BYP, and SYK contributed to the study design and conception, as well as the overall study planning. JKK, BYP, and SYK critically revised the manuscript and prepared the final version. All authors contributed to the revision of the manuscript and approved the final version for submission. SYK is responsible for the overall content as guarantor.

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Competing interests

None declared.

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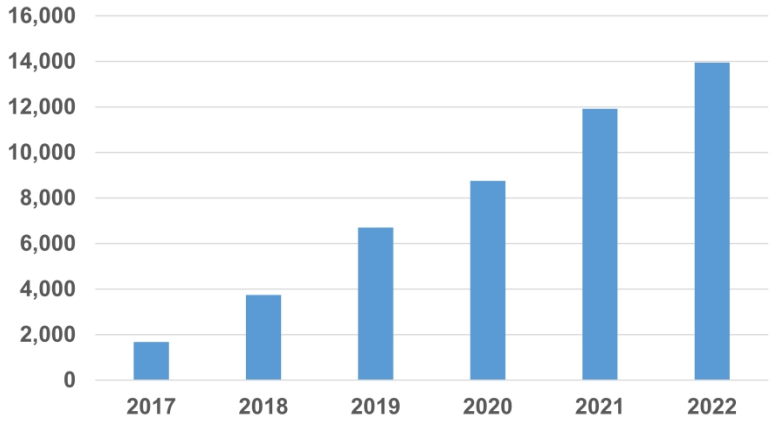
FIGURE LEGENDS

Figure 1. **Trends in hereditary cancer diagnostic testing in Korea from 2017 to 2022.** The data for this figure were sourced from the Health Insurance Review and Assessment Service Big Data Open Portal. It illustrates the increase in the number of next-generation sequencing-based genetic panel tests conducted annually to diagnose hereditary diseases in Korea.

Figure 2. Establishing a protocol logic for the hereditary cancer cohort.



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219x120mm (600 x 600 DPI)

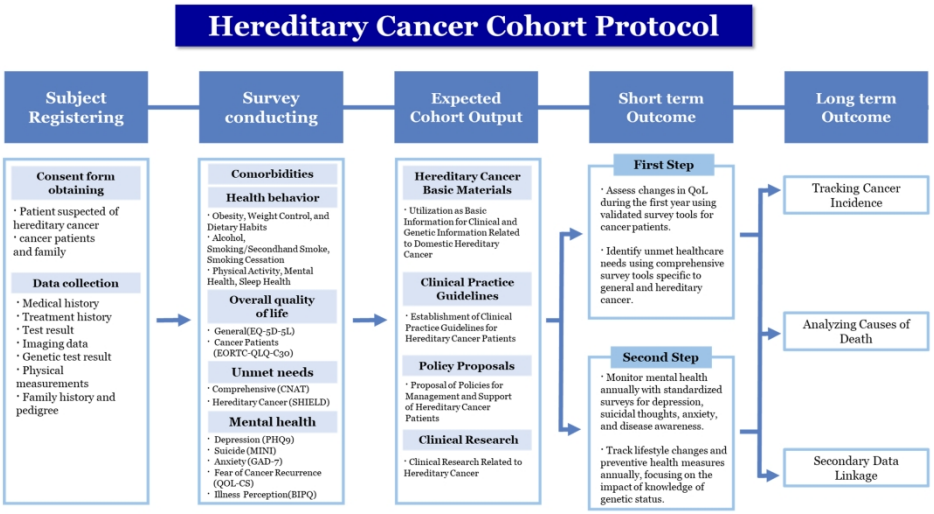

Figure 2. Establishing a protocol logic for the hereditary cancer cohort.

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Table S1. Gene lists included in next-generation sequencing (NGS) hereditary cancer panel

Panel	Updated date	Genes
Hereditary NGS panel (23 genes)	2018.02	*APC, ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, EPCAM, MEN1, MLH1, MSH2, MSH6, MUTYH, NBN, PALB2, PMS2, PTEN, RAD50, RAD51C, RET, STK11, TP53*
Hereditary NGS panel (25 genes)	2018.10	*APC, ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, EPCAM, MEN1, MLH1, MSH2, MSH6, MUTYH, NBN, PALB2, PMS2, PTEN, RAD50, RAD51C, RET, STK11, TP53, NF1, RAD51D*
Hereditary NGS panel (28 genes)	2019.11	*APC, ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, EPCAM, MEN1, MLH1, MSH2, MSH6, MUTYH, NBN, PALB2, PMS2, PTEN, RAD50, RAD51C, RET, STK11, TP53, NF1, RAD51D, POLD1, POLE, SMAD4*
Hereditary NGS panel (73 genes)	2022.02	*APC, ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, EPCAM, MEN1, MLH1, MSH2, MSH6, MUTYH, NBN, PALB2, PMS2, PTEN, RAD50, RAD51C, RET, STK11, TP53, NF1, RAD51D, POLD1, POLE, SMAD4, BMPR1A, CDKN2A, FH, HRAS, MAX, MET, MRE11, NF2, RB1, SDH, SDHAF2, SDHB, SDHC, SDHD, TMEM127, TSC1, TSC2, VHL, WT1, AIP, AXIN2, BAP1, CDC73, CDK4, CDKN1B, CHEK1, CTNNA1, DICER1, EXT1, EXT2, FANCL, FLCN, GREM1, HOXB13, KIT, MSH3, PHL1, PPP2R2A, PTCH1, RAD51B, RAD54L, SMARCA4, SMARCB1, SUFU*

*Abbreviation: NGS, next-generation sequencing

Table S2. Comparative Guidelines for Screening and Managing BRCA Gene Mutations: Korea, US, and UK

Guidelines	Country	Breast cancer	Ovarian cancer	Other cancers	Ref
10th Korean Breast Cancer Treatment Guidelines (2023)	Korea	Female carriers -Self-examination education from age 18. -Clinical breast examination every 6 months starting at age 25. -Annual MRI screening from age 25-29. -Annual MMG and MRI from age 30-75. Male carriers -Monthly self-examination and clinical breast examination every 12 months starting at age 35 -Annual MMG from age 50 for men with gynecomastia. Management -Bilateral RRM may be considered for BRCA1/2 carriers. -Contralateral mastectomy may be considered in carriers diagnosed with breast cancer.	Screening -Transvaginal ultrasound and CA125 blood test every 6 months starting at age 30. -Ultrasound is recommended between days 1-10 of the menstrual cycle; CA125 after day 5. Management -RRSO is recommended for BRCA1/2 carriers to lower ovarian and breast cancer risk. -RRSO is recommended at age 35-40 after family planning is complete. -Timing of RRSO should be individualized based on patient discussions.	**Prostate Cancer** -DRE and PSA blood test for early detection of prostate cancer from age 18. -Following prostate cancer screening is recommended for *BRCA* carriers. **Pancreatic Cancer** -Initiate screening with EUS, followed by alternating EUS and contrast-enhanced pancreatic MRI/MRCP, or annual MRI. **Gastric Cancer** -Endoscopy every 2 years starting at age 40, or 10 years earlier than the earliest age of onset in the family if there is a family history. **Colorectal Cancer** -Colonoscopy every 5 years starting at age 40, or 10 years earlier than the earliest age of onset in the family if there is a family history.	**[40]**
NCCN (2024)	US	Female carriers -Breast awareness from age 18. -Clinical breast examination every 6-12 months starting at age 25. -Annual MRI screening from age 25-29 (MMG if MRI unavailable). -Annual MMG and MRI from age 30-75. -Individualized management after age 75. Male carriers -Breast self-exam training and annual clinical breast examination starting at age 35 - Annual MMG from age 50 or earlier depending on family history. Management - RRM may be considered based on age, life expectancy, and residual breast cancer risk.	Screening -Undescribed Management -BRCA1 carriers: RRSO recommended at age 35-40. -BRCA2 carriers: RRSO can be delayed to age 40-45 unless family history suggests earlier intervention. -Pre-surgical CA125 testing and pelvic ultrasound recommended. -Combined OCP or hormonal IUDs can be considered to reduce ovarian cancer risk for women retaining their ovaries. -HRT may be considered post-RRSO, tailored to the presence or absence of the uterus.	**Prostate Cancer** -Screening should begin at age 40. -Screening may be considered for *BRCA1* PV/LPV carriers. -Screening is recommended for *BRCA2* PV/LPV carriers. **Pancreatic Cancer** -Screening for pancreatic cancer should be considered starting at age 50, or 10 years earlier than the earliest diagnosis of exocrine pancreatic cancer in a first- or second-degree relative with a germline PV/LPV, whichever comes first. -For individuals without a family history of exocrine pancreatic cancer, pancreatic cancer screening is not recommended for PV/LPV carriers in genes other than *ATM, BRCA2, STK11*, and *CDKN2A*.	**[41]**

				Melanoma - There are no specific guidelines for melanoma; however, annual full-body skin examinations are recommended. - General melanoma risk management, such as minimizing UV exposure, is appropriate.	
NICE (updated 2023)	UK	Female carriers -MRI and MMG not recommended from age 20-29. -Annual MRI and consider annual MMG from age 30-39. -Annual MRI and MMG from age 40-49. -Annual MMG from age 50-59 (MRI only for dense breasts). -Annual MMG from age 60-69 (MRI only for dense breasts). -MMG as part of the population screening program after 70. Male carriers -Undescrbied Management -RRM available for *BRCA1* carriers, with detailed counseling on benefits and risks. Immediate or delayed breast reconstruction should be offered by specialized teams.	Screening - Serial CA125 testing every 4 months using validated algorithms - Annual consultations to discuss results and risk-reducing surgery. Management - *BRCA1* carriers: RRSO recommended after age 35. - *BRCA2* carriers: RRSO recommended after age 40. - Surgery should occur after family planning is complete. - Comprehensive discussion of benefits and risks is required. Surgery is not recommended for patients with significant comorbidities or limited life expectancy.	**Not Applicable**	**[42]**

* CA125: Cancer Antigen 125; DRE: Digital Rectal Examination; EUS: Endoscopic Ultrasound; LPV: Likely Pathogenic Variant; MMG: Mammogram; MRCP: Magnetic Resonance Cholangiopancreatography; MRI: Magnetic Resonance Imaging; NCCN: National Comprehensive Cancer Network; NICE: National Institute for Health and Care Excellence; OCP: Oral Contraceptives PV: Pathogenic Variant; RRM: Risk-Reducing Mastectomy; RRSO: Risk-Reducing Salpingo-Oophorectomy; UV: Ultraviolet

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

Kim J-K, Jang M-A, Park JE, *et al*. Korean patients with hereditary cancer: a prospective multicentre cohort study protocol exploring psychosocial and health outcomes. *BMJ Open* 2025;15:e093905. doi:10.1136/bmjopen-2024–0 93 905

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BMJ Open 2025;**15**:e093905corr1. doi:10.1136/bmjopen-2024-093905corr1