Short Communication

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Ten-Year Follow-Up of Women at High Risk for Familial Breast and Ovarian Cancer in Otago and Southland, New Zealand

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Abstract

Background: Care for families affected by Familial Breast and Ovarian Cancer (FBOC) is challenging as a broad range of professions and specialties are involved. The aim was to review management and outcomes for a cohort of women at high risk for familial breast and ovarian cancer. **Methods:** Ten-year retrospective follow-up study of individuals in Southern New Zealand assessed by Genetic Health Service New Zealand to be high risk for FBOC and without a personal cancer diagnosis at time of consultation. **Results:** Twenty women were identified; twelve underwent genetic testing, and a pathogenic BRCA variant was identified in eleven. Eight women had no testing, as no index case was available. Guidelines had been fully adhered to in 55% of women, regardless of BRCA status. Six did not undergo appropriate breast surveillance. To date, seven of the 11 patients who tested positive for a pathogenic BRCA variant (64%) had risk-reducing surgeries. Two women were diagnosed with breast cancer on surveillance imaging; none were diagnosed with ovarian cancer. Four women were lost to follow-up, one of whom subsequently presented with a symptomatic breast cancer. **Conclusions:** To our knowledge, this is the first study providing long-term data for FBOC in New Zealand. Overall, guidelines were followed satisfactorily, but some women did not receive appropriate surveillance or referrals. An integrated interdisciplinary long-term care provision model in New Zealand might help to address gaps in FBOC surveillance and management.

Keywords: Hereditary cancer syndromes- prevention- New Zealand- breast cancer- practice guidelines as topic

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Introduction

About 5% of all breast cancers, and 15% of all high-grade epithelial ovarian cancers, are caused by variants in the *BRCA1* and *BRCA2* genes. Women who carry a pathogenic variant in these genes have an average lifetime risk of breast cancer of 72% (*BRCA1*) and 69% (*BRCA2*) and a lifetime ovarian cancer risk of 44% (*BRCA1*) and 17% (*BRCA2*) [1].

A broad range of professions and specialties are involved in managing familial breast and ovarian cancer (FBOC). Their aim is to implement risk management to mitigate the effect on the individual and the health system [2].

Genetic Health Service New Zealand (GHSNZ) is a national, publically funded service provided by Clinical Geneticists and Genetic Counsellors. Appropiate Primary Care and Specialists referrals as well as self referrals are accepted. GHSNZ assesses family cancer history to determine the level of risk, whether genetic testing is warranted and provides potiential screening recommendations.

The study was performed in New Zealand, which has a publicly funded health system. The regions relevant for this study of Otago and Southland have a population of approx. 300,000. The majority is of European descent (>80%), Māori compromise approx. 10%. Breast Cancer Rate for the region at the time the study cohort was recruited 2008/2009 was 93 per 1000,000 age-standardised, Ovarian Cancer Rate 10.7 per 100,000 [3]. The two underlying aims of risk management in FBOC are (1) early detection through appropriate evidence-based surveillance and (2) preventing cancer diagnoses through risk-reducing surgery or medication. Regular breast surveillance is recommended for the early detection of breast cancer [4]. Alternatively, prophylactic bilateral mastectomy can be offered as it reduces the risk of breast cancer [5]. Ovarian surveillance with ultrasound or tumour marker testing is not recommended as it is unsuccessful for early detection [4]. Long-term follow-up studies have shown that prophylactic bilateral salpingo-oophorectomy (BSO) reduces the risk of ovarian cancer by more than 90% [6, 7].

Referral to a specialist breast surgeon for discussion of surveillance and risk reducing strategies is recommended in women aged 25–30; referral to a specialist gynaecologist or gynaecologic oncologist for discussion about risk reducing BSO is recommended from 35 years (*BRCA1*)

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and 40 years (*BRCA2*) [4].

Management of these high-risk patients is complex and requires age-specific input from different specialist services.

This study aims to review the management and outcomes for women at high risk for FBOC. The primary aim is to assess adherence to guidelines. The secondary aims are to collect data on follow-up and outcomes to potentially identify aspects for improvement of care.

Materials and Methods

This retrospective descriptive 10-year follow-up study is based on a cohort of all-comers from Southern New Zealand (Regions Otago and Southland) seen by GHSNZ in 2008 and 2009 for suspected hereditary predisposition to breast and/or ovarian cancer. Inclusion criteria for this analysis was classification by GHSNZ to be at high risk for FBOC. Excluded were patients with breast and/or ovarian cancer diagnosis at the time of genetic consultation.

High risk for FBOC was defined as (1) being identified to carry a pathogenic gene variant or (2) to have an at least 10% likleyhood to carry an unidentified pathogenic variant based on strong family history. Patient - reported family history was cross checked to be correct via the New Zealand cancer registry by GHSNZ.

Data on patient management was collected from the South Island-wide clinical electronic documentation system Health Connect South (HCS), laboratory and radiology providers in the region or physical records as required. Patients were not contacted for this study. EviQ-based guidelines [4] have been applied. The version in use in 2010 for the identification and surveillance of women at high risk of familial ovarian and breast cancers were compared to assess adherence. Even though the guidelines have evolved over time, the key elements reviewed for this study were unchanged:

Breast

Referral to breast care service for consultation
Yearly breast imaging (MRI, mammogram)
Consideration of risk-reducing surgery

Ovarian

Referral to gynaecology/gynaecology oncology services for consultation from ages 35–40 years for risk-reducing BSO

No routine surveillance recommended (No serum CA125/transvaginal ultrasound)

Guidelines were deemed to have been adhered to if:

Breast

Patient had undergone >80% of recommended breast imaging.

Patient has been referred to breast care services for consultation (regardless of patient decision to undertake risk-reducing surgery).

Ovarian

Surveillance ultrasound for early detection of ovarian cancer was not performed. Pelvic ultrasound performed with symptomatic indication was disregarded.

Patient referral to gynaecology/gynaecology oncology services for consultation from ages 35–40 years (regardless of patient decision to undertake risk-reducing surgery) or currently awaiting referral at the recommended age.

Over the last 10 years, genetic testing technologies have improved, with full gene sequencing and the introduction of panel screening (with inclusion of additional *FBOC* genes). Therefore, data were also collected on whether patients meeting criteria had received updated gene analysis.

Ethics approval was granted and renewed for this follow up study by the Human Research Ethics Committee, University of Otago HD 19/050.

Results

Of the 120 individuals seen by GHSNZ for an assessment of Familal Breast and Ovarian Cancer in the two-year time period 2008/2009, 43 were classified as high risk for FBOC (Figure 1). Of these 23 had a personal diagnosis of breast or ovarian cancer at time of genetic assessment and were excluded from the study. The study cohort therefore included 20 non affected individuals i.e. without a personal cancer diagnosis at time of consultation process, who were identified to be at high risk for Familal Breast and Ovarian Cancer.

Median age at first consultation was 47 years (22 – 76 years) for the whole study cohort, lower for the subgroup identified to have a pathogenic BRCA variant (mean 26 years, range 20 – 63). One women in our cohort identified as Māori, she was found to carry a pathogenic BRCA variant, all others were NewZealand/European descent.

Eleven (55%) had a pathogenic variant (five *BRCA1* and six *BRCA2*). The remaining nine patients were classified as high risk based on (confirmed) family history.

Surveillance

Four asymptomatic women received (not recommended) pelvic ultrasound and CA125 testing. Six women (30%) did not have annual breast imaging and/or were not referred to breast care service for a consultation. Of these, three had a known pathogenic BRCA variant (Table 1).

Risk-reducing surgery

Among the 11 BRCA-positive patients in this study, five had completed both risk-reducing mastectomy (+/- mastectomy for cancer treatment) and BSO. Median time from initial genetic consultation to surgery was 86 months for mastectomy (range 6 – 110 months) and 40 months for BSO (range 2 - 68 months). Mastectomy was performed at a median age of 32.5 years (range 31 - 47), BSO at 43.5 years (range 32-63 years).

All four BRCA-positive patients who have not had risk-reducing mastectomy or BSO are currently under the age of 40 and either delaying surgery until their families are complete or awaiting referral to discuss surgical options at the recommended age. None of the women opted for medical management. Overall, eleven women (55%) were deemed to have received the recommended

Table 1. Adherence to Guidelines and Outcomes Since Initial Genetic Counselling

Genetic assessment	Adherence to guidelines *					Patient Outcome			
	Breast imaging	Breast referral	Gynae surveillance	Gynae referral	Overall	Risk-reducing Mastectomy	Risk-reducing BSO	Breast Cancer	Ovarian Cancer
All patients	14/20 (70%)	15/20 (75%)	16/20 (80%)	19/20 (95%)	11/20 (55%)	6/20 (30%)	8/20 (40%)	3/20 (15%)	0
BRCA positive	8/11 (73%)	9/11 (82%)	8/11 (73%)	10/11 (91%)	6/11 (55%)	6/11 # (55%)	6/11 (55%)	3/11 # (27%)	0
High Risk (not BRCA)	6/9 (67%)	6/9 (67%)	8/9 (89%)	9/9 (100%)	5/9 (55%)	0/9 (0%)	2/9 (22%)	0/9 (0%)	0

* Adherence to guidelines:Breast referral, Patient referred to breast care service for consultation (regardless of patient decision to undertake risk-reducing surgery); Gynae surveillance, Surveillance for early detection of ovarian cancer was not performed; Gynae referral, Patient has been referred to gynaecology/gynaecology oncology services for consultation from ages 35–40 years (regardless of patient decision to undertake risk-reducing surgery) or is currently awaiting referral at the recommended age.; # 3/11 of contralteral risk-reducing mastecomy at time of breast cancer treatment

breast/ovarian risk management (Table 1).

Cancer diagnosis after genetic consultation

Three patients were diagnosed with breast cancer after their original genetic consultation and all had a known familial pathogenic BRCA variant. Two were detected on recommended surveillance. The third patient was tested for the family variant only after her diagnosis of breast cancer so had not received appropriate surveillance prior to this. All three had contralateral risk-reducing mastectomies at the time of surgical treatment.

Further genetic consultations

In nine high-risk patients no pathogenic variant was identified. Updated gene screening was offered to three families during the follow up period due to affected relatives becoming available for testing. One patient was not offered an updated testing as a re-referral to GHSNZ did not occur.

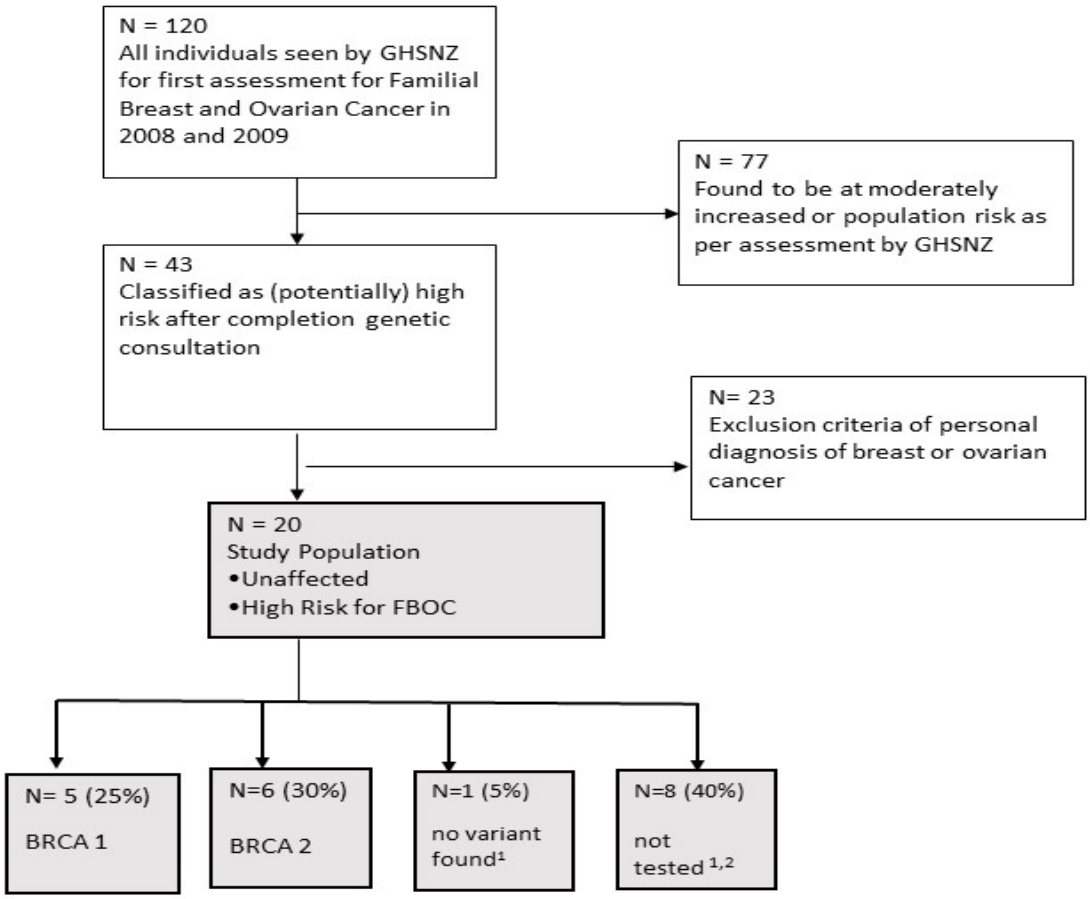

Figure 1. Study Population. Abbreviations: GHSNZ, Genetic Health Service New Zealand; FBOC, Familial Breast and Ovarian Cancer; BRCA 1, pathogenic BRCA 1 variant identified; BRCA 2, pathogenic BRCA 2 variant identified;
[1] Still (potentially), high risk due to strong family history, i.e.> 10% chance that pathogenic variant in family
[2] no index case with cancer diagnosis available for testing

Discussion

To our knowledge this is the first study to provide long-term follow-up data for FBOC patients in New Zealand. Over half of the women were managed fully within the recommended risk management guidelines. Thirty percent though did not receive appropriate breast surveillance, one of whom was diagnosed with a pathogenic BRCA variant only after developing a symptomatic breast cancer. Recommended breast surveillance was performed in 70% of the patients. This is within the range reported by other publications [8, 2].

Surveillance imaging found breast cancer in two of the twenty women, in line with a rate of 10.6% cancer found in a six-year surveillance interval reported by Warner et al. [9]. One patient developed a potentially avoidable breast cancer secondary to delayed genetic testing and lack of referral to breast surgeons for discussion about risk-reducing options. There is a high acceptance of risk-reducing surgeries in our cohort, with 75% (mastectomy) and 95% (BSO) of pathogenic BRCA-variant-positive patients in the appropriate age range proceeding with this option. International data show a broad range of acceptance of risk-reducing surgery in different countries ranging from 49.9% to 4.5% for mastectomy and . between 83.3% and 36.7% for BSO [10].

According to US data, the uptake of cancer risk management is higher when provided following genetic counselling, which may explain the high uptake of risk-reducing surgery in this cohort [11]. Long-term management programmes are deemed to be cost effective and could support to offer updated testing families within a systematic approach [12].

The limitations of this study include the small sample size and its retrospective nature. Additional surveillance or surgeries might have been performed but not captured. The sample might not be representative for New Zealand. Access to genetic consultations, testing, surveillance and risk-reducing surgery might differ throughout New Zealand. This study did not assess families who were not referred to GHSNZ for a consultation.

Overall, guidelines seem to have been followed satisfactorily. After being assessed and consulted regarding their risk for FBOC, women were able to participate in surveillance or undergo risk-reducing surgeries. However, 30% of women did not receive appropriate breast surveillance, four were lost to follow-up and one of the 20 women was diagnosed with a potentially avoidable breast cancer.

A bridge between genetic consultation, high-risk management and primary care is needed.

An integrated and coordinated interdisciplinary, long-term care provision programme could address many of the challenges.

Author Contribution Statement

All authors provided substantial contributions to conception and design, or analysis and interpretation of research.

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Declaration of Funding

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Approval by scientific body

The initial summerstudent project was approved by the Unviersity of Otago.

Data Availability Statement

The data that support this study will be shared upon reasonable request to the corresponding author.

Ethics approval

Ethics approval was granted and renewed for this follow up study by the Human Research Ethics Committee, University of Otago HD 19/050.

Conflict of Interest

The authors declare no conflicts of interest.

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