Awareness and Candidacy for Endocrine Prevention and Risk Reducing Mastectomy in Unaffected High-Risk Women Referred for Breast Cancer Risk Assessment

Basmah Alhassan, MBBS, MSc[1,3,4], Marianne Bou Rjeily, MD[1,2], Victor Villareal-Corpuz, RN, BSc[2], Ipshita Prakash, MD, MSc[1,2,4], Mark Basik, MD[1,4], Jean Francois Boileau, MD, MSc[1], Karyne Martel, MD[1], Michael Pollak, MD[2,4], William D. Foulkes, MBBS, PhD[2,4,5], and Stephanie M. Wong, MD, MPH[1,2,4]

[1]Department of Surgery, McGill University Medical School, Montreal, Canada; [2]Stroll Cancer Prevention Centre, Sir Mortimer B. Davis Jewish General Hospital, Montreal, Canada; [3]Department of Surgery, College of Medicine, King Saud University, Riyadh, Saudi Arabia; [4]Department of Oncology, McGill University Medical School, Montreal, Canada; [5]Division of Human Genetics, McGill University Medical School, Montreal, Canada

ABSTRACT

Introduction. Primary prevention of breast cancer in women at elevated risk includes several strategies such as endocrine prevention and risk-reducing mastectomy (RRM). The objective of this study was to evaluate awareness of different preventive strategies across high-risk subgroups.

Patients and Methods. Women referred for high risk evaluation between 2020 and 2023 completed an initial risk-assessment questionnaire that included questions around perceived lifetime risk and consideration of preventive strategies. One-way analysis of variance (ANOVA) and chi-squared tests were used to compare differences across different high-risk subgroups.

Results. 482 women with a median age of 43 years (20–79 years) met inclusion criteria; 183 (38.0%) germline pathogenic variant carriers (GPV), 90 (18.7%) with high-risk lesions (HRL) on breast biopsy, and 209 (43.4%) with strong family history (FH) without a known genetic predisposition. Most high-risk women reported that they had considered increased screening and surveillance (83.7%) and lifestyle strategies (80.6%), while fewer patients had considered RRM (39.8%) and endocrine prevention (27.0%). Prior to initial consultation, RRM was more commonly considered in GPV carriers (59.4%) relative to those with HRL (33.3%) or strong FH (26.3%, $p < 0.001$). Based on current guidelines, 206 (43%) patients were deemed eligible for endocrine prevention, including 80.5% with HRL and 39.0% with strong FH. Prior consideration of endocrine prevention was highest in patients with HRL and significantly lower in those with strong FH (47.2% HRL versus 31.1% GPV versus 18.7% FH, $p = 0.001$).

Conclusions. Endocrine prevention is the least considered preventive option for high-risk women, despite eligibility in a significant proportion of those presenting with HRL or strong FH.

Keywords Breast neoplasms · Endocrine prevention · High-risk lesions · Genetics · Risk-reducing surgery

For women without risk factors, the lifetime risk of developing breast cancer is estimated to be 13%, or 1 in 8 women.[1] However, select women are at increased risk for developing breast cancer, with lifetime risk that ranges between 20–80%. Elevated risk for breast cancer can be due to strong family history with or without a germline pathogenic variant (GPV), prior exposure to chest wall radiotherapy in young adulthood, or a history of atypical breast biopsies with high risk lesions (HRL), among other causes.[2–4] Several preventive strategies have been shown to effectively reduce the lifetime risk of developing breast cancer and are endorsed by international guidelines.[5]

While screening is the most widely promoted method for early detection and has been associated with a reduction in breast cancer-related mortality, it does not lower the likelihood of developing breast cancer.[6] Lifestyle modifications such as maintaining a normal body mass index, reducing alcohol consumption, avoiding smoking, a healthy diet, and moderate intensity exercise for 150 minutes per week have been shown to reduce breast cancer risk by up to 25% and are endorsed by National Comprehensive Cancer Network (NCCN) guidelines.[7–9] Bilateral risk-reducing mastectomy (RRM) is the most effective method to lower risk, resulting in a 90–95% relative risk reduction in GPV carriers.[10] However, because its impact on overall mortality remains controversial, RRM is not a requisite procedure for all GPV carriers who are already engaging in appropriate high-risk screening with annual mammography and magnetic resonance imaging. Furthermore, its use in most noncarriers is felt to be unnecessarily radical, given the potential for complications and the quality of life impact associated with major breast surgery and reconstruction.[11]

Over the last two decades, endocrine prevention (historically termed "chemoprevention") has become increasingly recognised as an effective long-term, risk-reducing strategy among certain groups of women with elevated risk.[12] Similar to RRM, endocrine prevention with tamoxifen, raloxifene, anastrozole, or exemestane offers no clear mortality benefit but does reduce the incidence of in situ or invasive breast cancer by 30–50% in high-risk women, and by up to 70% in women with HRL.[12–14] In 2019, the American Society of Clinical Oncology (ASCO) clinical practice guidelines endorsed the use of these medications in women with a history of atypical ductal or lobular hyperplasia, lobular carcinoma in situ (LCIS), or those with an estimated 10-year risk of developing breast cancer of 5% using the International Breast Intervention Study (IBIS)/Tyrer-Cuzick Risk Calculator.[15] Patients were also eligible if their estimated 5-year risk was at least 3% using the National Cancer Institute Breast Cancer Risk Assessment Tool (BCRAT), or if their relative risk was two or four times the average risk of their specific age groups.[15]

Despite multiple available and effective options, knowledge of preventive strategies among women at elevated risk for breast cancer is not well established. The primary objective of this study was to assess the awareness of risk-reducing strategies among women referred to high breast cancer risk clinic. A secondary aim was to evaluate eligibility of high-risk women for RRM and endocrine prevention and explore awareness of these options in eligible patients.

PATIENTS AND METHODS

Cohort Selection

Women referred to the Jewish General Hospital Stroll Cancer Prevention Centre for personalized evaluation of breast cancer risk between September 2019 and April 2023 were included. Demographic information and clinical history, risk factors for breast cancer, perceived lifetime risk of developing breast cancer, and consideration of different preventive strategies were surveyed using a risk assessment intake form. Following institutional review board approval, data obtained from prospectively collected questionnaires and clinic notes were extracted and managed using Research Electronic Data Capture (REDCap) tools hosted at McGill University.[16]

For analysis, patients were divided into the following three subgroups based on their primary indication for referral: strong family without a known GPV (FH); hereditary susceptibility due to a germline pathogenic variant (GPV) in *BRCA1/2*, *PALB2*, *CHEK2*, *ATM*, *CDH1*, *PTEN*, *TP53*, or other genes; or history of atypical breast biopsies with HRL including atypical lobular hyperplasia (ALH), atypical ductal hyperplasia (ADH), or classical LCIS. Due to the small number of patients with a personal history of chest wall radiation prior to age 30 years, this subgroup was excluded from the analysis. Women under 20 years of age, male patients, those with a personal history of breast cancer, and patients referred on the basis of family history alone with a lifetime breast cancer risk of less than 18% according to hereditary risk models were excluded from the analysis.

Perceived Breast Cancer Risk and Awareness of Preventive Strategies

At completion of the intake form, women were asked to describe on a Likert scale the anxiety they experience about a possible breast cancer diagnosis ("On a scale of 1 to 10, how concerned are you about the possibility of developing breast cancer?") and provide their own estimate of lifetime risk as a percentage ("What do you think is the risk of developing breast cancer over the course of your lifetime?"). Following these questions, women were asked to indicate if they were aware of and had ever considered any of the following strategies: (1) increased screening and surveillance, (2) lifestyle strategies to lower risk, (3) medications to lower breast cancer risk, and (4) risk-reducing surgery (prophylactic mastectomy).

Breast Cancer Risk Assessment Models

For those with strong FH of breast cancer and/or HRL, the IBIS/Tyrer-Cuzick Risk v8 model[17] was used to calculate 10-year and lifetime risk to age 85 using information derived from intake questionnaires combined with data from the medical record. In women over 40 years, breast density was obtained by American College of Radiology Breast Imaging Reporting and Data System (BI-RADS) category for all patients in whom mammographic reports were available.

For women with GPVs, 10-year and lifetime risk to age 80 were extracted from BOADICEA version 6/CanRisk estimates derived from genetic consultation notes, and when not available, the ASK2me™ online calculator.[18]

Eligibility for Risk Reducing Strategies

Eligibility for endocrine prevention was determined by applying the ASCO 2019 guidelines on "Use of Endocrine Therapy for Breast Cancer Risk Reduction".[15] All patients above the age of 40 who had completed childbearing and had a prior diagnosis of atypical hyperplasia or LCIS or a 10-year risk of 5% or more by IBIS/Tyrer-Cuzick v8 were eligible. Patients who completed 5-year endocrine prevention prior to their visit were analyzed as eligible. Premenopausal patients with a history of deep vein thrombosis or pulmonary embolism were deemed ineligible. Despite the controversial role of endocrine prevention in moderate and high-penetrance GPV carriers, *BRCA2, PALB2, CDH1, CHEK2, PTEN, BARD1,* and *ATM* carriers were considered eligible for endocrine prevention in this study using similar thresholds of 10-year risk (5%). Patients were considered eligible for risk reducing mastectomy if they had a high-penetrance GPV including *BRCA1/2, PALB2, CDH1,* or *PTEN* for which the 2023 NCCN guidelines recommend discussing the option of surgery.

Statistical Analyses

One-way ANOVA and chi-squared tests were used for continuous and categorical comparisons of breast cancer risk estimates and breast cancer-related anxiety across high-risk subgroups. Awareness and eligibility of different preventive strategies across subgroups were also compared using chi-squared and Fisher's exact tests, as appropriate. All analyses were conducted using SAS software version 9.4 (SAS Institute Inc., Cary, NC), with a two-sided p value of 0.05 used to indicate statistical significance.

RESULTS

Cohort Characteristics

Between September 2019 and April 2023, 558 patients were referred for high-risk evaluation and completed an individualized risk assessment. Following exclusions, a total of 482 were included in the analysis, including 183 (38.0%) GPV carriers, 209 (43.4%) with strong FH and 90 (18.7%) with HRL (Figure 1). The median age of the cohort was 43 years (range 20–79 years). Cohort characteristics are presented in Table 1. Among 183 GPV carriers, 77 (42.3%) were *BRCA1*, 80 (44.0%) *BRCA2*, 5 (2.8%) *PALB2*, 11 (6.0%) *CHEK2*, 3 (1.7%) *ATM*, and 7 had GPV in other genes. In 209 patients referred for strong FH, mean Tyrer–Cuzick lifetime risk estimates were 30.4% (range 18.0–55.2%) and 43 patients (20.5%) had undergone negative genetic testing or had an affected family member undergo negative genetic testing. In 90 patients referred for biopsy proven HRL, 30 (33.3%) presented with ADH, 20 (22.2%) presented with ALH, 17 (18.9%) with classical LCIS +/− ALH, 20 (22.2%) with a combination of ADH, LCIS/ALH or flat epithelial atypia, and 3 (3.3%) with atypical papilloma or pure flat epithelial atypia.

Perceived versus Calculated Lifetime Cancer Risk and Breast Cancer-Related Anxiety

Perceived and estimated lifetime breast cancer risks were subsequently compared across high-risk subgroups (Figure 1). Patients within different subgroups reported similarly high levels of perceived lifetime breast cancer risk (mean perceived lifetime risk; HRL 60.8% versus

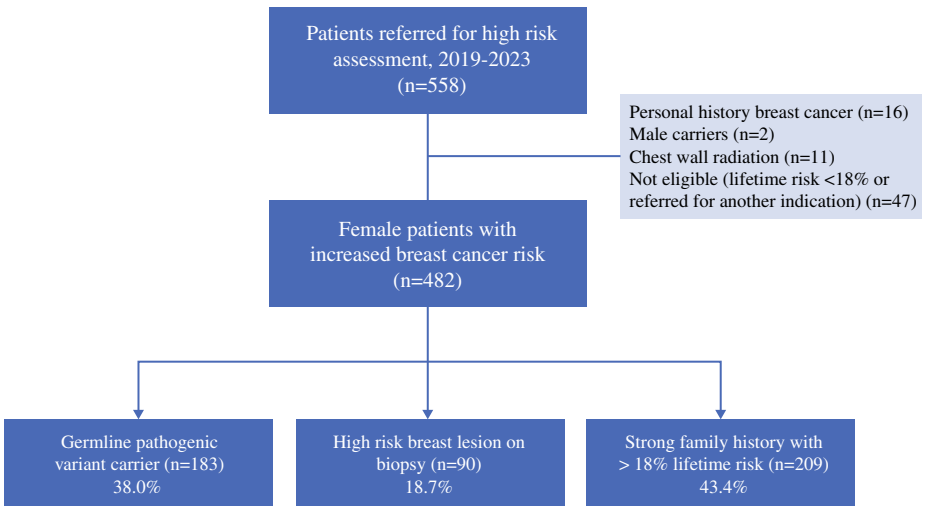

FIG. 1 Cohort selection and analysis

TABLE 1 Clinical characteristics (n = 482)

Characteristic	
Age—*n* (%)	
18–30 years	66 (13.7)
31–40 years	135 (28.0)
41–50 years	139 (28.8)
51–60 years	86 (17.8)
61+ years	56 (11.6)
Race/ethnicity—*n* (%)	
White	314 (65.15)
Black	11 (2.28)
Hispanic or Central/South American	16 (3.32)
Asian/Southeast Asian	42 (8.71)
North African/Middle Eastern	58 (12.03)
Other	41 (8.51)
Family history of breast cancer—*n* (%)	
None	186 (38.6)
One first-degree relative	244 (50.6)
Two or more first-degree relatives	52 (10.8)
Family history of ovarian cancer—*n* (%)	
Yes	117 (24.3)
No	365 (75.7)
Parity—*n* (%)	
Nulliparous	173 (35.8)
One or more pregnancy before age 25 years	71 (14.7)
One or more pregnancy after age 25 years	238 (49.5)
Median age of menarche—*years* (IQR)	12 (12–13)
Median age of menopause—*years* (IQR)	50 (45–52)
Menopausal status—*n* (%)	
Premenopausal	315 (66.0)
Postmenopausal	167 (34.0)
Oral contraceptive exposure—*n* (%)	
Yes	316 (65.6)
No	166 (34.4)
Hormone replacement therapy—*n* (%)	
Yes	447 (92.7)
No	35 (7.3)
ACR type breast density—*n* (% with mammographic density available)	
Type A (entirely fatty)	21 (7.0)
Type B (scattered fibroglandular)	90 (30.0)
Type C (heterogeneously dense)	139 (46.3)
Type D (extremely dense)	50 (16.7)
History of benign breast biopsies—*n* (%)	
Yes	166 (34.4)
No	316 (65.6)
High-risk subgroup—*n* (%)	
Germline pathogenic variant (GPV) carrier	183 (38.0)
Strong family history (FH) without known GPV	209 (43.4)
High risk lesion (HRL)	90 (18.6)

FH 68.7% versus GPV 68.7%; $p = 0.07$) and tended to overestimate residual lifetime risk calculated from hereditary risk models (mean calculated lifetime risk; HRL 38.4% versus FH 30.4% versus GPV 50.1%; $p < 0.001$). Although GPV carriers had the highest residual lifetime risk, patients referred for FH reported the highest levels of anxiety around developing breast cancer, while those with HRL reported significantly lower levels of breast cancer related anxiety (mean Likert score; HRL 6.4 versus FH 7.6 versus GPV 7.1; $p = 0.01$).

Awareness and Eligibility for Preventive Strategies

Prior to their risk assessment, most women had considered increased screening and surveillance, particularly patients with FH or GPV (HRL 70.6% versus FH 87.3% versus GPV 84.0%, $p = 0.02$). Lifestyle strategies to lower risk were strongly considered across all high-risk subgroups (HRL 72.6% versus FH 83.7% versus GPV 77.6%, $p = 0.15$). Overall, endocrine prevention was the least considered preventive strategy (HRL 34.6% versus FH 25.4% versus GPV 27.4%, $p = 0.41$), while risk-reducing mastectomy was considered by one-third of patients with HRL and FH as well as the majority of GPV carriers (HRL 30.0% versus FH 34.1% versus 58.9%, $p < 0.001$) (Figure 2).

Among the 206 (42.7%) women considered eligible for endocrine prevention, 12 (2.5%) patients had already completed a full course of treatment prior to initial visit. Eligibility for endocrine prevention was highest in women with HRL (92.2%) relative to 36.4% of FH patients and 25.7% of GPV carriers ($p < 0.001$). Of those eligible, only 34.5% reported having considered endocrine prevention in the past and 11.7% had tried or used endocrine prevention prior to initial visit. Relative to other subgroups, significantly more eligible women with HRL had been offered endocrine prevention (HRL 27.7% versus FH 4.0% versus GPV 12.8%, $p < 0.001$) and had tried or used endocrine prevention prior to their initial visit (HRL 15.7% versus FH 2.6% versus GPV 14.9%, $p = 0.01$) (Figure 3).

Among 183 unaffected GPV carriers, 8 patients (4.3%) referred for initial consultation had already undergone risk reducing mastectomy and 165 (90.2%) were eligible for surgical risk reduction. Within GPV carriers, there were significant differences in consideration of risk reducing mastectomy such that among unaffected *BRCA1/2* carriers, 68.2% had considered risk reducing mastectomy, whereas in other high penetrance GPVs (*PALB2*, *PTEN*, and *CDH1*) 50% had considered prophylactic surgery. Finally, in unaffected moderate penetrance carriers (*ATM*, *CHEK2*, *BARD1*, and *NF1*) for whom risk reducing mastectomy is not routinely recommended but rather considered on a case-by-case basis, 35.3% had considered surgery ($p = 0.02$).

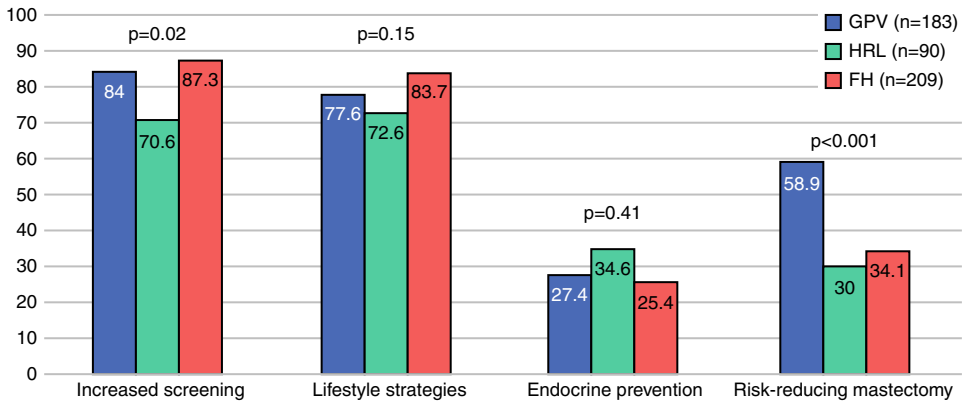

FIG. 2 Consideration of different risk reducing strategies by high-risk subgroups. *GPV* germline pathogenic variant carrier, *HRL* high-risk lesion, *FH* strong family history

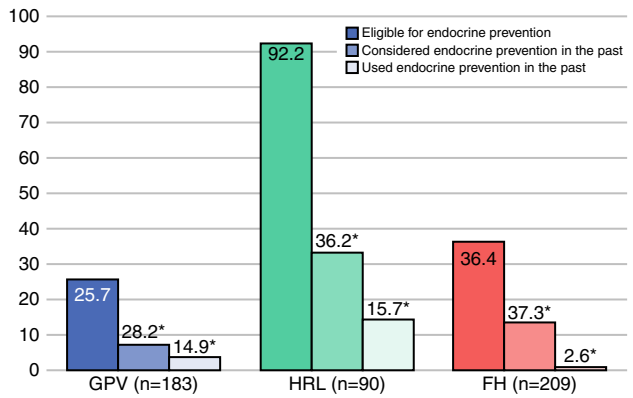

FIG. 3 Eligibility, awareness, and use of endocrine prevention in those eligible (* = % in those eligible). *GPV* germline pathogenic variant carrier, *HRL* high-risk lesion, *FH* strong family history

DISCUSSION

In this study of 482 high-risk women, we found high levels of perceived lifetime risk across all subgroups, with patients referred for strong FH reporting the highest levels of anxiety around developing a breast cancer despite having the lowest calculated lifetime risk estimates from hereditary risk models. With respect to different management strategies, we also found that while the majority of high-risk women are aware of screening and lifestyle strategies, more women had considered bilateral RRM over endocrine prevention to lower risk, despite greater eligibility for the latter. In the over 40% of women who were eligible for endocrine prevention in our cohort, 35% had considered endocrine prevention in the past, 12% had tried endocrine prevention, and only 2.5% had completed a full course of treatment.

Our findings on risk perception and breast cancer-related anxiety mirror those from earlier studies reporting minimal correlation between perceived lifetime risk and actual risk in women with a family history of breast cancer.[19] In a cross-sectional study of patients presenting to a breast cancer family history clinic, Rutherford et al. found that 84% of patients overestimated their lifetime risk compared with estimates calculated from the IBIS/Tyrer–Cuzick model.[20] In another survey of 11,365 women undergoing mammographic screening, most respondents overestimated their 5-year breast cancer risk as calculated by the Breast Cancer Risk Assessment Tool (BCRAT), while only 14.3% were accurate in their risk estimation.[21] Amplified risk perception has been shown to correlate directly with intensified level of worry and anxiety, and can impact uptake of screening, genetic testing, as well as adoption of risk reducing surgery and endocrine prevention.[22–24]

In our study, we found that 43% of patients met eligibility for endocrine prevention per 2019 ASCO guidelines but only one-third of eligible women had considered medication and fewer had taken it in the past. These findings are in line with a 2010 meta-analysis of nine studies by Ropka et al.[25] which noted real-world uptake of 14.8% compared with hypothetical interest reported by 24.7% of women. Despite longstanding approval for use in this setting, uptake of endocrine prevention remains low, between 7–11% in real-world studies.[25,26] In a meta-analysis including 21,423 women, factors associated with higher endocrine prevention uptake included having an abnormal biopsy, physician recommendation, fewer concerns around side effects, and older age.[26] Examining factors associated with decreased uptake following an educational intervention, Fagerlin et al. found that only 6% of women were willing to take tamoxifen despite 63% having reasonable knowledge around the topic, with most women citing concerns around medication side effects.[27] In another recent large study evaluating 575 endocrine prevention discussions in patients with no prior use, Flanagan et al. similarly reported fear of side effects as the most common factor prompting refusal.[28]

Our study was designed to address awareness of prevention strategies across different high-risk subgroups and suggests a significant awareness gap between surgical and pharmacologic options for breast cancer risk reduction. While increasing interest in RRM has been documented in carriers and noncarriers alike over the last decades,[29–32] the diffusion

of knowledge around endocrine prevention appears more limited. In a recent survey of 725 high-risk women and 221 Australian clinicians, only 48% of patients and 65% of family physicians reported being aware of endocrine prevention as an option.[33] Interestingly, the strongest barrier for family physicians to prescribe these medications was insufficient knowledge, suggesting that knowledge translation efforts around eligibility and efficacy of endocrine prevention are needed.

This study has several limitations, including the use of a nonvalidated questionnaire with a brief assessment of anxiety and awareness of preventive strategies, as well as the possibility of survey bias introduced by the questionnaire itself. Furthermore, perceived lifetime risk estimates and breast cancer-related anxiety were likely subject to selection bias by nature of patients referred and/or specifically presenting for "high risk assessment", and may not be representative of all women in the general population with these risk factors. In addition, women with HRL were less represented in this cohort, constituting only 18.7% of referred patients, which decreases generalizability to this group. Finally, we retained a small number of patients who had already undergone RRM or completed 5 years of endocrine prevention within our analytic cohort, which may have resulted in an overestimation of awareness of these preventive strategies. Fortunately, sensitivity analysis performed following removal of these 20 patients demonstrated similar levels of awareness across high-risk groups (data not shown), supporting the stability of our findings.

Despite the stated limitations, this study is one of few in the literature to prospectively explore awareness of high-risk women across different subgroups and risk strata. Furthermore, our assessment of eligibility for endocrine prevention and risk reducing surgery in relation to awareness gives valuable insight on specific groups which may be eligible for targeted interventions in the future. Further research that focuses on systematically evaluating candidacy and improving awareness and uptake of endocrine prevention options are warranted.

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