Original Article

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Genetic Counseling, Screening and Risk-Reducing Surgery in Patients with Primary Breast Cancer and Germline BRCA Mutations: Unmet Needs in Low- and Middle-Income Countries

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ABSTRACT

Objective: Worldwide genetic counseling practices are variable and often not reported in low- and middle-income countries (LMICs). We present the follow-up genetic counseling, breast screening, risk-reducing salpingo-oophorectomy (RRSO) and contralateral prophylactic mastectomy (CPM) in a cohort of study patients with either *BRCA* pathogenic mutations or *BRCA* variant of unknown significance (VUS).

Materials and Methods: Chart review and phone calls for the collection of information. Out of a cohort of 250 patients, 14 had deleterious mutations and 31 had a VUS, of whom 19 had primary early breast cancer. We collected information about genetic counseling, screening, CPM and RRSO.

Results: Fourteen patients with deleterious mutations (7 *BRCA1* and 7 *BRCA2*) and 19 patients with VUS mutations (20 VUS, 4 *BRCA1*, 16 *BRCA2*; 1 patient had both) were surveyed. Of 14 patients with deleterious *BRCA* mutations, 57.14% (8/14 patients) received genetic counseling from their oncologist. Subsequently 85.71% (12/14) are undergoing mammography screening and 35.71% (5/14) breast screening magnetic resonance imaging (MRI). Furthermore, 50% of them underwent CPM and 57.14% underwent RRSO. Of 19 patients with VUS mutations, 10.5% received genetic counseling from their oncologist; 78.9% were undergoing regular screening mammogram and 31.5% were undergoing breast MRI; one patient underwent CPM and two patients RRSO.

Conclusion: Within three years from knowing they have a mutation, 50% of patients with germline *BRCA* mutations had undergone CPM and 60% RRSO, the majority of them had screening mammography surveillance but only 50% had screening MRI. Follow-up of patients with VUS with mammography was 78% but MRI was only 31%. Lack of MRI surveillance reflects both limited resources and insufficient counseling. Genetic counseling was done by medical oncologists, which reflects a trend in LMIC. Our Data shows the importance of the need for professional genetic counselors and optimal surveillance in Lebanon and other LMICs.

Keywords: Hereditary breast cancer, genetic counseling, screening; contralateral prophylactic mastectomy, risk-reducing salpingo-oophorectomy, germline *BRCA* mutation, VUS mutation

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Key Points

- Optimal care, in terms of prevention and early intervention, is provided by identifying women and their family members who are at high risk of carrying mutations.
- Genetic counseling along with appropriate surveillance and interventions for *BRCA* mutations are recommended because of the known benefits from surveillance, chemoprevention and breast/ovarian risk reducing surgeries.
- Worldwide, the practice of genetic counseling among women with deleterious *BRCA* 1 and 2 variants classified as of unknown significance is variable and is limited in most low- and-middle income countries.

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Introduction

Breast cancer is the most common cancer among women, worldwide (1, 2). Hereditary breast cancer accounts for 5 to 10% of cases, 15 to 20% of breast cancer cases are familial and 70 to 80% are sporadic (3). At least 50% of hereditary breast cancer is due to germline autosomal dominant pathogenic *BRCA1* or *BRCA2* mutation (4). Breast cancers in patients with *BRCA1* mutations are usually of high-grade with rates of triple-negative breast cancer (TNBC) as high as 80 to 90% (5). Conversely, the rate of *BRCA* mutation in TNBC ranges between 11 to 35% (4, 6, 7). The risk of developing breast cancer in patients who have a *BRCA* mutation can be as high as 80% (40%–80%) (8), while the chance of having ovarian cancer is between 17 to 44% (9). In terms of prevention and early intervention, breast cancer care is optimized by identifying women and their family members at high-risk of carrying such mutations (10, 11). Individuals identified with a variant of unknown significance (VUS) should be counseled based upon their personal and family history, irrespective of the variant (12, 13). While recent American Cancer Society guidelines for breast cancer screening among average-risk women call for screening starting at the age of 45 years (14), the European Society of Medical Oncology calls for mammography screening for women aged 50–69 years with a Level 1A evidence while leaving it as an option for women in the age groups 40–49 and 70–74 years (15). For early detection in high-risk women and mutation carriers, guidelines call for annual screening with mammogram starting at age 30 years, or 10 years earlier than the first case in the family, along with a yearly breast screening magnetic resonance imaging (MRI), starting at 25 years old (16, 17).

Women who are carriers of *BRCA1/2* mutation and are newly diagnosed with breast cancer have a 17%–37% risk of developing a contralateral breast cancer within 10 years of their initial diagnosis (15, 16). Over 50% of *BRCA* mutation carriers opt for contralateral prophylactic mastectomy (CPM), thus decreasing the risk of breast cancer by 90%. Moreover, women with a *BRCA* variant are also at risk of developing ovarian cancer, ranging from 17% in *BRCA2* to 44% in *BRCA1* carriers, compared to a 2% risk in women without *BRCA* variants (18). Many genetic counseling practices are reported in the literature (19, 20). risk-reducing salpingo-oophorectomy (RRSO) around the age of 40, usually after completion of family plans, is recommended for women who are *BRCA1/2* mutation carriers. This prophylactic surgery reduces the risk of developing breast cancer by 50% and reduces the ovarian cancer risk by 80%–96% (21, 22).

Breast cancer represents 35% of all cancers affecting women in Lebanon and Arab countries, with a median age of diagnosis of 48–52 years (23, 24). We have previously reported the prevalence of *BRCA* mutations in 250 ethnic Lebanese Arab women with a high risk of having hereditary breast cancer and found that 5.6% had either *BRCA1* or *BRCA2* pathogenic mutations (23). Herein, we reported the results of surveillance three years after disclosure of the presence of a mutation to the patients.

Materials and Methods

Patients previously identified as carrying *BRCA* deleterious and VUS mutations were included (23). These patients were investigated in terms of follow-up processes, including genetic counseling, screening recommendations and risk reducing surgeries in patients with early breast cancer. The patients were included in the original study for *BRCA1* and *BRCA2* mutation and considered at high risk of genetic predisposition if: aged <40 years at diagnosis; aged ≤50 years with at least one relative with breast cancer; aged ≤50 years with one relative with ovarian cancer; ≥2 relatives with breast cancer; ≥2 relatives with ovarian cancer; or patient has personal history of breast or ovarian cancer (25, 26). No subjects were male.

The initial study plans included surveillance and follow-up of all patients. There was an additional approval by the Institutional Review Board (IRB) of the American University of Beirut Medical Center (IRB ID: IM.NS.06, date: 17.11.2016 and 29.06.2021) to complete clinical and follow up information via phone calls, when necessary. The content of phone conversations was strictly limited as specified by the IRB. Research Fellows conducted patient interviews and chart reviews. Patients were asked three specific questions about: 1) the screening modality used to detect a second primary breast cancer since they were discovered to have *BRCA* mutation; 2) if any preventive surgical procedure for breast and/or performed during or after treatment for the initial breast cancer; and 3) if they received any advice for genetic counseling for themselves and their families. The data and results were collected and simply analyzed for the processes of genetic counseling, screening, prophylactic CPM and RRSO interventions in this cohort of previously diagnosed patients with breast cancer, with high genetic predisposition according to the inclusion criteria and all of whom harbored either a deleterious or a VUS mutation for *BRCA1/2*.

Results

Study Cohort: In total there were 250 women identified from the earlier study who were at high risk of having hereditary BC. Of these 250, 14 (5.6%) had deleterious *BRCA1* or *BRCA2* mutations and 31 (12.4%) had VUS mutations, of whom 19 had early breast cancer. As reported earlier, 11.2% of patients were TNBC, and 25% of patients with TNBC had a *BRCA1* mutation (25). All patients with a *BRCA1* deletion had triple negative, grade 3, infiltrating ductal breast carcinoma. Of the 19 patients with *BRCA* VUS mutations, four were VUS *BRCA1* and 16 were VUS *BRCA2* while one patient had both *BRCA1* and *BRCA2* VUS detected (24).

Genetic counseling for patients with *BRCA* deleterious mutations: 57.14% of patients with *BRCA* pathogenic mutations said they received genetic counseling. All patients were counseled by their primary oncologist. None received information from a certified genetic counselor.

Genetic counseling for patients with VUS mutations: Only 10.5% reported having genetic counseling, and again this was only by their managing oncologist.

Screening mammography and MRI of the breasts in *BRCA* pathogenic mutation carriers: 85.71% of patients with a *BRCA* pathogenic mutation reported that they were undergoing regular screening mammography. Only 35.71% said they were receiving breast screening MRI in addition to yearly mammograms.

Genetic counseling and screening in family members of *BRCA1/2* pathogenic or VUS mutations: 57.14% reported that they had advised their family members (sisters and daughters) to undergo *BRCA* mutation testing. Furthermore, only 21.0% of the patients with VUS mutations advised their family members to undergo *BRCA* mutation testing.

Mammography and breast MRI in patients with VUS: Regular screening mammograms were consistently and persistently performed in 15 (78.9%) of patients with a VUS. However, only 31.5% had and continued to get regular screening MRI of the breasts (Graph 1).

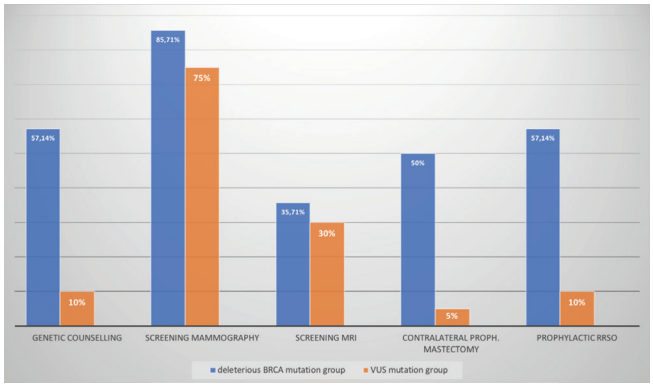
Risk reducing surgery in *BRCA* pathogenic mutation carriers: CPM was done in 50% of patients and RRSO in 57.14% of patients with a pathogenic mutation. 50% of the patients had both CPM and RRSO.

Risk reducing surgery in *BRCA* VUS mutation carriers: Of the patients with *BRCA1/2* VUS mutation, only 5.2% had CPM and 10.5% had RRSO (Graph 1). All patients who underwent these surgeries did so at the recommendation of their private oncologist who initiated discussion and counseling with them.

Chemoprevention: Chemoprevention was given for patients with a *BRCA* mutation in this study. Premenopausal women received tamoxifen, while post-menopausal women had either tamoxifen or aromatase inhibitor (AI). Chemoprevention with tamoxifen was done in 41% of patients. AI was used in 6% of patients. Premenopausal patients on AI also received ovarian function suppression (Goserelin subcutaneous tunnel injection 3.6 mg every 28 days) treatment as part of their adjuvant therapy.

Discussion and Conclusion

This was a follow-up study in a group of patients with pathogenic and VUS mutations in *BRCA*, identified as part of a study of 250 patients at high risk of having a hereditary breast cancer. In the full cohort the mean germline pathogenic mutation rate was 5.6%, with the highest rate (10.6%) in patients below 40 with a positive family history of breast cancer (25). Although the number of patients in the present study is small, we report real world rates of surveillance in patients with *BRCA* pathogenic and VUS mutations. It is notable that half of *BRCA1/2* patients underwent contralateral prophylactic mastectomy, which is consistent with the generally reported rate of prophylactic mastectomy, ranging from 29.9% to 55.4% (28). A meta-analysis had shown that the risk of contralateral breast cancer is 25% for *BRCA1* carriers and 13.5% for *BRCA2* carriers vs. 3.6% for non-carriers (29). There has been a recent trend towards prophylactic contralateral mastectomy or bilateral mastectomy at the time of initial breast cancer surgery (30).



Graph 1. Genetic counseling, screening mammography and MRI, risk reducing surgery in patients with *BRCA* pathogenic and VUS mutations

MRI: Magnetic resonance imaging, VUS: Variant of unknown significance, BRCA: Breast cancer gene

Published literature shows that around 56% of *BRCA1/2* patients undergo prophylactic oophorectomy (31). Prophylactic oophorectomy has been shown to reduce the risks of both breast and ovarian cancer by 50% and 95%, respectively, in women with *BRCA1* or *BRCA2* mutation. If prophylactic oophorectomy is performed by age 40, breast cancer risk can be also reduced by 56% and 43%, for *BRCA1* and *BRCA2* carriers, respectively (32). Once again, our rates of risk reducing prophylactic salpingo-oophorectomy of 57.14% is consistent with the literature.

Surveillance with MRI alternating with mammography is a recommended option in *BRCA1/2* carriers (33-35). In our cohort of patients, more than 80% with either mutation did undergo screening mammography, but only 25%–31% underwent screening MRI. This is likely due to suboptimal counseling and limited resources.

Genetic counseling together with appropriate surveillance and interventions for patients with *BRCA* mutations are recommended because of the known benefits from surveillance, chemoprevention and breast/ovarian risk reducing surgery. Availability of professional genetic counseling is variable and it is generally lacking in most LMICs (36-39), and even in many high income countries (HICs) (10, 12).

Although the National Comprehensive Cancer Network, US Preventive Services Task Force, and American College of Obstetricians and Gynecologists issued specific guidelines for genetic counseling referral, based on personal and family history including screening for hereditary breast and ovarian cancers, women meeting the criteria for genetic counseling and screening are often not referred (12). In the United States only 50% of those identified as high risk for carrying a genetic mutation are offered genetic counseling, highlighting the underuse of this type of recommended health care (10). The few published studies show that physicians have a positive attitude towards genetic counseling but lack sufficient knowledge to counsel adequately (13). In Lebanon, as in many other countries, and especially in LMIC, there is a lack of genetic counselors and there are no national guidelines for genetic screening. In addition, genetic counseling is not generally covered by health insurance companies.

Genetic counseling was documented in only about one third of our cohort of patients, and it was mostly done by the patients' own oncologists because of lack of professional counselors and high-risk breast clinics in the country. The 2015 American Society of Clinical Oncology (ASCO) Policy Statement on Genetic and Genomic Testing for Cancer Susceptibility included quality assurance, informed consent, patient privacy, protection from genetic discrimination, public and provider education, and efforts to identify and reduce disparities in access to clinical genetics services (40). These recommendations are based on studies in countries with robust health systems (41). Genetic counseling should be an integral part of these recommendation, not only for LMICs but also in HICs. In HICs, this is because of the now widely available access to genetic testing when there is a requirement for safe and appropriate counseling concerning prognostic and therapeutic information which is not always available from genetic testing service providers (42, 43).

As for patients with VUS mutations, most of our cohort underwent screening mammography (78.9%), but only 31% had screening MRI. This also reflects both suboptimal counseling and limited resources. As for risk reducing surgery, only one patient had CPM and two had RRSO. This is in line with literature and guidelines, as CPM and

RRSO are not recommended (14, 40, 44) unless the patient has a very strong family history and desires to have CPM and/or RRSO.

Follow up of high-risk patients and mutation-carriers is best done at specialized centers and clinics (45). However, in most parts of the world the majority of patients and carriers are followed by their private oncologists, with the exception of patients attending major cancer centers. Genetic counseling is included in the The European Society for Medical Oncology (ESMO)/ASCO Global Curriculum for training of medical oncologists (45). This issue needs a stepwise implementation. Coordination of care between referral cancer centers and general hospitals and general oncologists would help resolve this unmet need and improve surveillance and risk reducing surgeries (12). Professional genetic counselors are urgently needed in most LMICs and worldwide. Education and awareness of oncologists remains important as most patients are followed up by their primary oncologists. The widespread implementation of telemedicine during the coronavirus disease-2019 (COVID-19) era can be used to help *BRCA* carriers and the high-risk population for breast cancer as online consultations with genetic counselors may become more accessible for patients everywhere including both HICs and LMICs.

In conclusion, in this cohort of women living in the Lebanon, the majority of patients with *BRCA1/2* mutations underwent screening mammography but only a minority had breast screening MRI, despite recommendations. Genetic counseling for both the patients and their families was mostly given by medical oncologists. The requirement for optimal screening and genetic counseling is still not met in this cohort. We therefore believe that there remains a need for greater provision of professional genetic counselors and high-risk breast clinics, not only in our own country but also in other LMICs, and even among HICs, globally.

Ethics Committee Approval: This study approved by the Institutional Review Board (IRB) of the American University of Beirut Medical Center (IRB ID: IM.NS.06, date: 17.11.2016 and 29.06.2021).

Informed Consent: Informed consent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: N.S.E.S.; Design: N.S.E.S.; Data Collection and/or Processing: H.A.M., A.A.M., R.W.A., F.K., L.E.K., R.S., S.D., I.A.D., N.S.E.S.; Writing: H.A.M., A.A.M., R.W.A., F.K., L.E.K., R.S., S.D., I.A.D., N.S.E.S.; Critical Review: H.A.M., A.A.M., R.W.A., F.K., L.E.K., R.S., S.D., I.A.D., N.S.E.S.

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