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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

Hiba A. Moukadem, Ahmad Al Masry, Rula W. Atwani, Firas Kreidieh, Lana E. Khalil, Rita Saroufim, Sarah Daouk, Iman Abou Dalle, Nagi S. El Saghir

Division of Hematology Oncology, Department of Internal Medicine, American University of Beirut Medical Center, PO Box: 11-0236, Riad El Solh, 1107 2020, Beirut – Lebanon-

Corresponding author

Nagi S. El Saghir; ns23@aub.edu.lb

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Abstract

Background: 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) on a cohort of study patients with either BRCA pathogenic mutations or BRCA Variant of Unknown Significance (VUS).

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: 14 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 BRCA deleterious mutations, 57.14% (8/14 patients) received genetic counseling from their oncologist. 85.71% (12/14) are undergoing mammography screening, 35.71% (5/14) screening breast MRI. 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, 31.5% were undergoing MRI breasts; one patient underwent CPM and two patients RRSO.

Conclusions: Within 3 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 at 78% rate but MRI was only 31%. Lack of MRI surveillance reflects both limited resources and unsufficient counseling. Genetic counseling was done by medical oncologists which reflects a trend in LMIC and others. 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

Key Points

- Optimal care in terms of prevention and early intervention is optimized 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 practices of genetic counseling among women with BRCA 1 &2 deleterious and VUS mutations are variable and limited in most low- and- middle income countries.

Introduction

Breast cancer is the most common cancer among women worldwide[1,2]. Hereditary breast cancer accounts for 5 to 10% of the 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 triple-negative breast cancer (TNBC) as high as 80 to 90%[5]. The rate of BRCA mutation in triple negative breast cancer ranges between 11 to 35%[4,6,7]. The risk to develop 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]. Optimal care in terms of prevention and early intervention 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 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 45[14], the European Society of Medical Oncology calls for mammography screening for women age 50-69 with a Level 1A evidence while leaving it as an option for women ages 40-49 and 70-74[15]. For early detection in high-risk women and mutation carriers, guidelines call for annual screening with mammogram starting at age 30, or 10 years earlier than the first case in the family, along with a yearly screening breast MRI[16, 17] starting at 25 years old.

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 CPM, thus decreasing the risk of breast cancer by 90%. Moreover, women with a BRCA variant also have the risk to develop ovarian cancer which ranges from 17% in BRCA2 to 44% in BRCA1 carriers compared to 2% in average risk women[18]. Many genetic counseling practices are reported in the literature[19, 20]. 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 women cancers in Lebanon and Arab Countries with a median age of 48-52[23,24]. We have previously looked at the prevalence of BRCA mutations in 250 ethnic Lebanese Arab women with at a high-risk of having hereditary breast cancer and found that 5.6% had either BRCA1 or BRCA2 pathogenic mutation[23]. We report in this manuscript the results of surveillance after 3 years of disclosure of mutations to patients.

Methods

We identified the patients who carried BRCA deleterious and VUS mutations[23] and looked at genetic counseling, screening recommendations and risk reducing surgeries in patients with early breast cancer. The 250 patients were considered at high risk to carry genetic predisposition by virtue of having age less than 40 years at diagnosis, age equal or less than 50 years with at least one relative with breast cancer less or equal to 50 or one relative with ovarian cancer, patient has 2 or more relatives with breast cancer, patient has 2 or more relatives with ovarian cancer, or patient has personal history of breast or ovarian cancer[25,26] and were included in the original study for BRCA1 and BRCA2 mutations. We did not have any male patient in the study.

Our initial study plans included surveillance and follow-up of all patients. We had an additional approval by the Institutional Review Board (IRB) of the American University of Beirut Medical Center to complete clinical and follow up information via phone calls where necessary. We adhered strictly to the content of phone conversations as approved by the IRB. Research Fellows conducted patient interviews and chart reviews. Patients were asked 3 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 ovaries was done during or after treatment for the initial breast cancer, and 3) if they received any advice for genetic counseling for them and their families. We present data and results of genetic counseling, screening, CPM and RRSO prophylactic interventions in previously diagnosed patients with breast cancer with high genetic predisposition according to the inclusion criteria and who were found to harbor either a deleterious or a VUS mutation for BRCA1/2.

Results

Fourteen patients (5.6% of the total) had deleterious BRCA1 or BRCA2 mutations and 31 patients (12.4% of the total) had VUS mutations out 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[24,25]. All patients with BRCA1 deletions had triple negative, grade 3, infiltrating ductal breast carcinoma. 19 patients had VUS mutations; of which 4 were VUS BRCA1 and 16 were VUS BRCA2. One patient had both VUS of BRCA1 & BRCA2[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 own 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 this was only by their treating oncologist.

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

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

Mammography and breast MRIs in patients with VUS: regular screening with mammograms was and continues to be done by 15 78.9% of patients with a VUS. Only 31.5% were and continue getting regular screening MRI of the breasts as well (graph 1).

Risk Reducing Surgery in BRCA-pathogenic mutated patients: CPM was done in 50% of patients and RRSO in 57.14% of patients with pathogenic mutation. 50% of the patients had both CPM and RRSO.

Risk Reducing Surgery in BRCA VUS-mutated patients: Of patients with BRCA1/2 VUS mutation, only 5.2% of patients 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 BRCA mutated patients 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 were also on ovarian function suppression as part of their adjuvant therapy.

Discussion

In this group of patients with BRCA pathogenic and VUS mutations discovered as part of a study of 250 patients at high risk of having a hereditary breast cancer, where average germline pathogenic mutation rate was 5.6%, with the highest range in patients below 40 and a positive family history of breast cancer was up to 10.6%[27]. Although the number of patients in the study is small, we report in this article real world rates of surveillance in patients with BRCA pathogenic and VUS mutations and note that half of BRCA1/2 patients underwent contralateral prophylactic mastectomy, which was almost similar to the generally reported rate of prophylactic mastectomy in the literature that ranges from around 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].

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. Breast cancer risk can be also reduced by 56% and 43% if prophylactic oophorectomy is performed by age 40, for BRCA1 and BRCA2 carriers, respectively[32]. Our rates of risk reducing prophylactic salpingo-oophorectomy of 57.14% in patients with BRCA1/2 mutations parallel the literature.

Surveillance with MRI alternating with mammography intervals is a recommended option in BRCA1/2 carriers[33-35], In our cohort of patients, more than 80% of our patients with either mutation did undergo screening mammography, however, only 25-31% underwent screening MRI. This can be explained by suboptimal counseling and limited resources.

Genetic counseling along with appropriate surveillance and interventions for BRCA mutations detected patients are recommended because of the known benefits from surveillance, chemoprevention and breast/ovarian risk reducing surgeries. Availability of professional genetic counseling is variable and it is generally lacking in most low- and middle-income countries (LMICs) [36-39], and even in many High Income Countries[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 (US), 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, especially LMIC, there is a lack of genetic counselors and there are no national guidelines for genetic screening. Also, genetic counseling is generally not 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 ASCO Policy Statement on Genetic and Genomic Testing for Cancer Susceptibility includes 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 important companion of those statements for LMICs, and also in High-Income Countries (HICs) where the need of genetic counseling is further increased because of the explosion of genetic and genomic changes with related prognostic and therapeutic values[42,43].

As for patients with VUS mutations, the large majority of our cohort of patients underwent screening mammography (78.9%), and only 31% had screening MRI. This reflects also both suboptimal counseling and limited resources. As for risk reducing surgery, only one patient had CPM and 2 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, LMICs and even many HICs, the majority of patients and mutation carriers are followed by their private oncologists, except for major

cancer centers. Genetic counseling is included in the 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 in urgent need in most LMICs and worldwide. Education and sensibilization of oncologists remain important as most patients worldwide are followed up by their primary oncologists. The implementation of telemedicine in the medical system during the COVID-19 era can help BRCA carriers and the high-risk population for breast cancer living in the countryside and faraway places to have online consultations with genetic counselors usually available in large medical centers and university hospitals in major cities in most countries and particularly in LMICs.

Conclusion

We report real world data that the majority of patients with BRCA1 or BRCA2 mutations undergo screening mammography but only a minority undergoes MRI. We also report that genetic counseling for the patients and their families is mostly done by medical oncologists. We point out to and we emphasize the need for optimal screening and genetic counseling. Professional genetic counselors and high-risk breast clinics are needed in different LMICs in the world.

References:

1 Bray, Freddie, et al. "Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries." *CA: a cancer journal for clinicians* 68.6 (2018): 394-424.

2 Zaidi, Zoubida, and Hussain Adlane Dib. "The worldwide female breast cancer incidence and survival, 2018." (2019): 4191-4191.

3 Apostolou, Paraskevi, and Florentia Fostira. "Hereditary breast cancer: the era of new susceptibility genes." *BioMed research international* 2013 (2013).

4 King, Mary-Claire, Ephrat Levy-Lahad, and Amnon Lahad. "Population-based screening for BRCA1 and BRCA2: 2014 Lasker Award." *Jama* 312.11 (2014): 1091-1092.

5 Ellsworth, Darrell L., Clesson E. Turner, and Rachel E. Ellsworth. "A review of the hereditary component of triple negative breast cancer: High-and moderate-penetrance breast cancer genes, low-penetrance loci, and the role of nontraditional genetic elements." *Journal of oncology* 2019 (2019).

6 Greenup, Rachel, et al. "Prevalence of BRCA mutations among women with triple-negative breast cancer (TNBC) in a genetic counseling cohort." *Annals of surgical oncology* 20.10 (2013): 3254-3258.

7 Peshkin, Beth N., Michelle L. Alabek, and Claudine Isaacs. "BRCA1/2 mutations and triple negative breast cancers." *Breast disease* 32.1-2 (2011): 25-33.

8 Casaubon JT, Grewal US, Regan JP. BRCA 1 and 2. StatPearls. Treasure Island (FL): StatPearls Publishing Copyright © 2020, StatPearls Publishing LLC.; 2020.

9 Kuchenbaecker, Karoline B., et al. "Risks of breast, ovarian, and contralateral breast cancer for BRCA1 and BRCA2 mutation carriers." *Jama* 317.23 (2017): 2402-2416.

10 Evers, Christina, et al. "Familial breast cancer: Genetic counseling over time, including patients expectations and initiators considering the Angelina Jolie effect." *PloS one* 12.5 (2017): e0177893.
11 Chen, Sining, and Giovanni Parmigiani. "Meta-analysis of BRCA1 and BRCA2 penetrance." *Journal of clinical oncology: official journal of the American Society of Clinical Oncology* 25.11 (2007): 1329.
12 Wood, Marie E., et al. "Quality of cancer family history and referral for genetic counseling and testing among oncology practices: a pilot test of quality measures as part of the American Society of Clinical Oncology Quality Oncology Practice Initiative." *Journal of Clinical Oncology* 32.8 (2014): 824.
13 Van Riel, Els, et al. "BRCA testing of breast cancer patients: medical specialists' referral patterns, knowledge and attitudes to genetic testing." *European Journal of Cancer Care* 19.3 (2010): 369-376.
14 Mary B. Daly, et al. "Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic, Version 2.2021". JNCC. Jan 2021. Vol 19, Issue 1.
15 Cardoso, F., et al. "Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up." *Annals of Oncology* 30.8 (2019): 1194-1220.
16 Bitencourt AG, Rossi Saccarelli C, Kuhl C, et al: Breast cancer screening in average-risk women: towards personalized screening. Br J Radiol 92:20190660, 2019
17 Singer, Christian F., et al. "Genetic counselling and testing of susceptibility genes for therapeutic decision-making in breast cancer—An European consensus statement and expert recommendations." *European Journal of Cancer* 106 (2019): 54-60.
18 Harmsen, Marline G., et al. "Early salpingectomy (TUbectomy) with delayed oophorectomy to improve quality of life as alternative for risk-reducing salpingo-oophorectomy in BRCA1/2 mutation carriers (TUBA study): a prospective non-randomised multicentre study." *BMC cancer* 15.1 (2015): 1-9.

19 US Preventive Services Task Force, Owens DK, Davidson KW, Krist AH, Barry MJ, Cabana M, Caughey AB, Doubeni CA, Epling JW Jr, Kubik M, Landefeld CS, Mangione CM, Robert L, Silverstein M, Simon MA, Tseng CW, Wong JB. Risk Assessment, Genetic Counseling, and Genetic Testing for BRCA-Related Cancer: US Preventive Services Task Force Recommendation Statement. JAMA. 2019 Aug 20;322(7):652-665. DOI: 10.1001/jama.2019.10987. Erratum in: JAMA. 2019 Nov 12;322(18):1830. PMID: 31429903.

20 Forbes C, Fayter D, de Kock S, Quek RG. A systematic review of international guidelines and recommendations for the genetic screening, diagnosis, genetic counseling, and treatment of BRCA-mutated breast cancer. Cancer Manag Res. 2019 Mar 22;11:2321-2337. DOI: 10.2147/CMAR.S189627. PMID: 30962720; PMCID: PMC6434912.

21 Domchek, Susan M., et al. "Association of risk-reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality." *Jama* 304.9 (2010): 967-975.
22 Finch, Amy PM, et al. "Impact of oophorectomy on cancer incidence and mortality in women with a BRCA1 or BRCA2 mutation." *Journal of Clinical Oncology* 32.15 (2014): 1547.

23 El Khoury, Christiane J., et al. "Trends in Breast Cancer Staging at Diagnosis Associated with Screening Campaigns in Lebanon." *Women's Health Reports* 1.1 (2020): 521-528.

24 El Saghir, Nagi S., et al. "Trends in epidemiology and management of breast cancer in developing Arab countries: a literature and registry analysis." *International journal of surgery* 5.4 (2007): 225-233.

25 El Saghir, Nagi S., et al. "BRCA1 and BRCA2 mutations in ethnic Lebanese Arab women with high hereditary risk breast cancer." *The oncologist* 20.4 (2015): 357.

26 https://www.cancer.gov/about-cancer/causes-prevention/genetics/brca-fact-sheet#q6

27 Warner, Ellen. "Screening BRCA1 and BRCA2 mutation carriers for breast cancer." *Cancers* 10.12 (2018): 477.

28 Elsayegh, Nisreen, et al. "Contralateral prophylactic mastectomy rate and predictive factors among patients with breast cancer who underwent multigene panel testing for hereditary cancer." *Cancer medicine* 7.6 (2018): 2718-2726.

29 Engel, Christoph, et al. "Breast cancer risk in BRCA1/2 mutation carriers and noncarriers under prospective intensified surveillance." *International journal of cancer* 146.4 (2020): 999-1009.

30 Yao, Katharine, Mark Sisco, and Isabelle Bedrosian. "Contralateral prophylactic mastectomy: current perspectives." *International journal of women's health* 8 (2016): 213.

31 Nair N, Schwartz M, Guzzardi L, et al: Hysterectomy at the time of risk-reducing surgery in BRCA carriers. Gynecol Oncol Rep 26:71-74, 2018

32 Abildgaard, Julie, et al. "Mortality and risk of cancer after prophylactic bilateral oophorectomy in women with a family history of cancer." *JNCI cancer spectrum* 2.3 (2018): pky034.

33 Teoh, Victoria, Marios-Konstantinos Tasoulis, and Gerald Gui. "Contralateral prophylactic mastectomy in women with unilateral breast cancer who are genetic carriers, have a strong family history or are just young at presentation." *Cancers* 12.1 (2020): 140.

34 van den Broek, Alexandra J., et al. "Impact of age at primary breast cancer on contralateral breast cancer risk in BRCA1/2 mutation carriers." *J Clin Oncol* 34.5 (2016): 409-418.

35 Valachis, Antonis, Andreas D. Nearchou, and Pehr Lind. "Surgical management of breast cancer in BRCA-mutation carriers: a systematic review and meta-analysis." *Breast cancer research and treatment* 144.3 (2014): 443-455.

36 Anglian Breast Cancer Study Group. "Prevalence and penetrance of BRCA1 and BRCA2 mutations in a population-based series of breast cancer cases." *British Journal of Cancer* 83.10 (2000): 1301.

37 Papelard, H., et al. "Prevalence of BRCA1 in a hospital-based population of Dutch breast cancer patients." *British journal of cancer* 83.6 (2000): 719

38 Prince, Anya, and MPP JD. "Practical considerations in the delivery of genetic counseling and testing services for inherited cancer predisposition." *FROM THE EDITOR* (2013): 147.

39 Abu Bakar Hafeez Bhatti. Discussing Genetic Testing with Patients With Breast Cancer in Developing Countries: Should We Be Judicious? Journal of Clinical Oncology. Correspondence. Volume 33. Number 35. Dec 10, 2015

40 Robson, Mark E., et al. "American Society of Clinical Oncology policy statement update: genetic and genomic testing for cancer susceptibility." *J Clin Oncol* 28.5 (2010): 893-901.

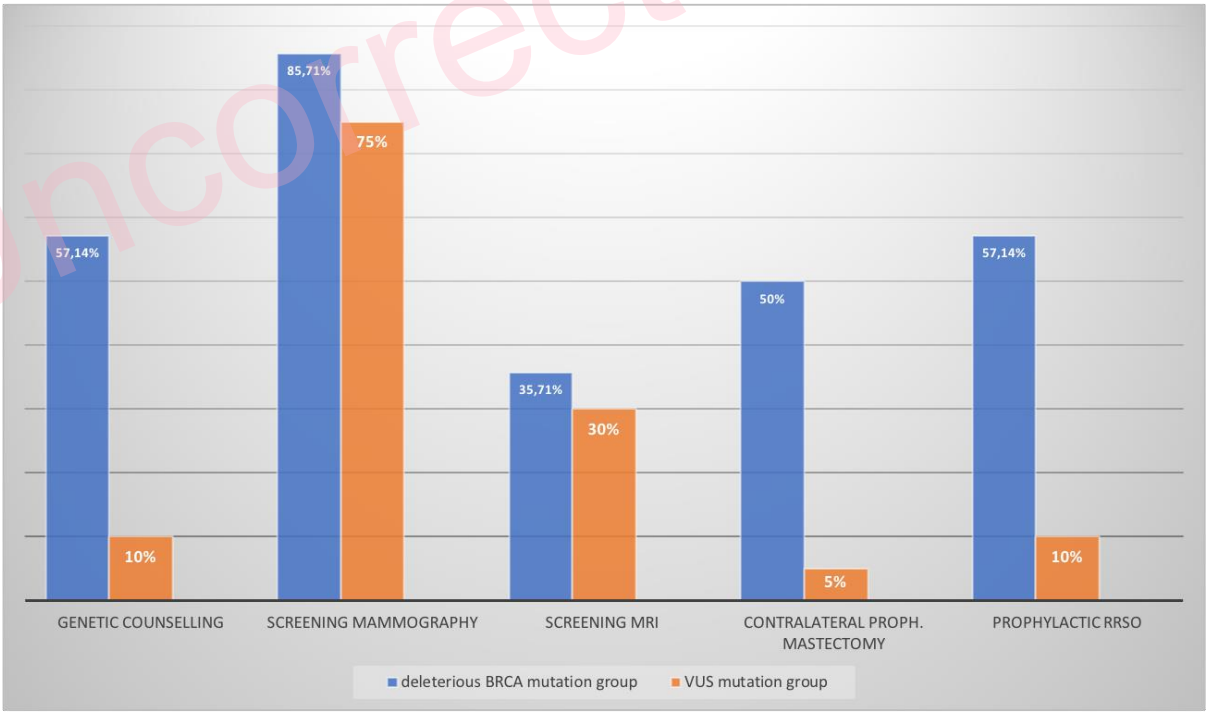
41 Ginsburg, Ophira, and Paul Brennan. "Genetic testing for breast cancer in the era of multigene panels: can we make an impact on population health?." *Journal of clinical oncology: official journal of the American Society of Clinical Oncology* 36.28 (2018): 2817-2819.

42 Pasick, Rena J., et al. "Effective referral of low-income women at risk for hereditary breast and ovarian cancer to genetic counseling: A randomized delayed intervention control trial." *American journal of public health* 106.10 (2016): 1842-1848.

43 Venetis, Maria K., et al. "Social network, surgeon, and media influence on the decision to undergo contralateral prophylactic mastectomy." *American journal of clinical oncology* 41.6 (2018): 519.

44 Cadiz, Fernando, et al. "Establishing a program for individuals at high risk for breast cancer." *Journal of Cancer* 4.5 (2013): 433.

45 Mateo, J., et al. "A framework to rank genomic alterations as targets for cancer precision medicine: the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT)." *Annals of Oncology* 29.9 (2018): 1895-1902.



Graph 1: Genetic counseling, screening mammography and MRI, Risk Reducing Surgery in patients with BRCA pathogenic and VUS mutations.