ISSN 2218-4333 (online)

World Journal of *Clinical Oncology*

World J Clin Oncol 2024 December 24; 15(12): 1459-1527

Published by Baishideng Publishing Group Inc

WJCO

World Journal of Clinical Oncology

Contents

Monthly Volume 15 Number 12 December 24, 2024

World Journal of Clinical Oncology

Monthly Volume 15 Number 12 December 24, 2024

Contents

ABOUT COVER

Editorial Board Member of *World Journal of Clinical Oncology*, Tomoyuki Takura, PhD, Professor, Department of Healthcare Economics and Health policy, Graduate School of Medicine, The University of Tokyo, Tokyo 113-8655, Japan. ttakura@m.u-tokyo.ac.jp

AIMS AND SCOPE

The primary aim of *World Journal of Clinical Oncology* (*WJCO*, *World J Clin Oncol*) is to provide scholars and readers from various fields of oncology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJCO mainly publishes articles reporting research results and findings obtained in the field of oncology and covering a wide range of topics including art of oncology, biology of neoplasia, breast cancer, cancer prevention and control, cancer-related complications, diagnosis in oncology, gastrointestinal cancer, genetic testing for cancer, gynecologic cancer, head and neck cancer, hematologic malignancy, lung cancer, melanoma, molecular oncology, neurooncology, palliative and supportive care, pediatric oncology, surgical oncology, translational oncology, and urologic oncology.

INDEXING/ABSTRACTING

The *WJCO* is now abstracted and indexed in PubMed, PubMed Central, Emerging Sources Citation Index (Web of Science), Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database. The 2024 Edition of Journal Citation Reports® cites the 2023 journal impact factor (JIF) for *WJCO* as 2.6; JIF without journal self cites: 2.6; 5-year JIF: 2.7; JIF Rank: 175/322 in oncology; JIF Quartile: Q3; and 5-year JIF Quartile: Q3.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Clinical Oncology

ISSN
ISSN 2218-4333 (online)

LAUNCH DATE
November 10, 2010

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Hiten RH Patel, Stephen Safe, Jian-Hua Mao, Ken H Young

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2218-4333/editorialboard.htm

PUBLICATION DATE
December 24, 2024

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

World Journal of Clinical Oncology

Submit a Manuscript: https://www.f6publishing.com

World J Clin Oncol 2024 December 24; 15(12): 1481-1490

DOI: 10.5306/wjco.v15.i12.1481

ISSN 2218-4333 (online)

ORIGINAL ARTICLE

Retrospective Study

Germline pathogenic variants among high hereditary risk patients with breast and ovarian cancer and unaffected subjects in Lebanese Arab women

Hiba A Moukadem, Mohammad A Fakhreddine, Nada Assaf, Nadine Safi, Ahmad Al Masry, Monita Al Darazi, Rami Mahfouz, Nagi S El Saghir

Specialty type: Oncology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade C

Novelty: Grade B

Creativity or Innovation: Grade B

Scientific Significance: Grade B

P-Reviewer: Zou YZ

Received: July 10, 2024

Revised: August 23, 2024

Accepted: October 11, 2024

Published online: December 24, 2024

Processing time: 103 Days and 11.4 Hours

Hiba A Moukadem, Mohammad A Fakhreddine, Nadine Safi, Ahmad Al Masry, Monita Al Darazi, Nagi S El Saghir, Division of Hematology/Oncology, Department of Internal Medicine, American University of Beirut Medical Center, Beirut 1107 2020, Lebanon

Nada Assaf, Rami Mahfouz, Department of Pathology and Laboratory Medicine, American University of Beirut Medical Center, Beirut 1001, Lebanon

Corresponding author: Nagi S El Saghir, MD, Professor, Division of Hematology Oncology, Department of Internal Medicine, American University of Beirut Medical Center, Cairo Street, PO Box 11-0236, Riad El Solh, Beirut 1107 2020, Lebanon. ns23@aub.edu.lb

Abstract

BACKGROUND

The prevalence of germline pathogenic variants in high hereditary risk breast and/or ovarian cancer patients and unaffected subjects referred for testing is an unmet need in low and middle-income countries.

AIM

To determine the prevalence of germline pathogenic variants in high hereditary risk patients with breast and/or ovarian cancer and unaffected individuals.

METHODS

We retrospectively reviewed records of patients and unaffected subjects referred for germline pathogenic variant testing due to high hereditary risk between 2010-2020. Data was collected and analyzed on Excel sheet.

RESULTS

In total, 358 individuals were included, including 257 patients and 101 unaffected individuals with relatives with breast or ovarian cancer. The prevalence of *breast cancer susceptibility gene (BRCA) 1/2* pathogenic variants was 8.63% (19/220) in patients with breast cancer, and 15.1% (5/33) in those with ovarian cancer. Among the 25 of 220 patients with breast cancer tested by next-generation sequencing, 3 patients had pathogenic variants other than *BRCA1/2*. The highest risk was observed in those aged 40 years with breast cancer and a positive family history, where the *BRCA1/2* prevalence was 20.1% (9/43). Among the unaffected subjects,

31.1% (14/45) had the same *BRCA1/2* pathogenic variants in their corresponding relatives. Among the subjects referred because of a positive family history of cancer without known hereditary factors, 5.35% (3/56) had pathogenic variants of *BRCA1* and *BRCA2*. The c.131G>T nucleotide change was noted in one patient and two unrelated unaffected subjects with a *BRCA1* pathogenic variant.

CONCLUSION

This study showed a 8.63% prevalence of pathogenic variants in patients with breast cancer and a 15.1% prevalence in patients with ovarian cancer. Among the relatives of patients with *BRCA1/2* pathogenic variants, 31% tested positive for the same variant, while 5.3% of subjects who tested positive due to a family history of breast cancer had a *BRCA* pathogenic variant.

Key Words: Breast cancer; Ovarian cancer; *Breast cancer susceptibility gene 1/2*; Germline pathogenic variant; High hereditary risk

Core Tip: This is the first study on referred patients with breast and/or ovarian cancer and subjects at high hereditary risk for germline pathogenic variant testing among ethnic Lebanese Arab women. The prevalence of pathogenic variants was 8.63% in patients with breast cancer and 15.1% in patients with ovarian cancer. Among the relatives of patients with *breast cancer susceptibility gene (BRCA) 1/2* pathogenic variants, 31% tested positive for the same variant, while 5.3% of subjects who tested positive due to a family history of breast cancer had a *BRCA* pathogenic variant. The results of this study support the hypothesis that the c.131G>T nucleotide change is a founder pathogenic variant in this population.

Citation: Moukadem HA, Fakhreddine MA, Assaf N, Safi N, Al Masry A, Al Darazi M, Mahfouz R, El Saghir NS. Germline pathogenic variants among high hereditary risk patients with breast and ovarian cancer and unaffected subjects in Lebanese Arab women. *World J Clin Oncol* 2024; 15(12): 1481-1490
URL: https://www.wjgnet.com/2218-4333/full/v15/i12/1481.htm
DOI: https://dx.doi.org/10.5306/wjco.v15.i12.1481

INTRODUCTION

According to the Global Cancer Observatory 2022, breast cancer is the most common cancer in females, accounting for 23.8% of new cancer cases worldwide, while ovarian cancer accounts for 3.4% of all cases[1]. In Lebanon, breast cancer constitutes 35%-40% of cancers in women, with 50% of cases diagnosed below the age of 50 years, and ovarian cancer constitutes 1.7% of cases[2-3]. The age-standardized incidence-rate of breast cancer was estimated at 91.7 per 100000 between 2005 and 2015, and 7.10 per 100000 for ovarian cancer between 2005 and 2016[3].

Most breast cancer cases are sporadic, with up to 15% familial and up to 10% hereditary[4]. High-penetrance genes, including *BRCA1* and *BRCA2*, are responsible for 50% of the hereditary breast cancer cases[5]. *BRCA1* and *BRCA2* are tumor suppressor genes located on chromosomes 17q and 13q, with 22 and 26 coding exons, respectively[6]. Most pathogenic variants in the coding sequences of these genes are point mutations, insertions, or deletions that cause shortening of the BRCA1 protein, ultimately leading to alterations in the DNA repair systems. The prevalence of pathogenic *BRCA* variants ranges from 0.6%-36.9% across different countries[5].

The criteria for testing for germline pathogenic variants in breast cancer cases include women with triple-negative breast cancer (TNBC) below the age of 60 years, young age at diagnosis, or a family history of breast or ovarian cancer[7-10]. Studies have shown that 15%-25% of ovarian cancer cases are associated with *breast cancer susceptibility gene (BRCA) 1/2* germline pathogenic variants[11,12]. The estimated lifetime risk of developing breast cancer in women with *BRCA1/2* pathogenic variants ranges between 59%-69% for *BRCA1* and 48%-72% for *BRCA2*; for ovarian cancer, the risk is between 39%-58% and 13%-29% for carriers of *BRCA1* and *BRCA2*, respectively[13]. Breast cancer predisposition is also significantly elevated in partner and localizer of *BRCA2* (*PALB2*) pathogenic variants, whose carriers have a 41%-60% lifetime risk of developing breast cancer[14,15].

In 2015, a prospective study of 250 Arab Lebanese women with breast cancer who met the criteria for genetic testing showed an overall prevalence of *BRCA1* and *BRCA2* pathogenic variants of 5.6%[16], while it was estimated to be 10%-15% in similar cohorts from the United States and Europe[17]. Studies from neighboring Arab countries showed a prevalence up to 20%[18]. Higher estimates have been reported in studies from Jordan (19.6% of *BRCA* pathogenic variants)[19] and Saudi Arabia (12.9%)[20]. For ovarian cancer, scarce data exist from Arab countries, and none from Lebanon.

The discovery of a pathogenic variant in either patient group (breast or ovarian cancer)[21-24] has implications not only for screening and early detection but also for patient management diagnosed with early or metastatic disease[25-27]. The detection of pathogenic variants could also benefit family members of patients with germline alterations, who are typically counseled about the risks of developing cancers and appropriate preventive and early detection options[28].

Identifying pathogenic variants in other moderate-risk genes [such as *PALB2*, *ataxia telengectasia mutated* (*ATM*), *checkpoint kinase 2* (*CHEK2*), *BRCA1 interacting protein C-terminal helicase 1* (*BRIP1*)] is also gaining clinical importance[29-32]. Antoniou *et al*[14] analyzed the risk of breast cancer in 362 patients with the *PALB2* pathogenic variant and found that carriers were associated with an 8-9 times higher probability of developing breast cancer in those younger than 40 years, 6-8 times higher in those aged between 40 years and 60 years, and 5 times higher in those older than 60 years. Data on these variants in Arab populations are either missing or scarce[20].

The aim of this study was to assess the prevalence of *BRCA1/2* and other germline pathogenic variants in patients and nonaffected subjects at high-risk for hereditary breast and/or ovarian cancer in ethnic Lebanese Arab referred for testing at the American University of Beirut Medical Center (AUBMC) Genetics Laboratory between 2010 and 2020. In our initial Institutional Review Board (IRB)-approved project, we planned to include the prevalence of pathogenic variants in patients with prostate cancer; however, the number of patients was only three. Therefore, we present and analyze data on patients with breast and/or ovarian cancer in this article.

MATERIALS AND METHODS

A retrospective chart review was conducted to retrieve the clinical, radiologic, pathologic, and genetic data of 358 individuals with a high hereditary risk for breast and ovarian cancer who were referred to the AUBMC laboratory for genetic testing between January 1, 2010, and August 25, 2020. Between January 1, 2010 and January 1, 2019, testing for *BRCA1* and *BRCA2* was performed by Sanger sequencing of all coding exons and immediately flanking introns. In 2019, Sanger sequencing was replaced by next-generation sequencing (NGS) panels of 70 cancer-related genes at Centogene Laboratories in Germany. The study was reviewed and approved by the IRB of AUBMC.

Data collection and analysis

Patient data were accessed through electronic medical records from papers and electronic (EPIC) medical records. The EPIC Program started at the AUBMC in November 2018. The data collection sheet included the following variables: (1) Demographics; (2) Age; (3) Tumor pathology; (4) Tumor staging; (5) Tumor characteristics; (6) Family history of cancer; (7) Treatment received; (8) Laboratory and imaging results; and (9) Outcomes. All male and female subjects with a family history of breast or ovarian cancer and patients with breast or ovarian cancer who underwent germline pathogenic variant testing performed between January 01, 2010, and August 25, 2020, at the AUBMC were included in this study. The National Comprehensive Cancer Network (NCCN) criteria were used for germline genetic testing. All the included participants were eligible for testing. The NCCN criteria for testing of unaffected individuals with a positive family history: (1) > 1 first-degree or second-degree relative with breast cancer at age ≤ 50 years, male breast, ovarian, pancreatic, metastatic prostate cancers; Or (2) > 3 first-degree or second-degree relatives with breast and/or prostate cancer. Because this was a retrospective study, the sample size was not calculated. All patients who fulfilled the eligibility criteria were enrolled. The patients and unaffected participants were referred from various hospitals and communities for testing. The principal investigator and research team had exclusive access to the patients' medical records for data collection and analysis. Data were de-identified after collection, and each patient was given a unique code, which was used for data analysis to ensure confidentiality. The list of code numbers with corresponding patient names was recorded on a separate datasheet accessible only to the research team. The linking documents were shredded after the data collection was completed. Consent forms were not required because the patients were not approached. All medical and genetic variants were verified against germline variants in the ClinVar international database. The collected data were entered on a Microsoft Excel sheet and analyzed, and the results were calculated using the same program.

Sanger sequencing

DNA was extracted from blood and saliva samples received (blood/saliva). It was then PCR amplified for sequence-based analysis to screen for mutations in all 24 coding exons of *BRCA1* and 27 coding exons of *BRCA2*. Sanger sequencing was performed using the Applied Biosystems strategy for automated fluorescent sequencing with a Big Dye Terminator. The analysis consisted of sequencing all coding exons immediately flanking the intronic regions of *BRCA1* and *BRCA2*. The sequence was obtained and analyzed by comparison with published *BRCA1* and *BRCA2* gene sequences. Software analysis was performed using Mutation Taster (http://mutationtaster.org), Polyphen-2 (http://genetics.bwh.harvard.edu), SIFT software (http://sift.jcvi.org), and the International Agency for Research on Cancer database (http://brca.iarc.fr) to predict the nature of the detected variants.

NGS testing

Starting with DNA isolated from the blood or saliva, sequencing-ready libraries are generated using highly multiplexed oligonucleotide probes. The sample-specific indices were added to each library. The pooled libraries were loaded onto a MiSeq system (Illumina) for automated sequencing and data analysis. The oligo pool targeted 65 full-length genes and 125 single nucleotide polymorphisms. This panel uses hybrid-capture chemistry to provide uniform coverage of the target regions (exons plus 10 bp flanking regions), enabling > 20 × coverage for > 99% of the amplicons. Known pathogenic and likely pathogenic variants described in Human Gene Mutation Database® and the CENTOGENE's Biodatabank, including relevant deep intronic and regulatory variants known at the time of the assay design. Genes tested in this panel include: (1) *Anaphase-promoting-complex*; (2) *ATM*; (3) *Axis inhibition protein 2*; (4) *BRCA associated protein 1*; (5) *Breast cancer susceptibility 1-associated RING domain*; (6) *Bleomycin*; (7) *Bone morphogenetic protein receptor, type IA*; (8) *BRCA1*; (9) *BRCA2*; (10) *BRIP1*; (11) *E-cadherin*; (12) *Cyclin-dependent kinases 4*; (13) *CDKN2A*; (14) *CHEK2*; (15) *Dicer*

1, *ribonuclease III*; (16) *DIS3 like 3'-5' exoribonuclease 2*; (17) *Epithelial cell adhesion molecule*; (18) *FANCC*; (19) *Fused hirudin*; (20) *Folliculin*; (21) *Polypeptide N-acetylgalactosaminyltransferase 12*; (22) *Homeobox protein B13*; (23) *KIT*; (24) *Melano-cortin 1 receptor*; (25) *Multiple endocrine neoplasia type 1*; (26) *Methylation*; (27) *Microphthalmia-associated transcription factor*; (28) *MutL homolog* (*MLH*) *1*; (29) *MLH3*; (30) *Meiotic recombination 11*; (31) *MutS homolog* (*MSH*)*2*; (32) *MSH3*; (33) *MSH6*; (34) *MutY human homologue*; (35) *Nitrogen balance*; (36) *Neurofibromatosis type 1*; (37) *N tabacum hybrid lethality 1*; (38) *PALB2*; (39) *PMS1 homolog 2*; (40) *Polymerase delta 1*; (41) *Polymerase (DNA) epsilon, catalytic subunit*; (42) *Peroxisomal 3-oxoacyl-CoA thiolase gene* ; (43) *Cationic trypsinogen gene*; (44) *Patched 1*; (45) *Chromosome 10*; (46) *RAD50*; (47) *RAD51C*; (48) *RAD51D*; (49) *RecQ like helicase*; (50) *Glial cell derived neurotrophic factor receptor-beta*; (51) *Ring finger protein 43*; (52) *Ribosomal protein S20*; (53) *Succinate dehydrogenase complex flavoprotein subunit A*; (54) *Succinate dehydrogenase assembly factor 2*; (55) *Succinate dehydrogenase B*; (56) *Shunt-dependent hydrocephalus*; (57) *Succinate dehydrogenase complex subunit D*; (58) *Mothers against decapentaplegic homolog 4*; (59) *Matrix-associated, actin-dependent regulator of chromatin, subfamily A, member 4*; (60) *Serine/threonine kinase 11*; (61) *Tumor protein p53* (TP53); (62) *Tuberous sclerosis complex* (*TSC*)*1*; (63) *TSC2*; (64) *Von hippel-lindau*; (65) *Wilms' tumor 1*; (66) *X-ray repair of cross-complementary* (*XRCC*) *2*; and (67) *XRCC3*. Unaffected family members with known familial pathogenic or likely pathogenic variants of a cancer predisposition gene were subjected to targeted sequencing for known familial variants. PCR analysis was performed by means of PCR followed by Sanger sequencing of the exons harboring a known mutation in the gene of interest.

RESULTS

Patients with breast cancer

Of the 358 individuals included in the study, 220 had breast cancer. Two hundred and nineteen were females and one was a male. Forty-three were diagnosed at age ≤ 40 years, 75 were aged between 41-50 years, and 102 were aged > 50 years at diagnosis. One hundred and seventy-five subjects underwent *BRCA1/2* Sanger sequencing, and 25 underwent NGS panel testing. One male patient with both breast and prostate cancers also underwent *BRCA1/2* Sanger sequencing (Figure 1, Tables 1 and 2).

Patients with ovarian cancer

Of the 358 individuals referred for genetic testing, 33 had ovarian cancer. Thirty patients underwent Sanger sequencing and three underwent NGS panel testing. Three patients had both ovarian and breast cancers (Figure 1, Tables 1 and 2).

In this study, the incidence of *BRCA1* and *BRCA2* pathogenic variants in women with breast and ovarian cancers was 8.63% (19/220) and 15.1% (5/33), respectively (Table 3). Of the three patients with both breast and ovarian cancers, two had a *BRCA1* pathogenic variant.

Pathogenic variants and age

Forty-three of the 220 patients with breast cancer were aged 40 years or younger, nine of whom had a *BRCA1/2* pathogenic variant (20.1%). Of the 19 patients with breast cancer and *BRCA1/2* pathogenic variants, 9 were ≤ 40 years old. Among the 28 patients who underwent NGS panel sequencing (25 with breast cancer and 13 with ovarian cancer), two had a *PALB2* pathogenic variant, and one had a *TP53* pathogenic variant. All three patients had breast cancer (Table 4).

Pathogenic variants and pathology data: Pathological data were available for all the 207 patients. Of these, 166 patients (80.19%) had Infiltrating Ductal Carcinoma, 10 patients (4.83%) had Infiltrating Lobular Carcinoma, 30 patients (14.49%) had ductal Carcinoma in situ, one had invasive tubulolobular carcinoma and one had a high-grade neuroendocrine tumor. Data were available for 205 patients; 22 patients (10.7%) had grade 1 disease, 70 patients (34.1%) had grade 2 disease, and 113 patients (55.1%) had grade 3 disease. Estrogen receptors were positive in 143/208 patients (68.75%), progesterone receptor was positive in 129/208 patients (62%), human epidermal growth factor receptor 2 (HER2) was overexpressed in 74/207 patients (35.74%), and HER2 was not available in one patient. TNBC was present in 43/208 patients (20.67%).

BRCA1 pathogenic variants were found in 23.25% (10/43) of patients with TNBC, and 62.5% of *BRCA1* pathogenic variant (10/16) had TNBC. Of the five *BRCA2* patients with breast cancer, one had TNBC, two had HER2 overexpression with hormone-receptor (HR)-positive sensitivity, and two had HR+. Complete pathological information was available for all patients with pathogenic variants.

Nonaffected subjects

A total of 101 individuals without a cancer diagnosis were referred for testing because of a positive family history of cancer or a known deleterious pathogenic variant in first-degree or second-degree family members. Of these, 31% were pathogenic *BRCA* variants. Eleven subjects (out of 30) who underwent targeted sequencing for *BRCA1* carried the familial variant, and three subjects (out of 15) with known familial *BRCA2* pathogenic variants were found to be carriers. Of the remaining 56 (out of 101) patients tested due to a positive family history of cancer, three (5.3%) had a *BRCA* pathogenic variant, two had a pathogenic *BRCA1* variant, and one had a pathogenic *BRCA2* variant (Figure 2, Table 5).

Table 1 *Breast cancer susceptibility gene 1* pathogenic variants identified in patients with breast and/or ovarian cancer

Nucleotide change	Molecular consequence	Location	Number of patients
Breast cancer			
C.1039_1040del	P.Leu347fs	Exon 10	1
C.2158G>T	P.Glu720Ter	Exon 11	2
C.5431C>T	P.Gln1811Ter	Exon 22	1
C.3257T>G	P.Leu1086Ter	Exon 10	1
C.679G>T	P.Glu227Ter	Exon 9	2
C.4065_4068delTCAA	P.Asn1355fs	Exon 10	1
C.3607C>T	P.Arg1203Ter	Exon 10	2
C.4096+1G>A	Splice donor	Intron 10	1
C.66dup	P.Glu23fs	Exon 2	1
C.131G>T	P.Cys44Phe	Exon 3	1
C.224_227del	P.Glu75fs	Exon 5	1
Ovarian cancer			
C.4065_4068del	P.Asn1355fs	Exon 10	1
C.2158G>T	P.Glu720Ter	Exon 11	1
C.34C>T	P.Gln12Ter	Exon 2	1
C.3381T>G[1]	P.Tyr1127Ter	Exon 10	1
C.2158G>T[1]	P.Glu720Ter	Exon 11	1

[1]One patient had both breast and ovarian cancer.

Table 2 *Breast cancer susceptibility gene 2* pathogenic variants identified in patients with breast/ovarian cancer

Nucleotide change	Molecular consequence	Location	Number of patients
Breast cancer			
C.9257-1G>A	Splice acceptor	Intron 24	3
C.3189_3192del	P.Ser1064fs	Exon 11	1
C.2808_2811del	P.Ala938fs	Exon 11	1
Ovarian cancer			
C.9257-1G>A	Splice acceptor	Intron 24	1
C.7806-2A>T	Splice acceptor	Intron 16	1

DISCUSSION

To our knowledge, this is the first study of germline pathogenic variants in ethnic Lebanese Arab patients with cancer and in unaffected subjects at high risk for hereditary breast and ovarian cancer referred for testing. The types of pathogenic variants observed were comparable to those described in the literature and genetic banks, including stop codons, frameshifts, and splice-site mutations. The total incidence of *BRCA1/2* pathogenic variants in our cohort of patients with breast cancer was 8.63% (19/220). Other small studies have shown a *BRCA1/2* prevalence of 7.4%[19] and 12.5%[33] among individuals with a high risk for hereditary breast or ovarian cancer genes. In Lebanon, approximately 50% of the patients with breast cancer are younger than 50 years[4]. The first *BRCA* testing study was published in 2012, in which 72 unrelated patients with a reported family history of breast and/or ovarian cancers were tested, and 9 subjects were identified to carry a deleterious mutation (12.5%)[33]. In a study of ethnic Arab patients with hereditary breast cancer in Saudi Arabia, 40 patients (12.9%) had *BRCA1/2* pathogenic variants (*BRCA1* in 10.7% and *BRCA2* in 2.2%)[20]. A recent study of 81 patients with breast cancer in Egypt showed a 14.8% risk of *BRCA1/2* pathogenic variants among this population[18].

Table 3 Genetic testing results for patients diagnosed with breast and/or ovarian cancer

Type of cancer	Affected gene	Pathogenic variant
Breast	*BRCA1*	6.36 (14/220)
	BRCA2	2.27 (5/220)
	BRCA1/2	8.63 (19/220)
Ovarian	*BRCA1*	9.09 (3/33)
	BRCA2	6.06 (2/33)
	BRCA1/2	15.15 (5/33)
Breast and ovarian	*BRCA1*	2/3

BRCA: *Breast cancer susceptibility gene*.

Table 4 Sequence mutations identified in patients with germline pathogenic variants other than *breast cancer susceptibility gene 1/2* (all 3 patients were diagnosed with breast cancer)

Genes	Nucleotide change	Molecular consequence	Location	Number of patients
PALB2	C.2257C>T	P.Arg753Ter	Exon 5	1
PALB2	C.93dupA	P.Leu32fs	Exon 2	1
Tumor protein p53	C.375G>A	P.(Thr125)	Exon 4	1

PALB2: Partner and localizer of breast cancer susceptibility gene 2.

Table 5 Sequence pathogenic variants identified in non-affected subjects with deleterious *breast cancer susceptibility gene 1* and *breast cancer susceptibility gene 2* variants

Nucleotide change	Molecular consequence	Location	Number of unaffected subjects
BRCA1			
C.2158G>T	P.Glu720Ter	Exon 11	3
C.3555del	P.Glu1185fs	Exon 10	3
C.34C>T	P.Gln12Ter	Exon 2	2
C.131G>T	P.Cys44Phe	Exon 3	2
C.679G>T	P.Glu227Ter	Exon 9	1
C.4065_4068del	P.Asn1355fs	Exon 10	1
C.3679C>T[1]	P.Gln1227Ter	Exon 9	1
BRCA2			
C.4342_4343del	P.Asn1448fs	Exon 11	2
C.9257-1G>A	Splice acceptor	Intron 24	1
C.5804del	P.Asn1935fs	Exon 11	1

[1]Unknown personal or family history of cancer.
BRCA: *Breast cancer susceptibility gene*.

In our study, almost all patients with hereditary breast cancer had a positive family history (11/14 for *BRCA1* and 5/5 for *BRCA2*) and most were younger than 40 years (8/14 for *BRCA1* and 2/5 for *BRCA2*). *BRCA1* pathogenic variants were found in 23.25% (10/43) of patients with TNBC and in 62.5% of *BRCA1* (10/16) of patients with TNBC. Of the five *BRCA2* patients with breast cancer, one had TNBC, two had HER2 overexpression with HR-positive sensitivity, and two had HR+. Data from Saudi Arabia showed that TNBC was present in 93.9% of patients with *BRCA1* and 57.1% of patients with *BRCA2*[20]. According to the present and previously reported data[16], the TNBC subtype, age at diagnosis < 40

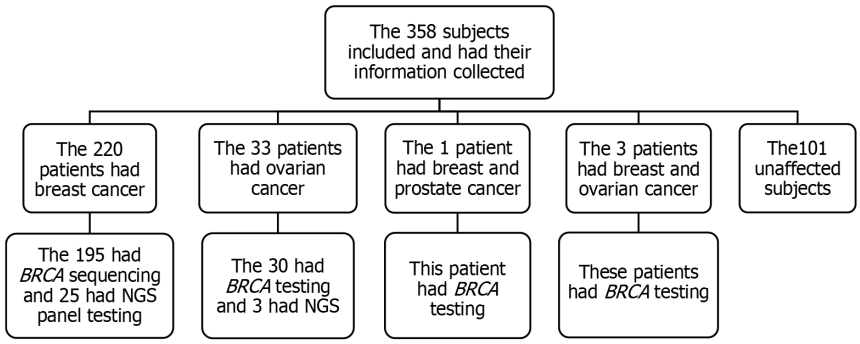

Figure 1 Patients and non-affected subjects distribution and testing. *BRCA*: *Breast cancer susceptibility* gene; NGS: Next-generation sequencing.

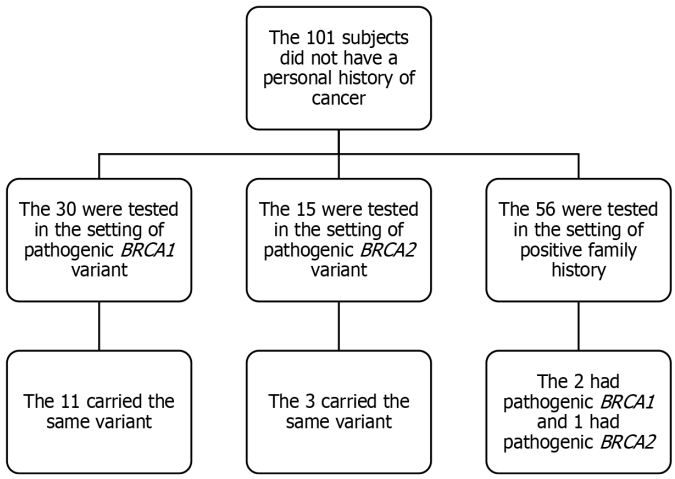

Figure 2 Non-affected subjects results. *BRCA*: *Breast cancer susceptibility* gene.

years, and positive family history are the most useful criteria for selecting patients with breast cancer for pathogenic variant testing, especially when resources are limited.

Additionally, the c.131G > T nucleotide change was present in one patient and two unaffected subjects harboring *BRCA1* pathogenic variants, which was reported in our previous study in a different Lebanese Arab patient cohort, whose DNA sequencing was performed at the Institut Jean Perrin in France[16], supporting the suggestion that this gene sequence found in several unrelated subjects is a founder pathogenic variant in this population.

For ovarian cancer, the overall incidence of *BRCA1/2* pathogenic variants was 15.1% (5/33), with all five patients having a positive family history of ovarian cancer. This is the first study to report almost a 15% rate of *BRCA1/2* pathogenic variants in patients with ovarian cancer in ethnic Lebanese Arab women. Other studies conducted in the Arab world reported 21.8% (14/64) of *BRCA1/2* pathogenic variants in ovarian cancer in Kuwait, with 10 having *BRCA1* and four having *BRCA2*[34]. Another study conducted in Saudi Arabia reported a prevalence of *BRCA1/2* pathogenic variants of 20.5% (24/117) in a high-risk Middle Eastern population[35]. Despite variable incidences reported due to small size studies, the average of *BRCA1/2* pathogenic variants in patients with ovarian cancer was approximately 20% in the Gulf Arab countries[36]. A prospective study from five Gulf countries tested *BRCA1/2* in 105 patients with ovarian cancer, of whom 17% harbored a pathogenic variant[37]. In an Arabian Peninsula study, 173 patients were tested for *BRCA1/2* pathogenic variants, with 10.2% pathogenic in 108 patients with breast cancer and 30.7% in 65 patients with ovarian cancer[38]. The largest epidemiological study of ovarian cancer in Arab countries was conducted by Younes and Zayed [39], which included 802 subjects, of whom 53 (approximately 15%) tested positive for a pathogenic variant in the *BRCA1/2* genes.

Testing relatives of patients with pathogenic variants yielded significant information about these subjects. Of the subjects, 36.7% (11/30) carried the same *BRCA1* pathogenic variant and 20% (3/15) carried the same *BRCA2* pathogenic variant. A smaller number of subjects with familial non-hereditary breast cancer had a pathogenic variant (two with *BRCA1* and one with a *BRCA2* variant). In this retrospective real-world study of unaffected individuals referred for genetic testing by virtue of a family history of malignancy, we recognize that the limitation of our study is that more than one unaffected individual per family may have been tested, which may have caused an increase in the variant frequency in this group.

The presence of a pathogenic variant in patients with diagnosed cancer or in unaffected subjects could have clinical implications at multiple levels, including the management of patients with cancer, screening for early detection with imaging of the breasts, such as mammography alternating with breast magnetic resonance imaging every 6 months, risk-

reducing surgeries (bilateral prophylactic mastectomies and bilateral salpingo-oophorectomy), and chemoprevention with tamoxifen. The use of poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitors such as olaparib is one example of a positive *BRCA* pathogenic variant affecting the medical management of patients with breast and/or ovarian cancer. In patients harboring a pathogenic variant of the *BRCA* gene, olaparib is indicated in an adjuvant setting for high-risk early breast cancer and for the treatment of patients with metastatic breast cancer[21,24]. PARP inhibitors are also used in advanced ovarian cancer after debulking surgery for maintenance or treatment of recurrent ovarian disease[25].

Variations among patients in the Middle East emphasize the need for periodic studies of germline variants in various ethnic populations, as penetrance and occurrence of cancer may be modified by other genetic alterations, reproductive factors, environmental factors, exercise, or diet. Recognizing population divergence underscores the need to deeply study population-specific genomes and environmental modifiers to better understand the fundamental genotype-phenotype correlations in such wide populations[40]. Pathogenic variants of *PALB2* and *TP53* were identified in patients who underwent NGS, emphasizing the importance of NGS in screening eligible patients.

CONCLUSION

In this cohort of patients and subjects with or at high hereditary risk for breast and/or ovarian cancer referred for germline testing, the prevalence of *BRCA1/2* pathogenic variants was approximately 8.63% in patients with breast cancer. Patients with breast cancer who had TNBC or were young and had a positive family history had a 23.25% or 20.1% chance to have a *BRCA1/2* pathogenic variant, respectively. Our study showed an almost 15% rate of *BRCA1/2* pathogenic variants. This high percentage highlights the need to refer all patients with ovarian cancer for counseling and genetic testing in accordance with the current international society guidelines. We report 31% positivity (14/45 subjects) in relatives of patients with hereditary breast cancer and emphasize the importance of testing healthy relatives of patients identified as carrying familial germline pathogenic variants. The introduction of NGS techniques for germline pathogenic variant testing has also allowed the detection of pathogenic variants in other inherited cancer genes and subsequent better counseling and management. One limitation of this study was its retrospective nature. Patients were referred for testing by different primary physicians and centers in the country; therefore, there was a potential selection bias. In addition, complete medical records were not available from our genetic laboratory for all patients.

FOOTNOTES

Author contributions: El Saghir NS was responsible for conception and design and administrative support; Mahfouz R and El Saghir NS were responsible for provision of study materials or patients; Moukadem HA, Fakhreddine MA, Assaf N, Safi N, Al Masry A, Al-Darazi MH and El Saghir NS were responsible for collection and assembly of data; Moukadem HA, Fakhreddine MA, Assaf N and El Saghir NS were responsible for data analysis and interpretation; Moukadem HA, Fakhreddine MA, Assaf N, Safi N, Al Masry A, Al Darazi M, Mahfouz R and El Saghir NS were responsible for manuscript writing and final approval of manuscript; all of the authors read and approved the final version of the manuscript to be published.

Institutional review board statement: The study was reviewed and approved by the Institutional Review board at the American University of Beirut Medical Center.

Informed consent statement: No consent form was required since patients were not approached.

Conflict-of-interest statement: All authors declare no conflict of interest in publishing the manuscript.

Data sharing statement: Study data are available upon request from the corresponding author.

Country of origin: Lebanon

ORCID number: Nada Assaf 0000-0002-3352-2660; Monita Al Darazi 0000-0002-6274-0464; Nagi S El Saghir 0000-0001-9612-4224.

S-Editor: Luo ML
L-Editor: A
P-Editor: Zhao S

REFERENCES

1 **Bray F**, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, Jemal A. Global cancer statistics 2022: GLOBOCAN estimates of

incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2024; **74**: 229-263 [PMID: 38572751 DOI: 10.3322/caac.21834]

2 **El Saghir NS**, Adib S, Mufarrij A, Kahwaji S, Taher A, Issa P, Shamseddine AI. Cancer in Lebanon: analysis of 10,220 cases from the American University of Beirut Medical Center. *J Med Liban* 1998; **46**: 4-11 [PMID: 9795515]

3 **Shamseddine A**, Sibai AM, Gehchan N, Rahal B, El-Saghir N, Ghosn M, Aftimos G, Chamsuddine N, Seoud M; Lebanese Cancer Epidemiology Group. Cancer incidence in postwar Lebanon: findings from the first national population-based registry, 1998. *Ann Epidemiol* 2004; **14**: 663-668 [PMID: 15380797 DOI: 10.1016/j.annepidem.2003.12.002]

4 **El Saghir NS**, Khalil MK, Eid T, El Kinge AR, Charafeddine M, Geara F, Seoud M, Shamseddine AI. Trends in epidemiology and management of breast cancer in developing Arab countries: a literature and registry analysis. *Int J Surg* 2007; **5**: 225-233 [PMID: 17660128 DOI: 10.1016/j.ijsu.2006.06.015]

5 **Armstrong N**, Ryder S, Forbes C, Ross J, Quek RG. A systematic review of the international prevalence of BRCA mutation in breast cancer. *Clin Epidemiol* 2019; **11**: 543-561 [PMID: 31372057 DOI: 10.2147/CLEP.S206949]

6 **Ramus SJ**, Gayther SA. The contribution of BRCA1 and BRCA2 to ovarian cancer. *Mol Oncol* 2009; **3**: 138-150 [PMID: 19383375 DOI: 10.1016/j.molonc.2009.02.001]

7 **Moyer VA**; U. S. Preventive Services Task Force. Risk assessment, genetic counseling, and genetic testing for BRCA-related cancer in women: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 2014; **160**: 271-281 [PMID: 24366376 DOI: 10.7326/M13-2747]

8 **Paluch-Shimon S**, Cardoso F, Sessa C, Balmana J, Cardoso MJ, Gilbert F, Senkus E; ESMO Guidelines Committee. Prevention and screening in BRCA mutation carriers and other breast/ovarian hereditary cancer syndromes: ESMO Clinical Practice Guidelines for cancer prevention and screening. *Ann Oncol* 2016; **27**: v103-v110 [PMID: 27664246 DOI: 10.1093/annonc/mdw327]

9 **Garutti M**, Foffano L, Mazzeo R, Michelotti A, Da Ros L, Viel A, Miolo G, Zambelli A, Puglisi F. Hereditary Cancer Syndromes: A Comprehensive Review with a Visual Tool. *Genes (Basel)* 2023; **14**: 1025 [PMID: 37239385 DOI: 10.3390/genes14051025]

10 **Tung NM**, Boughey JC, Pierce LJ, Robson ME, Bedrosian I, Dietz JR, Dragun A, Gelpi JB, Hofstatter EW, Isaacs CJ, Jatoi I, Kennedy E, Litton JK, Mayr NA, Qamar RD, Trombetta MG, Harvey BE, Somerfield MR, Zakalik D. Management of Hereditary Breast Cancer: American Society of Clinical Oncology, American Society for Radiation Oncology, and Society of Surgical Oncology Guideline. *J Clin Oncol* 2020; **38**: 2080-2106 [PMID: 32243226 DOI: 10.1200/JCO.20.00299]

11 **Kuchenbaecker KB**, Hopper JL, Barnes DR, Phillips KA, Mooij TM, Roos-Blom MJ, Jervis S, van Leeuwen FE, Milne RL, Andrieu N, Goldgar DE, Terry MB, Rookus MA, Easton DF, Antoniou AC; BRCA1 and BRCA2 Cohort Consortium, McGuffog L, Evans DG, Barrowdale D, Frost D, Adlard J, Ong KR, Izatt L, Tischkowitz M, Eeles R, Davidson R, Hodgson S, Ellis S, Nogues C, Lasset C, Stoppa-Lyonnet D, Fricker JP, Faivre L, Berthet P, Hooning MJ, van der Kolk LE, Kets CM, Adank MA, John EM, Chung WK, Andrulis IL, Southey M, Daly MB, Buys SS, Osorio A, Engel C, Kast K, Schmutzler RK, Caldes T, Jakubowska A, Simard J, Friedlander ML, McLachlan SA, Machackova E, Foretova L, Tan YY, Singer CF, Olah E, Gerdes AM, Arver B, Olsson H. Risks of Breast, Ovarian, and Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers. *JAMA* 2017; **317**: 2402-2416 [PMID: 28632866 DOI: 10.1001/jama.2017.7112]

12 **Antoniou A**, Pharoah PD, Narod S, Risch HA, Eyfjord JE, Hopper JL, Loman N, Olsson H, Johannsson O, Borg A, Pasini B, Radice P, Manoukian S, Eccles DM, Tang N, Olah E, Anton-Culver H, Warner E, Lubinski J, Gronwald J, Gorski B, Tulinius H, Thorlacius S, Eerola H, Nevanlinna H, Syrjäkoski K, Kallioniemi OP, Thompson D, Evans C, Peto J, Lalloo F, Evans DG, Easton DF. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case Series unselected for family history: a combined analysis of 22 studies. *Am J Hum Genet* 2003; **72**: 1117-1130 [PMID: 12677558 DOI: 10.1086/375033]

13 **Chen J**, Bae E, Zhang L, Hughes K, Parmigiani G, Braun D, Rebbeck TR. Penetrance of Breast and Ovarian Cancer in Women Who Carry a BRCA1/2 Mutation and Do Not Use Risk-Reducing Salpingo-Oophorectomy: An Updated Meta-Analysis. *JNCI Cancer Spectr* 2020; **4**: pkaa029 [PMID: 32676552 DOI: 10.1093/jncics/pkaa029]

14 **Antoniou AC**, Casadei S, Heikkinen T, Barrowdale D, Pylkäs K, Roberts J, Lee A, Subramanian D, De Leeneer K, Fostira F, Tomiak E, Neuhausen SL, Teo ZL, Khan S, Aittomäki K, Moilanen JS, Turnbull C, Seal S, Mannermaa A, Kallioniemi A, Lindeman GJ, Buys SS, Andrulis IL, Radice P, Tondini C, Manoukian S, Toland AE, Miron P, Weitzel JN, Domchek SM, Poppe B, Claes KB, Yannoukakos D, Concannon P, Bernstein JL, James PA, Easton DF, Goldgar DE, Hopper JL, Rahman N, Peterlongo P, Nevanlinna H, King MC, Couch FJ, Southey MC, Winqvist R, Foulkes WD, Tischkowitz M. Breast-cancer risk in families with mutations in PALB2. *N Engl J Med* 2014; **371**: 497-506 [PMID: 25099575 DOI: 10.1056/NEJMoa1400382]

15 **Gradishar WJ**, Moran MS, Abraham J, Abramson V, Aft R, Agnese D, Allison KH, Anderson B, Burstein HJ, Chew H, Dang C, Elias AD, Giordano SH, Goetz MP, Goldstein LJ, Hurvitz SA, Jankowitz RC, Javid SH, Krishnamurthy J, Leitch AM, Lyons J, Mortimer J, Patel SA, Pierce LJ, Rosenberger LH, Rugo HS, Schneider B, Smith ML, Soliman H, Stringer-Reasor EM, Telli ML, Wei M, Wisinski KB, Young JS, Yeung K, Dwyer MA, Kumar R. NCCN Guidelines® Insights: Breast Cancer, Version 4.2023. *J Natl Compr Canc Netw* 2023; **21**: 594-608 [PMID: 37308117 DOI: 10.6004/jnccn.2023.0031]

16 **El Saghir NS**, Zgheib NK, Assi HA, Khoury KE, Bidet Y, Jaber SM, Charara RN, Farhat RA, Kreidieh FY, Decousus S, Romero P, Nemer GM, Salem Z, Shamseddine A, Tfayli A, Abbas J, Jamali F, Seoud M, Armstrong DK, Bignon YJ, Uhrhammer N. BRCA1 and BRCA2 mutations in ethnic Lebanese Arab women with high hereditary risk breast cancer. *Oncologist* 2015; **20**: 357-364 [PMID: 25777348 DOI: 10.1634/theoncologist.2014-0364]

17 **Pourmasoumi P**, Moradi A, Bayat M. BRCA1/2 Mutations and Breast/Ovarian Cancer Risk: A New Insights Review. *Reprod Sci* 2024 [PMID: 39107554 DOI: 10.1007/s43032-024-01666-w]

18 **Azim HA**, Loutfy SA, Azim HA Jr, Kamal NS, Abdel Fattah NF, Elberry MH, Abdelaziz MR, Abdelsalam M, Aziz M, Shohdy KS, Kassem L. The Landscape of BRCA Mutations among Egyptian Women with Breast Cancer. *Oncol Ther* 2023; **11**: 445-459 [PMID: 37731153 DOI: 10.1007/s40487-023-00240-9]

19 **Abdel-Razeq H**, Al-Omari A, Zahran F, Arun B. Germline BRCA1/BRCA2 mutations among high risk breast cancer patients in Jordan. *BMC Cancer* 2018; **18**: 152 [PMID: 29409476 DOI: 10.1186/s12885-018-4079-1]

20 **Abulkhair O**, Al Balwi M, Makram O, Alsubaie L, Faris M, Shehata H, Hashim A, Arun B, Saadeddin A, Ibrahim E. Prevalence of BRCA1 and BRCA2 Mutations Among High-Risk Saudi Patients With Breast Cancer. *J Glob Oncol* 2018; **4**: 1-9 [PMID: 30199306 DOI: 10.1200/JGO.18.00066]

21 **Robson ME**, Tung N, Conte P, Im SA, Senkus E, Xu B, Masuda N, Delaloge S, Li W, Armstrong A, Wu W, Goessl C, Runswick S, Domchek SM. OlympiAD final overall survival and tolerability results: Olaparib versus chemotherapy treatment of physician's choice in patients with a germline BRCA mutation and HER2-negative metastatic breast cancer. *Ann Oncol* 2019; **30**: 558-566 [PMID: 30689707 DOI:

10.1093/annonc/mdz012]
22 **Litton JK**, Rugo HS, Ettl J, Hurvitz SA, Gonçalves A, Lee KH, Fehrenbacher L, Yerushalmi R, Mina LA, Martin M, Roché H, Im YH, Quek RGW, Markova D, Tudor IC, Hannah AL, Eiermann W, Blum JL. Talazoparib in Patients with Advanced Breast Cancer and a Germline BRCA Mutation. *N Engl J Med* 2018; **379**: 753-763 [PMID: 30110579 DOI: 10.1056/NEJMoa1802905]
23 **Diéras V**, Han HS, Kaufman B, Wildiers H, Friedlander M, Ayoub JP, Puhalla SL, Bondarenko I, Campone M, Jakobsen EH, Jalving M, Oprean C, Palácová M, Park YH, Shparyk Y, Yañez E, Khandelwal N, Kundu MG, Dudley M, Ratajczak CK, Maag D, Arun BK. Veliparib with carboplatin and paclitaxel in BRCA-mutated advanced breast cancer (BROCADE3): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol* 2020; **21**: 1269-1282 [PMID: 32861273 DOI: 10.1016/S1470-2045(20)30447-2]
24 **Geyer CE Jr**, Garber JE, Gelber RD, Yothers G, Taboada M, Ross L, Rastogi P, Cui K, Arahmani A, Aktan G, Armstrong AC, Arnedos M, Balmaña J, Bergh J, Bliss J, Delaloge S, Domchek SM, Eisen A, Elsafy F, Fein LE, Fielding A, Ford JM, Friedman S, Gelmon KA, Gianni L, Gnant M, Hollingsworth SJ, Im SA, Jager A, Jóhannsson ÓÞ, Lakhani SR, Janni W, Linderholm B, Liu TW, Loman N, Korde L, Loibl S, Lucas PC, Marmé F, Martinez de Dueñas E, McConnell R, Phillips KA, Piccart M, Rossi G, Schmutzler R, Senkus E, Shao Z, Sharma P, Singer CF, Španić T, Stickeler E, Toi M, Traina TA, Viale G, Zoppoli G, Park YH, Yerushalmi R, Yang H, Pang D, Jung KH, Mailliez A, Fan Z, Tennevet I, Zhang J, Nagy T, Sonke GS, Sun Q, Parton M, Colleoni MA, Schmidt M, Brufsky AM, Razaq W, Kaufman B, Cameron D, Campbell C, Tutt ANJ; OlympiA Clinical Trial Steering Committee and Investigators. Overall survival in the OlympiA phase III trial of adjuvant olaparib in patients with germline pathogenic variants in BRCA1/2 and high-risk, early breast cancer. *Ann Oncol* 2022; **33**: 1250-1268 [PMID: 36228963 DOI: 10.1016/j.annonc.2022.09.159]
25 **Banerjee S**, Moore KN, Colombo N, Scambia G, Kim BG, Oaknin A, Friedlander M, Lisyanskaya A, Floquet A, Leary A, Sonke GS, Gourley C, Oza A, González-Martín A, Aghajanian C, Bradley WH, Holmes E, Lowe ES, DiSilvestro P. Maintenance olaparib for patients with newly diagnosed advanced ovarian cancer and a BRCA mutation (SOLO1/GOG 3004): 5-year follow-up of a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol* 2021; **22**: 1721-1731 [PMID: 34715071 DOI: 10.1016/S1470-2045(21)00531-3]
26 **Vergote I**, González-Martín A, Ray-Coquard I, Harter P, Colombo N, Pujol P, Lorusso D, Mirza MR, Brasiuniene B, Madry R, Brenton JD, Ausems MGEM, Büttner R, Lambrechts D; European experts' consensus group. European experts consensus: BRCA/homologous recombination deficiency testing in first-line ovarian cancer. *Ann Oncol* 2022; **33**: 276-287 [PMID: 34861371 DOI: 10.1016/j.annonc.2021.11.013]
27 **Harvey-Jones EJ**, Lord CJ, Tutt ANJ. Systemic Therapy for Hereditary Breast Cancers. *Hematol Oncol Clin North Am* 2023; **37**: 203-224 [PMID: 36435611 DOI: 10.1016/j.hoc.2022.08.018]
28 **Ibrahim M**, Yadav S, Ogunleye F, Zakalik D. Male BRCA mutation carriers: clinical characteristics and cancer spectrum. *BMC Cancer* 2018; **18**: 179 [PMID: 29433453 DOI: 10.1186/s12885-018-4098-y]
29 **Timoteo AR**, Albuquerque BM, Moura PC, Ramos CC, Agnez-Lima LF, Walsh T, King MC, Lajus TB. Identification of a new BRCA2 large genomic deletion associated with high risk male breast cancer. *Hered Cancer Clin Pract* 2015; **13**: 2 [PMID: 25632310 DOI: 10.1186/s13053-014-0022-x]
30 **Rahman N**, Seal S, Thompson D, Kelly P, Renwick A, Elliott A, Reid S, Spanova K, Barfoot R, Chagtai T, Jayatilake H, McGuffog L, Hanks S, Evans DG, Eccles D; Breast Cancer Susceptibility Collaboration (UK), Easton DF, Stratton MR. PALB2, which encodes a BRCA2-interacting protein, is a breast cancer susceptibility gene. *Nat Genet* 2007; **39**: 165-167 [PMID: 17200668 DOI: 10.1038/ng1959]
31 **Zhang K**, Zhou J, Zhu X, Luo M, Xu C, Yu J, Deng M, Zheng S, Chen Y. Germline mutations of PALB2 gene in a sequential series of Chinese patients with breast cancer. *Breast Cancer Res Treat* 2017; **166**: 865-873 [PMID: 28825143 DOI: 10.1007/s10549-017-4425-z]
32 **Lee JEA**, Li N, Rowley SM, Cheasley D, Zethoven M, McInerny S, Gorringe KL, James PA, Campbell IG. Molecular analysis of PALB2-associated breast cancers. *J Pathol* 2018; **245**: 53-60 [PMID: 29431189 DOI: 10.1002/path.5055]
33 **Jalkh N**, Nassar-Slaba J, Chouery E, Salem N, Uhrchammer N, Golmard L, Stoppa-Lyonnet D, Bignon YJ, Mégarbané A. Prevalance of BRCA1 and BRCA2 mutations in familial breast cancer patients in Lebanon. *Hered Cancer Clin Pract* 2012; **10**: 7 [PMID: 22713736 DOI: 10.1186/1897-4287-10-7]
34 **Ashour M**, Ezzat Shafik H. Frequency of germline mutations in BRCA1 and BRCA2 in ovarian cancer patients and their effect on treatment outcome. *Cancer Manag Res* 2019; **11**: 6275-6284 [PMID: 31372034 DOI: 10.2147/CMAR.S206817]
35 **Siraj AK**, Masoodi T, Bu R, Parvathareddy SK, Al-Badawi IA, Al-Sanea N, Ashari LH, Abduljabbar A, Alhomoud S, Al-Sobhi SS, Tulbah A, Ajarim D, Alzoman K, Aljuboury M, Yousef HB, Al-Dawish M, Al-Dayel F, Alkuraya FS, Al-Kuraya KS. Expanding the spectrum of germline variants in cancer. *Hum Genet* 2017; **136**: 1431-1444 [PMID: 28975465 DOI: 10.1007/s00439-017-1845-0]
36 **Abdulrashid K**, AlHussaini N, Ahmed W, Thalib L. Prevalence of BRCA mutations among hereditary breast and/or ovarian cancer patients in Arab countries: systematic review and meta-analysis. *BMC Cancer* 2019; **19**: 256 [PMID: 30898109 DOI: 10.1186/s12885-019-5463-1]
37 **Azribi F**, Abdou E, Dawoud E, Ashour M, Kamal A, Al Sayed M, Burney I. Prevalence of BRCA1 and BRCA2 pathogenic sequence variants in ovarian cancer patients in the Gulf region: the PREDICT study. *BMC Cancer* 2021; **21**: 1350 [PMID: 34930165 DOI: 10.1186/s12885-021-09094-8]
38 **Alhuqail AJ**, Alzahrani A, Almubarak H, Al-Qadheeb S, Alghofaili L, Almoghrabi N, Alhussaini H, Park BH, Colak D, Karakas B. High prevalence of deleterious BRCA1 and BRCA2 germline mutations in arab breast and ovarian cancer patients. *Breast Cancer Res Treat* 2018; **168**: 695-702 [PMID: 29297111 DOI: 10.1007/s10549-017-4635-4]
39 **Younes N**, Zayed H. Genetic epidemiology of ovarian cancer in the 22 Arab countries: A systematic review. *Gene* 2019; **684**: 154-164 [PMID: 30352249 DOI: 10.1016/j.gene.2018.10.044]
40 **Abou-Alfa GK**, Norton L; Global Oncology Medical Diplomacy Working Group. Global Oncology Medical Diplomacy Working Group Inaugural Meeting: Defining Worldwide Barriers to Germline Genomics in Cancer Prevention and Management. *Ann Glob Health* 2023; **89**: 16 [PMID: 36843667 DOI: 10.5334/aogh.3967]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: office@baishideng.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com