Genetics in Medicine Open (2023) 1, 100824

ELSEVIER

Genetics in Medicine OPEN
An Official Journal of the ACMG

www.journals.elsevier.com/genetics-in-medicine-open

ARTICLE

Carrier screening program for *BRCA1/BRCA2* pathogenic variants among Ashkenazi Jewish women in Israel: An observational study

Rotem Greenberg[1,2], Efrat Aharonov-Majar[1], Ofer Isakov[1,2,3,4], Samah Hayek[1,5], Naama Elefant[1], Ran D. Balicer[1,2,5], Adi Berliner Senderey[1,4], Shay Ben-Shachar[1,2,3,*]

[1]*Clalit Research Institute, Innovation Division, Clalit Health Services, Ramat Gan, Israel;* [2]*Berkowitz Family Precision Medicine Clinic, Clalit Research Institute, Ramat Gan, Israel;* [3]*Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel;* [4]*Department of Biomedical Informatics, Harvard Medical School, Boston, MA;* [5]*Department of Epidemiology and Preventive Medicine, School of Public Health, Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel*

ARTICLE INFO

Article history:
Received 26 January 2023
Received in revised form
24 June 2023
Accepted 27 June 2023
Available online 6 July 2023

Keywords:
Ashkenazi Jewish
BRCA1
BRCA2
Cancer predisposition
Population carrier screening

ABSTRACT

Purpose: The aim of the study was to evaluate the results of a large-scale *BRCA1/2* carrier screening program among Ashkenazi Jewish (AJ) women.

Methods: We performed a cross-sectional study of women who were eligible for *BRCA1/2* screening program. Women who self-reported as complete or partial AJ were screened for 14 pathogenic variants in *BRCA1/2* genes, following the Israeli Ministry of Health's national screening program.

Results: The study included 13,502 women who underwent screening between June 2020 and June 2022. The prevalence of the pathogenic variants in *BRCA1/2* was 0.89% (120 of 13,502) among the tested women. Of the 14 variants tested, only 6 variants were detected. Three variants, known as the founder variants among AJ, accounted for 96.6% of identified variants (NM_000059.4(*BRCA2*):c.5946del, p.(Ser1982fs); NM_007294.4(*BRCA1*):c.68_69del, p.(Glu23fs); NM_007294.4(*BRCA1*):c.5266dup, p.(Gln1756fs)). The tested women were younger and of a higher socioeconomic status compared with the eligible non-tested women.

Conclusion: The study provides a new insight into a large carrier screening program for *BRCA1/2* pathogenic variants in AJ women in Israel. These findings present real-world prevalence of women who are heterozygous for *BRCA1/2* pathogenic variants in AJ population and the importance of such programs.

The Article Publishing Charge (APC) for this article was paid by Clalit Innovation.

*Correspondence and requests for materials should be addressed to Shay Ben-Shachar, Clalit Research Institute, Innovation Division, Clalit Health Services, Toval 40, Ramat Gan, 5252247, Israel. *Email address:* shayb@clalit.org.il

doi: https://doi.org/10.1016/j.gimo.2023.100824

Introduction

Pathogenic variants in the breast cancer susceptibility gene 1 (*BRCA1*, MIM 113705) and breast cancer susceptibility gene 2 (*BRCA2*, MIM 600185) are the most common cause of hereditary breast and/or ovarian cancer (HBOC) predisposition in women of all ethnicities. Variants in these genes are associated with increased risk for various cancer types among males and females.[1-5] Although most cases of breast and ovarian cancers in the Ashkenazi Jewish (AJ) population are sporadic, approximately 11% and 40% are predisposed by pathogenic variants in the *BRCA1/2* genes, respectively.[2-4,6]

More than 7000 pathogenic variants in *BRCA1/2* have been associated with increased risk for HBOCs.[7,8] Among AJ, only 3 founder variants in the *BRCA1/2* genes account for most HBOC cases: (1) NM_000059.4(*BRCA2*):c.5946del, p.(Ser1982fs); (2) NM_007294.4(*BRCA1*):c.68_69del, p.(Glu23fs); and (3) NM_007294.4(*BRCA1*):c.5266dup, p.(Gln1756fs). Approximately 1 in 40 (2.5%) AJ individuals were found to carry one of these variants previously.[9] The frequency of these variants among AJ was previously reported to range between 0.96% and 1.14% for *BRCA1* c.68_6del, 0.13% and 0.28% for *BRCA1* c.5266dup, and 1.52% for *BRCA2* c.5946del.[9-12]

This phenomenon of few variants associated with the majority of *BRCA1/2*- related HBOC cases is unique. In the past decades, there has been an increased rate of mixed ancestry marriages; thus, many individuals are only partially AJ, and the real frequency of women who are heterozygous for *BRCA1/2* pathogenic variants in the Israeli population is unknown.

To decrease breast and ovarian cancer–related morbidity and mortality among heterozygotes, the National Comprehensive Cancer Network issued recommendations for an intensive follow-up program for individuals who are heterozygous for *BRCA1/2* pathogenic variants and for testing family members for carrier status.[9,13] These follow-up programs have been shown to significantly reduce cancer-related morbidity and mortality.[13]

Despite the increased risk of cancer and the high penetrance in women, approximately half of women who are heterozygous for *BRCA1/2* pathogenic variants lack suggestive family history, mostly because of the sex of family members, small pedigrees, incomplete penetrance, cancer-risk modifying variants (often incorporated into polygenic risk score [PRS]), and other nongenetic risk modifiers such as lifestyle.[2,13,14] Therefore, a testing strategy based only on a family history may fail to detect about 50% of at-risk individuals positive for the *BRCA1/2* variants.[2,13,14]

In 2020, the Israeli Ministry of Health initiated a funded *BRCA1/2* carrier screening program for AJ women, without requiring pretesting genetic counseling. Since 2020, women meeting the following criteria were encouraged to complete the screening test: (1) full or partial AJ origin based on self-report, (2) age $\geq$ 18 years, and (3) self-report of no personal history of breast, ovarian, or pancreatic cancer.

In this study, with the aim to evaluate the results of the *BRCA1/2* carrier screening program, we characterized individuals who underwent *BRCA1/2* screening test at Clalit Health Services (CHS) and estimated the frequency of women who are heterozygous for *BRCA1/2* pathogenic variants of those who were screened. The results of this study are important for improving the *BRCA1/2* screening program, defining the target population, and tailoring specific interventions for better health outcomes.

Materials and Methods

Data sources

The data were extracted from CHS, the largest health care provider in Israel, insuring more than half of the Israeli population.

CHS has a comprehensive data warehouse that combines administrative and clinical data from community and hospital records, including demographic information, laboratory results, diagnoses given in a community or hospital setting, clinical and behavioral markers, and medical procedures. The raw data extracted were coded, viewed, and stored only within the Clalit Research Institute.

Study population and design

We performed a cross-sectional study. The study population includes individuals who were CHS members and met the following eligibility criteria: (1) women, (2) age $\geq$ 25 years, (3) fully or partially of AJ origin (at least 1 grandparent of AJ by self-report), (4) have no personal history of *BRCA1/2*-associated cancer (breast, ovarian, and pancreatic cancer),[10,13] and (5) women with no known familial pathogenic variant in a cancer susceptibility gene, by self-report.

Pretest process

Information regarding the implications of the test and the risk of being positive for *BRCA1/2* variants were provided by physicians, nurses, or geneticists from various clinics and hospitals. Women who showed interest were required to schedule an appointment to the test.

Two days before the test, participants were provided with a link to an explanatory webpage on the CHS website and an explanatory video through a text message.

The test was performed without requiring pretesting genetic counseling. Upon arrival for the test, participants were provided with an oral explanation by a genetic nurse who had received prior training. Written informed consent, containing information regarding the implications and potential outcomes of the test, was also obtained.

Women with a known first-degree family history of relevant cancer were recommended to undergo genetic counseling alongside the test.

Women who did not meet the eligibility test criteria did not perform the test and were referred for genetic counseling.

Genetic test

The test was performed at 6 CHS hospitals, and the date of performing the genetic test was defined as the index date. For CHS members who were not tested, the index date was defined as the end of research (July 1, 2022). Peripheral blood leukocyte DNA was extracted with the PureGene kit (Gentra, Inc) according to the manufacturer's recommended protocol. Specimens were analyzed for 14 common pathogenic variants in *BRCA1/2* in the Israeli population including the known AJ founder variants with NanoCHIP (Gamidor Diagnostics) (Supplemental Table 1).

Test results

Women positive for *BRCA1/2* variants were promptly invited to genetic counseling to receive the test results and follow-up recommendations.

Women whose carrier status was negative were informed of their test results, through a letter, email, or online (based on their preference), along with a written/electronic communication of the implications and recommendations to continue with general follow-up, according to the recommendations of the attending physician. Moreover, they were advised to seek genetic counseling if they had a personal or family history of cancer.

Ethnicity definition

Self-reported ethnicity was validated based on CHS electronic medical records (EMRs) of maternal and paternal grandparents' country of birth.[15] For each individual, EMR-based ethnicity was derived in a stepwise manner: (1) based on the birth country of each grandparent; (2) if information regarding the grandparent was unavailable, the birth country of the parent was used; and (3) finally, if both were unavailable, the birth country of the patient was used. Each birth country is assigned one of these ethnicities—AJ, Sephardic, Ethiopian Jewish, and Arab.

For this study, the EMR-based ethnicity was divided into 6 groups: having 1 grandparent AJ (at least 25% AJ), having 2 grandparents AJ (at least 50% AJ), having 3 grandparents AJ (at least 75% AJ), having 4 grandparents AJ (100%), having 4 grandparents Sephardic/other (100% non-AJ), and in case of missing information on the 4 grandparents, the members were recorded as unknown.

Baseline measurements

Sociodemographic information was retrieved from the EMR CHS database. It included biological sex, age at index date (years), socioeconomic status (SES; low, medium, high; based on clinic-degree data), population sector (Jewish—general sector, Jewish—ultraorthodox), place of residence (rural, urban), and ethnicity. All the study population characteristics were extracted up to 5 years before the index date.

Statistical analysis

Descriptive statistics were conducted for the study population, and we compared the characteristics of individuals who underwent the *BRCA1/2* screening test with those who did not undergo *BRCA1/2* screening. Among the tested individuals, we compared the characteristics of women who were heterozygous for *BRCA1/2* pathogenic variants with those carrier status was not positive. Continuous and categorical variables were compared using an unpaired *t* test and the χ^2 test, respectively. Two-sided tests were used, and *P* value of <.05 was defined as significant. Statistical analyses were conducted using the R language (version 4.1.0, R Foundation for Statistical Computing).

Results

During the study period, of 420,418 women at CHS who met criteria for testing, 13,502 underwent screening for *BRCA1/2* pathogenic variants. Most of the tested women (carrier status both positive and negative) were in the age group of 25 to 44 years (Table 1 and Supplemental Table 2). The overall frequency of individuals positive for *BRCA1/2* variants was 0.89% (120 of 13,502). Among women from different age groups, we did not find significant difference in *BRCA1/2* carrier frequency ($P = .14$). Specifically, the carrier frequency among younger women (aged 25-44 years) was 0.98% (83 of 8464), whereas the carrier frequency among older women (aged 45-65 years) was 0.73% (37 of 5038) (Table 1 and Supplemental Table 2).

According to the EMR, the carrier frequency for AJ were 0.96% (89 of 9190), 1.18% (2 of 169) for Sephardic, and 0.69% (29 of 4143) for women of unknown origin. The carrier frequency for the various degrees of AJ origin were as follows: 1.02% (46 of 4489) for full AJ, 1.6% (9 of 562) for at least 75% AJ, 0.94% (31 of 3285) for at least 50% AJ, and 0.35% (3 of 854) for at least 25% AJ (Figure 1).

Of the 14 variants included in the screening test, only 6 variants were detected among our tested population. Unsurprisingly, among AJ, the 3 known founder variants were the most common with the *BRCA2* c.5946del variant being the most common (64, 53%), followed by *BRCA1* c.68_69del (42, 35%) and *BRCA1* c.5266dup (10, 8.4%). The remaining variants identified by the screening test included the *BRCA2* c.7007G>C variant (2, 1.7%) and the *BRCA1* c.181T>G in and *BRCA2* c.2158G>T variants (1, 0.8% each). As expected, no variant was detected in a homozygous or compound heterozygous state in this healthy population.

Table 1 Sociodemographic characteristics of the study population

Characteristic	Eligible Population $N = 420,418$	Tested $n = 13,502$	Not Tested, $n = 406,916$	P Value[a]
Age, mean (SD)[b]	52 (18)	43 (12)	53 (19)	<.001
Age category, n (%)[b]				<.001
25-34	83,594 (20)	3747 (28)	79,847 (20)	
35-44	95,683 (23)	4717 (35)	90,966 (22)	
45-54	62,419 (15)	2608 (19)	59,811 (15)	
55-64	56,590 (13)	1327 (9.8)	55,263 (14)	
65+	122,132 (29)	1103 (8.2)	121,029 (30)	
Ethnicity, n (%)[b]				<.001
AJ	416,106 (99)	9190 (68)	406,916 (100)	
At least 25%	23,162 (5.5)	854 (6.3)	22,308 (5.5)	
At least 50%	89,342 (21)	3285 (24)	86,057 (21)	
At least 75%	9932 (2.4)	562 (4.2)	9370 (2.3)	
100% AJ	293,670 (70)	4489 (33)	289,181 (71)	
100% Sephardic	169 (0.1)	169 (1.4)	–	
Unknown/other	4143 (1.0)	4143 (31)	–	
Sector, n (%)				<.001
Jewish, general	397,969 (95)	13,224 (98)	384,745 (95)	
Jewish, ultraorthodox	21,322 (5.1)	251 (1.9)	21,071 (5.2)	
Other	1127 (0.3)	27 (0.2)	1100 (0.3)	
Place of residence, n (%)				<.001
Rural	52,527 (13)	3220 (24)	49,307 (12)	
Urban	366,180 (87)	10,173 (76)	356,007 (88)	
(Missing)	1711	109	1602	
Socioeconomic status, n (%)				<.001
Low	216,439 (51)	3288 (24)	213,151 (52)	
Medium	195,081 (46)	9681 (72)	185,400 (46)	
High	8777 (2.1)	530 (3.9)	8247 (2)	
(Missing)	121	3	118	

AJ, Ashkenazi Jewish; *CHS*, Clalit Health Services.
[a]Significant difference with $P < .05$.
[b]Mean (SD); n (%); Median (IQR).

The age, ethnicity, sector, SES, and type of residence of tested women ($n = 13,502$) and the eligible non-tested women ($n = 406,916$) were compared. The average age was lower among the tested individuals (mean = 43, SD = 12) compared with the eligible not tested group (mean = 53, SD = 19). Among the tested cohort, younger women had a lower rate of full AJ ancestry compared with older women (Figure 2).

Additionally, most of the tested women were from medium-high SES (76%), and only 24% were from low SES. Nevertheless, only 6% (3220 of 52,527) of the low SES eligible population underwent the screening test. Overall, out of the total eligible population, the compliance of individuals from urban area was higher (76%) compared with individuals from a rural area (24%). However, when considering the compliance in relation to the population sizes of rural and urban areas, a higher percentage of women underwent the test in rural areas-6.1% (3220 of 52,527) compared to urban areas-2.8% (10,173 of 366,180). Following this, only 1.9% of the tested women were orthodox, and only 1.17% (251 of 21,322) from the eligible orthodox population were tested (Table 1).

Discussion

Screening programs for early detection of breast and ovarian cancer have been shown to reduce morbidity and mortality. Individuals who are heterozygous for *BRCA1/2* pathogenic variants are at increased risk for breast and ovarian cancer, and advances in knowledge, technology, and patient awareness have led to the identification of more *BRCA1/2* heterozygotes than in the past. The prognosis of individuals screening positive for *BRCA1/2* variants has improved because of prevention and early detection programs, the use of prophylactic medication (eg, tamoxifen), and even targeted treatments such as Poly ADP ribose polymerase (PARP) inhibitors.[16] Yet, many individuals who are heterozygous for *BRCA1/2* pathogenic variants remain incognito and unaware of a positive carrier status. Therefore, better testing strategies are required, as well as a reassessment of the current strategy, in which only women with high risk because of AJ origin or a family history are recommended to be tested.

Our results indicate that the carrier frequency of the 3 AJ founder variants in *BRCA1/2* is 0.95% (88 of 9190) among all AJ groups and 1.02% (46 of 4489) among the full AJ

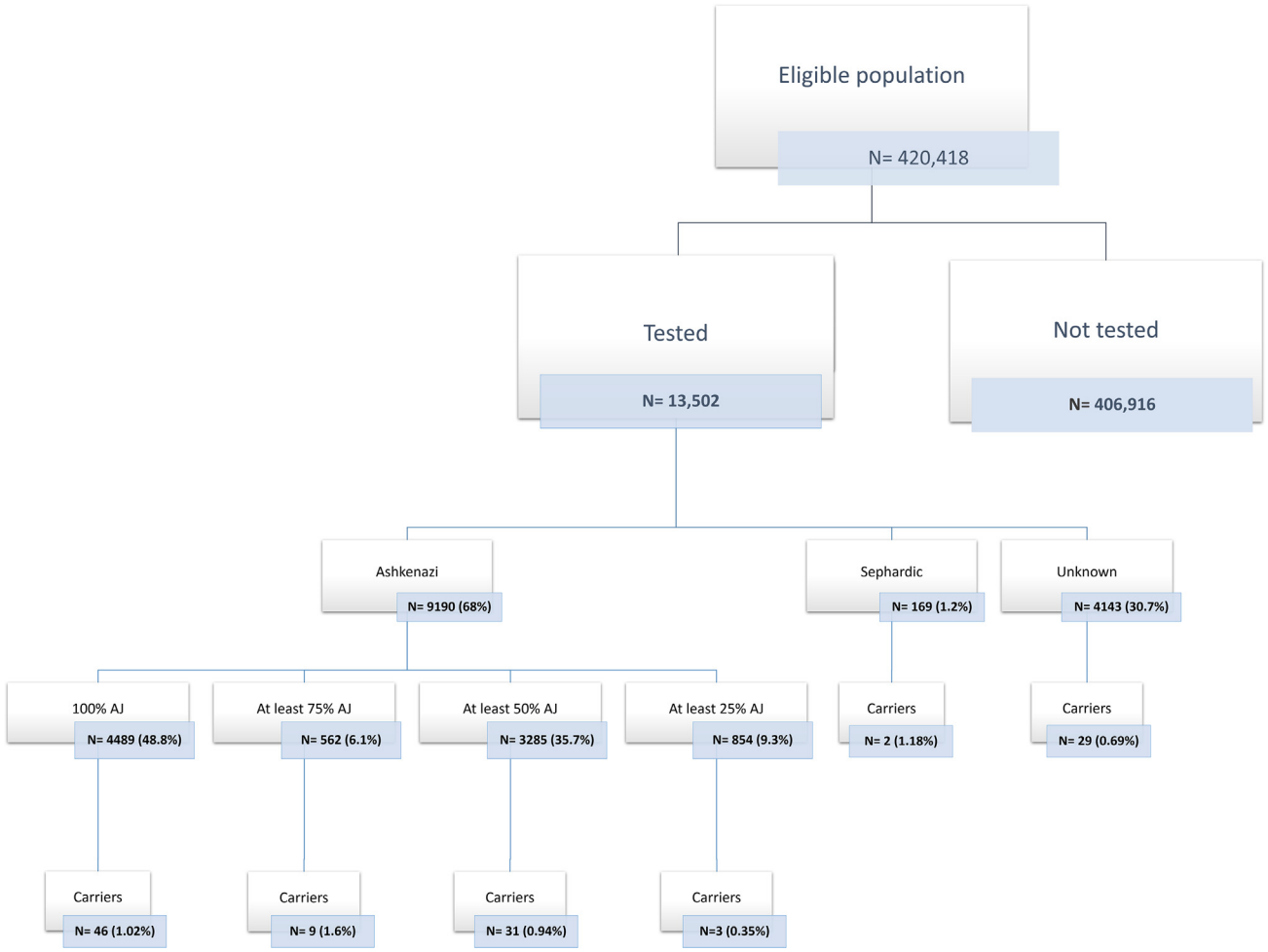

Figure 1 **Study population flowchart.** AJ, Ashkenazi Jewish.

group. These frequencies are lower than the reported frequency in previous studies (2.5%).[9,10] In contrast to these studies, our cohort included women from varying degrees of AJ and only unaffected women, without known familial *BRCA1/2* variant, who inherently have a lower carrier frequency compared with affected women and those with known familial *BRCA1/2* variant. In addition, we excluded men, who rarely have breast cancer and should therefore have a higher carrier frequency compared with a parallel unaffected women cohort. Nevertheless, more recent studies that used inclusion and exclusion criteria that were more similar to our study (eg, unaffected women, without known family history of *BRCA1/2* variant, tested women age ranges) reported more similar prevalence rates—1.3% to 1.8%.[17-19]Similarly, our carrier frequency was lower than that reported in the Genome Aggregation Database (gnomAD) v2.1.1, for AJ women without cancer[20]: *BRCA1* c.5266dup (0.3%, n = 4676 alleles); *BRCA1* c.68_69del (0.3%, n = 4676 alleles), and *BRCA2*, c.5946del (0.57%, n = 4672 alleles). However, the carrier frequency was more similar when comparing our findings with the carrier frequencies in gnomAD v3.1.2: *BRCA1* c.5266dup (0.0%, n = 1744 alleles; 0.03% in the CHS group),[21] *BRCA1* c.68_69del (0.11%, N = 1744 alleles; 0.15% in the CHS group),[22] and *BRCA2* c.5946del (0.23% n = 1744 alleles; 0.23% in the CHS group).[23] This may stem from the difference in ancestry assignment methodology between the 2 gnomAD versions. Specifically, the models for ancestry assignment were developed using different data sets, and different probability thresholds for assignment were used (90% in v2.1.1 vs 75% in v3.1.2).[20-23] This difference in probability thresholds suggests that the population composition is more heterogeneous in gnomAD v3.1.2 and therefore more closely resembles our cohort, compared with v2.1.1 and previous studies.

Although, 14 *BRCA1/2* variants were tested, the 3 known *BRCA1/2* founder variants in AJ were found in 96.6%. In light of these findings, in the setting of a screening test, it might be more efficient to consider testing individuals of full AJ only for these 3 founder variants. However, the admixture of populations that continue to grow, may cause, over time, to miss many carriers and create a false reassurance. Therefore, we expect broad testing of known and common pathogenic variants in the population and even a full sequencing of *BRCA1/2* genes to become the most efficient screening method while maintaining cost-effectiveness.

The well-known success of the Israeli carrier screening programs for reproductive purposes[24] demonstrates the

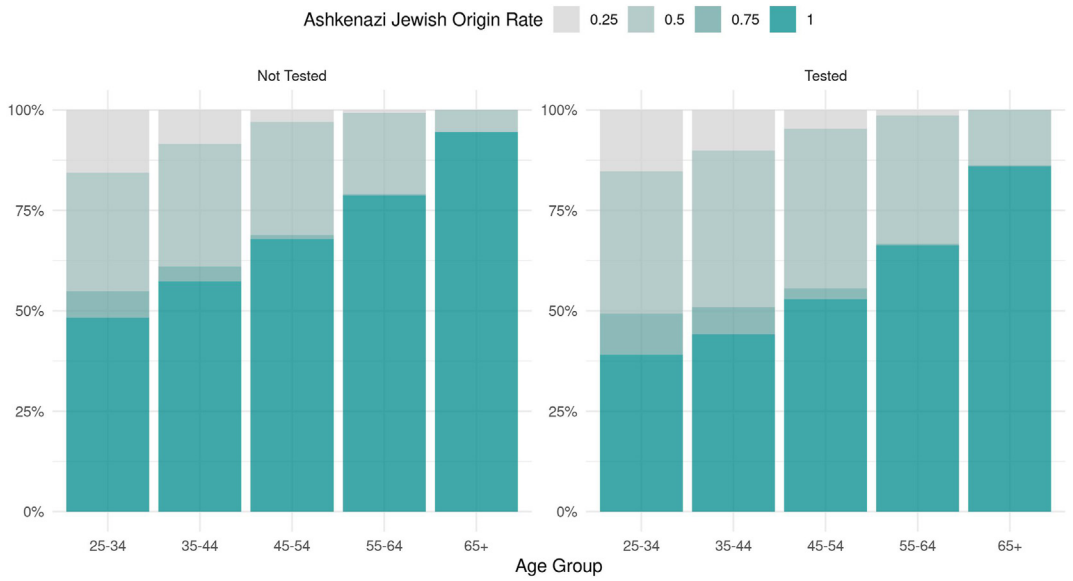

Figure 2 The distribution of AJ degree by age group, tested vs nontested individuals. AJ, Ashkenazi Jewish.

Israeli public's interest in proactive genetics tests. Therefore, the relatively low compliance to the *BRCA1/2* carrier screening (3%) calls for an evaluation of the behavioral factors that may influence the compliance rate and for ways to increase compliance.

In our study, women from the general Jewish population, with higher SES, were more likely to get tested than those with lower SES. This finding is consistent with previous studies and demonstrates that there is a positive relationship between SES and health-seeking behavior.[25]

Considering the potential impact of population characteristics, including an older population, lower SES, and variations in health-seeking behavior,[25] among others, the variation in compliance rate, may also be explained by the limited accessibility to health services. However, further investigation is needed. These results demonstrate that measures and decisions should be taken by policy makers to design strategies that will increase awareness and accessibility of tests and address any issues preventing women from completing this important screening.

In summary, this large-scale real-world study revealed that the carrier frequency of *BRCA1/2* pathogenic variants is lower than reported in previous studies, but it is still substantial. Even when considering the lower carrier frequency detected in this large-scale study, previous studies have shown that it still supports its cost-effectiveness.[26,27]

Our findings show that younger women have a lower rate of full AJ origin compared with older women and a higher frequency of those heterozygous for *BRCA1/2* pathogenic variants. As the admixture of populations continue to grow, determining an woman's precise origin is expected to be increasingly challenging. Therefore, expanding the carrier screening test to include women of diverse origins, rather than just women of AJ origin, should be considered.

Finally, the higher prevalence rate of women who are heterozygous for *BRCA1/2* pathogenic variants among younger women (25-45 years), as well as the low compliance among women with lower SES, emphasizes the importance of reexamining the current strategy. Increasing compliance among these populations will exhaust the advantage of early detection to reduce morbidity and mortality and, as a result, will improve the cost-effectiveness of this screening program.

Data Availability

The raw data remain confidential and cannot be shared; however, we are allowed to provide limited individuals' data, which can be requested from the corresponding author.

Acknowledgments

The authors appreciate the genetic counseling, laboratory services, and database assistance provided by the medical and laboratory staff at Clalit's genetic institutes. The authors would also like to thank Ronit Vizer, Ruth Baruch, and all Clalit's genetic nurses for their assistance in putting the screening program in place.

Funding

No funding was obtained or used in this study.

Author Information

Conceptualization: R.G., O.I., S.B.-S.; Data Curation: A.B.S., O.I., S.B.-S., N.E.; Formal Analysis: E.A.-M., R.G.;

Writing-original draft: R.G., E.A.-M., S.B.-S.; Supervision: A.B.S., S.B.-S., S.H., R.D.B.; Methodology: S.H., A.B.S., S.B.-S., N.E., R.G.; Validation: O.I., A.B.S., S.H., N.E.; Investigation: R.G., E.A.-M., A.B.S., S.B.-S.

Ethics Declaration

Because the study deals only with secondary data, the study was exempted by institutional review board committee of CHS (COM1-0078-21).

Conflict of Interest

The authors declare no conflicts of interest related to the manuscript.

Additional Information

The online version of this article (https://doi.org/10.1016/j.gimo.2023.100824) contains supplemental material, which is available to authorized users.

References

1. Parmigiani G, Berry D, Aguilar O. Determining carrier probabilities for breast cancer–susceptibility genes BRCA1 and BRCA2. *Am J Hum Genet*. 1998;62(1):145-158. http://doi.org/10.1086/301670
2. Levy-Lahad E, Catane R, Eisenberg S, et al. Founder BRCA1 and BRCA2 mutations in Ashkenazi Jews in Israel: frequency and differential penetrance in ovarian cancer and in breast-ovarian cancer families. *Am J Hum Genet*. 1997;60(5):1059-1067.
3. Tung N, Lin NU, Kidd J, et al. Frequency of germline mutations in 25 cancer susceptibility genes in a sequential series of patients with breast cancer. *J Clin Oncol*. 2016;34(13):1460-1468. http://doi.org/10.1200/JCO.2015.65.0747
4. Zhang S, Royer R, Li S, et al. Frequencies of BRCA1 and BRCA2 mutations among 1,342 unselected patients with invasive ovarian cancer. *Gynecol Oncol*. 2011;121(2):353-357. http://doi.org/10.1016/j.ygyno.2011.01.020
5. Kuchenbaecker KB, Hopper JL, Barnes DR, et al. Risks of breast, ovarian, and contralateral breast cancer for BRCA1 and BRCA2 mutation carriers. *JAMA*. 2017;317(23):2402-2416. http://doi.org/10.1001/jama.2017.7112
6. King MC, Levy-Lahad E, Lahad A. Population-based screening for BRCA1 and BRCA2: 2014 Lasker award. *JAMA*. 2014;312(11):1091-1092. http://doi.org/10.1001/jama.2014.12483
7. BRCA1[gene] – ClinVar. National Center for Biotechnology Information. Accessed October 15, 2022. https://www.ncbi.nlm.nih.gov/clinvar/?gr=0&term=BRCA1%5Bgene%5D&redir=gene
8. BRCA2[gene] – ClinVar. National Center for Biotechnology Information. Accessed October 15, 2022. https://www.ncbi.nlm.nih.gov/clinvar/?gr=0&term=BRCA2%5Bgene%5D
9. Roa BB, Boyd AA, Volcik K, Richards CS. Ashkenazi Jewish population frequencies for common mutations in BRCA1 and BRCA2. *Nat Genet*. 1996;14(2):185-187. http://doi.org/10.1038/ng1096-185
10. Gabai-Kapara E, Lahad A, Kaufman B, et al. Population-based screening for breast and ovarian cancer risk due to *BRCA1* and *BRCA2*. *Proc Natl Acad Sci U S A*. 2014;111(39):14205-14210. http://doi.org/10.1073/pnas.1415979111
11. Bahar AY, Taylor PJ, Andrews L, et al. The frequency of founder mutations in the BRCA1, BRCA2, and APC genes in Australian Ashkenazi Jews: implications for the generality of U.S. population data. *Cancer*. 2001;92(2):440-445. http://doi.org/10.1002/1097-0142(20010715)92:2<440::AID-CNCR1340>3.0.CO;2-O
12. Hartge P, Struewing JP, Wacholder S, Brody LC, Tucker MA. The prevalence of common BRCA1 and BRCA2 mutations among Ashkenazi Jews. *Am J Hum Genet*. 1999;64(4):963-970. http://doi.org/10.1086/302320
13. Genetic/familial high-risk assessment: breast and ovarian. Version 2. 2022. National Comprehensive Cancer Network. Accessed June 10, 2022. https://www.nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf
14. Lee A, Mavaddat N, Wilcox AN, et al. BOADICEA: a comprehensive breast cancer risk prediction model incorporating genetic and nongenetic risk factors. *Genet Med*. 2019;21(8):1708-1718. http://doi.org/10.1038/s41436-018-0406-9
15. Updated guidance on the reporting of race and ethnicity in medical and science journals. JAMA Network. Accessed March 24, 2023. https://jamanetwork.com/journals/jama/fullarticle/2783090
16. Lee JM, Ledermann JA, Kohn EC. PARP inhibitors for BRCA1/2 mutation-associated and BRCA-like malignancies. *Ann Oncol*. 2014;25(1):32-40. http://doi.org/10.1093/annonc/mdt384
17. Lieberman S, Lahad A, Tomer A, Cohen C, Levy-Lahad E, Raz A. Population screening for BRCA1/BRCA2 mutations: lessons from qualitative analysis of the screening experience. *Genet Med*. 2017;19(6):628-634. http://doi.org/10.1038/gim.2016.175
18. Metcalfe KA, Poll A, Royer R, et al. A comparison of the detection of BRCA mutation carriers through the provision of Jewish population-based genetic testing compared with clinic-based genetic testing. *Br J Cancer*. 2013;109(3):777-779. http://doi.org/10.1038/bjc.2013.309
19. Tiller JM, Cousens NE, Kaur R, et al. Population-based BRCA1/2 testing programmes are highly acceptable in the Jewish community: results of the JeneScreen Study. *J Med Genet*. 2023;60(3):265-273. http://doi.org/10.1136/jmedgenet-2022-108519
20. gnomAD. v2.1.1. Genome Aggregation Database. Accessed October 12, 2022. https://gnomad.broadinstitute.org/
21. Insertion (1 base): 17-43057062-T-TG (GRCh38). gnomAD v3.1.2 (non-cancer). gnomAD. Accessed December 21, 2022. https://gnomad.broadinstitute.org/variant/17-43057062-T-TG?dataset=gnomad_r3_non_cancer
22. Deletion (2 bases): 17-43124027-ACT-A. gnomAD v3.1.2 (non-cancer). gnomAD. Accessed December 21, 2022. https://gnomad.broadinstitute.org/variant/17-43124027-ACT-A?dataset=gnomad_r3_non_cancer
23. Deletion (1 base): 13-32340300-GT-G (GRCh38). gnomAD v3.1.2 (non-cancer). gnomAD. Accessed December 21, 2022. https://gnomad.broadinstitute.org/variant/13-32340300-GT-G?dataset=gnomad_r3_non_cancer
24. Singer A, Sagi-Dain L. Impact of a national genetic carrier-screening program for reproductive purposes. *Acta Obstet Gynecol Scand*. 2020;99(6):802-808. http://doi.org/10.1111/aogs.13858
25. Amornsiripanitch N, Ameri SM, Goldberg RJ. Impact of age, race, and socioeconomic status on women's perceptions and preferences regarding communication of estimated breast cancer risk. *Acad Radiol*. 2021;28(5):655-663. http://doi.org/10.1016/j.acra.2020.03.041
26. Manchanda R, Patel S, Antoniou AC, et al. Cost-effectiveness of population based BRCA testing with varying Ashkenazi Jewish ancestry. *Am J Obstet Gynecol*. 2017;217(5):578.e1-578.e12. http://doi.org/10.1016/j.ajog.2017.06.038
27. Michaan N, Leshno M, Safra T, Sonnenblick A, Laskov I, Grisaru D. Cost effectiveness of whole population BRCA genetic screening for cancer prevention in Israel. *Cancer Prev Res (Phila)*. 2021;14(4):455-462. http://doi.org/10.1158/1940-6207.CAPR-20-0411