OPEN ACCESS

Original research

Damaging missense variants in innate immunity genes are associated with earlier age of breast cancer onset in *BRCA1* 185delAG carriers

Sapir Shemesh,[1] Rinat Bernstein-Molho,[2,3] Shelley Shoval,[2] Yael Laitman,[2] Dana Madorsky-Feldman,[4] Eitan Friedman,[3,4] Ran Elkon [1]

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/jmg-2025-111394).

[1]Department of Human Genetics and Computational Medicine, Gray Faculty of Medical & Health Sciences, Tel Aviv University, Tel Aviv-Yafo, Israel
[2]The Suzanne Levy-Gertner Oncogenetics Unit, Danek Gertner Institute of Human Genetics, Sheba Medical Center, Tel HaShomer, Israel
[3]Gray Faculty of Medical & Health Sciences, Tel Aviv University, Tel Aviv-Yafo, Israel
[4]The Meirav High-Risk Clinic, Sheba Medical Center, Tel HaShomer, Tel Aviv District, Israel

Correspondence to
Professor Ran Elkon; ranel@tauex.tau.ac.il and Professor Eitan Friedman; feitan@tauex.tau.ac.il

Received 25 November 2025
Accepted 4 February 2026

To cite: Shemesh S, Bernstein-Molho R, Shoval S, *et al*. *J Med Genet* Epub ahead of print: [please include Day Month Year]. doi:10.1136/jmg-2025-111394

ABSTRACT

Background Penetrance of breast cancer (BC) among women who carry pathogenic variants (PVs) in *BRCA1* is incomplete, and the age at BC diagnosis varies considerably, even among carriers of the same PV, suggesting the involvement of genetic and non-genetic risk modifying factors. Polygenic Risk Score (PRS) models based on common sequence variants account for less than 10% of the total risk variability among *BRCA1* PV carriers, indicating that further genetic modifiers remain to be identified.

Methods Here, for the first time, we applied whole-exome sequencing for this challenge, investigating a cohort of 321 Israeli women carrying the *BRCA1* 185delAG founder PV.

Results In our cohort, we found that harbouring additional putatively damaging missense variants in genes involved in innate immunity was significantly associated with earlier BC onset. The HR for carrying a missense variant in genes annotated to the top-scoring immune-related gene set *NATURAL_KILLER_CELL_ACTIVATION* was 3.62 (95% CI 1.96 to 6.67; $p=3.8\times10^{-5}$).

Conclusion These findings highlight a potential role for innate immune pathways as modifiers of *BRCA1* penetrance and support the development of more refined, personalised risk prediction models.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The age at breast cancer (BC) diagnosis varies considerably among carriers of pathogenic *BRCA1* variants.

⇒ However, current knowledge about genetic risk modifiers in *BRCA1* carriers remains limited.

WHAT THIS STUDY ADDS

⇒ By applying whole-exome sequencing to a large cohort of Ashkenazi Jewish *BRCA1* carriers, we found that the presence of additional putatively damaging missense variants in genes involved in innate immunity is significantly associated with earlier BC onset.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our findings highlight a novel role for innate immune pathways as potential modifiers of BC risk in *BRCA1* carriers.

INTRODUCTION

BRCA1 (MIM# 113705) is one of the two prominent breast cancer (BC) susceptibility genes. Women harbouring a pathogenic variant (PV) in *BRCA1* have an estimated 60–80% lifetime risk of developing BC, along with a substantially elevated risk (30–40%) of ovarian cancer.[1 2] Current risk mitigation options for female *BRCA1* carriers range from intensive early-age (25–30 years) BC screening, primarily by MRI, to chemoprevention and active risk-reducing surgical removal of the breasts (risk-reducing mastectomy (RRM)) and of the fallopian tubes and ovaries (risk-reducing salpingo-oophorectomy (RRSO)).[3] Critical clinical decisions include the decision to opt for RRM and determining the optimal age for RRSO. These surgical options are invasive, irreversible, associated with substantial life-changing effects and may have adverse psychological impacts.[4] Although penetrance for BC in *BRCA1* carriers is high, it is incomplete, and age at BC diagnosis among *BRCA1* carriers varies widely, even among carriers of identical PV in the same families.[5] Combined, this variability suggests the effects of modifying factors—genetic and non-genetic—that affect *BRCA1*-associated BC risk. Our limited understanding of these risk-modifying factors hampers personalised clinical decision-making, including decisions regarding surveillance and the appropriate type and timing of risk-reducing strategies. Therefore, there is a major clinical need for refined, personalised risk models for *BRCA1* carriers. This need is particularly important in Israel, where a predominant founder PV in *BRCA1* (c.68_69del; p.Glu23fs, also known as 185delAG-rs80357914) makes Ashkenazi Jews (AJ) the ethnic group with the highest population-wide prevalence of *BRCA1* carriers worldwide. The prevalence of *BRCA1* carriers among AJ is approximately five to six times higher (~1:100[2]) compared with ~1:500–1:600 in most other genetically heterogeneous populations.[6]

Efforts to identify genetic variants that modify cancer risk in *BRCA1* carriers have been ongoing for the past two decades, led primarily by the large international Consortium of Investigators of Modifiers of *BRCA1/2* (CIMBA).[7] Several recent studies have demonstrated the utility of Polygenic Risk Score (PRS) models in stratifying BC risk in *BRCA1* carriers.[8–11] Notably, a recent CIMBA study showed that a PRS model incorporating 313 BC risk SNPs

(BC PRS_{313}) is significantly associated with BC risk in *BRCA1* carriers of European ancestry. For example, *BRCA1* carriers in the 5th and 95th percentiles of BC PRS_{313} showed an approximately twofold difference in absolute BC risk by age 50 (31% vs 58%, respectively).[12] Despite this notable difference, the PRS model explains less than 10% of the overall variation in *BRCA1* carrier risk, highlighting the likely existence of many additional risk modifying factors.[11 13]

Current PRS models, including BC PRS_{313}, are based on genome-wide association studies (GWAS) findings, which are limited by design to common variants (minor allele frequency (MAF) >1%). Pioneering studies have begun to explore the roles of other forms of genetic variation, not captured by GWAS, in modifying BC risk among *BRCA* carriers. For example, the potential contributions of low-frequency germline CNVs,[14] variable number of tandem repeats[15] and sequence variants within candidate modifier genes[16] have been investigated. In particular, given the role of *BRCA1* protein product in DNA repair, a recent study hypothesised that reduced activity of additional genes involved in DNA damage repair (DDR) may further increase *BRCA1* PV penetrance, as manifested in earlier age at BC diagnosis.[17] Focusing on a curated set of 311 genes known to function in DDR pathways—and using extreme-phenotype sampling of *BRCA1* PV carriers with either early BC onset (before age 35) or who remained cancer-free by age 60—their results suggested that carrying additional PTVs in DDR genes might be associated with earlier BC onset in *BRCA1* PV carriers (OR 3.1; 95% CI 0.92 to 11.5; p=0.07).[17]

In this study, we further hypothesised that—given the pivotal role the immune system plays in cancer pathogenesis and surveillance[18–22]—impaired immune function may also modify BC risk among *BRCA1* PV carriers. Leveraging a large whole-exome sequencing (WES) cohort of Israeli women carrying the *BRCA1* 185delAG AJ founder PV, we examined whether carrying additional putatively damaging variants in genes involved in distinct arms of the immune system was associated with age at BC diagnosis.

METHODS

Cohort

Our study included a cohort of 321 Israeli women carrying the *BRCA1* 185delAG PV, 98 of whom were diagnosed with BC (online supplemental table S1). The cohort was recruited through the Meirav High-Risk Clinic at Sheba Medical Center (SMC), where participants are enrolled in a clinical surveillance programme that includes biannual breast clinical examinations and breast MRI alternating with ultrasound and/or mammography. Recruitment was conducted under an ethically approved protocol, carried out in collaboration with Regeneron at SMC, and each participant provided written informed consent.

Whole-exome sequencing

WES was carried out at the Regeneron Genetics Center following previously published protocols.[23] In brief, genomic DNA was sheared and used to prepare 75 bp paired-end libraries for exome sequencing. Samples were captured using the IDT XGen exome capture reagent and sequenced on an Illumina NovaSeq instrument. Captured fragments were sequenced to achieve a minimum of 85% of the target bases covered at 20× or greater. Following sequencing, data were processed using a DNAnexus implemented cloud-based pipeline that runs standard tools for sample-level data production and analysis. Sequence reads were aligned to the GRCh38/hg38 human genome reference assembly using BWA-mem, and SNP and InDel variants were called using GATK's *HaplotypeCaller* in accordance with the best practices for germline short variant discovery.

Principal Component Analysis (PCA)

PCA was performed using PLINK V.1.9 on genotype data, including only variants with no missing genotypes (geno=0). The top five principal components (PCs) were extracted for downstream analyses.

Variant annotation and filtering

All variants were annotated with the Ensembl Variant Effect Predictor (VEP, cache V.109).[24] Variants were filtered by population frequency using gnomAD.[25] Variants with a general or AJ-specific MAF greater than 0.05 were excluded. In addition, variants whose MAF in our study's cohort was greater than 0.2 were excluded too. For VEP annotations, only protein-coding transcripts (ie, transcripts annotated with the protein_coding, TR genes or IG genes biotypes) were considered, using ENSEMBL annotations. For each variant, the most impactful annotation was selected according to the following hierarchy: loss-of-function (LoF)>missense>inframe insertion/deletion>synonymous>non-coding annotations (eg, downstream, intronic).

Association tests with BC age at diagnosis

We used multivariate Cox regression models to assess the association between age at BC diagnosis and mutational status in the examined genes or gene sets. The model controlled for the top five PCs and for the total number of damaging alleles across the exome of each woman. Specifically, we applied the following Cox proportional hazards model for the hazard function $h(t)$:

$$\log h_i(t) = \alpha(t) + \beta_{IN} Xin_i + \beta_{Tot} Xtot_i + \sum_{j=1}^{5} \beta_{PCj} PC_{i,j}$$

where i is an index for individuals, Xin is the number of putatively damaging variants in the tested gene or gene set and $Xtot$ is the total number of putatively damaging variants in all the protein-coding genes. Time was either the age at BC diagnosis or censoring age at last follow-up. To appropriately account for the impact of risk-reducing surgeries, for women who underwent such procedures, we considered the timing of cancer diagnosis in relation to the surgical intervention. Specifically, (1) if a woman underwent RRM or bilateral salpingo-oophorectomy (BSO) and had not been diagnosed with cancer, the age at surgery was used as the age of censoring. (2) If cancer developed prior to surgery, the age at diagnosis was used. (3) In cases where surgery preceded a subsequent cancer diagnosis, the age at surgery was taken as the relevant event age, reflecting the preventive intent of the operation.

We ran the model separately for the low frequency LoF variants and low frequency putatively damaging missense variants (alphaMissense score >0.85).

Gene set-level control tests with synonymous variants

As a negative control, we ran the same analysis using low-frequency synonymous variants. In each run, for every woman, we randomly sampled synonymous variants in the same number as her damaging variants (LoF or missense). We repeated these control runs 100 times.

In the gene set-level tests, overlaps between Gene Ontology Biological Process (GOBP) gene sets create dependencies between tests, leading to substantial deviations of the observed p value

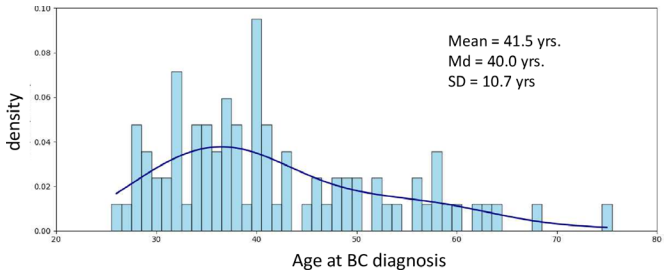

Figure 1 Distribution of age at breast cancer (BC) diagnosis among women in our cohort who developed BC and did not undergo bilateral salpingo-oophorectomy surgery (n=84).

distribution from the expected null. To construct a null distribution of p values that accounts for these dependencies (used for comparison with the observed p values in the QQ plots), we permuted the assignment of genes to GOBP gene sets. This gene permutation preserves both the sizes of the gene sets and their overlaps. We ran the Cox model on 100 such random iterations and constructed the null p value distribution by averaging the ranked p values across iterations.

RESULTS

We analysed a cohort of 321 Israeli women carrying the *BRCA1* 185delAG AJ founder PV. Most participants were of AJ ancestry (207/321; 64%), but Israeli women of other Jewish ethnic backgrounds were also included: Middle Eastern, Balkan, North African and admixed ancestries (online supplemental figure S1). Of the participants, 84 women (26%) developed BC (excluding the 14 women who developed BC after undergoing BSO), with a mean age at diagnosis of 41.5 years (median 40.0 years). Age at BC onset showed considerable variation, with an SD of 10.7 years and a range of 26–75 years (figure 1). After filtering by MAF, we identified 111 627 unique protein-coding variants (485 413 variants in total): 42 966 unique synonymous (201 623 in total), 64 861 unique missense (270 251 in total) and 3800 unique LoF (13 539 in total) variants. We evaluated the potential functional impact of the missense variants using the alphaMissense score,[26] identifying 3113 unique variants having a putatively damaging effect (9004 in total, alphaMissense score >0.85).

First, we performed gene-level tests to identify genes whose mutational status may be associated with *BRCA1* penetrance. We applied a multivariate Cox regression model to assess the association between carrying additional low-frequency, putatively damaging variants in each tested gene and BC age at diagnosis in our *BRCA1* carriers cohort. The model controlled for the top five PCs and the total protein-coding mutational burden of each woman (see the Methods section). We conducted separate analyses for missense and LoF variants and tested all protein-coding genes that harboured at least 10 damaging variants (153 genes for missense; 247 genes for LoF). Only one gene, *KMT2C*, in the missense variant analysis—and none in the LoF variant analysis—was identified at a 5% false discovery rate (FDR) (online supplemental table S2 and figure S2). *KMT2C*, a gene that encodes a nuclear protein involved in histone methylation and transcriptional activation, has previously been implicated in BC pathogenesis.[27]

Next, we conducted gene-set level analyses. We first tested the previously reported association between LoF variants in DDR genes and earlier age at BC diagnosis among *BRCA1* PV carriers.[17] However, this association could not be replicated in our cohort (online supplemental figure S3). Given the critical role the immune system plays in the tumour microenvironment and its pivotal effect on tumour progression, we then investigated whether carrying additional damaging variants in immune-related genes was associated with age at BC diagnosis. To this end, we queried GOBP categories containing the terms '*innate_immune*' or '*adaptive_immune*.' This yielded four innate immunity–related gene sets and four adaptive immunity–related gene sets. Notably, multivariate Cox regression analysis revealed a significant association between carrying additional putatively damaging missense variants in genes involved in the innate immune response and age at BC onset among *BRCA1* PV carriers in our cohort (table 1). The estimated HR for carrying a missense variant in genes from the GOBP category *REGULATION_OF_INNATE_IMMUNE_RESPONSE* was 1.55 (95% CI 1.15 to 2.08; p=0.0037) (figure 2; online supplemental figure S4). This association was unique to genes involved in the activation of the innate immune response and was not observed for genes involved in its negative regulation (table 1) None of the individual genes within the set reached statistical significance, indicating that, given the current cohort size, the observed effect becomes apparent only when the innate immune genes are analysed collectively. Furthermore, the associations were specific to innate immunity gene sets and were not detected for gene sets related to adaptive immunity (table 1). Additionally, no significant associations were found in the gene set-level analysis of LoF variants (table 2).

Finally, we extended the gene set-level analysis by performing a hypothesis-free exploration of biological processes that may be associated with BC risk in *BRCA1* PV carriers. We tested

Table 1 Low-frequency putatively damaging missense variants

GOBP gene set	GOBP ID (# of genes)	P value	HR (95% CI)
Innate immune			
Regulation of innate immune response	GO:0045088 (428)	0.0037	1.55 (1.15 to 2.08)
Activation of innate immune response	GO:0002218 (280)	0.012	1.5 (1.1 to 2.05)
Innate immune response activating cell-surface receptor signalling	GO:0002220 (93)	0.028	1.72 (1.06 to 2.8)
Negative regulation of innate immune response	GO:0045824 (91)	0.86	1.1 (0.4 to 3)
Adaptive immune			
Negative regulation of adaptive immune response	GO:0002820 (64)	0.15	0.5 (0.195 to 1.28)
Regulation of adaptive immune response	GO:0002819 (208)	0.3	0.8 (0.51 to 1.23)
Positive regulation of adaptive immune response	GO:0002821 (130)	0.13	0.42 (0.14 to 1.3)
Adaptive immune response based on somatic recombination of immune receptors built from immunoglobulin superfamily domains	GO:0002460 (371)	0.85	0.97 (0.68 to 1.37)

GOBP, Gene Ontology Biological Process.

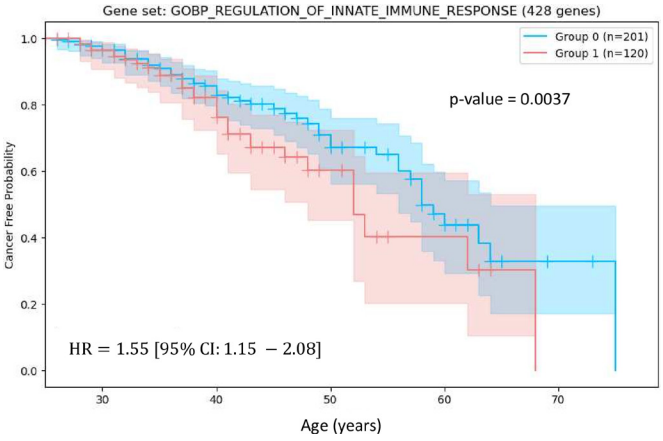

Figure 2 Carrying additional low-frequency putatively damaging missense variants in innate immunity genes is associated with earlier breast cancer (BC) diagnosis among *BRCA1* carriers. Kaplan-Meier plot comparing age at BC diagnosis between *BRCA1* PV carriers who do (group 1) or do not (group 0) carry such variants in any gene included in the Gene Ontology Biological Process (GOBP) '*REGULATION_OF_INNATE_IMMUNE_RESPONSE*' gene set. P value and HR were calculated using a multivariate Cox regression model, controlling for the top five principal components and the total number of low-frequency putatively damaging missense variants each woman carries.

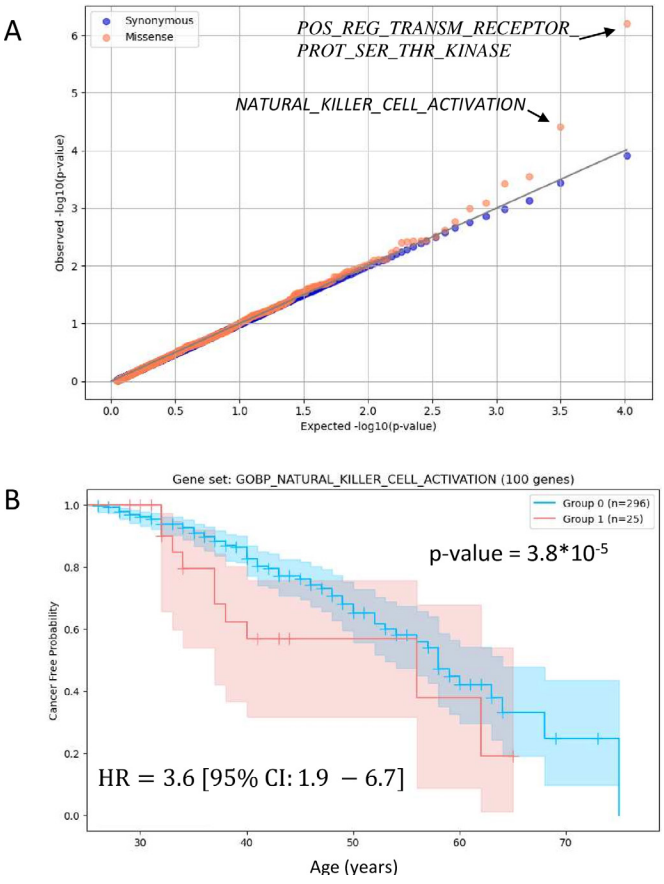

Figure 3 (A) QQ plot for the gene set-level tests assessing the association of low-frequency putatively damaging missense variants with breast cancer (BC) age at diagnosis among *BRCA1* PV carriers. For the expected p values under the null (x-axis), we used random sampling of low-frequency synonymous variants and permutations of gene assignments to gene sets (see the Methods section). The x-axis represents the average ranked p values over 100 iterations. (B) Kaplan-Meier plot comparing BC age at diagnosis between *BRCA1* PV carriers who do (group 1) or do not (group 0) carry additional low-frequency putatively damaging missense variants in any gene included in the Gene Ontology Biological Process (GOBP) '*NATURAL_KILLER_CELL_ACTIVATION*' gene set. P value and HR were calculated using a multivariate Cox regression model.

approximately 1500 GOBP gene sets—each containing between 50 and 500 genes and including at least 20 low-frequency missense or LoF variants in our cohort—to assess whether carrying additional damaging variants in genes within a given set was associated with age at BC diagnosis. These analyses were conducted separately for putatively damaging missense variants and LoF variants. As a negative control, we repeated the analysis using low-frequency synonymous variants (see the Methods section). The distribution of the observed p values from the damaging variant analysis, compared with that from the synonymous variants control, indicated that the missense variant analysis (figure 3A), but not the LoF variant analysis (online supplemental figure S5), captured genuine association signals with age at BC onset. While no gene set passed the 5% FDR threshold in the LoF variant analysis, two gene sets were identified in the missense variant analysis (online supplemental table S3). The top-scoring gene set in this analysis was *POS_REG_TRANSM_RECEPTOR_SER_THR_KINASE_SIGPATH*, which comprised 104 genes (online supplemental figure S6). Notably, the second gene set was related to natural killer (NK) cells, which are a pivotal arm of the innate immune system, and was *NATURAL_KILLER_CELL_ACTIVATION* ($p=3.82\times10^{-5}$; figure 3B). The estimated HR for carrying an additional missense

Table 2 Low-frequency LoF variants

GOBP gene set	GOBP ID (# of genes)	P value	HR (95% CI)
Innate immune			
Regulation of innate immune response	GO:0045088 (428)	0.27	0.9 (0.76 to 1.08)
Activation of innate immune response	GO:0002218 (280)	0.62	0.95 (0.77 to 1.17)
Innate immune response activating cell-surface receptor signalling	GO:0002220 (93)	0.52	1.15 (0.75 to 1.76)
Negative regulation of innate immune response	GO:0045824 (91)	0.64	0.95 (0.76 to 1.18)
Adaptive immune			
Negative regulation of adaptive immune response	GO:0002820 (64)	0.47	0.86 (0.56 to 1.3)
Regulation of adaptive immune response	GO:0002819 (208)	0.4	0.9 (0.72 to 1.14)
Positive regulation of adaptive immune response	GO:0002821 (130)	0.43	0.93 (0.7 to 1.16)
Adaptive immune response based on somatic recombination of immune receptors built from immunoglobulin superfamily domains	GO:0002460 (371)	0.19	0.88 (0.72 to 1.07)

GOBP, Gene Ontology Biological Process; LoF, loss-of-function.

variant in genes within this set was 3.62 (95% CI 1.96 to 6.67). This gene set comprised 100 genes; among them, the gene most frequently carrying a damaging missense variant was *IFNA10*—a member of the type I interferon family—detected in 13 women (online supplemental table S4). The overlap between the two top-scoring gene sets was minimal (only one gene—*JAK2*), indicating that they captured distinct association signals with age at BC diagnosis in our cohort.

DISCUSSION

To the best of our knowledge, our study is the first large-scale WES analysis aimed at identifying genetic modifiers of BC risk in *BRCA1* PV carriers. All participants in our cohort carry an identical *BRCA1* 185delAG AJ founder PV, which facilitates the detection of modifiers by avoiding confounding from variant-specific effects.[28] We found that the presence of additional putatively damaging missense variants in genes involved in innate immunity was significantly associated with earlier BC diagnosis. This effect was noted for several overlapping gene sets; the strongest one was for the genes annotated as involved in the activation of NK cells. It remains to be determined whether these preliminary findings can be replicated in independent, ethnically diverse, larger cohorts of carriers of heterogeneous PVs in *BRCA1*.

Previous studies have demonstrated that PRS models can stratify BC risk in BRCA1 carriers. Specifically, the 313-SNP PRS model for estrogen receptor (OR)-negative BC showed a HR per SD of 1.29 (95% CI 1.25 to 1.33).[12] Assuming approximate normality of the standardised PRS, the implied HR comparing individuals at the 95th versus 5th percentile is ~2.3, and the HR comparing the 99th versus 1st percentile is ~3.3. Thus, the HR of 3.62 that we observed for carriers of damaging missense variants in genes related to NK cell activation is comparable in magnitude to, and even larger than, the risk difference associated with the extreme tails of the PRS distribution. However, due to the small cohort size, the margins of our estimation are wide (95% CI 1.96 to 6.67). It will be of interest to investigate whether the effects of common risk SNPs, as captured by PRS, and those of rare missense variants in immunity-related genes are additive. Since most PRS SNPs are non-coding, they were not captured by our WES analysis. Assessing the combined impact of common non-coding and rare coding variants will require large cohorts of *BRCA1* carriers with available whole-genome sequencing data.

The risk-modifying effect observed in the current study was specific to genes involved in innate immunity, with no significant association detected for genes related to the adaptive immune system. However, although not statistically significant after correction for multiple testing, the top-scoring gene set in our LoF variant analysis was *GOBP_REGULATION_OF_B_CELL_ACTIVATION* (p=0.0003; online supplemental table S3), suggesting that compromised activity of the adaptive arm might also increase BC risk in *BRCA1* PV carriers. As for the innate immunity genes, the strongest signal was observed for genes implicated in the activation of NK cells. Prior studies provide biological plausibility for this association between impaired NK cell activation and increased BC risk in *BRCA1* PV carriers. First, triple-negative breast cancer (TNBC)—the predominant BC subtype in *BRCA1* carriers[29]—exhibits a significantly higher frequency of major histocompatibility complex class I (MHC I) loss compared with other BC subtypes.[30] Second, the loss of MHC I likely shifts the burden of immune surveillance from cytotoxic T cells to NK cells, which function as 'missing self' sensors; their activity is enhanced in response to cells with reduced MHC I expression.[31] Therefore, if BRCA1-deficient tumours rely more heavily on NK cells for immune control, then NK cell dysfunction could promote immune escape and development of these tumours, as suggested by our findings. Furthermore, it would be interesting to examine whether our observation can also be generalised to BC risk modulation in the general population, and whether this effect is specific to, or stronger in, the TNBC subtype.

Interestingly, while our manuscript was under review, a related study by Kuligina *et al* was published.[32] In that work, the authors specifically investigated potential modifying effects of damaging variants in immune-related genes on BC risk in BRCA1 carriers. Their analysis identified a missense variant in PRF1 (PRF1 p.Ala91Val; rs35947132) as a candidate associated with an earlier age at BC diagnosis in carriers. Notably, PRF1 encodes a pore-forming protein that is essential for immune function in cytotoxic T lymphocytes and NK cells, enabling these cells to eliminate infected or tumour cells by creating pores in target cell membranes.[33] The PRF1 p.Ala91Val variant was also detected in our cohort; however, its predicted AlphaMissense deleteriousness score (0.70) was below the threshold applied in our analyses (0.85). Evaluation of this specific variant in our data suggested an effect consistent with that reported by Kuligina *et al*. Nevertheless, because it was observed in only 17 carriers in our cohort, it did not approach statistical significance (p=0.20; online supplemental figure S7) and therefore can be considered only weak supportive evidence.

In summary, our findings in the Israeli cohort of identical *BRCA1* PV carriers highlight a potential role for innate immune pathways as modifiers of *BRCA1* penetrance and may support the development of more refined, personalised BC risk prediction models for *BRCA1* PV carriers. Future studies should assess whether these observations replicate in independent, ethnically diverse cohorts.

Acknowledgements We would like to thank Regenron's team for generating the WES data in the context of a collaborative effort with the Sheba Medical Center. This study was supported by funds from the Israel Cancer Research Fund (ICRF) (RE), the joint programme from the Cancer Biology Research Center (CBRC), Djerassi Oncology Center, Edmond J. Safra Center for Bioinformatics and Center for AI and Data Science (TAD) at Tel Aviv University (RE). RE is a Faculty Fellow of the Edmond J. Safra Center for Bioinformatics at Tel Aviv University. SS was partially supported by a fellowship from the Edmond J. Safra Center for Bioinformatics at Tel Aviv University.

Contributors RE, EF and RB conceived and supervised the study; RE designed the analysis; S Shemesh performed the data analysis; RE, S Shemesh, EF and RB wrote the manuscript. S Shoval, YL and DM-F contributed to the cohort recruitment. RE is the guarantor. AI (ChatGPT) was used to proof-edit the English.

Funding This study was funded by Israel Cancer Research Fund, Edmond J. Safra Center for Bioinformatics and Center for AI and Data Science (TAD) at Tel Aviv University, Edmond J. Safra Center for Bioinformatics at Tel Aviv University, Cancer Biology Research Center (CBRC), Djerassi Oncology Center.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study was conducted under an ethics protocol approved by SMC IRB (Reference number SMC 1492-14). All participants provided written informed consent. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. As per the ethically approved protocol, individual-level data cannot be shared. Aggregated, deidentified data may be made available on a specific, justified request to the corresponding authors.

ORCID iD
Ran Elkon https://orcid.org/0000-0003-3440-1286

REFERENCES

1 Petrucelli N, Daly MB, Pal T, *et al*. BRCA1- and brca2-associated hereditary breast and ovarian cancer. In: Adam MP, Everman DB, Mirzaa GM, et al, eds. *GeneReviews*. Seattle, 1993.
2 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;111:14205–10.
3 Clark AS, Domchek SM. Clinical management of hereditary breast cancer syndromes. *J Mammary Gland Biol Neoplasia* 2011;16:17–25.
4 Bertozzi S, Londero AP, Xholli A, *et al*. Risk-Reducing Breast and Gynecological Surgery for BRCA Mutation Carriers: A Narrative Review. *J Clin Med* 2023;12:1422.
5 Friebel TM, Domchek SM, Rebbeck TR. Modifiers of cancer risk in BRCA1 and BRCA2 mutation carriers: systematic review and meta-analysis. *J Natl Cancer Inst* 2014;106.
6 Maxwell KN, Domchek SM, Nathanson KL, *et al*. Population Frequency of Germline BRCA1/2 Mutations. *J Clin Oncol* 2016;34:4183–5.
7 Chenevix-Trench G, Milne RL, Antoniou AC, *et al*. An international initiative to identify genetic modifiers of cancer risk in BRCA1 and BRCA2 mutation carriers: the Consortium of Investigators of Modifiers of BRCA1 and BRCA2 (CIMBA). *Breast Cancer Res* 2007;9:104.
8 Gallagher S, Hughes E, Wagner S, *et al*. Association of a Polygenic Risk Score With Breast Cancer Among Women Carriers of High- and Moderate-Risk Breast Cancer Genes. *JAMA Netw Open* 2020;3:e208501.
9 Mars N, Widén E, Kerminen S, *et al*. The role of polygenic risk and susceptibility genes in breast cancer over the course of life. *Nat Commun* 2020;11:6383.
10 Gao C, Polley EC, Hart SN, *et al*. Risk of Breast Cancer Among Carriers of Pathogenic Variants in Breast Cancer Predisposition Genes Varies by Polygenic Risk Score. *J Clin Oncol* 2021;39:2564–73.
11 Borde J, Laitman Y, Blümcke B, *et al*. Polygenic risk scores indicate extreme ages at onset of breast cancer in female BRCA1/2 pathogenic variant carriers. *BMC Cancer* 2022;22:706.
12 Barnes DR, Rookus MA, McGuffog L, *et al*. Polygenic risk scores and breast and epithelial ovarian cancer risks for carriers of BRCA1 and BRCA2 pathogenic variants. *Genet Med* 2020;22:1653–66.
13 Zhang H, Ahearn TU, Lecarpentier J, *et al*. Genome-wide association study identifies 32 novel breast cancer susceptibility loci from overall and subtype-specific analyses. *Nat Genet* 2020;52:572–81.
14 Hakkaart C, Pearson JF, Marquart L, *et al*. Copy number variants as modifiers of breast cancer risk for BRCA1/BRCA2 pathogenic variant carriers. *Commun Biol* 2022;5:1061.
15 Ding YC, Adamson AW, Bakhtiari M, *et al*. Variable number tandem repeats (VNTRs) as modifiers of breast cancer risk in carriers of BRCA1 185delAG. *Eur J Hum Genet* 2023;31:216–22.
16 Peterlongo P, Chang-Claude J, Moysich KB, *et al*. Candidate genetic modifiers for breast and ovarian cancer risk in BRCA1 and BRCA2 mutation carriers. *Cancer Epidemiol Biomarkers Prev* 2015;24:308–16.
17 Sepahi I, Faust U, Sturm M, *et al*. Investigating the effects of additional truncating variants in DNA-repair genes on breast cancer risk in BRCA1-positive women. *BMC Cancer* 2019;19:787.
18 Swann JB, Smyth MJ. Immune surveillance of tumors. *J Clin Invest* 2007;117:1137–46.
19 Corthay A. Does the immune system naturally protect against cancer? *Front Immunol* 2014;5:197.
20 Ribatti D. The concept of immune surveillance against tumors. The first theories. *Oncotarget* 2017;8:7175–80.
21 Wu B, Zhang B, Li B, *et al*. Cold and hot tumors: from molecular mechanisms to targeted therapy. *Signal Transduct Target Ther* 2024;9:274.
22 Emens LA, Romero PJ, Anderson AC, *et al*. Challenges and opportunities in cancer immunotherapy: a Society for Immunotherapy of Cancer (SITC) strategic vision. *J Immunother Cancer* 2024;12:e009063.
23 Strauss KA, Gonzaga-Jauregui C, Brigatti KW, *et al*. Genomic diagnostics within a medically underserved population: efficacy and implications. *Genet Med* 2018;20:31–41.
24 McLaren W, Gil L, Hunt SE, *et al*. The Ensembl Variant Effect Predictor. *Genome Biol* 2016;17:122.
25 Karczewski KJ, Francioli LC, Tiao G, *et al*. The mutational constraint spectrum quantified from variation in 141,456 humans. *Nature New Biol* 2020;581:434–43.
26 Cheng J, Novati G, Pan J, *et al*. Accurate proteome-wide missense variant effect prediction with AlphaMissense. *Science* 2023;381.
27 Gala K, Li Q, Sinha A, *et al*. KMT2C mediates the estrogen dependence of breast cancer through regulation of ERα enhancer function. *Oncogene* 2018;37:4692–710.
28 Rebbeck TR, Mitra N, Wan F, *et al*. Association of type and location of BRCA1 and BRCA2 mutations with risk of breast and ovarian cancer. *JAMA* 2015;313:1347–61.
29 Engel C, Rhiem K, Hahnen E, *et al*. Prevalence of pathogenic BRCA1/2 germline mutations among 802 women with unilateral triple-negative breast cancer without family cancer history. *BMC Cancer* 2018;18:265.
30 Dusenbery AC, Maniaci JL, Hillerson ND, *et al*. MHC Class I Loss in Triple-negative Breast Cancer: A Potential Barrier to PD-1/PD-L1 Checkpoint Inhibitors. *Am J Surg Pathol* 2021;45:701–7.
31 Ljunggren HG, Kärre K. In search of the "missing self": MHC molecules and NK cell recognition. *Immunol Today* 1990;11:237–44.
32 Kuligina ES, Martianov AS, Yanus GA, *et al*. Germline Variants in the Immune Response-Related Genes: Possible Modifying Effect on Age-Dependent *BRCA1* Penetrance in Breast Cancer Patient. *Cancers (Basel)* 2025;17:3756.
33 Voskoboinik I, Whisstock JC, Trapani JA. Perforin and granzymes: function, dysfunction and human pathology. *Nat Rev Immunol* 2015;15:388–400.