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Title

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Permalink

<https://escholarship.org/uc/item/5fd4g4bz>

Journal

Gynecologic Oncology, 209

ISSN

0090-8258

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Publication Date

2026-06-01

DOI

10.1016/j.ygyno.2026.05.007

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Peer reviewed



Published in final edited form as:

Gynecol Oncol. 2026 June ; 209: 77–87. doi:10.1016/j.ygyno.2026.05.007.

Real-World Genetic Testing Data of Ovarian Cancer Patients: Informing Counseling and Risk Reduction in Patients over age Seventy

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Abstract

Background: Older women are underrepresented in hereditary cancer guidelines, and the prevalence of pathogenic or likely pathogenic (P/LP) germline variants in ovarian cancer (OC) patients aged ≥ 70 remains poorly characterized. Current recommendations for risk-reducing interventions and surveillance rely heavily on variant and family history (FH), yet their

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Declaration of Generative AI and AI-Assisted Technologies in the Manuscript Preparation Process

During the preparation of this work, the authors used Claude (Anthropic) to assist in the generation of Figures 2, 3B, and Supplementary Figure S1. The authors subsequently reviewed, verified, and edited all outputs as appropriate and assume full responsibility for the accuracy and integrity of the final content.

applicability in older populations is uncertain. We evaluated age-stratified prevalence of P/LP variants at OC diagnosis to identify at-risk older patients and inform more inclusive genetic counseling strategies.

Methods: We conducted a retrospective analysis of 113,236 OC patients undergoing germline testing through the Myriad Collaborative Research Registry (1996–2024). Variant prevalence, ancestry, FH, and testing patterns were evaluated across age groups, with focus on patients ≥ 70 .

Results: Overall, 14,513 patients (12.8%) harbored a P/LP variant, including 13,049 (11.5%) in established OC susceptibility genes. Among patients ≥ 70 (20%, $n=22,593$), 6.6% carried variants in established genes compared with 12.8% in those < 70 ($p < 0.01$). *BRCA1/2* and Lynch syndrome variants declined with age; *BRCA2* exceeded *BRCA1* in patients ≥ 70 . Moderate-penetrance variants (*BRIP1*, *PALB2*) were relatively enriched, while *ATM* and *RAD51C/D* remained stable. *PMS2* were more common than previously reported and declined with age ($p=0.03$). Patients ≥ 70 were 1.5-fold less likely to report a cancer FH.

Conclusion: Despite lower prevalence, a clinically meaningful proportion of patients ≥ 70 harbor actionable P/LP variants, often without FH that would prompt risk-reducing interventions. These findings suggest reduced sensitivity of FH-based risk assessment in older individuals, supporting age-inclusive genetic counseling and testing strategies extending beyond FH-based criteria.

Keywords

ovarian cancer; hereditary cancer; BRCA; Lynch syndrome; elderly; risk reduction; prevention

Introduction

Hereditary cancer risk assessment relies on personal and family history, with key susceptibility genes including *BRCA1* and *BRCA2*, as well as *ATM*, *BRIP1*, *CHEK2*, *PALB2*, *RAD51C*, *RAD51D*, and Lynch syndrome-associated genes (*MLH1*, *MLH2*, *MSH6*, *PMS2*, *EPCAM*).¹ Identification of pathogenic or likely pathogenic (P/LP) variants informs cancer prevention, surveillance, and treatment for patients and at-risk relatives. Detection of hereditary susceptibility enables targeted interventions, including risk-reducing surgery and cascade testing, reducing cancer incidence and mortality.^{2,3}

Ovarian cancer (OC) has a substantial hereditary component, with 18–25% of patients harboring germline P/LP variants, most commonly *BRCA1/2* (86–90%).² High-penetrance genes, such as *BRCA1/2*, confer well-established risk, whereas moderate-penetrance genes have more variable risk estimates and remain an area of active investigation.⁴ Risk-reducing bilateral salpingo-oophorectomy (RRSO) decreases OC incidence and improves survival, forming the cornerstone of management.^{1,5}

In the general U.S. population, the lifetime risk of OC is approximately 1.3% by age 80.⁶ Family history remains an important modifier of risk; individuals with a first degree relative (FDR) affected by OC have an estimated relative risk of 3.1 (95% CI, 2.6–3.7) compared with the general population.^{1,7} Cost-effectiveness analyses suggest that RRSO becomes cost-effective when lifetime OC risk exceeds approximately 4%, setting a benchmark for intervention.⁸

The National Comprehensive Cancer Network (NCCN) provides gene-specific management recommendations based on absolute lifetime cancer risk estimates, recommending enhanced screening or consideration of RRSO when OC risk exceeds population-level lifetime risk (1–2%).^{1,4,7} Earlier studies proposed lower thresholds, such as double the population risk or 2.6% for consideration of RRSO,⁷ which is less than the risk of OC conferred by having a FDR with OC. The NCCN (v.2.2026) adopts a 5% threshold to recommend discussion of RRSO for genes with risk estimates below this benchmark but above population levels, with individualized recommendations based on family history and patient preferences.⁹

The expansion of multigene panel testing has outpaced evidence, creating uncertainty in risk estimates and management.^{7,10} Advances in targeted therapies, including PARP inhibitors and immune checkpoint inhibitors, have improved survival.^{11,12} As the survivor population ages, new challenges arise regarding long-term surveillance and prevention in older carriers.

Current NCCN guidelines recommend individualized breast cancer screening ≥ 75 , leaving management of older *BRCA1/2* carriers largely to clinical discretion.¹ Similarly, although RRSO is recommended at younger ages for carriers of *BRCA1/2*, *BRIP1*, *RAD51C/D*, *MLH1*, *MSH2/EPCAM*, and *MSH6*, guidance is limited when variants are identified later in life. Evidence to inform management in individuals ≥ 70 remains sparse. Given the lack of effective OC screening, reliance on conservative management in older high-risk women may contribute to delayed diagnosis and worse outcomes despite available risk-reducing interventions.

Among Lynch syndrome variants, estimated lifetime OC risk varies, with higher risk observed in *MSH2/EPCAM* (8–38%), and *MLH1* (4–20%), compared to *MSH6* (≤ 1 –13%) and *PMS2* (1.3–3%).^{1,13–15} Recommendations are even less well defined for moderate-risk OC genes; consideration of RRSO is suggested for variants associated with lower absolute risk ($< 5\%$), such as *PALB2* (3–5%). *ATM*, confers a lower estimated lifetime risk (2–3%), below thresholds at which routine RRSO is typically recommended.^{1,16} Current guidelines often rely on family history in addition to variant status to guide management.^{1,17}

While age has been studied in relation to treatment toxicity and dosing, it has not been adequately examined as a distinct population with a meaningful burden of P/LP variants. A prior study of 1,231 patients reported a 7.9% prevalence of P/LP variants in OC-associated genes.¹⁸ However, the genetic landscape of older patients is insufficiently characterized in larger cohorts. Despite increasing emphasis on individualized, patient-centered care, older adults remain underrepresented in hereditary cancer guidelines. Limited age-specific data and guidance on continuation, modification, or discontinuation of surveillance and preventive interventions create uncertainty in clinical decision-making, particularly for carriers of moderate-penetrance variants.

We evaluated the prevalence and distribution of germline of P/LP variants in women with OC, with a focus on those aged ≥ 70 years, to better characterize hereditary cancer burden and inform age-specific risk assessment and management. We hypothesized that a clinically meaningful proportion of older patients harbor actionable variants, often independent

of family history, supporting the need for more age-inclusive genetic counseling and consideration of RRSO in later life.

Study Objectives

The primary objective was to determine the prevalence of germline P/LP variants by age at OC diagnosis, categorized by decade and dichotomized as <70 versus ≥70 years. Secondary objectives included evaluating age-related patterns in P/LP variant prevalence in relation to family history (including degree of relatedness and age at diagnosis of affected relatives) and assessing differences by ancestry. Exploratory analyses examined patterns of germline testing by provider type, geographic region, and state-level uptake, as well as testing characteristics, including panel size and gene composition.

Methods

Study Population

This retrospective study analyzed germline testing data from the Myriad Collaborative Research Registry v.3 (1996–2024). Ovarian, fallopian tube, and primary peritoneal cancers were collectively defined as OC. Patients were stratified by P/LP variant status: (1) carriers harboring alterations in established OC susceptibility genes per NCCN Guidelines v2.2026 (*BRCA1*, *BRCA2*, *RAD51C*, *RAD51D*, *BRIP1*, *PALB2*, *ATM*, *MLH1*, *MSH2*, *MSH6*, *EPCAM*); (2) carriers of P/LP variants in other hereditary cancer genes not associated with heightened OC risk. *PMS2* was included in the OC susceptibility cohort given limited and evolving evidence.

Inclusion criteria were female sex at birth, age ≥18 years at OC diagnosis, and completed germline testing. Patients with missing age at diagnosis were excluded. Variant analyses were limited to individuals with ≥1 P/LP variant. Variants of uncertain significance (VUS) were excluded unless accompanied by a P/LP variant. Of all tested individuals, 859 were excluded (43 age <18; 816 missing age), yielding a final cohort of 113,236 OC patients. State-level testing uptake was categorized as high versus moderate/low based on prior definitions.^{19,20}

Variables and Statistical Analysis

Descriptive statistics summarized demographic and clinical characteristics, including age, family cancer history, ancestry and gene classification (OC susceptibility vs other). Ancestry was self-reported at the time of genetic testing. Ashkenazi Jewish ancestry was categorized as mutually exclusive from other race/ethnicity groups. P/LP variant prevalence was assessed across age groups (by decade and <70 vs ≥70 years) using Chi-square or Fisher's exact tests. Age at diagnosis between carriers and non-carriers was compared using the Mann–Whitney U test, with effect size quantified by Cohen's *d*. Gene-specific associations with older-onset OC (<70 vs ≥70) were evaluated using Chi-square tests, with odds ratios (ORs) and 95% confidence intervals (CIs). Familial cancer burden was quantified using a degree-weighted score (1.0 first-degree, 0.5 second-degree, 0.25 third-degree, 0.125 other relatives).

Multivariable logistic regression assessed independent associations with older-onset OC, including all P/LP variants and adjusting for family history and covariates. Separate models were constructed adjusting for self-reported race and ancestry. Ancestry-adjusted models were predefined as the primary analysis, with race-adjusted models evaluated as sensitivity analyses. Associations between age at onset and affected relatives were evaluated using Spearman correlation and linear regression. Group comparisons used Mann–Whitney U tests, with false discovery rate (FDR) controlled using the Benjamini–Hochberg method. All tests were two-sided ($p < 0.05$; FDR $q < 0.05$), and performed using SAS 9.4 (SAS Institute Inc., Cary, NC) and Python version 3.12 (pandas, SciPy, and statsmodels). The study received IRB approval (IRB-25–0847).

Results

Study Population

This retrospective analysis of the MCRR included 1,230,321 patients undergoing germline testing, of whom 1,018,299 (82.8%) were female. Among these, 113,236 (11.1%) had OC. A total of 14,513 OC patients (12.8%) harbored at least one P/LP germline variant (Figure 1), including 90.0% ($n=13,049$, 11.5% of the overall OC cohort) with variants in established OC susceptibility genes.

Across the overall OC cohort, the greatest proportion of diagnoses occurred between ages 50–69, with 20% of patients diagnosed at ≥ 70 years (Figure 2). Among P/LP carriers, prevalence was highest between ages 40–59 years. Among P/LP variant carriers, 12.9% ($n=1,868$) were ≥ 70 years at diagnosis. Across all OC patients diagnosed at age ≥ 70 years, 6.6% ($n=1,484/22,593$) carried a P/LP variant in an OC susceptibility gene.

Median age at diagnosis was 58.0 years (IQR 48.0–68.0), for the overall OC cohort ($n=113,236$), compared with 55.0 years (IQR 48.0–63.0) among carriers of established P/LP susceptibility variants ($n=13,049$). Patients harboring exclusively a non-OC-associated hereditary cancer variant ($n=1464$) had a median age of 59.0 years (IQR 47.0–70.0).

Spectrum of Germline Variants

Among 14,513 OC patients with P/LP variants, *BRCA1/2* accounted for 74.9% of variants, with *BRCA1* ($n=6,561$, 45.2%) more frequent than *BRCA2* ($n=4,314$, 29.7%, Supplementary Figure S1). Other established OC susceptibility genes collectively comprised 19.5% ($n=2,829$), including *ATM* ($n=518$, 3.6%), *BRIP1* ($n=503$, 3.5%), *MSH6* ($n=341$, 2.3%), *RAD51C* ($n=333$, 2.3%), *MSH2* ($n=311$, 2.1%), *PMS2* ($n=277$, 1.9%), *PALB2* ($n=227$, 1.6%), *RAD51D* ($n=192$, 1.3%), *MLH1* ($n=122$, 0.8%), and *EPCAM* ($n=5$, $<0.1\%$). Lynch syndrome-associated genes (*MSH2*, *MSH6*, *MLH1*, *PMS2*, and *EPCAM*) were identified in 7.1% of carriers ($n=1,028$).

Variants in Other hereditary cancer genes without established OC risk were identified in 2,792 patients; 1,464 (10.1% of the P/LP variant cohort) harbored these variants exclusively, representing 1.3% of the total OC cohort.

Gene Prevalence in the Overall Cohort

BRCA1 and *BRCA2* were the most frequently altered genes, identified in 6.4% (n=6,561) and 4.2% (n=4,314) of all OC patients, respectively, and together accounting for 10.4% of the total OC cohort (n=10,774/113,236; Table 1). Lynch syndrome–associated genes were identified in 2.0% (n=1,028), while moderate-penetrance genes were less frequent, (*ATM* n=518, 1.1%; *BRIP1* n=503, 1.0%; *RAD51C* n=333, 0.7%; *PALB2* n=227, 0.5%; *RAD51D* n=192, 0.4%).

Age at Diagnosis by Gene

Age at OC diagnosis varied by P/LP variant. *BRCA1* and *BRCA2* carriers were diagnosed at median ages of 52 and 59 years, respectively. Moderate-penetrance genes showed generally older onset (*ATM* 58, *RAD51D* 60, *PALB2* 61, *RAD51C* 61, *BRIP1* 64 years; Figure 3). Lynch syndrome genes were associated with earlier onset (*MSH2* 44, *MLH1* 45, *MSH6* 51, *PMS2* 55 years).

Age-Stratified Patterns

Age-stratified patterns emerged across OC susceptibility genes. *BRCA1/2* and Lynch syndrome variants (*MSH2*, *MLH1*, and *MSH6*) were enriched in patients <70 years, with *PMS2* demonstrating attenuated age-related decline compared with other MMR genes (Table 1, Figure 3). Moderate penetrance genes (*ATM*, *RAD51C*, and *RAD51D*) showed stable prevalence across age groups. *BRIP1* and *PALB2* were enriched in older-onset disease. *BRIP1* prevalence increased with age (1.5% at 70–79; 1.6% at ≥80; p<0.01) and was higher in patients ≥70 versus <70 (1.5% vs 0.9%, p<0.01). *BRCA1/2* prevalence declined with age; patients diagnosed at ≥70 years had significantly lower relative frequencies of *BRCA1* (1.9% vs 7.4%) and *BRCA2* (3.3% vs 4.4%) compared with those <70 years (both p<0.01). The distribution of *BRCA* mutations shifted with age, with *BRCA2* exceeding *BRCA1* in OC patients ≥70, contrasting with both the overall cohort and the <70 group, in which *BRCA1* remained the most common P/LP variant. Lynch syndrome variants similarly declined with age (2.3% <70 vs 0.8% ≥70; p<0.01), driven by reductions in *MSH2*, *MSH6*, and *MLH1*.

Age-Associated Odds of Gene Carriage

Patients ≥70 years had significantly lower odds of *BRCA1* (OR 0.24, 95% CI 0.21–0.27), *BRCA2* (OR 0.71; 95% CI 0.65–0.77) and Lynch syndrome variants *MSH2*, *MSH6*, *MLH1* (OR range 0.09–0.36; Figure 4). *PMS2* showed a similar but attenuated trend toward lower prevalence in older patients (OR 0.70, 95% CI 0.51–0.96). Moderate-penetrance genes (*ATM*, *RAD51C/D*, *PALB2*) showed no strong association with age. In contrast, *BRIP1* was enriched in older-onset OC (OR=1.73, 95% CI 1.44–2.08).

Ancestry Race/Ethnicity

Ancestry distributions differed by age among OC patients harboring P/LP variants in OC susceptibility genes (Supplementary Table S1–S3; P<0.01). Patients diagnosed at ≥70 were more frequently of White/European ancestry compared with younger patients (60.8% vs 54.3%) and less frequently of Asian (2.9% vs 3.3%), Black/African (4.0% vs 5.1%), or

Hispanic/Latino ancestry (4.4% vs 7.3%). Ashkenazi Jewish ancestry was similar across age groups (6.7% vs 6.5%).

However, gene specific ancestry analyses, showed enrichment of *BRCA1* carriers of Ashkenazi Jewish (OR 2.5, 95% CI 1.6–3.6), Asian (OR 2.4, 95% CI 1.2–4.3), and Mixed ancestries (OR 1.7, 95% CI 1.1–2.5) among older patients (≥ 70), with relative underrepresentation of White/European carriers (OR=0.5, 95% CI 0.4–0.6). Carriers of *BRCA2* showed enrichment of Middle Eastern (OR 4.3, 1.7–9.0), Asian (OR 2.2, 1.3–3.5), and Ashkenazi Jewish carriers (OR 1.9, 1.3–2.6), and under-representation of White/European carriers (OR 0.7, 0.6–0.9) in the ≥ 70 cohort. (Supplementary Figure S2). The remaining OC susceptibility genes did not demonstrate specific ancestry or race-based predispositions across the overall cohort or within the elderly population.

In ancestry-adjusted models, *BRCA1* (OR 0.20, 95% CI 0.18–0.23; $p < 0.01$), *BRCA2* (OR 0.60, 95% CI 0.54–0.66; $p < 0.01$), *MSH2* (OR 0.08, 95% CI 0.04–0.17; $p < 0.01$), *MLH1* (OR 0.24, 95% CI 0.11–0.50; $p < 0.01$), and *MSH6* (OR 0.37, 95% CI 0.26–0.53; $p < 0.01$) were significantly associated with younger age at diagnosis. In contrast, *BRIP1* (OR 1.98, 95% CI 1.64–2.41; $p < 0.01$) and *PALB2* (OR 1.35, 95% CI 0.99–1.82; $p < 0.01$) were independently associated with OC ≥ 70 years. *ATM*, *PMS2*, *RAD51C*, and *RAD51D* showed no significant age association.

Race-adjusted models confirmed lower odds of older-onset OC among Asians (OR 0.52, 95% CI 0.46–0.58), Black/African American (OR 0.68, 95% CI 0.63–0.74), and Hispanic/Latino (OR 0.50, 95% CI 0.46–0.54) compared with White patients.

Family History

Family history of OC was less common among patients ≥ 70 (23.2% [n=345/1,484] vs 32.5% [n=3,759/11,565]). Among families with reported cancer history, relatives of older OC probands (≥ 70 years) were diagnosed at later ages, with a higher median age at cancer diagnosis (57 vs 55 years; $p < 0.01$) and a higher minimum age at diagnosis (47 vs 45 years; $p < 0.01$). Consistent with this pattern, relatives of younger probands were more likely to have cancers diagnosed before age 50 compared with relatives of older probands (63.6% vs 54.2%; $p < 0.01$).

In the adjusted multivariate model, the degree-weighted family history score was not independently associated with age of OC diagnosis (OR 1.01, 95% CI 0.98–1.04; $p = 0.46$). However, the presence of any family history of OC was significantly associated with younger age at diagnosis (OR 0.70, 95% CI 0.63–0.78; $p < 0.01$), with family history-positive patients diagnosed a median of 5 years earlier (53 vs 58 years; $p < 0.01$).

Prevalence of family history of cancer declined significantly with increasing age at OC diagnosis (Figure 5). Among PV carriers, the prevalence of reported family history was 1.5-fold lower in patients aged ≥ 70 years compared with those aged < 50 years (23.2% vs 34.9%), with a strong inverse correlation across age groups (Spearman $\rho = -0.94$, $p = 0.005$).

In gene-specific analyses, P/LP variant carriers with a positive family history were generally diagnosed at younger ages than carriers without family history; however, the magnitude of this association varied by gene. Genes typically associated with later-onset OC (e.g., *BRIP1*, *ATM*, and *RAD51D*) demonstrated the largest age shifts, with family history-positive carriers diagnosed approximately 3–4 years earlier than carriers without a family history. In contrast, younger-onset OC susceptibility genes (e.g., *MLH1* and *MSH6*) showed minimal or no difference in age at diagnosis based on family history.

Secondary Malignancies

Older-onset OC patients had a higher prevalence of metachronous or synchronous malignancies (39.9% vs 31.7%, $p<0.01$). When secondary cancer burden was evaluated across gene-specific subgroups, no significant differences between older-onset and younger patients were observed for carriers of Lynch syndrome-associated genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*), *RAD51C/D*, *ATM*, *PALB2*, or *BRIP1*. This difference was most pronounced among *BRCA1/2* carriers, where older patients had substantially higher rates of multiple primary cancers. Among *BRCA1* carriers, 32.1% of all OC patients had multiple malignancies, more commonly in patients ≥ 70 versus <70 (51.2% vs 30.9%, $p<0.01$). A similar pattern was observed for *BRCA2* (31.7% overall; 41.1% vs 30.0%, $p<0.01$). Among *BRCA1* and *BRCA2* carriers, 25.0% and 23.1%, respectively, had a prior cancer diagnosis preceding OC.

Genetic Testing Patterns

Genetic testing uptake was lower among older patients (52.5% ≥ 70 vs 57% <70 , $p<0.01$; Supplementary Table S4). Oncologists ordered the majority of tests (71.8%), with increasing reliance on oncologist-directed testing with age and declining involvement of genetic specialists. Testing patterns shifted with age, with decreased use of BRCA-only testing and increased use of multigene panels. Genetic testing was most frequently completed in historically high-uptake states.

Discussion

The decline in P/LP variant prevalence with age aligns with the known peak incidence of hereditary cancer in midlife. However, a clinically meaningful proportion of patients ≥ 70 years harbor actionable variants in hereditary cancer predisposition genes, supporting universal testing irrespective of age.¹ Identification of P/LP variants in older patients informs individualized treatment and serves as a critical gateway to cascade testing among at-risk relatives. Our findings from this large cohort are consistent with prior studies in smaller populations.^{18,21} While the prevalence of high-penetrance variants declines with older age, we identified distinct gene-specific patterns among moderate-penetrance genes, with *BRIP1* and *PALB2* enriched in later-onset disease, while *RAD51C/D* and *ATM* remain stable across the lifespan.

Despite guidelines, only 30% of OC patients undergo genetic testing, with further underutilization observed in older individuals.^{22–24} This gap may reflect “outgrowing” hereditary cancer risk based on modeling, whereby age-specific penetrance appears to

decline and residual lifetime risk decreases, potentially leading some clinicians and patients to defer genetic testing in older individuals.

Limitations of Family History in Risk Assessment

Family history of OC was less frequently reported in patients ≥ 70 years, despite greater time for cancer manifestation in relatives, likely reflecting truncated pedigrees and underreporting, reducing its utility for risk stratification. Testing should not rely solely on family history.

Within gene-specific analyses, family history remained a risk-modifying factor, with carriers reporting a positive family history generally diagnosed at younger ages. This effect was most pronounced for later-onset genes such as *BRIP1*. However, attenuation of this association in gene-specific analyses likely reflects limited power. Current NCCN guidelines rely on family history to guide management recommendations such as RRSO of moderate-penetrance variants; our findings suggest this approach may miss at-risk older individuals and support more age-inclusive strategies.

BRCA1 and *BRCA2*

Consistent with prior literature, *BRCA1* carriers presented at younger ages and with greater familial burden, whereas *BRCA2* carriers demonstrated later-onset disease with similar familial patterns across age groups. Both genes showed enrichment of Ashkenazi Jewish ancestry among older carriers. The apparent underrepresentation of White/European ancestry in older *BRCA1/2* carriers likely reflects classification methods and historical testing patterns, including earlier reliance on ancestry-based referral prior to universal testing recommendations. Ancestry categories in the dataset were mutually exclusive; individuals classified as Ashkenazi Jewish were not concurrently categorized as White/European.

Older *BRCA1/2* carriers exhibited a higher burden of secondary cancers compared with younger patients, without similar differences across other gene subgroups. These findings support continued high-risk breast surveillance beyond age 70. While the benefit of risk-reducing mastectomy declines with age, ongoing MRI-based surveillance is a reasonable strategy in select older carriers.^{25–29}

Lynch Syndrome Genes

Lynch syndrome–associated variants were identified in approximately 2% of the OC cohort, consistent with prior reports.³⁰ Although prevalence declined after age 60, secondary cancer burden remained comparable across age groups, underscoring the lifelong secondary cancer risk. Prior literature of Lynch syndrome-associated OC predominantly reflects patients diagnosed before age 70, with gene-specific lifetime risks by age 70 well established for *MLH1* and *MSH2*.^{13,14} Clinical guidelines recommend discussion of risk-reducing hysterectomy and RRSO for all women with Lynch syndrome, along with intensive multisystem surveillance.^{31,32}

Data regarding *PMS2*-associated OC risk remain limited and inconsistent,³³ with several studies failing to demonstrate a statistically significant increased OC risk. Similarly, evidence for *MSH6*-associated OC risk is limited in prospective cohorts, although, case-control studies have reported elevated risk (OR 1.92–5.04).^{34–37} Notably, In our cohort, *PMS2* and *MSH6* variants were observed at measurable frequencies comparable to *RAD51C/D*. These findings support consideration of tailored surveillance strategies in appropriate carriers, including those identified later in life.

Moderate-Penetrance Genes

BRIP1 was the most common moderate-penetrance gene in older patients (≥ 70), consistent with prior literature.³⁸ Previous works demonstrated lifetime OC risks of 5–12% and support RRSO at ages 45–50. Approximately one-quarter of *BRIP1* carriers developed synchronous or metachronous malignancies, without a clear age-dependent pattern, highlighting the sustained cancer burden. The stable prevalence of moderate-risk variants (*ATM*, *PALB2*, *RAD51C/D*), supports lifelong genetic risk assessment and individualized management, rather than age-based de-escalation.

Limitations

This retrospective registry analysis is limited by reported data accuracy and completeness. Missing treatment and outcome data precluded evaluation of survival or treatment-response associations, and information on chemoprevention and risk-reducing interventions (e.g., surgery) was unavailable. The longitudinal design spans major changes in genetic testing practices, with earlier reliance on limited assays, including Ashkenazi Jewish founder mutation testing, and more recent adoption of multigene panel testing. Accordingly, earlier cohorts likely underascertain P/LP variant prevalence, resulting in lower observed rates compared with contemporary estimates. As a result, the burden of clinically relevant germline variants in older patients with OC is likely underestimated. Furthermore, given known underutilization of genetic testing in older patients, the lower prevalence observed with increasing age may partly reflect selection bias rather than true population-level differences.

Additionally, some variants may represent incidental findings rather than true disease drivers. The absence of paired germline–somatic data limits assessment of causal contributions to tumorigenesis. Limited post-test follow-up may also have resulted in underascertainment of secondary malignancies. Exclusion of VUS likely further underestimated true P/LP variant prevalence, particularly given evidence that 8.7–17.9% of VUS are subsequently reclassified as pathogenic.^{39,40}

Clinical Implications

Despite declining prevalence with age, hereditary cancer risk remains clinically significant in older patients. While *BRCA* and Lynch syndrome associated variant frequency decreases with age, lifetime cancer risk is maintained, reflecting underlying biological heterogeneity influenced by variant-specific effects, polygenic risk, and epigenetic modifiers.

As survival in OC improves, risk-reduction strategies in older carriers warrant individualized consideration. Many older patients maintain good functional status and may benefit from tailored approaches, including continued surveillance or risk-reducing interventions. These decisions should be guided by performance status, competing risks, and patient preferences, rather than age alone.

Family history was less informative in older patients, likely reflecting smaller family size, incomplete ascertainment, and competing mortality risks across generations. In contrast, our findings suggest that personal cancer history may represent an informative indicator of hereditary cancer risk in this population. The high burden of prior malignancies observed among older patients represents a missed prevention window, where earlier genetic evaluation could have enabled risk-reducing strategies prior to OC development. Among *BRCA1/2* carriers, approximately one quarter of patients had a preceding primary malignancy, highlighting missed opportunities for earlier identification of hereditary cancer risk. These findings support greater integration of personal cancer history into genetic testing decision-making.

Notably, genetic testing in elderly patients serves as a critical gateway to cascade testing among at-risk relatives, as identification of a P/LP variant in an older individual may have its greatest impact on cancer prevention in younger family members. Furthermore, identification of germline P/LP variants retains direct clinical relevance for the patient, providing prognostic information and informing therapeutic decision-making, including eligibility for targeted therapies such as PARP inhibitors. Despite these implications, current guidelines provide limited direction for the management of older carriers, reflecting the urgent need to develop age-specific management strategies. Collectively, these findings support universal genetic testing irrespective of age, not only to inform patient care but also to extend the benefits of cancer prevention and precision oncology to families and future generations.

Conclusion

Women aged ≥ 70 with OC harbor clinically meaningful rates of pathogenic germline variants and remain at risk for hereditary breast and ovarian cancers, supporting genetic testing and risk-reducing interventions regardless of age. Although the prevalence of high-penetrance variants declines with age, their continued clinical relevance, together with the burden of synchronous and metachronous malignancies, underscores the need for ongoing, individualized surveillance and prevention strategies in older adults. The sustained prevalence of moderate-penetrance variants, including *ATM*, *RAD51C/D*, *PALB2*, and *BRIP1*, reinforces the importance of lifelong genetic risk assessment and personalized management. The diminished reliability of family history in older patients highlights the limitations of conventional risk stratification. Collectively, these findings support lifespan- and gene-specific approaches to genetic counseling, testing, and consideration of RRSO beyond traditional family history-based criteria.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding:

Eliya Shachar received T32 NIH funding for the Patient-Centered Outcomes Research Training in Urologic and Gynecologic Cancers (PCORT UroGynCan) grant number T32CA251072

Conflicts of Interest

Eliya K. Shachar- T32 NIH funding for the Patient-Centered Outcomes Research Training in Urologic and Gynecologic Cancers (PCORT UroGynCan) (grant number T32CA251072) Ritu Salani,- Advisory board: Merck, Genmab, Eisai, Abbvie, Pfizer, WhiteHawk, Daiichi Sankyo; Royalties: Up to Date.

Dana M. Chase: Speaker and consultant for GSK, Astra Zeneca, Abbvie, Pfizer, Eisai Consultant for Corcept, Merck; Research funding from GSK and Merck Breanna Roscow- Myriad Genetics employee and stockholder Paul Spellman- Consultant for 10X Genomics, Illumina, Foresight Diagnostics, Natera, and Twinstrand.

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Highlights

- 20% of OC patients are ≥ 70 ; 6.6% harbor pathogenic variants
- *BRCA2* exceeds *BRCA1* ≥ 70 years, indicating age-related shift
- *BRIP1/PALB2* enriched ≥ 70 ; *ATM/RAD51C/D* stable across lifespan
- Family history less sensitive ≥ 70 , limiting risk assessment
- RRSO may be considered given limited effective OC surveillance

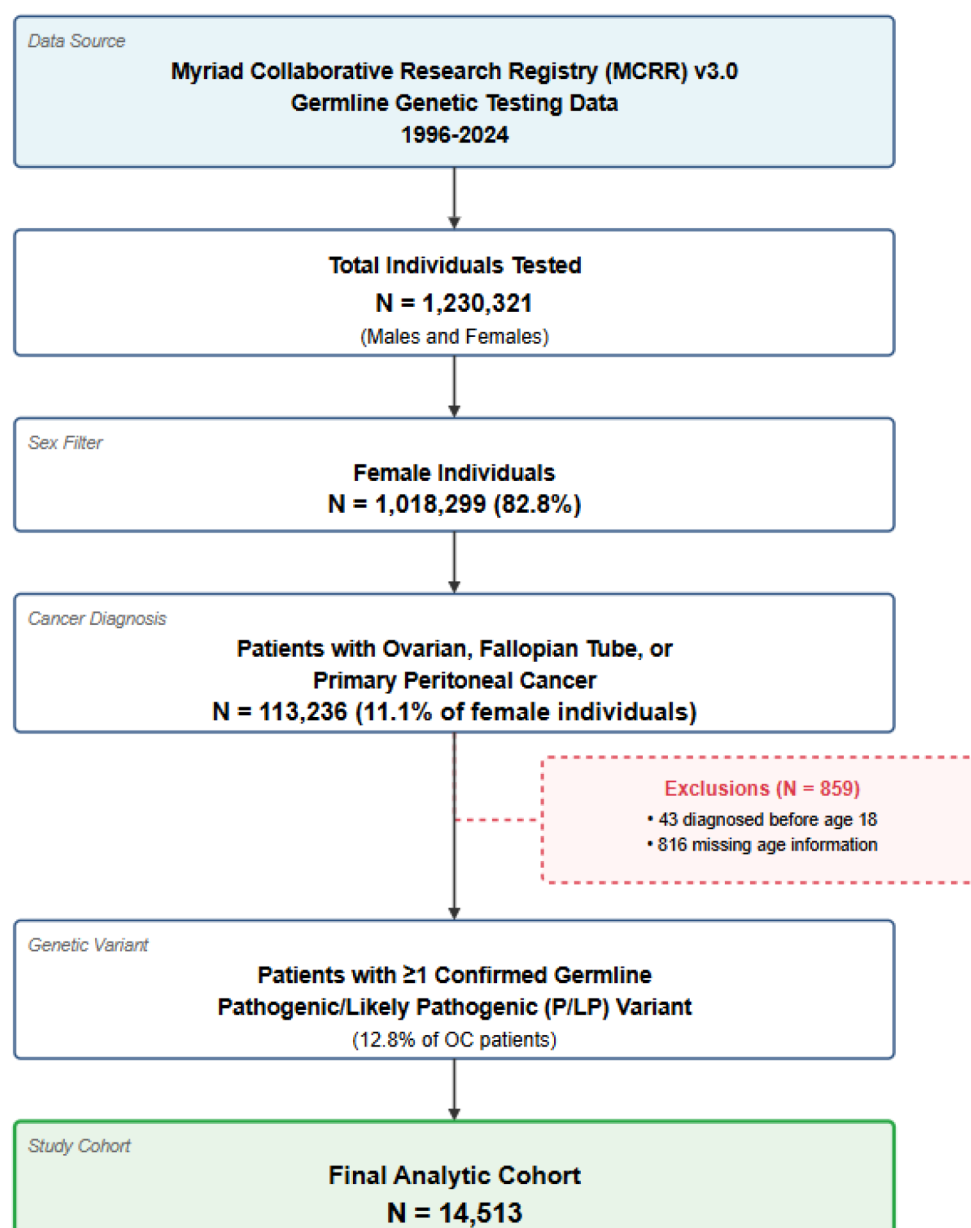


Figure 1. Study population flow diagram.

This flow diagram summarizes the derivation of the final analytic cohort from the Myriad Collaborative Research Registry (MCRR) v3.0 germline genetic testing database (1996–2024). Only female individuals with a confirmed diagnosis of ovarian, fallopian tube, or primary peritoneal cancer were included. Patients were excluded if diagnosed before age 18 or if age at diagnosis was missing. The full ovarian cancer cohort comprises all patients with completed germline testing; analyses requiring variant status were performed in the analytic subset of patients with at least one confirmed pathogenic or likely pathogenic germline variant.

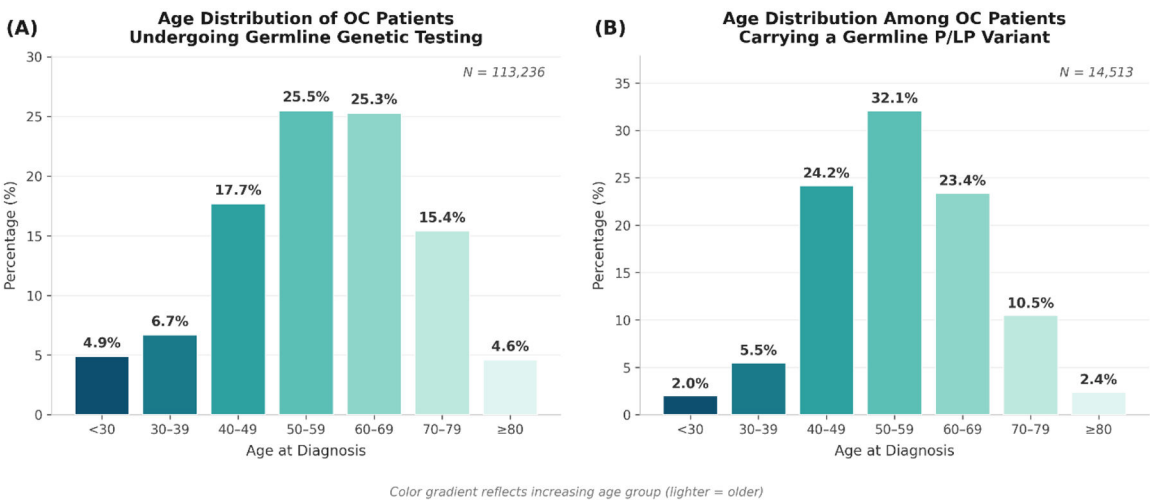


Figure 2. Age distribution of ovarian cancer patient by age at diagnosis.
Age distribution of ovarian cancer patients at diagnosis stratified by germline testing status and pathogenic variant carrier status. (A) Age distribution at diagnosis among all ovarian cancer (OC) patients who underwent germline genetic testing (n = 113,236). **(B)** Age distribution among OC patients harboring at least one germline pathogenic or likely pathogenic (P/LP) variant across OC susceptibility genes (n = 14,513). Bar color reflects a sequential gradient from dark (younger age groups) to light (older age groups), emphasizing the ordinal nature of age at diagnosis. Because some individuals carried more than one P/LP variant, panel B reflects the distribution of patients with at least one variant rather than the total number of variants identified.

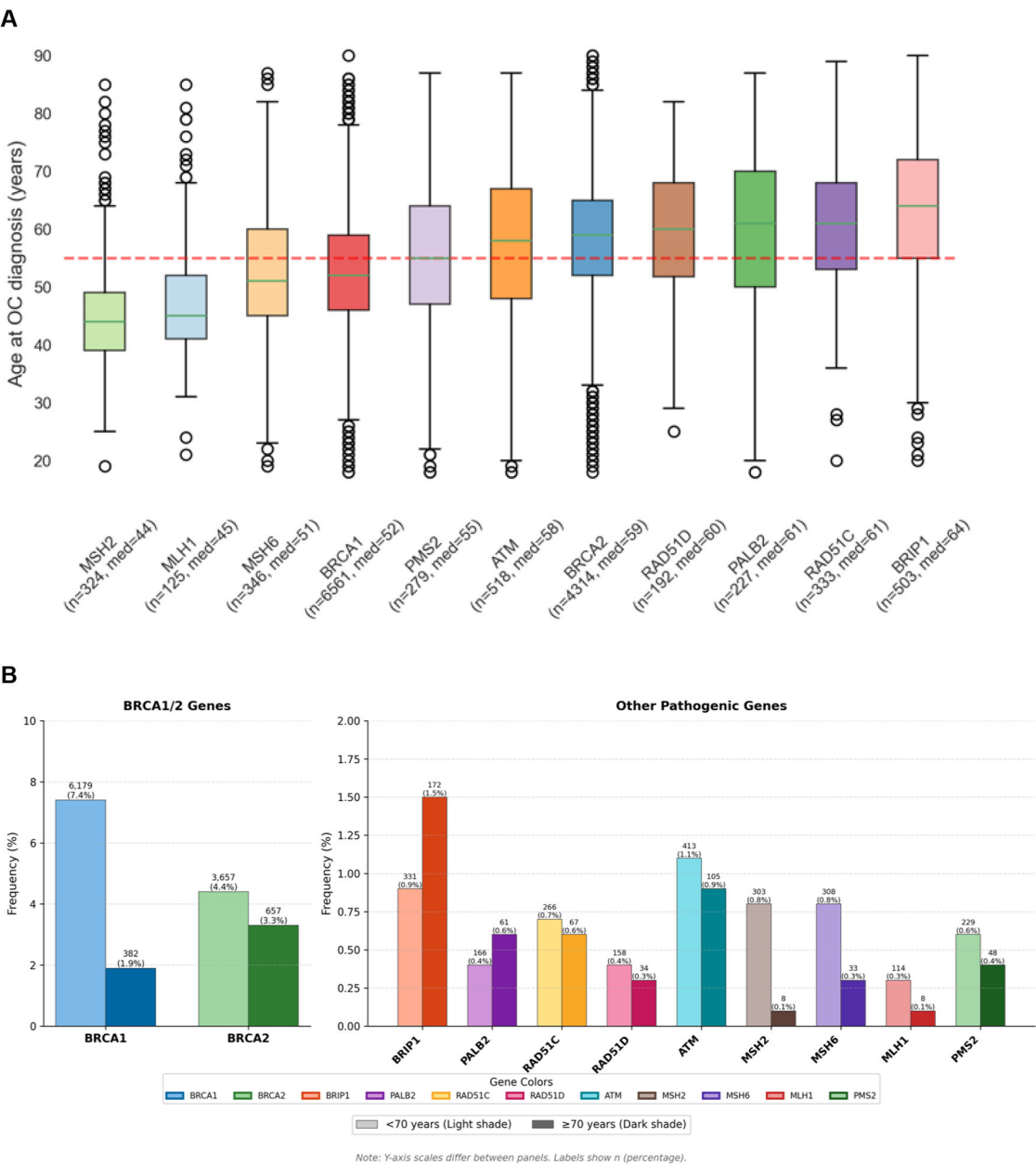
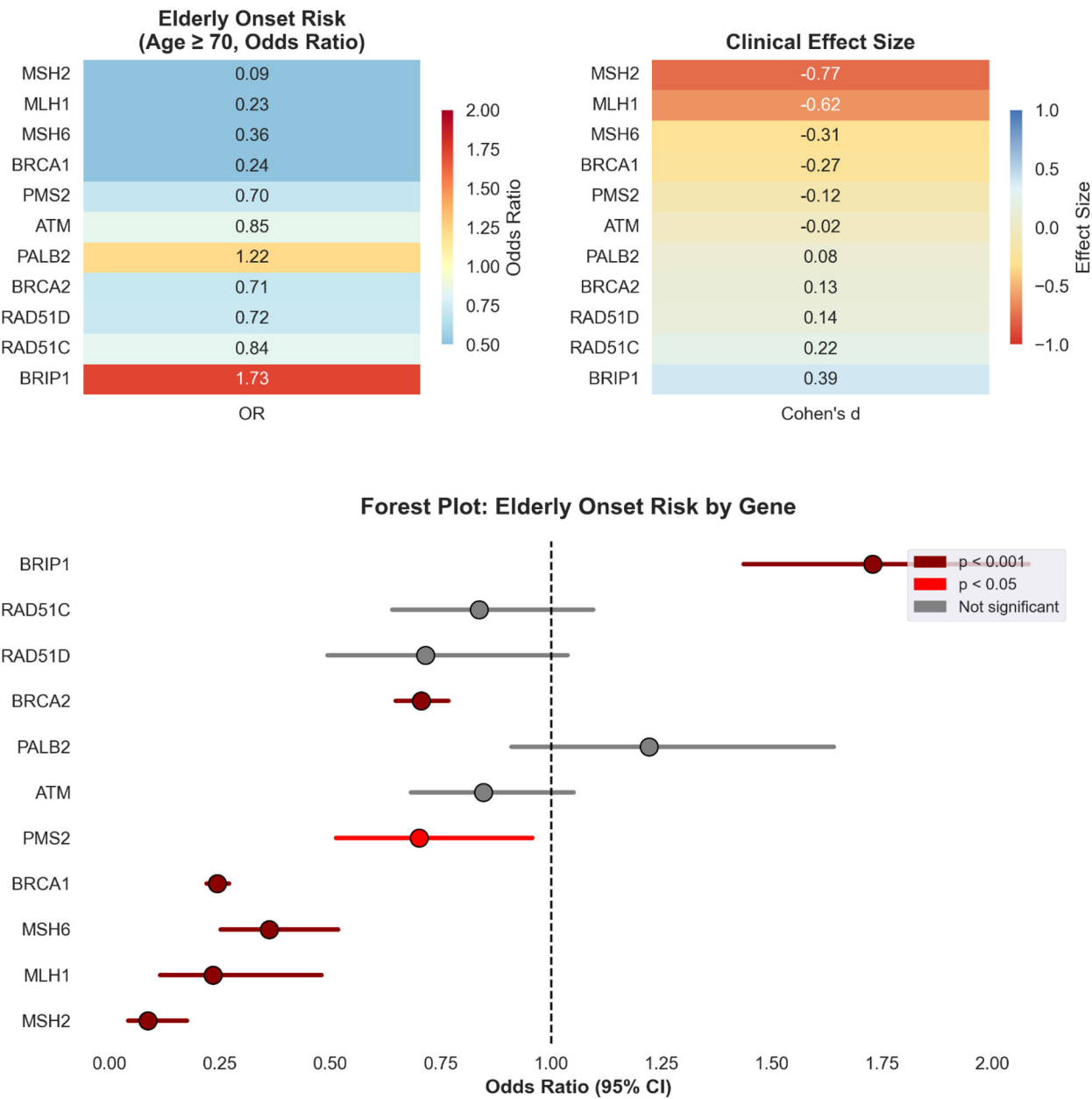
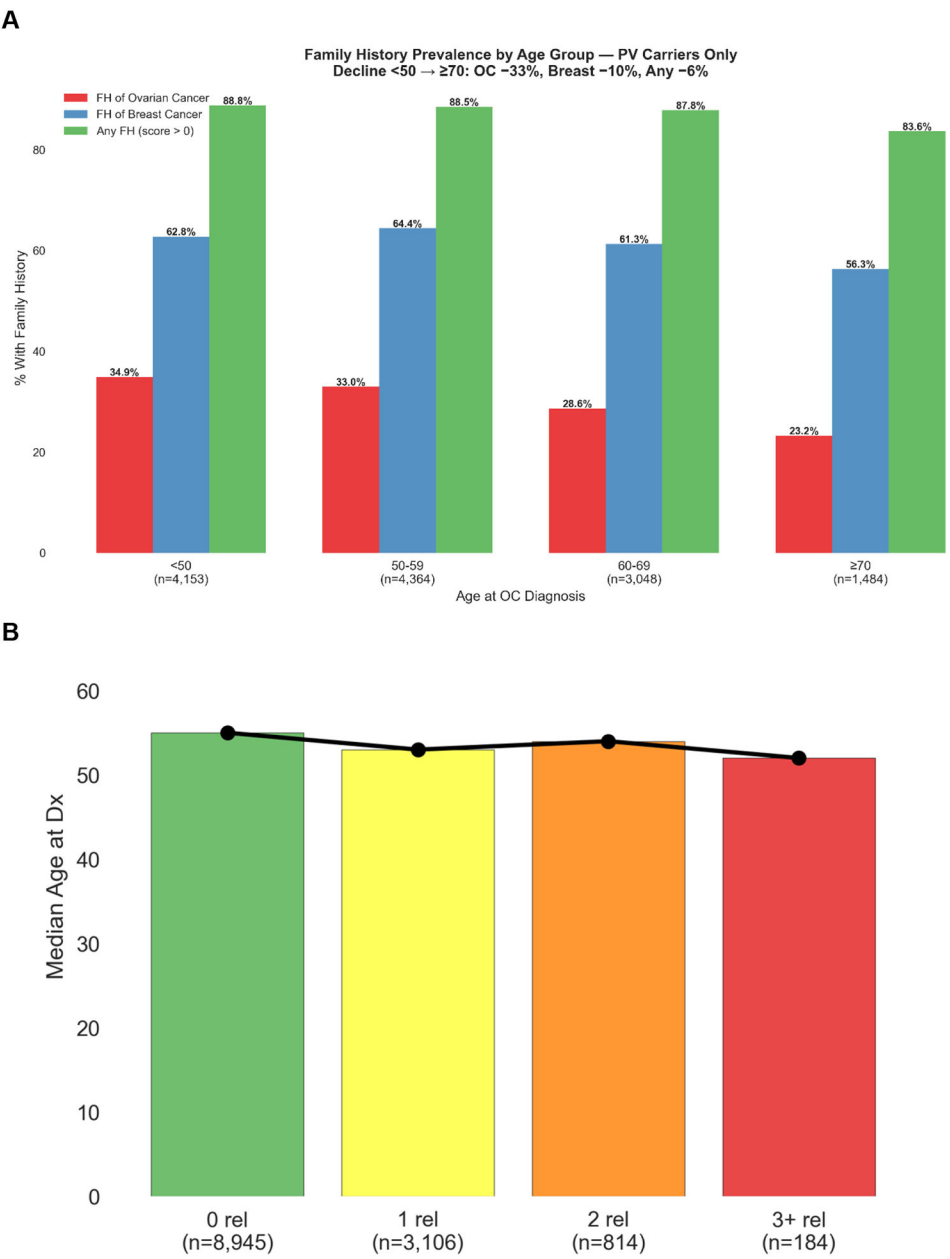


Figure 3.
(A) Age distribution by pathogenic variant and ovarian cancer presentation. **(B)** Prevalence of pathogenic variants in ovarian cancer susceptibility genes comparison by age group (<70 vs ≥70 years) among ovarian cancer patients.





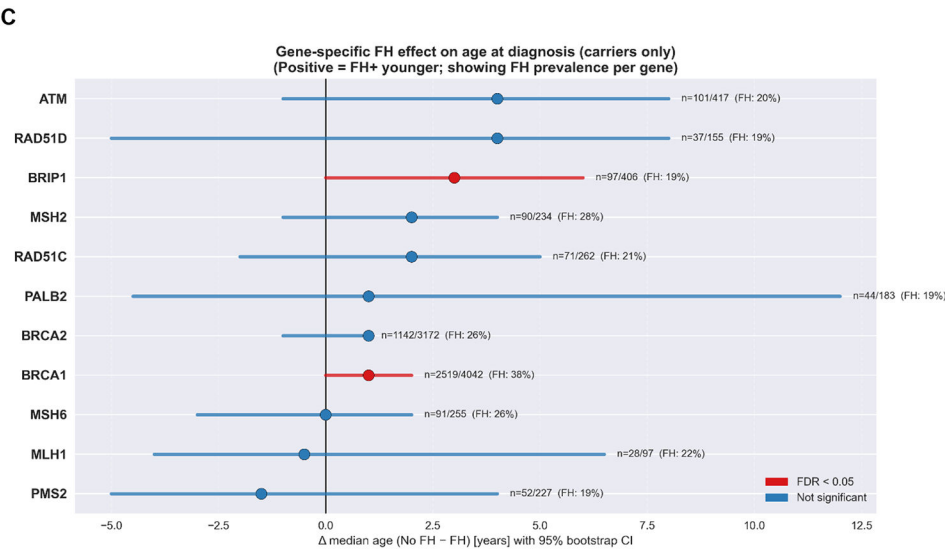


Figure 5.
(A) Family History of Ovarian, Breast Cancer and Any Cancer Family History Across Ovarian Cancer patients by Age at Ovarian Cancer Disease Onset **(B)** Age of Diagnosis with variable number of relatives with a Family history of Cancer **(C)** Gene-Specific Family History effect on Age at Ovarian Cancer Disease Onset Across Pathogenic Variants

Table 1.

Gene Variants Prevalence among the Ovarian Cancer Patients Completing Germline Testing by age at Diagnosis (N=113,236)

	Age at OC Diagnosis			p-value
	Total	<70	≥ 70	
BRCA1 , n (%)	6,561 (6.4%)	6,179 (7.4%)	382 (1.9%)	<.0001 ¹
BRCA2 , n (%)	4,314 (4.2%)	3,657 (4.4%)	657 (3.3%)	<.0001 ¹
BRIP1 , n (%)	503 (1.0%)	331 (0.9%)	172 (1.5%)	<.0001 ¹
PALB2 , n (%)	227 (0.5%)	166 (0.4%)	61 (0.6%)	0.1211 ¹
RAD51C , n (%)	333 (0.7%)	266 (0.7%)	67 (0.6%)	0.2817 ¹
RAD51D , n (%)	192 (0.4%)	158 (0.4%)	34 (0.3%)	0.1061 ¹
ATM , n (%)	518 (1.1%)	413 (1.1%)	105 (0.9%)	0.2134 ¹
MSH2 , n (%)	311 (0.6%)	303 (0.8%)	8 (0.1%)	<.0001 ¹
EPCAM , n (%)	5 (0.0%)	5 (0.0%)	0 (0.0%)	0.5936 ²
MSH6 , n (%)	341 (0.7%)	308 (0.8%)	33 (0.3%)	<.0001 ¹
MLH1 , n (%)	122 (0.2%)	114 (0.3%)	8 (0.1%)	0.0001 ¹
PMS2 , n (%)	277 (0.6%)	229 (0.6%)	48 (0.4%)	0.0452 ¹
Lynch , n (%)	1,028 (2.0%)	933 (2.3%)	95 (0.8%)	<.0001 ¹
Other P/LP variants , n (%)	2,792 (5.6%)	2,168 (5.6%)	624 (5.6%)	0.9624 ¹

¹ Chi-Square;

² Fisher's Exact;

The gene prevalence is calculated by considering the total number of patients tested for the gene

Abbreviations: P/LP- pathogenic or likely pathogenic