WAGO 2025 ANNUAL MEETING
ORAL ABSTRACT

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Ovarian Cancer in Patients with Pathogenic Variants over 70 years old: Real-World Data Informing Screening and Risk Reduction in Older Age

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Objectives
The optimal management of women with hereditary cancer mutations requires accurate, age-specific cancer risk estimates to guide screening initiation and cessation, as well as recommendations for risk-reducing interventions. Current guidelines underrepresent women over age 70, particularly those diagnosed with epithelial ovarian cancer (EOC), leaving gaps in evidence-based recommendations. This study leverages real-world data from the Myriad Collaborative Research Registry (MCRR) to assess the prevalence of pathogenic (PV) and likely pathogenic variants (LPV) in EOC patients aged ≥70, ≥80, and ≥90 years, alongside cumulative rates of metachronous and synchronous malignancies.

Methods
We analyzed MCRR v.3 (1996-2024), comprising 1,230,321 participants. A total of 93,224 EOC patients who underwent germline testing were assessed for PV/LPV prevalence across different age groups. We evaluated synchronous and metachronous malignancies and evaluated cumulative cancer risk by age of EOC diagnosis. Chi-square tests determined the significance of age-related prevalence changes ($p \leq 0.05$).

Results
Among 93,224 EOC patients, 18,851 (20.22%) were ≥70 years old, 4,387 (4.71%) were ≥80 years old, and 286 (0.31%) were ≥90 years old. The prevalence of PV/LPV decreased with age: from 15.68% in the total population to 9.88% at ≥70 years, 7.84% at ≥80 years, and 5.59% at ≥90 years ($p < 0.0001$). BRCA1 and BRCA2 were the most commonly identified PV/LPVs (11.87% combined). BRCA1 prevalence decreased significantly with age (8.53% in patients < 70 years vs. 2.02% in ≥70 years, $p < 0.001$). BRCA2 declined less markedly (4.94% < 70 years vs. 3.52% ≥70 years, $p < 0.001$). Lynch syndrome-associated genes (MLH1, MSH2, MSH6) also showed age-related decreases ($p < 0.001$). Conversely, PALB2, BRIP1, and TP53 were more frequently observed in older patients ($p < 0.05$). A subset of EOC patients with PV/LPV developed multiple synchronous or metachronous malignancies, most commonly breast and gastrointestinal cancers. Among BRCA1 carriers, breast cancer prevalence increased from 29.02% in the overall population to 44.88% in ≥70-year-old carriers ($p < 0.0001$). For BRCA2 carriers, breast cancer prevalence rose from 27.09% in the total population to 35.80% in ≥70-year-old carriers ($p < 0.0001$). PALB2 carriers demonstrated a higher cumulative prevalence of breast cancer in older age groups (40% vs. 18.46%). Lynch syndrome-associated PV/LPV carriers had stable colon cancer prevalence across all age groups, with a notable increase in MSH2 carriers aged ≥70 ($p < 0.001$), while endometrial cancer prevalence slightly declined with advancing age.

Conclusions
Hereditary cancer risk persists into older age, with sustained prevalence of PMS2, RAD51C, RAD51D, PTEN, CHEK2, BARD1, and APC PV/LPVs among women diagnosed with EOC at ≥70 years. The decline in BRCA1, BRCA2, and BRIP1 prevalence may reflect reduced survival associated with these variants. The stable prevalence of certain PV/LPVs suggests lower penetrance or later-onset cancers. Importantly, they underscore the continued importance of recommending risk-reducing salpingo-oophorectomy, as well as continued breast and colon cancer surveillance, for elderly PV/LPV carriers. Current guidelines should evolve to better reflect these age-specific risks, ensuring tailored cancer prevention and screening approaches across the lifespan.

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