

The Difference in Contralateral Breast Cancer (CBC) and Ovarian Cancer (OC) Risks for *BRCA1* Founder Variant (c.5266dup, c.4035del) Carriers with Primary Breast Cancer (PBC)

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Abstract

Purpose: To compare the risks of CBC and OC following a diagnosis of PBC in carriers of founder germline PV's of *BRCA1* gene (c.5266dup and c.4035del), and to evaluate the impact of age at PBC diagnosis on subsequent CBC and OC risks.

Subjects and Methods: This retrospective bicentric cohort study included 1,364 female *BRCA1* PV carriers diagnosed with and PBC. The control cohort comprised 11,350 unselected female PBC cases without known *BRCA1* PVs. Follow-up begun at PBC diagnosis and continued until CBC or OC occurrence, censoring at risk-reducing surgery, death, or last follow-up. Risks were estimated using Kaplan-Meier analysis, log-rank testing and Cox proportional hazards modelling.

Results: The 10-year cumulative risk of CBC was 3.3% in controls, 25.0% in the c.5266dup carriers, and 13.1% in the c.4035del carriers. *BRCA1* PV carriers had significantly higher CBC risks compared with controls ($p < 0.001$), with c.5266dup conferring greater risk than c.4035del ($p = 0.045$). Age < 40 years at PBC diagnosis independently increased CBC risk (HR 2.06, 95% CI 1.83-2.29, $p < 0.001$). For OC, the 10-year cumulative risk was 1.0% in controls, 13.0% in the c.5266dup carriers and 22.1% in the c.4035del carriers. *BRCA1* PV carriers had higher OC risks compared with controls ($p < 0.001$), and c.4035del conferred higher risk than c.5266dup, ($p = 0.043$). Age < 40 years at PBC did not significantly affect OC risk (HR 1.03, 95% CI 0.77-1.29, $p = 0.23$).

Conclusion: Both *BRCA1* founder PVs confer substantially increased risks of CBC and OC compared with the general breast cancer population. The PV c.5266dup is associated with relatively higher CBC risk and lower OC risk, whereas PV c.4035del is associated with relatively lower CBC risk but higher OC risk. Age < 40 years at PBC further increases CBC risk, but does not influence OC risk. These findings highlight the importance of PV location in refining individualized risk-reduction strategies for *BRCA1* carriers.