Category II

Characterizing Breast Cancer Prevalence Among Female SDHx Pathogenic Variant Carriers in a Laboratory Research Registry

Kimberly Van Ysseldyk, Monique Tiffany

Myriad Genetics, Inc., Utah, USA

Objective: Germline pathogenic or likely pathogenic variants (PV/LPVs) in *SDHx* (*SDHA, SDHB, SDHC, SDHD*) cause hereditary paraganglioma and pheochromocytoma (PPGL) syndromes and are linked to other tumors, such as renal cell carcinoma (RCC) and gastrointestinal stromal tumors (GIST). As *SDHx* variants are increasingly identified on multigene panels, questions have arisen about a possible association with breast cancer (BC). Prior literature is mixed, underscoring the need for clearer characterization. This study assesses BC prevalence among female *SDHx* carriers in a large laboratory-based research registry.

Materials and Methods: We performed a retrospective cohort analysis using the Myriad Collaborative Research Registry (MCRR) v7. Females with a confirmed *SDHx* PV/LPV were included; those with co-occurring PV/LPVs in other cancer predisposition genes were excluded. Personal BC history was summarized overall and by gene. Indications for genetic testing were unavailable.

Results: The MCRR includes 222,111 females with a personal history of cancer who underwent germline testing that included the *SDHx* genes; 135,712 (61%) had BC, with a mean diagnosis age of 57 years. Among all females tested, 508 *SDHx* PV/LPV carriers were identified. Of these, 286 (56.3%) had BC, including 7 with two primary BCs (293 total). Mean age at diagnosis among carriers was 57.4 years. By gene:

- *SDHA:* 376 carriers; 218 (58%) with BC, 7 had 2 BC primaries.

Mean age of diagnosis (dx): 57.4y

- *SDHB:* 61 carriers; 32 (52.5%) with BC

Mean age of dx: 55.2y

- *SDHC:* 50 carriers; 25 (50%) with BC

Mean age of dx: 58.8y

- *SDHD:* 23 carriers; 11 (47.8%) with BC

Mean age of dx: 60.5y

Compared with the overall affected cohort, *SDHx* carriers had a lower proportion of BC (61% *vs.* 56.3%), with no gene specific enrichment and no evidence of earlier onset.

Conclusion: In a large cohort of women with cancer who underwent multigene testing, *SDHx* PV/LPV carriers did not show higher BC prevalence than the overall group, and age at diagnosis was similar. The proportion of breast cancer in *SDHx* carriers was lower, but it remains unclear whether their risk differs from the general population or if findings are incidental. Since *SDHx* is often found incidentally, breast care teams should prioritize surveillance for tumors known to be associated with *SDHx* (PPGL, RCC, and GIST) and refer patients as appropriate to genetics or specialty care. Further prospective studies with cancer-free controls are needed to define breast cancer risk in *SDHx* carriers and guide screening.

Keywords: *SDHx*; germline