Clinical presentation and management considerations for 68 breast cancer patients with germline PALB2 mutations

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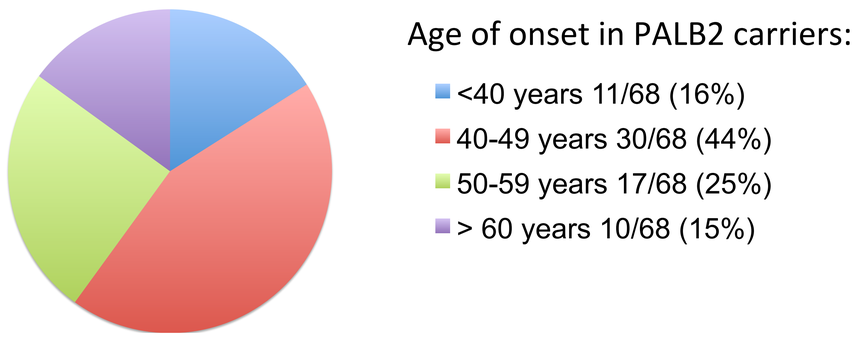
Background

PALB2 is considered to be a moderate- to high-penetrance breast cancer predisposition gene, and recently revised National Comprehensive Cancer Network (NCCN) 1.2016 guidelines recommend that PALB2 mutation carriers undergo an annual breast MRI and consider surgical prophylaxis. Growing implementation of multigene hereditary breast cancer panels is expected to discover more patients with moderate- to high-penetrance gene findings. Our study describes the clinical presentation of 68 PALB2 mutation carriers and reviews risk management considerations for the purpose of helping clinicians prepare themselves and their patients to deal with actionable results.

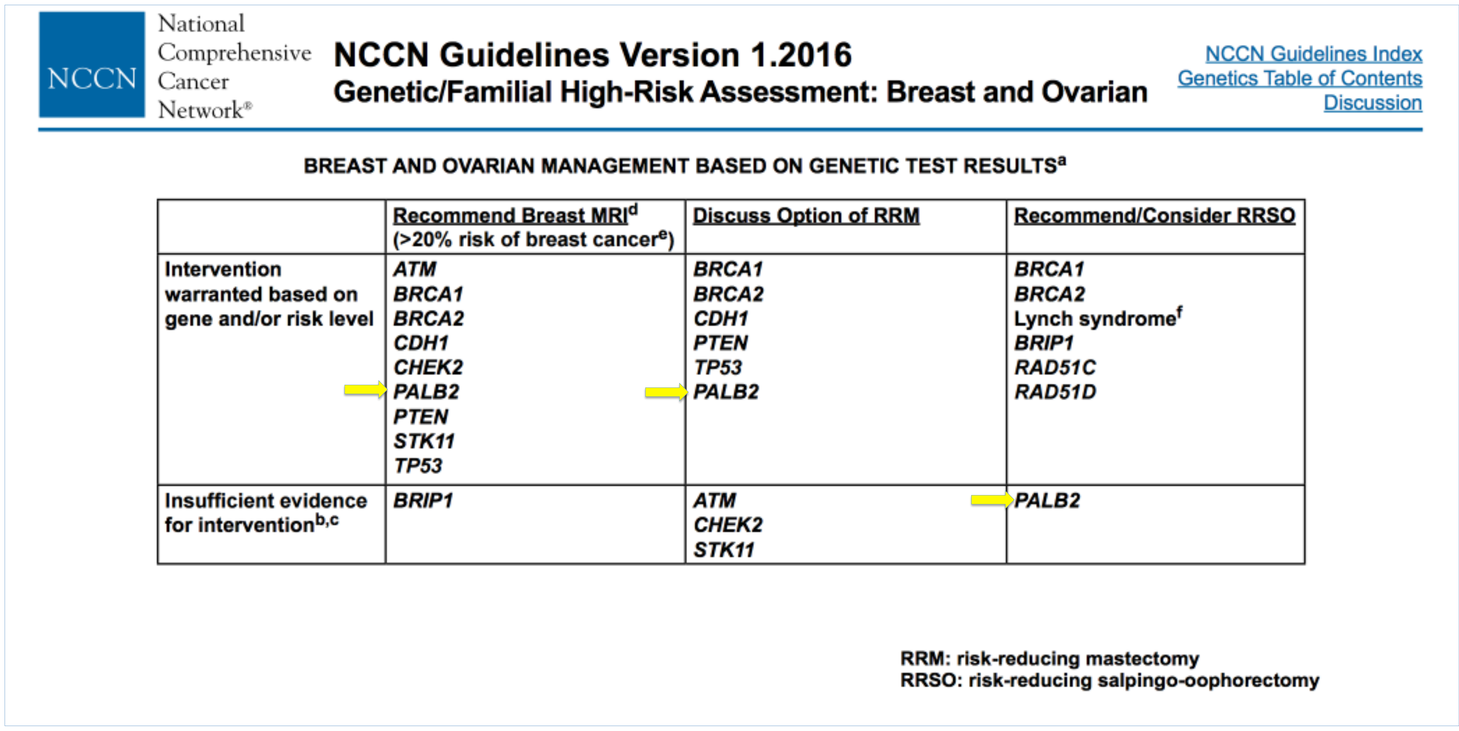
Methods

Sixty-eight (68) sequential patients who had been referred for genetic testing were selected based on the identification of a Pathogenic or Likely Pathogenic (P/LP) variant in PALB2 and on a personal history of cancer. De-identified personal and family histories, which had been provided by ordering clinicians, were examined.

Results



Among the 68 breast cancer patients, 29% presented with bilateral breast cancer or had a history of multiple primaries, 18% had triple-negative breast cancer, and 67% reported having a significant family history of cancer.



NCCN National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2016
Genetic/Familial High-Risk Assessment: Breast and Ovarian

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Discussion

BREAST AND OVARIAN MANAGEMENT BASED ON GENETIC TEST RESULTS[a]

	Recommend Breast MRI[d] (>20% risk of breast cancer[e])	Discuss Option of RRM	Recommend/Consider RRSO
Intervention warranted based on gene and/or risk level	*ATM* *BRCA1* *BRCA2* *CDH1* *CHEK2* *PALB2* *PTEN* *STK11* *TP53*	*BRCA1* *BRCA2* *CDH1* *PTEN* *TP53* *PALB2*	*BRCA1* *BRCA2* Lynch syndrome[f] *BRIP1* *RAD51C* *RAD51D*
Insufficient evidence for intervention[b,c]	*BRIP1*	*ATM* *CHEK2* *STK11*	*PALB2*

RRM: risk-reducing mastectomy
RRSO: risk-reducing salpingo-oophorectomy

Figure 1. Screen shot of recently revised NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian, Version 1.2016

Conclusions

- This patient series highlights clinical aspects of PALB2-related breast cancer suggestive of a high-penetrance gene, including presentation of early-onset and multiple primary cancers.
- PALB2 is mutated in the germline of roughly 1% of appropriately tested patients. It confers lifetime cancer risks from 30% to 60% based on family history (Antoniou, AC, *et al. NEJM*. 2014; 371(6):497–506), which, at the high end, is comparable to risk from BRCA2.
- Management of PALB2-positive patients with a strong family history may warrant special consideration, including breast MRI and risk-reducing mastectomy.
- More research is needed to understand the relationship between PALB2 and other cancers.

Limitations of study: ascertainment bias, limited information on tumor pathology, and an unconfirmed family history.