# The expanding phenotype of PALB2-related cancer: clinical presentations of 144 identified carriers

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## Background

PALB2 is now known to be a moderate- to high-penetrance breast cancer predisposition gene. Other cancer types, including ovarian, pancreatic, and prostate, may also be prevalent in PALB2-positive individuals; however, data supporting these associations are limited. In this case series, we describe the clinical presentation of 144 PALB2 mutation carriers to further delineate the spectrum of cancers reported in PALB2-positive individuals and their families.

## Methods

A total of 174 sequential clinical cases identified through April 1, 2016, with a pathogenic or likely pathogenic variant in PALB2 were analyzed. Six individuals with mutations in more than one hereditary cancer susceptibility gene were excluded. To ensure that only unique families were included, we excluded 24 additional individuals because their relative(s) previously tested positive through Invitae. De-identified personal and family histories were provided by ordering clinicians. Variants were classified by using a point-based system that closely adheres to ACMG guidelines.

## Results

Of the 144 individuals assessed (138 females, six males), 116 had cancer and the remaining 28 were unaffected carriers (Figure 1). Of the 111 affected females, 101 (91%) had breast cancer. Triple-negative histology was mentioned in 18 cases, 19 individuals had bilateral breast cancer or multiple breast cancer primaries, and 22 individuals had breast cancer and one additional primary (excluding breast cancer). Additional primary cancers included: pancreatic, thyroid, endometrial, colon, gastric, ovarian, squamous cell carcinoma (SCC) of the anus, melanoma, and sarcoma (Figure 2). The average age at initial breast cancer diagnosis was 47.9 years (Figure 3).

**Figure 1. Clinical characteristics of 144 PALB2-positive patients**

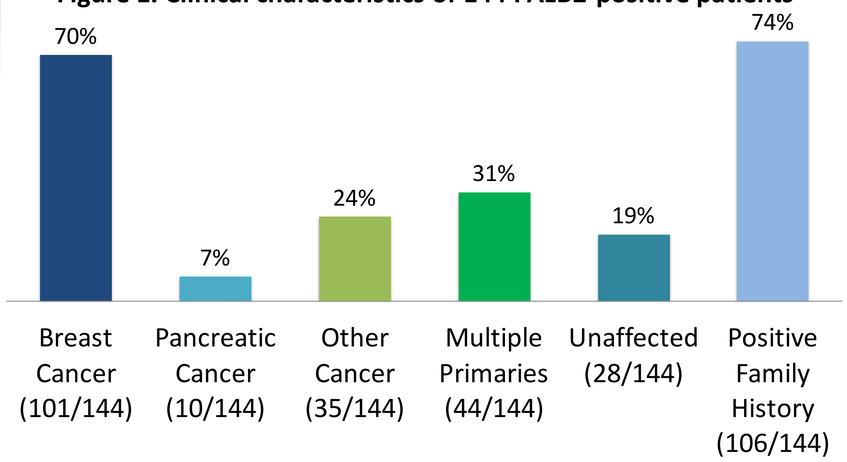



**Figure 1.** Frequency of clinical characteristics reported by clinician as the indication for testing. "Multiple primaries" includes patients with bilateral breast cancer or breast and any other type of cancer. "Positive family history" includes individuals with at least one relative with breast or pancreatic cancer, or both.

**Figure 2. Other Cancer Types in Affected Probands**

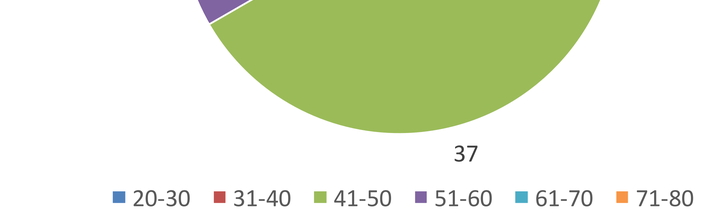


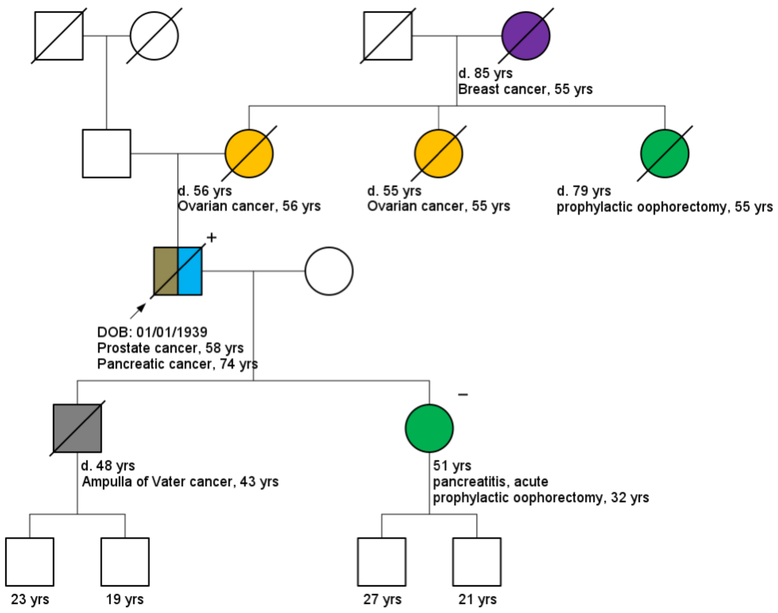

**Figure 3. Age at Breast Cancer Diagnosis**




## Results (cont.)

Of the six males, five were diagnosed with pancreatic cancer and one was unaffected. Three of the five affected males had at least one additional primary cancer, including: prostate, thyroid, bile duct, and urothelial cancers (Figure 2).

**Figure 4. Male proband with a PALB2 mutation**




## Conclusions

- This series highlights the clinical aspects of PALB2-related cancers, including the presentation of early-onset and multiple primary cancers.
- PALB2 is mutated in the germline of roughly 1% of tested patients (data not shown). It confers lifetime breast cancer risks of 30–60% based on family history (Antoniou, AC, *et al. NEJM.* 2014; 371(6):497-506), which is comparable to the risk from germline BRCA2 mutations.
- This study suggests that clinicians must consider PALB2 mutation status in a broadening spectrum of cancer phenotypes to inform risk assessment and management decisions, and that more research is needed to understand the relationship between PALB2 and other cancer risks.
- Study limitations: ascertainment bias, limited information on tumor pathology and hormone receptor status, unconfirmed family history.