The aim of this analysis was to examine the spectrum of individuals with two breast cancer diagnoses who underwent multiplex testing of multiple breast cancer associated genes, including RAD51C, RAD51D, and BARD1, in a commercial diagnostic laboratory. Deleterious or Suspected pathogenic variants were found to have more than one PV compared to those with a single breast cancer. The most common combination of PVs in individuals with two breast cancers was CHEK2 and PALB2, with 34% of women having this combination among women with two primary breast cancers; this rate persisted across single or dual breast cancer status. A p-value <0.05 was considered statistically significant.

- Among the 135,609 tested individuals, 38,440 had a single breast cancer diagnosis and 4,845 were diagnosed with two primary breast cancers. 12.4% (n = 603) of individuals with two breast cancers had at least one PV. This is significantly higher than the 9% PV prevalence in individuals with one breast cancer (p < 0.0001).

- The remaining 7.1% of PVs were in genes associated with other cancer risks.

- The median age of diagnosis for individuals with a PV and two breast cancers was 45 years, compared to 49 years of age for those without a PV.

- Individuals with two breast cancers were statistically more likely to have a PV if the first diagnosis occurred before age 45 (p < 0.0001).

- 22% (range 18-35%) of individuals whose first breast cancer was diagnosed ≤ 40 years of age had a PV if the first diagnosis occurred before age 45. This may be explained, in part, by the younger median age at first diagnosis for metachronous (45 years) versus synchronous (48 years) breast cancers.

- The prevalence of PVs was >10% for individuals with metachronous breast cancers, regardless of time between diagnoses (Figure 2).

- This is significantly higher than the 88/38,440 (0.2%) of individuals with a single breast cancer found to have more than one PV.

- The most common combination of PVs in individuals with two breast cancers was CHEK2 and PALB2 (n=6), representing 30% of the total; this combination only represented 6% of cases with 2 PVs among women with one breast cancer.

- There were significantly more PVs among individuals with metachronous disease (14.1%) than among those with synchronous breast cancers (9.7%) (p < 0.0001).

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