Cancer Predisposition Variants and Subsequent-Malignancy-related late-mortality among long-term survivors of childhood cancer.

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BACKGROUND: We previously reported that among 3,006 survivors of childhood cancer in the St. Jude Lifetime Cohort (SJLIFE), 5.8% (95% CI = 5.0% to 6.7%) carried a cancer predisposition variant (CPV) in one of the 60 genes implicated in autosomal dominant cancer predisposition, and had increased risk of developing subsequent malignancies (SMNs). Among long-term survivors of childhood cancer, the rate of SMN-related late-mortality among carriers of CPV versus non-carriers is unknown.

METHODS: Whole-genome sequencing (WGS) or whole-exome sequencing (WES) data for 12,475 five-year survivors were used to classify CPV status as previously described (Wang et al., JCO, 2018), including 4,402 from SJLIFE and 8,073 from the Childhood Cancer Survivor Study (CCSS; the CCSS original cohort data was downloaded from dbGaP, phs001327.v2). Mortality data were obtained through a search of the National Death Index. SMN-related mortality was analyzed using cmprsk R package implementing Fine & Gray method where other-cause mortality was treated as the competing risk. Deaths with unknown causes were excluded.

RESULTS: A total of 263 SMN-related and 396 other-cause deaths occurred among the survivors. 642 (5.1%, 95% CI = 4.8% to 5.5%) survivors were CPV carriers. Overall, cumulative SMN-related mortality was significantly increased in CPV carriers versus non-carriers ($P = 2.9 \times 10^{-7}$) whereas cumulative other-cause mortality was not (P = 0.38). By 40 years from achieving 5-year survival, the cumulative SMN-related mortality was 12.8% (95% CI = 10.0% to 15.6%) among CPV carriers as compared to 6.2% (95% CI = 5.7% to 6.7%) among non-carriers, and the cumulative other-cause mortalities were comparable (9.3% vs. 9.5%). After adjusting for genetically-determined race, sex, age at diagnosis and cancer treatment exposures, carrying a CPV was associated with increased rate of SMN-related mortality (Relative Rate [RR] = 3.34, 95% CI = 2.13 to 5.24, $P = 1.5 \times 10^{-7}$ for the combined cohorts; RR = 5.24, 95% CI = 2.15 to 12.79, $P = 2.7 \times 10^{-4}$ in SJLIFE; and RR = 3.02, 95% CI = 1.79 to 5.10, $P = 3.7 \times 10^{-5}$ in CCSS). Notably, the association between CPV status and SMN-related mortality was substantially higher (RR = 4.82, 95% CI = 3.09 to 7.52) among those received higher doses of chest irradiation (≥ 20 Gy) than lower doses or none (<20 Gy) (RR = 1.45, 95% CI = 0.42 to 4.97), suggesting gene-treatment interactions.

CONCLUSION: Carrying a CPV will not only increase the risk of developing SMN but also the risk of SMN-related mortality among long-term survivors of childhood cancer, highlighting the importance of genetic testing for CPVs to guide precision preventive survivorship care.