Title: Joint effects of general population polygenic risk scores and radiation treatment on subsequent neoplasm risk among childhood cancer survivors: A report from the Childhood Cancer Survivor Study (CCSS)

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BACKGROUND:

We examined whether PRS from general population studies are associated with risk of subsequent neoplasms (SNs) in childhood cancer survivors and evaluated joint associations between PRS and radiation treatment (RT), an established SN risk factor.

METHODS:

Common genetic variants associated with risk of basal cell carcinoma (BCC), breast cancer, thyroid cancer, squamous cell carcinoma (SCC) or melanoma in general population studies were used to calculate cancer-specific PRS among 5,911 5-year cancer survivors diagnosed <21 years of age and between 1970-1986 in the CCSS. We examined associations between each PRS and SN risk using conditional logistic regression in nested case-control studies, with incidence density sampling and matching on childhood cancer type, age at diagnosis, sex, RT dose to the SN site, and chemotherapy exposure. Further analyses matching only on non-treatment factors assessed joint associations considering potential combinations of PRS and RT exposure. We calculated the relative excess risk due to interaction (RERI) to determine whether joint associations were consistent with additivity of the individual risk factors (RERI > 0 indicates a more-than-additive joint association).

RESULTS:

Among survivors (median age at follow-up 40 years, range 3-67; 62% exposed to RT), cancer-specific PRS were associated with risk of subsequent BCC (N = 626; quartile 4 versus 1, OR [95% CI] = 1.9 [1.5-2.4]), breast cancer (N = 277; 4.5 [2.8-7.1]), thyroid cancer (N = 149; 1.9 [1.2-3.1]), and melanoma (N = 76; 2.7 [1.3-5.6]). Both PRS and RT were independently associated with SN risk, but joint analyses using a common reference group (PRS < median, RT < 1 Gy) found that both risk factors together resulted in more-than-additive increases in risk of BCC (RERI [95% CI] = 6.9 [2.0-11.8], breast cancer (6.6 [2.2-10.1], and thyroid cancer (4.8 [0.5-9.2]). Specifically, BCC risk was increased 28.8-fold for both PRS $\geq$ median and RT $\geq$ 1 Gy together, but only 3.3-fold for PRS $\geq$ median alone and 19.7-fold for RT $\geq$ 1 Gy alone. Similarly, breast cancer risk was increased 14.1-fold for both risk factors together, 2.5-fold for PRS $\geq$ median alone, and 6.5-fold for RT $\geq$ 1 Gy alone, and thyroid cancer risk was increased 12.3-fold for both risk factors together, 2.4-fold for PRS $\geq$ median alone, and 6.0-fold for RT $\geq$ 1 Gy alone. In joint analyses using more detailed RT categories, we found more-than-additive joint associations at both low and high RT doses.

CONCLUSION:

General population PRS were associated with SN risks after childhood cancer. More-than-additive increased risks with the combination of PRS and RT suggest that established markers of genetic susceptibility remain important in the context of treatment-related risks and may be useful in further refining risk assessment and follow-up guidelines for survivors.