Title: Pan-cancer polygenic risk distinctly contributes to prediction of heterogeneous subsequent malignancies across treatment profiles in survivors of childhood cancer

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Subsequent malignant neoplasms (SMNs) contribute substantially to late morbidity/mortality among long-term survivors of childhood cancer. Given growing evidence of common biological hallmarks for cancers including indications of a shared genetic basis (pleiotropy), we explored the impact of pan-cancer polygenic risk factors on overall SMN risk in 10,137 childhood cancer survivors. Participants in the Childhood Cancer Survivor Study and St. Jude Lifetime Cohort Study (European genetic ancestry) with genotype data, medical record-abstracted treatment exposures, and pathology-confirmed SMNs were analyzed. Top-performing published genome-wide polygenic risk scores (PRSs) for specific cancers and "any cancer" in the Michigan Genomics Initiative (MGI) study (Cancer-PRSWeb; prsweb.sph.umich.edu) were computed, where pan-cancer PRSs came from UK Biobank GWAS (N>300K). Hazard ratios (HRs) for any SMN incidence were estimated by Cox regression, with age, sex, batch/cohort, fine-scale ancestry, and primary cancer diagnosis/treatment (e.g., radiation therapy [RT], alkylating agents, anthracyclines, epipodophyllotoxins) as covariates. A total of 1,022 SMNs were observed among 922 survivors (total N=10,137; 242,962 person-years of follow-up), including subsequent breast (25.5% of SMNs, N=237) and thyroid (23.6%; N=218) cancers and basal cell carcinomas (BCCs; 21.8%, N=201). Since the top pan-cancer PRS in MGI (lassosum with 179 variants, PRS_{179}) performed similarly across the two cohorts and combined sample, we report combined results. PRS_{179} was significantly associated with pan-SMN risk (HR per PRS SD=1.12, $P=6.2\times10^{-4}$). This association was consistently attenuated among survivors who received any RT (top vs. bottom PRS_{179} quartiles, HR=2.13, $P=4.5\times10^{-4}$ if no RT vs. HR=1.19, P=0.13 if any RT), while anthracyclines enhanced risk (HR=2.79, $P=1.1\times10^{-3}$ if no RT, anthracyclines >0 mg/m^2). Top PRSs for breast cancer, thyroid cancer, and BCC in MGI were significantly associated with corresponding specific SMN risks (HRs=1.29 to 1.37, $P=5.9\times10^{-14}$ to 1.5×10^{-4}). Although these cancer subtypes were common (~60% of SMNs), pan-cancer PRS_{179} remained significantly associated with pan-SMN risk (HR per PRS SD=1.11, $P=4.1\times10^{-3}$) while the three cancer-specific PRSs did not (P>0.06) in a model with all four scores. In summary, pan-cancer polygenic risk factors can predict overall SMN risk among childhood cancer survivors despite the heterogeneity of SMNs, depending on treatments received. Further research to refine pan-SMN genetic risk predictors reflecting common carcinogenic hallmarks and their effect modification by treatments is needed.

Table 1: Pan-SMN risk associations with UK Biobank GWAS-based pan-cancer PRS (179 variants: PRS_{179}) in childhood cancer survivors

	First SMN (any) analysis				Multiple SMN (any) analysis			
Survivor dataset	N	N_{event}	HR (95% CI)	P	N	N_{event}	HR (95% CI)	P
CCSS	6444	656	1.116 (1.032-1.208)	$6.1x10^{-3}$	6444	759	1.099 (1.022-1.183)	0.011
CCSS, RT=0 stratified	2830	154	1.277 (1.083-1.507)	$3.7x10^{-3}$	2830	168	1.282 (1.096-1.500)	$1.9x10^{-3}$
CCSS, RT=1 stratified	3614	502	1.067 (0.977-1.166)	0.151	3614	591	1.051 (0.968-1.142)	0.235
CCSS, stratified: RT=0 and chemotherapy=0	1261	47	1.235 (0.932-1.637)	0.142	1261	53	1.303 (1.003-1.694)	0.048
CCSS, stratified: RT=0 and chemotherapy=1	1571	107	1.288 (1.048-1.583)	0.016	1571	115	1.260 (1.035-1.534)	0.021
CCSS, stratified: RT=0 and alkylating agents≥Q1 dose	818	65	1.212 (0.969-1.517)	0.092	818	70	1.190 (0.962-1.473)	0.110
CCSS, stratified: RT=0 and anthracyclines≥Q1 dose	975	73	1.262 (0.979-1.627)	0.073	975	79	1.235 (0.965-1.582)	0.094
CCSS, stratified: RT=0 and epipodophyllotoxins≥Q1 dose	253	16	1.419 (0.724-2.779)	0.308	253	17	1.681 (0.930-3.038)	0.085
SJLIFE	3352	234	1.138 (0.999-1.297)	0.053	3352	263	1.139 (1.008-1.288)	0.037
SJLIFE, RT=0 stratified	1642	45	1.457 (1.089-1.951)	0.011	1642	49	1.453 (1.082-1.952)	0.013
SJLIFE, RT=1 stratified	1710	189	1.067 (0.920-1.237)	0.392	1710	214	1.081 (0.946-1.234)	0.252
SJLIFE, stratified: RT=0 and chemotherapy=0	531	16	1.453 (0.886-2.384)	0.139	531	17	1.472 (1.041-2.083)	0.029
SJLIFE, stratified: RT=0 and chemotherapy=1	1111	29	1.606 (1.107-2.329)	0.013	1111	32	1.512 (1.000-2.286)	0.050
SJLIFE, stratified: RT=0 and alkylating agents≥Q1 dose	586	21	1.469 (0.951-2.269)	0.083	586	24	1.417 (0.852-2.356)	0.179
SJLIFE, stratfied: RT=0 and anthracyclines≥Q1 dose	574	20	2.094 (1.321-3.320)	$1.7x10^{-3}$	574	23	1.923 (1.103-3.353)	0.021
SJLIFE, stratfied: RT=0 and epipodophyllotoxins≥Q1 dose	398	11	1.533 (0.842-2.790)	0.162	398	12	2.109 (1.189-3.742)	0.011
Combined (CCSS + SJLIFE)	9796	890	1.124 (1.051-1.201)	$6.2x10^{-4}$	9796	1022	1.112 (1.044-1.185)	$9.3x10^{-4}$
Combined, RT=0 stratified	4472	199	1.310 (1.135-1.512)	$2.3x10^{-4}$	4472	217	1.312 (1.143-1.506)	$1.1x10^{-4}$
Combined, RT=1 stratified	5324	691	1.070 (0.993-1.154)	0.076	5324	805	1.063 (0.991-1.141)	0.088
Combined, stratified: RT=0 and chemotherapy=0	1792	63	1.292 (1.029-1.622)	0.027	1792	70	1.339 (1.084-1.653)	$6.7x10^{-3}$
Combined, stratified: RT=0 and chemotherapy=1	2682	136	1.310 (1.094-1.569)	$3.3x10^{-3}$	2682	147	1.291 (1.084-1.539)	$4.2x10^{-3}$
Combined, stratified: RT=0 and alkylating agents≥Q1 dose	718	50	1.146 (0.899-1.462)	0.271	718	55	1.154 (0.915-1.454)	0.226
Combined, stratified: RT=0 and anthracyclines≥Q1 dose	1083	76	1.245 (1.019-1.520)	0.032	1083	83	1.225 (0.996-1.507)	0.055
Combined, stratified: RT=0 and epipodophyllotoxins≥Q1 dose	439	24	1.687 (0.955-2.980)	0.071	439	26	1.949 (1.129-3.363)	0.017
Combined, stratified: RT=1 chemotherapy=0	1633	218	1.050 (0.925-1.193)	0.450	1633	257	1.064 (0.940-1.205)	0.326
Combined, stratified: RT=1 chemotherapy=1	3692	474	1.079 (0.985-1.182)	0.100	3692	549	1.059 (0.973-1.152)	0.184

HR per PRS SD; see PGS Catalog: PGS000356 for PRS details (Cancer-PRSWeb, University of Michigan). "RT" refers to any exposure to radiation therapy (any field).
"Chemotherapy" refers to any exposures to alkylating agents, anthracylines, or epipodophyllotoxins. Q1 dose = first quartile dose.

Table 2: Pan-SMN risk associations for pan-cancer PRS_{179} quartiles (relative to the first quartile) in childhood cancer survivors

Sample	Quartile (Q1 Ref.)	N (N_{case})	HR (95% CI)	P
All survivors	Q2	9795 (890)	1.259 (1.037-1.527)	0.020
	Q3		1.256 (1.032-1.530)	0.023
	Q4		1.371 (1.125-1.671)	$1.8x10^{-3}$
CCSS, all	Q2	6444 (656)	1.229 (0.983-1.536)	0.070
	Q3		1.214 (0.965-1.528)	0.097
	Q4		1.339 (1.065-1.684)	0.013
SJLIFE, all	Q2	3351 (234)	1.321 (0.891-1.957)	0.165
	Q3		1.383 (0.939-2.038)	0.101
	Q4		1.438 (0.970-2.131)	0.071
All survivors, RT=0	Q2	4472 (199)	1.291 (0.827-2.017)	0.261
	Q3		1.567 (0.998-2.460)	0.051
	Q4		2.129 (1.396-3.248)	$4.5x10^{-4}$
All survivors, RT=1	Q2	5323 (691)	1.242 (1.001-1.539)	0.049
	Q3		1.177 (0.945-1.465)	0.147
	Q4		1.193 (0.952-1.494)	0.125
All survivors, RT=0 and chemotherapy=0	Q2	1792 (63)	0.858 (0.370-1.988)	0.720
	Q3		1.720 (0.832-3.556)	0.143
	Q4		1.783 (0.851-3.735)	0.126
All survivors, RT=0 and chemotherapy <median	Q2	2744 (83)	1.203 (0.600-2.414)	0.603
	Q3		1.861 (0.931-3.723)	0.079
	Q4		2.015 (1.048-3.872)	0.036
All survivors, RT=0 and chemotherapy ≥median	Q2	1594 (103)	1.592 (0.851-2.977)	0.145
	Q3		1.431 (0.751-2.729)	0.276
	Q4		2.330 (1.269-4.278)	$6.4x10^{-3}$
All survivors, RT=0 and chemotherapy=1	Q2	2682 (136)	1.540 (0.906-2.619)	0.111
	Q3		1.499 (0.849-2.645)	0.163
	Q4		2.311 (1.375-3.883)	$1.6x10^{-3}$
All survivors, RT=0 and anthracyclines>0	Q2	2179 (104)	1.761 (0.942-3.292)	0.076
	Q3		1.784 (0.910-3.496)	0.092
	Q4		2.793 (1.509-5.168)	$1.1x10^{-3}$
All survivors, RT=0 and alkylating agents>0	Q2	2010 (103)	1.500 (0.825-2.726)	0.183
	Q3		1.299 (0.694-2.431)	0.413
	Q4		1.961 (1.095-3.511)	0.023
All survivors, RT=0 and epipodophyllotoxins>0	Q2	876 (30)	1.408 (0.470-4.216)	0.541
	Q3		0.568 (0.134-2.414)	0.443
	Q4		3.415 (1.015-11.491)	0.047
All survivors, RT=1 and chemotherapy=1	Q2	1633 (218)	1.246 (0.841-1.844)	0.273
	Q3	NA	1.421 (0.961-2.102)	0.078
	Q4	NA	1.118 (0.754-1.658)	0.579
All survivors, RT=1 and chemotherapy=1	Q2	3691 (474)	1.248 (0.966-1.613)	0.091
	Q3		1.116 (0.855-1.457)	0.419
	Q4		1.241 (0.945-1.629)	0.120

"RT" refers to any exposure to radiation therapy (any field). "Chemotherapy" refers to any exposures to alkylating agents, anthracylines, or epipodophyllotoxins. "Median" refers to median dose.

Table 3: Pan-cancer PRS_{179} and cancer treatment interaction associations with SMN risk in the combined childhood cancer survivor sample (N=10,137)

	First SMN (any) analysis	
Pan-cancer PRS x treatment interaction	HR (95% CI)	P
PRS_{179}	1.307 (1.133-1.509)	$2.5x10^{-4}$
PRS_{179} x any RT	0.822 (0.699-0.966)	0.017
PRS_{179}	1.058 (0.972-1.152)	0.192
PRS_{179} x any anthracyclines	1.142 (0.999-1.306)	0.052
PRS_{179}	1.097 (0.995-1.211)	0.063
PRS_{179} x any alkylating agents	1.040 (0.910-1.188)	0.566
PRS_{179}	1.123 (1.045-1.207)	$1.6x10^{-3}$
PRS_{179} x any epipodophyllotoxins	1.005 (0.830-1.218)	0.956
PRS_{179}	1.225 (1.048-1.432)	0.011
PRS_{179} x any RT	0.834 (0.710-0.979)	0.027
PRS_{179} x any anthracyclines	1.136 (0.983-1.312)	0.084
PRS_{179} x any alkylating agents	1.007 (0.875-1.158)	0.925
PRS_{179} x any epipodophyllotoxins	0.946 (0.771-1.161)	0.598

HR per PRS SD.

Table 4: Pan-cancer PRS_{179} associations with pan-SMN risk in the combined childhood cancer survivor sample, adjusting for published cancer-specific PRS

		First SMN (any) analysis	
Study sample	PRS type	HR (95% CI)	P
All survivors	PRS_{179}	1.106 (1.033-1.185)	$4.1x10^{-3}$
	$PRS_{thyroid}$	1.042 (0.976-1.113)	0.214
	PRS_{BCC}	1.027 (0.953-1.106)	0.488
	PRS_{breast}	1.085 (0.996-1.182)	0.062
All survivors, stratified: RT=0	PRS_{179}	1.312 (1.136-1.515)	$2.1x10^{-4}$
	$PRS_{thyroid}$	1.036 (0.903-1.187)	0.617
	PRS_{BCC}	1.025 (0.876-1.200)	0.758
	PRS_{breast}	0.941 (0.793-1.117)	0.487

HR per PRS SD. See Cancer-PRSWeb (prsweb.sph.umich.edu) and corresponding publication for PRS details.