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ORIGINAL RESEARCH

Contribution of Genome-Wide Polygenic Score to Risk of Coronary Artery Disease in Childhood Cancer Survivors

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ABSTRACT

BACKGROUND Adverse cardiovascular outcomes such as coronary artery disease (CAD) are the leading noncancer causes of morbidity and mortality among childhood cancer survivors.

OBJECTIVES The aim of this study was to assess the role of a genome-wide polygenic score (GPS) for CAD, well validated in the general population, and its interplay with cancer-related risk factors among childhood cancer survivors.

METHODS In a cohort study of 2,472 5-year childhood cancer survivors from the St. Jude Lifetime Cohort, the association between the GPS and the risk of CAD was performed using Cox regression models adjusted for age at cancer diagnosis, sex, cumulative dose of anthracyclines, and mean heart radiation dose.

RESULTS Among survivors of European ancestry, the GPS was significantly associated with the risk of CAD (HR per 1 SD of the GPS: 1.25; 95% CI: 1.04-1.49; $P = 0.014$). Compared with the first tertile, survivors in the upper tertile had a greater risk of CAD (1.51-fold higher HR of CAD [95% CI: 0.96-2.37; $P = 0.074$]), although the difference was not statistically significant. The GPS-CAD association was stronger among survivors diagnosed with cancer at age <10 years exposed to >25 Gy heart radiation (HR top vs. bottom tertile of GPS: 15.49; 95% CI: 5.24-45.52; $P_{trend} = 0.005$) but not among those diagnosed at age ≥10 years ($P_{trend} \geq 0.77$) and not among those diagnosed at age <10 years exposed to ≤25 Gy heart radiation ($P_{trend} = 0.23$). Among high-risk survivors, defined by an estimated relative hazard ≥3.0 from fitted Cox models including clinical risk factors alone, the cumulative incidence of CAD at 40 years from diagnosis was 29% (95% CI: 13%-45%). After incorporating the GPS into the model, the cumulative incidence increased to 48% (95% CI: 26%-69%).

CONCLUSIONS Childhood cancer survivors are at risk for premature CAD. A GPS may help identify those who may benefit from targeted screening and personalized preventive interventions. (J Am Coll Cardiol CardioOnc 2022;4:258-267)

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Long-term survivors of childhood cancer are at risk for various treatment-related late effects including coronary artery disease (CAD). Compared with the general population, survivors have more than a 10-fold higher risk of developing CAD[1] that is strongly associated with exposure to chest or mediastinal radiation.[2-4] In a study from the St. Jude Lifetime Cohort (SJLIFE), survivors treated with cardiac radiation exposure >15 Gy were at a significantly higher risk for CAD (OR: 10.5; 95% CI: 4.2-26.3) compared with unexposed survivors.[2] CAD was observed in 3.8% of cardiotoxic-exposed survivors and 10.5% of those ≥40 years of age. Similar findings have also been noted in the Childhood Cancer Survivor Study with radiation exposure to the heart increasing the risk of myocardial infarction in a dose-dependent manner.[4,5] However, the role of anthracyclines in the development of CAD is less clear. Prior studies have shown evidence of vascular inflammation, early atherogenesis, and dyslipidemia in survivors exposed to anthracyclines[6] and suggested a potential indirect association through alteration of brachial artery reactivity[7] and impaired endothelial relaxation,[8] but these associations are not firmly established.

In the general population, both heritable and lifestyle risk factors are known to contribute to the risk of CAD. Estimates of heritability range from 40% to 50%, and genome-wide association studies have identified more than 160 genetic variants affecting the risk of CAD.[9] Individually, these variants contribute a small proportion to the overall risk, but together, in the form of a polygenic score, they can stratify the population by heritable CAD risk. The use of polygenic scores enhances the ability to predict the development of CAD.[10] Khera et al[11] used novel approaches to generate polygenic scores that considered genome-wide common variation and showed improved predictive performance compared with traditional polygenic scores that involve only genome-wide significant variants. Their genome-wide polygenic score (GPS) using approximately 6.63 million common genetic variants identified 8% of the population at >3-fold increased risk for CAD. Notably, the prevalence of this GPS-defined high-risk group was 20-fold higher than the carrier frequency of rare monogenic mutations conferring the comparable risk, implying a greater clinical and public health impact. The GPS for CAD risk, initially developed, validated, and tested in the general population of European ancestry from the UK Biobank, has now been validated in independent populations of French Canadian[12] and South Asian descents[13] with similar results.

However, it is unknown whether this GPS can also inform CAD risk in high-risk clinical populations such as childhood cancer survivors. No studies have been conducted to examine the role of genetic factors in estimating risk of CAD among childhood cancer survivors. It is conceivable that cancer-related clinical and treatment factors may modify the contribution of genetic determinants of CAD risk among survivors. To this end, we conducted a study to assess the previously validated general-population GPS for CAD risk, and its potential interplay with survivor-specific factors, among childhood cancer survivors participating in the SJLIFE cohort.

ABBREVIATIONS AND ACRONYMS

AUC = area under the receiver-operating characteristic curve

CAD = coronary artery disease

GPS = genome-wide polygenic score

NRI = net reclassification index

SJLIFE = St. Jude Lifetime Cohort

SJCRH = St. Jude Children's Research Hospital

METHODS

STUDY POPULATION. The SJLIFE is a retrospective cohort study initiated in 2007 with prospective clinical follow-up and ongoing enrollment of 5-year survivors of childhood cancer treated at St. Jude Children's Research Hospital (SJCRH) since it opened in 1962.[14,15] The SJCRH Institutional Review Board approved the study. All participants provided written informed consent, and the investigation conformed to the principles outlined in the Declaration of Helsinki.

Given that the existing GPS for CAD risk was derived from individuals of European ancestry,[11] our analyses were initially restricted to survivors of European descent followed by an analysis of African-American survivors. Genetic ancestry was determined by principal component analysis using the 1000 Genomes Project as the reference population (Supplemental Methods, Supplemental Figure 1).

GENETIC DATA. Genotype data were obtained using paired-end whole genome sequencing with approximately 30× coverage using the HiSeq X10 (Illumina) and/or NovaSeq (Illumina) sequencers. Details of the whole genome sequencing, data processing, and quality control measures are provided elsewhere.[16-18] Principal components were generated based on the genotype data of an independent set of common variants using EIGENSTRAT in PLINK version 1.9[19] and used to control for potential population stratification.

PHENOTYPE DATA. Participants returned to SJCRH for a comprehensive clinical evaluation including history and physical examination, anthropometric measurements, a fasting laboratory battery (including metabolic and lipid panels), a 12-lead electrocardiogram, an echocardiogram, neurocognitive testing, and a physical function

assessment.[14] Additionally, survivors completed a series of health questionnaires including sociodemographic characteristics, interval medical events, family history, health behaviors, and quality of life. Detailed medical record abstractions were performed by trained abstractors to confirm cumulative doses of specific chemotherapeutic agents, radiation fields and doses, surgical interventions, cancer recurrences, subsequent neoplasms, and acute or late organ toxicities. Cumulative anthracycline exposure was recorded in doxorubicin equivalents and reported as milligrams per square meter.[20] The mean radiation dose to the heart (in Gy) was determined using established methods by radiation physicists at MD Anderson Cancer Center, Houston, TX, including energy source, tumor dose, and treatment fields.[21] Chronic health conditions were uniformly assessed and severity graded according to a modified version of the National Cancer Institute's Common Terminology Criteria for Adverse Events (version 4.03)[22] (Supplemental Table 1). No survivors had grades 1 or 2 CAD, so only grades 3 (severe/disabling) and 4 (life-threatening/urgent intervention required) were included. Acquired cardiovascular risk factors including diabetes, hypertension, dyslipidemia, and obesity were also assessed, and survivors with grade 2 (moderate/minimal noninvasive intervention required) to grade 4 conditions before the CAD diagnosis were included.

GPS. Khera et al[11] created a GPS for CAD risk using 6,630,150 common genetic variants based on a meta-analysis of genome-wide association studies including a total of 60,801 cases and 123,504 controls.[23] This GPS was then validated and tested in 120,280 and 288,978 participants in the UK Biobank, respectively.[11] In the SJLIFE cohort, genotype data were available for 6,616,870 variants (99.98%) of the GPS calculation. Using the natural logarithm of the reported OR of the 6,616,870 variants as their weights, the GPS was constructed as a weighted sum of the number of risk alleles carried by a childhood cancer survivor.

STATISTICAL ANALYSES. Continuous variables are reported as their median (25th and 75th percentiles [Q1-Q3]), and categoric variables are presented as counts with percentages. Multivariable analyses assessing the association between the GPS and the risk of CAD were performed using Cox regression with censoring at the end of follow-up and death (cause specific), and the results are presented with estimated HRs and corresponding 95% CIs and *P* values. The at-risk follow-up time started at 5 years from childhood cancer diagnosis and ended at the presentation of CAD, the last date of contact, or death, whichever came first. The nongenetic (clinical risk factors alone) baseline model for CAD risk was fit first adjusting for age at cancer diagnosis (<10 vs ≥10 years), sex, cumulative anthracycline dose (none, 1-250 mg/m^2, and >250 mg/m^2), average heart radiation dose (≤25 Gy vs >25 Gy), and the top 5 principal components to adjust for a fine-scale population structure within individuals of European ancestry.[24,25] The cumulative anthracycline dose was converted to a categoric variable using the cutpoints in the previously published studies.[26,27] Exposure to higher doses of average heart radiation and younger age at diagnosis are known risk factors for CAD in childhood cancer survivors.[2] To assess the GPS-CAD association with respect to these high-risk survivors, age at cancer diagnosis and the average heart radiation dose were also categorized. The median age at diagnosis among survivors with CAD in this study population was 9.8 years; thus, 10 years was chosen as a cutpoint. Exposure to chest radiation is the strongest risk factor for CAD among childhood cancer survivors, which was first recognized among survivors of Hodgkin lymphoma.[28] Treatment protocols for pediatric Hodgkin lymphoma include chest irradiation of approximately 25 Gy. Given that Hodgkin lymphoma was the largest diagnostic group in survivors with CAD in our analysis, we selected 25 Gy as the cutpoint to categorize the average heart radiation dose (the average heart radiation dose and protocol dose of chest radiation are highly correlated with $r = 0.91$). The GPS was then added in 2 ways: 1) as a continuous variable (the *z*-score normalized across all SJLIFE survivors), assessing the adjusted HR of CAD per SD change in the GPS; and 2) as a categoric variable (tertiles) using the first tertile as the reference. The analysis was conducted for survivors of European ancestry and those of African ancestry separately. Additionally, among survivors of European ancestry, we assessed potential modifications of the GPS-CAD association in 4 subgroups of heart radiation dose (>25 Gy vs ≤25 Gy) × age at cancer diagnosis (<10 years vs ≥10 years of age at cancer diagnosis), performing a test for trend in the CAD risk over the tertiles of GPS in each subgroup. Potential modifications of the GPS-CAD association by survivor-specific clinical and treatment risk factors were further adjusted for cardiovascular risk factors as time-dependent covariates. Similar analyses in survivors of African ancestry could not be performed because of the limited number of survivors with African ancestry and CAD.

To summarize individual European-descent survivors' predicted CAD risk, the linear predictor of the fitted nongenetic baseline model with clinical risk factors alone was exponentiated and used as risk scores, including age at cancer diagnosis, sex, the cumulative anthracycline dose, the average heart radiation dose, and the top 5 principal components. Low-,

TABLE 1 Characteristics of Childhood Cancer Survivors From the St. Jude Lifetime Cohort

	Survivors of African Ancestry			
	Without CAD (n = 1,999)	With CAD (n = 120)	Without CAD (n = 335)	With CAD (n = 18)
Age at childhood cancer diagnosis	6.8 (3.1-12.9)	9.8 (4.4-15.4)	8.2 (3.4-13.0)	6.2 (4.4-10.4)
Age at last contact or death	37.8 (31.9-45.0)	47.7 (41.4-52.3)	35.0 (30.1-42.3)	46.8 (43.4-50.7)
Age at CAD	NA	39.7 (33.3-45.9)	NA	38.4 (36.4-43.5)
Sex				
Female	968 (48.4)	39 (32.5)	182 (54.3)	5 (27.8)
Male	1,031 (51.6)	81 (67.5)	153 (45.7)	13 (72.2)
Cumulative anthracycline dose (mg/m^2)				
None	823 (41.2)	58 (48.3)	166 (49.6)	13 (72.2)
1-250	906 (45.3)	39 (32.5)	128 (38.2)	3 (16.7)
>250	270 (13.5)	23 (19.2)	41 (12.2)	2 (11.1)
Average heart radiation (Gy)				
≤25	1,877 (93.9)	91 (75.8)	318 (94.9)	9 (50.0)
>25	122 (6.1)	29 (24.2)	17 (5.1)	9 (50.0)
Hypertension				
No	1,382 (69.1)	69 (57.5)	210 (62.7)	9 (50.0)
Yes	617 (30.9)	51 (42.5)	125 (37.3)	9 (50.0)
Diabetes				
No	1,764 (88.2)	105 (87.5)	291 (86.9)	16 (88.9)
Yes	235 (11.8)	15 (12.5)	44 (13.1)	2 (11.1)
Dyslipidemia				
No	1,648 (82.4)	95 (79.2)	305 (91.0)	16 (88.9)
Yes	351 (17.6)	25 (20.8)	30 (9.0)	2 (11.1)
Obesity				
No	548 (27.4)	81 (67.5)	90 (26.9)	12 (66.7)
Yes	1,451 (72.6)	39 (32.5)	245 (73.1)	6 (33.3)

Values are median (Q1-Q3 [25th-75th percentiles]) or n (%).
CAD = coronary artery disease; NA = not applicable.

intermediate-, and high-risk groups for CAD were defined by the cutoff values of this risk score at −0.5 and 1.1 (ie, the thresholds of estimated relative hazard for the low- and high-risk groups were approximately <0.6 and >3, respectively). The same definition of the risk groups was also applied to the model that added the effect modification (an interaction term) of the GPS by >25 Gy heart radiation and <10 years age at diagnosis to the nongenetic baseline model. To evaluate how well CAD risk is discriminated by the 2 sets of 3 risk groups defined by the 2 models (the nongenetic baseline with and without the GPS interaction term), we estimated the cumulative incidence curves of CAD for each risk group. Death was considered a competing risk event when estimating cumulative incidence. Gray's method[29] was used to evaluate the statistical significance of the differences in cumulative incidence curves across all risk groups.

We performed receiver-operating characteristic analyses to assess the predictive ability of 1) the nongenetic baseline model including an interaction term for age at cancer diagnosis (≥10 years vs < 10 years) and the average heart radiation dose (>25 Gy vs ≤25 G) and 2) the nongenetic baseline model plus the GPS for the risk of CAD. The predictive performance of each model was measured by the area under the receiver-operating characteristic curve (AUC). Specifically, we obtained predicted probabilities of CAD for each survivor based on the Cox regression model with and without the GPS at 40 years using the time-dependent AUC method of Heagerty and Zhang[30] with their risksetROC R package. We used 1,000 bootstraps sampled with replacement from the original population to calculate 95% CIs of the AUC estimates. Statistical significance of the AUC difference with and without the GPS was calculated using the DeLong test.[31] Analyses were performed for all survivors and for those diagnosed at <10 years of age and exposed to >25 Gy of average heart radiation dose only. All statistical analyses were performed using R 3.5.1, and all statistical tests were 2-sided with a P value <0.05 considered statistically significant.

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TABLE 2 Modification of GPS-CAD Associations by Childhood Cancer Survivor–Specific Risk Factors

	Age at Diagnosis <10 Years			
	Average Heart Radiation ≤25 Gy (n = 698, 32.9%)	Average Heart Radiation >25 Gy (n = 105, 5.0%)	Average Heart Radiation ≤25 Gy (n = 1,270, 59.9%)	Average Heart Radiation >25 Gy (n = 46, 2.2%)
Bottom	1.00 (Reference)	3.65 (1.35-9.89)	1.01 (0.47-2.18)	0.96 (0.12-7.44)
Intermediate	1.00 (0.46-2.17)	2.59 (0.90-7.47)	1.50 (0.71-3.15)	6.13 (1.91-19.61)
Top	1.11 (0.52-2.39)	3.72 (1.49-9.28)	1.54 (0.73-3.27)	15.49 (5.27-45.52)
Trend test *P* value	0.77	0.93	0.23	0.005

Values are HR (95% CI) unless otherwise indicated.
CAD = coronary artery disease; GPS = genome-wide polygenic score.

RESULTS

There were 2,472 five-year survivors in SJLIFE available for this analysis. Of these, 2,119 and 353 survivors were of European and African ancestries, including 120 (5.7%) and 18 (5.1%) with grade 3 to 4 CAD, respectively. Clinical, demographic, and treatment characteristics are provided in **Table 1**. Survivors of European ancestry with CAD were slightly older at cancer diagnosis (median age at diagnosis = 9.8 years [Q1-Q3: 4.4-15.4]) compared with their counterparts without CAD (median age at diagnosis = 6.8 years [Q1-Q3: 3.1-12.9]). The median age at CAD diagnosis was 39.7 years (Q1-Q3: 33.3-45.9 years). The proportion of males was higher (67.5%) among survivors with CAD compared with those without (51.6%). Approximately 24% of survivors with CAD had received >25 Gy of heart radiation compared with 6.1% without CAD. A total of 1,639 (77.3%) had at least 1 cardiovascular risk factor before their CAD diagnosis. The GPS distribution among the 2,119 survivors approximated a normal distribution (Supplemental Figure 2). Characteristics of survivors of African ancestry were generally comparable with those of European ancestry.

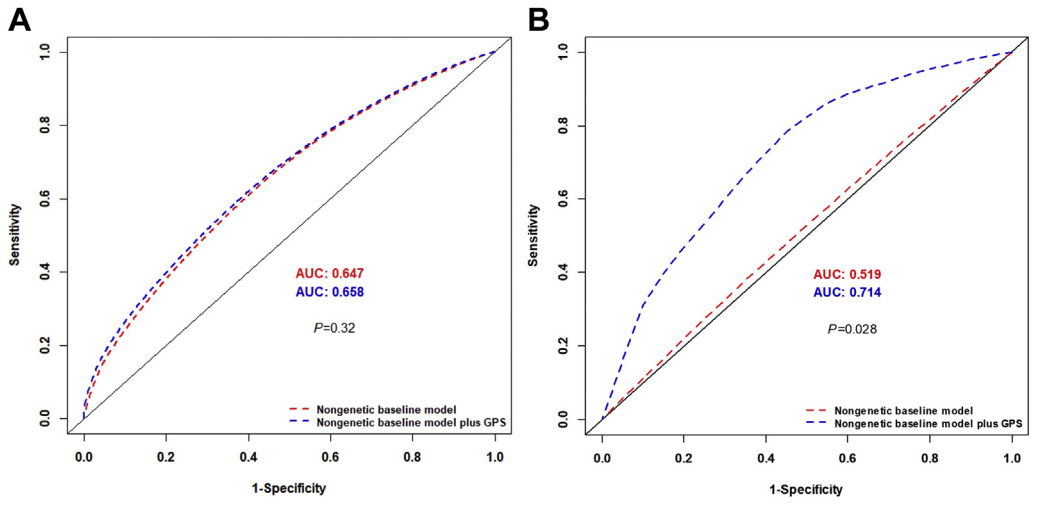
In the multivariable Cox regression analysis among survivors of European ancestry, the GPS was significantly associated with the risk of CAD (HR per 1 SD of the GPS: 1.25; 95% CI: 1.04-1.49; $P = 0.014$). Compared with the first tertile, survivors in the upper tertile had greater risks of CAD (1.51-fold higher HR of CAD [95% CI: 0.96-2.37; $P = 0.074$ in the highest tertile]), although the differences were not statistically significant. Among survivors of African ancestry, the GPS was not significantly associated with the risk of CAD (HR per 1 SD of the GPS: 0.79; 95% CI: 0.41-1.51; $P = 0.47$ and HR for top vs bottom tertile of the GPS: 1.17; 95% CI: 0.28-4.96; $P = 0.83$).

Among survivors of European ancestry, the association of the GPS with CAD risk was modified by age at cancer diagnosis and the average heart radiation dose (**Table 2**). Specifically, compared with survivors diagnosed at ≥10 years, treated with ≤25 Gy heart radiation, and in the bottom tertile of the GPS, those diagnosed at age <10 years, exposed to >25 Gy heart radiation, and in the top tertile of the GPS had an increased risk of CAD (HR: 15.49; 95% CI: 5.24-45.52; $P_{trend} = 0.005$). However, the GPS was not associated with CAD risk among those diagnosed at ≥10 years regardless of heart radiation exposure ($P_{trend} = 0.77$ and 0.93) or among survivors diagnosed at <10 years and exposed to ≤25 Gy heart radiation ($P_{trend} = 0.23$). These results persisted even after adjusting for hypertension, diabetes, dyslipidemia, and obesity (HR among survivors diagnosed at age <10 years, exposed to >25 Gy heart radiation, and with GPS in the top tertile: 17.26; 95% CI: 5.83-51.09; $P_{trend} = 0.003$ compared with those diagnosed at ≥10 years, treated with ≤25 Gy heart radiation, and in the bottom tertile of the GPS) (Supplemental Table 2).

Based on the nongenetic baseline model with clinical risk factors alone, survivors of European ancestry were classified into the low-risk (n = 352), intermediate-risk (n = 1,707), and high-risk (n = 60) groups. The cumulative incidence estimates of CAD at 30 years from cancer diagnosis in each risk group were 3.2%, 7.5%, and 22.9%, respectively, and at 40 years from diagnosis, they were 3.2%, 15.3%, and 28.6% (**Central Illustration**). Inclusion of the GPS and an interaction term with age at cancer diagnosis and the average heart radiation dose increased the cumulative incidence of CAD in each risk group to 3.4%, 7.0%, and 33.0% and 3.4%, 14.5%, and 48.0% at 30 and 40 years from diagnosis, respectively.

Among all survivors, the AUC estimate of the nongenetic baseline model including age at cancer diagnosis, sex, the cumulative anthracycline dose, the average heart radiation dose, an interaction term for age at cancer diagnosis and the average heart radiation dose, and the top 5 principal components was 0.65 (95% CI: 0.62-0.71). The addition of GPS increased the AUC estimate by 0.01, but the improvement was not

FIGURE 1 The Predictive Ability of the GPS for CAD



Area under the receiver-operating characteristic (AUC) estimates without **(red)** and with **(blue)** the genome-wide polygenic score (GPS) for coronary artery disease from the general population among **(A)** all childhood cancer survivors of European ancestry and **(B)** only those diagnosed <10 years of age and exposed to >25 Gy of average heart radiation dose are shown.

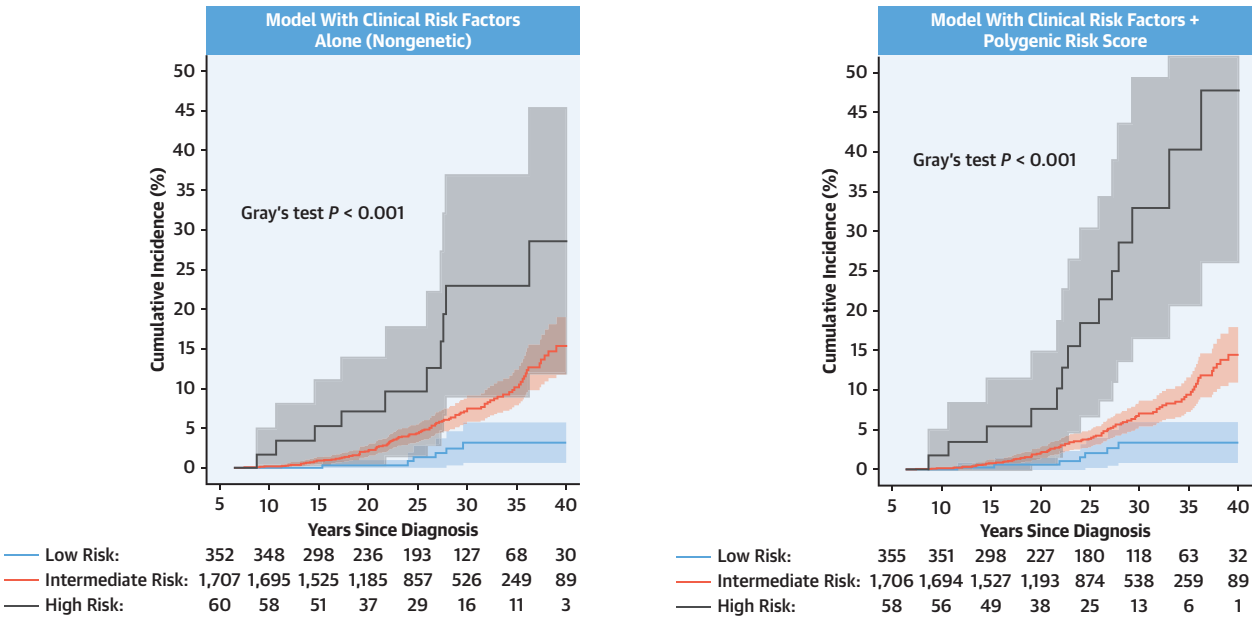
statistically significant ($P = 0.32$). The net reclassification index (NRI) comparing the models with and without the GPS was 0.027 (95% CI: −0.002 to 0.0102) for survivors with CAD and −0.011 (95% CI: −0.054 to 0.012) for those without CAD. Continuous NRI was used considering its sensitivity to the number and choice of thresholds selected, as suggested earlier.[32,33] Among survivors diagnosed <10 years of age and exposed to >25 Gy of average heart radiation dose, the AUC estimate of the nongenetic baseline model with clinical risk factors alone at 40 years since diagnosis was 0.52 (95%: CI 0.49-0.77), which significantly ($P = 0.028$) increased to 0.71 (95% CI: 0.53-0.90) when the GPS was included in the model (**Figure 1**). Further inclusion of acquired cardiovascular risk factors (diabetes, hypertension, dyslipidemia, and obesity) improved the AUC estimates of the nongenetic baseline models without (0.56 [95% CI: 0.49-0.81]) and with the GPS (0.76 [95% CI: 0.57-0.93]). The NRI comparing the models with and without the GPS was 0.171 (95% CI: 0.035-0.435) for survivors with CAD and −0.054 (95% CI: −0.152 to 0.082) for those without CAD. Corresponding calibration plots based on the models with and without the GPS are provided in Supplemental Figure 3.

DISCUSSION

To our knowledge, this is the first investigation to apply a validated GPS for CAD to clinically confirmed outcomes in a well-characterized cohort of childhood cancer survivors. We identified a significant association between GPS and the risk of CAD (HR 1.25 per 1 SD of the GPS), and we identified significant interactions with treatment exposures. The improvement in AUC caused by the GPS was small (1%) and not statistically significant among all survivors. However, in the younger subset of survivors exposed to higher average heart radiation doses, the AUC improvement by GPS was substantial (19%); the GPS remained independently predictive even with the inclusion of age-acquired traditional cardiovascular risk factors in this subgroup. The NRI estimates were also similar, although caution is needed in their interpretation.[34-36] Including the GPS had the greatest impact on the highest-risk group, increasing the estimated cumulative incidence of CAD at 30 and 40 years from diagnosis to 33% and 48%, respectively, in this young adult population. These observations are consistent with the cumulative incidence estimates and demonstrate the ability of the GPS to predict CAD risk in a subset of survivors. Although these results need to be applied to larger survivor populations, the GPS may better define survivors who may benefit from more focused health counseling and lifestyle interventions.

Primary prevention of CAD largely relies on the determination of risk for a future event as measured by a variety of available risk calculators, with intervention determined by the level of risk

CENTRAL ILLUSTRATION **The Cumulative Incidence of Coronary Artery Disease Among Childhood Cancer Survivors According to Nongenetic and Genome-Wide Polygenic Score Models**



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Survivors were classified into low-, intermediate-, and high-risk groups based on the nongenetic baseline model. Curves based on the nongenetic baseline model (the left panel) and those based on the nongenetic baseline model plus the genome-wide polygenic score for coronary artery disease (CAD) and its interaction with age at diagnosis and the average heart radiation dose (the right panel). The nongenetic baseline model for CAD risk was based on clinical risk factors alone based on age at cancer diagnosis, sex, the cumulative anthracycline dose, the average heart radiation dose, and the top 5 principal components.[24,25]

(ie, high, intermediate, or low). For the general population, numerous prediction models exist and have often been a source of debate.[37] Weighted by age, these calculators are not capable of accurately predicting risk for young patients previously exposed to cardiotoxic cancer therapies. Irradiated survivors are specifically known to be at high risk for CAD, and, to date, only 1 prediction model has been proposed.[38] Using data from 5-year cancer survivors participating in the Childhood Cancer Survivor Study, Chow et al[38] developed and externally validated a model that included sex and chest radiation exposure (C-index = 0.69). Performance improved only slightly with the addition of radiation dose (C-index = 0.70). Investigators reported a near 20% cumulative incidence of CAD by age 50 years (95% CI: 15.0-24.7). However, most general population models do not even include patients <50 years old. Including the GPS, we estimated the cumulative incidence at 30 and 40 years from diagnosis to be substantially higher.

Including the GPS may have implications for clinical survivorship care, potentially differentiating patients needing intensified preventive efforts from those at lower risk who may not require additional screening beyond that of the general population.[39] Although the number of high-risk survivors identified in our models with (n = 58) and without (n = 60) the GPS was approximately the same, inclusion of the GPS improved risk stratification. Fifteen (2 with CAD) of 60 clinically high-risk survivors were reclassified into the intermediate-risk subgroup, and 13 (6 with CAD) clinically intermediate-risk survivors moved into the high-risk subgroup.

Importantly, early evidence suggests the knowledge of genetic risk scores may impact health behaviors,[40] and lifestyle factors may particularly alter the trajectory for those at highest risk. Pooling genetic data from 3 large cohort studies (Atherosclerosis Risk in Communities Study, Women's Genome Health Study, and Malmö Diet and Cancer Study), Khera

et al[41] demonstrated the independent effect of lifestyle. A favorable lifestyle (defined as at least 3 of 4 factors: absence of smoking, lack of obesity, regular physical activity, and a healthy diet) reduced the risk of CAD among those at high genetic risk by 46% (HR: 0.54; 95% CI: 0.47-0.63). In fact, the 10-year cumulative incidence of CAD was reduced by nearly half in each respective cohort. Additionally, Mega et al[42] demonstrated a differential effect of statin therapy across polygenic risk groups, reducing risk by 13%, 29%, and 48% in the low-, intermediate-, and high-risk groups, respectively. In a 6-month clinical trial of 203 intermediate-risk (10-year congenital heart disease risk of 5%-20%) adults, those randomized by clinical plus genetic risk scores had lower low-density cholesterol levels and were more likely to have initiated statin therapy compared with participants randomized by clinical risk factors alone. Germline genotypes allow for the estimation of genetic risk for many diseases with a 1-time, minimally invasive DNA extraction at any time point in the life span. The addition of this low-cost genetic test (currently <$100) may fill an identified knowledge gap for surveillance of cancer survivors[43] as well as guide clinical decision making and motivate future health counseling.

STUDY LIMITATIONS. Some limitations should be noted when interpreting our data. Although we identified the highest risk in a very select survivor population, mostly Hodgkin lymphoma survivors diagnosed at a young age, our data importantly suggest that genetic profiles may enhance the identification of patients at risk for therapy-induced CAD, even before treatment exposures. These findings have the potential to alter future treatment protocols as well as long-term care. However, additional external validation/replication and prospective evaluation are required before incorporating polygenic risk scores in clinical risk stratification of childhood cancer survivors. Because of the limited sample size, we were unable to adequately assess the role of the GPS risk among survivors of African ancestry. Considering widespread differences in linkage disequilibrium and allele frequencies between individuals of European and African ancestries,[44,45] the GPS developed in individuals of European ancestry may not necessarily be associated with the risk of CAD in survivors of African ancestry. Further research is needed to develop population-specific polygenic risk scores across racial and ethnic groups for testing in larger survivor populations.

CONCLUSIONS

The clinical presentation and severity of cardiovascular outcomes in survivors of childhood cancer can be varied. We demonstrate the discerning role of adding genetic risk factors for CAD, especially among those diagnosed at younger ages and treated with higher doses of heart radiation. Thus, identifying a population who may benefit from personalized preventive interventions.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In long-term survivors of childhood cancer, a GPS for CAD is predictive of CAD incidence, specifically among those diagnosed with cancer before 10 years of age and exposed to >25 Gy heart radiation.

TRANSLATIONAL OUTLOOK: Future studies should consider incorporating the polygenic risk score with treatment exposures to identify at-risk survivors for CAD who may benefit from targeted screening and personalized preventive interventions.

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APPENDIX For an expanded Methods section and supplemental figures and tables, please see the online version of this paper.