Published in final edited form as:

Cancer Epidemiol Biomarkers Prev. 2019 February ; 28(2): 417–419. doi: 10.1158/1055-9965.EPI-18-0972.

Telomere length-associated genetic variants and the risk of thyroid cancer in survivors of childhood cancer: a report from the Childhood Cancer Survivor Study (CCSS)

Maria M. Gramatges[1], **Lindsay M. Morton**[2], **Yutaka Yasui**[3], **Michael A. Arnold**[4], **Joseph P. Neglia**[5], **Wendy M. Leisenring**[6], **Mitchell J. Machiela**[2], **Casey L. Dagnall**[2,7], **Stephen J. Chanock**[2,7], **Gregory T. Armstrong**[3], **Leslie L. Robison**[3], **Smita Bhatia**[8], and **Philip J. Lupo**[1]

[1]Department of Pediatrics, Baylor College of Medicine, Houston, TX

[2]Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD

[3]Department of Epidemiology and Cancer Control, St. Jude Children's Research Hospital, Memphis, TN

[4]Department of Pathology and Laboratory Medicine, Nationwide Children's Hospital

[5]Department of Pediatrics, University of Minnesota, Seattle, WA

[6]Division of Clinical Research, Fred Hutchinson Cancer Research Center, Seattle, WA

[7]Cancer Genomics Research Laboratory, Leidos Biomedical Research, Inc, Frederick National Laboratory for Cancer Research

[8]Institute for Cancer Outcomes and Survivorship, University of Alabama at Birmingham, Birmingham, AL

Abstract

Background: Given the inverse relationship previously described between telomere content and thyroid subsequent malignant neoplasm (thyroid SMN) in survivors of childhood cancer, we investigated the relationship between known genetic determinants of leukocyte telomere length and thyroid SMN among survivors.

Methods: Leveraging data from a large, genotyped survivor cohort, the Childhood Cancer Survivor Study, we used a well-described genetic risk score method to estimate the hazard ratio for thyroid SMN among 5,324 genotyped survivors.

Results: We identified 118 survivors with thyroid SMN and 5,206 without thyroid SMN. No association between genetically-estimated leukocyte telomere length and risk for thyroid SMN was identified.

Corresponding author: Maria Monica Gramatges, MD, PhD, Baylor College of Medicine, 1102 Bates St, Suite 1200, Houston, TX 77030, (p) 832-824-4678 (f) 832-825-4651 (e) gramatge@bcm.edu.

Conflict of interest statement: The authors declare no conflicts of interest.

Conclusions: Our results suggest that variation in common SNPs influencing leukocyte telomere length is not strongly associated with risk for thyroid SMN in survivors of childhood cancer.

Impact: The previously-observed inverse relationship between leukocyte telomere length and thyroid SMN risk in survivors of childhood cancer may be related to alternative molecular mechanisms, and warrants further study.

Keywords

telomere length; thyroid cancer; genetic risk score; survivor

Introduction

Subsequent malignant neoplasm of the thyroid (thyroid SMN) is one of the most common SMNs among survivors of childhood cancer. Established risk factors for thyroid SMN include female sex, younger age at primary cancer diagnosis, and exposure to radiation (1); however, these factors do not fully explain the observed variability in thyroid SMN risk for survivors. We previously reported less telomere content detected by quantitative PCR among childhood cancer survivors who developed thyroid SMN, compared with matched survivor controls without SMN (2). Given this finding, and emerging evidence for associations between genetically-predicted leukocyte telomere length (LTL) and increased risk for specific cancers (3), we extended this work to investigate the relationship between single nucleotide polymorphisms (SNPs) associated with LTL, as previously determined by genome-wide meta-analyses, and thyroid SMN in a cohort of childhood cancer survivors.

Materials and Methods

This study leveraged existing genotype data from participants enrolled in the Childhood Cancer Survivor Study (CCSS), a multicenter, retrospective cohort of five-year survivors of childhood cancer diagnosed between 1970 and 1986 (4). Survivors are prospectively followed, and incidence of thyroid SMN ascertained through self-report questionnaires. SMN cases were validated by pathology reports and verified by a CCSS pathologist (M.A.). A comparison group of survivors without thyroid SMN were censored by date of other SMN, death, or date of last follow up. Inclusion in this analysis was restricted to CCSS participants with genome-wide SNP data. Genotype data were generated by the Cancer Genomics Research Laboratory of the National Cancer Institute using the Illumina HumanOmni5Exome array. Imputation was based on the 1000 Genomes Project reference haplotypes, as described previously (5). Analyses were restricted to those of European ancestry to limit bias due to population stratification. Genetically-estimated LTL was determined using methods described by Machiela *et al.* (3). In brief, participant genotypes were extracted from nine common SNPs previously identified as associated with LTL by genome-wide meta-analyses (6–8). Assuming an additive genetic model, we used a multivariable Cox proportional hazards model to estimate the hazard ratio (HR), 95% confidence interval (CI), and *P* value for the association between each individual SNP and thyroid SMN risk. We then estimated the HR for thyroid SMN risk using the weighted sum of nine SNPs. An un-weighted genetic risk score (GRS) was determined for each participant

from the number of risk alleles present (0, 1, or 2), and a weighted GRS was generated using the published beta estimate for each effect allele. Based on the thyroid SMN risk prediction model described by Kovalchik *et al.* (9), covariates included sex, primary cancer diagnosis, neck radiation exposure (yes/no), and alkylating agent exposure (yes/no). Results were stratified on radiation exposure and primary diagnosis, and the false discovery rate was used to account for multiple comparisons. Power was calculated using Quanto Version 1.2.4. Based on a sample size of 5,324 genotyped survivors of European descent (118 with thyroid SMN and 5,206 without thyroid SMN), we were powered to detect a HR of 1.7 for thyroid SMN, using the lowest tertile of genetically-estimated LTL. As this is in keeping with previous assessments evaluating LTL genetic risk scores and subsequent cancer (3,6–8), we were adequately powered to detect the proposed associations.

Results

The majority of the 118 survivors with a verified diagnosis of thyroid SMN had papillary carcinoma (papillary, n=106 [89.8%]; follicular, n=11 [9.3%]; carcinoma not otherwise specified, n=1 [0.9%]). Participants were predominantly survivors of Hodgkin lymphoma, leukemia, and central nervous system tumors and diagnosed before the age of 15 years (Table 1). Thyroid SMN cases were more likely to have been born before 1970 ($p=0.002$), exposed to an alkylating agent ($p=0.016$) or radiation ($p<0.001$), and have a history of thyroid nodules ($p<0.001$). Of the nine SNPs evaluated, four were directly genotyped and five were imputed, all with imputations scores that were greater than 0.89. No association was observed between the individual LTL-related SNPs and risk for thyroid SMN. When considering the total burden of the effect alleles for these SNPs on thyroid SMN risk, there was no significant relationship observed for either the un-weighted or weighted GRS (Table 2). Given the strong dose-dependent relationship between radiation and risk for thyroid SMN, we then restricted the analysis to radiation to the neck-exposed individuals (yes/no, considered yes if >10% of the region was directly within the radiation field) and, similarly, no association was observed (Supplementary Table S1).

Discussion

In the largest available cohort of childhood cancer survivors with comprehensive genotype data, our results suggest that variation in common SNPs influencing LTL is not strongly associated with risk for thyroid SMN in survivors of childhood cancer. No prior studies have investigated common variation in SNPs influencing LTL and risk for thyroid SMN. Of note, our observations are in contrast with evidence for genetically increased LTL in adults with primary thyroid cancer, though that study was underpowered to detect associations within this cancer subtype (10). The previously-observed inverse relationship between LTL and thyroid SMN risk in survivors may therefore be due to alternative molecular mechanisms, such as rare variants interacting with therapy-related exposures, defects in specific genes related to telomere maintenance, or environmental factors (e.g. differential effects of chemotherapy and/or radiation). Investigations that expand this assessment and comprehensively evaluate the role of telomere maintenance genes on risk for thyroid SMN are ongoing.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding support: This work was supported by the National Cancer Institute (CA194473: M.G., Principal Investigator) and a CCSS Career Development Award to P.L. CCSS is supported by the National Cancer Institute (CA55727: G.A., Principal Investigator), the St. Jude Children's Research Hospital Cancer Center Support (CORE) grant (CA21765, C. Roberts, Principal Investigator), and the American Lebanese-Syrian Associated Charities (ALSAC). Genotyping for the study also was supported by the Intramural Research Program of the National Cancer Institute, National Institutes of Health.

Abbreviations:

SMN	Subsequent malignant neoplasm
CCSS	Childhood Cancer Survivor Study
LTL	leukocyte telomere length
GRS	Genetic risk score

References:

1. Veiga LH, Lubin JH, Anderson H, de Vathaire F, Tucker M, Bhatti P, et al. A pooled analysis of thyroid cancer incidence following radiotherapy for childhood cancer. Radiat Res 2012;178(4):365–76. [PubMed: 22857014]
2. Gramatges MM, Liu Q, Yasui Y, Okcu MF, Neglia JP, Strong LC, et al. Telomere content and risk of second malignant neoplasm in survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. Clin Cancer Res 2014;20(4):904–11. [PubMed: 24277454]
3. Machiela MJ, Lan Q, Slager SL, Vermeulen RC, Teras LR, Camp NJ, et al. Genetically predicted longer telomere length is associated with increased risk of B-cell lymphoma subtypes. Hum Mol Genet 2016;25(8):1663–76. [PubMed: 27008888]
4. Robison LL, Armstrong GT, Boice JD, Chow EJ, Davies SM, Donaldson SS, et al. The Childhood Cancer Survivor Study: a National Cancer Institute-supported resource for outcome and intervention research. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2009;27(14):2308–18. [PubMed: 19364948]
5. Morton LM, Sampson JN, Armstrong GT, Chen T, Hudson MM, Dagnall CL, et al. Genome-wide association study identifies susceptibility loci that modify radiation-related risk for breast cancer after childhood cancer. J Natl Cancer Inst 2017;in press(in press).
6. Codd V, Nelson CP, Albrecht E, Mangino M, Deelen J, Buxton JL, et al. Identification of seven loci affecting mean telomere length and their association with disease. Nat Genet 2013;45(4):422–7, 7e1–2. [PubMed: 23535734]
7. Mangino M, Hwang SJ, Spector TD, Hunt SC, Kimura M, Fitzpatrick AL, et al. Genome-wide meta-analysis points to CTC1 and ZNF676 as genes regulating telomere homeostasis in humans. Hum Mol Gen 2012;21(24):5385–94. [PubMed: 23001564]
8. Mangino M, Christiansen L, Stone R, Hunt SC, Horvath K, Eisenberg DT, et al. DCAF4, a novel gene associated with leucocyte telomere length. J Med Genet 2015;52(3):157–62. [PubMed: 25624462]
9. Kovalchik SA, Ronckers CM, Veiga LH, Sigurdson AJ, Inskip PD, de Vathaire F, et al. Absolute risk prediction of second primary thyroid cancer among 5-year survivors of childhood cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2013;31(1):119–27. [PubMed: 23169509]

10. Telomeres Mendelian Randomization C, Haycock PC, Burgess S, Nounu A, Zheng J, Okoli GN, et al. Association Between Telomere Length and Risk of Cancer and Non-Neoplastic Diseases: A Mendelian Randomization Study. JAMA Oncol 2017;3(5):636–51. [PubMed: 28241208]

Table 1:

Study population characteristics

Characteristic	Survivors with Thyroid SMN, n (%) (n=118)	Survivors without Thyroid SMN, n (%) (n=5,206)	p value
Female	76 (64.4)	2,663 (51.2)	0.004
Type of first cancer			
Leukemia	32 (27.1)	1,662 (31.9)	<0.001
CNS	15 (12.7)	628 (12.1)	
Hodgkin lymphoma	39 (33.1)	685 (13.2)	
Non-Hodgkin lymphoma	6 (5.1)	431 (8.3)	
Wilms tumor	5 (4.2)	493 (9.5)	
Neuroblastoma	4 (3.4)	386 (7.4)	
Soft tissue sarcoma	6 (5.1)	469 (9.0)	
Bone cancer	11 (9.3)	452 (8.7)	
Age at first cancer diagnosis			
<15 years	96 (81.4)	4,251 (81.7)	0.934
≥15 years	22 (18.6)	955 (18.3)	
Year of birth			
1970 or before	71 (60.2)	2,373 (45.6)	0.002
After 1970	47 (39.8)	2,833 (54.4)	
Chemotherapy – alkylator	71 (62.2)	2,495 (50.9)	0.016
Radiation	100 (87.0)	3,216 (65.1)	<0.001
Radiation to neck	69 (60.5)	1,074 (22.2)	<0.001
Thyroid nodules	91 (83.5)	523 (10.4)	<0.001

Table 2:

Risk for thyroid SMN associated with previously-established leukocyte telomere length-related SNPs

SNP	Chr	Nearby gene	Effect Allele	Other Allele	EAF in EUR*	Published beta	Published P value	Reference	Unadjusted HR (95% CI)	P value	Adjusted HR& (95% CI)	P value
rs11125529	2	*ACYP2*	A	C	0.11	0.065	7.5E-10	Codd et al.	1.08 (0.75–1.55)	0.67	1.10 (0.74–1.64)	0.64
rs10936599	3	*TERC*	C	T	0.76	0.100	2.5E-31	Codd et al.	0.99 (0.73–1.33)	0.95	1.04 (0.75–1.44)	0.83
rs7675998	4	*NAF1*	G	A	0.76	0.048	4.4E-16	Codd et al.	0.88 (0.65–1.19)	0.41	0.93 (0.67–1.29)	0.67
rs2736100	5	*TERT*	C	A	0.50	0.085	4.4E-19	Codd et al.	0.89 (0.69–1.15)	0.36	0.83 (0.63–1.08)	0.17
rs9420907	10	*OBFC1*	C	A	0.13	0.142	6.9E-11	Codd et al.	1.09 (0.78–1.52)	0.60	1.06 (0.74–1.52)	0.74
rs2535913	14	*DCAF4*	G	A	0.78	0.103	6.4E-10	Mangino et al.	0.81 (0.62–1.06)	0.13	0.80 (0.59–1.06)	0.12
rs3027234	17	*CTC1*	C	T	0.28	0.064	2.3E-08	Mangino et al.	1.18 (0.85–1.63)	0.32	1.10 (0.78–1.53)	0.60
rs8105767	19	*ZNF208*	G	A	0.12	0.019	1.1E-09	Codd et al.	1.25 (0.95–1.63)	0.11	1.08 (0.79–1.48)	0.62
rs755017	20	*RTEL1*	G	A	0.69	0.049	6.7E-09	Codd et al.	0.80 (0.52–1.22)	0.30	0.91 (0.59–1.42)	0.68
Un-weighted Genetic Risk Score									0.98 (0.89–1.09)	0.76	0.96 (0.86–1.07)	0.47
Weighted Genetic Risk Score									1.17 (0.34–4.00)	0.80	0.81 (0.22–2.98)	0.76

*Estimated allele frequency (EAF) in Europeans (EUR) from the 1000 Genomes Project

&Adjusted for birth year, initial cancer type, age at diagnosis, sex, thyroid nodules, radiation, radiation to the neck (Y/N), radiation dose to the neck, alkylating agent

Cancer Epidemiol Biomarkers Prev. Author manuscript; available in PMC 2020 February 01.