Genetic variants, treatment exposures, and their associations with the development of colorectal cancer as a subsequent malignant neoplasm in long-term survivors of childhood cancer

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BACKGROUND & RATIONALE:

Long-term survivors of childhood cancer face an increased risk of developing subsequent malignant neoplasms (SMNs), with colorectal cancer (CRC) emerging as a significant concern.[1,2] Compared to the general population, childhood cancer survivors have a 2 to 10.9-fold[2-4] higher risk of developing CRC. CRC as an SMN in this vulnerable population presents a unique challenge due to its potential for early onset and the unknown interplay between genetic predisposition and treatment-related factors.[3,5-8] While previous research has described genetic risk factors[9] for CRC in the general population and characterized risk of subsequent CRC in childhood cancer survivors associated with treatment-related exposures (i.e., chemotherapies, radiotherapy),[2,3,10] there is limited knowledge regarding the role of genetic variants in subsequent CRC development in childhood cancer survivors.

Previous studies through the Childhood Cancer Survivor Study (CCSS)[3] and the St. Jude Children's Research Hospital[2] have demonstrated that the risk of CRC is elevated among childhood cancer survivors who received abdominal/pelvic radiation and alkylating chemotherapy agents, such as procarbazine and cisplatin. In a case-control analysis, the risk of subsequent CRC increased by 70% for each 10-Gray increase in radiation dose to the colon; further, an 8.8-fold increased risk of subsequent CRC was seen with alkylating agent exposure.[2] Similar findings have been found in cohorts of European childhood cancer survivors.[4,11,12] On a cellular level, abdominal or pelvic radiation can induce ongoing DNA damage accumulation below the threshold of cell

death in gastrointestinal tissues.[13-15] Comparably, alkylating agents are genotoxic chemicals that can cause DNA mutations outside of signaling cell death.[16,17] Both mechanisms can increase the oncogenic potential of cells through genetic alterations.

Genetic predisposition also plays a critical role in SMN development, including CRC. Certain genetic variants associated with hereditary syndromes, such as Lynch syndrome (caused by mutations in *MLH1, MSH2, MSH6*, and *PMS2*) and Familial Adenomatous Polyposis (caused by mutations in the *APC* gene), are known to increase CRC risk.[18-20] However, the role of rare variants in these genes on the risk of developing subsequent CRCs in childhood cancer survivors has not been explored. Across the genes listed in the American College of Medical Genetics and Genomics (ACMG) Secondary Findings,[21] in the 60 genes (SJCPG60) known to be associated with autosomal dominant cancer predisposition syndromes,[22] and in the 96 genes inherited in an autosomal dominant or autosomal recessive manner,[22] we have identified 17 genes associated with increased risk of CRC (Table 1). We hypothesize that pathogenic/likely pathogenic variants (P/LP) variants in these 17 CRC-related genes contribute to the development of subsequent CRCs in childhood cancer survivors, particularly for those with early onset CRCs. Early onset CRC is defined as a diagnosis of CRC in individuals at age 50 or younger.[23] Additionally, we hypothesize that genetic risk from pathogenic/likely pathogenic variants in CRC-related genes may be modified by treatment exposures—specifically abdominal/pelvic radiation and alkylating agents (procarbazine or cisplatin)—such that survivors treated with these modalities will exhibit different prevalence and distributions of P/LP variants compared to unexposed survivors across treatment-defined subgroups, reflecting a potential interaction between genetic predisposition and treatment-related DNA damage. Whole-exome sequencing (WES) data from >12,000 survivors of childhood cancer from the CCSS and SJLIFE offers a unique opportunity to preliminarily explore the role of rare P/LP in the risk of subsequent CRCs, as well as their interactions with treatment exposures.

Building on previous work in the CCSS characterizing the risk of subsequent CRCs, our study will address the current knowledge gap described above by leveraging the extensive data available through the CCSS and St. Jude Lifetime Cohort (SJLIFE). Based on an initial review with the CCSS Genetics Working Group, there are approximately 100 survivors with a CRC SMN with WES (31 cases from SJLIFE, 68 cases from CCSS) that can be analyzed for this study. By characterizing the prevalence and distribution of rare P/LP variants in the identified 17 CRC-related genes from the ACMG, SJCPG60, and 96 genes, our study aims to elucidate the interplay between genetic variants and treatment-related exposures related to subsequent CRCs in these survivors. Findings could ultimately play a critical role in the development of targeted interventions, ranging from informing counseling to survivor and survivor families to updating screening guidelines, thus contributing to an improvement in long-term outcomes.

SPECIFIC AIMS:

Aim 1: To characterize the prevalence and distribution of P/LP variants, as listed in Table 1, in survivors diagnosed with a cancer < 21 years of age who subsequently develop CRC and compare results to (i) survivors without a subsequent CRC diagnosis, (ii) individuals in the general population (e.g., SJLIFE community controls), and (iii) an external reference panel (gnomAD) – overall, by treatment exposure, and by age at CRC diagnosis.

Aim 2: To estimate the associations of genetic variants with subsequent CRC in childhood cancer survivors and explore whether primary cancer treatment exposures moderate these associations.

Exploratory Aim 1: To describe the proportion of individuals who received a colonoscopy among childhood cancer survivors who (a) are diagnosed with CRC, and separately (b) report a CRC-related genetic condition.

METHODS/ANALYTIC APPROACH:

Study population (eligibility criteria): Five-year survivors of childhood cancer participating in the CCSS and SJLIFE with WES data. Aim 1 will also utilize SJLIFE community controls.

Dependent/outcome variables:

- Development of CRC as a SMN, and age at time of SMN.

Independent/predictor variables:

- Genetic data
    - **Whole exome sequencing:** We will utilize WES data in the CCSS and SJLIFE cohorts. Currently, WES data of 12,000+ survivors of childhood cancer in the CCSS and SJLIFE are being jointly processed at St. Jude Children's Research Hospital. We expect this process to be complete prior to undertaking this analysis. Once this process is complete, we will create a binary variable (yes/no) indicating carrier status of rare (minor allele frequency, MAF <0.1%)[24] P/LP variants in CRC-related cancer predisposition genes to utilize for analysis. We recognize that there is overlap between the CCSS and SJLIFE cohorts; thus, we will keep the identified survivors in SJLIFE and remove the duplicates found in CCSS. We have compiled a list of 17 genes that are associated with increased CRC risk[25] across the ACMG, SJCPG60, and 96 genes (genes are listed in Table 1).
    - In line with previous studies,[20,21,26,27] we will analyze variants in cancer predisposition genes with a focus on rare genetic variants. For P/LP variants, the National Center for Biotechnology Information (NCBI) ClinVar[28] will be utilized and annotated for these variants. Variants with an aggregate interpretation indicating a consensus in ClinVar will be utilized. In addition, we

will analyze loss-of-function (LOF) and predicted deleterious missense variants. Loss-of-Function Transcript Effect Estimator (LOFTEE; plug-in implemented in the Variant Effect Predictor tool, or VEP[29], version 108) will be utilized to annotate LOF variants. If LOF variants are flagged by LOFTEE as "dubious," such as "LOFs affecting poorly conserved exons,[30] then they will be excluded. For predicted deleterious missense variants, we will utilize SnpEff[31] and dbNSFP[32] (version 4.1a) for annotations. If more than 90% of annotations predict deleteriousness across the previously mentioned tools/databases, then they will be classified as deleterious.

- Sociodemographic/clinical variables
    - Sex
    - Attained age (i.e., date of birth and date of last contact or death)
    - Vital status (dead/alive)
    - Primary cancer diagnosis
    - Age at primary cancer diagnosis (i.e., date of primary cancer diagnosis)
    - Reported race/ethnicity
    - Family history of CRC (yes/no)
    - Family history of any cancer (yes/no)
    - Self-reported personal history of colonic polyps (I5 from Follow-up Survey 7 and Follow-up Survey 5; I4 in Follow-up Survey 4; I4 from SJLIFE HOME Survey):
        - Yes" will comprise of self-reported survey answers of:
            - Yes, and the condition is still present
            - Yes, but the condition is no longer present
            - Note: If Yes is marked by the participant, please provide age that participant filled in
        - "No" will comprise of self-reported survey answers of:
            - No
            - Not sure
    - Date of CRC diagnosis and length of time from primary cancer diagnosis to CRC diagnosis
    - Date of sample collection from participants with genetic data
    - Recurrence of primary cancer and date of diagnosis
    - Other SMN diagnoses and date(s) of diagnosis
    - Specific cancer treatment exposures of interest (delivered within 5 years of primary cancer diagnosis):
        - Abdominal radiotherapy (RT) (yes/no and dose)
        - Pelvic RT (yes/no and dose)
        - Total body irradiation (yes/no and dose)
        - Chemotherapy (yes/no and dose, if available)
            - Alkylating agents

        - Yes/no and dose quantified as cyclophosphamide-equivalent dose[33] (CED)
        - Specific alkylating agents (procarbazine, cisplatin) informing CED (yes/no and dose)
- Self-reported having abdominal or rectal surgery (Item K16 and K17 from Survey Follow up-7; Item J16 and J17 from Survey Follow-up 5; Item J17 and J18 from SJLIFE Home Survey)
    - "Yes" will comprise of self-reported survey answers of:
        - Yes
        - Note: If Yes is marked by participant, please provide age that participant filled in
    - "No" will comprise of self-reported survey answers of:
        - No
        - Not sure
- Self-reported a genetic condition related to CRC (Item W1 from Survey Follow up-7 and Survey Follow-up 5; Item "Hereditary Conditions" from Survey Follow-up 4 and Survey Follow-up 2; Item 4 from Survey Follow-up 1)
    - Survey Follow-up 7 and Survey Follow-up 5:
        - Bloom's syndrome (yes/no/not sure) (Item W1d)
        - Familial adenomatous polyposis (FAP or Gardner syndrome) (yes/no/not sure) (Item W1i)
        - Other (yes/no/not sure and open-ended written response) (Item W1p)
    - In Survey Follow-up 4 and Survey Follow-up 2, if participant circles the following answers under "Hereditary Conditions":
        - Bloom's syndrome
        - Polyposis coli (Gardner syndrome)
    - Survey Follow-up 1:
        - Bloom's syndrome (yes/no/not sure) (Item 4d)
        - Polyposis coli (Gardner syndrome) (yes/no/not sure) (Item 4i)
        - Other (yes/no/not sure and open-ended written response) (Item 4p)
- Self-reported a genetic condition related to CRC (Item P1 from SJLIFE Home Survey)
    - Bloom's syndrome (yes/no/not sure) (Item P1d)
    - Familial adenomatous polyposis (FAP or Gardner syndrome) (yes/no/not sure) (Item P1i)
    - Li-Fraumeni syndrome (p53 gene abnormality) (Item P1r)
    - Other (yes/no/not sure and open-ended written response) (Item P1s)
- Self-reported receipt of colonoscopy (yes/no) (Item C1f from Survey Follow-up 7, Survey Follow-up 6 Long, and Survey Follow-up 5; Item C4 from Survey Follow-up 4; Item B2 from Survey Follow-up 2)

        - “Yes” will comprise of self-reported survey answers of:
            - Less than 1 year ago
            - 1-2 years ago
            - More than 2 years ago but less than 5 years ago
            - 5 or more years
            - I had one but I don't recall when
        - “No” will comprise of self-reported survey answers of:
            - Never
            - I don’t know if I ever had one
            - Don’t know (from Item C4 from Survey Follow-up 4; Item B2 from Survey Follow-up 2)
    - Self-reported receipt of colonoscopy (yes/no) (Item N12 from SJLIFE Home Survey)
        - “Yes” will comprise of self-reported survey answers of:
            - Less than 1 year ago
            - 1-2 years ago
            - More than 2 years ago but less than 5 years ago
            - 5 or more years
            - I had one but I don't recall when
        - “No” will comprise of self-reported survey answers of:
            - Never
            - I don’t know if I ever had one
    - Self-reported body mass index data (Item A1 and A2 from Survey Follow-up 7, Survey Follow-up 6 Long, Survey Follow-up 5, Survey Follow-up 4; Item 7 and 8 in Survey Follow-up 2; Item A3 and A4 from SJLIFE Home Survey)
        - Date of survey collection (“Today’s Date”)
        - Height
        - Weight
    - Self-reported tobacco exposure (yes/no) (Item M7, M9, M10, M11, M13, M14 from Survey Follow-up 7; Item N7, N9, N10, N11, N13, N14 from Survey Follow-up 5 and Survey Follow-up 4; Item L1, L2, L3, L4, L6 from Survey Follow-up 2)
        - “Yes” will comprise of self-reported survey answers of:
            - “Yes” to the question: “Have you smoked at least 100 cigarettes since you last provided us this information”
            - “Yes” to the question: “Do you smoke cigarettes now?”
            - Any number greater than 0 to the question: “On average, how many cigarettes a day do/did you smoke?”
            - Any number greater than 0 to the question: “How many years, in total, have you smoked?”
            - Any positive answer (respondent checks occasionally use or regularly use) to one or more of the items listed (chewing

tobacco, snuff tobacco, pipes, cigars, or e-cigarettes/vaping) in the question: “In the past year, have you ever used any of these products?”

- Any positive answer (respondent checks less than 1 year, 1-2 years, 3-4 years, 5-10 years, or 11+ years) to the items listed (chewing tobacco, snuff tobacco, pipes, cigars, or e-cigarettes/vaping) in the question: “For any of those that you have used or are currently using, how long how you used it?”

- “No” will comprise of self-reported survey answers of:
  - “No” to the question: “Do you smoke cigarettes now?”

Analysis:

Aim 1: Across the set of 17 CRC-related cancer predisposition genes identified (Table 1), the prevalence and distribution of variants will be tabulated and described among survivors who developed a subsequent CRC and among survivors who did not develop a subsequent CRC. The summary will include variant classes characterization, such as P/LP, LOF, and missense variants, and their frequency. These characteristics will be compared to individuals from the general population via a control sample (the SJLIFE community controls). Since treatment with abdominal/pelvic radiotherapy and specific alkylating agents (procarbazine or cisplatin) has been found to be associated with increased subsequent CRC risk, we will also tabulate distributions of variants for the following subgroups of survivors:

(i) individuals treated with abdominal/pelvic radiation and no procarbazine or cisplatin

(ii) individuals treated with procarbazine or cisplatin and no abdominal/pelvic radiation; and

(iii) individuals not exposed to abdominal/pelvic radiation, procarbazine, or cisplatin

Analyses will be repeated restricted to CRC diagnosed prior to age 50 to explore distributions in early-onset CRC.

Aim 2: To evaluate associations between P/LP variants and the development of CRC as an SMN, we will utilize cause-specific Cox regression models with time since diagnosis as the time scale using methods for delayed entry data to reflect that participants enter risks sets at the time a sample for WES was collected. In the primary analysis, all variants across the 17 genes of interest will be grouped, and the presence of any genetic variant will be indicated by a single binary variable (Y/N). In exploratory analysis, if the data permit (large enough numbers of participants with relevant variants), we will repeat the analysis separately for LOF and missense variants. Ideally we would like to analyze associations with variants for each gene separately, but recognize the numbers are likely to be small for such an analysis. We aim to adjust these analyses for sex, age at childhood cancer diagnosis, attained age, family history of CRC, and the genetic ancestry derived from genotype data.

The primary analysis will be repeated adjusting the model for treatment exposures. We will include binary variables of Y/N indicating whether patients received

abdominal/pelvic radiation or alkylating chemotherapies. Our ultimate interest is whether there are interactions between the treatment exposures and the presence of P/LP variant. We can explore this by including interaction terms in our model, but recognize that analyses will be underpowered for formally testing of whether such interactions are present. Further, we will explore whether lifestyle factors available in the data (smoking status and obesity) modify associations, but recognize the limitations of these factors in CCSS survey data. We will adjust for these factors in a simplified manner, based on indicators if participants were ever a smoker or if participants were ever overweight or obese.

Cumulative incidence of CRC will be estimated for survivors stratified by P/LP variant carrier status, accounting for death or lost to follow-up as a competing risk and reflecting the delayed entry data.

Exploratory Aim 1: To obtain the number of childhood cancer survivors who report a CRC-related genetic condition, the total number of individuals who provided a positive response to survey items eliciting a self-reported genetic condition related to CRC will be ascertained via all available CCSS and SJLIFE surveys. A positive response will be counted if the individual reports a CRC-related genetic condition in any of the available CCSS or SJLIFE surveys. Then, the number of positive and negative responses for receipt of a colonoscopy will be determined as per the response groupings from the "self-reported receipt of colonoscopy" variable described above. For participants without CRC, if they ever report having received a colonoscopy in any of the surveys, they will be classified as having received colonoscopy; otherwise, they will be classified as not having received one. For participants with CRC, we will aim to capture responses restricted to surveys completed prior to the CRC diagnosis. To estimate the proportion of individuals who received a colonoscopy among childhood cancer survivors who report a CRC-related genetic condition, the number of individuals who provided a positive response to the "self-reported receipt of colonoscopy" variable will be divided by the total number of individuals who provided a positive response to survey items eliciting a self-reported a genetic condition related to CRC. The same process will be repeated to determine the proportion of individuals who did not receive a colonoscopy among childhood cancer survivors who report a CRC-related genetic condition, except we will utilize the number of individuals who provided a negative response to the "self-reported receipt of colonoscopy" variable as the numerator.

Example tables and figures

Table 1: Complied list of 17 genes associated with increased risk of CRC

HGNC symbol*	HGNC approved name	Phenotype	Inheritance Pattern**
APC	adenomatous polyposis coli	Familial Adenomatous Polyposis	AD

BMPR1A	bone morphogenetic protein receptor, type IA	Hereditary Mixed Polyposis Syndrome	AD
EPCAM	epithelial cell adhesion molecule	Lynch Syndrome	AD
GREM1	gremlin 1, DAN family BMP antagonist	Hereditary mixed polyposis syndrome	AD
MLH1	mutL homolog 1	Lynch Syndrome; Constitutional mismatch repair deficiency	AD; AR
MSH2	mutS homolog 2	Lynch Syndrome; Constitutional mismatch repair deficiency	AD; AR
MSH3	mutS homolog 3	MSH3-associated polyposis	AR
MSH6	mutS homolog 2	Lynch Syndrome; Constitutional mismatch repair deficiency	AD; AR
PMS2	PMS1 homolog 2, mismatch repair system component	Lynch Syndrome; Constitutional mismatch repair deficiency	AD; AR
PTEN	phosphatase and tensin homolog	Cowden Syndrome, increased risk for cancers of the breast, thyroid, endometrium, colorectum, kidney, and skin (i.e. melanoma)	AD
SMAD4	SMAD family member 4	Hereditary Hemorrhagic Telangiectasia; Juvenile Polyposis	AD
STK11	serine/threonine kinase 11	Peutz Jeghers Syndrome, including increased risk for cancers of the gastrointestinal tract, pancreas, cervix, ovary, and breast	AD
TP53	tumor protein p53	Li Fraumeni Syndrome	AD
MUTYH	mutY DNA glycosylase	MUTYH-associated polyposis	AR
NTHL1	nth like DNA glycosylase 1	NTHL1 Tumor Syndrome; NTHL1-Associated Polyposis	AR
POLD1	polymerase (DNA directed), delta 1, catalytic subunit	POLD1 & POLE associated Colorectal Adenomas and Cancer	AD
POLE	polymerase (DNA directed), epsilon, catalytic subunit	POLD1 & POLE associated Colorectal Adenomas and Cancer	AD

*HGNC symbol is the unique identifier assigned to every known human gene by the Human Genome Organization Gene Nomenclature Committee (HGNC).
**Inheritance patterns are autosomal dominant (AD) and/or autosomal recessive (AR).

Table 2: Demographic and clinical characteristics of childhood cancer survivors in CCSS and St. Jude Lifetime Cohort

	CRC (n=99)	Total (n=)
Characteristic		
Age at time of childhood cancer diagnosis		
0-4 years old		
5-9 years old		
10-14 years old		
15-20 years old		
Race and Ethnicity		
White, Non-Hispanic		
Black, Non-Hispanic		
Hispanic/Latin		
Other		
Sex		
Female		
Male		
Childhood cancer diagnosis		
Leukemia		
Lymphoma		
Non-Hodgkin lymphoma		
Soft tissue sarcoma		
Bone cancer		
Neuroblastoma		
CNS tumor		
Kidney (Wilms) tumor		
Family history of colorectal cancer		
Yes		
No		
Age at time of subsequent colorectal cancer (CRC)		
<15 years old		NA
15-29 years old		NA
30-39 years old		NA
40-49 years old		NA
>50 years old		NA

Length of time from primary cancer diagnosis to CRC diagnosis		
<5 years		NA
5-10 years		NA
11-20 years		NA
21-30 years		NA
30+ years		NA
Alkylating agents, in CED* (mg/m^2)		
None		
>0 to < 4,000		
≥ 4,000 to < 8,000		
≥ 8,000		
Procarbazine dose (mg/m^2)		
None		
>0 to ≤ 4200		
>4200 to ≤ 7036		
>7036		
Cisplatin (mg/m^2)		
None		
1-400		
401-750		
>750		
Abdominal radiotherapy for primary malignancy (Gy)		
None		
Yes		
<10		
>10 to <20		
≥ 20		
Pelvic radiotherapy for primary malignancy (Gy)		
None		
Yes		
<10		
>10 to < 20		
≥ 20		
Total body irradiation (Gy)		

None		
Yes		
<10		
>10 to < 20		
≥ 20		
Body Mass Index (BMI) at time of survey		
Underweight (BMI<18.5)		
Normal weight (18.5≤BMI<25)		
Overweight (25≤BMI<30)		
Obese (BMI≥30)		
Tobacco exposure		
Yes		
No		

*CED=cyclophosphamide-equivalent dose

Table 3: ACMG genotypes

		Survivors with CRC SMN carrying variant, n(%)	Survivors without CRC SMN carrying variants, n(%)	General Population, n(%)
Total, n				
Number who carry a rare variant				
Gene	Variant class			
APC	P/LP			
	LOF			
	Missense			
BMPR1A	P/LP			
	LOF			
	Missense			
*Other genes listed from Table 1, etc.**				

* Will list all cancer predisposition genes from the ACMG Secondary Findings, $SJCPG_{60}$, and 96 genes that are known to be associated with CRC-related cancer predisposition syndromes

Table 4: ACMG genotypes among CRC SMN cases by treatment exposure (n=99)

Gene	Variant class	Treated with abdominal/pelvic radiation and no procarbazine or cisplatin, n(%)	Treated with procarbazine or cisplatin and no abdominal/pelvic radiation, n(%)	No exposures to abdominal/pelvic radiation, procarbazine, or cisplatin, n(%)
Total, n				
APC	P/LP			
	LOF			
	Missense			
BMPR1A	P/LP			
	LOF			
	Missense			
*Other genes listed in Table 1, etc.**				

* Will list all cancer predisposition genes from the ACMG Secondary Findings, $SJCPG_{60}$, and 96 genes that are known to be associated with CRC-related cancer predisposition syndromes

Table 5: Hazard ratios for genetic variants, clinical factors, and treatment exposures for CRC SMN development in childhood cancer survivors

Factors	Hazard ratio	95% confidence interval	p value
Genetic Variant			
P/LP			
Missense			
LOF			
Sex			
Male			
Female			
Age at time of childhood cancer diagnosis			
0-4 years old			
5-9 years old			
10-14 years old			
15-20 years old			

Family history of colorectal cancer			
Yes			
No			
Treatment exposures			
Alkylating agents, in CED* (mg/m^2)			
None			
>0 to < 4,000			
≥ 4,000 to < 8,000			
≥ 8,000			
Procarbazine dose (mg/m^2)			
None			
>0 to ≤ 4200			
>4200 to ≤ 7036			
>7036			
Cisplatin (mg/m^2)			
None			
1-400			
401-750			
>750			
Abdominal radiotherapy for primary malignancy (Gy)			
None			
Yes			
<10			
>10 to <20			
≥ 20			
Pelvic radiotherapy for primary malignancy (Gy)			
None			
Yes			
<10			
>10 to < 20			
≥ 20			

Total body irradiation (Gy)			
None			
Yes			
<10			
>10 to < 20			
≥ 20			

Table 6: Self-reported genetic conditions related to CRC and receipt of colonoscopy

	Total, n (%)
Total number of participants who responded to survey, n	
Genetic conditions	
Bloom's syndrome	
Yes	
No	
Not sure	
Familial adenomatous polyposis (FAP or Gardner syndrome)	
Yes	
No	
Not sure	
Other**	
Yes	
No	
Not sure	
Total number of participants who reported having a CRC-related genetic condition, n	
Never received a colonoscopy	
Received a colonoscopy	
Less than 1 year ago	
1-2 years ago	
>2 years to <5 years ago	
5 or more years	
I had one but I don't recall	
I don't know if I ever had one or don’t know	

**Other includes written responses of _____. We will only include if the condition(s) written is related to CRC (i.e., Lynch syndrome/Hereditary Nonpolyposis Colorectal Cancer, Li-Fraumeni syndrome, etc.)

Figure 1: Cumulative Incidence of Colorectal Cancer Stratified by P/LP Variant Carrier Status in Childhood Cancer Survivors

- X-Axis: Age (in years)
- Y-Axis: Cumulative incidence of CRC (expressed as a proportion).
- Stratification: Separate curves for P/LP variant carriers versus non-carriers.

Figure 2: Forest plots for adjusted hazard ratios and 95% confidence intervals for Colorectal Cancer Risk Factors in Childhood Cancer Survivors

- X-axis: Hazard ratio on a logarithmic scale, with a vertical line at HR = 1 indicating no association.
- Y-Axis: Would list the predictor variables, including:
    - P/LP variant carrier status
    - Sex
    - Age at childhood cancer diagnosis
    - Family history of CRC
    - Treatment exposures (e.g., radiation, chemotherapy)

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