Increased Burden of Familial-associated Early-onset Cancer Risk among Minority Americans Compared to non-Latino Whites.

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Abstract

Background. The role of race/ethnicity in genetic predisposition of early-onset cancers can be estimated by comparing family-based cancer concordance rates among ethnic groups.

Methods. We used linked California health registries to evaluate the relative cancer risks for first degree relatives of patients diagnosed between ages 0-26, and the relative risks of developing distinct second primary malignancies (SPMs). From 1989-2015, we identified 29,631 cancer patients and 62,863 healthy family members. We calculated the standardized incident ratios (SIRs) of early-onset primary cancers diagnosed in proband siblings and mothers, as well as SPMs detected among early-onset patients. Analyses were stratified by self-identified race/ethnicity.

Results. Given probands with cancer, there were increased relative risks of any cancer for siblings and mothers [SIR=3.32;95% confidence interval (CI):2.85-3.85] and of SPMs (SIR=7.27;95%CI:6.56-8.03). Higher relative risk of any cancer in siblings and mothers given a proband with solid cancer (P<0.05) was observed for both Latinos (SIR=4.98;95%CI:3.82-6.39) and for non-Latino Blacks (SIR=7.35;95%CI:3.36-13.95) compared to non-Latino White subjects (SIR=3.02;95%CI:2.12-4.16). For hematologic cancers, higher familial risk was evident for Asian/Pacific Islanders (SIR=7.56;95%CI:3.26-14.90) compared to non-Latino whites (SIR=2.69;95%CI:1.62-4.20).

Conclusions. The data support a need for increased attention to the genetics of early-onset cancer predisposition and environmental factors in race/ethnic minority families in the US.

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Keywords: Early-onset cancer; Familial risk; Linked cancer registry; Race/ethnicity; Latino Americans; Hispanic paradox.
Key Messages

- We identified 29,631 cancer patients and their 62,863 healthy family members in California from 1989 to 2015.

- The risk of early-onset cancer in siblings and mothers was elevated by having a proband with cancer in the same family.

- The relative risk of early-onset cancers given a proband with solid cancer was higher for Latinos and Blacks when compared to non-Latino Whites.
Introduction

Both genetic and environmental factors play a role in the causes of early-onset cancer. Several well-defined genetic syndromes contribute to early-onset cancer risk, along with a wider array of common alleles that influence risk marginally and detected at the population level. As an example of the former, Li-Fraumeni syndrome caused by mutations in the tumor suppressor gene \textit{TP53}, is associated with an increased risk of a spectrum of cancers diagnosed at early ages\(^1\). An example of low penetrance common genetic variations associated with cancer risk include \textit{IKZF1} and \textit{ARID5B} genes in pediatric acute lymphoblastic leukemia (ALL)\(^2\). Both of these classes of variants may vary in frequency by race/ethnic group and cluster by families\(^3-5\).

Examination of cancer predisposition requires investigation in ethnic strata particularly where cancer incidence rates are known to differ as they do for many pediatric cancer types, such as leukemia\(^6\) and brain cancer\(^7\).

In addition to primary cancers, incidence patterns of second independent malignancies may also provide a perspective of underlying genetic predisposition. Among childhood cancer survivors, more second primary malignancy cases are observed among non-Latino Whites (NLW) than Latino subjects\(^8\). This is also reflected in adult cancers, where Latino breast cancer survivors had lower risk of second cancers than NLW and NL Black women\(^9\).

Germline pathogenic/likely pathogenic variants in cancer predisposition genes are found in approximately 10\% of pediatric cancer patients\(^1,10-12\), and may be inherited or arise \textit{de novo}. Highly penetrant inherited variants will contribute to clustering of cancer cases within the family. Shared environments within the family unit may also be considered alongside genetic risk as potential causes for family-based cancer concordance.
Familial concordance of a wide variety of cancers has been assessed using the Swedish Family-Cancer Database, leading to a deep understanding of familial relative risks. The Victorian Paediatric Cancer Family Study in Australia also explored the cancer risks for relatives of children with cancer in a small population. In the US, the Utah Population database may be the best-known population for studying familial risk. Importantly, these studies largely comprise families of European ancestry, and therefore have not examined potential ethnic-specific familial risks. Here, we utilized linked population registries with over 64,000 individuals to quantify the familial risks (siblings and mothers) and the risks of early-onset second primary malignancies in the highly diverse and large population of California. Risk patterns suggest that race/ethnic minority subjects in the US may harbor a higher burden of familial risks for some types of cancers compared with the majority population – non-Latino whites.
Methods

Source of Data

We used linked population-based registries in California to evaluate the relative risks of early-onset cancers (0-26 years age of onset) for siblings and mothers of children, adolescents, and young adults (AYA) aged 0-26 diagnosed with cancer, as well as the relative risks of early-onset second primary malignancies (SPMs) among the proband patients. The dataset was created by linking information from the California Cancer Registry (CCR) and California Birth Statistical Master File, allowing the capture of siblings and parents of cancer probands, along with their cancer incidence. The linked dataset comprehensively encompassed all cancer cases 0-26 years old, as well as their sibling and mother cancers, diagnosed from 1989 to 2015 in California. Our upper age limit of 26 was set based on the available age range covered by this relatively young cohort. Overall, the dataset included a total of 121 571 individuals. The information on healthy siblings and mothers was available during the whole study period, whereas the information on fathers was not available until 2004 in the birth files and therefore is not included in the current analysis.

For the analysis of cancer familial risks, we included all primary incident cancer cases diagnosed from 1989 to 2015 among patients aged 0-26 years, with patient age-at-diagnosis limited by the study time period for which California maintained a statewide SEER gold-standard cancer registry. For the analysis of secondary cancer risks, we included all SPMs diagnosed over the same years and patient age ranges. Although the CCR only records primary malignancies, some misclassification of relapsed or recurrent disease is possible. A physician (E.N.) reviewed diagnosis codes of all the cases diagnosed after the first primary case to prevent the misclassification of relapsed first primary malignancies (FPMs) as SPMs. For both analyses, we classified the cancers into twelve-broad groups and subgroups as defined by the International Classification of Childhood Cancer, Third edition (ICCC-3, November 2012).
The abbreviations for cancer types are included in Table 1. We also grouped the cancers into hematologic or solid categories in the analyses. Hematologic cancers were defined as leukemias and lymphomas. Solid cancers were defined as CNS tumors, neuroblastomas, retinoblastomas, renal tumors, hepatic tumors, bone tumors, sarcomas, germ cell tumors, epithelial neoplasms and other and unspecified malignant neoplasms.

**Statistical Analysis**

We quantified the relative risks for siblings and mothers, and the relative risks of SPMs by calculating the standardized incident ratios (SIRs) of a given cancer or of SPMs among the healthy siblings, and the SIRs of a given cancer among healthy mothers of probands using a previous published method. We defined a proband as a pediatric or AYA patient with a given cancer. Only one child/AYA in each family can be a proband, so that in families with two or more cases, the proband is defined as the patient with the earliest date of diagnosis. Given a proband with cancer, we calculated the SIRs for a sibling or a mother in the same family for all types of cancers. Separately, we calculated the SIRs for a sibling for the same type of cancer as the proband. We also stratified the analyses by self-identified race/ethnicity of the mother in each family. The SIRs in siblings, mothers or of SPMs can be denoted as:

$$SIR = \frac{O}{E} = \frac{\sum_{i=1}^{N} \sum_{j=1}^{n_{i}} D_{ij}}{\sum_{i=1}^{N} \sum_{j=1}^{n_{i}} \sum_{k=1}^{K_{max}} \lambda_{k}^{ij} t_{ijk}}$$

Where N is the number of families, n_i is the number of non-proband individuals of interest (siblings/SPMs/mothers) in family i, and K_max is the total number of age intervals. The data for each individual includes a disease indicator (D_{ij}) and the number of years “at risk” during the k^{th} age interval (t_{ijk}). A given individual is defined to be at risk beginning at their age when the proband in their family is diagnosed and ending either when they become affected themselves or they are censored due to end of study follow-up. For siblings and mothers, age was stratified...
into seven groups as 0, 0-4, 5-9, 10-14, 15-19, 20-24 and 25-29 years. For the calculation of SIRs within a given race group, $\lambda_k$ is the race-, sex- and age-specific incidence rate of a given cancer. We compared the SIRs across race/ethnic groups with approximate Chi-squared tests. The approximate chi-square method compares the probability of occurrence of events in one group to another, based on a binomial distribution. This comparison is not related to the 95% confidence intervals for the SIRs. We designated that all events occurred right at the middle point of each calendar year. We also stratified the analysis by 5-year age groups. The 95% confidence intervals (CIs) were calculated assuming a Poisson distribution for categories with less than 100 observed cases. For categories with more than 100 observed cases, we adopted the method as indicated by Breslow and Day (1987) to calculate the 95% CIs, as suggested by Washington State Department of Health\textsuperscript{22,23}. Statistical analyses were performed using R software (v 3.6.0). Any two-sided p-value less than 0.05 was considered statistically significant. A supplement is included with this manuscript with more information on the statistical tests and computational codes used. Please access this supplement “Statistics and coding supplement: Familial\_risk\_CCR\_eLife” for more information.

Results

**Demographics of the study population**

From 1989 to 2015, we identified a total of 29,249 pediatric and AYA patients with a primary malignancy, comprising 29,072 probands, 112 affected siblings (from 110 families) and 65 affected mothers. All siblings were diagnosed after the proband’s diagnosis as defined, and 56 (86%) of the 65 mothers were diagnosed after the proband’s diagnosis. We also identified 387 SPMs among all pediatric and AYA probands (Table 2).

**Familial relative risks of early-onset cancers**
Overall, we found a 3.32-fold (95%CI:2.85-3.85) increased relative risk of any cancer among siblings and mothers who have a proband with cancer in the same family. Briefly, we found a 2.97-fold (95%CI:2.30-3.78) increased relative risk of any cancer given a proband with hematologic cancers and a 4.54-fold (95%CI:3.82-5.35) increased relative risk of any cancer given a proband with solid cancers. When stratified by cancer type, higher relative risks among siblings and mothers were observed given probands with leukemias, lymphomas, CNS tumors, retinoblastomas, renal tumors, sarcomas, GCTs, epithelial neoplasms, and other unspecified neoplasms (Figure 1A).

For the relative risk of specific cancer types, we found a 2.68-fold (95%CI:1.68-4.06) increased risk of hematologic cancers among siblings and mothers of a proband with hematologic cancer, and a 6.78-fold (95%CI:5.58-8.16) increased relative risk of solid cancers among siblings and mothers of a proband with solid cancer (Supplementary Table 1). Furthermore, leukemias, lymphomas, CNS tumors, retinoblastoma, sarcomas, GCT, and epithelial neoplasms exhibited statistically significantly increased relative risk for the same type of cancer as the proband (Figure 2 & Supplementary Table 2).

When stratified by more finely defined cancer subtypes, increased relative risks of any cancer for siblings and mothers were observed given a proband with lymphoid leukemia, acute myeloid leukemia, Hodgkin lymphomas, non-Hodgkin lymphomas, astrocytomas, intracranial and intraspinal embryonal tumors, certain gliomas, certain specified intracranial and intraspinal neoplasms, nephroblastoma and other nonepithelial renal tumors, rhabdomyosarcomas, fibrosarcomas, peripheral nerve sheath tumors and other fibrous neoplasms, certain specified soft tissue sarcomas, malignant gonadal germ cell tumors, and certain unspecified carcinomas (Supplementary Table 3).
When stratified by race/ethnicity, the relative risk of any cancer for siblings and mothers given a proband with solid cancer was significantly higher among Latino and non-Latino black subjects than non-Latino White (NLW) subjects [Latino: SIR=4.98;95%CI:3.82-6.39; NLW: SIR=3.02;95%CI:2.12-4.16; \( P=0.019 \)] (Figure 1B). Non-Latino Asians/Pacific Islanders (API) had higher SIRs than NLW given a proband with hematologic cancer (SIR=7.56; 95%CI: 3.26-14.90, \( p=0.023 \) compared to NLW), and non-Latino Blacks had higher SIRs than NLW given a proband with any cancer (SIR=6.96;95%CI:3.71-11.91, \( p=0.002 \) compared to NLW) or solid cancer (SIR=7.35;95%CI: 3.36-13.95, \( p=0.026 \) compares to NLW) (Figure 1B&Supplementary Table 4). For the relative risk of the same category of cancers given a proband with that type of cancer, Latino subjects also showed higher relative risk of solid cancers than NLW subjects [Latino: SIR=7.94;95%CI:5.89-10.47; NLW: SIR=4.41;95%CI:2.99-6.25; \( P=0.012 \)] (Figure 1B& Supplementary Table 1). Data on other minority groups (Asians, non-Latino Blacks) were too sparse to make this comparison.

Relative risks of second primary malignancies

Overall, SPMs among all childhood patients were enriched in families that exhibited familial risks; that is, those families with two or more primary cancer patients. We found 14 SPMs out of 2,432 members (0.58%) in the families that exhibited familial risks (two or more primary cancers), and 373 SPMs out of 119,136 members (0.31%) in families that did not exhibit familial risk (\( p=0.023 \)) (Supplementary Table 5).

For relative risks, we found a 7.27-fold increased risk of SPMs relative to the general population among children/AYAs with a FPM (SIR=7.27;95%CI:6.56-8.03). Most primary cancer types were associated with an elevated relative risk of SPMs (Figure 3A). When stratified by race/ethnicity, a similar relative risk of all SPMs given a proband with cancer was observed among Latino subjects and NLW subjects [Latino: SIR=6.85;95%CI:5.83-8.00; NLW: SIR=6.65;95%CI:5.55-
7.91; \( P=0.869 \) (Figure 3B). The relative risk of all SPMs given a proband with any cancer and solid cancers were higher among Non-Latino API subjects compared to NLW subjects [any cancer, Non-Latino API: SIR=15.41; 95%CI:10.85-21.24; \( P<0.001 \); hematologic cancers, Non-Latino API: SIR=18.90; 95%CI:11.55-29.20; \( P<0.001 \)] (Figure 3B).

For the relative risks of SPMs of the same cancer types as the FPM, we found elevated risks for both hematologic and solid cancers. When stratified by race/ethnicity, similar relative risks were observed among NLW subjects compared to Latino subjects given a proband with hematologic or solid cancer (Supplementary Table 6); numbers were too sparse to compare Asian and non-Latino Blacks.
Discussion

To our knowledge, this is the first study to quantify the familial clustering risks and risks of SPMs among early-onset cancer patients with an emphasis on racial/ethnic differences. Using linked population registry data in the California population, we found that the risk for a sibling child/AYA or mother to have early-onset cancer was elevated once a proband was identified with an early-onset cancer. Likewise, the relative risks for SPMs were elevated among children/AYAs who contracted a first primary cancer. Due to the rarity of childhood cancers, the absolute risk of early-onset cancer is very small, but still higher among young siblings and mothers in the current study (0.074%) compared to general population (0.023%, calculated from SEER) of the same age group. The findings were consistent across race/ethnic groups; however, the magnitude was different. Latinos and non-Latino Blacks had higher sibling/maternal relative risks compared to NLWs for solid cancers, and APIs exhibited a higher risk of hematologic neoplasms.

Consistent with our results, a rich literature with a primary focus on European ancestry populations has reported excessive familial risks of hematologic malignancies\textsuperscript{13}, lymphomas\textsuperscript{24-26}, brain tumors\textsuperscript{27,28}, neuroblastomas\textsuperscript{29}, retinoblastomas\textsuperscript{26,29}, germ cell tumors\textsuperscript{30}, sarcomas\textsuperscript{31} and melanomas\textsuperscript{32}. In terms of secondary cancers, studies have reported excessive risks of second primary malignancies among of survivors of hereditary retinoblastoma\textsuperscript{33}, chronic myeloid leukemia\textsuperscript{34}, chronic lymphocytic leukemia\textsuperscript{35}, Hodgkin's lymphoma\textsuperscript{36}, non- Hodgkin's lymphoma\textsuperscript{37}, and neuroblastoma\textsuperscript{38}. The excessive familial risks of certain cancers are highly likely to be associated with genetic predisposition. The archetypic examples are germline loss-of-function mutations in \textit{RB1}, which are found in ~40% of retinoblastoma cases\textsuperscript{29}, and adrenal cortical cancer, with germline \textit{TP53} mutations accounting for most familial cases\textsuperscript{29}. Low penetrance common genetic variations, for instance in \textit{CEBPE}, \textit{IKZF1}, and \textit{ARID5B} genes in ALL, are associated with cancer risk and may also contribute to familial concordance as combinations of
low frequency alleles or “polygenic risk scores” have been shown to be as impactful as single

strong predisposition mutations in adult cancers\textsuperscript{39,40}, however, their contribution to cancer clustering among children and their families has not yet been studied.

Our data demonstrate a higher degree of familial-based clustering of solid cancers among Latinos and non-Latino Blacks compared to non-Latino Whites, and hematologic cancers among Asian/Pacific Islanders. This familial concordance is likely due to both shared genetic and environmental causes and appears to affect some cancer types differentially by race/ethnicity. Latinos are an admixed population, comprising an ancestral mixture from Native American, European, and African sources; likewise, non-Latino Blacks are admixed with African and smaller levels of European ancestry. Asian/Pacific Islanders constitute a particularly diverse group in California with origins in multiple countries. California Latinos, particularly the youth population are largely from Mexico, and harbor a higher risk of certain cancers particularly pediatric leukemias, the most common cancer in children\textsuperscript{41}; however this higher risk is partially accounted for by a higher frequency of common risk alleles which do not address strong familial predisposition loci\textsuperscript{4} and obviously cannot account for their higher familial risk of solid tumors. Clearly, this higher risk identified in relation to the family units in US minorities has not been systematically studied, and our results here beg for an analysis of comparative sources of genetic and environmental risk that contribute to the higher risk and familial clustering of certain cancers in Latinos, Blacks, and Asian/Pacific Islanders.

Therapy of the first primary cancer is a major factor in the induction of secondary independent malignancies\textsuperscript{42-44}. Multiple primary cancer diagnoses are considered a key feature of hereditary cancer predisposition syndromes\textsuperscript{45}. As such secondary cancers are rare, genetics are still likely to play a strong role\textsuperscript{46}, and our overall SPM results here emphasize a similar patterning as
cancer clustering in first primary malignancies. Of note, our analysis was not designed to
distinguish risk influences from therapies for the primary cancers on secondary cancers.

For some tumor types the germline predisposition was readily noted in this cohort, for example
ten of the fourteen affected relatives who had a proband with retinoblastoma were diagnosed
with the same cancer, an unsurprising finding given that germline RB1 mutations account for a
significant proportion of retinoblastoma are highly penetrant and those tumors tend to be
diagnosed young. We also observed increased relative risks for sarcomas given a proband with
leukemias, suggesting the presence of families with Li-Fraumeni syndrome, which is
characterized by a spectrum of childhood and adult-onset cancers including adrenocortical
carcinoma, breast cancer, CNS tumors, sarcomas, and leukemia45.

Population-level selection pressures are thought to influence the relative frequencies of alleles.
For instance, genetic adaptations that shaped the Native American genome to cold and warm
environments47, and immune response following colonization by Europeans48. Our result
suggests that some adaptive selection pressures, or simply genetic drift, in specific ethnic
groups may differentially influence familial cancer clustering as it does for immune and
metabolic phenotypes among several ethnic groups49,50. If replicated in other study settings, this
contrast between genetic risk of child and adult onset cancers by ethnicity should be studied
further for a fuller understanding of familial risks.

Our analyses capitalized on the highly diverse population in California, allowing us to quantify
the relative risks across different ethnic groups. Moreover, the utilization of linked population-
based registries in California enabled us to minimize the selection and information biases
introduced by a case-control study design or other strategies that only sample portions of the
population. There are also some limitations of our study. Despite the large number of total
cancer cases, the number of affected siblings and second primaries are very small for some
cancer types, thus limiting the power to detect significant relative risks. Also, we are unable to
track cancer incidence for affected siblings, maternal cancers, and SPMs that may have been
diagnosed outside of California. In addition, the follow-up time of 26 years is not enough for a
comprehensive detection of SPMs in the probands, nor for cancers arising in proband mothers
at older ages. These insufficient follow-up time and loss-to-follow-up issues have limited our
ability to quantify the relative risks among mothers with cancer onset at older ages (>40 yrs).
Furthermore, it is likely that the low number of mothers with cancer is a result of bias against
some very strong cancer predispositions, so the patients could not survive long enough or be
healthy enough to reproduce. Lastly, the lack of records on fathers reduces our ability to
quantify the relative risks among other first-degree relatives and may reduce the appreciation of
the potential contribution of high-risk cancer predisposition syndromes which can be inherited
from either parent.

Accepting those limitations with the current dataset, our study has several important implications
that may open windows to future research. First, the genetic predispositions driving the
excessive early-onset cancer risks among the Latino, non-Latino Black and Asian populations,
whether from higher frequencies of known cancer predisposition syndromes or mutations in
novel genes, or a higher burden of common or rare genetic risk alleles, warrants further
investigation. Second, the comparative attributable fraction of familial risk based on
environmental risk factors interacting with genetic predispositions warrants further investigation.
Lastly, descriptive studies on familial and secondary cancer risks among race/ethnic groups
other than non-Latino Whites may provide additional insights into cancer incidence variation
leading to incidence disparities by race/ethnicity, and provide critical information for tailoring
appropriate messages for familial genetic counseling.

(3199 words)
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**Declaration of interests**

None.

**List of Supplementary materials**

Supplementary File

Source Code File
1. Saletta F, Dalla Pozza L, Byrne JA. Genetic causes of cancer predisposition in children and adolescents. *Transl Pediatr*. 2015;4(2):67-75.

2. Moriyama T, Relling MV, Yang JJ. Inherited genetic variation in childhood acute lymphoblastic leukemia. *Blood*. 2015;125(26):3988-3995.

3. Caswell-Jin JL, Gupta T, Hall E, et al. Racial/ethnic differences in multiple-gene sequencing results for hereditary cancer risk. *Genet Med*. 2018;20(2):234-239.

4. Walsh KM, Chokkalingam AP, Hsu LI, et al. Associations between genome-wide Native American ancestry, known risk alleles and B-cell ALL risk in Hispanic children. *Leukemia*. 2013;27(12):2416-2419.

5. Ricker C, Culver JO, Lowstuter K, et al. Increased yield of actionable mutations using multi-gene panels to assess hereditary cancer susceptibility in an ethnically diverse clinical cohort. *Cancer Genet*. 2016;209(4):130-137.

6. Feng Q, de Smith AJ, Vergara-Lluri M, et al. Trends in Acute Lymphoblastic Leukemia Incidence in the US from 2000-2016: an Increased Risk in Latinos Across All Age Groups. In. *Am J Epidemiol*. Vol In press2020.

7. Ostrom QT, Adel Fahmideh M, Cote DJ, et al. Risk factors for childhood and adult primary brain tumors. *Neuro Oncol*. 2019;21(11):1357-1375.

8. Brown AL, Arroyo VM, Agrusa JE, Scheurer ME, Gramatges MM, Lupo PJ. Survival disparities for second primary malignancies diagnosed among childhood cancer survivors: A population-based assessment. *Cancer*. 2019;125(20):3623-3630.

9. Calip GS, Law EH, Ko NY. Racial and ethnic differences in risk of second primary cancers among breast cancer survivors. *Breast Cancer Res Treat*. 2015;151(3):687-696.

10. Zhang J, Walsh MF, Wu G, et al. Germline Mutations in Predisposition Genes in Pediatric Cancer. *N Engl J Med*. 2015;373(24):2336-2346.

11. Plon SE, Lupo PJ. Genetic Predisposition to Childhood Cancer in the Genomic Era. *Annu Rev Genomics Hum Genet*. 2019;20:241-263.

12. Ripperger T, Bielack SS, Borkhardt A, et al. Childhood cancer predisposition syndromes—A concise review and recommendations by the Cancer Predisposition Working Group of the Society for Pediatric Oncology and Hematology. *Am J Med Genet A*. 2017;173(4):1017-1037.

13. Sud A, Chattopadhyay S, Thomsen H, et al. Analysis of 153,115 patients with hematological malignancies refines the spectrum of familial risk. *Blood*. 2019;134(12):960-969.

14. Kharazmi E, Fallah M, Sundquist K, Hemminki K. Familial risk of early and late onset cancer: nationwide prospective cohort study. *BMJ*. 2012;345:e8076.

15. Hemminki K, Czene K. Attributable risks of familial cancer from the Family-Cancer Database. *Cancer Epidemiol Biomarkers Prev*. 2002;11(12):1638-1644.

16. Heath JA, Smibert E, Algar EM, Dite GS, Hopper JL. Cancer risks for relatives of children with cancer. *J Cancer Epidemiol*. 2014;2014:806076.

17. Curtin K, Smith KR, Fraser A, Pimentel R, Kohlmann W, Schiffman JD. Familial risk of childhood cancer and tumors in the Li-Fraumeni spectrum in the Utah Population Database: implications for genetic evaluation in pediatric practice. *Int J Cancer*. 2013;133(10):2444-2453.

18. Kohli DR, Smith KR, Wong J, et al. Familial pancreatic cancer risk: a population-based study in Utah. *J Gastroenterol*. 2019;54(12):1106-1112.

19. Samadder NJ, Curtin K, Wong J, et al. Epidemiology and familial risk of synchronous and metachronous colorectal cancer: a population-based study in Utah. *Clin Gastroenterol Hepatol*. 2014;12(12):2078-2084 e2071-2072.
20. Wang X, Harmon J, Zabrieskie N, et al. Using the Utah Population Database to assess familial risk of primary open angle glaucoma. *Vision Res.* 2010;50(23):2391-2395.

21. Goldgar DE, Easton DF, Cannon-Albright LA, Skolnick MH. Systematic population-based assessment of cancer risk in first-degree relatives of cancer probands. *J Natl Cancer Inst.* 1994;86(21):1600-1608.

22. Guidelines for Using Confidence Intervals for Public Health Assessment. Washington State Department of Health. [https://www.doh.wa.gov/Portals/1/Documents/1500/ConfIntGuide.pdf](https://www.doh.wa.gov/Portals/1/Documents/1500/ConfIntGuide.pdf). Published 2012. Accessed March 29, 2021.

23. Breslow NE, Day NE. Statistical methods in cancer research. Volume II--The design and analysis of cohort studies. *IARC Sci Publ.* 1987(82):1-406.

24. Cerhan JR, Slager SL. Familial predisposition and genetic risk factors for lymphoma. *Blood.* 2015;126(20):2265-2273.

25. Fallah M, Kharazmi E, Pukkala E, et al. Familial risk of non-Hodgkin lymphoma by sex, relationship, age at diagnosis and histology: a joint study from five Nordic countries. *Leukemia.* 2016;30(2):373-378.

26. Madanat-Harjuoja LM, Pitkaniemi J, Hirvonen E, Malila N, Diller LR. Linking population-based registries to identify familial cancer risk in childhood cancer. *Cancer.* 2020;126(13):3076-3083.

27. Couldwell WT, Cannon-Albright LA. A description of familial clustering of meningiomas in the Utah population. *Neuro Oncol.* 2017;19(12):1683-1687.

28. Crump C, Sundquist J, Sieh W, Winkleby MA, Sundquist K. Perinatal and familial risk factors for brain tumors in childhood through young adulthood. *Cancer Res.* 2015;75(3):576-583.

29. Kamihara J, Bourdeaut F, Foulkes WD, et al. Retinoblastoma and Neuroblastoma Predisposition and Surveillance. *Clin Cancer Res.* 2017;23(13):e98-e106.

30. Landero-Huerta DA, Vigueras-Villasenor RM, Yokoyama-Rebollar E, et al. Epigenetic and risk factors of testicular germ cell tumors: a brief review. *Front Biosci (Landmark Ed).* 2017;22:1073-1098.

31. Lynch HT, Deters CA, Hogg D, Lynch JF, Kinarsky Y, Gatalica Z. Familial sarcoma: challenging pedigrees. *Cancer.* 2003;98(9):1947-1957.

32. Frank C, Sundquist J, Hemminki A, Hemminki K. Risk of other Cancers in Families with Melanoma: Novel Familial Links. *Sci Rep.* 2017;7:42601.

33. Marees T, Moll AC, Imhof SM, de Boer MR, Ringens PJ, van Leeuwen FE. Risk of second malignancies in survivors of retinoblastoma: more than 40 years of follow-up. *J Natl Cancer Inst.* 2008;100(24):1771-1779.

34. Sasaki K, Kantarjian HM, O'Brien S, et al. Incidence of second malignancies in patients with chronic myeloid leukemia in the era of tyrosine kinase inhibitors. *Int J Hematol.* 2019;109(5):545-552.

35. Molica S. Second neoplasms in chronic lymphocytic leukemia: incidence and pathogenesis with emphasis on the role of different therapies. *Leuk Lymphoma.* 2005;46(1):49-54.

36. Baker H. Second cancer risk for Hodgkin's lymphoma survivors. *Lancet Oncol.* 2016;17(2):e50.

37. Chattopadhyay S, Sud A, Zheng G, et al. Second primary cancers in non-Hodgkin lymphoma: Bidirectional analyses suggesting role for immune dysfunction. *Int J Cancer.* 2018;143(10):2449-2457.

38. Applebaum MA, Henderson TO, Lee SM, Pinto N, Volchenboum SL, Cohn SL. Second malignancies in patients with neuroblastoma: the effects of risk-based therapy. *Pediatr Blood Cancer.* 2015;62(1):128-133.
39. Fantus RJ, Helfand BT. Germline Genetics of Prostate Cancer: Time to Incorporate Genetics into Early Detection Tools. *Clin Chem.* 2019;65(1):74-79.

40. Yadav S, Couch FJ. Germline Genetic Testing for Breast Cancer Risk: The Past, Present, and Future. *Am Soc Clin Oncol Educ Book.* 2019;39:61-74.

41. Barrington-Trimis JL, Cockburn M, Metayer C, Gauderman WJ, Wiemels J, McKean-Cowdin R. Trends in childhood leukemia incidence over two decades from 1992 to 2013. *Int J Cancer.* 2017;140(5):1000-1008.

42. McNerney ME, Godley LA, Le Beau MM. Therapy-related myeloid neoplasms: when genetics and environment collide. *Nat Rev Cancer.* 2017;17(9):513-527.

43. Mazonakis M, Kachris S, Damilakis J. Second Cancer Risk from Radiation Therapy for Common Solid Tumors Diagnosed in Reproductive-Aged Females. *Radiat Prot Dosimetry.* 2018;182(2):208-214.

44. Turcotte LM, Liu Q, Yasui Y, et al. Chemotherapy and Risk of Subsequent Malignant Neoplasms in the Childhood Cancer Survivor Study Cohort. *J Clin Oncol.* 2019;37(34):3310-3319.

45. Valdez JM, Nichols KE, Kesserwan C. Li-Fraumeni syndrome: a paradigm for the understanding of hereditary cancer predisposition. *Br J Haematol.* 2017;176(4):539-552.

46. Churpek JE, Marquez R, Neistadt B, et al. Inherited mutations in cancer susceptibility genes are common among survivors of breast cancer who develop therapy-related leukemia. *Cancer.* 2016;122(2):304-311.

47. Reynolds AW, Mata-Miguez J, Miro-Herrans A, et al. Comparing signals of natural selection between three Indigenous North American populations. *Proc Natl Acad Sci U S A.* 2019;116(19):9312-9317.

48. Lindo J, Huerta-Sanchez E, Nakagome S, et al. A time transect of exomes from a Native American population before and after European contact. *Nat Commun.* 2016;7:13175.

49. O'Fallon BD, Fehren-Schmitz L. Native Americans experienced a strong population bottleneck coincident with European contact. *Proc Natl Acad Sci U S A.* 2011;108(51):20444-20448.

50. Vatsiou AI, Bazin E, Gaggiotti OE. Changes in selective pressures associated with human population expansion may explain metabolic and immune related pathways enriched for signatures of positive selection. *BMC Genomics.* 2016;17:504.
### Tables

Table 1. Abbreviations of the twelve broad groups defined by the International Classification of Childhood Cancer, Third edition.

| Abbreviation | Definition                                      |
|--------------|------------------------------------------------|
| Leukemias    | I. Leukemias, myeloproliferative diseases, and myelodysplastic diseases |
| Lymphomas    | II. Lymphomas and reticuloendothelial neoplasms |
| CNS tumors   | III. CNS and miscellaneous intracranial and intraspinal neoplasms |
| Neuroblastomas | IV. Neuroblastoma and other peripheral nervous cell tumors |
| Retinoblastoma | V. Retinoblastoma |
| Renal tumors | VI. Renal tumors |
| Hepatic tumors | VII. Hepatic tumors |
| Bone tumors  | VIII. Malignant bone tumors |
| Sarcomas     | IX. Soft tissue and other extraosseous sarcomas |
| GCT          | X. Germ cell tumors, trophoblastic tumors, and neoplasms of gonads |
| Epithelial neoplasms | XI. Other malignant epithelial neoplasms and malignant melanomas |
| Other        | XII. Other and unspecified malignant neoplasms |

*Cancers were classified into groups as defined by the International Classification of Childhood Cancer, Third edition (ICCC-3, November 2012)* [https://seer.cancer.gov/icc3/iccc3.html](https://seer.cancer.gov/icc3/iccc3.html).
Table 2. Selected demographic characteristic of probands, affected siblings and second primary malignancies among the early-onset cancer patients in the linked population-based registries in California, 1989 to 2015.

| Overall * | No. of probands | No. of affected siblings | No. of affected mothers | No. of second primaries † |
|-----------|-----------------|--------------------------|-------------------------|--------------------------|
| Overall 29,249 | 29,072 | 112 | 65 | 387 |
| Age at diagnosis (years) ‡ | | | | |
| 0 | 2592 (8.75) | 2611 (8.98) | 10 (8.93) | 0 (0.00) |
| 1-4 | 8683 (29.3) | 8719 (29.99) | 15 (13.39) | ≤5 (3.08) |
| 5-9 | 5054 (17.06) | 5057 (17.39) | 12 (10.71) | 0 (0.00) |
| 10-14 | 4224 (14.26) | 4180 (14.38) | 22 (19.64) | 0 (0.00) |
| 15-19 | 4734 (15.98) | 4664 (16.04) | 37 (33.04) | 7 (10.77) |
| 20+ | 4344 (14.66) | 3841 (13.21) | 16 (14.29) | 56 (86.15) |
| Gender | | | | |
| Male | 15,528 (52.40) | 15,467 (53.20) | 56 (50.00) | NA |
| Female | 14,102 (47.59) | 13,605 (46.80) | 56 (50.00) | 65 (100.00) |
| Race/ethnicity | | | | |
| Latino (all races) | 13,281 (44.82) | 13,059 (44.92) | 51 (45.54) | 26 (40.00) |
| Non-Latino White | 11,410 (38.51) | 11,193 (38.50) | 39 (34.82) | 17 (26.15) |
| Non-Latino Black | 1772 (5.98) | 1716 (5.90) | 9 (8.04) | 7 (10.77) |
| Asian/Pacific Islander | 2605 (8.79) | 2551 (8.77) | 12 (10.71) | 0 (0.00) |
| Other | 563 (1.94) | 553 (1.90) | ≤5 (0.89) | 15 (4.62) |

* All early-onset cancer patients diagnosed from 1989 to 2015 identified in the linked population-based registries in California.
† Number of second primary malignancies diagnosed from 1989 to 2015 within all children (probands and affected siblings, excluding mothers) with early-onset cancers in the linked population-based registries in California.
Figures

Figure legend:

Figure 1: Relative risks of early-onset cancers among siblings and mothers.
A. Relative risks among siblings and mothers of any early-onset cancer (diagnosed under 26 years of age) given a proband with cancer, 1989 to 2015, California, USA.
B. Relative risks by ethnic group among siblings and mothers of any early-onset cancer (diagnosed under 26 years of age) given a proband with cancer, 1989 to 2015, California, USA.

Cancers were classified into groups as defined by the International Classification of Childhood Cancer, Third edition (ICCC-3, November 2012) (https://seer.cancer.gov/iccc/iccc3.html).

Hematologic cancers include leukemias and lymphomas. Solid cancers include CNS tumors, neuroblastomas, retinoblastomas, renal tumors, hepatic tumors, bone tumors, sarcomas, GCT, epithelial neoplasms and others.

The axis for SIR was natural log-transformed. SIR and 95% CI were not calculatable for cancers with zero observed case.

P was calculated assuming a Poisson distribution.

Abbreviations: SIR, Standardized incidence ratio. CI, confidence interval. API, Asian/Pacific Islander.

Figure 2: Relative risks of siblings and mothers of specific cancers.

Cancers were classified into groups as defined by the International Classification of Childhood Cancer, Third edition (ICCC-3, November 2012) (https://seer.cancer.gov/iccc/iccc3.html).

Standardized incidence ratios greater than 10 were recoded to 10.

Siblings and mothers of a proband were diagnosed with cancer from 1989 to 2015 at 0 to 26 years of age.

P was calculated assuming a Poisson distribution.

Abbreviations: SIR, Standardized incidence ratio. CI, confidence interval. GCT, germ cell tumors, trophoblastic tumors, and neoplasms of gonads.

Figure 3. Relative risks of second primary malignancies.
A. Relative risks of second primary malignancies of any early-onset cancer (diagnosed under 26 years of age) given a proband with cancer, 1989 to 2015, California, USA.
B. Relative risks of second primary malignancies of any early-onset cancer (diagnosed under 26 years of age) given a proband with cancer by ethnic group, 1989 to 2015, California, USA.

Cancers were classified into groups as defined by the International Classification of Childhood Cancer, Third edition (ICCC-3, November 2012) (https://seer.cancer.gov/iccc/iccc3.html).

Hematologic cancers include leukemias and lymphomas. Solid cancers include CNS tumors, neuroblastomas, retinoblastomas, renal tumors, hepatic tumors, bone tumors, sarcomas, GCT, epithelial neoplasms and others.

The axis for SIR was natural log-transformed. SIR and 95% CI were not calculatable for cancers with zero observed case.

P was calculated assuming a Poisson distribution.

Abbreviations: SIR, Standardized incidence ratio. CI, confidence interval. FPM, first primary malignancy. SPM, second primary malignancy. API, Asian/Pacific Islander.
### Fig. 1

#### A.

| Group            | No. of probands | No. of affected siblings and mothers | SIR of any cancer (95% CI) |
|------------------|-----------------|--------------------------------------|---------------------------|
| Overall          | 29072           | 177                                  | 3.32 (2.85, 3.85)         |
| Hematologic cancers | 11404         | 66                                   | 2.97 (2.30, 3.78)         |
| Solid cancers    | 17849           | 141                                  | 4.54 (3.82, 5.35)         |
| Hematologic cancers |             |                                       |                           |
| Leukemias        | 8500            | 51                                   | 2.87 (2.14, 3.78)         |
| Lymphomas        | 2928            | 21                                   | 4.66 (2.89, 7.13)         |
| Solid cancers    |                 |                                       |                           |
| CNS tumors       | 5739            | 38                                   | 3.50 (2.48, 4.8)          |
| Neuroblastomas   | 1445            | 7                                    | 2.01 (0.81, 4.15)         |
| Retinoblastomas  | 718             | 14                                   | 8.03 (4.39, 13.48)        |
| Renal tumors     | 1069            | 9                                    | 3.62 (1.66, 6.88)         |
| Hepatic tumors   | 414             | less than or equal to 5              | 2.20 (0.27, 7.94)         |
| Bone tumors      | 249             | less than or equal to 5              | 5.59 (0.68, 20.18)        |
| Sarcomas         | 2915            | 40                                   | 7.85 (5.61, 10.69)        |
| GCT              | 2423            | 20                                   | 5.97 (3.65, 9.22)         |
| Epithelial neoplasms | 3050         | 36                                   | 12.51 (8.76, 17.32)       |
| Other            | 255             | less than or equal to 5              | 9.17 (2.50, 23.49)        |

#### B.

| Group              | Ethnicity      | SIR (95% CI)     | P comparing SIRs to Non-Latino White |
|--------------------|----------------|------------------|--------------------------------------|
| Overall            | Non-Latino White | 2.60 (1.93, 3.43) |                                     |
|                    | Latino all races  | 3.36 (2.66, 4.19) | 0.183                                |
|                    | Non-Latino API   | 4.58 (2.29, 8.20) | 0.128                                |
|                    | Non-Latino Black  | 6.96 (3.71, 11.91)| 0.002                                |
| Hematologic cancers| Non-Latino White  | 2.69 (1.62, 4.20) |                                     |
|                    | Latino all races  | 2.48 (1.64, 3.61) | 0.91                                 |
|                    | Non-Latino API   | 7.56 (3.26, 14.90)| 0.023                                |
|                    | Non-Latino Black  | 6.14 (1.67, 15.73)| 0.242                                |
| Solid cancers      | Non-Latino White  | 3.02 (2.12, 4.16) |                                     |
|                    | Latino all races  | 4.98 (3.82, 6.39) | 0.019                                |
|                    | Non-Latino API   | 5.07 (2.04, 10.44)| 0.306                                |
|                    | Non-Latino Black  | 7.35 (3.36, 13.95)| 0.026                                |
Fig. 3

A.

| Group               | No. of FPMs | No. of SPMs | SIR of any cancer (95% CI) |
|---------------------|-------------|-------------|---------------------------|
| Overall             | 30,059      | 387         | 7.27 (6.56, 8.03)         |
| Hematologic cancers | 11,553      | 146         | 6.57 (5.54, 7.72)         |
| Solid cancers       | 18,893      | 241         | 7.75 (6.80, 8.80)         |
| Hematologic cancers |             |             |                           |
| Leukemias           | 8,543       | 116         | 6.53 (5.40, 7.83)         |
| Lymphomas           | 2,960       | 30          | 6.66 (4.50, 9.51)         |
| Solid cancers       |             |             |                           |
| CNS tumors          | 5,877       | 64          | 5.89 (4.54, 7.52)         |
| Neuroblastomas      | 1,450       | 24          | 6.91 (4.43, 10.28)        |
| Retinoblastomas     | 728         | 24          | 13.77 (8.82, 20.49)       |
| Renal tumors        | 1,078       | 13          | 5.24 (2.79, 8.95)         |
| Hepatic tumors      | 417         | less than or equal to 5 | 5.49 (1.78, 12.82) |
| Bone tumors         | 250         | 8           | 22.35 (9.65, 44.03)       |
| Sarcomas            | 3,028       | 68          | 13.35 (10.37, 16.93)      |
| GCT                 | 2,468       | 13          | 3.88 (2.07, 6.63)         |
| Epithelial neoplasms| 3,479       | 21          | 7.30 (4.52, 11.15)        |
| Other               | 261         | less than or equal to 5 | 2.29 (0.06, 12.78) |

B.

| Group               | Ethnicity     | SIR (95% CI)                      | P comparing SIRs to Non-Latino White |
|---------------------|---------------|-----------------------------------|--------------------------------------|
| Overall             | Non-Latino White | 6.65 (5.55, 7.91)                |                                      |
|                     | Latino all races | 6.85 (5.83, 8.00)                | 0.869                                |
|                     | Non-Latino API  | 15.41 (10.85, 21.24)             | <0.001                               |
|                     | Non-Latino Black | 5.36 (2.57, 9.85)                | 0.609                                |
| Hematologic cancers | Non-Latino White | 5.80 (4.16, 7.87)                |                                      |
|                     | Latino all races | 5.61 (4.29, 7.21)                | 0.949                                |
|                     | Non-Latino API  | 18.90 (11.55, 29.20)             | <0.001                               |
|                     | Non-Latino Black | 6.14 (1.67, 15.73)               | 0.874                                |
| Solid cancers       | Non-Latino White | 7.09 (5.68, 8.75)                |                                      |
|                     | Latino all races | 7.87 (6.39, 9.60)                | 0.525                                |
|                     | Non-Latino API  | 12.31 (7.17, 19.71)              | 0.052                                |
|                     | Non-Latino Black | 4.90 (1.80, 10.66)               | 0.483                                |