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Authors

Wang, Rong
Metayer, Catherine
Morimoto, Libby
[et al.](#)

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Original Contribution

Parental Age and Risk of Pediatric Cancer in the Offspring: A Population-Based Record-Linkage Study in California

Rong Wang, Catherine Metayer, Libby Morimoto, Joseph L. Wiemels, Juan Yang, Andrew T. DeWan, Alice Kang, and Xiaomei Ma*

* Correspondence to Dr. Xiaomei Ma, Yale School of Public Health, 60 College Street, PO Box 208034, New Haven, CT 06520-8034 (e-mail: xiaomei.ma@yale.edu).

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Linking birth records and cancer registry data from California, we conducted a population-based study with 23,419 cases and 87,593 matched controls born during 1978–2009 to investigate the relationship of parental age to risk of pediatric cancer. Compared with children born to mothers aged 20–24 years, those born to mothers in older age groups had a 13%–36% higher risk of pediatric cancer; the odds ratio for each 5-year increase in maternal age was 1.06 (95% confidence interval (CI): 1.04, 1.09). For cancer diagnosed in children in age groups 0–14 years and 15–19 years, the odds ratios for each 5-year increase in maternal age were 1.05 (95% CI: 1.02, 1.07) and 1.14 (95% CI: 1.09, 1.19), respectively. Having an older father also conferred an increased risk, with an odds ratio for each 5-year increase of 1.03 (95% CI: 1.02, 1.05) for cancer diagnosed at ages 0–19 years and 1.03 (95% CI: 1.02, 1.05) for cancer diagnosed at ages 0–14 years. While advancing maternal age increased risk of leukemia and central nervous system tumors, older paternal age was not associated with risk of either type. Both maternal and paternal older ages were associated with risk of lymphoma. In this large, population-based record-linkage study, advancing parental age, especially advancing maternal age, was associated with higher pediatric cancer risk, with variations across types of cancer.

adolescent; case-control study; children; parental age; pediatric cancer

Abbreviations: CCR, California Cancer Registry; CI, confidence interval; CNS, central nervous system; OR, odds ratio.

Approximately 16,000 new cases of pediatric cancer (in persons aged 0–19 years) are diagnosed in the United States annually (1), with few well-established risk factors, including certain genetic conditions, ionizing radiation, prior chemotherapy, male predominance, and white race (2–4).

In the United States, the age at which individuals give birth to children has been rising. The average age of first-time mothers was 21.4 years in 1970 (5), 24.9 years in 2000 (5), and 26.3 years in 2014 (6). The average age of fathers at the birth of their first child increased from 25.3 years during 1987–1988 to 29.4 years during 2006–2010 (7). Over the period of 1975–2012, the incidence of pediatric cancer rose at an annual rate of 0.6% (8). Although similar temporal trends in parental age and pediatric cancer incidence do not necessarily suggest an association between the two, it is plausible that parental age plays a role in the etiology of pediatric

cancer. Genomic sequencing studies in parent-offspring trios have found a higher number of de novo mutations in the offspring of older parents (9–11), and accumulation of germ-cell mutations may increase cancer risk (12). In addition, older parental age correlated with decreased DNA methylation level in newborns; many of the loci where methylation changes occurred have been linked to oncogenesis (13).

The potential relationship of parental age to risk of pediatric cancer has been examined previously, but the findings are inconsistent (14–21). Although 2 of these studies included over 10,000 cases (14, 15), most existing studies had limited or moderate sample sizes. To elucidate the etiologic role of parental age, we conducted a population- and record-based case-control study with an unprecedented sample size and a low likelihood of bias, evaluating all pediatric cancer as a group as well as by age at diagnosis and types of cancer

(e.g., leukemia, central nervous system (CNS) tumors). The racial/ethnic diversity of our study population also enabled us to assess the relationship of parental age to pediatric cancer risk according to race/ethnicity, which had not been evaluated in previous studies.

METHODS

Study population

We linked statewide birth records maintained by the California Department of Public Health for the years of 1978–2009 to cancer diagnosis data for the years of 1988–2011 from the California Cancer Registry (CCR). Beginning in January 1988, California law has required that all new cancer cases diagnosed in state residents be reported to the CCR. CCR data meet all standards of the Surveillance, Epidemiology, and End Results Program and National Program of Cancer Registries for quality, timeliness, and completeness (22). Included in this analysis were children born in California and diagnosed with cancer at the ages of 0–19 years. Children who were born in California during the same period and did not have cancer cases reported to CCR were considered potential controls. For each cancer case, up to 4 controls were randomly selected from the pool of potential controls and matched to the case on birth year and month, sex, and race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic/Latino, Asian/Pacific Islander, other). The study protocol was approved by the institutional review boards at the California Health and Human Services Agency, University of California (Berkeley and San Francisco), and Yale University.

From the 24,734 cases that were identified, we excluded cases: 1) whose mothers resided outside California at the time of delivery (out of concern that these children might not have been reported to the CCR had they developed pediatric cancer) ($n = 18$); 2) who were reported as having Down syndrome, an established, strong risk factor for childhood leukemia (23) ($n = 85$); 3) whose birth records did not include information on maternal or paternal age, the primary exposure of interest ($n = 1,094$); and 4) who had missing data on other variables that might reflect a less than optimal quality of birth record, including birth weight ($n = 10$), birth order ($n = 58$), mode of delivery (vaginal versus cesarean, $n = 37$), plurality (single or multiple birth, $n = 1$), or mother's country of birth ($n = 11$). The final number of cases after exclusions was 23,420. The same exclusion criteria were applied to the 93,667 matched control subjects selected for the 23,420 cases, and 87,593 controls remained after exclusions. One case without matched controls was further excluded. The final sample consisted of 23,419 cases and 87,593 individually matched controls. Each case had at least 1 matched control, and about 77% of cases had 4 matched controls.

Variables of interest

Both maternal and paternal ages (in years) were abstracted from birth records and categorized into 5-year age groups (<20 years, 20–24 years, 25–29 years, 30–34 years, 35–39 years, ≥ 40 years). To account for potential confounding by other infant and parental characteristics, we also abstracted data

on birth weight, length of gestation, birth order, mode of delivery, plurality, maternal country of birth, maternal smoking during pregnancy, maternal history of miscarriage or still-birth (i.e., fetal loss <20 or ≥ 20 weeks of gestation), maternal education, and paternal education.

Statistical analysis

Mean values and standard deviations were calculated for parental age. Pearson's χ^2 test was used to compare characteristics between cases and controls. Odds ratios and 95% confidence intervals were obtained from conditional logistic regression models. Maternal and paternal ages were modeled as categories (5-year age groups), using the age group of 20–24 years as a referent. Parental ages as continuous variables were used to assess possible trends. Both maternal and paternal ages were included in the models simultaneously. All factors/characteristics listed in Table 1 were considered potential confounding variables in the initial model, but only covariates that had a P value of less than 0.05 after using the SAS (SAS Institute, Inc., Cary, North Carolina) stepwise function were retained in the final model. These included birth weight (grams: <2,500, 2,500–2,999, 3,000–3,499, 3,500–3,999, $\geq 4,000$), length of gestation (weeks: 22–36, 37–41, 42–44, or unknown), birth order (first, second, third or higher), maternal country of birth (United States, foreign countries), maternal smoking during pregnancy (no, yes, or unknown), and maternal and paternal education (up to 8th grade, 9–12th grade, at least some college, or unknown).

In the United States, cancers in the pediatric population have traditionally been categorized in 2 different age groups: 0–14 years and 0–19 years. We conducted the analyses separately for age groups 0–14 years and 15–19 years so our results could be compared with those from previous studies, most of which focused on the younger age group of 0–14 years. Additionally, we conducted analyses in children diagnosed with cancer at the age of 0–5 years (early childhood), because a pooled analysis by Johnson et al. (14) reported a stronger association between advancing maternal age and cancer risk in younger children.

Because the California population is diverse in terms of race and ethnicity, we also conducted subgroup analyses for different racial/ethnic groups, including non-Hispanic white, non-Hispanic black, Hispanic/Latino, and Asian/Pacific Islander. The likelihood ratio test was used to assess whether a statistical interaction existed between race/ethnicity and parental age.

In addition to analyzing pediatric cancer as a group, we conducted separate analyses for 11 major diagnostic groups in the *International Classification of Childhood Cancer, Third Edition* (24), as well as major subtypes of the 3 most common diagnostic groups: leukemia, lymphoma, and CNS tumors.

For different subgroup analyses, the covariates selected by the SAS (SAS Institute, Inc.) stepwise function were not always the same. We compared the odds ratios for parental age, the primary exposure of interest, from the model that included covariates selected for the analysis of overall pediatric cancer and the model that included covariates selected for any specific subgroup analysis. Because the results were

Table 1. Characteristics of the Study Population, California, 1978–2009

Characteristic	Case Group (n = 23,419)		Control Group (n = 87,593)		P Value
	No. of Individuals	% ^a	No. of Individuals	% ^a	
Maternal age, years					<0.01
<20	2,084	8.9	8,780	10.0	
20–24	5,434	23.2	22,405	25.6	
25–29	7,070	30.2	25,660	29.3	
30–34	5,632	24.0	19,915	22.7	
35–39	2,578	11.0	8,985	10.3	
≥40	621	2.7	1,848	2.1	
Paternal age, years					<0.01
<20	817	3.5	3,655	4.2	
20–24	4,094	17.5	16,800	19.2	
25–29	6,454	27.6	24,512	28.0	
30–34	6,180	26.4	22,254	25.4	
35–39	3,692	15.8	13,119	15.0	
≥40	2,182	9.3	7,253	8.3	
Sex					0.83
Female	10,557	45.1	39,418	45.0	
Male	12,862	54.9	48,175	55.0	
Race/ethnicity					0.40
Non-Hispanic white	9,851	42.1	37,325	42.6	
Non-Hispanic black	1,448	6.2	5,213	6.0	
Hispanic	9,743	41.6	36,116	41.2	
Asian/Pacific Islander	2,107	9.0	7,965	9.1	
Other	270	1.2	974	1.1	
Birth weight, g					<0.01
<2,500	1,313	5.6	5,067	5.8	
2,500–2,999	8,316	35.5	32,173	36.7	
3,000–3,499	3,261	13.9	13,151	15.0	
3,500–3,999	7,436	31.8	27,071	30.9	
≥4,000	3,093	13.2	10,131	11.6	
Gestational age, weeks					0.24
22–36	2,251	9.6	8,085	9.2	
37–41	17,585	75.1	65,891	75.2	
42–44	2,118	9.0	7,946	9.1	
Unknown	1,465	6.3	5,671	6.5	
Birth order					0.37
First	9,233	39.4	34,836	39.8	
Second	7,596	32.4	27,991	32.0	
Third or higher	6,590	28.1	24,766	28.3	
Mode of delivery					<0.01
Vaginal	17,735	75.7	67,401	76.9	
Cesarean	5,684	24.3	20,192	23.1	
Plurality					0.41
Singleton	22,874	97.7	85,473	97.6	
Multiple	545	2.3	2,120	2.4	
Maternal country of birth					<0.01
United States	14,988	64.0	54,269	62.0	
Foreign	8,431	36.0	33,324	38.0	

Table continues

Table 1. Continued

Characteristic	Case Group (n = 23,419)		Control Group (n = 87,593)		P Value
	No. of Individuals	% ^a	No. of Individuals	% ^a	
Maternal smoking during pregnancy					<0.01
No	14,663	62.6	54,188	61.9	
Yes	239	1.0	1,077	1.2	
Unknown	8,517	36.4	32,328	36.9	
Maternal history of miscarriage					0.13
No	19,451	83.1	73,129	83.5	
Yes	3,944	16.8	14,389	16.4	
Unknown	24	0.1	75	0.1	
Maternal history of stillbirth					0.40
No	23,026	98.3	86,180	98.4	
Yes	359	1.5	1,277	1.5	
Unknown	34	0.1	136	0.2	
Maternal education					<0.01
Up to 8th grade	1,574	6.7	7,107	8.1	
9th–12th grade	7,141	30.5	26,412	30.2	
At least some college	6,820	29.1	23,963	27.4	
Unknown	7,884	33.7	30,111	34.4	
Paternal education					<0.01
Up to 8th grade	1,624	6.9	7,123	8.1	
9th–12th grade	6,867	29.3	25,509	29.1	
At least some college	6,786	29.0	23,785	27.2	
Unknown	8,142	34.8	31,176	35.6	

^a Percentages may not add up to 100.0% due to rounding.

essentially the same, we used the set of covariates selected for overall pediatric cancer for subgroup analyses as well. SAS, version 9.4 (SAS Institute, Inc.), was used for all analyses, and all tests were 2-sided, with a type I error of 5%.

RESULTS

Among 23,419 cases, 10,396 (44.4%), 7,778 (33.2%), and 5,245 (22.4%) were diagnosed at the age of 0–5, 6–14, and 15–19 years, respectively. Compared with controls, cases appeared to have higher birth weight ($P < 0.01$), be more likely to be delivered by cesarean section ($P < 0.01$), have US-born mothers ($P < 0.01$), and have parents with higher education ($P < 0.01$) (Table 1). Among those with known smoking information, mothers of controls were more likely to have smoked during pregnancy than those of cases ($P < 0.01$). No differences were observed with regard to length of gestation, birth order, plurality, and maternal history of miscarriage or stillbirth (Table 1).

Pearson's correlation coefficient between maternal and paternal age was 0.74. The mean age of case mothers at delivery (27.6 (standard deviation, 6.0) years) was slightly older than that of control mothers (27.2 (standard deviation, 5.9) years; $P < 0.01$), and more cases than controls were delivered

by mothers who were at least 30 years old (37.7% of cases versus 35.1% of controls; $P < 0.01$) (Table 1). Similarly, the mean age for fathers of cases (30.3 (standard deviation, 6.8) years) was higher than that of controls (29.8 (standard deviation, 6.8) years; $P < 0.01$). As shown in Figure 1, both maternal and paternal ages became more advanced over the study period of 1978–2009, and the parents of cases were consistently older than parents of controls across all birth years.

After adjusting for multiple covariates including paternal age, compared with children whose mother were aged 20–24 years at delivery, those born to mothers in the older age groups had a 13%–36% increased risk of pediatric cancer (all $P < 0.05$), and the odds ratio for each 5-year increase in maternal age was 1.06 (95% confidence interval (CI): 1.04, 1.09; P -trend < 0.01) (Figure 2A, Web Table 1, available at <https://academic.oup.com/aje>). Similarly, having an older father also conferred an increased risk of pediatric cancer (while adjusting for maternal age and other covariates), but the magnitude of association was smaller than that observed with maternal age; the highest odds ratio was 1.15 (95% CI: 1.07, 1.24) for the paternal age group of ≥ 40 years. The odds ratio for each 5-year increase in paternal age was 1.03 (95% CI: 1.02, 1.05; P -trend < 0.01) (Figure 2B).

Advancing maternal age was associated with pediatric cancer diagnosed at different ages, and the odds ratios for

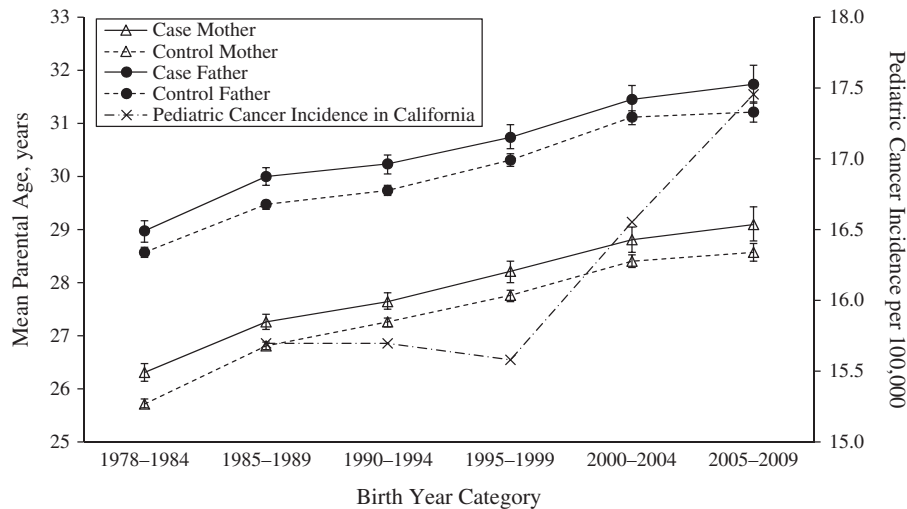


Figure 1. Mean parental age at delivery, according to year of birth, and pediatric cancer incidence data, California, 1978–2009. Pediatric cancer incidence data were obtained from the California Cancer Registry.

each 5-year increase in maternal age were 1.05 (95% CI: 1.02, 1.07; P -trend < 0.01) for cancer diagnosed in the age group 0–14 years and 1.14 (95% CI: 1.09, 1.19; P -trend < 0.01) for cancer diagnosed in the age group 15–19 years (Figure 2A). Advancing paternal age also increased the risk of cancer diagnosed both at the age of 0–14 years (per 5-year increase in paternal age, odds ratio (OR) = 1.03, 95% CI: 1.02, 1.05; P -trend < 0.01) and 15–19 years (per 5-year increase in paternal age, OR = 1.04, 95% CI: 1.00, 1.07; P -trend = 0.03). As for cancer diagnosed in early childhood (age 0–5 years), results regarding parental age were generally comparable to those observed in the diagnostic age group of 0–14 years (Figure 2).

Mean parental ages at delivery differed by racial/ethnic groups, with Asian/Pacific Islander parents having the oldest mean ages at delivery of their children (Table 2). Across all groups, mean ages of cases' parents were older than those of controls. Pearson's correlation coefficient between maternal and paternal age ranged from 0.69 in Asians/Pacific Islanders to 0.75 in non-Hispanic whites. Among non-Hispanic white children, having an older mother or father elevated the risk of pediatric cancer, with a magnitude of nearly 5% increase in pediatric cancer risk per 5-year increase in parental age (P -trend < 0.01) (Web Table 2). Among non-Hispanic black mothers, being in the age group ≥ 40 years had a higher likelihood of having offspring with pediatric cancer, but few mothers were in this age group (29 case mothers and 57 control mothers). For Hispanic children, older maternal age also increased their cancer risk; older paternal age did not appear to influence disease risk, although there was indication that having a young father, under the age of 20 years, might confer protection against pediatric cancer. Among Asians/Pacific Islanders, maternal age did not influence pediatric cancer risk. Compared with Asian/Pacific Islander fathers aged 20–24 years, those older than 30 years had a higher likelihood of having offspring with pediatric cancer. The likelihood ratio test for statistical interaction between race/ethnicity and parental age was

not significant ($P = 0.19$ and 0.12 for interaction with maternal and paternal age, respectively).

When assessing the association between parental age and risk of specific types of cancer, we found that each 5-year increase in maternal age elevated the risk of pediatric leukemia overall (OR = 1.07, 95% CI: 1.03, 1.11) and acute lymphoblastic leukemia (OR = 1.06, 95% CI: 1.02, 1.10) but not acute myeloid leukemia (Table 3). Similarly, older maternal age also increased the risk of CNS tumors overall (OR = 1.08, 95% CI: 1.03, 1.13), ependymomas and choroid plexus tumor (OR = 1.26, 95% CI: 1.10, 1.45), astrocytomas (OR = 1.09, 95% CI: 1.01, 1.16), renal tumors (OR = 1.15, 95% CI: 1.04, 1.26), and hepatic tumors (OR = 1.19, 95% CI: 1.01, 1.40). On the other hand, we did not find statistical evidence to reject a null association between paternal age and the risk of leukemia, CNS tumors, renal tumors, or hepatic tumors in our study. Older maternal and paternal ages were both associated with risk of pediatric lymphoma overall and Hodgkin lymphoma. Only older paternal age increased risk of non-Hodgkin lymphoma. No associations were observed between parental age and other types of cancer (Table 3).

DISCUSSION

In this largest-to-date, population-based record-linkage study that is less prone to bias, advancing parental age, especially advancing maternal age, was associated with increased risk of pediatric cancer. Compared with previous studies that focused on the age group of 0–14 years, our study also included cases diagnosed at the ages of 15–19 years; in this group, there was a larger magnitude of association between maternal age and cancer risk. We also observed variations across different cancer sites.

Previously, a pooled analysis of population-based record-linkage studies reported that each 5-year increase in maternal age raised risks of overall childhood cancer, leukemia, and

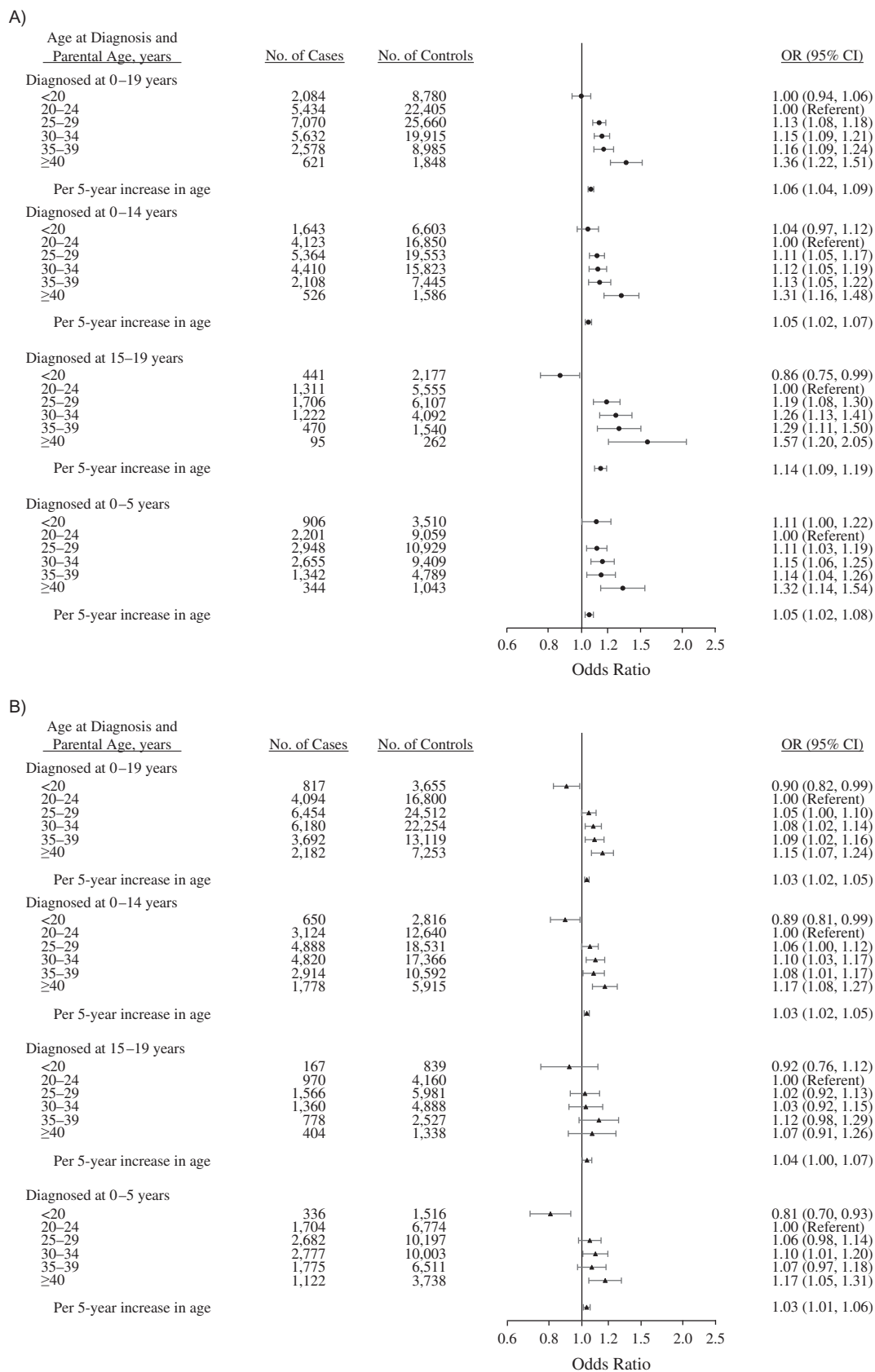


Figure 2. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for parental age and risk of pediatric cancer according to age at diagnosis, California, 1978–2009. A) Maternal age at delivery. B) paternal age at delivery.

Table 2. Mean Values and Standard Deviations for Parental Ages at Delivery According to Race/Ethnicity, California, 1978–2009

Race/Ethnicity	Maternal Age, years Mean (SD)		Paternal Age, years Mean (SD)	
	Case Group	Control Group	Case Group	Control Group
Non-Hispanic white	28.7 (5.6)	28.2 (5.7)	31.4 (6.5)	30.8 (6.5)
Non-Hispanic black	25.8 (6.1)	25.4 (5.9)	29.0 (7.8)	28.5 (7.4)
Hispanic	26.3 (6)	25.9 (5.9)	28.7 (6.7)	28.4 (6.7)
Asian/Pacific Islander	30.1 (5.3)	29.6 (5.5)	33.4 (6.4)	32.7 (6.5)
Other	28.0 (5.9)	27.1 (6.1)	30.7 (6.6)	29.8 (7.3)

Abbreviation: SD, standard deviation.

CNS tumors by 7%–8% (14). The pooled analysis also found that, for childhood cancer overall, the risk associated with each 5-year increase in maternal age was higher among children diagnosed at ages 0–4 years (OR = 1.08) than among those diagnosed in age group 5–9 years (OR = 1.05) or 10–14 years (OR = 1.04). In our study, the comparable odds ratios were 1.05, 1.05, and 1.03, respectively. In a Swedish study, investigators observed a nearly 50% higher risk of childhood leukemia, but not brain tumors, among the children of mothers aged over 35 years (25). Emerson et al. (16) reported that having a mother over 35 years of age was associated with an increased risk of astrocytoma (but not overall brain tumor or other subtypes of CNS tumors) in children ≤ 10 years of age. Similar to our study, in a large case-control study in Great Britain, investigators observed an association of maternal age with childhood acute lymphoblastic leukemia but not acute myeloid leukemia (15). Using a study design similar to ours, Oksuzyan et al. (19) observed a slight but not significant increased risk (OR = 1.14, 95% CI: 0.88, 1.49) of childhood leukemia among mothers aged over 35 years in a California-based study that included 5,788 cases born in 1986–2007 and diagnosed in 1988–2008. Our study included subjects who were born as early as 1978 (7,180 leukemia cases) and matched controls by race/ethnicity. Hispanic ethnicity accounts for more than 30% of California population (26) and nearly 50% of pediatric leukemia cases in our study. Hispanic mothers are younger at first delivery than mothers from other racial/ethnic groups (6). In the study by Oksuzyan et al. (19), it was possible for a Hispanic case to have a non-Hispanic control, which may have narrowed the apparent difference in maternal age between cases and controls when compared with our study. Many other studies did not observe associations between maternal age and childhood leukemia (17, 21, 27–30) or CNS tumors (21, 31, 32). Because the magnitude of association we observed between maternal age and pediatric cancer risk was not substantial, moderate sample size and limited statistical power from many existing studies could have contributed to inconsistent findings in the literature. Null findings, especially those from studies with relatively small sample sizes, probably should not be interpreted as providing evidence against an etiological role of advancing maternal age.

In our study, older paternal age also increased pediatric cancer risk, but no association was observed for most specific types of cancer. Because maternal and paternal ages were highly

correlated, we also fitted models with paternal age alone, in which advancing paternal age increased the risk of leukemia overall, acute lymphoblastic leukemia, CNS tumors overall, ependymomas and choroid plexus tumor, and other specified intracranial and intraspinal neoplasms (detailed results not presented). This indicated that the role of paternal age may not be independent of maternal age, which is consistent with the finding of a large pooled analysis (14). A few previous studies did not observe an association between older paternal age and childhood leukemia risk (17, 25, 27, 28), while others did (15, 18–20). As for CNS tumors, a positive association with advancing paternal age was observed in 2 Swedish studies (21, 25) but not in other studies (31–33). In addition to possible differences in sample size, whether maternal age was accounted for in the analysis of paternal age might have contributed to inconsistent findings.

The mechanism(s) through which parental age influences pediatric cancer risk are uncertain. Adkins et al. (13) reported that advancing parental age was correlated with decreased DNA methylation level in newborns; the association with maternal age was stronger and involved more sites. In addition, many of the loci where methylation changes occurred have been linked to oncogenesis (13). In addition, maternal age is correlated with aneuploidy in the offspring (34–36), including Down syndrome, and children with such birth defects have a higher risk of developing childhood cancers (37–40). It is also possible that advancing maternal age could be a marker for other factors, such as contaminant levels in maternal blood (41) and breast-milk (42) and age-related changes in hormonal levels during pregnancy (43, 44). Furthermore, genomic sequencing studies revealed a higher frequency of de novo mutations in the offspring as parents (especially fathers) aged (9–11). A majority of paternal age-related germline mutations have also been reported as somatic oncogenic mutations for various tumor types (45). Recently, Mills et al. (46) reported a weak paternal age association for retinoblastoma resulting from de novo germline mutations. Overall, accumulation of mutations may increase cancer risk (12, 45, 46).

Strengths of the current study include an unprecedented sample size and improved statistical power, population-based ascertainment of cases and controls that minimizes selection bias, reliance on data from preexisting birth and cancer registry records (therefore minimizing information bias), adjustment for multiple covariates to reduce confounding, and the

Table 3. Adjusted Odds Ratios and 95% Confidence Intervals for Parental Age and Risk of Pediatric Cancers Among Children Aged 0–19 Years, California, 1978–2009

Cancer Type and Parental Age Group, years	Maternal Age					Paternal Age				
	No. of Cases	No. of Controls	OR ^a	95% CI	P Value	No. of Cases	No. of Controls	OR ^a	95% CI	P Value
Leukemias, myeloproliferative diseases, and myelodysplastic diseases										
All										
<20	673	2,754	0.97	0.87, 1.09	0.62	283	1,165	0.98	0.84, 1.14	0.79
20–24	1,689	6,809	1.00	Referent		1,264	5,138	1.00	Referent	
25–29	2,082	7,750	1.08	1.00, 1.17	0.06	1,988	7,503	1.06	0.97, 1.16	0.20
30–34	1,682	6,038	1.13	1.02, 1.24	0.02	1,819	6,714	1.06	0.96, 1.17	0.28
35–39	829	2,869	1.17	1.04, 1.32	0.01	1,145	4,020	1.09	0.97, 1.22	0.15
≥40	225	603	1.53	1.26, 1.84	<0.01	681	2,283	1.10	0.96, 1.26	0.17
Per 5-year increase in age			1.07	1.03, 1.11	<0.01			1.02	0.99, 1.05	0.16
Acute lymphoblastic leukemia										
<20	531	2,174	0.99	0.87, 1.13	0.93	223	917	0.99	0.83, 1.18	0.88
20–24	1,293	5,340	1.00	Referent		980	4,043	1.00	Referent	
25–29	1,666	6,063	1.13	1.03, 1.24	<0.01	1,550	5,844	1.07	0.97, 1.18	0.20
30–34	1,334	4,728	1.16	1.04, 1.30	<0.01	1,455	5,299	1.08	0.96, 1.21	0.21
35–39	657	2,309	1.17	1.02, 1.34	0.02	898	3,203	1.09	0.95, 1.24	0.22
≥40	164	477	1.40	1.13, 1.74	<0.01	539	1,785	1.16	0.99, 1.35	0.06
Per 5-year increase in age			1.06	1.02, 1.10	<0.01			1.03	0.99, 1.06	0.10
Acute myeloid leukemia										
<20	108	410	1.01	0.75, 1.34	0.97	43	179	0.89	0.59, 1.34	0.58
20–24	292	1,070	1.00	Referent		207	798	1.00	Referent	
25–29	297	1,219	0.90	0.73, 1.10	0.29	325	1,202	1.09	0.87, 1.36	0.45
30–34	248	932	0.99	0.78, 1.26	0.93	260	1,003	1.03	0.79, 1.33	0.84
35–39	122	399	1.16	0.85, 1.59	0.36	170	592	1.07	0.79, 1.44	0.67
≥40	39	94	1.61	1.00, 2.58	0.05	101	350	0.97	0.68, 1.39	0.89
Per 5-year increase in age			1.08	0.99, 1.18	0.09			1.00	0.93, 1.08	0.95
Lymphomas and reticuloendothelial neoplasms										
All										
<20	231	1,096	0.96	0.79, 1.16	0.65	92	426	1.05	0.80, 1.38	0.72
20–24	615	2,767	1.00	Referent		446	2,139	1.00	Referent	
25–29	924	3,082	1.26	1.11, 1.44	<0.01	790	2,962	1.18	1.02, 1.36	0.03
30–34	671	2,302	1.18	1.01, 1.38	0.03	747	2,641	1.24	1.06, 1.46	<0.01
35–39	260	950	1.07	0.87, 1.31	0.54	436	1,432	1.41	1.17, 1.70	<0.01
≥40	59	168	1.37	0.97, 1.94	0.07	249	765	1.51	1.21, 1.88	<0.01
Per 5-year increase in age			1.07	1.01, 1.13	0.02			1.08	1.03, 1.13	<0.01
Hodgkin lymphoma										
<20	101	534	0.85	0.64, 1.14	0.28	46	208	1.32	0.89, 1.96	0.16
20–24	276	1,281	1.00	Referent		188	1,012	1.00	Referent	
25–29	423	1,431	1.31	1.09, 1.59	<0.01	382	1,356	1.34	1.08, 1.66	<0.01
30–34	311	1,007	1.36	1.08, 1.71	<0.01	322	1,223	1.21	0.95, 1.55	0.12
35–39	119	422	1.17	0.87, 1.58	0.31	216	610	1.72	1.30, 2.27	<0.01
≥40	28	65	1.94	1.15, 3.27	0.01	104	331	1.42	1.01, 1.98	0.04
Per 5-year increase in age			1.15	1.06, 1.25	<0.01			1.07	1.00, 1.15	0.04

Table continues

Table 3. Continued

Cancer Type and Parental Age Group, years	Maternal Age					Paternal Age				
	No. of Cases	No. of Controls	OR ^a	95% CI	P Value	No. of Cases	No. of Controls	OR ^a	95% CI	P Value
Non-Hodgkin lymphomas (except Burkitt lymphoma)										
<20	92	395	1.04	0.77, 1.42	0.79	37	153	1.00	0.65, 1.55	1.00
20–24	221	1,003	1.00	Referent		166	767	1.00	Referent	
25–29	342	1,084	1.33	1.07, 1.65	<0.01	269	1,048	1.08	0.85, 1.38	0.53
30–34	214	815	1.04	0.80, 1.35	0.76	280	931	1.33	1.02, 1.74	0.04
35–39	86	318	1.03	0.72, 1.46	0.88	133	514	1.21	0.87, 1.67	0.25
≥40	21	59	1.24	0.69, 2.25	0.47	91	261	1.67	1.15, 2.42	<0.01
Per 5-year increase in age			1.03	0.93, 1.13	0.57			1.10	1.02, 1.19	0.01
Central nervous system and miscellaneous intracranial and intraspinal neoplasms										
All										
<20	407	1,647	1.08	0.93, 1.25	0.33	158	681	0.91	0.74, 1.12	0.39
20–24	978	4,285	1.00	Referent		758	3,113	1.00	Referent	
25–29	1,408	5,038	1.24	1.11, 1.37	<0.01	1,231	4,768	1.00	0.89, 1.13	0.96
30–34	1,100	3,986	1.22	1.08, 1.38	<0.01	1,261	4,468	1.06	0.93, 1.20	0.40
35–39	556	1,801	1.39	1.20, 1.62	<0.01	742	2,654	1.01	0.87, 1.17	0.92
≥40	133	397	1.51	1.19, 1.92	<0.01	432	1,470	1.03	0.86, 1.22	0.76
Per 5-year increase in age			1.08	1.03, 1.13	<0.01			1.02	0.98, 1.05	0.32
Ependymomas and choroid plexus tumor										
<20	40	135	1.64	0.99, 2.72	0.06	20	71	1.14	0.60, 2.14	0.69
20–24	78	429	1.00	Referent		57	285	1.00	Referent	
25–29	125	488	1.41	0.99, 2.02	0.06	122	451	1.27	0.85, 1.91	0.24
30–34	120	382	1.93	1.29, 2.89	<0.01	126	423	1.17	0.75, 1.83	0.48
35–39	74	204	2.57	1.60, 4.12	<0.01	82	291	0.95	0.57, 1.55	0.82
≥40	19	39	3.71	1.77, 7.76	<0.01	49	156	0.97	0.56, 1.69	0.92
Per 5-year increase in age			1.26	1.10, 1.45	<0.01			0.99	0.89, 1.11	0.88
Astrocytomas										
<20	157	714	0.92	0.73, 1.16	0.47	59	296	0.82	0.59, 1.14	0.24
20–24	433	1,800	1.00	Referent		333	1,302	1.00	Referent	
25–29	609	2,166	1.20	1.02, 1.40	0.03	531	2,056	0.93	0.78, 1.10	0.39
30–34	484	1,745	1.16	0.96, 1.40	0.12	531	1,937	0.94	0.77, 1.14	0.52
35–39	215	737	1.25	0.98, 1.58	0.07	332	1,090	1.02	0.81, 1.28	0.85
≥40	52	173	1.38	0.95, 2.01	0.09	164	654	0.82	0.62, 1.07	0.15
Per 5-year increase in age			1.09	1.01, 1.16	0.02			1.00	0.95, 1.06	0.99
Intracranial and intraspinal embryonal tumors										
<20	102	383	0.98	0.71, 1.34	0.88	47	164	1.06	0.71, 1.59	0.76
20–24	230	916	1.00	Referent		172	667	1.00	Referent	
25–29	313	1,095	1.18	0.95, 1.47	0.13	270	1,027	0.99	0.78, 1.27	0.95
30–34	229	869	1.09	0.84, 1.41	0.54	287	1,007	1.09	0.83, 1.44	0.52
35–39	103	422	1.01	0.72, 1.40	0.97	136	615	0.89	0.64, 1.23	0.48
≥40	25	82	1.17	0.69, 2.01	0.56	90	287	1.29	0.88, 1.89	0.19
Per 5-year increase in age			1.02	0.93, 1.12	0.70			1.03	0.96, 1.12	0.41

Table continues

Table 3. Continued

Cancer Type and Parental Age Group, years	Maternal Age					Paternal Age				
	No. of Cases	No. of Controls	OR ^a	95% CI	P Value	No. of Cases	No. of Controls	OR ^a	95% CI	P Value
Other gliomas										
<20	55	190	1.51	1.00, 2.28	0.05	16	76	0.71	0.38, 1.33	0.29
20–24	115	568	1.00	Referent		104	398	1.00	Referent	
25–29	167	638	1.28	0.94, 1.73	0.11	130	602	0.82	0.59, 1.14	0.23
30–34	133	461	1.27	0.89, 1.81	0.18	154	555	0.97	0.67, 1.39	0.86
35–39	81	223	1.49	0.97, 2.28	0.07	105	329	1.09	0.72, 1.64	0.70
≥40	22	56	1.57	0.83, 2.95	0.16	64	176	1.14	0.71, 1.85	0.59
Per 5-year increase in age			1.03	0.91, 1.16	0.69			1.05	0.95, 1.16	0.30
Other specified intracranial and intraspinal neoplasms										
<20	48	212	1.05	0.68, 1.62	0.82	16	72	1.05	0.55, 2.02	0.88
20–24	113	533	1.00	Referent		86	425	1.00	Referent	
25–29	182	603	1.30	0.97, 1.75	0.08	166	591	1.32	0.95, 1.84	0.10
30–34	122	488	1.12	0.79, 1.59	0.53	144	505	1.36	0.94, 1.98	0.10
35–39	78	198	1.83	1.19, 2.81	<0.01	84	302	1.28	0.83, 1.97	0.27
≥40	15	41	1.65	0.82, 3.33	0.16	62	180	1.48	0.92, 2.39	0.11
Per 5-year increase in age			1.11	0.98, 1.26	0.09			1.05	0.95, 1.16	0.32
Neuroblastoma and other peripheral nervous cell tumors										
<20	111	380	1.35	1.01, 1.81	0.04	39	191	0.62	0.41, 0.94	0.03
20–24	253	1,021	1.00	Referent		196	735	1.00	Referent	
25–29	359	1,309	1.06	0.87, 1.30	0.55	309	1,183	1.05	0.84, 1.32	0.66
30–34	335	1,181	1.05	0.84, 1.33	0.66	349	1,216	1.21	0.94, 1.56	0.13
35–39	139	610	0.84	0.63, 1.12	0.24	210	823	1.14	0.86, 1.50	0.38
≥40	36	116	1.17	0.74, 1.84	0.49	130	469	1.28	0.93, 1.76	0.13
Per 5-year increase in age			0.98	0.90, 1.06	0.61			1.07	1.00, 1.14	0.05
Retinoblastoma										
<20	57	232	0.88	0.60, 1.31	0.54	22	86	0.92	0.53, 1.60	0.78
20–24	139	513	1.00	Referent		106	368	1.00	Referent	
25–29	177	613	1.04	0.78, 1.39	0.77	139	606	0.77	0.56, 1.07	0.12
30–34	131	501	0.85	0.61, 1.19	0.35	154	547	0.98	0.68, 1.41	0.92
35–39	64	261	0.74	0.48, 1.13	0.16	98	366	1.01	0.67, 1.52	0.96
≥40	22	71	0.88	0.48, 1.62	0.68	71	218	1.26	0.79, 2.00	0.34
Per 5-year increase in age			0.99	0.88, 1.11	0.83			1.07	0.97, 1.18	0.15
Renal tumors										
<20	83	349	1.10	0.79, 1.52	0.59	34	156	0.88	0.56, 1.38	0.58
20–24	204	955	1.00	Referent		161	731	1.00	Referent	
25–29	288	1,043	1.36	1.09, 1.69	<0.01	282	969	1.24	0.97, 1.58	0.08
30–34	294	868	1.74	1.35, 2.25	<0.01	249	940	1.02	0.77, 1.34	0.91
35–39	112	407	1.40	1.01, 1.94	0.05	174	555	1.22	0.89, 1.67	0.23
≥40	25	90	1.46	0.86, 2.49	0.16	106	361	1.13	0.79, 1.62	0.49
Per 5-year increase in age			1.15	1.04, 1.26	<0.01			1.00	0.93, 1.08	0.97

Table continues

Table 3. Continued

Cancer Type and Parental Age Group, years	Maternal Age					Paternal Age				
	No. of Cases	No. of Controls	OR ^a	95% CI	P Value	No. of Cases	No. of Controls	OR ^a	95% CI	P Value
Hepatic tumors										
<20	38	118	1.80	1.06, 3.05	0.03	12	44	0.86	0.40, 1.85	0.70
20–24	48	269	1.00	Referent		48	209	1.00	Referent	
25–29	86	344	1.49	0.95, 2.33	0.09	83	309	1.10	0.69, 1.76	0.69
30–34	93	305	2.04	1.23, 3.39	<0.01	89	326	0.97	0.58, 1.64	0.92
35–39	50	146	2.35	1.27, 4.36	<0.01	50	211	0.70	0.38, 1.29	0.25
≥40	12	33	2.22	0.91, 5.38	0.08	45	116	1.09	0.57, 2.09	0.78
Per 5-year increase in age			1.19	1.01, 1.40	0.04			1.03	0.91, 1.17	0.66
Malignant bone tumors										
<20	91	416	0.83	0.62, 1.12	0.23	31	169	0.74	0.48, 1.16	0.19
20–24	297	1,066	1.00	Referent		219	822	1.00	Referent	
25–29	298	1,143	0.91	0.74, 1.12	0.38	286	1,094	1.01	0.81, 1.27	0.93
30–34	222	846	0.93	0.72, 1.19	0.54	263	911	1.13	0.87, 1.47	0.35
35–39	96	306	1.16	0.84, 1.62	0.37	141	568	0.93	0.68, 1.26	0.63
≥40	16	66	0.85	0.45, 1.62	0.62	80	279	1.10	0.76, 1.60	0.60
Per 5-year increase in age			1.02	0.93, 1.13	0.63			1.00	0.93, 1.08	0.94
Soft tissue and other extrasosseous sarcomas										
<20	134	571	0.97	0.76, 1.26	0.84	52	251	0.78	0.55, 1.12	0.18
20–24	373	1,452	1.00	Referent		279	1,102	1.00	Referent	
25–29	435	1,643	1.03	0.86, 1.23	0.76	411	1,558	1.06	0.88, 1.28	0.56
30–34	367	1,259	1.13	0.92, 1.39	0.25	405	1,422	1.11	0.90, 1.38	0.34
35–39	154	560	1.06	0.81, 1.39	0.67	200	797	1.00	0.78, 1.29	0.99
≥40	25	91	1.01	0.61, 1.67	0.96	141	446	1.28	0.95, 1.73	0.10
Per 5-year increase in age			1.03	0.95, 1.11	0.48			1.05	0.99, 1.12	0.09
Germ-cell tumors, trophoblastic tumors, and neoplasms of gonads										
<20	149	585	0.96	0.76, 1.22	0.75	48	223	0.76	0.53, 1.10	0.15
20–24	389	1,475	1.00	Referent		315	1,124	1.00	Referent	
25–29	418	1,609	1.03	0.86, 1.23	0.75	396	1,555	0.92	0.76, 1.11	0.39
30–34	325	1,168	1.11	0.89, 1.37	0.36	365	1,371	0.94	0.75, 1.16	0.55
35–39	136	471	1.13	0.85, 1.50	0.40	208	774	0.94	0.72, 1.21	0.62
≥40	33	105	1.16	0.73, 1.85	0.52	118	366	1.13	0.83, 1.53	0.45
Per 5-year increase in age			1.07	0.99, 1.15	0.10			1.04	0.98, 1.11	0.18
Other malignant epithelial neoplasms and malignant melanomas										
<20	98	569	0.73	0.56, 0.96	0.03	43	235	0.99	0.67, 1.45	0.94
20–24	402	1,598	1.00	Referent		268	1,179	1.00	Referent	
25–29	533	1,889	1.03	0.87, 1.21	0.77	480	1,830	1.07	0.89, 1.28	0.50
30–34	378	1,340	0.96	0.79, 1.18	0.72	432	1,532	1.13	0.91, 1.40	0.26
35–39	162	534	1.02	0.78, 1.32	0.89	265	820	1.33	1.04, 1.70	0.02
≥40	31	99	1.14	0.71, 1.82	0.58	116	433	1.07	0.79, 1.44	0.67
Per 5-year increase in age			1.06	0.98, 1.14	0.16			1.05	0.99, 1.12	0.11

Abbreviations: CI, confidence interval; OR, odds ratio.

^a Odds ratios and 95% confidence intervals were derived from multivariable conditional logistic regression models that included maternal and paternal ages, birth weight (in grams: <2,500, 2,500–2,999, 3,000–3,499, 3,500–3,999, ≥4,000), length of gestation (in weeks: 22–36, 37–41, 42–44, or unknown), birth order (first, second, third or higher), maternal country of birth (United States, foreign countries), maternal smoking during pregnancy (no, yes, or unknown), and maternal and paternal education (up to 8th grade, 9–12th grade, at least some college, or unknown).

racial/ethnic diversity of the study population. In addition, this is a single-site study with uniform criteria for subject selection and data abstraction, therefore bypassing challenges inherent in pooled analyses (14) that stem from heterogeneity across individual studies. Furthermore, we included many adolescents aged 15–19 years, who are understudied and underserved in cancer research (47, 48).

The record-linkage design also gave rise to some important limitations. First, we were restricted to the use of existing data without verification. While errors in existing records are definitely possible, most birth variables included in our analysis are considered accurate (49), and any deviation from truth is unlikely to be differential by case/control status. Second, data on parental education were missing for a rather large proportion of the subjects because the data elements were not always included in California birth records. To address this issue, we conducted sensitivity analyses by excluding subjects with unknown covariate information and the primary results remained the same (detailed data not presented). However, there could still be residual confounding due to missing information on parental education or other markers of socioeconomic status (e.g., household income). Third, some controls could have moved out of California and developed pediatric cancer elsewhere, or they could have developed pediatric cancer within California but were not captured by the CCR. Under the extreme assumption that all controls were lost to follow-up, we would expect about 138 cases of cancer to arise from the 87,593 controls with 800,101 person-years of follow-up, at an incidence rate of 17.3 per 100,000 person-years (50). Relative to the 23,419 cases included in our study, it is unlikely that 138 cases would have biased our results to a measurable degree. Fourth, we were unable to ascertain cancer cases in children who were born in 1978–1987 and diagnosed with cancer over the same time period, most of whom would have been very young at cancer diagnosis. Because the control subjects were matched to cases on year of birth, and we conducted separate analyses for cases diagnosed at 0–5 years, the association is likely on precision (i.e., statistical power) and not on internal validity. Fifth, in this study we were able to include only adolescents who were born before 1996. As parental age has continued to rise, further study with adolescents born more recently is needed. Last, we were unable to account for other putative risk factors of pediatric cancer, such as ionizing radiation, although we did adjust for many covariates.

In summary, in this large population-based study, older parental age, especially older maternal age, increased the risk of pediatric cancer, with variations across different ages of diagnosis, and specific cancer sites. Future studies are needed to clarify the underlying biological mechanisms, given the growing number of children born to older parents in the United States and worldwide.

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Author affiliations: Department of Chronic Disease Epidemiology, Yale School of Public Health, New Haven, Connecticut (Rong Wang, Andrew T. DeWan, Xiaomei

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