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Meta-Analysis

Parental Age and Childhood Lymphoma and Solid Tumor Risk: A Literature Review and Meta-Analysis

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Abstract

Background: Although advanced parental age has been definitively linked to pediatric acute lymphoblastic leukemia, studies of parental age and pediatric solid tumors have not reached firm conclusions. This analysis aimed to elucidate the relationship between parental age and pediatric solid tumors through meta-analysis of existing studies based in population registries. **Methods:** We searched Medline (PubMed) and Embase for registry-based studies of parental age and solid tumors through March 2022. We performed random-effects meta-analysis to estimate pooled effects and 95% confidence intervals (CIs). All statistical tests were 2-sided. **Results:** A total of 15 studies covering 10 childhood solid tumor types (30 323 cases and 3 499 934 controls) were included in this analysis. A 5-year increase in maternal age was associated with an increased risk of combined central nervous system tumors (odds ratio [OR] = 1.07, 95% CI = 1.04 to 1.10), ependymoma (OR = 1.19, 95% CI = 1.09 to 1.31), astrocytoma (OR = 1.10, 95% CI = 1.05 to 1.15), rhabdomyosarcoma (OR = 1.14, 95% CI = 1.03 to 1.25), and germ cell tumors (OR = 1.06, 95% CI = 1.00 to 1.12). A 5-year increase in paternal age was associated with an increased risk of non-Hodgkin lymphoma (OR = 1.06, 95% CI = 1.00 to 1.12). **Conclusions:** This meta-analysis of registry-based analyses of parental age and childhood cancer supports the association between older maternal age and certain childhood solid cancers. There is also some evidence that paternal age may be associated with certain cancers such as non-Hodgkin lymphoma. However, as maternal and paternal age are highly correlated, disentangling potential independent causal effects of either factor will require large studies with extensive data on potential confounders.

In the last several decades, there has been a trend toward delayed childbearing across the globe (1). This has been attributed to a number of factors including higher educational attainment, women working outside the home, improved contraception methods, and access to assisted reproductive technologies (1). Within the United States, this rise in age is seen in both men and women and across races and ethnicities and geographic regions (2). Delaying childbearing can benefit families individually through greater socioeconomic attainment, however, the association between older parental age and adverse perinatal outcomes such as Down syndrome, preterm birth, and perinatal and neonatal death, among others, is well established in the literature (1,3).

Previous studies have shown a clear link between older parental age and acute lymphoblastic leukemia (ALL), the most common childhood cancer. The Childhood Cancer and Leukemia International Consortium (CLIC) recently published on this association in a pooled analysis, stratifying by original study type (questionnaire-based case-control studies vs registry-based linkage studies) (4). They found a positive association between both older maternal (odds ratio [OR] = 1.05, 95% confidence interval [CI] = 1.01 to 1.08) and paternal age (OR = 1.04, 95% CI = 1.01 to 1.07) per 5-year increase but only in the registry-based studies. This discrepancy likely reflects selection bias in participation in questionnaire-based case-control studies. CLIC has also investigated this association in acute myeloid leukemia (AML), again stratifying by original study design (5). They found a strong association (OR = 6.87, 95% CI = 2.12 to 22.25) between advanced maternal age and AML in children aged younger than 1 year, again only in the registry-based studies. There were no associations found for paternal age or in AML risk among older children (1-14 years).

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The association between parental age and other childhood cancers has been studied without any firm conclusions (6-9). This likely results from limitations in study sizes among these rarer solid childhood tumors and, again, the likelihood of selection bias in questionnaire-based case-control studies. We planned to overcome these limitations by conducting a thorough literature review and meta-analysis of the current literature on the association between parental age and solid tumors in children focusing only on population-based studies to minimize bias.

Methods

Search Strategy

We searched for English-language publications in Medline (PubMed) and Embase through March 2022. We used the MeSH terms "neoplasms," "maternal age," "paternal age," and "registries," along with text words "child*," "pediatric," "paediatric," "neoplas*," "malignan*," "cancer*," "tumor*," "sarcoma," "lymphoma," "maternal," "paternal," "parent*," "age*," "characteristic*," "register*," "registry," and "registries."

Finally, we also included the text words "leukemia" and "leukaemia" to capture any studies that only focused descriptions of their findings on these more common types of cancer but also presented other cancer types within their articles.

Study Selection

For inclusion, we required that articles used data derived from registry-based or birth certificate data and be published in peer-reviewed journals. Only articles that examined childhood (ages 0-19 years) cancer, with effect estimates for maternal or paternal age, or including information from which a crude estimate could be determined, were included. One author (KM) screened all titles, abstracts, and full-text publications based on these criteria and abstracted relevant effect estimates. Figure 1 outlines our search and selection process.

Many of the articles used similar datasets or individual datasets that had been pooled. We allowed for small overlap (1 year or less) between studies in similar or overlapping populations to minimize double-counting participants. As one author (LS) was an original investigator of the 5-state pooled dataset described in Johnson et al. (8), odds ratios were re-estimated excluding California data so as to allow for inclusion of the larger Wang et al. (10) study without double-counting some participants.

Data Extraction and Quality Assessment

Two authors (KM, AD) extracted descriptive information from the methods of each publication including International Classification of Childhood Cancer, Third Edition (ICCC-3) grouping, ICCC-3 subgrouping if applicable, year of publication, population characteristics, age range for cancer diagnoses, and time frame for cancer diagnoses. The maximally adjusted effect estimate, as well as adjustment factors, were extracted from each study. Data was presented in multiple ways in the manuscripts included. When available, estimates associated with 5-year increases in maternal or paternal age were extracted. If age categories were presented, estimates from all categories were recorded. Any discrepancies in data extraction were reviewed by a third author (EM).

Synthesis of Data and Analysis

In studies that only included categorical estimates, these age categories were collapsed using methods described in Greenland and Longnecker (11) and Berlin, Longnecker, and Greenland (12). Briefly, all participants within each age category were given the midpoint age within that group. In the oldest age category, participants were assigned an age of 1.2 times that of the lower endpoint age and, in the youngest age category, the mean value between the upper endpoint and a value that was determined to be a possible lower bound—in this case age 12 years. We then determined the odds ratio for a 5-year increase in parental age.

For each childhood cancer grouping, the effect of a 5-year increase in age was estimated using random-effects meta-analysis (13). Where possible, the analyses were conducted by ICCC-3 subgroup, but as certain studies only classified cases by broader diagnostic groups, some analyses were conducted by both levels. For example, central nervous system (CNS) tumors were analyzed in the broader CNS group as well as in individual subgroups such as ependymoma and astrocytoma. In these random-effects meta-analysis models, the weights given to each study are inversely related to the total variance within that study. We additionally estimated the effect of a 5-year increase in parental age on all cancers included together to assess the overall effect of delayed childbearing on childhood cancer. For each cancer category, random-effects models were used to estimate summary odds ratios and 95% confidence intervals. Statistical significance of a summary effect was assessed using these confidence intervals to determine if the effect was statistically significantly different from the null. We used the I^2 statistic, a measure of heterogeneity ranging from 0% to 100% and corresponding P value to assess between-study heterogeneity ($P_{\text{heterogeneity}}$). Publication bias was assessed by funnel plot asymmetry and Egger test for small study effects. All tests were 2-sided with P values of less than .05 indicating statistical significance.

Several studies included in this analysis only provided crude estimates of the association between parental age and cancer risk. To assess the effect that these studies had on the meta-analysis, the analysis was reconducted excluding these crude estimates.

Additionally, as birth records are often missing paternal age (14), a sensitivity analysis was conducted to estimate the effect of missing paternal age on results. This sensitivity analysis was conducted using the 5-state pooling data from the Johnson et al. (8) study, one of the larger studies in this analysis, by assigning fathers with missing ages to the youngest and oldest age categories to determine the bounds within which the true effect estimate might lie.

Data analysis was conducted using Stata (version 16.1).

Results

Our initial search yielded 1540 nonduplicate records from Medline and Embase (Figure 1). We conducted a review of titles and abstracts, screening for manuscripts that either directly examined the association between parental age and childhood cancer and for manuscripts that may contain sufficient data in tables allowing for calculation of crude odd ratios. A total of 163 records were deemed eligible for a full-text review. Of these studies, 83 were excluded during full-text review, and 80 studies were identified for further review. From these studies, we analyzed those with nonoverlapping dates, regions, and tumor types of inclusion. If multiple studies were conducted in the

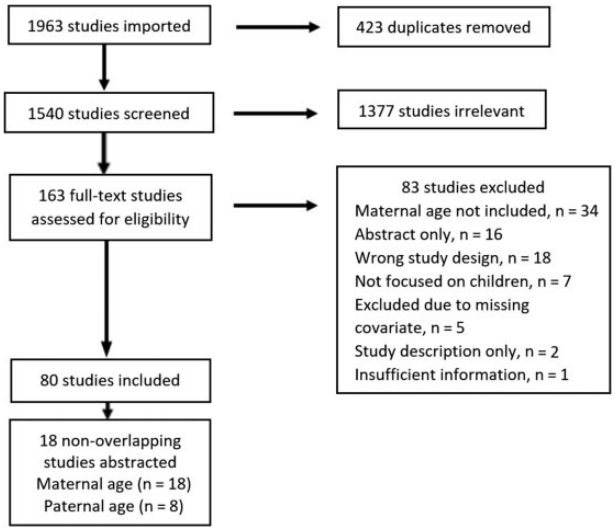

Figure 1. Search results and study selection flowchart.

same dataset, we chose the study that presented the most fully adjusted model or that had the most recent date of publication. Estimates of associations were abstracted from 18 publications covering 10 childhood solid tumor types and 33 847 cases and 3 675 858 controls (Table 1). Each study's quality was assessed using the Newcastle-Ottawa Scale (NOS) (15). The NOS rates study quality based on selection of cases and controls, the comparability of cases and controls, and exposure ascertainment and has a maximum score of 9. We considered a study high quality if it had a score of 7 or higher. Using this criterion, all included studies with adjusted effect estimates were considered high quality. The average NOS of all studies included was 7.2.

Maternal Age

There were several statistically significant associations between maternal age at birth and the odds of certain cancer types. A 5-year increase in age was statistically significantly associated with an increased odds of CNS tumors (OR = 1.07, 95% CI = 1.04 to 1.10; I^2 = 0.04%, $P_{heterogeneity}$ = .73), ependymoma (OR = 1.17, 95% CI = 1.07 to 1.29; I^2 = 4.19%, $P_{heterogeneity}$ = .38), astrocytoma (OR = 1.10, 95% CI = 1.05 to 1.15; I^2 = 0.02%, $P_{heterogeneity}$ = .19), rhabdomyosarcoma (OR = 1.13, 95% CI = 1.01 to 1.26; I^2 = 12.34%, $P_{heterogeneity}$ = .26), and germ cell tumors (OR = 1.06, 95% CI = 1.00 to 1.12 [lower bound rounded down to 1.00]; I^2 = 0.02%, $P_{heterogeneity}$ = .58). No other statistically significant associations were observed; however, several point estimates and confidence intervals were suggestive of an association. Results were considered suggestive of an association if 95% confidence interval lower bounds were between 0.97 and 1.00 for a point estimate above 1.00 and upper bounds between 1.00 and 1.03 for a point estimate below the null. Such suggestive positive associations between a 5-year increase in maternal age and cancer odds were observed for non-Hodgkin lymphoma (OR = 1.05, 95% CI = 0.99 to 1.12; I^2 = 0.00%, $P_{heterogeneity}$ = .30), medulloblastoma (OR = 1.04, 95% CI = 0.98 to 1.12; I^2 = 0.01%, $P_{heterogeneity}$ = .46), neuroblastoma (OR = 1.05, 95% CI = 0.99 to 1.12; I^2 = 42.77%, $P_{heterogeneity}$ = .17), combined renal tumors (OR = 1.09, 95% CI = 0.99 to 1.20; I^2 = 78.23%, $P_{heterogeneity}$ < .001), combined hepatic tumors (OR = 1.09, 95% CI = 0.98 to 1.21; I^2 = 14.94%, $P_{heterogeneity}$ = .34), combined bone tumors (OR = 1.05, 95% CI = 0.99 to 1.11; I^2 = 0.00%, $P_{heterogeneity}$ = .72), osteosarcoma (OR = 1.06, 95% CI = 0.97 to 1.17; I^2 = 11.77%, $P_{heterogeneity}$ = .29), and soft tissue sarcomas (OR = 1.04, 95% CI = 0.97 to 1.13; I^2 = 39.89%, $P_{heterogeneity}$ = .14). These statistically significant and suggestive meta-analysis results are displayed in Figure 2. Full results may be found in Supplementary Figure 1 (available online). The overall effect of a 5-year increase in maternal age on the odds of combined childhood lymphoma and solid tumors was also statistically significant (OR = 1.05, 95% CI = 1.03 to 1.07).

Paternal Age

A 5-year increase in paternal age at birth was associated with a statistically significant increase in the odds of non-Hodgkin lymphoma (OR = 1.07, 95% CI = 1.01 to 1.13; I^2 = 0.00%, $P_{heterogeneity}$ = .45). Using the same criteria for suggestive results as outlined in the maternal results, suggestive positive associations were observed between a 5-year increase in paternal age and combined lymphoma (OR = 1.03, 95% CI = 0.98 to 1.09; I^2 = 51.80%, $P_{heterogeneity}$ = .09), combined CNS tumors (OR = 1.01, 95% CI = 0.99 to 1.03; I^2 = 1.15%, $P_{heterogeneity}$ = .39), neuroblastoma (OR = 1.03, 95% CI = 0.97 to 1.09; I^2 = 28.49%, $P_{heterogeneity}$ = .28), retinoblastoma (OR = 1.05, 95% CI = 0.98 to 1.13; I^2 = 0.01%, $P_{heterogeneity}$ = .43), combined bone tumors (OR = 1.03, 95% CI = 0.97 to 1.09; I^2 = 0.00%, $P_{heterogeneity}$ = .63), and germ cell tumors (OR = 1.04, 95% CI = 0.98 to 1.09; I^2 = 0.00%, $P_{heterogeneity}$ = .92). These statistically significant and suggestive paternal meta-analysis results are displayed in Figure 3. Full results may be found in Supplementary Figure 2 (available online). The overall effect of a 5-year increase in paternal age on the odds of combined childhood lymphoma and solid tumors was also statistically significant (OR = 1.02, 95% CI = 1.01 to 1.04).

Publication Bias

Publication bias was assessed through visual inspection of funnel plots as well as Egger test for small study effects. In the case that there was not publication bias, funnel plots are roughly symmetrical, and 95% of studies fall between the pseudo 95% confidence lines. In this analysis, there is evidence of potential publication bias in the studies of maternal age and any lymphoma, Hodgkin lymphoma, and renal tumors based on visual evaluation of funnel plots by cancer type (Figure 4). However, none of this asymmetry was statistically significant at the 0.05 level as determined by Egger test. There was no evidence of strong publication bias for the other cancer types investigated by maternal age.

There is some evidence of publication bias in paternal studies of lymphomas based on visual inspection of funnel plots by cancer type. This asymmetry was statistically significant as determined by Egger test, indicating the possibility of publication bias in studies of paternal age and lymphoma. There was not strong evidence of publication bias for the other cancers investigated with paternal age (Figure 5).

Sensitivity Analysis Excluding Crude Estimates

Comparisons between the estimated associations observed when the crude estimates were included vs the estimated associations observed with the exclusion of these studies may be found in Table 2. No large differences in odds ratios were observed.

Sensitivity Analysis of Missing Paternal Age

The sensitivity analysis of the Johnson et al. (8) study estimated the effect of missing paternal age by assigning missing fathers

Table 1. Characteristics of studies on parental age and solid childhood cancers

Study	Study population	Parental age variable	Odds ratio available	Adjustment variables	Cancer type(s)	No. of controls
Contreras ZA et al. (16)	Denmark Children younger than 16 years Born 1968-2014 and diagnosed 1968- 2015	Maternal, paternal	Adjusted	Parental place of birth, parity, other parent's age	Lymphoma (n = 578), CNS (n = 1548), neuroblastoma (n = 346), retinoblastoma (n = 163), renal tumor (n = 293), hepatic tumor (n = 73), bone tumor (n = 266), soft tissue sarcoma (n = 342), germ cell tumor (n = 166), other/nonspecific (n = 342)	585 594
Johnson KJ et al. (8)	Pooled 5 state: CA (excluded), MN, NY, TX, WA Children younger than 15 years Born 1970-2004 and diagnosed 1980-2004	Maternal, paternal	Adjusted	Maternal race, sex, birthweight, gestational age, birth order, birth year category, plurality, state, other parent's age	Lymphoma (n = 1248), CNS (n = 2863), neuroblastoma (n = 993), retinoblastoma (n = 399), renal tumor (n = 776), hepatic tumor (n = 181), bone tumor (n = 492), soft tissue sarcoma (n = 810), germ cell tumor (n = 395)	49 236
Wang R et al. (10)	California Children younger than 19 years Born 1978-2009 and diagnosed 1988-2011	Maternal, paternal	Adjusted	Other parent's age, birth weight, length of gestation, birth order, maternal country of birth, maternal smoking during pregnancy	Lymphoma (n = 2760), CNS (n = 4582), neuroblastoma (n = 1233), retinoblastoma (n = 590), renal tumor (n = 1006), hepatic tumor (n = 327), bone tumor (n = 1020), soft tissue sarcoma (n = 1488), germ cell tumor (n = 1450), other/nonspecific (n = 1604)	87 593
Petridou et al. (17)	Sweden Children younger than 15 years Born 1973-2007 and diagnosed 1973-2007	Maternal	Adjusted	Sex, maternal education, gestational age, birth order	Lymphoma (n = 684)	2 334 346
Wong and Dockerty (18)	New Zealand Children younger than 15 years (non-Hodgkins disease) younger than 25 (Hodgkins disease) Born 1961-1987 (non-Hodgkins) Born 1951-1987 (Hodgkins) Diagnosed 1976-1987	Maternal, paternal	Adjusted	Parity, social class, marital status, other parent's age, urban or nonurban status	Lymphoma (n = 236)	585
Cantwell MM et al. (19)	Northern Ireland Born 1971-1986 and diagnosed 1975-1997	Maternal, paternal	Crude	—	CNS (n = 155)	420 436
Danysh HE et al. (20)	Texas Children younger than 5 years Born 2003-2009 and diagnosed 2003-2009	Maternal	Crude	—	CNS (n = 315)	1575
de Paula Silva N et al. (21)	Brazil Born after 1999 and diagnosed 2000-2010	Maternal	Crude	—	CNS (n = 119), other/nonspecific (n = 221)	1580

(continued)

Table 1. (continued)

Study	Study population	Parental age variable	Odds ratio available	Adjustment variables	Cancer type(s)	No. of controls
Bluhm E et al. (22)	Sweden Born 1973-1995 and diagnosed until 1995	Maternal	Conditional	Sex, birth year and month	Neuroblastoma (n = 245)	1225
Kumar SV et al. (23)	Texas Children younger than 5 years Born 2003-2009 and diagnosed 2003-2009	Maternal	Crude	—	Neuroblastoma (n = 252), retinoblastoma (n = 121)[a], renal tumor (n = 143), hepatic tumor (n = 55)[a]	2855
Schuz J et al. (24)	Denmark, Norway, Sweden (diagnosed 1985-2006), Finland (diagnosed 1987-2006)	Maternal, paternal	Conditional	Birth month and year, sex, and country	Renal tumor (n = 690)	3298
de Fine Licht S et al. (26)	Denmark, Finland, Norway, Sweden Children younger than 15 years Born 1985-2006	Maternal	Conditional	Sex, age, country	Hepatic tumor (n = 155)	775
Troisi R et al. (27)	Norway (birth years 1970-2009), Sweden (birth years 1974-2009), Denmark (birth years 1980-2010); younger than 43 years	Maternal	Conditional	Birth year and sex	Bone tumor (n = 510)	9140
Ghali MH et al. (28)	Connecticut Children younger than 19 years Born 1946-1985 and diagnosed 1960-1988	Maternal, paternal	Crude	—	Soft tissue sarcoma (n = 103)	205
Stephansson O et al. (29)	Denmark, Norway, Sweden, Finland Children younger than 15 years Born 1967-2006 and diagnosed	Maternal	Adjusted	Birth weight, gestational age, and parity	Germ cell tumor (n = 152)	1491
Fahmideh et al. (25)	Texas Children 16 years and younger Born 1995-2011	Maternal	Adjusted	Birth year, sex, maternal race and ethnicity, maternal education, tumor malignancy	CNS (n = 217)	2170
Lombardi et al. (30)	California Children 5 years and younger Diagnosed 1988-2013	Maternal	Crude	—	CNS (n = 157)	123 154
Deziel et al. (31)	California Children 19 years and younger Born 1978-2015 and diagnosed 1988-2015	Maternal, paternal	Adjusted	Sex, race and ethnicity, gestational age, other parent's age, maternal education, maternal birthplace, birth order, mode of delivery, history of miscarriage, history of pregnancy complications, previous c-section	Other or nonspecific (n = 1012)	50 600
Total	NA	NA	NA	NA	Lymphoma (n = 5506), CNS (n = 9927), neuroblastoma (n = 3069), retinoblastoma (n = 1273), renal tumor (n = 2908), hepatic tumor (n = 791), bone tumor (n = 2288), soft tissue sarcoma (n = 2743), germ cell tumor (n = 2163), other or nonspecific (n = 3179)	3 675 858

[a]Odds ratios could not be estimated for these cancers as certain cell counts were omitted from the publication because of confidentiality concerns. However, these cases were included in the estimated effect of all cancers pooled.
CNS = central nervous system; NA = not applicable.

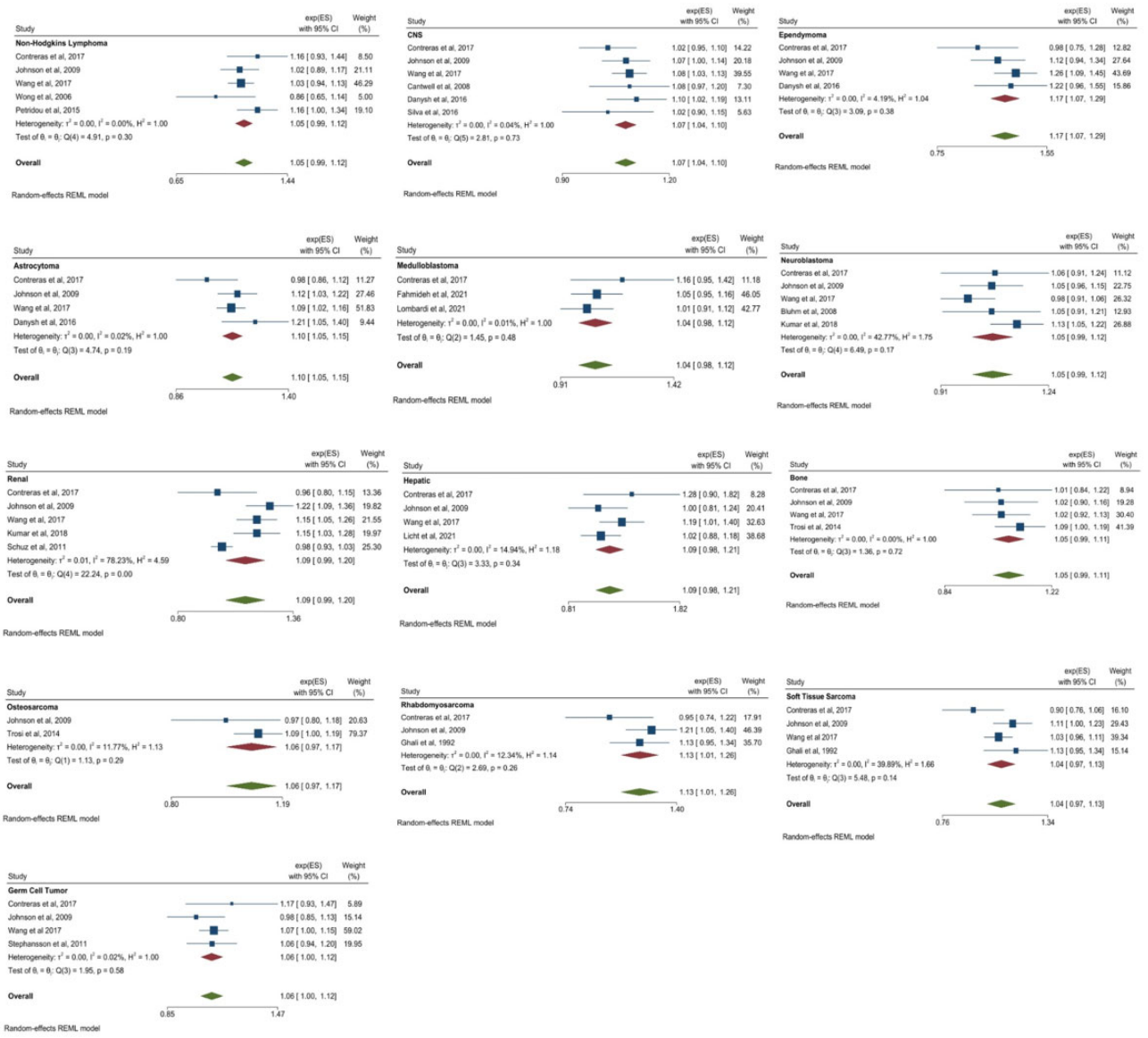

Figure 2. Maternal statistically significant and suggestive meta-analysis results for a 5-year increase in maternal age at birth. Error bars represent 95% confidence intervals. Between-study heterogeneity is presented in terms of the τ^2, I^2, and H^2 statistic. Test of $\theta_i = \theta_j$ refers to the Cochran Q test of between-study homogeneity. Random effects modeling using restricted maximum likelihood methods was used to produce summary estimates. All tests were 2-sided. CI = confidence interval; ES = estimate (β); REML = restricted maximum likelihood.

to the youngest and oldest age categories. This analysis did not detect any meaningful differences (>10% change) in estimated effect sizes because of missing paternal age with the exception of the effect maternal age on ependymoma risk in which the point estimate changed by 11.2%. However, this sensitivity analysis investigated the most extreme cases—that all missing fathers belonged to the youngest and oldest categories—which is highly unlikely. Additionally, none of the new estimates were statistically significantly different from the original estimates.

Discussion

Overall, through this meta-analysis of population-based studies of parental age and childhood solid tumors, we observed statistically significant associations between higher maternal age and CNS tumors, ependymoma, astrocytoma, rhabdomyosarcoma, and germ cell tumors as well as between higher paternal age and non-Hodgkin lymphoma. Increasing maternal age has been shown to be a risk factor for a number of adverse perinatal outcomes; it has also been shown to be associated with ALL (4) and AML (5). This analysis provides evidence that increasing maternal age may be associated with an increased odds of many solid tumors as well, particularly CNS tumors. Though several point estimates highlighted in this analysis were relatively small, each point estimate is reported in reference to a 5-year increase in parental age; thus, the differences across the full reproductive age span would be much greater. For example, a 5-year increase in maternal age was associated with a 7% increase in odds of combined CNS tumors in this analysis (OR = 1.07), but a 20-year difference in maternal age (for example, comparing a mother aged 20 years to a mother aged 40 years) is associated with a 31% increase (OR = 1.31).

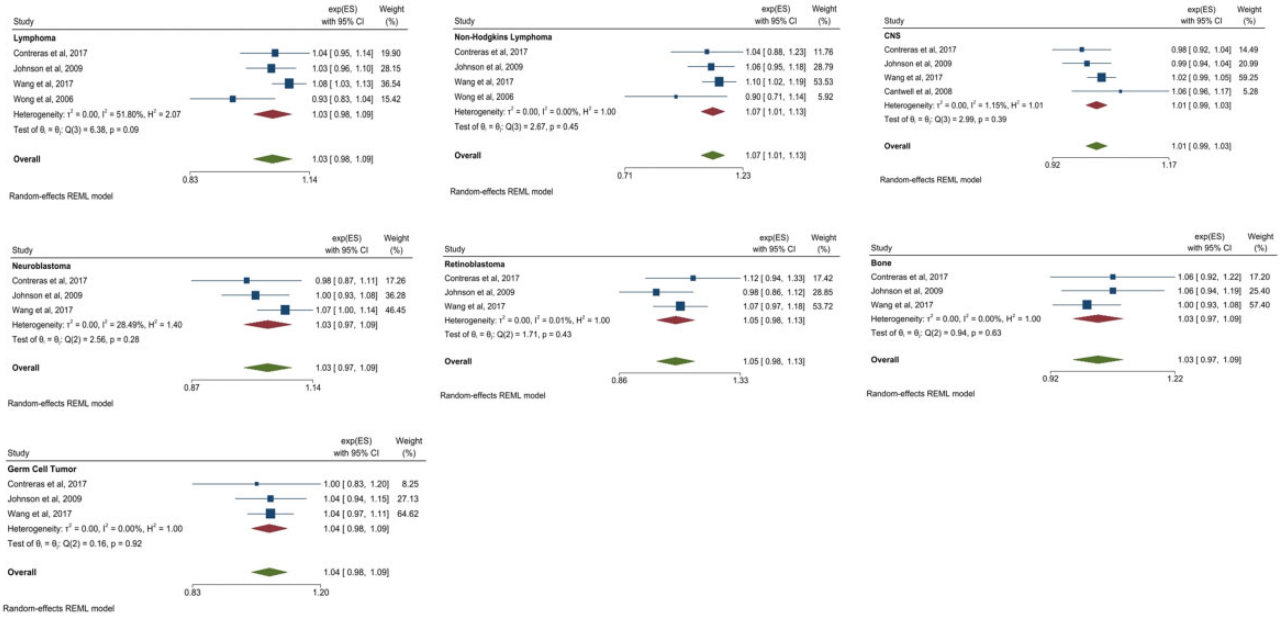

Figure 3. Paternal statistically significant and suggestive meta-analysis results for a 5-year increase in paternal age at birth. Error bars represent 95% confidence intervals. Between-study heterogeneity is presented in terms of the τ^2, I^2, and H^2 statistic. Test of $\theta_i = \theta_j$ refers to the Cochran Q test of between-study homogeneity. Random effects modeling using restricted maximum likelihood methods was used to produce summary estimates. All tests were 2-sided. CI = confidence interval; ES = estimate (β); REML = restricted maximum likelihood.

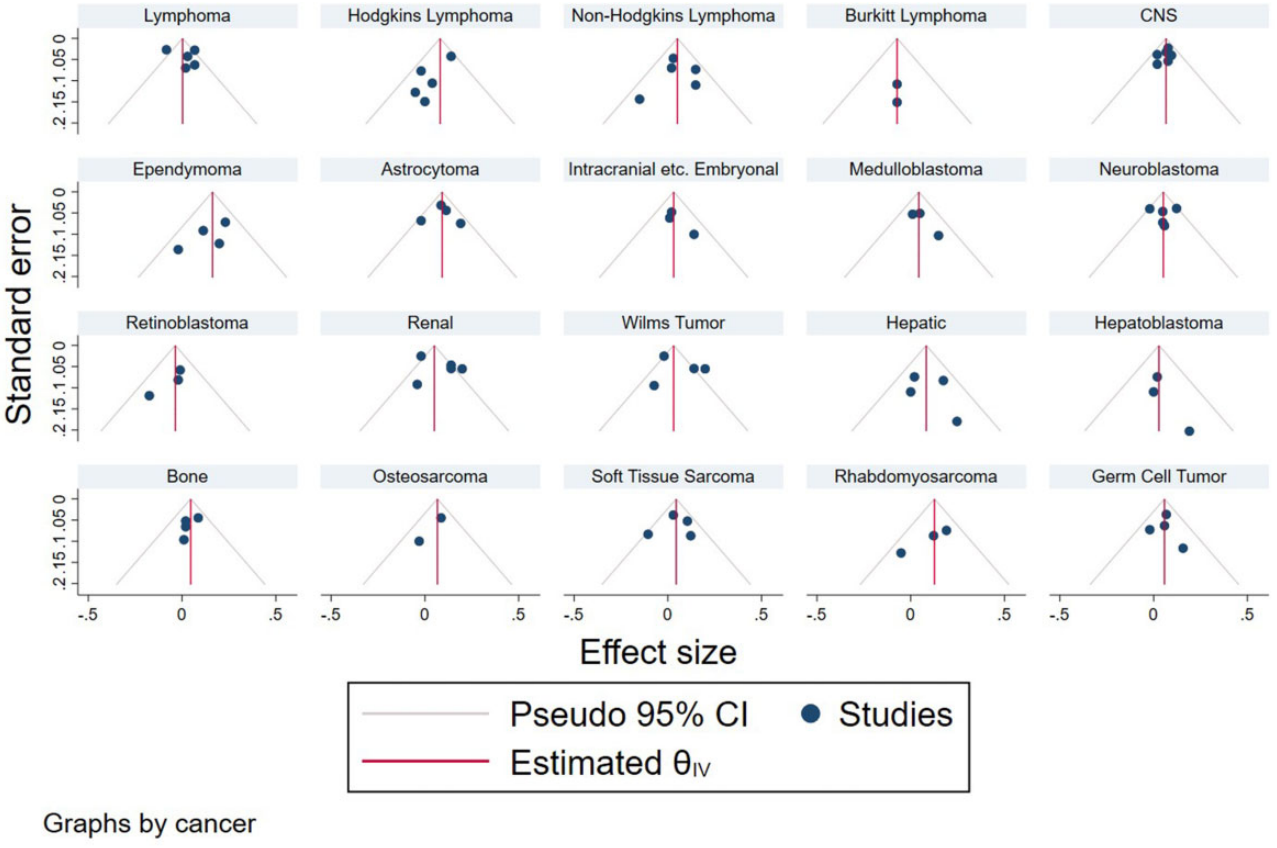

Figure 4. Funnel plots for maternal age publications by cancer type. θ is the log summary odds ratio. CI = confidence interval; CNS = central nervous system; IV = inverse variance.

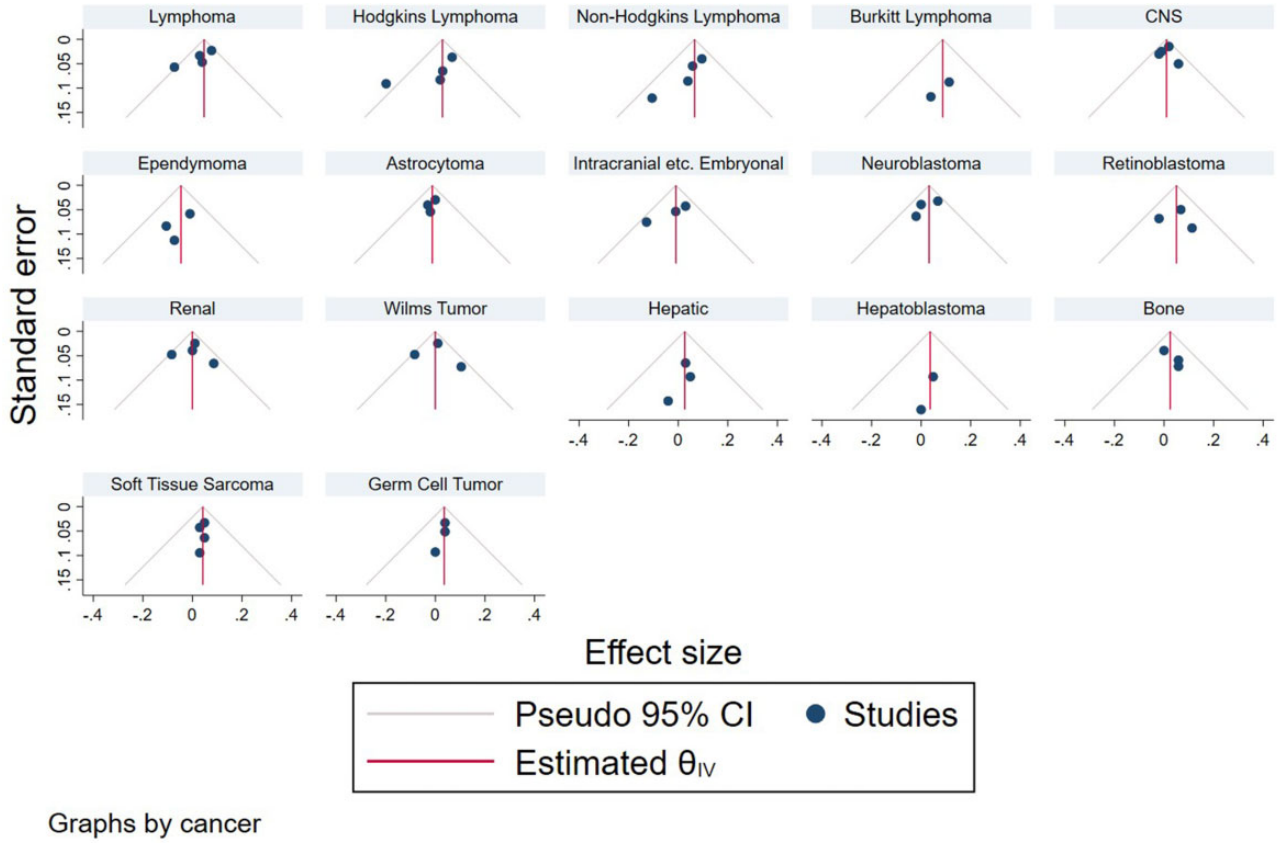

Figure 5. Funnel plots for paternal age publications by cancer type. θ is the log summary odds ratio. CI = confidence interval; CNS = central nervous system; IV = inverse variance .

Table 2. Odds ratio estimates including and excluding studies with crude estimates only[a]

Cancer	Maternal OR including crude estimates (95% CI)	Maternal OR excluding crude estimates (95% CI)	Paternal OR including crude estimates (95% CI)	Paternal OR excluding crude estimates (95% CI)
CNS tumor	1.07 (1.04 to 1.10)	1.07 (1.03 to 1.10)	1.01 (0.99 to 1.03)	1.01 (0.98 to 1.03)
Ependymoma	1.17 (1.07 to 1.29)	1.15 (1.01 to 1.31)	NA	NA
Astrocytoma	1.10 (1.05 to 1.15)	1.08 (1.03 to 1.14)	NA	NA
Medulloblastoma	1.04 (0.98 to 1.12)	1.07 (0.98 to 1.17)	NA	NA
Neuroblastoma	1.05 (0.99 to 1.12)	1.02 (0.97 to 1.07)	NA	NA
Renal tumor	1.09 (0.99 to 1.20)	1.08 (0.96 to 1.21)	NA	NA
Wilms tumor	1.07 (0.95 to 1.21)	1.04 (0.89 to 1.22)	NA	NA
Soft tissue sarcoma	1.04 (0.97 to 1.13)	1.03 (0.93 to 1.13)	1.04 (1.00 to 1.09)	1.04 (1.00, 1.09)
Rhabdomyosarcoma	1.13 (1.01 to 1.26)	1.10 (0.87 to 1.38)	NA	NA

[a]CI = confidence interval; CNS = central nervous system; NA = not applicable; OR = odds ratio.

A priori, we expected to observe an association between paternal age and childhood cancer risk. The rate of germline mutations increases with paternal age, which has been hypothesized to be due to increased number of cell division during spermatogenesis (32). On average, it has been found that with each year in paternal age, the number of mutations in the child increases approximately linearly by 2.9 mutations (33), and on an average, the father transmits 3.44 times more de novo mutations than the mother (34). As germline pathogenic or likely pathogenic variants are associated with childhood cancer risk (35-37), it seemed likely that paternal age influences cancer risk in offspring through this increase in de novo mutations. Previous large, pooled analyses such as the previously mentioned CLIC analyses of ALL (4) (16 720 cases and 42 632 controls) and AML (5) (3182 cases and 8377 controls) have reported that higher paternal age is associated with an increased risk of ALL, though there was no association seen with AML. Our analysis demonstrated a statistically significant association between paternal age and non-Hodgkin lymphoma but no other cancers. As the mechanism through which paternal age may influence childhood cancer risk is both plausible and well understood, the abundance of null findings in this analysis was contrary to expectation. However, at present, there are a limited number of registry-based studies of paternal age available for analysis, and certain registries do not contain paternal age data, thus it is possible that there may be an association

that is undetectable with current literature. It is also difficult to disentangle the independent associations of maternal and paternal age on childhood cancer risk, given their strong correlation (38). However, several of the included studies, and notably the largest studies included in this meta-analysis (8,10,16), did adjust for the other parent's age in all effect estimates. Furthermore, exclusion of studies that only reported crude estimates did not substantially change observed effect estimates.

Somewhat against our expectations, maternal age showed more and greater associations with childhood cancer than paternal age. The observed association between increasing maternal age and odds of childhood lymphoma and solid tumors could be due to multiple potential biological mechanisms. The rate of germline de novo mutations increases with both maternal and paternal age (39), although the association with maternal age is much less strong (34), and certain cancer predisposition syndromes may occur as a result of de novo germline mutations (40). Chromosomal abnormalities and nondisjunction such as Down syndrome are also associated with older maternal age (41). Down syndrome is associated with an increased risk of leukemia (42), and chromosomal abnormalities are associated with an increased risk of any cancer (43); thus, this represents a pathway through which advanced maternal age may affect childhood cancer risk. Advanced maternal age is also associated with an increase in nonchromosomal birth defects (44), which are linked with an increased risk of cancer, including strong associations with CNS tumors and germ cell tumors (43). Additionally, mitochondrial DNA heteroplasmy, or the occurrence of more than 1 mitochondrial DNA haplotype in a cell or tissue, is associated with maternal age (45,46) and has been linked to an increased risk of conditions such as cancer (47). Lastly, advanced maternal age influences patterns of DNA methylation in offspring, and some of the CpG sites found to be influenced by maternal age are also potentially associated with cancer, such as *KLHL35* (48). As proof of principle, transgenerational inheritance of aberrant epigenetic patterns from mother to son has been reported in a case of epimutation, which silenced the *MLH1* DNA mismatch repair gene, resulting in Lynch syndrome in the affected son (49).

There are some important limitations to the current analysis. Though one of the strengths of meta-analyses is the ability to pool multiple studies to increase the sample size, we are still limited by the rarity of some of the cancer types we included, and the relatively limited number of registry-based studies of certain cancer types. If the effect of parental age on cancer incidence is small, current pooling efforts still may not be enough to detect statistically significant effect estimates. We are also limited to what has been published in the current literature. If studies found null associations, these may not be reported in the literature. We tried to minimize the potential for publication bias by using a more liberal inclusion criteria for full text review, however, the funnel plots assessing publication bias appear to show publication bias may be present for certain cancers and parental age. Additionally, there was some evidence of within-study heterogeneity in some of the cancers investigated. This heterogeneity may be partially explained by the inclusion of differing confounders in the individual studies. Additionally, as included studies were conducted in a variety of regions including North and South America, Europe, and Oceania, it is likely that lifestyle and genetic factors that may contribute to cancer risk in children as well as the detection of such cancers may vary. For example, smoking prevalence and age at initiation of smoking varies regionally across the globe (53), and parental smoking is a potential risk factor for multiple childhood cancers (50-52,54-56). Included studies also vary by years of diagnosis, which may additionally add heterogeneity in risk factor prevalence and cancer detection. Many existing registry-based studies were missing paternal age data more often than maternal age—for example, Johnson et al. (8) reported that though maternal age was available for almost all subjects, paternal age was missing in 10% of cases and 11% of controls. We evaluated the influence that this missingness could have on effect estimates in a sensitivity analysis of the 5-state pooling data from the Johnson et al. (8) study, one of the larger studies in this analysis. We assigned fathers with missing ages to both the youngest and oldest age categories to determine the bounds within which the true effect estimate might lie. We found that in this case, missing ages for fathers were unlikely to have a meaningful impact on effect estimates. It is also possible that there are unmeasured confounders affecting these results. Socioeconomic status is associated with parental age (57) and childhood cancer risk (58,59), and only 2 of the included studies controlled for a socioeconomic status proxy: maternal education (17,18). There are also other potential confounders that are associated with both offspring cancer risk and parental age, such as parental smoking (51,60) and maternal prenatal vitamin use (61,62), which are generally not available in registry-based studies. In the case of smoking, older mothers are less likely to smoke than younger mothers (63), and very young paternal age is associated with substance use (64), whereas parental smoking is associated with an increased risk of cancer in children (51,65). In the case of vitamin use, older mothers are more likely to take supplements than younger mothers (61), although maternal vitamin use may decrease the risk of certain childhood cancers (62). In both of the mentioned situations, uncontrolled confounding could lessen observed associations. However, it is important to note that these trends in smoking and vitamin use may not hold constant across all birth years and regions investigated. Another factor limiting this analysis is that some registry-based studies did not have access to paternal age because of the respective registries used, for example, the Swedish and Danish birth registries used in a number of studies included in this analysis do not collect data on paternal age, and thus, these studies could neither estimate the effect of paternal age on the odds of cancer nor control for paternal age in their analyses of maternal age. Maternal and paternal age are strongly correlated variables (38), and a number of studies included in our analysis did not control for paternal age in their analyses of maternal age and cancer risk. Thus, it is possible that some of the observed effect of maternal age on cancer risk is actually due to paternal age. However, removing studies with only crude estimates did not have undue effects on estimates. Of the additional studies that did not control for paternal age in their analysis of maternal age, only one, Stephan sson et al. (29), was a study of a cancer where a statistically significant result was observed—germ cell tumors.

We also must emphasize several strengths to this analysis. We chose to include only population-based registry studies, leading to more valid findings as recall bias is not a concern and selection bias should be minimal. Additionally, we had access to the 5-state pooling data, allowing for re-analysis of the data without the California data, which allowed for the inclusion of the Wang et al. (10) paper and the data from the Johnson et al. (8) paper, thus increasing sample size.

In conclusion, this meta-analysis of registry-based analyses of parental age and childhood cancer supports the association between older maternal age and certain childhood solid cancers—namely, CNS tumors, ependymoma, astrocytoma,

rhabdomyosarcoma, and germ cell tumors—in addition to the previously investigated association between maternal age and leukemia. There was also some evidence of an association between older paternal age and non-Hodgkin lymphoma. The observed associations are also supported by numerous potential biological mechanisms such as germline mutations, DNA methylation, and chromosomal and nonchromosomal birth defects. However, the number of registry-based studies of certain cancers and parental age is relatively limited at this time; thus, further research into the association between parental age and certain cancers is warranted in the future. Additionally, mechanistic studies may also be used to investigate the relationship between parental age and cancer risk, for example, an analysis of tumor profiles and parental age could determine whether or not mutation profiles differ with age.

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Data Availability

The data underlying this meta-analysis are available in the article itself and the referenced articles.

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