HHS Public Access

Author manuscript

Paediatr Perinat Epidemiol. Author manuscript; available in PMC 2018 April 16.

Published in final edited form as:

Paediatr Perinat Epidemiol. 2017 November ; 31(6): 563–572. doi:10.1111/ppe.12412.

Parental age and risk of infant leukemia: a pooled analysis

Erin L Marcotte[a,b,*], **Todd E Druley**[c], **Kimberly J Johnson**[d], **Michaela Richardson**[a], **Julie von Behren**[e], **Beth A Mueller**[f], **Susan Carozza**[g], **Colleen McLaughlin**[h], **Eric J Chow**[f], **Peggy Reynolds**[e], and **Logan G Spector**[a,b]

[a]Division of Epidemiology & Clinical Research, Department of Pediatrics, University of Minnesota, Minneapolis, MN

[b]Masonic Cancer Center, Minneapolis, MN

[c]Departments of Pediatrics and Genetics, Washington University, St Louis, MO

[d]Brown School and Department of Pediatrics, Washington University, St Louis, MO

[e]Northern California Cancer Center, Berkeley, CA

[f]Public Health Sciences Division, Fred Hutchinson Cancer Research Center, Seattle, WA

[g]Epidemiology Program, College of Public Health & Human Sciences, Oregon State University, Corvallis, OR

[h]Department of Population Health Sciences, Albany College of Pharmacy and Health Sciences, Albany, NY

Abstract

Background—Infant leukemia (IL) is extremely rare with fewer than 150 cases occurring each year in the United States. Little is known about its causes. However, recent evidence supports a role of *de novo* mutations in IL etiology. Parental age has been associated with several adverse outcomes in offspring, including childhood cancers. Given the role of older parental age in *de novo* mutations in offspring, we carried out an analysis of parental age and IL.

Methods—We evaluated the relationship between parental age and IL in a case-control study using registry data from New York, Minnesota, California, Texas and Washington. Records from 402 cases (219 acute lymphoblastic leukemia [ALL], 131 acute myeloid leukemia [AML], 52 other) and 45,392 controls born during 1981–2004 were analyzed. Odds ratios (ORs) and 95% confidence intervals (CI) were calculated by logistic regression. Estimates were adjusted for infant sex, birth year category, maternal race, state, and mutually adjusted for paternal or maternal age, respectively.

Results—Infants with mothers age ≥40 years had an increased risk of developing AML (OR 4.80, 95% CI 1.80, 12.76). In contrast, paternal age <20 was associated with increased risk of ALL (OR 3.69, 95% CI 1.62, 8.41).

[*]Corresponding author: Erin L Marcotte, PhD, Department of Pediatrics, Division of Epidemiology & Clinical Research, MMC 715, 420 Delaware St. S.E., Minneapolis, MN 55455; phone: 612-626-3281, fax: 612-624-7147, marcotte@umn.edu.

Conclusion—Ours is the first study to show an association with young paternal age and infant ALL. Given record linkage, there is little concern with recall or selection bias, although data are lacking on *MLL* gene status and other potentially important variables. Parent of origin effects, *de novo* mutations and/or carcinogenic exposures may be involved in IL etiology.

Keywords

infant leukemia; epidemiology; childhood cancer; maternal age; paternal age

Background

Leukemia that occurs in infancy (< 12 months of age) is distinct from leukemia in older children. Infants with leukemia are more often female (compared to ~30% greater incidence in males overall for childhood leukemia), have a nearly equal distribution of acute lymphoblastic (ALL) to acute myeloid leukemia (AML) diagnosis (compared to about 4 times greater incidence of ALL in older children)[1] and have an increased frequency of somatic *MLL* gene rearrangements (50–80% of infant ALL and 34–50% of infant AML compared to approximately 6% and 14% for ALL and AML in older children, respectively)[2, 3].

The *MLL* gene rearrangement in infant leukemia is especially remarkable given that similar *MLL* rearrangements are observed in chemotherapy related leukemias (mostly, AML) associated with modalities that inhibit DNA topoisomerase II[4]. There have been a few epidemiological investigations of infant leukemia[5, 6], and there is some evidence that maternal exposure to DNA topoisomerase II inhibitors during pregnancy through diet and medications may play a causal role, especially for infant AML with *MLL* gene rearrangements[7]. Infants with leukemia, especially ALL with *MLL* gene rearrangements, experience survival rates of less than 50%, which is considerably lower than childhood ALL overall which currently experiences over 80% five year survival[1]. As the causes of infant leukemia are largely unknown, it is important to continue to study risk factors in order to understand the underlying etiology.

Recent observations show that there is a high burden of germline genetic variation in the *MLL3* gene among infants with *MLL*-negative leukemia[8]. In this study, twenty three infant-mother pairs (12 ALL, 13 AML) underwent whole exome sequencing. *MLL3* was a compound heterozygote in 100% of infants with AML and 50% of those with ALL, suggesting that germline mutations may be important for leukemogenesis in the absence of *MLL* rearrangements or a high burden of somatic mutations. While 47% of the germline variation in the infants could be tracked to maternal alleles, this study did not have paternal DNA available, but these results suggest that the additional germline variation is either of paternal or *de novo* origin (or both).

Advanced parental age has been associated with several outcomes in offspring, including autism[9], congenital abnormalities and syndromes[10], and childhood cancers[11]. Given the role of older parental age in *de novo* mutations in offspring, and the potential role of parental age in gene rearrangements, we carried out an analysis of parental age and infant leukemia in a population-based study using pooled data from five US states.

Methods

Childhood cancer cases were identified in the population-based cancer registries of California, Minnesota, New York (excluding New York City), Texas and Washington; recent estimates show at least 95% case completeness[12]. Eligibility criteria, matching factors and inclusion years have been published previously[11]. Briefly, cases were classified according to the International Classification of Childhood Cancer 3rd edition. Controls were randomly selected from each state's birth certificates. Original datasets which were pooled for this study varied in case:control ratios that ranged from 1:1 to 10:1. Controls were matched to cases by birth year in all states; California and Texas additionally matched by sex. Individual matching was performed in California, while frequency matching was used for the other four states. Table 1 shows characteristics of original datasets which were pooled for this study.

Additional criteria were applied for consistency. Since cases were permitted to be selected as controls for Minnesota and New York, we excluded them from the control group in this analysis. The California registry included cases diagnosed < 28 days of age; these were excluded for consistency with the other states. For this analysis, we restricted cases to infants diagnosed with acute leukemia before they reached one year of age. Our final dataset consisted of 402 infants diagnosed with acute leukemia between the ages of 1 month and 1 year (219 ALL, 131 AML, 52 other) and 45,392 controls.

Available birth record information included parental age, birth weight, gestational age, plurality, sex, birth order, birth year and maternal race. California provided gestational age based on the last menstrual period (LMP) while the other four states calculated gestational age using LMP and a clinical estimate. We calculated gestational age using the LMP when available and, when LMP was unavailable, we used the clinical estimate of gestational age. Clinical estimate was used for 2749 (6%) of the births in our dataset.

Statistical analysis

Odds ratios (OR) and 95% confidence intervals (CI) were estimated by unconditional logistic regression (SAS version 9.4, SAS Institute, Cary, NC, USA); individual-level matching in the California dataset was not retained to allow for this method. Cases and controls were restricted to those with birth years after 1981. Records with Down syndrome were removed (16 controls and 6 cases), although Down syndrome was not recorded before 1989 in Washington. Covariates were selected *a priori* for inclusion based on established associations with childhood cancers and were retained in the final multivariate models if they changed the OR estimate substantially (eg, ≥10%). Variables considered include birthweight, gestational age, birth order, maternal education, maternal race/ethnicity, paternal education, paternal race/ethnicity, and plurality. Final models included maternal race (non-Hispanic white, Hispanic, other), maternal and paternal age (≤19, 20–24, 25–29, 30–34, 35–39, 40+ years), state of birth, and the matching variables (birth year and infant sex).

The association between parental age and infant leukemia was analyzed utilizing two methods. The first method was complete case analysis in which a total of 5,547 controls and 72 cases were excluded due to missing maternal race, maternal age, paternal age, or sex (see

Table 2). Due to the large number of records missing paternal age, our second method employed fully conditional specification (FCS) logistic regression multiple imputation procedures (PROC MI and PROC MIANALYZE) to impute paternal and maternal age. FCS is an iterative Markov chain Monte Carlo (MCMC) method wherein a model is specified for each partially observed variable conditional on all other variables, then missing values are imputed for the variable being fit. The method continues until the maximum number of iterations is reached, and the imputed values at the maximum iteration are saved to the imputed dataset. Forty iterations and ten imputation datasets were used. Missing paternal age was most prevalent among children of the youngest mothers:. Of the 834 mothers aged 16 years or younger, 41.4% were missing paternal ages. By contrast, of the 45,463 mothers aged > 16 years, 10.9% were missing paternal ages. The correlation between maternal and paternal age was lower in this age group ($r_{\leq 16\ years}$=0.11 vs. $r_{\geq 17\ years}$=0.74). To reduce any potential bias attributable to this distribution of missing data, we conducted a sensitivity analysis of the complete case method, restricting cases and controls to those with a maternal age ≥16 years. Finally, we conducted a sensitivity analysis excluding births prior to 1989 from Washington, as Down syndrome was not recorded during those years. We also conducted a bias analysis to assess the impact of underreporting of Down syndrome cases in our dataset. We calculated the observed and expected numbers of Down syndrome cases and reconstructed the dataset using maternal age to determine the probability that the infant had Down syndrome, based on published maternal age-specific incidence rates[13], taking into account the number of observed cases and assuming a sensitivity and specificity of 18% and 99%, respectively, for birth certificate reports of Down syndrome[14]. To perform a single reconstruction, we conducted a Bernoulli trial for all subjects, based on their probabilities, to assign whether they were classified as a Down syndrome case. We then subjected each reconstructed dataset to the logistic regression models, excluding the subjects classified as Down syndrome cases in that iteration. We conducted 100 reconstructions.

Utilizing these methods, we examined the association between parental age and infant leukemia overall, as well as stratified by leukemia type (ALL and AML) and by infant's age at diagnosis (1–5 months, 6–11 months).

Results

We did not observe any differences between cases and controls with regard to plurality, birth weight or gestational age (Table 2), and exclusions of twins/multiples did not alter this (data not shown). AML cases were more likely than controls to have a birth order of third or higher. The mean age of control mothers at birth was slightly younger (27.0 [SD = 5.8]) than case mothers overall (27.3 [SD = 6.3]), mothers of ALL cases (27.4 [SD = 6.2]), and mothers of AML cases (27.3 [SD = 6.7]) (data not shown). The mean age of control fathers was slightly younger (29.9 [SD = 6.3]) than case fathers overall (30.0 [SD = 7.0]) and fathers of AML cases (30.6 [SD = 7.5]), while control fathers were slightly older than fathers of ALL cases (29.5 [SD = 6.9]).

In multivariate analyses of complete records, we did not observe associations between maternal age and infant leukemia overall (Figure 1A) or ALL, although point estimates for the risk of ALL were decreased for mothers age ≤ 19 years (OR 0.51, 95% CI 0.24, 1.09)

and 20–24 years (OR 0.77, 95% CI 0.47, 1.24) (Figure 1B). Older maternal age was associated with increased point estimates for risk of infant AML in our complete records analysis, and we observed a strong estimated effect for AML in relation to maternal age 40+ years (OR 4.80, 95% CI 1.80, 12.76; Figure 1C). This association remained when we used imputed parental ages (OR 4.27, 95% CI 1.72, 10.64; Supplementary Table 1).

In complete records analyses of paternal age, very young paternal age (≤ 19 years) was associated with infant leukemia overall (OR 2.21, 95% CI 1.16, 4.21; Figure 2A), with a particularly strong effect estimate for infant ALL (OR 3.69, 95% CI 1.62, 8.41; Figure 2B). This association was somewhat attenuated with imputed parental ages (OR 2.55, 95% CI 1.08, 6.04; Supplementary Table 2). The estimated effect for paternal age 20–24 years and infant ALL was also increased (OR 1.47, 95% CI 0.88, 2.45) in our complete records analysis. Also using complete records for analysis, we did not observe an association between advanced paternal age and infant ALL, and there was no association between either younger or advanced paternal age and infant AML (Figure 2C).

Sensitivity analyses excluding births prior to 1989 from Washington and bias analysis to assess the effect of under ascertainment of Down syndrome cases did not change our results (data not shown). Analyses stratified by infant's age at diagnosis yielded generally similar results but were based on very few numbers of cases in the extremes of the parental age spectrum (data not shown).

Comment

Main findings

We observed associations between older maternal age and infant AML and younger paternal age and infant ALL. These results remained consistent both when we used imputed parental ages and conducted sensitivity analyses limiting to mothers age 16 years and older.

Interpretation

Although several studies have investigated the relationship between parental age and childhood cancer, few previous studies have examined infant leukemia specifically. One analysis which combined data from three population-based case-control studies investigated maternal age among all infant leukemias (ALL and AML combined, n=303) reported a suggestive u-shaped relationship, where offspring of both younger and older mothers had increased risk of infant leukemia compared to mothers age 20–35 years[15]. Another population-based case-control study did not find an association between maternal age and all infant leukemias (ALL and AML, n=238)[16]. Neither of these analyses accounted for paternal age or stratified by leukemia subtype, which may explain the inconsistency of these results compared to our study; also both relied on active participation and may have been susceptible to selection bias. A recent meta-analysis of parental age and childhood leukemia showed associations between both younger and older maternal age and childhood AML and young paternal age and childhood AML[17]. However, the comparability of the meta-analysis to the current study is limited due to inclusion of children diagnosed at older ages, variation

between studies on classification of parental age categories, and the fact that only a subset of included studies mutually adjusted for maternal and paternal age.

The mechanisms through which advanced maternal age could affect infant leukemia risk might include aberrant gene expression or genomic alterations. Maternal age is known to play an important role in the etiology of other offspring outcomes involving chromosomal anomalies[18]; given the importance of the MLL rearrangements in infant leukemia, it is possible that maternal age plays a role in these novel mutational events. Furthermore, *de novo* point mutations increase with maternal age[19], and these maternally derived mutational signatures may be distinct from those that are paternally derived. A prior study has reported that germline variation may play an important role in infant leukemia without *MLL* translocations, with a particularly striking association between variations in the *MLL3* gene among AML cases[8]. Interestingly, in that study, 38% (5 of 13) of mothers of AML cases were >35 years of age. Given that the gene regulatory functions of the MLL family of proteins rely on histone modification with known histone methyltransferase functions and suspected histone ubiquitination functions, epigenetic alterations in oocytes that are transmissible to offspring are another possible mechanism. Studies in both humans[20] and mice[21] have demonstrated age-associated differential gene expression in oocytes among cell cycle control and DNA repair pathways. Furthermore, several studies have reported aberrant methylation patterns in infant leukemia[22], including a study within a mouse model of *MLL*-rearranged leukemia[23]. It is also possible that a longer period of cumulative exposure to environmental mutagens in older mothers also plays a role. Environmental toxins have been shown to induce global hypermethylation, de novo germline mutations, and DNA damage in germ cells, and can have long-term developmental effects in offspring[24].

Older mothers are more likely to have used assisted reproductive technology (ART)[25] and fertility treatment has been implicated as a possible cause of childhood cancer among offspring[26]. While we did not have information on use of fertility treatments, we do not believe that this contributed significantly to our findings as there are very few twins and higher order multiples among our cases (n=6). Although in the last two decades efforts have been made within the medical community to reduce the number of multiple births resulting from ART, our study covers birth years prior to most of these efforts, when nearly 60% of live births from ART were twin gestations or higher order multiples[27]. It is also possible that older maternal age is a proxy for other factors that could increase risk of infant leukemia in the offspring, such as age-associated changes in hormonal levels during pregnancy[28].

The mechanisms through which young paternal age could affect infant leukemia risk are less clear, although adverse outcomes among offspring of young fathers, including an increased risk of chromosomal aneuploidies[29], schizophrenia[30], preterm birth[31], and birth defects[32] have been reported. A recent study reported a 6.7-fold increase in germline mutation rate for teenage fathers compared to teenage mothers[33]. From this mutation rate among young fathers, the authors estimated that approximately 147 cell divisions may occur in the male germline during pre-puberty spermatogenesis, which is much higher than previously estimated. Therefore there may be a high burden of *de novo* germline mutations among offspring of young fathers which could account for the excess risk observed in these children. Furthermore, young men with drug and other substance abuse problems are more

likely to become teenage fathers[34], and these behaviors are also associated with increased germline mutations in sperm and other deleterious effects in spermatozoa[35].

We were not able to exclude children with Down syndrome for early birth years from Washington state, although sensitivity analysis excluding years in which birth records did not record Down syndrome did not change our results. However, birth certificates may not capture all cases of Down syndrome even when it is recorded. As children with Down syndrome are predisposed to leukemia[36] and one study reported an increased risk of Down syndrome among offspring of young fathers[29], this may have influenced our results. However the children for whom we do not have these data represent a small proportion of our overall study population and bias analysis accounting for underreporting of Down syndrome did not change our results. Furthermore, although children with Down syndrome are occasionally diagnosed with leukemia in infancy, most are diagnosed at older ages[36]. Therefore we do not believe this accounts for the association we observed between young paternal age and infant ALL.

Parental ages have been steadily increasing in the United States over the last several decades, particularly among mothers. Birth rates for women age 30–34 years increased by 64% between 1980 and 2015, while rates for women age 35–39 and 40–44 each increased over 150% within the same period[37]. The largest increases have been observed among older women, with a 300% increase in birth rate among women age 45–49 between 1980 and 2015. By contrast, birth rates among women younger than age 30 years have decreased, with particularly sharp decreases among the youngest age groups. Birth rates among older men have also increased since 1980, although not as dramatically as those among older women. Notable for the current study, birth rates among young men age 15–19 decreased by 45% between 1980 and 2015[37].

Strengths of the study

Strengths of our study include the population-based data and use of high quality cancer registries to ascertain cases and birth registries from which we randomly sampled controls. The large sample size allowed stratification of infant leukemia subtype and also provided sufficient power to detect associations among the two extremes of the parental age spectrum. Our study did not rely on active participation and therefore selection bias is not expected to have impacted our results. We expect that our main exposure variable, parental age, is accurately reported on birth certificates[38].

Limitations of the data

Misclassification of other covariates is possible, however any misclassification would be nondifferential with respect to disease status and therefore would bias estimates toward the null. Although this study did not include infant leukemia cases from the entire US population, we expect that the results are generalizable to all infant leukemias in the US given that this was a population-based sample and we do not believe the factors that distinguish the study population from the general US population modify the effect of parental age on risk of infant leukemia. Furthermore, the racial and ethnic diversity of controls mirrors that of the US as a whole, and the maternal and paternal ages of controls

follows national trends from the past three decades. Paternal age was missing in 10.9% of records for mothers age > 16 years and 41.4% of those for mothers age ≤ 16 years. We accounted for this by imputation for parental ages and by performing a sensitivity analysis, excluding children whose mothers were age ≤ 16 years; associations were slightly attenuated using imputation methods, but remained statistically significant. Our study was limited by lack of data available on other variables of interest, such as MLL rearrangement status, use of ART, and complete ascertainment of Down syndrome.

Conclusions

Our results suggest associations between advanced maternal age and risk of infant AML and young paternal age and risk of infant ALL. Since most etiological studies of infant leukemia focus on pregnancy-related events, our results suggest that future studies need to consider both maternal and paternal contributions. In particular, parent of origin *de novo* mutations and/or carcinogenic exposures may be involved. Additionally, future studies on whether these results vary by *MLL* status or use of ART will be useful for a thorough analysis of these potential associations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by Children's Cancer Research Fund, Minneapolis, MN; National Cancer Institute at the National Institutes of Health (N01-CN-05230 to WA, R01CA717450 to CA, R01CA92670 to TX); Fred Hutchinson Cancer Research Center; and the Centers for Disease Control and Prevention's National Program of Cancer Registries by cooperative agreement (U58DP000783-01 to NY).

Abbreviations used

ALL	acute lymphoblastic leukemia
AML	acute myeloid leukemia
ART	artificial reproductive technology
CI	confidence interval
FCS	fully conditional specification
IL	infant leukemia
LMP	last menstrual period
MCMC	Markov chain Monte Carlo
OR	odds ratio

References

1. Howlader, N., Noone, AM., Krapcho, M., Miller, D., Bishop, K., Altekruse, SF., et al. SEER Cancer Statistics Review, 1975–2013, National Cancer Institute. Bethesda, MD: National Cancer Institute; 2016. Available from: https://seer.cancer.gov/csr/1975_2013/ [cited 2016 December 11, 2016]
2. Greaves MF, Wiemels J. Origins of chromosome translocations in childhood leukaemia. Nat Rev Cancer. 2003; 3:639–649. [PubMed: 12951583]
3. Felix CA, Lange BJ. Leukemia in infants. Oncologist. 1999; 4:225–240. [PubMed: 10394590]
4. Kumar L. Epipodophyllotoxins and secondary leukaemia. Lancet. 1993; 342:819–820. [PubMed: 8104269]
5. Ross JA, Davies SM, Potter JD, Robison LL. Epidemiology of childhood leukemia, with a focus on infants. Epidemiol Rev. 1994; 16:243–272. [PubMed: 7713179]
6. Ross JA, Potter JD, Reaman GH, Pendergrass TW, Robison LL. Maternal exposure to potential inhibitors of DNA topoisomerase II and infant leukemia (United States): a report from the Children's Cancer Group. Cancer Causes Control. 1996; 7:581–590. [PubMed: 8932918]
7. Spector LG, Xie Y, Robison LL, Heerema NA, Hilden JM, Lange B, et al. Maternal diet and infant leukemia: the DNA topoisomerase II inhibitor hypothesis: a report from the children's oncology group. Cancer Epidemiol Biomarkers Prev. 2005; 14:651–655. [PubMed: 15767345]
8. Valentine MC, Linabery AM, Chasnoff S, Hughes AE, Mallaney C, Sanchez N, et al. Excess congenital non-synonymous variation in leukemia-associated genes in MLL- infant leukemia: a Children's Oncology Group report. Leukemia. 2014; 28:1235–1241. [PubMed: 24301523]
9. Sandin S, Hultman CM, Kolevzon A, Gross R, MacCabe JH, Reichenberg A. Advancing maternal age is associated with increasing risk for autism: a review and meta-analysis. J Am Acad Child Adolesc Psychiatry. 2012; 51:477–486 e471. [PubMed: 22525954]
10. Baird PA, Sadovnick AD. Maternal age in Down syndrome. Am J Med Genet. 1988; 29:947–948. [PubMed: 2969683]
11. Johnson KJ, Carozza SE, Chow EJ, Fox EE, Horel S, McLaughlin CC, et al. Parental age and risk of childhood cancer: a pooled analysis. Epidemiology. 2009; 20:475–483. [PubMed: 19373093]
12. Thoburn KK, German RR, Lewis M, Nichols PJ, Ahmed F, Jackson-Thompson J. Case completeness and data accuracy in the Centers for Disease Control and Prevention's National Program of Cancer Registries. Cancer. 2007; 109:1607–1616. [PubMed: 17343277]
13. Bray I, Wright DE, Davies C, Hook EB. Joint estimation of Down syndrome risk and ascertainment rates: a meta-analysis of nine published data sets. Prenat Diagn. 1998; 18:9–20. [PubMed: 9483635]
14. Boulet SL, Shin M, Kirby RS, Goodman D, Correa A. Sensitivity of birth certificate reports of birth defects in Atlanta, 1995–2005: effects of maternal, infant, and hospital characteristics. Public Health Rep. 2011; 126:186–194. [PubMed: 21387948]
15. Ross JA, Potter JD, Shu XO, Reaman GH, Lampkin B, Robison LL. Evaluating the relationships among maternal reproductive history, birth characteristics, and infant leukemia: a report from the Children's Cancer Group. Ann Epidemiol. 1997; 7:172–179. [PubMed: 9141639]
16. Spector LG, Davies SM, Robison LL, Hilden JM, Roesler M, Ross JA. Birth characteristics, maternal reproductive history, and the risk of infant leukemia: a report from the Children's Oncology Group. Cancer Epidemiol Biomarkers Prev. 2007; 16:128–134. [PubMed: 17220341]
17. Sergentanis TN, Thomopoulos TP, Gialamas SP, Karalexi MA, Biniaris-Georgallis SI, Kontogeorgi E, et al. Risk for childhood leukemia associated with maternal and paternal age. Eur J Epidemiol. 2015; 30:1229–1261. [PubMed: 26537708]
18. Ginsburg C, Fokstuen S, Schinzel A. The contribution of uniparental disomy to congenital development defects in children born to mothers at advanced childbearing age. Am J Med Genet. 2000; 95:454–460. [PubMed: 11146466]
19. Goldmann JM, Wong WS, Pinelli M, Farrah T, Bodian D, Stittrich AB, et al. Parent-of-origin-specific signatures of de novo mutations. Nat Genet. 2016; 48:935–939. [PubMed: 27322544]
20. Steuerwald NM, Bermudez MG, Wells D, Munne S, Cohen J. Maternal age-related differential global expression profiles observed in human oocytes. Reprod Biomed Online. 2007; 14:700–708. [PubMed: 17579982]

21. Hamatani T, Falco G, Carter MG, Akutsu H, Stagg CA, Sharov AA, et al. Age-associated alteration of gene expression patterns in mouse oocytes. Hum Mol Genet. 2004; 13:2263–2278. [PubMed: 15317747]
22. Zhang Y, Chen A, Yan XM, Huang G. Disordered epigenetic regulation in MLL-related leukemia. Int J Hematol. 2012; 96:428–437. [PubMed: 23054645]
23. Ng RK, Kong CT, So CC, Lui WC, Chan YF, Leung KC, et al. Epigenetic dysregulation of leukaemic HOX code in MLL-rearranged leukaemia mouse model. J Pathol. 2014; 232:65–74. [PubMed: 24122813]
24. Yauk C, Polyzos A, Rowan-Carroll A, Somers CM, Godschalk RW, Van Schooten FJ, et al. Germ-line mutations, DNA damage, and global hypermethylation in mice exposed to particulate air pollution in an urban/industrial location. Proc Natl Acad Sci U S A. 2008; 105:605–610. [PubMed: 18195365]
25. Prevention CfDCa. 2014 Assisted Reproductive Technology Fertility Clinic Success Rates Report. US Dept of Health and Human Services; 2016.
26. Hargreave M, Jensen A, Toender A, Andersen KK, Kjaer SK. Fertility treatment and childhood cancer risk: a systematic meta-analysis. Fertil Steril. 2013; 100:150–161. [PubMed: 23562045]
27. Reynolds MA, Schieve LA, Martin JA, Jeng G, Macaluso M. Trends in multiple births conceived using assisted reproductive technology, United States, 1997–2000. Pediatrics. 2003; 111:1159–1162. [PubMed: 12728130]
28. Troisi R, Potischman N, Roberts J, Siiteri P, Daftary A, Sims C, et al. Associations of maternal and umbilical cord hormone concentrations with maternal, gestational and neonatal factors (United States). Cancer Causes Control. 2003; 14:347–355. [PubMed: 12846366]
29. Steiner B, Masood R, Rufibach K, Niedrist D, Kundert O, Riegel M, et al. An unexpected finding: younger fathers have a higher risk for offspring with chromosomal aneuploidies. Eur J Hum Genet. 2015; 23:466–472. [PubMed: 25005732]
30. Miller B, Messias E, Miettunen J, Alaraisanen A, Jarvelin MR, Koponen H, et al. Meta-analysis of paternal age and schizophrenia risk in male versus female offspring. Schizophr Bull. 2011; 37:1039–1047. [PubMed: 20185538]
31. Abel EL, Kruger M, Burd L. Effects of maternal and paternal age on Caucasian and Native American preterm births and birth weights. Am J Perinatol. 2002; 19:49–54. [PubMed: 11857096]
32. Archer NP, Langlois PH, Suarez L, Brender J, Shanmugam R. Association of paternal age with prevalence of selected birth defects. Birth Defects Res A Clin Mol Teratol. 2007; 79:27–34. [PubMed: 17120236]
33. Forster P, Hohoff C, Dunkelmann B, Schurenkamp M, Pfeiffer H, Neuhuber F, et al. Elevated germline mutation rate in teenage fathers. Proc Biol Sci. 2015; 282:20142898. [PubMed: 25694621]
34. Thornberry, TP., Wei, EH., Stouthamer-Loeber, M., Van Dyke, J. Teenage Fatherhood and Delinquent Behavior. Justice USDo. , editor. Washington, DC: Office of Juvenile Justice and Delinquency Prevention; 2000.
35. Yauk CL, Berndt ML, Williams A, Rowan-Carroll A, Douglas GR, Stampfli MR. Mainstream tobacco smoke causes paternal germ-line DNA mutation. Cancer Res. 2007; 67:5103–5106. [PubMed: 17545587]
36. Ross JA, Spector LG, Robison LL, Olshan AF. Epidemiology of leukemia in children with Down syndrome. Pediatr Blood Cancer. 2005; 44:8–12. [PubMed: 15390275]
37. Martin JA, Hamilton BE, Osterman MJ, Driscoll AK, Mathews TJ. Births: Final Data for 2015. Natl Vital Stat Rep. 2017; 66:1.
38. Northam S, Knapp TR. The reliability and validity of birth certificates. J Obstet Gynecol Neonatal Nurs. 2006; 35:3–12.

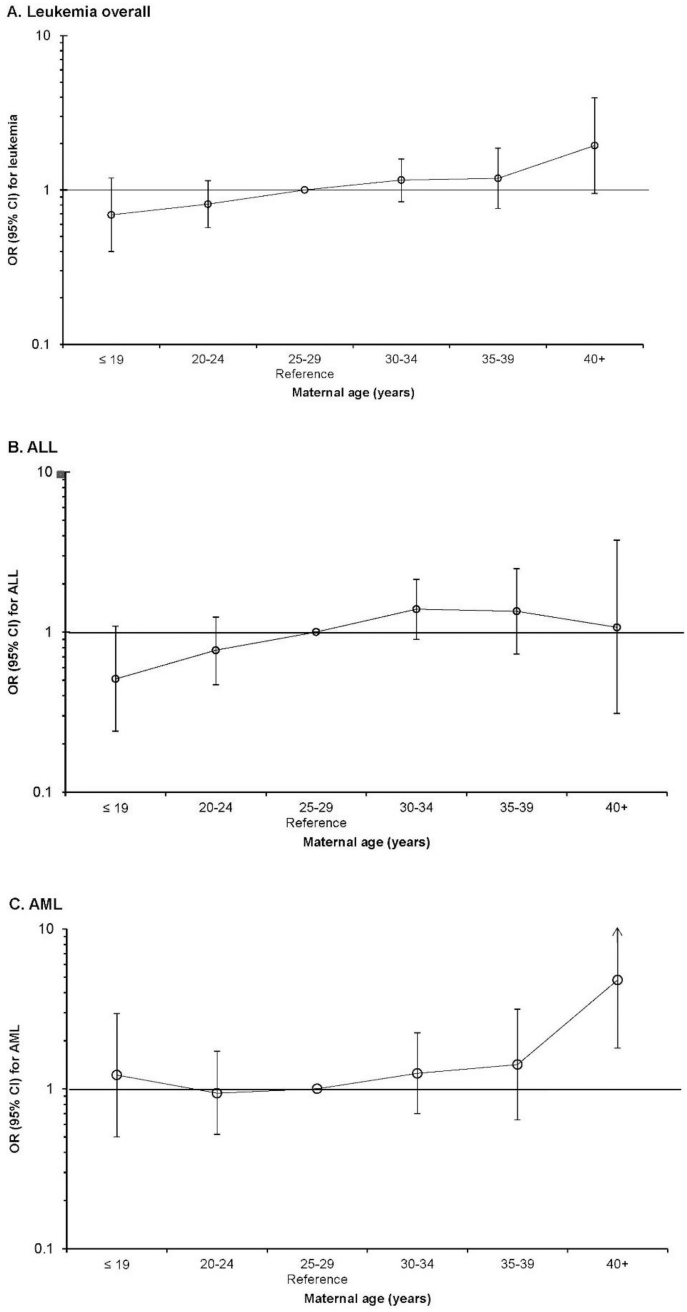

Figure 1.

Association of maternal age with infant leukemia using complete case analysis, plotted on the log scale, and adjusted for sex, birth year category, maternal race (white, Hispanic, other), state, and paternal age. Figures shown are: (A): all infant leukemias; (B) infant ALL; (C) infant AML.

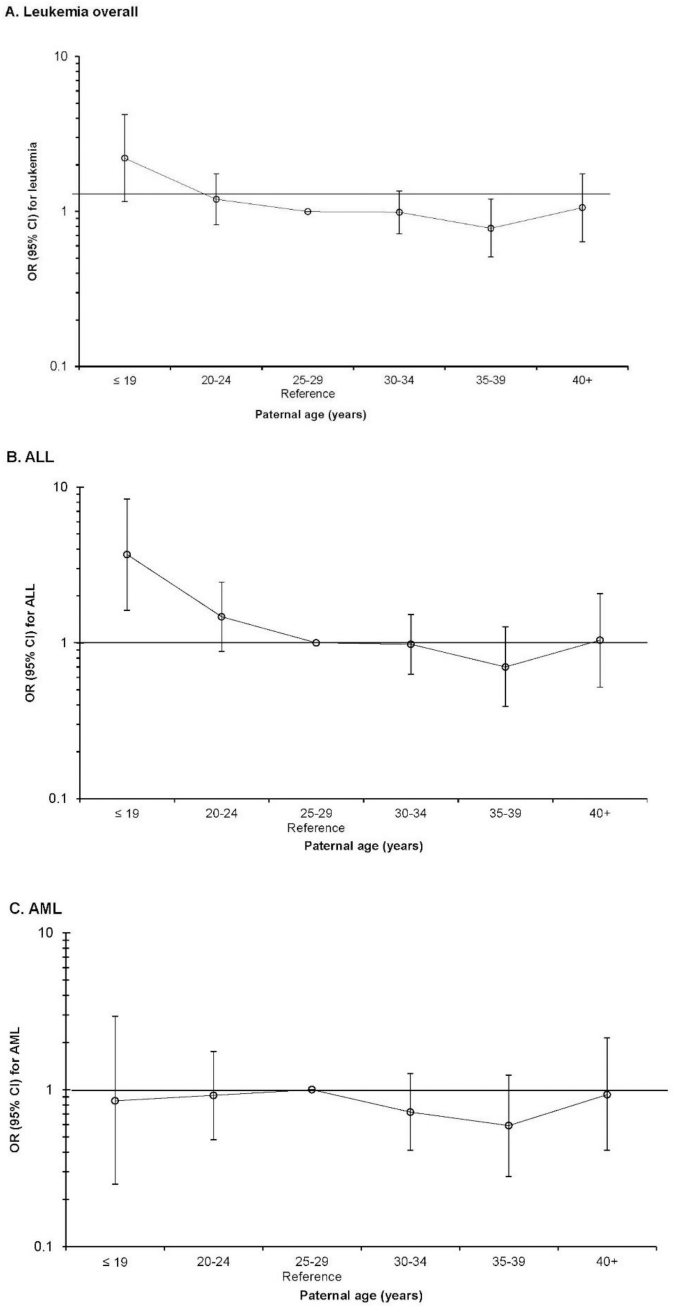

Figure 2.

Association of paternal age with infant leukemia using complete case analysis, plotted on the log scale, and adjusted for sex, birth year category, maternal race (white, Hispanic, other), state, and maternal age. Figures shown are: (A): all infant leukemias; (B) infant ALL; (C) infant AML.

Table 1

Characteristics of original state datasets

State	Years of diagnosis	Years of birth	No. cases	No. controls	Matching factors
California	1988–1997	1987–1997	152	7607	Birth year, Sex
Minnesota	1988–2004	1987–2004	44	5999	Birth year
New York	1985–2001	1984–2001	68	6663	Birth year
Texas	1990–1998	1989–1998	87	2385	Birth year, Sex
Washington	1980–2004	1980–2004	51	22738	Birth year

Paediatr Perinat Epidemiol. Author manuscript; available in PMC 2018 April 16.

Table 2

Selected descriptive statistics for the study population

	Controls N = 45,392 N (%)	All Infant Leukemias[a] N = 402 N (%)	ALL N = 219 N (%)	AML N = 131 N (%)
Sex				
Male	23,935 (53)	199 (50)	110 (50)	60 (46)
Female	21,455 (47)	203 (50)	109 (50)	71 (54)
Missing	2	0	0	0
Birth Year Category				
1981–1989	17,444 (38)	92 (23)	42 (19)	36 (27)
1990–1997	22,523 (50)	262 (65)	156 (71)	75 (57)
1998–2004	5,425 (12)	48 (12)	21 (10)	20 (15)
Missing	0	0	0	0
Plurality				
Singleton	44,318 (98)	396 (99)	216 (99)	128 (98)
Twin +	1,046 (2)	6 (1)	3 (1)	3 (2)
Missing	28	0	0	0
Birth Weight				
< 2500 g	2,483 (5)	17 (4)	7 (3)	8 (6)
2500 – < 4000 g	36,909 (82)	332 (83)	181 (83)	110 (85)
4000 +	5,890 (13)	51 (13)	31 (14)	12 (9)
Missing	110	2	0	1
Gestational Age				
< 37	3,509 (8)	29 (7)	15 (7)	11 (9)
37–38	7,274 (17)	72 (18)	35 (16)	30 (23)
39–40	18,981 (43)	177 (45)	97 (45)	52 (41)
41	7,702 (18)	69 (18)	36 (17)	22 (17)
42 +	6,384 (15)	47 (12)	33 (15)	13 (10)
Missing	1,542	8	3	3
Birth Order				
First	18,305 (41)	156 (40)	91 (42)	44 (34)
Second	14,557 (33)	111 (28)	57 (27)	38 (29)
Third	11,871 (27)	127 (32)	67 (31)	47 (36)
Missing	659	8	4	2
Age at Diagnosis				
1–5 months	-	174 (43)	101 (46)	47 (36)
6–11 months	-	228 (57)	118 (54)	84 (64)
Missing	0	0	0	0
Maternal Age				

	Controls N = 45,392 N (%)	All Infant Leukemias[a] N = 402 N (%)	ALL N = 219 N (%)	AML N = 131 N (%)
≤ 19	4,750 (10)	48 (12)	23 (11)	20 (15)
20–24	11,333 (25)	88 (22)	51 (23)	27 (21)
25–29	14,166 (31)	120 (30)	63 (29)	37 (28)
30–34	10,334 (23)	95 (24)	56 (26)	27 (21)
35–39	4,060 (9)	37 (9)	21 (10)	11 (8)
40 +	732 (2)	14 (3)	5 (2)	9 (7)
Missing	17	0	0	0
Paternal Age				
≤ 19	1,310 (3)	20 (6)	13 (7)	5 (5)
20–24	6,943 (17)	57 (17)	33 (18)	19 (17)
25–29	11,878 (29)	87 (26)	44 (25)	33 (30)
30–34	11,320 (28)	96 (29)	52 (29)	26 (24)
35–39	5,956 (15)	42 (13)	21 (12)	13 (12)
40 +	2,907 (7)	31 (9)	15 (8)	14 (13)
Missing	5,078	69	41	21
Maternal Race				
White	32,846 (73)	221 (55)	112 (51)	77 (59)
Hispanic	6,201 (14)	138 (35)	85 (39)	37 (28)
Other	5,795 (13)	40 (10)	21 (10)	16 (12)
Missing	550	3	1	1
Paternal Race				
White	29,704 (74)	210 (58)	102 (52)	77 (63)
Hispanic	5,910 (15)	124 (34)	76 (39)	35 (29)
Other	4,767 (12)	30 (8)	18 (9)	10 (8)
Missing	5,011	38	23	9
State				
CA	7,607 (17)	152 (38)	85 (39)	49 (37)
MN	5,999 (13)	44 (11)	23 (11)	16 (12)
NY	6,663 (15)	68 (17)	30 (14)	24 (18)
TX	2,385 (5)	87 (22)	53 (24)	26 (20)
WA	22,738 (50)	51 (13)	28 (13)	16 (12)
Missing	0	0	0	0

[a]All leukemias includes: Lymphoid leukemia, Acute myeloid leukemia, Chronic myelogenous diseases, Myelodysplastic syndrome, Leukemia NOS