Cancer Epidemiology 49 (2017) 202–215

Contents lists available at ScienceDirect

Cancer Epidemiology

The International Journal of Cancer Epidemiology, Detection, and Prevention

journal homepage: www.cancerepidemiology.net

Parental age and childhood cancer risk: A Danish population-based registry study

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ARTICLE INFO

Article history:
Received 9 February 2017
Received in revised form 27 June 2017
Accepted 30 June 2017
Available online 14 July 2017

Keywords:
Childhood cancer
Parental age
Paternal age
Maternal age
Epidemiology
Risk factors

ABSTRACT

Background: Though the association between parental age at child's birth and the risk of childhood cancer has been previously investigated, the evidence to date is inconclusive and scarce for rarer cancer types.
Methods: Cancer cases (N = 5,856) were selected from all children born from 1968 to 2014 and diagnosed from 1968 to 2015 in Denmark at less than 16 years of age listed in the nationwide Danish Cancer Registry. Cases were individually matched to controls (1:100) on sex and year of birth with a total of 585,594 controls randomly sampled from all live births in Denmark from the Danish Central Population Registry. Parental age at child's birth was extracted from the Central Population Registry. Conditional logistic regression models were used to estimate odds ratios for the association between parental age at child's birth and childhood cancer risk. Parental age was modeled as both categorical (referent group, parents aged 25–29) and continuous per 5-year increase in age.
Results: Offspring of older mothers were at an increased risk of acute lymphoblastic leukemia [OR = 1.10, 95% CI: (1.02, 1.19) per 5-year increase in age]. Older maternal age (40+) increased the risk of non-Hodgkin lymphoma [OR = 1.96, 95%CI: (1.12, 3.43)]. The risk of Wilms' tumor also appeared elevated with older paternal age [OR = 1.11, 95% CI: (0.97, 1.28) per 5-year increment in age].
Conclusion: Older parental age was a risk factor for various childhood cancers in Danish children. Further investigation of the biological and social factors that may be contributing to these associations is warranted.

1. Introduction

Parental age at child's birth has increased in the US, Europe, and elsewhere. In the United States in 2013, the birth rate for women over 35 years of age (49.3 births per 1000 women) was at the highest level in 50 years, while the birth rate for all women younger than 30 has dropped, with a 61% drop in the teen birth rate since 1970. The rates of children born to older fathers (ages 35–54) have also increased although less steeply than among mothers [1]. In Denmark, there has been an increasing trend in the average age of first childbirth from 23.1 years in 1960 to 29 years in 2014 [2]. Pregnancy outcomes related to advanced maternal age include low birth weight, preterm birth, and sharp increases in the risk of chromosomal anomalies. Advanced paternal age has been less studied than maternal age, but is related to birth defects associated with single gene mutations (achondroplasia, neurofibromatosis) and chromosomal abnormalities as well as neurodevelopmental disorders [3].

Cancer is the leading cause of death from disease among children younger than 14 and Denmark has among the highest incidence rates of childhood cancer worldwide [4]. Little is known about the etiology of these diseases, with established risk factors limited to ionizing radiation, certain rare genetic syndromes, genetic polymorphisms, congenital anomalies, and parental smoking (only in the case of hepatoblastoma) [5,6].

Older parental age has been associated with several childhood cancer types, but results across studies have been inconsistent. The most extensively studied cancer type has been leukemia. A recent meta-analysis, including results from 69 case-control studies and 8 cohort studies, found an increased risk of acute lymphoblastic leukemia (ALL) in offspring of older mothers and fathers when examining age as a continuous and categorical variable. Additionally, offspring of younger fathers also had an increased risk of ALL.

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http://dx.doi.org/10.1016/j.canep.2017.06.010
1877-7821/

In terms of acute myeloid leukemia (AML), there was a U-shaped risk with maternal age and the risk of AML was increased only in offspring born to younger fathers. Only 4 of the 77 studies included in this analysis examined the impact of mutual adjustment for maternal and paternal age, and the only notable association that persisted with mutual adjustment was an increased risk of AML with younger maternal age [7].

Population-based studies that have assessed several, rarer cancer types are more limited. A recent study using California Cancer Registry data examined parental age (categorical/per 5-year increment) and found an overall increased risk of ALL, central nervous system (CNS) tumors, hepatic tumors, renal tumors, and lymphomas with older maternal age when adjusting for paternal age. For paternal age, only an increased risk of lymphomas with older paternal age when mutual adjusting was found [8]. A pooled-analysis of registry data from 5 US States (California, Minnesota, New York, Texas, Washington) found an increased risk of several childhood cancer types with advanced maternal age. In particular, leukemia, CNS tumors, neuroblastoma, Wilms' tumors, and soft tissue sarcomas were associated with older maternal age when adjusting for paternal age. Additionally, paternal age was not associated with most childhood cancer types after adjusting for maternal age [9]. A registry-based study in Denmark, including children born 1978–2010, examined paternal age (categorical/per 5-year increment) in relation to various cancer types and found an increased risk of ALL and decreased risk of CNS tumors with older parental age [10]. Specific cancer types have also been individually studied in relation to parental age with varying associations [11–20]. Thus, overall the strongest support exists for a relation between older parental age and ALL. The purpose of this study was to assess the association between parental age and childhood cancer in a large population-based sample of children born in Denmark. Though a previous Danish study has examined paternal age, maternal age was not examined and our study includes more years thus it would expand on this previous study's findings [10].

2. Methods

Cases for the present study were selected from all primary cancers diagnosed in Denmark born from 1968 to 2014 and diagnosed from 1968 to 2015 among children less than 16 years of age and listed in the Danish Cancer Registry [21]. Childhood cancers were grouped according to the International Childhood Cancer Classification (ICCC); ICCC-1 based on the original notification forms corresponding to ICD-O-1- codes until 1977, and ICD-O-1 codes from 1978 until 2003 and ICCC-3 based on ICD-O-3 codes thereafter [22,23]. We included in analyses the main ICCC groups and specific cancer types with at least 50 cases.

We linked children with cancer to the Central Population Registry (CPR) based on the unique 10-digit Central Person number which is assigned to all persons living in Denmark [24]. From the CPR, we randomly selected controls from all children born in Denmark. We individually matched each case to 100 controls on sex and year of birth. The parent study of this project was designed to assess parental occupational exposures, thus 100 controls were selected to ensure sufficient sample size for rarer exposures. Eligible controls were children who were free of cancer and living in Denmark at the date of their corresponding case's diagnosis.

To obtain covariate information, we also linked children to the Medical Births Registry (MBR) (data available from 1973+) and the Danish National Patient Registry (DNPR) based on their Central Person number. The MBR includes pregnancy information and the DNPR includes all hospital admissions in Denmark since 1977, as well as records for all outpatient visits and emergency room consultations since 1994. Diagnoses are coded according to a modified Danish version of the eighth revision of the International Classification of Diseases (ICD-8) up to 1993, and thereafter to the tenth revision of the Classification (ICD-10) [25,26].

As this was a record-based study, we did not seek informed consent from individual subjects. The study received approvals from the human subject's protection boards of the University of California Los Angeles and the Danish Data Protection Agency.

Parental age at child's birth was determined from the date of birth information in the CPR. Given that the previous literature has found mixed results with some studies finding a U-shaped risk with age and others linear increases in risk, we analyzed parental age as both categorical and continuous. We grouped parental age categories as <25, 25–29, 30–34, 35–39, 40–45, 45+, collapsing the top three categories when the number of cases was less than five. The reference group was those in the 25–29 age category. We excluded 6 controls who were born outside of Denmark. Thus, our final sample includes 5,856 cases and 585,594 controls. Supplementary file 1 provides more detailed information on the registries we linked.

We performed conditional logistic regression to assess the effect of parental age on childhood cancer risk. All analyses were conducted using SAS 9.3 software (Cary, NC) and the Proc logistic method with a strata statement to identify our matched sets. We considered covariates for inclusion in the models that have been previously associated with childhood cancer risk, including multiple births, parity, and urban versus rural place of birth [19,27–30]. Although ethnic group is associated with childhood cancer risk [31], information on ethnic group is not collected in Danish national databases. As a proxy for ethnic group we assessed the inclusion of parental place of birth as a covariate in analyses and categorized it using the definitions of a previous Danish study (Danish/Western/non-Western) [10]. We left parental place of birth and parity in our final models as they changed estimates the most (>5% change). We also performed mutual adjustment for parental age. Due to the large change in estimates with mutual adjustment and the potential collinearity between maternal and paternal age, we present multiple models to show how the estimates changed. Additionally, we conducted a stratified analysis examining the effect of older paternal age (30–34 years and 35+ years vs. <30 yrs) among children with younger (<30 years) mothers to try to tease apart the independent effect of paternal age for ALL. We were unable to look at the effect of older maternal age (35+ years) in younger fathers (<30 years) since there were too few cases that fell into this category (n = 5). To assess linear trends in risk we modeled maternal and paternal age as continuous variables per 5-year increase in age.

We also conducted analyses stratified by laterality of the tumor for retinoblastoma and Wilms' tumor. Due to its greater frequency of origin in the father's germline [32], bilateral retinoblastoma is typically examined in relation to paternal pre-conception exposures, whereas unilateral disease results from somatic changes in pregnancy or early life, and is studied in relation to maternal exposures [33]. The evidence for a similar presentation of Wilms' tumor is hypothesized but results have been more tenuous for a parent-specific origin.

Social class was defined based on parental job title from criteria developed by the Danish National Center for Social Research (academics or executive managers, middle managers or 3–4 years of further education, other white-collar workers, skilled blue-collar workers, unskilled workers, and unknown or unclassified) [34]. Earlier in the study, job title was reported on income tax forms, whereas in the latter years of the study parents were not required to report their job title in every year, thus the proportion of missing data increased over time. A combined measure of socioeconomic status (SES) for the family was calculated based on the SES of the parent with the highest level. Given the large