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Birth weight and the risk of histological subtypes of ovarian and endometrial cancers: Results from the Copenhagen School Health Records Register

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HIGHLIGHTS

- Low and high birthweights increase risk of ovarian cancer.
- Birthweight was not associated with most types of endometrial cancer.
- In utero exposures may be relevant for ovarian & endometrial cancers.

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ABSTRACT

Background. Studies of birth weight associations with ovarian and endometrial cancer risks are limited with inconsistent results, and none has evaluated associations by histologic subtype. We utilized prospectively collected birth weight information to investigate the association with risk of ovarian and endometrial cancers overall and by histologic subtype.

Methods. 162,559 girls, born from 1930 to 1989, from the Copenhagen School Health Records Register (CSHRR) were followed prospectively via linkage with the Danish health registers. Ovarian (n = 666) and endometrial (n = 694) cancers were identified from 1978 to 2014. Cox regression was used to estimate hazard ratios (HR) and 95% confidence intervals (CI).

Results. Women with lower (2.0–3.25 vs. 3.26–3.75 kg) and higher (3.75–5.5 vs. 3.26–3.75 kg) birth weights had increased risks of ovarian cancer overall [HR (95% CI): 1.27 (1.06–1.52); 1.51 (1.21–1.87), respectively] and serous ovarian cancers [1.54 (1.19–1.98); 1.98 (1.47–2.67), respectively]. A decreased risk of Type II endometrial tumors was suggested per kilogram increase in birth weight [HR (95% CI): 0.63 (0.40–1.00)].

Conclusions. Our results suggest that both lower and higher birth weights were associated with increased ovarian cancer risk and associations were particularly strong for serous ovarian cancer, the most common subtype. Birth weight was not associated with most types of endometrial cancer.

1. Introduction

Ovarian cancer is the deadliest gynecological cancer, with 553 new cases and 376 deaths estimated in Denmark per year between 2011 and 2014 [1]. Endometrial cancer is the most common and second deadliest gynecological cancer among women in Denmark, with an estimated 769 new cases, and 93 deaths over the same time period [1]. For both tumors many reproductive factors are associated with risk, suggesting an etiological role of hormonal exposure [2]. Early age at menarche, an indicator of early hormonal exposure and increased number of lifetime ovulations, is associated with increased risk of both ovarian and endometrial cancer [2]. It has been suggested that in utero and early life sex-steroid hormone exposures may affect gonadotropin

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release and subsequent fetal imprinting that could result in earlier ages at menarche [3–5]. Associations with early age at menarche and taller adult height also support that early life may be a critical period for ovarian and/or endometrial cancer initiation [2]. Further, it has been suggested that birth weight may reflect in utero exposures of the individual that may influence later life risk of cardiovascular disease and some cancers [6].

Evidence supporting female cancer risk associations with birth weight only exists for breast cancers, as studies evaluating relations between birth weight and ovarian or endometrial cancers have been limited and showed inconsistent results [7–12]. Further, none of these studies has evaluated etiologic heterogeneity in this context, despite the compelling evidence that adult body size and/or height as well as many other hormonally-related reproductive factors are associated with differing risks for ovarian and endometrial cancer subtypes [13–16]. The aim of this study therefore is to examine birth weight and its association with ovarian and endometrial cancers overall and by histologic subtype.

2. Materials and methods

2.1. Cohort

Data on birth weight were obtained from the Copenhagen School Health Records Register (CSHRR), which has been described previously [17]. Briefly, the CSHRR contains health records for 372,636 children born 1930 through 1989 who attended school in Copenhagen, Denmark. Information on name, sex, and date of birth was systematically recorded on individual health cards along with height and weight measurements collected as part of school-related annual health examinations [17]. From the birth year 1936 onwards birth weight, as reported by parents or guardians, was recorded on each child's health card [17]. At birth, families are issued an infancy health book with the infants' birth weight recorded by a visiting health nurse. These books are commonly used as a continuous health record for children and may have been referenced by parents to report birth weight [18]. Correlations above 0.93 have been found between recalled birth weights from the cohort and birth records [18].

2.2. Linkage

Unique government-issued identification numbers, from the Danish Civil Registration System of vital statistics [19], were recorded on health cards for children who attended school in 1968 or after, and the identification numbers were retrieved for children who left school before this time. Individuals were followed for information in national health registers based on record linkages using these personal identification numbers. Information on vital status was obtained from the Danish Civil Registration System [19]. Hysterectomy and bilateral oophorectomy or salpingo-oophorectomy information was obtained by linkage to the Danish National Patient Register, which contains information on all hospital discharge diagnoses from 1977 onwards [20].

2.3. Cancer registration

Ovarian and endometrial cancers were identified through linkage to the Danish Cancer Registry, which has very high validity [19,21], using ICD-10 codes, which were available from 1 January 1978, due to a Danish recoding project, through 31 December 2014; ovary: C56.0, C56.2–3 and C56.9 and endometrial: C54.0–C54.1, C54.3–C54.6, C54.9 and C55. Using the ICD—O—3 morphology codes (Supplemental Table 1), epithelial ovarian cancers were subdivided into serous, endometrioid, clear cell, mucinous, and other epithelial ovarian cancers. Endometrial cancers were classified as Type I and Type II cancers based on the dualistic model [22], given that it has long been speculated that hormonal exposures are strongly related to Type I tumors, whereas Type II tumors are considered to be unrelated to hormonal exposure. We also evaluated associations with the most common subtype endometrioid adenocarcinoma and other Type I tumors.

2.4. Study population

Women eligible for this study were born from 1936 to 1989, had an identification number, were alive and living in Denmark on January 1, 1978 and were 18 years of age or older. Among 184,276 women in the cohort, 161,498 were born 1936–1989. Records from 17,052 women did not have an identification number and were excluded and 3244 were additionally excluded due to emigration, death or loss to follow-up prior to age 18 years or January 1, 1978 leaving 141,202 women.

For ovarian cancer analyses, we excluded women with an oophorectomy or salpingo-oophorectomy prior to age 18 years ($n = 2$) or 1978 ($n = 20$), with an ovarian cancer diagnosis prior to 1978 ($n = 29$), or without a date for the ovarian cancer diagnosis ($n = 2$). For endometrial cancer analyses, women with a hysterectomy prior to age 18 years ($n = 5$) or 1978 ($n = 327$), with an endometrial cancer diagnosis prior to 1978 ($n = 1$), or without a date for the endometrial cancer diagnosis ($n = 1$) were excluded. For both outcomes, we further excluded women without information on birth weight ($n = 19{,}767$ ovarian, 19,717 endometrial) and with birth weight values <2 kg ($n = 2117$ ovarian, 2112 endometrial) or >5.5 kg ($n = 414$ ovarian, 411 endometrial). Given these exclusions, 118,851 women were included in ovarian cancer analyses and 118,628 women were included in endometrial cancer analyses.

Each woman was followed from the age of 18 years or from her age in 1978, whichever came later. When investigating ovarian cancer, women were followed up until a diagnosis of ovarian cancer, oophorectomy/salpingo-oophorectomy, death, emigration, loss to follow-up, or December 31, 2014, whichever came first. In the analyses with endometrial cancer as the endpoint, women were followed up until a diagnosis of endometrial cancer, hysterectomy, death, emigration, loss to follow-up, or December 31, 2014, whichever came first.

2.5. Statistical analyses

Analyses for ovarian and endometrial cancer outcomes were conducted separately using Cox proportional hazard models. We used age as the underlying time scale and stratified by 5-year birth cohorts to allow the baseline hazard to differ by birth cohorts. We assessed linearity of the birth weight-cancer association using linear splines with 2 knots positioned at 3.25 and 3.75 kg using the likelihood ratio test. When the linear assumptions for the model were not satisfied, birth weight was evaluated with 3 a priori chosen categories (2.0–3.25, 3.26–3.75, 3.76–5.5 kg), with birth weight in the normal range (3.26–3.75 kg) serving as the referent category. We selected these categories to reduce the influence of digit preference [23].

We examined the proportional hazards assumptions underlying the Cox models by testing if associations between birth weight and ovarian or endometrial cancer risks, differed by categories of age at diagnosis using likelihood ratio tests. We assessed heterogeneity in the birth weight association across ovarian and endometrial cancer subtypes via a likelihood ratio test by including an interaction term between birth weight and cancer subtype. Interactions of birth cohort with the associations between birth weight and cancer risk were similarly investigated using likelihood ratio tests. We did not identify violations of the proportional hazards assumption or birth cohort effects in any of these associations (results not shown). Statistical analyses were performed using Stata (version 14.1, StataCorp LP College Station, TX).

This study was approved by the Danish Data Protection Agency. According to Danish law, ethical approval is not required for register-based studies.

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