 Childhood Overweight, Tallness, and Growth Increase Risks of Ovarian Cancer

Julie Aarestrup1, Britton Trabert2, Lian G. Ulrich3, Nicolas Wentzensen2, Thorkild I.A. Sørensen4,5, and Jennifer L. Baker1,4

Abstract

Background: Adult body size is related to ovarian cancer risks, but size in childhood may also influence risks. We investigated if childhood body mass index (kg/m²), height, and growth patterns were associated with ovarian cancer overall and by histologic subtypes, including effects of birthweight.

Methods: A cohort of 155,958 girls from the Copenhagen School Health Records Register, born 1930 to 1989 with measured weights and heights from 7 to 13 years, were included. During follow-up, 1,041 ovarian cancers were recorded. Overweight was defined using International Obesity Task Force criteria. Cox regressions were performed.

Results: Compared with non-overweight girls, at most ages girls with overweight had increased risks of ovarian cancer overall (HR range: 1.24–1.34), mucinous, endometrioid, and clear cell ovarian cancers, but not serous and other ovarian cancers. Childhood height had positive and significant associations with ovarian cancer overall (HR range: 1.07–1.10 per z-score) and the endometrioid subtype but not with the other subtypes. Adjusting for birthweight minimally altered the associations with childhood body size. In growth analyses, girls with overweight or who were tall at 7 and 13 years had increased risks of ovarian cancer overall compared with average-sized girls at both ages.

Conclusions: Ovarian carcinogenesis is linked to childhood overweight, tallness, and growth, with variations across histologic subtypes, suggesting that early life plays a role in the origins of this disease.

Impact: These findings emphasize that healthy body size and growth during childhood are important as they may contribute to reducing ovarian cancer risks.

Introduction

Ovarian cancer is the deadliest gynecological malignancy, and it ranks as the seventh most common cancer among women worldwide and the tenth most common cancer in Denmark (1, 2). Currently, there are no effective ovarian cancer screening approaches and as clinical symptoms are uncommon at early stages, it is often diagnosed at advanced stages (3, 4). The etiology of ovarian cancer is complex and heterogeneous with respect to genomic pathways, histologic presentation, and prognosis (5, 6).

Few risk factors for ovarian cancer are established, and these include older age, family history, reproductive factors (nulliparity, history of infertility, early age at menarche, and late age at menopause), and hormone replacement therapy (3, 7). There are also indications that excess body fatness in adult life increases risks for ovarian malignancies (3, 8, 9); however, evidence is more convincing for taller adult height (3, 8). Excessive weight gain in adult life may also be associated with increased risks of developing ovarian cancer (10). Although not investigated in the majority of previous studies on adult women, risk factors, including body size, most likely differ by tumor subtype (11–13).

The timing of the development and the duration of exposure to excess body fatness may be important for risks of ovarian cancer. Two studies that examined links between childhood or adolescent adiposity and ovarian cancer overall yielded inconsistent results; child size did not matter whereas adolescent size did, and neither study investigated effects of weight patterns during childhood (14, 15). Although it is plausible that childhood height and growth matter as well, previous studies have not reported on this nor have they examined the associations with ovarian cancer subtypes or the influence of birthweight on these associations—each of which may be important factors for the risks of this disease.

We examined if childhood overweight and height at each age from 7 to 13 years are associated with risks of ovarian cancer overall and its different histologic subtypes. In addition, we investigated if associations between childhood body size and ovarian cancer overall were influenced by birthweight and whether growth patterns were associated with risks of ovarian cancer overall.

Materials and Methods

The Copenhagen School Health Records Register (CSHRR) contains information from mandatory school health examinations on 184,276 girls born 1930 to 1989. Weight and height at
Proportional hazards analyses stratiﬁed by 5-year birth cohorts using age at risk as the underlying time scale to investigate the associations between childhood body size and ovarian cancer risks. In the subsample of women born 1936 to 1989, we repeated these analyses only adjusting for birthweight. Among these cases, 570 (54.8%) were serous, 110 (10.6%) mucinous, 104 (10.0%) endometrioid, 39 (3.7%) clear cell, and 218 (20.9%) were other epithelial ovarian cancers (Supplementary Table S2). The median age at diagnosis was 57 years (range: 20–82) for ovarian cancers overall and it varied slightly across subtypes (Table 1). As expected, median values for BMI and height increased with childhood age (Table 1).

**Statistical analyses**

BMI (kg/m²) values were calculated. BMI and height were transformed into z-scores using an internal reference and interpolated or extrapolated to exact ages. For BMI, the values were subsequently back-transformed so that girls could be classiﬁed using International Obesity Task Force criteria into non-overweight or overweight (including obesity). At age 7 years, the cutoff corresponds to 17.69 kg/m² and cutoffs for other ages are using International Obesity Task Force criteria into non-overweight or overweight (including obesity). Identiﬁcation numbers for girls who were in school in 1968 or later were recorded on the health cards for girls leaving school prior to this time identiﬁcation numbers were retrieved. Incident ovarian cancers were identiﬁed in the comprehensive and valid Danish Cancer Registry (18). Using International Classiﬁcation of Disease (ICD)-10 codes, ovarian tumors were classiﬁed as C56.0, C56.2–3, and C56.9. Using ICD-O-3 morphology codes, the epithelial ovarian cancers were deﬁned and subclassiﬁed as serous, mucinous, endometrioid, clear cell, and other epithelial ovarian cancers (Supplementary Table S1). We excluded nonepithelial ovarian cancers, very rare and unspeciﬁc ovarian cancers, cancers with uncertain primary origin, and cancers without morphology information from all analyses. Information on vital status was obtained from the Danish Civil Registration System (17) and information on bilateral oophorectomy or salpingo-oophorectomy from the Danish National Patient Register, which contains information on all hospital discharge diagnoses since 1977 (19).

Among the total population of girls in the CSHRR, we excluded women without an identiﬁcation number (N = 21,717), who emigrated, died, or were lost to follow-up prior to age 18 or January 1, 1978 (N = 3,784), who had an oophorectomy or salpingo-oophorectomy prior to age 18 (N = 2) or 1978 (N = 50), an ovarian cancer diagnosis prior to 1978 (N = 49), lacked a date for the ovarian cancer diagnosis (N = 2), were missing height and/or weight measurements at all childhood ages (N = 2,710) or with outlying height or body mass index (BMI) z-scores at all ages (z-score < −4.5 or >4.5; N = 4), resulting in 155,958 women available for the analyses (Supplementary Fig. S1). Women were followed from 18 years or from her age in 1978, whichever came later. Follow-up ended on the date of a diagnosis of ovarian cancer, oophorectomy/salpingo-oophorectomy, death, emigration, loss to follow-up, or December 31, 2014, whichever came ﬁrst.

**Statistical analyses**

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Childhood weight status at age 7 years and the risks of ovarian cancer overall and by histologic subtype. The figure shows the risk estimates for ovarian cancer risk per z-score increase in height. Hazard ratios including 95% CIs were estimated by Cox proportional hazards regression models stratified by 5-year birth cohorts.

Adjustment for birthweight

In the subsample of 118,229 women with information available on birthweight there were 663 cases of ovarian cancer. In this subsample, the associations between childhood overweight and height, respectively, and ovarian cancer overall were minimally affected by adjustment for birthweight (Supplementary Tables S5–S6).

Growth and ovarian cancer overall

Among 126,700 girls with measurements of body size at ages 7 and 13 years there were 920 diagnoses of ovarian cancer. In these analyses we found that girls with overweight at both ages had an increased risks of ovarian cancer overall compared with non-overweight girls. Girls who became overweight or who changed from being classified as overweight to non-overweight during childhood did not have increased risks of ovarian cancer overall (Table 2). Girls who were tall throughout childhood (represented by the age 7 estimate in the growth model) had significantly increased risks of ovarian cancer overall compared with average-height girls [HR = 1.04 (95% confidence interval [CI], 1.01–1.08) per 0.5 z-score increase]. In contrast, girls who grew tall (represented by the change estimate in the growth model) during

Table 1. Age at diagnosis among cases and BMI (kg/m^2) and height (cm) values for 155,958 girls included in this study from the Copenhagen School Health Records Register

<table>
<thead>
<tr>
<th>Age at diagnosis (years)</th>
<th>N</th>
<th>Median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>1,041</td>
<td>57 (20-82)</td>
</tr>
<tr>
<td>Serous</td>
<td>570</td>
<td>58 (20-82)</td>
</tr>
<tr>
<td>Mucinous</td>
<td>110</td>
<td>55 (29-76)</td>
</tr>
<tr>
<td>Endometrioid</td>
<td>104</td>
<td>53 (21-81)</td>
</tr>
<tr>
<td>Clear cell</td>
<td>39</td>
<td>56 (35-76)</td>
</tr>
<tr>
<td>Other epithelial</td>
<td>218</td>
<td>60 (20-81)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BMI (kg/m^2)</th>
<th>N</th>
<th>Median (5–95 percentiles)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>145,821</td>
<td>15.3 (13.5–18.0)</td>
</tr>
<tr>
<td>8</td>
<td>147,519</td>
<td>15.6 (13.7–17.7)</td>
</tr>
<tr>
<td>9</td>
<td>142,518</td>
<td>16.0 (13.9–19.6)</td>
</tr>
<tr>
<td>10</td>
<td>159,003</td>
<td>16.4 (14.2–20.4)</td>
</tr>
<tr>
<td>11</td>
<td>158,103</td>
<td>16.8 (14.4–21.5)</td>
</tr>
<tr>
<td>12</td>
<td>137,041</td>
<td>17.5 (14.8–22.2)</td>
</tr>
<tr>
<td>13</td>
<td>135,130</td>
<td>18.3 (15.3–23.2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Height (cm)</th>
<th>N</th>
<th>Median (5–95 percentiles)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>145,821</td>
<td>121.7 (113.0–130.4)</td>
</tr>
<tr>
<td>8</td>
<td>147,519</td>
<td>126.9 (117.9–135.0)</td>
</tr>
<tr>
<td>9</td>
<td>142,518</td>
<td>132.1 (122.7–142.0)</td>
</tr>
<tr>
<td>10</td>
<td>159,003</td>
<td>137.3 (127.3–148.0)</td>
</tr>
<tr>
<td>11</td>
<td>158,103</td>
<td>142.9 (132.0–154.8)</td>
</tr>
<tr>
<td>12</td>
<td>137,041</td>
<td>149.3 (137.1–161.7)</td>
</tr>
<tr>
<td>13</td>
<td>135,130</td>
<td>155.5 (143.0–167.0)</td>
</tr>
</tbody>
</table>

Table 2. Weight status patterns and the risks of ovarian cancer overall including women born 1930–1989

<table>
<thead>
<tr>
<th>Overweight status</th>
<th>N</th>
<th>Cases</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-overweight at 7 and 13 years</td>
<td>114,229</td>
<td>839</td>
<td>1.00 (ref.)</td>
</tr>
<tr>
<td>Non-overweight at 7 years, overweight at 13 years</td>
<td>4,828</td>
<td>32</td>
<td>1.09 (0.77-1.55)</td>
</tr>
<tr>
<td>Overweight at 7 years, non-overweight at 13 years</td>
<td>3,435</td>
<td>21</td>
<td>0.98 (0.64-1.51)</td>
</tr>
<tr>
<td>Overweight at 7 and 13 years</td>
<td>4,208</td>
<td>36</td>
<td>1.67 (1.19-2.33)</td>
</tr>
</tbody>
</table>

Cox proportional hazards regression models stratified by 5-year birth cohorts.

Overweight defined using International Obesity Task Force criteria.

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childhood did not have increased risks of ovarian cancer overall compared with girls who had average growth [HR 0.95 (95% CI, 0.89–1.01) per 0.5 z-score increase, corresponding approximately to 20.6 cm of growth].

**Discussion**

In this large population-based study, with an extensive follow-up period of 37 years, girls with overweight had greater risks of ovarian cancer overall than girls who were not classified as overweight. Similar patterns were identified for the histologic subtypes of mucinous, endometrioid and clear cell ovarian cancers, but not with serous and other ovarian cancers. Taller girls had increased risks of ovarian cancer overall and the endometrioid subtype, but not the other subtypes. Adjusting for birthweight minimally affected the associations with childhood body size. Finally, girls with overweight or who were tall at ages 7 and 13 years had elevated risks of ovarian cancer overall compared with girls who were not overweight or not tall at both ages.

Our findings on childhood overweight, although not directly comparable due to age differences, are in accord with those from a Norwegian study of adolescents (14–19 years) that also used measured values of height and weight (15). Our results differ from an American study that combined data from the Nurses’ Health Study and Nurses’ Health Study II and did not find strong indications of associations between body size at 5 to 10 years and risks of ovarian cancer. As this previous study used recalled and self-reported somatypes from childhood, differences with our study findings may be explained by differences in the ascertainment of childhood body size (14).

Although ovarian epithelial cancers are recognized to differ histologically, the majority of epidemiological studies are unable to explore associations by subtype due to low numbers of cases and a lack of available histological information. A growing body of evidence suggests that many ovarian cancer risk factors are differentially associated with histologic subtypes, but findings are generally inconsistent, and this also applies to adult BMI and height (11–13). Risk factors are well-established only for the rare non-serous subtypes. In analyses on associations with ovarian cancer subtypes, we generally found positive associations between childhood overweight and mucinous, endometrioid, and clear cell ovarian cancers as well as positive associations between childhood height and the endometrioid subtype. These subtype analyses offer an insight into how childhood overweight and height relate to these forms, and consistent with previous studies, we do not find indications of associations with the common and fatal serous ovarian cancers.

We and others have previously shown u-shaped associations between birthweight and ovarian cancer risks (21, 22). However, adjusting for birthweight minimally changed our findings for childhood body size, suggesting that size at birth, as an indicator of fetal growth, does not affect these associations with ovarian cancer risks.

Our novel analyses on growth found that girls with overweight at 7 and 13 years had higher risks of ovarian cancer overall than girls who were not overweight at both ages. Becoming overweight or reducing size to being classified as non-overweight, however, was surprisingly not associated with ovarian cancer as compared with girls who were not overweight at both ages. One other study on growth and ovarian cancer risks examined BMI trajectories from childhood to midlife, but likely due to few cases it did not detect associations with ovarian cancer (23). We also found that girls who were consistently tall, compared with girls who were not, had significantly increased risks of ovarian cancer overall. As we did not find that girls who became overweight or grew tall during these ages were at increased risks of ovarian cancer, these findings suggest that the biological processes underlying these associations may be initiated earlier in childhood.

Biological mechanisms underlying the association between childhood body size and ovarian cancer risks are likely to vary across histologic subtypes, and they remain largely unknown. Adult adiposity may be linked to ovarian carcinogenesis through influences on the bioavailability or synthesis of endogenous sex hormones (24, 25). Similarly, excess childhood body fatness is speculated to contribute to a continuous accumulation of risk throughout the life-course or alternatively, the timing of developing excess body fatness may be critically important. As child and adult BMI are only moderately correlated at ages when ovarian cancers emerge (r values of 0.26–0.43; ref. 26), which is typically from the 5th decade of life, body size tracking is unlikely to entirely explain these findings. Height is a marker for underlying etiologic factors such as genetic predispositions, environmental and nutritional factors, exposure to insulin, and sex steroid and growth hormones (27, 28). In addition, taller height and excess body fatness may be indicators of earlier puberty (29, 30) and contribute to an increased lifetime number of ovulatory cycles (31) that may be critical for ovarian cancer risks.

Our study included a large population of school-aged girls with measured heights and weights from nationally based examinations enhancing the validity as compared with self-reported data. Girls in this study were largely of Western European origin, thus our results likely apply to significant portions of populations outside of Denmark. These girls were followed through national health registers for an extensive period with minimal loss to follow-up. A distinct strength includes the detailed pathology information on morphologically-verified tumors from the high-quality Danish Cancer Registry (18), which allowed us to divide ovarian cancers into subtypes based on histologic traits. Information on tumor grade is not electronically available in Danish registers, thus, we could not evaluate associations with serous ovarian malignancies depend on the degree of differentiation as suggested for adult body size (32). Even though information on birthweight was available in this study, we lack information on body size from the period after birth to age 7 years making us unable to evaluate these ages in childhood, where associations with body size may be established. Moreover, we do not have information available on potential confounding factors in childhood. Finally, apart from adjusting for birthweight, other covariates of potential interest, such as adult body size, menopausal hormone therapy, and reproductive factors, were not taken into account. These factors are unlikely to confound the associations but could potentially act as mediators. Nonetheless, it was beyond the scope of the current study to examine the potential mediating roles of these factors.

In conclusion, our study suggests that childhood overweight and tallness increase the risks of ovarian cancer overall and that girls who had patterns of overweight or tallness at both ages 7 and 13 had increased risks of ovarian cancer overall. Interestingly, there were indications that the associations may vary by histological subtype. We did not find any associations with serous ovarian cancer, which is the most common type of ovarian cancer,
and future studies therefore need to identify other risk factors for this subtype. Whether the associations are independent of adult body size remains to be explored. Nonetheless, the identification of factors early in life associated with later ovarian cancer risks, although they may only be indicators of risks, adds to the currently limited understanding of ovarian cancer etiology.

Disclosure of Potential Conflicts of Interest

L.G. Ulrich has ownership interest in Novo Nordisk. No potential conflicts of interest were disclosed by the other authors.

Disclaimer

The funding sources had no involvement in the study design, collection, analysis and interpretation of data, writing the article, and decision to submit.

Authors' Contributions

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Development of methodology: J. Aarestrup, T.I.A. Sørensen, J.L. Baker

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): J. Aarestrup, T.I.A. Sørensen, J.L. Baker

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): J. Aarestrup, B. Trabert, L.G. Ulrich, N. Wentzensen, T.I.A. Sørensen, J.L. Baker

Writing, review, and/or revision of the manuscript: J. Aarestrup, B. Trabert, L.G. Ulrich, N. Wentzensen, T.I.A. Sørensen, J.L. Baker

Study supervision:

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): J. Aarestrup, T.I.A. Sørensen, J.L. Baker

Other (revision of different types of ovarian cancer and interpretation of hormonal dependency): L.G. Ulrich

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