Childhood overweight, tallness and growth increase risks of ovarian cancer

Julie Aarestrup[1], Britton Trabert[2], Lian G Ulrich[3], Nicolas Wentzensen[2], Thorkild I.A. Sørensen[4,5], Jennifer L. Baker[1,4]

[1] Center for Clinical Research and Prevention, Bispebjerg and Frederiksberg Hospital, Capital Region, Denmark

[2] Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD, USA

[3] Copenhagen University Hospital Rigshospitalet, Department of Gynecology and Obstetrics, Copenhagen, Denmark

4 Novo Nordisk Foundation Center for Basic Metabolic Research, Section on Metabolic Genetics, University of Copenhagen, Copenhagen, Denmark

[5] Department of Public Health, Faculty of Medical and Health Sciences, University of Copenhagen, Copenhagen, Denmark

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Corresponding author:
Jennifer L. Baker
Center for Clinical Research and Prevention
Nordre Fasanvej 57
2000 Frederiksberg
Denmark
E-mail: Jennifer.Lyn.Baker@regionh.dk
Phone: +4538163058

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The authors declare no potential conflicts of interest**.**

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Abstract

Background: Adult body size is related to ovarian cancer risk, but size already in childhood may influence risks many years later. Thus, we investigated if childhood body mass index (BMI; kg/m^2), height, and growth patterns were associated with ovarian cancer overall and by histologic subtypes, also including effects of birthweight.

Methods: A cohort of 155,958 girls from the Copenhagen School Health Records Register, born 1930-1989 with measured weights and heights from 7-13 years were followed through national health registers. 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 normal-weight girls, at most ages girls with overweight had increased risks of ovarian cancer overall (hazard ratio (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. 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 potential variations by histological subtypes, suggesting that early life may play 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 risk.

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, histological presentation, and prognosis (5, 6).

Few risk factors for ovarian cancer are established, and these include older age, family history, and reproductive factors (nulliparity, history of infertility, early age at menarche, and late age at menopause) (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 type (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 influence of birthweight or ovarian cancer sub-types; each of which may be important factors for the risk of this disease.

We examined if childhood BMI and height at each age from 7 to 13 years are associated with risks of ovarian cancer overall and its different histological subtypes. Additionally we investigated if

associations between childhood body size and ovarian cancer overall were influenced by birthweight and whether patterns of childhood growth 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 372,636 children born 1930-1989. Weight and height at ages 7-13 years were measured by trained school personnel. Parents or guardians reported their child's birthweight from the birth year 1936 onwards.(16)

Women were followed for information in national health registers based on record linkages using a unique government-issued personal identification number assigned to all Danish residents alive in 1968 or born thereafter (17). The information was systematically recorded on individual health cards along with the child's name, sex and date of birth (16). Identification numbers for children who were in school in 1968 or later were recorded on the health cards and for children leaving school prior to this time identification numbers were retrieved (16). 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 sub-classified as serous, mucinous, endometrioid, clear cell and other epithelial ovarian cancers. We excluded non-epithelial ovarian cancers, very rare and unspecific ovarian cancers, cancers with uncertain primary origin and cancers without morphology information from all analyses (Supplementary Table S1).

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). 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 BMI z-scores at all ages (z-score <-4.5 or >4.5) (N=4). 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

Based on calculated BMI (kg/m^2) values that were transformed to BMI values at exact ages using z-scores, it was categorized into normal-weight and overweight (including obesity) using International Obesity Task Force (IOTF) criteria (corresponds to 17.69 kg/m^2 at age 7 years; other ages in Table S2) (20). We conducted Cox 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 risk. In the sub-sample of women born 1936-1989 with information available on birthweight, we repeated these analyses on the outcome of overall ovarian cancer and tested for effect modification by birthweight. As this was not found (all p-values ≥ 0.09) we conducted these analyses only adjusting for birthweight.

Non-linearity was assessed by linear splines, the likelihood ratio test and visual inspections of graphs. We detected non-linearity in associations between childhood BMI and ovarian cancer, thus categorical analyses using IOTF cut-offs were conducted. Non-linearity was not identified for associations with childhood height.

Growth in relation to ovarian cancer overall was assessed in girls with body size available at 7 and 13 years. In analyses on changes in weight status, girls with normal-weight at both ages were the

reference group. Growth in height was examined in a model with height at age 7 years and change in height from age 7 to 13 years.

We examined the proportional hazards assumptions underlying the Cox models by testing if associations between childhood body size and ovarian cancer risk differed by categories of age at risk using likelihood ratio tests. Interactions of birth cohort with the associations between childhood body size and ovarian cancer were similarly investigated using likelihood ratio tests. No violations of the proportional hazards assumption or birth cohort effects were detected. Potential heterogeneity in the associations with childhood body size across subtypes was evaluated using likelihood ratio tests by including an interaction term between childhood BMI and height, respectively, and ovarian cancer sub-types.

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

Results

During 37 years and 4.61 million woman-years of follow-up of 155,958 women, 1,041 were diagnosed with epithelial ovarian cancer. Among these 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 58 years (range: 20-82) for ovarian cancers overall and varied slightly across subtypes (Table 1). As expected, median values for BMI and height increased with childhood age (Table 1).

BMI and ovarian cancer overall and by sub-type

Girls with overweight had an increased risk of ovarian cancer overall at all ages (hazard ratio (HR) range: 1.24-1.33), compared with normal-weight girls, although the estimates did not reach statistical significance at a few ages (Figure 1, Supplementary Table S2). For the subtypes, childhood overweight was positively and significantly associated with mucinous, endometrioid and clear cell ovarian cancers, with few exceptions, but not with serous or other epithelial ovarian cancers (Figure 1, Supplementary Table S2). Despite indications of differences in the BMI associations with the different subtypes, the tests for heterogeneity were not statistically significant (P-values range: 0.35-0.75).

Height and ovarian cancer overall and by sub-type

Childhood height was positively and significantly associated with ovarian cancer overall and associations were similar across all ages (HR range: 1.07-1.10 per z-score, corresponding approximately to 5.2 cm at age 7 years) (Figure 2, Supplementary Table S3). For the endometrioid subtype, the associations were similarly positive (HR range: 1.19-1.34 per z-score), whereas associations with serous, mucinous, clear cell and other epithelial ovarian cancers were generally

not statistically significant (Figure 2, Supplementary Table S3). The tests for heterogeneity between sub-types were not statistically significant (P-value range: 0.21-0.63).

Adjustment for birthweight

In the sub-sample of 118,229 women, including 663 overall ovarian cancers, with information available on birthweight, the associations between childhood overweight and height, respectively, and ovarian cancer overall were minimally affected by adjustment for birthweight (Supplementary Table S4-5).

Growth and ovarian cancer overall

Among 126,700 girls, including 920 diagnoses of overall ovarian cancers, with measurement of body size at ages 7 and 13 years, we found that girls with overweight at both ages had an increased risk of ovarian cancer overall compared with normal-weight girls. Girls who became overweight or became normal-weight during childhood did not have an increased risk of ovarian cancer overall (Table 2). Girls who were tall throughout childhood (represented by the change 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 age 7 estimate in the growth model) during childhood did not have an increased risk of ovarian cancer 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 a greater risk of ovarian cancer overall than normal-weight girls. Similar patterns were identified for the histological subtypes of mucinous, endometrioid and clear cell ovarian cancers, but not with serious and other ovarian cancers. Taller girls had increased risks of ovarian cancer overall and for the endometrioid subtype, but not for other subtypes. Adjusting for birthweight minimally affected the associations with childhood body size. Finally, girls who were overweight or tall at age 7 and 13 years had elevated risks of ovarian cancer overall compared with girls who were averaged-sized 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 (14). Our results differ from an American study of children (5 and 10 years) that yielded inconsistent results, but this may be explained by methodological differences as it used recalled and self-reported somatotypes from childhood (15). In analyses on associations with ovarian cancer sub-types, we generally found positive associations between childhood overweight and mucinous, endometrioid and clear cell ovarian cancer as well as positive associations between childhood height and the endometrioid subtype. Our sub-type analyses offer an insight into how childhood overweight and height relate to these forms, as this type of division is largely lacking even in adult studies. Even though birthweight may have independent associations with ovarian cancer risk (21), adjusting for birthweight minimally changed the estimates, suggesting that size at birth, as an indicator of fetal growth, does not affect the associations with childhood body size.

Our novel analyses on growth found that girls with overweight at 7 and 13 years had a higher risk of ovarian cancer overall than girls who were normal-weight at both ages. Becoming overweight or

reducing size to normal-weight, however, was surprisingly not associated with ovarian cancer as compared with girls who were normal-weight at both ages. One other study on growth and ovarian cancer risk examined BMI trajectories from childhood to midlife, but as it was limited by few cases it did not detect associations with ovarian cancer (22). 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.

Adiposity may be linked to ovarian carcinogenesis through influences on the bioavailability or synthesis of endogenous sex hormones (23, 24). As such, excess childhood body fatness may 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 0.26-43) (25), which is typically from the 5th decade of life, body size tracking is unlikely to entirely explain these findings. Height is likely a marker for underlying etiologic factors such as genetic predispositions, environmental and nutritional factors and exposure to insulin, insulin-like growth factors and sex steroid and growth hormones (26, 27). Additionally, taller height and excess body fatness may be indicators of earlier puberty (28, 29) and contribute to an increased lifetime number of ovulatory cycles (30) that may be critical for ovarian cancer risk.

Our study included a large population of school-aged girls with measured heights and weights from mandatory school-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 histological traits. Information on tumor grade is not electronically available in Danish registers, thus, we could not evaluate if associations with serous ovarian malignancies depend on the degree of differentiation as suggested for adult body size (31). Finally, 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.

In conclusion, our study suggests that childhood overweight and tallness increase the risk of ovarian cancer overall and that girls who had growth patterns of overweight or tallness at ages 7 and 13 had increased risks of ovarian cancer overall. Interestingly, there were indications that the associations may vary by histological sub-type. 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 risk, although they may only be indicators of risk, adds to the currently limited understanding of ovarian cancer etiology.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Study concept and design: JA, BT, JLB

Data acquisition TIAS, JLB

Data analyses: JA

Interpretation of data: JA, BT, LGU, NW, TIAS, JLB

Manuscript preparation: JA, BT, JLB

Manuscript review: JA, BT, LGU, NW, TIAS, JLB

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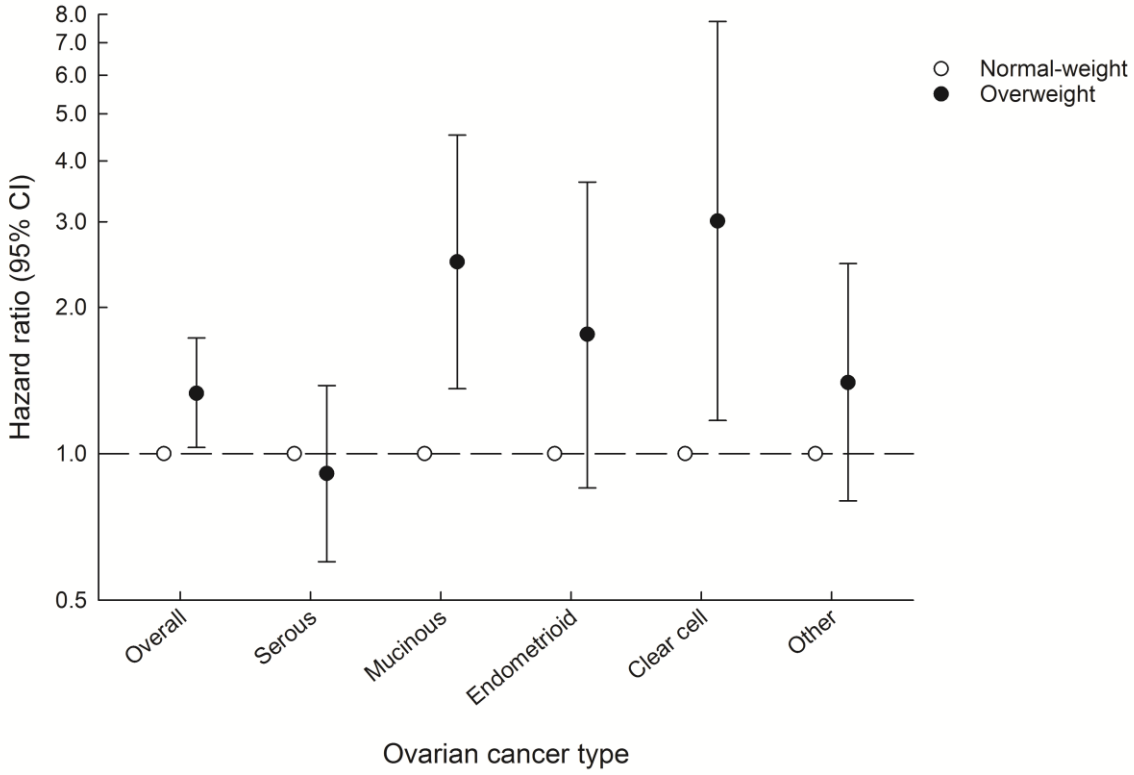
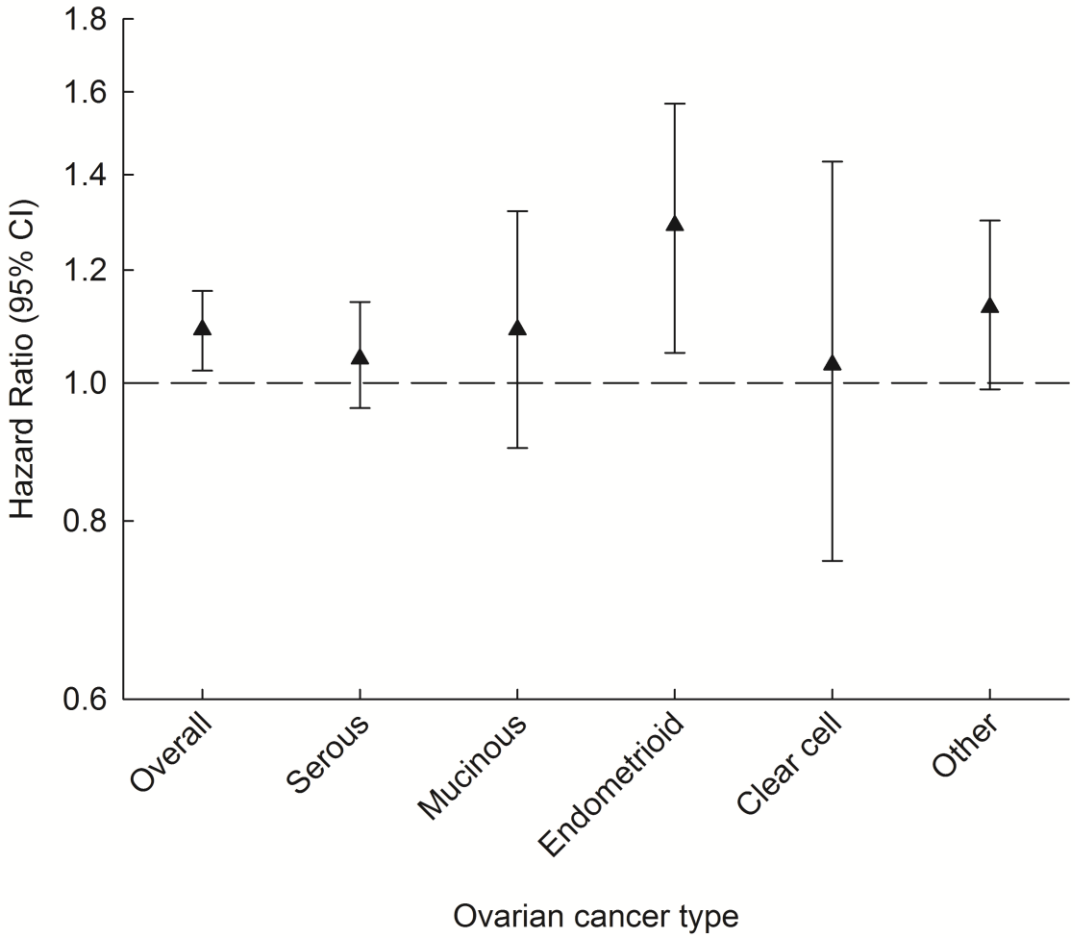
Figure 1. Childhood weight status at age 7 years and the risk of ovarian cancer overall and by histological subtype [a]



CI, confidence intervals.

[a] Cox models stratified by 5-year birth cohorts.

Figure 2. Childhood height at age 7 years and the risk of ovarian cancer overall and by histological subtype (per z-score increase)[a]



CI, confidence intervals.

[a] Cox models stratified by 5-year birth cohorts.

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

	N	Median (range)
Age at diagnosis (years)		
Overall	1,041	58 (20-82)
Serous	570	58 (20-82)
Mucinous	110	55 (29-76)
Endometrioid	104	53 (21-81)
Clear cell	39	56 (35-76)
Other epithelial	218	60 (20-81)
	N	Median (5-95 percentiles)
BMI (kg/m^2)		
7	145,821	15.3 (13.5-18.0)
8	147,519	15.6 (13.7-18.7)
9	142,518	16.0 (13.9-19.6)
10	139,003	16.4 (14.2-20.4)
11	138,103	16.8 (14.4-21.3)
12	137,041	17.5 (14.8-22.2)
13	135,13	18.3 (15.3-23.2)
Height (cm)		
7	145,821	121.7 (113.0-130.4)
8	147,519	126.9 (117.9-136.0)
9	142,518	132.1 (122.7-142.0)
10	139,003	137.3 (127.3-148.0)
11	138,103	142.9 (132.0-154.8)
12	137,041	149.3 (137.1-161.7)
13	135,130	155.5 (143.0-167.0)

BMI, body mass index.

Table 2. Weight status patterns and the risk of ovarian cancer overall including women born 1930-1989[a]

Overweight status[b]	N	Cases	HR (95% CI)
Normal-weight at 7 and 13 years	114,229	839	1.00 (ref.)
Normal-weight at 7 years, overweight at 13 years	4,828	32	1.09 (0.77-1.55)
Overweight at 7 years, normal-weight at 13 years	3,435	21	0.98 (0.64-1.51)
Overweight at 7 and 13 years	4,208	36	1.67 (1.19-2.33)

BMI, body mass index; CI, confidence interval; HR, hazard ratio.

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

[b] Overweight defined using International Obesity Task Force criteria

Supplementary Table S1. Specification of ovarian cancers

Type	Morphology (ICD-O-3)	Specification	N
Serous	8050	Papillary carcinoma, NOS	2
	8260	Papillary adenocarcinoma, NOS	38
	8441	Serous cystadenocarcinoma, NOS	371
	8450	Papillary cystadenocarcinoma, NOS	23
	8460	Papillary serous cystadenocarcinoma	120
	8461	Serous surface papillary carcinoma	16
Sub-total			*570*
Mucinous	8470	Mucinous cystadenocarcinoma, NOS	59
	8471	Papillary mucinous cystadenocarcinoma	4
	8480	Mucinous adenocarcinoma	47
Sub-total			*110*
Endometrioid	8380	Endometrioid carcinoma	98
	8560	Adenosquamous carcinoma	5
	8570	Adenocarcinoma with squamous metaplasia	1
Sub-total			*104*
Clear cell	8310	Clear cell adenocarcinoma, NOS	39
Sub-total			*39*
Other epithelial	8010	Carcinoma, NOS	23
	8020	Carcinoma, undifferentiated type, NOS	9
	8070	Planocellulært carcinom, NOS	3
	8140	Adenocarcinoma, NOS	149
	8230	Solid carcinoma, NOS	3
	8246	Neuroendocrine carcinoma	2
	8440	Cystadenocarcinoma, NOS	14
	8950	Mullerian mixed tumor	3
	8951	Mesodermal mixed tumor	2
	8980	Carcinosarcoma, NOS	10
Sub-total			218
Total			*1,041*
Excluded ovarian cancers	8000	Neoplasm, malignant	4
	8001	Tumor cells, malignant	3
	8021	Carcinoma, anaplastic type, NOS	1
	8041	Small cell carcinoma, NOS	1
	8042	Oat cell carcinoma	1
	8130	Papillary urotelial carcinoma	1
	8141	Scirrhous adenocarcinoma	1
	8240	Carcinoid tumor, NOS	1
	8243	Goblet cell carcinoid	1
	83809	Endometrioid carcinoma uncertain primary	1
	84609	Papillary serous cystadenocarcinoma uncertain primary	1
	8490	Signet ring cell carcinoma	1
	8600	Thecoma, malignant	1
	8620	Granulosa cell tumor, malignant	12
	8810	Fibrosarcoma, NOS	1

Supplementary Table S1., *continued*

Type	Morphology (ICD-O-3)	Specification	N
Excluded ovarian cancers	8890	Leiomyosarcoma, NOS	1
	9000	Brenner tumor, malignant	6
	9060	Dysgerminoma	4
	9071	Yolk sac tumor	1
	9080	Teratoma, malignant, NOS	3
	9110	Mesonephroma, malignant	2
	9580	Granular cell tumor, malignant	1
	9680	Malignant Lymfom, large B-cell, diffust, NOS	1
	9690	Follicular lymphoma, NOS	1
	9990	No morphology	15
Total			*66*

NOS, Not otherwise specified.

Supplementary Table S2. Childhood overweight status and risks of ovarian cancer overall and its subtypes including women born 1930-1989[a]

Age (years)	Overweight status[b]	N	Overall		Serous		Mucinous		Endometrioid		Clear cell		Other	
			Cases	HR (95% CI)	Cases	HR (95% CI)	Cases	HR (95% CI)	Cases	HR (95% CI)	Cases	HR (95% CI)	Cases	HR (95% CI)
7	Normal-weight	136,366	923	1.00 (ref.)	510	1.00 (ref.)	95	1.00 (ref.)	91	1.00 (ref.)	32	1.00 (ref.)	195	1.00 (ref.)
	Overweight	9,455	61	1.33 (1.03-1.73)	23	0.91 (0.60-1.38)	12	2.48 (1.36-4.52)	8	1.76 (0.85-3.62)	5	3.01 (1.17-7.74)	13	1.40 (0.80-2.46)
8	Normal-weight	137,382	932	1.00 (ref.)	521	1.00 (ref.)	94	1.00 (ref.)	90	1.00 (ref.)	31	1.00 (ref.)	196	1.00 (ref.)
	Overweight	10,137	62	1.24 (0.96-1.60)	21	0.75 (0.48-1.16)	11	2.11 (1.13-3.95)	9	1.82 (0.92-3.62)	6	3.41 (1.42-8.19)	15	1.48 (0.88-2.51)
9	Normal-weight	132,145	931	1.00 (ref.)	505	1.00 (ref.)	94	1.00 (ref.)	86	1.00 (ref.)	31	1.00 (ref.)	197	1.00 (ref.)
	Overweight	10,373	71	1.34 (1.05-1.71)	30	1.02 (0.71-1.48)	11	1.97 (1.05-3.69)	11	2.16 (1.15-4.06)	7	3.71 (1.63-8.46)	12	1.09 (0.61-1.96)
10	Normal-weight	128,979	917	1.00 (ref.)	509	1.00 (ref.)	92	1.00 (ref.)	87	1.00 (ref.)	32	1.00 (ref.)	197	1.00 (ref.)
	Overweight	10,024	67	1.29 (1.01-1.65)	31	1.07 (0.75-1.54)	11	2.06 (1.10-3.86)	9	1.78 (0.90-3.55)	6	3.14 (1.31-7.53)	10	0.93 (0.49-1.75)
11	Normal-weight	128,602	930	1.00 (ref.)	512	1.00 (ref.)	96	1.00 (ref.)	87	1.00 (ref.)	34	1.00 (ref.)	201	1.00 (ref.)
	Overweight	9,501	63	1.27 (0.98-1.64)	28	1.03 (0.70-1.50)	10	1.89 (0.98-3.63)	10	2.12 (1.10-4.09)	4	2.09 (0.74-5.90)	11	1.07 (0.58-1.96)
12	Normal-weight	127,551	922	1.00 (ref.)	510	1.00 (ref.)	96	1.00 (ref.)	87	1.00 (ref.)	33	1.00 (ref.)	196	1.00 (ref.)
	Overweight	9,49	65	1.31 (1.02-1.69)	30	1.09 (0.76-1.58)	9	1.68 (0.85-3.34)	10	2.11 (1.09-4.06)	6	3.27 (1.36-7.83)	10	0.99 (0.52-1.87)
13	Normal-weight	125,366	908	1.00 (ref.)	512	1.00 (ref.)	93	1.00 (ref.)	86	1.00 (ref.)	32	1.00 (ref.)	185	1.00 (ref.)
	Overweight	9,764	71	1.33 (1.05-1.70)	28	0.93 (0.63-1.36)	11	1.98 (1.06-3.70)	10	1.96 (1.01-3.77)	6	3.11 (1.30-7.47)	16	1.52 (0.91-2.53)

BMI: Body Mass Index, CI: Confidence Interval HR: Hazard Ratio

[a] Cox proportional hazards regression models stratified by 5-year birth cohorts

[b] Overweight defined using International Obesity Task Force criteria. BMI 7 years: 17.69, BMI 8 years: 18.28, BMI 9 years: 18 99, BMI 10 years: 19.78, BMI 11 years: 20.66, BMI 12 years: 21.59, BMI 13 years: 22.49.

Supplementary Table S3. Childhood height at 7-13 years and risks of ovarian cancer overall and its subtypes per z-score increase including women born 1930-1989[a]

Age (years)	N	Overall		Serous		Mucinous		Endometrioid		Clear cell		Other		p[b]
		Cases	HR (95% CI)	Cases	HR (95% CI)	Cases	HR (95% CI)	Cases	HR (95% CI)	Cases	HR (95% CI)	Cases	HR (95% CI)	
7	145,821	984	1.09 (1.02-1.16)	533	1.04 (0.96-1.14)	107	1.09 (0.90-1.32)	99	1.29 (1.05-1.57)	37	1.03 (0.75-1.43)	208	1.13 (0.99-1.30)	0.41
8	147,519	994	1.09 (1.02-1.16)	542	1.03 (0.95-1.12)	105	1.11 (0.92-1.35)	99	1.33 (1.09-1.62)	37	1.06 (0.76-1.47)	211	1.11 (0.97-1.28)	0.24
9	142,518	984	1.09 (1.02-1.16)	535	1.03 (0.95-1.13)	105	1.09 (0.90-1.32)	97	1.34 (1.09-1.64)	38	1.15 (0.83-1.58)	209	1.13 (0.99-1.30)	0.21
10	139,003	984	1.10 (1.04-1.18)	540	1.06 (0.97-1.15)	103	1.06 (0.87-1.29)	96	1.32 (1.08-1.62)	38	1.12 (0.81-1.55)	207	1.16 (1.01-1.34)	0.31
11	138,103	993	1.10 (1.04-1.18)	540	1.05 (0.97-1.15)	106	1.03 (0.85-1.25)	97	1.30 (1.06-1.59)	38	1.12 (0.81-1.55)	212	1.19 (1.04-1.36)	0.26
12	137,041	987	1.10 (1.04-1.17)	540	1.07 (0.98-1.17)	105	1.02 (0.84-1.23)	97	1.26 (1.03-1.54)	39	1.02 (0.75-1.40)	206	1.18 (1.03-1.35)	0.40
13	135,130	979	1.07 (1.00-1.14)	540	1.05 (0.97-1.15)	104	1.01 (0.83-1.22)	96	1.19 (0.97-1.45)	38	0.96 (0.69-1.32)	201	1.13 (0.98-1.30)	0.63

CI, confidence interval; HR, hazard ratio.

[a] Cox models stratified by 5-year birth cohorts.

[b] Test for heterogeneity using the likelihood ratio tests by including an interaction term between childhood height and the ovarian cancer subtype.

Supplementary Table S4. Childhood overweight status and risks of ovarian cancer overall including women born 1936-1989 with information on birthweight in models unadjusted and adjusted for birthweight[a]

				Unadjusted	Adjusted for birthweight[a]
Age (years)	Overweight status*	N	Cases	HR (95% CI)	HR (95% CI)
7	Normal-weight	105,115	592	1.00 (ref.)	1.00 (ref.)
	Overweight	7,866	43	1.32 (0.97-1.79)	1.29 (0.94-1.76)
8	Normal-weight	105,325	598	1.00 (ref.)	1.00 (ref.)
	Overweight	8,429	44	1.21 (0.89-1.64)	1.19 (0.87-1.62)
9	Normal-weight	100,514	586	1.00 (ref.)	1.00 (ref.)
	Overweight	8,594	53	1.36 (1.03-1.81)	1.35 (1.02-1.79)
10	Normal-weight	97,647	588	1.00 (ref.)	1.00 (ref.)
	Overweight	8,235	50	1.31 (0.98-1.75)	1.30 (0.97-1.73)
11	Normal-weight	97,098	594	1.00 (ref.)	1.00 (ref.)
	Overweight	7,757	46	1.25 (0.93-1.69)	1.24 (0.92-1.67)
12	Normal-weight	96,125	586	1.00 (ref.)	1.00 (ref.)
	Overweight	7,675	50	1.37 (1.03-1.83)	1.35 (1.01-1.81)
13	Normal-weight	94,556	575	1.00 (ref.)	1.00 (ref.)
	Overweight	7,731	55	1.46 (1.11-1.93)	1.44 (1.09-1.89)

BMI, body mass index; CI, confidence interval; HR, hazard ratio.

[a] Cox proportional hazards regression models stratified by 5-year birth cohorts. Birthweight was modelled categorically (2.0-3.25, 3.26-3.75, 3.76-5.5).

[b] Overweight defined using International Obesity Task Force criteria.

Supplementary Table S5. Childhood height and risks of ovarian cancer overall per z-score increase including women born 1936-1989 with information on birthweight in models unadjusted and adjusted for birthweight[a]

Age (years)	N	Cases	Unadjusted	Adjusted for birthweight
			HR (95% CI)	HR (95% CI)
7	112,981	635	1.08 (1.00-1.17)	1.08 (1.00-1.17)
8	113,754	642	1.07 (0.99-1.16)	1.07 (0.99-1.16)
9	109,108	639	1.08 (1.00-1.17)	1.08 (1.00-1.17)
10	105,882	638	1.09 (1.00-1.18)	1.09 (1.00-1.18)
11	104,855	640	1.09 (1.01-1.18)	1.09 (1.01-1.18)
12	103,800	636	1.10 (1.02-1.19)	1.10 (1.02-1.19)
13	102,287	630	1.08 (1.00-1.17)	1.08 (0.99-1.17)

CI, confidence interval; HR, hazard ratio.

[a] Cox proportional hazards regression models stratified by 5-year birth cohorts. Birthweight was modelled categorically (2.0-3.25, 3.26-3.75, 3.76-5.5).