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ORIGINAL ARTICLE

Associations of early life and adulthood adiposity with risk of epithelial ovarian cancer

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Background: Few studies have evaluated the association between early life adiposity and ovarian cancer risk. Adiposity during different periods of life may be differentially associated with the risk.

Patients and methods: We prospectively followed 133 526 women in the Nurses' Health Study (NHS; 1980–2012) and NHSII (1989–2013). Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for incident ovarian cancer ($N = 788$) according to validated measures for early life adiposity [body mass index (BMI) at age 10 imputed from somatotype and recalled BMI at age 18) as well as BMI change between age 10 and 18 and after age 18 (current weight assessed on every biennial questionnaire since baseline).

Results: After mutual adjustment for BMI at age 10, BMI at age 18 and current BMI, the HR (95% CI) for ovarian cancer risk per 5 kg/m^2 was 0.84 (0.74–0.96) for BMI at age 10 (P-trend = 0.01), 1.17 (1.03–1.33) for BMI at age 18 (P-trend = 0.02), and 1.06 (0.99–1.14) for current BMI (P-trend = 0.08). However, the inverse association with BMI at age 10 was attenuated after adjusting for BMI change between age 10 and 18 and BMI change after age 18 (HR per 5 kg/m^2: 1.04; 95% CI 0.91–1.20; P-trend = 0.55). By contrast, BMI change between age 10 and 18 was strongly positively associated with ovarian cancer risk (HR per 5 kg/m^2 increase: 1.24; 95% CI 1.11–1.39; P-trend = 0.0002), whereas BMI change since age 18 was only slightly associated with risk (HR per 5 kg/m^2 increase: 1.06; 95% CI 0.99–1.14; P-trend = 0.10). These associations were in general stronger for premenopausal cases or non-serous tumors.

Conclusion: Early life changes in adiposity were more strongly associated with ovarian cancer risk than adulthood changes. The specific mechanisms underlying the associations with adiposity changes during early life warrant further investigation.

Key words: adiposity, early life exposure, life course approach, ovarian cancer, pediatric obesity

Introduction

Growing evidence supports obesity as a risk factor for several cancers in women [1]. Multiple mechanisms were proposed for obesity-related cancer risk, including endogenous sex hormone dysregulation, inflammation, and insulin resistance [1]. While these mechanisms seem relevant and plausible for ovarian carcinogenesis, evidence regarding the association between obesity and ovarian cancer has been weak and mixed from more than 50 epidemiologic studies [2]. Most studies evaluated adult body mass index (BMI) with ovarian cancer risk overall; however, it is important to consider the etiologically relevant window of susceptibility by integrating adiposity during different life periods, timing of ovarian cancer development and tumor histologic features.

Adipose tissues play critical roles in hormonal balance by serving as a reservoir for steroid hormones [3]. Given that the ovary is hormone sensitive with distinct functions and hormonal profiles across the female life span, adiposity during developmental, reproductive, and postmenopausal years may have different influences on ovarian functions, including carcinogenic effects on ovarian cancer development [4]. Indeed, a pooled analysis of 12 cohort studies reported a positive association of BMI with ovarian cancer risk among premenopausal, but not

postmenopausal, women [5]. Less is known about the associations with adiposity during early life (e.g. childhood, adolescence, early adulthood). These life periods are important from both etiologic and public health perspectives, considering the long latency of cancer development, the rising trend in childhood/adolescence obesity [6], and the established association between early life adiposity and breast cancer risk [7–9]. Therefore, we conducted the current analysis in the Nurses' Health Study (NHS) and NHSII to examine the associations of BMI at age 10 and 18, BMI change between age 10 and 18, and BMI change since age 18 with ovarian cancer risk overall, by menopausal status, and by histologic subtype.

Patients and methods

Study population

The NHS was established in 1976 among 121 700 US nurses aged 30–55, and the NHSII was a similar cohort initiated in 1989 among 116 429 nurses aged 25–42. At baseline, all participants completed a questionnaire on their lifestyles and disease history. Biennial follow-up questionnaires were mailed to all participants to update health-related information. We excluded women with bilateral oophorectomy, prevalent cancer (at baseline except non-melanoma skin cancer), or missing data on early life adiposity and reproductive factors. The study was approved by the Institutional Review Board of the Brigham and Women's Hospital.

Ascertainment of incident ovarian cancer

Incident cases were identified by self-reports on each biennial questionnaire, through family members, or via linkage with the US National Death Index or the US Postal Service. For all identified cases, we obtained relevant medical records or linked to cancer registry to confirm the diagnosis. A gynecologic pathologist blinded to exposure status reviewed the pathology reports and classified the tumors according to morphology, histology, grade, and stage. Concordance between the pathology report and a tumor slide review was 98% for morphology and 83% for histology.

Weight and height measures

Adult height was reported at enrollment, and current weight on every biennial questionnaire. Weight at age 18 was recalled in 1980 (NHS) or 1989 (NHSII), the beginning of the follow-up for this analysis. We categorized BMI at age 18 as <20.0, 20.0–24.9, 25.0–29.9, ≥30 kg/m^2. BMI change since age 18 was calculated as the difference between current BMI (updated every 2 years) and BMI at 18 and categorized as BMI loss (<−2.0 kg/m^2), stable BMI (−2.0 to 2.0 kg/m^2), intermediate BMI gain (2.1–4.0 kg/m^2), and large BMI gain (>4.0 kg/m^2). Somatotype at age 10 was assessed in 1988 (NHS) and 1989 (NHSII) using the nine-figure Stunkard somatotype pictogram [10]. Self-reported weight was strongly correlated with measured weight ($r = 0.97$) [11]. Validity of recalled weight at age 18 was assessed by comparison against nursing school admission physical exam records ($r = 0.87$) [12]. We imputed BMI at age 10 using data from the Growing Up Today Study, which collected both Stunkard pictograms and BMI in girls at age 10 [13].

Statistical analyses

We used the Cox proportional hazards model to evaluate the associations of early life adiposity and BMI change with risk of epithelial ovarian cancer. Person-time accrued from baseline until death, bilateral oophorectomy, any cancer diagnosis (except non-melanoma skin cancer), or the end of follow-up (NHS: June 2012; NHSII: June 2013), whichever occurred first. First, we estimated hazard ratios (HRs) for incident ovarian cancer according to adiposity measures during different life periods, including imputed BMI at age 10, recalled BMI at age 18 and current BMI. These adiposity factors were included individually or simultaneously in two separate models, with adjustment for potential confounders as listed in Table 2. We used BMI change per 5 kg/m^2 to report the continuous associations. To avoid reverse causation that preclinical ovarian cancer may influence body weight, BMI at time *t*-2 was used to represent current BMI rather than BMI at time *t*.

Second, we subdivided current BMI (at time *t*-2) into components as follows:

BMI at time *t*-2 = BMI at age 10 + (BMI at age 18–BMI at age 10) + (BMI at time *t*-2 – BMI at age 18) ≡ BMI at age 10 + BMI change between age 10 and 18 + BMI change after age 18.

Individual components in the equation were mutually adjusted for in the same model. The advantage of the BMI decomposition is that each component is only weakly correlated (supplementary Table S1, available at *Annals of Oncology* online), thus reducing collinearity, whereas the absolute adiposity measures during different life periods have moderate-to-strong correlations (supplementary Table S2, available at *Annals of Oncology* online). Separate analyses were carried out for NHS, NHSII, and combined, as well as by menopausal status.

Third, subtype analyses were performed for serous and non-serous tumors using a competing risks Cox model [14]. Secondarily, we examined the associations for endometrioid tumors, which may be more related to adiposity due to similar histologic origin to endometrial tissues [15]. Analyses were performed in SAS 9.4 (SAS Institute, Cary, NC).

Results

Current BMI was positively related to somatotype at age 10, BMI at age 18, and BMI change since age 18 (Table 1). In both cohorts, women with higher current BMI were more likely to have earlier age at menarche, tubal ligation, surgical menopause, and physical inactivity, but less likely to use estrogen + progesterone HT or currently smoke. The distributions of these population characteristics were similar when comparing across categories of somatotype at age 10, except that women with larger body size at age 10 were more likely to be current smokers (supplementary Table S3, available at *Annals of Oncology* online). Of note, 94% of NHS and 92% of NHSII women had menarche between age 10 and 18.

We documented 562 incident ovarian cancers in NHS and 226 in NHSII during 32 years of follow-up, with consistent associations observed across the two cohorts with imputed BMI at age 10 and recalled BMI at age 18 (*P*-heterogeneity > 0.69; supplementary Table S4, available at *Annals of Oncology* online). In the pooled multivariable analysis (Table 2), BMI at age 10 was not associated with ovarian cancer risk (*P*-trend = 0.14), whereas there was a positive association with BMI at age 18 (*P*-trend = 0.006). Mutual adjustment for adiposity measures yielded a significant inverse association for BMI at age 10 (*P*-trend = 0.01) and a similar positive association for BMI at age 18 (*P*-trend = 0.02). Specifically, every 5-unit higher BMI at age 10 was associated with 16% lower risk [95% confidence interval (CI) 0.74–0.96], and every 5-unit higher BMI at age 18 was associated with 17% higher risk (95% CI 1.03–1.33). By contrast, current BMI was more modestly associated with ovarian cancer risk after accounting for early life adiposity (HR per 5 kg/m^2 higher BMI: 1.06; 95% CI 0.99–1.14; *P*-trend = 0.08). This was only observed in NHSII (*P*-heterogeneity = 0.02; supplementary Table S4,

Table 1. Population characteristics by current body mass index (BMI) in the Nurses' Health Study (NHS) (1996) and NHSII (1997)

	NHS (1996)			NHSII (1997)		
	Current BMI categories					
n	<24.9 20 320	25–29.9 14 537	30+ 9 156	<24.9 48 484	25–29.9 22 827	30+ 18 204
Age, years	62.3 ± 7.3	62.0 ± 7.2	61.1 ± 7.0	41.5 ± 4.6	42.2 ± 4.6	42.5 ± 4.5
Postmenopausal, %	92	91	90	6	8	8
Surgical menopause, %[a,b]	15	17	19	21	29	31
Age at menarche, years	12.7 ± 1.4	12.5 ± 1.4	12.2 ± 1.4	12.7 ± 1.4	12.3 ± 1.4	12.0 ± 1.4
Parous, %	94	94	95	81	83	77
Number of children[c]	3.1 ± 1.5	3.3 ± 1.5	3.2 ± 1.5	2.3 ± 0.9	2.3 ± 1.0	2.3 ± 1.0
Ever use OC, %	51	50	51	86	86	84
Duration of OC use, years	4.3 ± 4.0	4.1 ± 3.9	3.9 ± 3.8	5.3 ± 4.6	5.2 ± 4.5	4.8 ± 4.3
Tubal ligation, %	20	21	23	23	27	28
Family history, %[d]	16	16	17	10	11	11
Physical activity, MET-hrs/week	21.4 ± 23.8	17.1 ± 20.2	11.9 ± 15.7	21.8 ± 25.3	16.5 ± 19.9	11.9 ± 16.4
Ever use E-only HT[a]	25	23	20	24	26	27
Years of E-only HT	6.1 ± 5.7	6.0 ± 5.6	5.4 ± 5.2	2.5 ± 2.4	2.6 ± 2.2	2.7 ± 2.6
Ever use E + P HT[a]	36	31	25	41	37	30
Years of E + P HT	4.8 ± 3.1	4.5 ± 3.0	4.1 ± 2.9	2.7 ± 2.3	2.8 ± 2.3	2.7 ± 2.3
Ever use other HT[a]	19	17	13	12	10	13
Years of other HT	3.1 ± 3.0	2.8 ± 2.6	2.6 ± 2.5	1.3 ± 1.2	1.4 ± 1.5	1.3 ± 1.5
Current smokers, %	15	11	8	12	11	10
Height, inches	64.6 ± 2.4	64.5 ± 2.4	64.3 ± 2.5	64.9 ± 2.5	64.9 ± 2.6	64.7 ± 2.8
Somatotype at age 10	2.3 ± 1.3	2.5 ± 1.4	3.1 ± 1.5	2.4 ± 1.2	2.9 ± 1.3	3.9 ± 1.4
BMI at age 18	20.4 ± 2.2	21.4 ± 2.6	23.3 ± 3.6	19.9 ± 2.1	21.5 ± 2.7	24.3 ± 4.3
Current BMI	22.3 ± 1.9	27.2 ± 1.4	34.4 ± 4.3	21.9 ± 1.8	27.2 ± 1.4	35.7 ± 5.3
BMI change since age 18	1.9 ± 2.7	5.8 ± 2.8	11.2 ± 4.6	2.0 ± 2.3	5.6 ± 2.9	11.4 ± 5.1

[a]Among postmenopausal women.
[b]Menopause due to hysterectomy.
[c]Among parous women.
[d]Family history of breast cancer or ovarian cancer.
E, estrogen; HT, hormone therapy; MET, metabolic equivalent; OC, oral contraceptive; P, progesterone.

available at *Annals of Oncology* online), possibly due to cohort differences in age and menopausal status.

The changes in estimates after mutual adjustment for BMI at different ages suggested that BMI change during different life periods may be the underlying driver. Further analyses showed that imputed BMI at age 10 was no longer associated with ovarian cancer risk after accounting for BMI change from age 10 to 18 (HR per 5 kg/m^2 higher BMI: 1.04; 95% CI 0.91–1.20; *P*-trend = 0.55; Table 3). However, BMI change from age 10 to 18 was more strongly associated with ovarian cancer risk than BMI change after age 18. The pooled HR (95% CI) associated with 5 kg/m^2 BMI increase was 1.24 (1.11–1.39) for BMI change between age 10 and 18 (*P*-trend = 0.0002) and 1.06 (0.99–1.14) for BMI change after age 18 (*P*-trend = 0.10). Of note, while the association with BMI change between age 10 and 18 was similar in NHS/NHSII (*P*-heterogeneity = 0.51), the association with BMI change after age 18 differed significantly by cohort (*P*-heterogeneity = 0.002; supplementary Table S5, available at *Annals of Oncology* online). BMI increase after age 18 was positively associated with risk in NHSII (*P*-trend = 0.001), but not in NHS (*P*-trend = 0.72), similar to the cohort-specific association with current BMI described above.

After adjusting for BMI change between age 10 and 18, imputed BMI at age 10 was not associated with either premenopausal (*P*-trend = 0.23) or postmenopausal ovarian cancer risk (*P*-trend = 0.63; supplementary Table S6, available at *Annals of Oncology* online). The positive association with BMI change between age 10 and 18 was stronger for premenopausal (HR per 5 kg/m^2: 2.41; 95% CI 1.38–4.19; *P*-trend = 0.002) than for postmenopausal cases (HR per 5 kg/m^2: 1.31; 95% CI 0.90–1.92; *P*-trend = 0.16; *P*-heterogeneity = 0.08). BMI change during premenopausal years (i.e. between age at menopause and age 18) was only associated with increased risk of premenopausal ovarian cancer (*P*-trend = 0.02), consistent with the strong positive association observed in NHSII. Neither premenopausal BMI change nor BMI change after menopause was associated with postmenopausal ovarian cancer risk.

Similarly, after adjustment for BMI change between age 10 and 18, imputed BMI at age 10 was not associated with serous (*P*-trend = 0.72) or non-serous ovarian cancer (*P*-trend = 0.79;

Table 2. Association of imputed body mass index (BMI) at age 10, BMI at age 18, and current BMI with risk of epithelial ovarian cancer

	Cases	P-Ys	HR (95% CI) Model 1[a]	Model 2[b]
Imputed BMI at age 10				
<14.0	133	233 450	1.00 (Ref)	1.00 (Ref)
14.0–15.9	278	528 018	0.93 (0.76–1.15)	0.93 (0.75–1.14)
16.0–17.9	192	434 683	0.80 (0.64–1.00)	0.78 (0.62–0.97)
18.0–19.9	101	189 037	0.99 (0.76–1.28)	0.93 (0.71–1.20)
≥20.0	84	185 030	0.82 (0.62–1.08)	0.74 (0.56–0.98)
Per 5 BMI units			0.91 (0.81–1.03)	0.84 (0.74–0.96)
P-trend			0.14	0.01
BMI at age 18				
<20.0	260	581 454	0.87 (0.74–1.01)	0.86 (0.73–1.01)
20.0–24.9	444	837 416	1.00 (Ref)	1.00 (Ref)
25.0–29.9	63	119 249	0.98 (0.75–1.28)	0.98 (0.75–1.29)
≥30.0	21	32 099	1.32 (0.85–2.05)	1.32 (0.84–2.08)
Per 5 BMI units			1.16 (1.04–1.29)	1.17 (1.03–1.33)
P-trend			0.006	0.02
Current BMI				
<25.0	381	841 626	1.00 (Ref)	1.00 (Ref)
25.0–29.9	230	429 093	1.02 (0.87–1.21)	1.00 (0.85–1.18)
≥30.0	177	299 499	1.20 (1.00–1.44)	1.15 (0.95–1.40)
Per 5 BMI units			1.09 (1.03–1.16)	1.06 (0.99–1.14)
P-trend			0.005	0.08

[a]Stratified by calendar time, and adjusted for age at menarche, tubal ligation, duration of OC use, duration of premenopause, duration of postmenopause, menopausal status, type of menopause, duration of estrogen-only HT use, duration of estrogen and progesterone HT use, duration of other HT use, height, parity and smoking status.

[b]Model 1 + mutually controlling for imputed BMI at age 10, BMI at age 18, and current BMI.

HR, hazard ratio; CI, confidence interval; P-Y, person-years; HT, hormone therapy.

Table 3. Associations of imputed body mass index (BMI) at age 10, BMI change between age 10 and 18, and BMI change after age 18 with risk of epithelial ovarian cancer

	Cases	P-Ys	HR (95% CI)[a]
Imputed BMI at age 10			
<14.0	133	233 450	1.00 (Ref)
14.0–15.9	278	528 018	0.99 (0.80–1.23)
16.0–17.9	192	434 683	0.91 (0.72–1.16)
18.0–19.9	101	189 037	1.21 (0.91–1.60)
≥20.0	84	185 030	1.16 (0.81–1.59)
Per 5 BMI units			1.04 (0.91–1.20)
P-trend			0.55
BMI change between age 10 and 18			
<2.0	101	294 188	0.62 (0.48–0.81)
2.0–3.9	191	371 462	1.00 (Ref)
4.0–5.9	213	422 330	0.97 (0.79–1.19)
6.0–7.9	158	276 497	1.08 (0.87–1.35)
≥8.0	125	205 741	1.16 (0.91–1.48)
Per 5 BMI units			1.24 (1.11–1.39)
P-trend			0.0002
BMI change since age 18			
<−2.0	35	61 374	1.01 (0.70–1.47)
−2.0 to 1.9	188	463 958	1.00 (Ref)
2.0–3.9	165	334 053	1.15 (0.93–1.42)
≥4.0	400	710 833	1.12 (0.94–1.34)
Per 5 BMI units			1.06 (0.99–1.14)
P-trend			0.10

[a]Stratified by calendar time, mutually controlling for imputed BMI at age 10, BMI change between age 10 and 18 and BMI change since age 18, and adjusted for age at menarche, tubal ligation, duration of OC use, duration of premenopause, duration of postmenopause, menopausal status, type of menopause, duration of estrogen-only HT use, duration of estrogen and progesterone HT use, duration of other HT use, height, parity and smoking status.

HR, hazard ratio; CI, confidence interval; P-Y, person-years; HT, hormone therapy.

Table 4). However, the positive associations with BMI change were suggestively stronger for non-serous tumors than for serous ovarian tumors. For BMI change between age 10 and 18, the HR (95% CI) for every 5 kg/m^2 increase was 1.35 (1.10–1.65) for non-serous cancer and 1.08 (0.90–1.28) for serous cancer (*P*-heterogeneity = 0.10). BMI increase after age 18 was modestly associated with non-serous cancer (HR per 5 kg/m^2: 1.14; 95% CI 1.00–1.30; *P*-trend = 0.04), but was not associated with serous cancer (HR per 5 kg/m^2: 0.97; 95% CI 0.87–1.08; p-trend = 0.61; *P*-heterogeneity = 0.06). The results for BMI at age 10 and BMI change between age 10 and 18 were similar when further dividing non-serous tumors into endometrioid versus other tumors, whereas BMI change since age 18 was only positively associated with endometrioid tumors (data not shown).

Discussion

Several meta-analyses/pooled analyses reported weak-to-moderate positive associations between adult BMI and ovarian cancer risk, noting significant between-study heterogeneity with weaker associations in prospective versus case–control studies [5, 16–20]. As a result, body fatness is considered as a probable risk factor for ovarian cancer by WCRF/AICR, with similar conclusions reached by other cancer organizations [21–23]. However, an IARC report suggested a causal link between body fatness and ovarian cancer risk [24], although the conclusion was based on one meta-analysis reporting a weak positive association with significant heterogeneity by study design [18]. Further, most studies did not assess the associations with early life adiposity and whether these associations differed by menopausal status or histology.

Interestingly, a Norwegian study found significantly increased ovarian cancer risk for women who were obese in adolescence (age 14–19) or early adulthood (age 20–29), but no associations were observed for adiposity at age ≥30 years [25]. Similarly, analyses of 12 prospective studies showed no overall association with adult BMI [5]. However, BMI was positively associated with risk among premenopausal, but not among postmenopausal, women. In the Iowa Women's Health Study, higher BMI at age 18, but

Table 4. Associations of imputed body mass index (BMI) at age 10, early life BMI change, and adulthood BMI change with risk of epithelial ovarian cancer for serious and non-serous subtypes

	Non-serous			Serous			*P*-het[b]
	Cases	P-Ys	HR (95% CI)[a]	Cases	P-Ys	HR (95% CI)[a]	
Imputed BMI at age 10							
<14.0	37	233 707	1.00 (ref)	64	233 707	1.00 (ref)	0.65
14.0–15.9	75	528 385	0.94 (0.63–1.42)	140	528 385	1.00 (0.73–1.35)	
16.0–17.9	60	434 118	0.96 (0.62–1.50)	99	434 118	0.96 (0.69–1.35)	
18.0–19.9	34	189 001	1.33 (0.80–2.22)	51	189 001	1.28 (0.86–1.92)	
≥20.0	15	185 023	0.65 (0.33–1.28)	44	185 023	1.25 (0.80–1.96)	
Per 5 BMI units			0.96 (0.74–1.26)			1.04 (0.85–1.27)	
P-trend			0.79			0.72	
BMI change between age 10 and18							
<2.0	25	294 095	0.56 (0.34–0.92)	55	294 095	0.73 (0.51–1.05)	0.10
2.0–3.9	60	372 078	1.00 (ref)	89	372 078	1.00 (ref)	
4.0–5.9	55	421 995	0.82 (0.56–1.19)	123	421 995	1.19 (0.90–1.58)	
6.0–7.9	41	276 541	0.92 (0.60–1.40)	86	276 541	1.25 (0.91–1.72)	
≥8.0	40	205 525	1.14 (0.74–1.77)	45	205 525	0.91 (0.62–1.33)	
Per 5 BMI units			1.35 (1.10–1.65)			1.08 (0.90–1.28)	
P-trend			0.004			0.42	
BMI change since age 18							
<−2.0	13	61 383	1.49 (0.79–2.81)	17	61 383	0.98 (0.58–1.67)	0.06
−2.0 to 1.9	53	463 965	1.00 (ref)	97	463 965	1.00 (ref)	
2.0–3.9	45	334 053	1.14 (0.77–1.70)	86	334 053	1.14 (0.85–1.53)	
≥4.0	110	710 833	1.22 (0.87–1.70)	198	710 833	1.04 (0.81–1.33)	
Per 5 BMI units			1.14 (1.00–1.30)			0.97 (0.87–1.08)	
P-trend			0.04			0.61	

[a]Stratified by calendar time, mutually controlling for imputed BMI at age 10, BMI change between age 10 and 18 and BMI change since age 18, and adjusted for age at menarche, tubal ligation, duration of OC use, duration of premenopause, duration of postmenopause, menopausal status, type of menopause, duration of estrogen-only HT use, duration of estrogen and progesterone HT use, duration of other HT use, height, parity and smoking status.
[b]Test for heterogeneity between serous versus non-serous ovarian cancer.
P-Y, person-years; HT, hormone therapy.

not current BMI, was associated with higher ovarian cancer risk [26]. Overall, findings were similar to our results that BMI at age 18 was significantly associated with ovarian cancer risk, particularly in premenopausal years. In contrast to a recent meta-analysis of two prospective studies reporting a positive association between adult weight gain and postmenopausal ovarian cancer risk [relative risk (RR) per 5 kg increase: 1.13; 95% CI 1.03–1.23] [27], our data suggest that additional BMI increase in adulthood was only associated with premenopausal cancer. This may be a reflection of the stronger association with non-serous tumors, which are more common in this period.

Few studies have evaluated early life adiposity with ovarian cancer. An earlier study in NHS/NHSII (372/131 cases) reported conflicting results, with body size at age 10 associated with lower risk in NHS, but suggestively higher risk in NHSII [28]. With extended follow-up and more incident cases, the current study revealed more consistent association patterns. Several studies have observed an inverse association of childhood body size with both premenopausal and postmenopausal breast cancer risk, although the association with BMI at age 18 was in the opposite direction between breast cancer and ovarian cancer [7–9]. Our results highlight that adiposity in puberty/adulthood was more strongly associated with non-serous than serous tumors. Similar differences by histologic subtype were also noted in prior studies of adult BMI [18, 20]. Notably, this is consistent with other reproductive and hormonal factors generally having stronger associations with non-serous subtypes [29].

It is unclear why early life BMI change, compared with adulthood change, was more strongly associated with ovarian cancer risk. From a life course perspective, early life BMI increase was likely a reflection of the life-long exposure to adiposity and adiposity-induced biologic alterations, which may result in greater impact cumulatively over decades of cancer development. Given that our early life adiposity assessment straddled puberty when ovaries underwent development and maturation, it is possible that the peripubertal period represents a critical window of ovarian carcinogenic susceptibility to adiposity. For example, onset of puberty is accompanied by increased androgen secretion, which may be further aggravated among girls with substantial weight gain through puberty [30]. Circulating androgen levels are more strongly associated with non-serous tumors, potentially explaining the stronger associations consistently observed between early life adiposity and non-serous cancer risk [31]. Hyperinsulinemia and inflammation may also be

important linking childhood weight gain and adult ovarian cancer risk [32, 33]. In light of the differential associations with peripubertal, premenopausal and postmenopausal BMI change, future investigation is needed to confirm our findings and elucidate the etiologic roles of adiposity that may be distinct between female developmental, reproductive, and postmenopausal periods.

The strength of the study included large sample size, long follow-up, and a wide age distribution that allowed assessment by menopausal status. The results were robust after adjusting for reproductive, hormonal, and lifestyle risk factors for ovarian cancer. Importantly, we were able to dissect the independent association for adiposity measures during specific life periods while controlling for relevant anthropometric measures in other periods. Although our analysis relied on self-reported current weight, recalled weight and imputed BMI from somatotype in early life, these measures have been extensively validated in our cohort and the influence of potential measurement error was likely minimal, attenuating the observed associations. Our analysis by histology and menopausal status was limited by a relatively small number of cases. Future consortium efforts are needed to fully understand these relationships. As our study population included predominantly white nurses, extrapolation to other populations should be cautious.

In conclusion, our results suggest that adiposity changes during peripubertal period are more strongly associated with ovarian cancer risk than adulthood changes. This study provides additional evidence to support that maintaining a healthy weight throughout the life course may have moderate benefits on ovarian cancer prevention, particularly non-serous subtypes diagnosed during premenopausal years. Further studies are needed to understand the specific mechanisms linking peripubertal adiposity and adult ovarian cancer risk.

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Disclosure

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