Height, Body Mass Index, and Ovarian Cancer: A Pooled Analysis of 12 Cohort Studies

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Abstract

Background: **Although many studies have investigated the association between anthropometry and ovarian cancer risk, results have been inconsistent.**

Methods: **The associations of height, body mass index (BMI), and ovarian cancer risk were examined in a pooled analysis of primary data from 12 prospective cohort studies from North America and Europe. The study population consisted of 531,583 women among whom 2,036 epithelial ovarian cancer cases were identified. To summarize associations, study-specific relative risks (RR) were estimated using the Cox proportional hazards model and then combined using a random-effects model.**

Results: **Women with height ≥1.70 m had a pooled multivariate RR of 1.38 [95% confidence interval (95% CI), 1.16-1.65] compared with those with height <1.60 m. For the same comparison, multivariate RRs were 1.79 (95% CI, 1.07-3.00) for premenopausal and 1.25 (95% CI, 1.04-1.49) for postmenopausal ovarian cancer ($P_{interaction}$ = 0.14). The multivariate RR for women with a BMI ≥30 kg/m^2 was 1.03 (95% CI, 0.86-1.22) compared with women with a BMI from 18.5 to 23 kg/m^2. For the same comparison, multivariate RRs were 1.72 (95% CI, 1.02-2.89) for premenopausal and 1.07 (95% CI, 0.87-1.33) for postmenopausal women ($P_{interaction}$ = 0.07). There was no statistically significant heterogeneity between studies with respect to height or BMI. BMI in early adulthood was not associated with ovarian cancer risk.**

Conclusion: **Height was associated with an increased ovarian cancer risk, especially in premenopausal women. BMI was not associated with ovarian cancer risk in postmenopausal women but was positively associated with risk in premenopausal women.** (Cancer Epidemiol Biomarkers Prev 2008;17(4):902–12)

Introduction

With >200,000 cases diagnosed worldwide in 2002 ovarian cancer is the sixth most frequent type of cancer in women (1). Ovarian cancer is diagnosed often in advanced stages and survival rates are poor (2, 3). Use of oral contraceptives, parity, tubal ligation, and hysterectomy have been associated with decreased risk, while use of hormone replacement therapy, a family history of ovarian cancer and infertility have been associated with increased risk of ovarian cancer (4-6).

Height has been positively associated with several types of cancer (7, 8). Several studies have investigated the association with ovarian cancer risk (9-22), but results are inconsistent.

Obesity is an important risk factor for many cancers; the evidence is strongest for breast, colorectal, endometrial, gallbladder, kidney, pancreas, and gastric cardia cancer and esophageal adenocarcinoma (23, 24). Obesity

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might be a risk factor for ovarian cancer also, because several clinical conditions (e.g., polycystic ovarian syndrome and infertility) have been associated with both obesity and ovarian cancer (5, 25-27). In a recent review, it was concluded that obesity is associated with a modestly increased risk of ovarian cancer. The association was heterogeneous and stronger in case-control studies than in prospective studies, however (28).

Given the observed heterogeneity in results across studies, we investigated the association between height and body mass index (BMI) and risk of ovarian cancer in 12 cohort studies (13, 19, 29-38), meeting the inclusion criteria for participation in the analyses of dietary factors and ovarian cancer risk as part of the Pooling Project of Prospective Studies of Diet and Cancer. We also investigated whether the associations with height and BMI varied by several risk factors for ovarian cancer. Additionally, because particular histologic subtypes of ovarian cancer resemble different gynecologic tissue (39), behave different clinically, and may have genetic differences (40), we studied whether the associations differed by histologic subtype.

Materials and Methods

Population. A pooled analysis of the primary data from 12 prospective cohort studies (13, 19, 29-38) based in North America and western Europe was conducted in the Pooling Project of Prospective Studies of Diet and Cancer. The methods have been described in detail elsewhere (41). To be included in the ovarian cancer analyses, each study needed to have a publication on a diet and cancer association, a minimum of 50 incident ovarian cancer cases, an assessment of usual food and nutrient intake and validation of the dietary assessment tool, or a closely related instrument (Table 1). The current analysis used the same data sets that have been used in the analyses of dietary factors and ovarian cancer risk in the Pooling Project of Prospective Studies of Diet and Cancer. As done previously, the follow-up of the Nurses' Health Study (NHS) was divided into two sections where part A (NHSa) followed individuals from the completion of the 1980 food frequency questionnaire to 1986 and part B (NHSb) followed individuals from the completion of the 1986 questionnaire to 2000. The standard theory of survival data has established that blocks of person-time in different time periods are asymptotically uncorrelated regardless of the extent to which they are derived from the same subjects (42). Thus, pooling estimates from these two time periods, and the cases that arise within them, produces estimates and estimated SEs that are as valid as those from a single combined period.

Exposure Assessment. Information on current height and weight was self-reported by the subjects and collected from the baseline self-administered questionnaires within each individual study. Weight during early adulthood (asked in the questionnaires as either age 18 or 20) was also collected in six of the studies (Table 1). Baseline BMI and BMI during early adulthood were calculated using baseline weight and weight at early adulthood, respectively, divided by height at baseline squared (kg/m^2). Information on dietary and nondietary factors was also collected on the baseline self-administered questionnaires within each study. The majority of studies obtained information on other known and suspected risk factors for ovarian cancer, including several reproductive factors, energy intake, smoking status, and physical activity.

The association between BMI and ovarian cancer has been observed to vary according to menopausal status in several studies (28). Most studies had information on menopausal status at baseline only. To assign changing menopause status during follow-up, an algorithm was developed based on an analysis of 42,531 NHS participants who were premenopausal in 1976 and remained premenopausal or had natural menopause by 1992. Using Kaplan-Meier (43) curves for time to menopause, we determined the ages at which ~50% (age 51 years) and 90% (age 55 years) of the women had become postmenopausal. These ages were used to define the upper and lower bounds for the premenopausal and postmenopausal categories, respectively, in the algorithm. The menopausal status of women whose ages were between 51 and 55 years was considered uncertain (44).

Exclusions. In addition to applying the exclusions that each study had predefined for their cohort, we excluded individuals if they had a prior cancer diagnosis other than nonmelanoma skin cancer at baseline, had a bilateral oophorectomy before baseline, had $\log_e$-transformed energy intakes beyond 3 SDs from the study-specific $\log_e$-transformed mean energy intake of their respective population, or had missing information on weight or height. For the analyses of height, BMI at baseline, and BMI during early adulthood, we also excluded individuals with a BMI at baseline of <18.5 kg/m^2 and a BMI >50 kg/m^2. In the analysis regarding BMI during early adulthood, individuals whose BMI at that time was <14 or >50 kg/m^2 were excluded. The Adventist Health Study (37) and New York State Cohort (29) did not obtain information on oophorectomy at baseline; thus, we were not able to exclude individuals who had a bilateral oophorectomy before baseline in these studies.

Outcome Assessment. Participants were followed from the date of the baseline questionnaire until date of diagnosis of ovarian cancer, date of death, date the participant moved out of the study area (if applicable), or end of follow-up, whichever came first. Invasive epithelial ovarian cancer was ascertained by self-report with subsequent medical record review (30, 36, 45), cancer registry linkage (13, 19, 29, 34, 35), or both (32, 33, 37, 38). Some studies also obtained incident outcome and mortality information from death registries (13, 29-34, 36, 38). Invasive epithelial ovarian cancer was defined by *International Classification of Diseases for Oncology, First Edition* code 183.0 or second edition C56. Borderline and nonepithelial ovarian cancer cases were not included as cases. Histologic information was ascertained from the *International Classification of Diseases for Oncology* morphology codes (46) or the histologic information supplied by individual studies.

Statistical Analysis. Anthropometric measures were modeled continuously and categorically as predefined categories. Height was classified into the following categories: <1.60, 1.60 to <1.65, 1.65 to <1.70, and ≥ 1.70 m. BMI at baseline was classified into the following categories: 18.5 to <23, 23 to <25, 25 to <27, 27 to <30,

Table 1. Study characteristics and mean height, weight, and BMI at baseline and at early adulthood by cohort study in the ovarian cancer analyses, the Pooling Project of Prospective Studies of Diet and Cancer

Cohort	Country	Follow-up years	Baseline cohort size*	Baseline age range (y)
Adventist Health Study	United States	1976-1988	16,254	28-90
Breast Cancer Detection Demonstration Project Follow-up Study	United States	1987-1999	29,682	40-93
Canadian National Breast Screening Study‡	Canada	1980-2000	49,613	40-60
Cancer Prevention Study II Nutrition Cohort	United States	1992-2001	59,166	40-87
Iowa Women's Health Study	United States	1986-2001	27,952	52-71
The Netherlands Cohort Study ‡	The Netherlands	1986-1995	62,412	55-69
New York State Cohort	United States	1980-1987	21,183	15-107
New York University Women's Health Study	United States	1985-1998	12,089	31-70
NHSa	United States	1980-1986	78,066	34-67
NHSb	United States	1986-2000	57,303¶	40-67
NHS II	United States	1991-2002	86,279	26-46
Swedish Mammography Cohort	Sweden	1987-2004	57,430	38-76
Women's Health Study	United States	1993-2004	31,457	38-89
Total			531,583	

*Baseline cohort size determined after specific exclusions (that is, missing information on height and weight, prior cancer diagnosis other than nonmelanoma skin cancer at baseline, had a bilateral oophorectomy before baseline, or had $\log_e$-transformed energy intakes beyond 3 SDs from the study-specific $\log_e$-transformed mean energy intake of the population).
† Not applicable, because no information was available on weight in early adulthood in the questionnaire.
‡ The Canadian National Breast Screening Study and The Netherlands Cohort Study are analyzed as case-cohort studies so the baseline cohort size does not reflect the above exclusions.
§Not applicable because this study does not include women that were premenopausal at baseline.
‖Not applicable, because information on menopausal status was not available.
¶NHSb is not included as part of total cohort size because they are included in NHSa.

and ≥30 kg/m^2. The combined categories 25 to <27 and 27 to <30 kg/m^2 correspond to the ''overweight'' category as defined by WHO, whereas the ≥30 kg/m^2 category corresponds to the obese categories as defined by WHO (47). BMI in early adulthood was classified into the following categories: <18.5, 18.5 to <21, 21 to <23, 23 to <25, and ≥25 kg/m^2.

Relative risks (RR) and 95% confidence intervals (95% CI) were calculated by Cox proportional hazards models for each individual study. The model included stratification by age at baseline (in years) and the year the baseline questionnaire was returned and treated the follow-up time (in days) as the timescale, resulting in a time metric that simultaneously accounted for age, calendar time, and time since entry into the study. Multivariate RRs were adjusted for age at menarche, menopausal status, oral contraceptive use, hormone replacement therapy use among postmenopausal women, parity, smoking status, physical activity, and energy intake. A missing indicator variable for each covariate was also generated within a study, if needed. In general, data on covariates were missing for <10% of each study population (41).

Two of these studies, the Canadian National Breast Screening Study and The Netherlands Cohort Study, were analyzed as case-cohort studies (48) because the investigators of these two studies had processed questionnaires for only a random sample of the cohort at baseline plus all incident cases.

SAS software (49) was used to analyze each cohort. The study-specific results were pooled using a random-effects model (50), weighted by the inverse of their variance. Between-studies heterogeneity was investigated using the Q test statistic (50, 51). To test whether there was a linear trend in the risk of disease with increasing height or BMI, a variable with values corresponding to the median value for each exposure category was included in the model and the coefficient for that variable was evaluated using the Wald test. If heterogeneity was present between studies, mixed-effects meta-regression analyses (52) were conducted to evaluate whether there was heterogeneity by follow-up time, menopausal status, and age at diagnosis.

To assess visually whether the association between height, BMI, and the risk of ovarian cancer was linear, we examined nonparametric regression curves using stepwise restricted cubic splines (53, 54). For these analyses, all studies were combined into a single data set and analysis was stratified by study. To test for nonlinearity, the model including the linear and cubic spline terms selected by a stepwise regression procedure was compared with the model with only the linear term using the likelihood ratio test.

Separate analyses were conducted for serous, endometrioid, and mucinous subtypes among those studies having >10 cases of the specific histologic subtype. We tested whether results differed across the subtypes using a contrast test (41, 55).

Results

Table 1 presents the study-specific characteristics of the 12 cohorts and mean height, weight, BMI at baseline, and BMI in early adulthood per cohort. Studies had a maximum follow-up time ranging from 7 years in the New York State Cohort to 22 years in the NHS. In total, 2,036 cases of invasive epithelial ovarian cancer were recorded in the 531,583 women in the 12 cohort studies, of whom 170 diagnoses occurred in premenopausal women and 1,336 occurred in postmenopausal women. The mean BMI at baseline was the lowest in the

Table 1. Study characteristics and mean height, weight, and BMI at baseline and at early adulthood by cohort study in the ovarian cancer analyses, the Pooling Project of Prospective Studies of Diet and Cancer (Cont'd)

No. cases			Mean (SD)			
Total	Premenopausal at diagnosis	Postmenopausal	Height (m)	Weight (kg)	BMI at baseline (kg/m^2)	BMI (kg/m^2) in early adulthood
43	2	37	1.63 (0.07)	65.4 (12.8)	24.5 (4.5)	NA[†]
126	3	116	1.62 (0.06)	66.5 (12.3)	25.2 (4.4)	NA
221	27	91	1.62 (0.06)	64.9 (11.3)	24.8 (4.1)	21.0 (2.7)
265	1	255	1.64 (0.06)	69.8 (12.9)	25.7 (4.6)	20.7 (2.8)
205	NA[§]	205	1.63 (0.06)	69.4 (13.0)	26.2 (4.7)	21.0 (3.0)
197	NA[§]	197	1.65 (0.06)	68.8 (9.9)	25.2 (3.4)	21.4 (2.7)
72	NA[‖]	NA[‖]	1.62 (0.07)	65.0 (12.0)	24.7 (4.3)	NA
64	13	39	1.62 (0.07)	66.3 (12.3)	25.0 (4.4)	NA
118	43	50	1.64 (0.06)	65.7 (12.5)	24.5 (4.4)	21.4 (3.0)
306	19	189	1.64 (0.06)	68.1 (13.3)	25.4 (4.7)	21.4 (2.9)
46	46	NA	1.65 (0.07)	67.3 (14.7)	24.7 (5.1)	21.3 (3.2)
273	8	89	1.64 (0.06)	66.8 (10.8)	24.8 (3.8)	NA
100	8	68	1.64 (0.06)	70.1 (14.0)	26.0 (4.9)	NA
2,036	170	1,336				

Adventist Health Study and NHSa (24.5 kg/m^2) and the highest in the Iowa Women's Health Study (26.0 kg/m^2). BMI in early adulthood ranged from 20.7 kg/m^2 (Cancer Prevention Study II Nutrition Cohort) to 21.4 kg/m^2 (in three cohort studies).

Height was positively associated with the risk of ovarian cancer (Table 2). The pooled multivariate adjusted RR for women at least 1.70 m tall was 1.38 (95% CI, 1.16-1.65) compared with women shorter than 1.60 m ($P_{trend} < 0.001$). Although the study-specific RRs ranged from 0.36 in the Adventist Health Study to 3.29 in the NHS II, almost all study-specific results for this comparison were higher than one (Fig. 1; *P* for between-studies heterogeneity = 0.14). The nonparametric regression curve and a formal test showed that the association between height and risk of ovarian cancer was reasonably linear (*P* for curvature = 0.27). The RR per 5 cm increment in height was 1.10 (95% CI, 1.05-1.15).

The association between height and risk of ovarian cancer was stronger in premenopausal women than in postmenopausal women (*P* for interaction by menopausal status = 0.14). The pooled multivariate RR for continuous height (per 5 cm) and ovarian cancer risk was 1.20 (95% CI, 1.05-1.37) in premenopausal women and was 1.07 (95% CI, 1.02-1.13) in postmenopausal women. The pooled multivariate RR for the association between continuous height (per 5 cm) was 1.16 (95% CI, 1.08-1.25) in women ages <63 years at diagnosis (median age at diagnosis in these studies) and 1.08 (95% CI, 1.03-1.13) in women ages ≥63 years (*P* for interaction by age group = 0.08).

The association was slightly different with respect to histologic subtypes, although the difference was not statistically significant (*P* for difference by histologic type = 0.64). Of the total 2,036 cases, 984 cases were classified as serous carcinoma, 253 as endometrioid carcinoma, and 120 as mucinous carcinoma. Height was not associated with risk of mucinous carcinoma [RR for continuous height (per 5 cm), 1.05; 95% CI, 0.90-1.22], whereas it was positively associated with risk of serous (RR, 1.13; 95% CI, 1.06-1.20) and endometrioid carcinoma (RR, 1.18; 95% CI, 1.06-1.32).

BMI at baseline was not associated with the risk of ovarian cancer overall (P_{trend} = 0.90; see Table 3). The study-specific results for the ≥30 kg/m^2 category compared with the <23 kg/m^2 category were not statistically heterogeneous (*P* for between studies heterogeneity = 0.21; Fig. 2). The study-specific and pooled multivariate RRs did not change substantially when energy intake and physical activity were removed from the model (data not shown). The nonparametric regression curve and a formal test did not suggest departure from linearity (*P* for curvature = 0.53). The pooled multivariate RR for the association between continuous BMI per 4 kg/m^2 and ovarian cancer risk was 1.06 (95% CI, 0.95-1.17) in the first 5 years of follow-up and 0.98 (95% CI, 0.92-1.03) in the remaining years of follow-up (*P* for difference by follow-up period = 0.11). The pooled multivariate RR for women with a BMI ≥30 kg/m^2 was 1.23 (95% CI, 0.87-1.74) in the first 5 years of follow-up compared with women with a BMI of 18.5 to 23.0 kg/m^2. The results were similar when the first 2 years of follow-up were excluded (data not shown).

The association between BMI at baseline and ovarian cancer risk appeared to differ by menopausal status. The *P* for interaction with menopausal status was 0.07. The pooled multivariate RR for continuous BMI (per 4 kg/m^2) and ovarian cancer risk was 1.12 (95% CI, 0.96-1.31) in premenopausal women and 1.02 (95% CI, 0.95-1.08) in postmenopausal women. The pooled multivariate RR for the association between continuous BMI (per 4 kg/m^2) and ovarian cancer risk was not different in women ages <63 years of age at diagnosis compared with women ages ≥63 years (*P* for difference by age group = 0.73). BMI at baseline was not associated with the risk of serous, endometrioid, or mucinous carcinomas when these endpoints were examined individually (Table 3).

Data on BMI in early adulthood were collected in six studies (Table 1), in which a total of 1,305 cases were ascertained. BMI in early adulthood was not associated with the risk of ovarian cancer overall (Table 4). The pooled multivariate RR for women with a BMI ≥25 kg/m^2 at early adulthood was 1.01 (95% CI, 0.72-1.43) compared with women with a BMI <18, 5 kg/m^2 (P_{trend} = 0.95). The study-specific RRs were quite different (*P* for between studies heterogeneity = 0.14), although only one was statistically significant. The study specific RR of women with a BMI ≥25 kg/m^2 at early adulthood compared with

Table 2. Pooled RRs and 95% CIs for ovarian cancer according to height, the Pooling Project of Prospective Studies of Diet and Cancer

	Height per 5 cm increment	*P* for between studies-heterogeneity	Height, categorical (m)	
			<1.60	1.60 to <1.65
All females				
n cases			455	570
Age-adjusted RR (95% CI)	1.10 (1.05-1.15)	0.15	1 (Reference)	1.06 (0.94-1.20)
Multivariate adjusted RR†,‡,§ (95% CI)	1.10 (1.05-1.15)	0.13	1 (Reference)	1.06 (0.94-1.21)
Postmenopausal females (at baseline)‖				
n cases			314	372
Age-adjusted RR (95% CI)	1.07 (1.02-1.13)	0.25	1 (Reference)	1.01 (0.87-1.18)
Multivariate adjusted RR†,§ (95% CI)	1.07 (1.02-1.13)	0.21	1 (Reference)	1.02 (0.87-1.19)
Premenopausal females (at diagnosis)¶				
n cases			29	32
Age-adjusted RR (95% CI)	1.20 (1.05-1.37)	0.43	1 (Reference)	0.90 (0.53-1.53)
Multivariate adjusted RR† (95% CI)	1.20 (1.05-1.37)	0.48	1 (Reference)	0.92 (0.54-1.59)
All females, serous carcinoma**				
n cases			201	275
Age-adjusted RR (95% CI)	1.12 (1.06-1.18)	0.32	1 (Reference)	1.12 (0.93-1.35)
Multivariate adjusted RR†,‡,§ (95% CI)	1.13 (1.06-1.20)	0.22	1 (Reference)	1.14 (0.95-1.37)
All females, endometrioid carcinoma**,††				
n cases			49	74
Age-adjusted RR (95% CI)	1.18 (1.05-1.32)	0.29	1 (Reference)	1.25 (0.86-1.80)
Multivariate adjusted RR†,‡,§ (95% CI)	1.18 (1.06-1.32)	0.33	1 (Reference)	1.28 (0.88-1.86)
All females, mucinous carcinoma**,‡‡				
n cases			30	32
Age-adjusted RR (95% CI)	1.07 (0.92-1.25)	0.32	1 (Reference)	0.21 (0.48-1.37)
Multivariate adjusted RR†,‡,§ (95% CI)	1.05 (0.90-1.22)	0.51	1 (Reference)	0.85 (0.51-1.44)

*Based on the highest category versus the reference category.
† Multivariate RRs were adjusted for age at menarche (<13, 13, >13 y), oral contraceptive use (ever, never), parity (0, 1, 2, >2), BMI (<23, 23-24.9, 25-29.9, >30 kg/m^2), smoking status (never, past, current), physical activity (low, medium, high), and energy intake (continuously).
‡ Multivariate RRs were also adjusted for menopausal status at baseline.
§Multivariate RRs were also adjusted for hormone replacement therapy use among postmenopausal women (never, past, current).
‖NHS II was not included in these analyses because this study has <10 cases and New York State Cohort was not included because this study had no information on menopausal status.
¶Only Canadian National Breast Screening Study, New York University Women's Health Study, NHSa, NHSb, and NHS II were included in the analyses because the other studies have <10 cases per study or had no premenopausal women included at baseline.
**Adventist Health Study was not included in these analyses because information on histologic subtypes was not available.
†† New York State Cohort and New York University Women's Health Study were not included in these analyses because each study had <10 cases.
‡‡ Breast Cancer Detection Demonstration Project Follow-up Study, NHS II, New York State Cohort, New York University Women's Health Study, and Women's Health Study were not included because each study had <10 cases.

women with a BMI <18.5 kg/m^2 was the highest in NHS II (RR, 2.81; 95% CI, 0.83-9.53) and the lowest in The Netherlands Cohort Study (RR, 0.55; 95% CI, 0.21-1.43).

Discussion

In this pooled analysis of the individual data from 12 prospective cohort studies, height was associated with a modest increase in the risk of epithelial ovarian cancer, especially in premenopausal women. Height was associated with an increased risk of endometrioid and serous carcinoma but not with mucinous carcinoma, although the difference between histologic subgroups was not statistically significant. BMI at baseline was not associated with the risk of epithelial ovarian cancer overall; however, being obese was associated with an increased risk of premenopausal ovarian cancer.

The association between height and the risk of ovarian cancer has been studied in several epidemiologic studies. Most case-control studies have reported no statistically significant associations between height and risk (9-12, 14-18). Only one case-control study (22) observed a statistically significant elevated risk. In contrast, most prospective cohort studies have reported positive associations with height. Of the six published prospective studies (13, 19-21, 32, 33), three (13, 19, 33) were included in this analysis. One other report was from a cohort in which we only included the subset of women who completed a dietary assessment in 1992 (32). The cohorts not included in this analysis have either not assessed diet or did not use a validated assessment of usual dietary intake or been able to control for other ovarian cancer risk factors such as parity and oral contraceptive use. Jonsson et al. (20) reported an increased risk for the tallest 25% of the women (≥166 cm) compared with the second quartile (159 to <163 cm), which had been defined as the reference category. A Norwegian cohort (21) of 1.1 million women with 7,882 cases of ovarian cancer reported a positive association between height and ovarian cancer: women taller than 175 cm had a RR of 1.29 (95% CI, 1.11-1.51) compared with women between 160 and 164 cm.

The observation that most case-control studies have not reported statistically significant odds ratios may be caused by a relative lack of power, because 5 (9, 11, 14, 18, 22) of 10 (9-12, 14-18, 22) have published odds ratios (≥1.3) that are in range with our result (1.37) for the

Table 2. Pooled RRs and 95% CIs for ovarian cancer according to height, the Pooling Project of Prospective Studies of Diet and Cancer (Cont'd)

Height, categorical (m)		P_{trend}	P for between studies-heterogeneity*
1.65 to <1.70	≥1.70		
571	440		
1.17 (1.03-1.33)	1.38 (1.17-1.64)	<0.001	0.15
1.18 (1.04-1.34)	1.38 (1.16-1.65)	<0.001	0.14
377	273		
1.13 (0.97-1.32)	1.23 (1.04-1.46)	0.006	0.47
1.14 (0.98-1.34)	1.25 (1.04-1.49)	0.004	0.42
43	44		
1.16 (0.66-2.04)	1.79 (1.07-2.97)	0.01	0.58
1.20 (0.67-2.13)	1.79 (1.07-3.00)	0.009	0.62
293	215		
1.30 (1.07-1.57)	1.43 (1.17-1.75)	<0.001	0.57
1.33 (1.10-1.60)	1.47 (1.20-1.81)	<0.001	0.53
63	67		
1.15 (0.78-1.69)	1.75 (1.18-2.60)	0.002	0.87
1.21 (0.82-1.78)	1.76 (1.18-2.64)	0.002	0.90
30	28		
0.09 (0.49-1.63)	1.12 (0.64-1.94)	0.35	0.55
0.89 (0.49-1.63)	1.12 (0.64-1.94)	0.42	0.61

highest category of height. Odds ratios in the other five studies were all above unity, between 1.08 and 1.26 (10, 12, 15-17). For the few studies that have investigated whether the association between height and ovarian cancer risk is modified by menopausal status, the association was stronger in or restricted to premenopausal women (21, 56), which is in agreement with our analysis. Whether height is associated with histologic subtypes has been investigated in a few studies only. In the Norwegian cohort study (21), height was positively associated with endometrioid ovarian cancer risk, which is in accordance with our findings: the association with other histologic subtypes was not reported. In an Australian case-control study, height was associated with risk of mucinous borderline invasive ovarian cancer, but the 95% CIs were wide because of small numbers (12); no associations were observed with invasive serous, mucinous, or endometrioid cancers (12). In our pooled analysis, only invasive ovarian cancers were included, so we were not able to evaluate borderline invasive ovarian cancers.

In this pooled analysis, no association was observed between BMI at baseline and risk of ovarian cancer in all women. This finding is not in agreement with a systematic review from Olsen et al. (28) who concluded that overweight and obesity were associated with a small to moderately increased risk of ovarian cancer in population-based case-control studies and prospective cohort studies (pooled effect estimate for adult obesity versus normal BMI, 1.3; 95% CI, 1.1-1.5). The association was weaker and not statistically significant in prospective cohort studies in the systematic review (RR, 1.12; 95% CI, 0.95-1.32), and results between cohort studies were heterogeneous (28). Of the 17 (13, 19-21, 31-33, 37, 56-64) published cohort studies, 5 (13, 19, 31, 33, 37) were included in our pooled analysis and 2 were included in part (32, 56). The 10 cohorts not included in this analysis have published mostly null associations, with the exception of Garfinkel (57), Wolk et al. (60), Lukanova et al. (63), and Reeves et al. (64) who published positive associations.

However, in our analysis, we observed that BMI was positively associated with ovarian cancer risk in women who were premenopausal. The number of cases in premenopausal women was limited. Heterogeneity with respect to menopausal status, however, has been

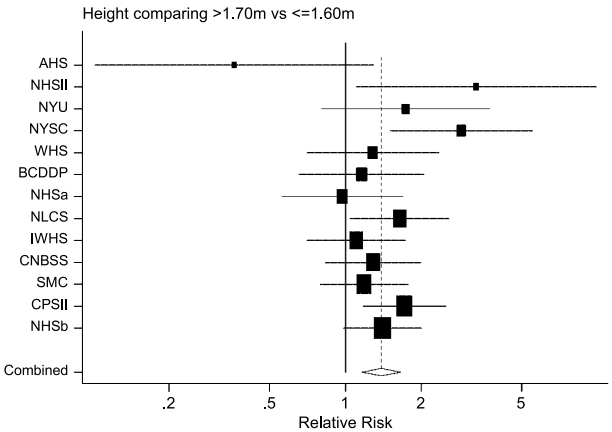

Figure 1. Study-specific and pooled multivariate RRs and 95% CIs of ovarian cancer and height, category ≥1.70 versus ≤1.60 m. *Black squares* and *horizontal lines,* study-specific multivariate RRs and 95% CIs for the comparison of the highest versus the lowest category of height. The area of the *black square* reflects the study-specific weight (inverse of the variance). *Diamond,* pooled multivariate RR and 95% CI.

Table 3. Pooled RRs and 95% CIs for ovarian cancer according to BMI, the Pooling Project of Prospective Studies of Diet and Cancer

	BMI per 4 kg/m^2 increment	*P* for between studies-heterogeneity	BMI, categorical (kg/m^2)	
			<23	23 to <25
All females				
n cases			718	441
Age-adjusted RR (95% CI)	0.99 (0.94-1.05)	0.10	1 (Reference)	0.89 (0.79-1.01)
Multivariate adjusted RR†,‡,§ (95% CI)	1.01 (0.95-1.07)	0.05	1 (Reference)	0.91 (0.80-1.03)
Postmenopausal females (at baseline)‖				
n cases			426	291
Age-adjusted RR (95% CI)	1.00 (0.94-1.07)	0.15	1 (Reference)	0.90 (0.77-1.05)
Multivariate adjusted RR†,§ (95% CI)	1.02 (0.95-1.08)	0.19	1 (Reference)	0.91 (0.78-1.06)
Premenopausal females (at diagnosis)¶				
n cases			64	34
Age-adjusted RR (95% CI)	1.10 (0.95-1.28)	0.34	1 (Reference)	1.25 (0.81-1.92)
Multivariate adjusted RR† (95% CI)	1.12 (0.96-1.31)	0.32	1 (Reference)	1.29 (0.83-2.00)
All females, serous carcinoma††				
n cases			352	209
Age-adjusted RR (95% CI)	0.98 (0.93-1.04)	0.60	1 (Reference)	0.87 (0.72-1.05)
Multivariate adjusted RR†,‡,§ (95% CI)	1.00 (0.94-1.06)	0.55	1 (Reference)	0.88 (0.72-1.06)
All females, endometrioid carcinoma††,‡‡			<23	23-<25
n cases			93	62
Age-adjusted RR (95% CI)	0.97 (0.81-1.16)	0.02	1 (Reference)	1.04 (0.71-1.53)
Multivariate adjusted RR†,‡,§ (95% CI)	0.99 (0.82-1.19)	0.02	1 (Reference)	1.06 (0.72-1.56)
All females, mucinous carcinoma††,‡‡,§§				
n cases			40	25
Age-adjusted RR (95% CI)	1.02 (0.85-1.22)	0.48	1 (Reference)	0.83 (0.50-1.36)
Multivariate adjusted RR†,‡,§ (95% CI)	1.03 (0.84-1.27)	0.32	1 (Reference)	0.84 (0.51-1.38)

*Based on the highest category versus the reference category.
† Multivariate RRs were adjusted for age at menarche (<13, 13, >13 y), oral contraceptive use (ever, never), parity (0, 1, 2, >2), smoking status (never, past, current), physical activity (low, medium, high), and energy intake (continuously), modeled identically across studies.
‡ Multivariate RRs were also adjusted for menopausal status at baseline.
§ Multivariate RRs were also adjusted for hormone replacement therapy use among postmenopausal women (never, past, current).
‖ NHS II was not included in these analyses because this study has <10 cases and New York State Cohort was not included because this study had no information on menopausal status.
¶ Only Canadian National Breast Screening Study, New York University Women's Health Study, NHSa, NHSb, and NHS II (cohorts with >10 cases) were included in these analyses.
**New York University Women's Health Study was not included in the category ≥30 because there were no cases in that category. The participants who were not cases who would have been in this highest category were included in the next highest category (25 to <30 kg/m^2).
†† Adventist Health Study was not included in these analyses because information on histologic subtypes was not available.
‡‡ New York State Cohort and New York University Women's Health Study were not included in these analyses because each study had <10 cases.
§§ Breast Cancer Detection Demonstration Project Follow-up Study, NHS II, and Women's Health Study were not included because each study had <10 cases.

observed in almost all studies that have investigated whether the association between BMI and ovarian cancer is modified by menopausal status or age (17, 31, 58, 59, 63-68). Only one case-control study (69) has not reported a higher risk in younger women. That BMI has different effects depending on menopausal status is plausible, as this also has been observed with breast cancer, another hormone-dependent cancer (7).

Olsen et al. (28) attributed the weaker association in prospective cohort studies to the fact that some had used a single measurement of body mass and had a very long follow-up. Weight change during the follow-up may have caused attenuation of the risk estimates. In our analysis, the association was stronger in the first 5 years of follow-up but not statistically significant. It is therefore possible that a weak association was attenuated in our analysis because of the single (baseline) measurement of BMI and the long follow-up. Our finding that the association is stronger in premenopausal and younger women may also be an explanation for the time-dependent association. Cases with longer follow-up in the cohort studies are more likely to be postmenopausal at diagnosis than cases with a short follow-up. The difference in risk estimates between study types could also be caused by selection and information bias in the case-control studies.

Because of the small numbers of ovarian cancer cases in most studies, few studies have investigated whether the association with BMI differs among specific histologic subtypes of ovarian cancer and the findings have been inconsistent (31, 65-68, 70). In our pooled analysis, we did not observe an association with any of the investigated subtypes of invasive ovarian cancer.

We found no association between BMI in early adulthood and ovarian cancer risk. Four (13, 19, 21, 31) cohort studies [of which three (13, 19, 31) are included in this analysis] and six case-control studies (14-17, 66, 71) have published inconsistent results. The Norwegian cohort study published increased risks for women with a ''high'' or ''very high'' BMI in early adulthood compared with women of medium BMI (21). Of the case-control studies, one published an inverse association for BMI at age 18 (66), two published null results (15, 16), and three published positive associations (14, 17, 71).

Table 3. Pooled RRs and 95% CIs for ovarian cancer according to BMI, the Pooling Project of Prospective Studies of Diet and Cancer (Cont'd)

BMI, categorical (kg/m^2)			P_{trend}	P for between studies-heterogeneity*
25 to <27	27 to <30	≥30		
316	285	276		
0.89 (0.76-1.03)	0.88 (0.76-1.02)	0.98 (0.84-1.14)	0.60	0.31
0.91 (0.78-1.07)	0.91 (0.78-1.05)	1.03 (0.86-1.22)	0.90	0.21
222	206	191		
0.92 (0.78-1.09)	0.93 (0.78-1.10)	1.02 (0.83-1.25)	0.91	0.24
0.95 (0.80-1.13)	0.96 (0.80-1.14)	1.07 (0.87-1.33)	0.53	0.22
14	14	22		
0.95 (0.52-1.71)	1.23 (0.59-2.53)	1.62** (0.97-2.70)	0.21	0.53
0.95 (0.50-1.81)	1.28 (0.59-2.79)	1.72** (1.02-2.89)	0.13	0.49
145	146	132		
0.85 (0.69-1.03)	0.92 (0.75-1.12)	0.91 (0.74-1.12)	0.40	0.77
0.86 (0.70-1.04)	0.93 (0.76-1.14)	0.95 (0.77-1.17)	0.64	0.78
≥25				
98				
0.88 (0.59-1.30)			0.56	0.11
0.92 (0.62-1.36)			0.74	0.16
55				
0.97 (0.65-1.47)			0.89	0.56
1.02 (0.66-1.57)			0.74	0.45

Height has been associated with several types of cancer, especially breast cancer (8). Height as such does not cause cancer but probably acts as a marker for some other exposure (8). Suggested hypotheses include genetic factors, energy intake in early life, and exposure to sex and growth hormones. For instance, insulin-like growth factor-I is associated with height and also inhibits apoptosis of damaged cells and stimulates cell turnover and cell proliferation (8, 72, 73). Insulin-like growth factor-I was associated with an increased risk of ovarian cancer before age 55 in one study (74). In a small Italian case-control study, these findings were not confirmed, however (75), but in this study blood samples were not collected prospectively. A nested case-control analysis within the European Prospective Investigation into Cancer and Nutrition cohort using prediagnostic blood samples observed that insulin-like growth factor-I levels were increased in women that developed ovarian cancer at premenopausal or perimenopausal age (76). The link between height and increased risk of ovarian cancer therefore seems plausible.

Obesity has multiple effects on the hormonal status of premenopausal and postmenopausal women. In premenopausal women, obesity lowers sex hormone-binding globulin but does not influence levels of estrogens and androgens significantly, because the ovaries produce more steroids than the peripheral fat tissue (23, 77). A recent publication from the NHS II showed that BMI was inversely associated with sex hormone-binding globulin and progesterone and positively associated with free testosterone in premenopausal women (78). This is in agreement with the hypothesis of Risch who suggested that high serum levels of androgens increase the risk of ovarian cancer, whereas progestagens protect against ovarian cancer (79).

The results from the Pooling Project of Prospective Studies of Diet and Cancer are not likely to have been affected by selection or information bias as only data from prospective cohort studies have been analyzed and the follow-up rate in these studies generally exceeded 90% (41). Although some cohorts have measured height and weight, all anthropometric results used in this analysis were self-reported, however, and misclassification of exposure is a potential source of bias. Although

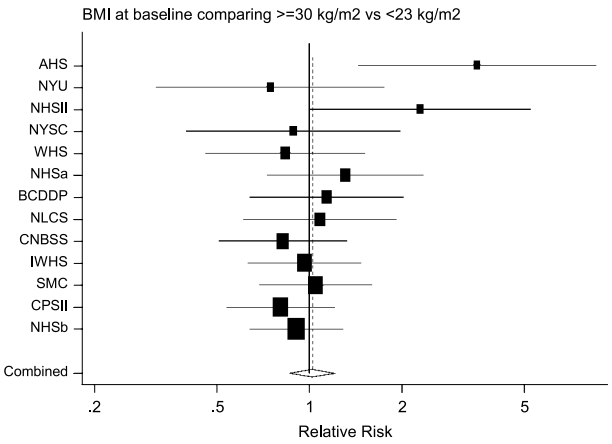

Figure 2. Study-specific and pooled multivariate RRs and 95% CIs of ovarian cancer and BMI, category ≥30 versus ≤23 kg/m^2. *Black squares* and *horizontal lines,* study-specific multivariate RRs and 95% CIs for the comparison of the highest versus the lowest category of BMI. The area of the *black square* reflects the study-specific weight (inverse of the variance). *Diamond,* pooled multivariate RR and 95% CI.

Table 4. Pooled RRs and 95% CIs for ovarian cancer according to BMI in early adulthood, the Pooling Project of Prospective Studies of Diet and Cancer

	BMI in early adulthood per 4 kg/m^2 increment	*P* for between studies-heterogeneity	BMI in early adulthood categorical (kg/m^2)	
			<18.5	18.5 to <21
All females[†,‡]				
n cases			175	543
Age-adjusted RR (95% CI)	1.01 (0.88-1.17)	0.002	1 (Reference)	1.01 (0.92-1.30)
Multivariate adjusted RR (95% CI)	1.00 (0.87-1.15)	0.004	1 (Reference)	1.09 (0.92-1.30)
Multivariate adjusted RR[§] (95% CI)	0.98 (0.87-1.11)	0.05	1 (Reference)	1.09 (0.92-1.30)
Postmenopausal females[‖]				
n cases			131	389
Age-adjusted RR (95% CI)	1.00 (0.86-1.16)	0.02	1 (Reference)	1.15 (0.93-1.43)
Multivariate adjusted RR (95% CI)	0.99 (0.85-1.15)	0.03	1 (Reference)	1.14 (0.93-1.40)

*Based on the highest category versus the reference category.
† Multivariate RRs were adjusted for age at menarche (<13, 13, >13 y), menopausal status at baseline, oral contraceptive use (ever, never), hormone replacement therapy use among postmenopausal women (never, past, current), parity (0, 1, 2, >2), smoking status (never, past, current), physical activity (low, medium, high), and energy intake (continuously), modeled identically across studies.
‡ Only Canadian National Breast Screening Study, Cancer Prevention Study II Nutrition Cohort, Iowa Women's Health Study, The Netherlands Cohort Study, NHSa, NHSb, and NHS II were included in these analyses; other studies did not have information regarding body mass at early adulthood.
§ Multivariate RRs were also adjusted for BMI at baseline (continuously).
‖ NHS II was not included in these analyses because this study has <10 cases and New York State Cohort was not included because this study had no information on menopausal status.

several studies have reported high correlations (>0.8) between self-reported and measured anthropometric data (80-82), other publications have reported that despite high correlations weight tends to be slightly underestimated and height slightly overestimated, thus leading to lower estimates of body mass (83, 84). Weight at early adulthood was used to calculate BMI in early adulthood, and misclassification might have occurred because this is difficult to remember. Misclassification is expected to be nondifferential and therefore would tend to bias towards the null.

Not all covariates were measured in each study. Within our models, we adjusted for most of the important ovarian cancer risk factors (e.g., age at menarche, oral contraceptive use, and parity) if they were measured in a study; results from age-adjusted and multivariate models were similar, suggesting that any residual or unmeasured confounding was small. A major advantage of the method of pooling primary data compared with a literature-based meta-analysis is the ability to characterize and control for covariates uniformly and classify the main exposures similarly. Due to the inclusion of 12 cohort studies from North America and Europe, we had far greater statistical power than the individual cohort studies to examine specific histologic subtypes or effect modification by menopausal status.

In summary, this prospective study with >2,000 cases found that height was associated with a modestly increased risk of ovarian cancer, especially in premenopausal women. No association was observed between recent BMI or BMI in early adulthood and overall ovarian cancer risk. Being obese was associated with an increased risk of premenopausal ovarian cancer, however. Further research is warranted to investigate possible heterogeneous effects with respect to specific histologic subtypes and menopausal status.

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Table 4. Pooled RRs and 95% CIs for ovarian cancer according to BMI in early adulthood, the Pooling Project of Prospective Studies of Diet and Cancer (Cont'd)

BMI in early adulthood categorical (kg/m^2)			P_{trend}	P for between studies-heterogeneity*
21 to <23	23 to <25	≥25		
348	143	96		
1.09 (0.89-1.34)	1.01 (0.76-1.34)	1.04 (0.72-1.50)	0.90	0.09
1.08 (0.88-1.33)	0.99 (0.74-1.33)	1.01 (0.72-1.43)	0.95	0.14
1.08 (0.88-1.31)	0.99 (0.74-1.33)	0.97 (0.73-1.30)	0.71	0.41
262	106	63		
1.17 (0.92-1.49)	1.09 (0.73-1.62)	1.06 (0.70-1.60)	0.97	0.15
1.17 (0.91-1.50)	1.11 (0.72-1.70)	1.03 (0.70-1.52)	0.92	0.21

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