# Body Mass Index, Height, and the Risk of Ovarian Cancer Mortality in a Prospective Cohort of Postmenopausal Women

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## Abstract

**Endogenous hormones may play a role in ovarian carcinogenesis. Postmenopausal obesity, although associated with higher circulating levels of estrogen and androgens, has not been linked consistently to ovarian cancer. The present study examined the relationship between body mass index (BMI), height, and ovarian cancer mortality among postmenopausal women in a large prospective mortality study of 300,537 women who were cancer free at enrollment in 1982 and had no history of hysterectomy or ovarian surgery. During 16 years of follow-up, 1,511 deaths occurred from ovarian cancer. Cox proportional hazard modeling was used to compute rate ratios (RRs) and to adjust for confounders. Ovarian cancer mortality rates were higher among overweight [BMI ≥25; RR, 1.16; 95% confidence interval (CI), 1.04–1.30] and obese women (BMI ≥30; RR, 1.26; 95% CI, 1.07–1.48) compared with women with BMI <25. Use of postmenopausal estrogens modified the association between BMI and ovarian cancer mortality ($P = 0.05$). The increased risk associated with obesity (BMI ≥30) was limited to women who never used postmenopausal estrogens (RR, 1.36; 95% CI, 1.12–1.66) and was not seen among ever users (RR, 0.93; 95% CI, 0.62–1.41). Height was positively associated with ovarian cancer mortality. Compared with women 152–156 cm tall, ovarian cancer mortality rates were lowest for the shortest women (RR, 0.72; 95% CI, 0.47–1.10 for women <152 cm) and highest for the tallest (RR, 1.41; 95% CI, 0.95–2.09 for women ≥177 cm). In this study, obesity and height appear to be independently associated with ovarian cancer mortality. The 36% increase in risk associated with obesity among women who had never used postmenopausal estrogens may have important public health implications because obesity is a growing problem in the United States.**

## Introduction

Endogenous hormones are hypothesized to be involved in the etiology of ovarian cancer (1–3). Postmenopausal circulating levels of estrogens and androgens are higher among obese women, and obesity is a well-established risk factor for hormone-related cancers, such as breast and endometrial cancer (4). Ovarian cancer, however, has not been linked consistently to obesity.

Eighteen case-control studies (5–22) have been examined for the association between BMI[2] and ovarian cancer. Five (6, 9–11, 14) of nine hospital-based case-control studies found no association, three reported a positive association (7, 8, 18), and one (13) found increased risk with lower BMI. In contrast, six (5, 12, 15–17, 20) of the nine population-based case-control studies (5, 12, 15–17, 19–22) found moderately increased risk with higher BMI. The results from case-control studies may reflect selection bias in the hospital-based case-control studies if hospital controls tended to be more obese than general population controls.

Only three prospective studies, all relatively small, have examined the association between obesity and ovarian cancer. The largest study (23), including 175 cases, reported 60% increased risk of ovarian cancer mortality in women with a weight index at least 40%-plus above the average weight of the cohort. No increased risk was observed in a Danish cohort of women discharged with diagnoses of obesity (24). Limitations of this study were its reliance on the use of an external comparison group and an inability to control for other well-defined ovarian cancer risk factors that may be associated with obesity. Risk of ovarian cancer increased with increasing waist:hip ratio in the Iowa Women's Health Study cohort (25), suggesting an association with abdominal adiposity, but no increased risk was seen with increasing BMI. The Iowa study included only 97 ovarian cancer cases and may have had limited power to detect modest increases in risk.

Previous studies have not examined whether the effect of BMI on ovarian cancer risk was modified by use of postmenopausal estrogen, which has been associated with increased ovarian cancer risk in this study (2) and another prospective study (26). In this analysis, we hypothesized that obesity might increase ovarian cancer risk only among women who did not use postmenopausal estrogen. Effect modification by postmenopausal estrogen use is biologically plausible because obesity may increase ovarian cancer risk by increasing circulating levels of estrogens because of peripheral aromatization of androgens in adipose tissue (27–29). Therefore, obesity might be expected to have little effect on ovarian cancer risk among women who already had high levels of circulating estrogen

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[2] The abbreviations used are: BMI, body mass index; RR, rate ratio; CI, confidence interval; CPS-II, Cancer Prevention Study II; ERT, estrogen replacement therapy; IGF, insulin-like growth factor.

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because of the use of postmenopausal estrogen. This type of interaction between obesity and postmenopausal estrogen use has been documented previously for breast cancer (30, 31).

No trend of increasing risk with increasing height has been reported in three previous studies (14, 18, 32) that assessed the association between height and ovarian cancer incidence. Two studies (14, 18) were conducted in Japan and had as a maximum height category women taller than 158 cm. The third study (32) was conducted in Greece and reported no significant increase in risk among women ≥165 cm tall.

We examined the association between BMI, height, and the risk of ovarian cancer mortality in a large prospective cohort of postmenopausal women and whether use of postmenopausal estrogens modified this association.

## Materials and Methods

**Participants.** Women in this study were selected from the 676,288 female participants in the CPS-II, a prospective mortality study of ~1.2 million women and men begun by the American Cancer Society in 1982. Participants were identified and enrolled by >77,000 American Cancer Society volunteers throughout the United States and Puerto Rico (33). Participants completed a confidential, self-administered questionnaire in 1982 that included personal identifiers, demographic characteristics, personal and family history of cancer and other diseases, reproductive history, and various behavioral, environmental, occupational, and dietary exposures.

The vital status of study participants was determined through December 31, 1998, using two approaches. Volunteers made personal inquiries in 1984, 1986, and 1988 to determine whether their enrollees were alive or dead and to record the date of all deaths. Subsequent to 1988, automated linkage using the National Death Index was used to extend follow-up through 1998 (34) and to identify deaths among the few participants lost to follow-up between 1982 and 1988. Ascertainment of death was 99% complete from the time of enrollment through September 1988 (the end of volunteer follow-up) and ~93% complete from that time through December 31, 1988 (34). All aspects of the CPS-II cohort are approved by the Emory University School of Medicine Human Investigations Committee. Informed consent to participate in the study was implied by the return of a completed self-administered questionnaire in 1982.

At a completion of mortality follow-up in December 1998, a total of 131,039 women (19.4%) had died, 543,408 (80.3%) were still living, and 2,079 (0.3%) had follow-up truncated on September 1, 1988 because of insufficient data for National Death Index linkage. Death certificates were obtained for 98.4% of all women known to have died and were coded according to the International Classification of Diseases, Ninth Revision (35). Deaths from ovarian cancer were defined as those women who died with ovarian cancer (International Classification of Diseases-9 codes 183.0–183.9) as the underlying cause of death through December 31, 1998. We made the following exclusions for our analytic cohort: women with a history of cancer at the time of enrollment (except nonmelanoma skin cancer; $n = 57{,}106$); women who were premenopausal or who had unknown menopausal status ($n = 134{,}884$); and women with missing values of height or weight or with extreme ≤0.10th percentile or ≥99.90th percentile values of height, weight, or BMI ($n = 15{,}277$). We also excluded women who reported having had hysterectomy or previous ovarian surgery, because we could not distinguish partial from total oophorectomy ($n = 168{,}484$). After these exclusions, a total of 300,537 women and 1,511 ovarian cancer deaths were eligible for analysis.

**Assessment of Anthropometric Variables.** BMI (weight in kg/height in $m^2$) was calculated from reported height and weight and was categorized as follows: <18.50, 18.50–20.49, 20.50–21.99, 22.0–23.49, 23.50–24.99, 25.0–26.49, 26.50–27.99, 28.0–29.99, 30.0–34.99, and ≥35.00. We used BMI = 18.50–20.49 as the referent group for analyses. These categories correspond to cutpoints proposed by the WHO (36) for underweight (BMI <18.50), normal range (BMI 18.50–24.99), overweight grade 1 (BMI 25.00–29.99), and overweight grade 2 or obese (BMI 30.00–39.99). We conducted addition analyses using these WHO-recommended categories with BMI <25.00 as the referent category. Height in centimeters was categorized in increments of 5 cm. The minimum category was <152 cm, and the maximum was ≥177 cm. We used height of 152–156 cm as the referent group.

**Statistical Analysis.** Age-standardized death rates and RRs were calculated at each level of BMI and height. Death rates were directly standardized to the age distribution of the female population of the CPS-II cohort. We used Cox proportional hazards modeling to compute RRs and to adjust for potential confounders. For all of the Cox models, we stratified on the exact year of age at enrollment and controlled for race (white, nonwhite), duration of oral contraceptive use (never, <5 years, ≥5 years), number of full-term pregnancies (0, 1, 2–3, ≥4), age at menarche (<12, ≥12 years), age at menopause (<40, 40–49, ≥50 years), status and duration of ERT use (never, former <10 years of use, former ≥10 years of use, current <10 years of use, current ≥10 years of use). BMI and height were included in all models. Education, family history of breast and/or ovarian cancer, and smoking were also examined as potential confounders. However, we did not adjust for these factors in the final models because such adjustment had virtually no effect on our results. The Mantel-Haenszel (37) test for trend was used to assess the statistical significance of the association between the risk of ovarian cancer deaths and levels of increased BMI or height.

To test whether any of the potential risk factors modified the association between BMI and height and ovarian cancer, we entered multiplicative interaction terms between BMI or height and all of the other covariates into the multivariate models one at a time. We grouped BMI in three categories (<25.0, 25.0–29.99, and ≥30.0). The statistical significance of the interaction terms was assessed at the $P = 0.05$ level using the likelihood ratio test (38).

## Results

About 3% ($n = 8{,}024$) of women in the study population were underweight (BMI <18.5), 58% ($n = 174{,}622$) were in the normal range (BMI = 18.5 to <25.0), 28% ($n = 83{,}370$) were grade 1 overweight (BMI = 25.0 to <30.0), and 11% ($n = 34{,}002$) were grade 2 overweight or obese (BMI ≥30.0) as defined by WHO.

The age-adjusted percent distribution of certain ovarian cancer risk factors varied considerably by BMI (Table 1). Leaner women were more likely to be white, to be taller, and to be more educated. They were also more likely to have used oral contraceptives or postmenopausal estrogens, to have fewer number of pregnancies, to exercise more, and to be current smokers. Smaller differences were observed between BMI levels for other potential ovarian cancer risk factors. Shorter women were older at study entry, had younger age at menarche, were more likely to be of a race other than white, and to be less

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*Table 1* Demographic characteristics of women by BMI, CPS-II, 1982–1998

| Covariate | BMI <25.0[b] (*n* = 182,646) | | BMI, age adjusted %[a] 25.0 to <30.0[b] (*n* = 83,889) | | BMI ≥30.0[b] (*n* = 34,002) | |
|---|---|---|---|---|---|---|
| | No. | % | No. | % | No. | % |
| Race/Ethnicity | | | | | | |
| White | 173583 | 95.0 | 76387 | 91.1 | 29262 | 86.1 |
| Other | 8192 | 4.5 | 6983 | 8.3 | 4541 | 13.4 |
| Age at entry, yr | | | | | | |
| <40 | 253 | 0.1 | 107 | 0.1 | 98 | 0.3 |
| 40–49 | 18888 | 10.3 | 6699 | 8.0 | 3334 | 9.8 |
| 50–59 | 76852 | 42.1 | 32739 | 39.0 | 14044 | 41.3 |
| 60–69 | 55795 | 30.5 | 29363 | 35.0 | 11558 | 34.0 |
| >69 | 30858 | 16.9 | 14981 | 17.9 | 4968 | 14.6 |
| Family history of ovarian and/or breast cancer | | | | | | |
| No | 167880 | 91.9 | 77408 | 92.3 | 31575 | 92.9 |
| Yes | 14766 | 8.1 | 6481 | 7.7 | 2427 | 7.1 |
| Height, cm | | | | | | |
| <152 | 3380 | 1.9 | 2083 | 2.5 | 1542 | 4.5 |
| 152 to <157 | 18174 | 9.9 | 10786 | 12.9 | 5240 | 15.4 |
| 157 to <162 | 48401 | 26.5 | 23339 | 27.8 | 10842 | 31.9 |
| 162 to <167 | 55273 | 30.3 | 22513 | 26.8 | 9142 | 26.9 |
| 167 to <172 | 40759 | 22.3 | 18247 | 21.8 | 5244 | 15.4 |
| 172 to <177 | 13310 | 7.3 | 5596 | 6.7 | 1587 | 4.7 |
| ≥177 cm | 3349 | 1.8 | 1325 | 1.6 | 405 | 1.2 |
| Age at menarche, yr | | | | | | |
| <12 | 23862 | 13.1 | 14018 | 16.7 | 7691 | 22.6 |
| ≥12 | 150599 | 82.5 | 65658 | 78.3 | 24628 | 72.4 |
| Age at menopause, yr | | | | | | |
| <40 | 4501 | 2.5 | 2270 | 2.7 | 1041 | 3.1 |
| 40–49 | 54949 | 30.1 | 23812 | 28.4 | 9214 | 27.1 |
| ≥50 | 80152 | 43.9 | 39065 | 46.6 | 15310 | 45.0 |
| Oral contraceptive use, yr | | | | | | |
| Never | 137908 | 75.5 | 66797 | 79.6 | 27041 | 79.5 |
| <5 | 17674 | 9.7 | 6362 | 7.6 | 2605 | 7.7 |
| ≥5 | 18083 | 9.9 | 5819 | 6.9 | 2229 | 6.5 |
| Estrogen replacement therapy, yr | | | | | | |
| Nonuser | 105555 | 57.8 | 49574 | 59.1 | 21671 | 63.7 |
| Current oral, <10 | 6994 | 3.8 | 2085 | 2.5 | 569 | 1.7 |
| Current oral, ≥10 | 2810 | 1.5 | 844 | 1.0 | 180 | 0.5 |
| Former oral, <10 | 22712 | 12.4 | 9178 | 10.9 | 2821 | 8.3 |
| Former oral, ≥10 | 3490 | 1.9 | 1328 | 1.6 | 316 | 0.9 |
| No. of full-term pregnancies | | | | | | |
| None | 22579 | 12.4 | 9486 | 11.3 | 3825 | 11.2 |
| One | 19606 | 10.7 | 8302 | 9.9 | 3182 | 9.4 |
| 2–3 | 84951 | 46.5 | 35823 | 42.7 | 13268 | 39 |
| 4–9 | 42347 | 23.2 | 23328 | 27.8 | 10813 | 31.8 |
| Exercise | | | | | | |
| None | 3652 | 2.0 | 2256 | 2.7 | 1565 | 4.6 |
| Slight | 35454 | 19.4 | 20289 | 24.2 | 10660 | 31.4 |
| Moderate | 128048 | 70.1 | 54807 | 65.3 | 19141 | 56.3 |
| Heavy | 11536 | 6.3 | 4431 | 5.3 | 1599 | 4.7 |
| Education | | | | | | |
| Less than high school | 23207 | 12.7 | 16482 | 19.6 | 8608 | 25.3 |
| High school graduate | 54635 | 29.9 | 26940 | 32.1 | 10805 | 31.8 |
| Some college | 54285 | 29.7 | 22222 | 26.5 | 8230 | 24.2 |
| College graduate or more | 47471 | 26.0 | 16479 | 19.6 | 5556 | 16.3 |
| Cigarette smoking | | | | | | |
| Never | 90552 | 49.6 | 47937 | 57.1 | 20279 | 59.7 |
| Current | 42355 | 23.2 | 13565 | 16.2 | 4431 | 13.0 |
| Former | 37192 | 20.4 | 15387 | 18.3 | 6194 | 18.2 |

[a] Percentages are directly adjusted to the age distribution of the entire study population.
[b] Percentages not summing to total reflect missing data.

educated than taller women (data not shown). Taller women were more likely to have used oral contraceptives (data not shown). Differences by height across other potential risk factors were small.

Ovarian cancer mortality rates (using WHO categories) were higher among overweight (BMI ≥25.0; RR, 1.16; 95% CI, 1.04–1.30) and obese women (BMI ≥30.0; RR, 1.26; 95% CI, 1.07–1.48) compared with women with BMI <25 (Table 2).

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*Table 2* Ovarian cancer mortality by BMI, CPS-II, 1982–1998

| | No. of deaths | No. of person-years | Age-standardized rate[a] | RR (95% CI)[b] | RR (95% CI)[c] |
|---|---|---|---|---|---|
| BMI | | | | | |
| <25.0 | 853 | 2,702,979 | 26.6 | 1 | 1 |
| 25.0 to <30.0 | 467 | 1,238,126 | 31.2 | 1.16 (1.03–1.30) | 1.16 (1.04–1.30) |
| ≥30.0 | 191 | 493,218 | 33.2 | 1.25 (1.06–1.46) | 1.26 (1.07–1.48) |
| | | | | | *P* for trend = 0.001 |
| BMI | | | | | |
| <18.5 | 32 | 103,133 | 23.9 | 0.99 (0.67–1.45) | 0.98 (0.67–1.45) |
| 18.5 to <20.5 | 138 | 458,984 | 26.2 | 1 | 1 |
| 20.5 to <22.0 | 258 | 716,466 | 31.2 | 1.19 (0.97–1.46) | 1.18 (0.96–1.46) |
| 22.0 to <23.5 | 226 | 765,845 | 24.6 | 0.96 (0.77–1.18) | 0.95 (0.77–1.17) |
| 23.5 to <25.0 | 199 | 658,551 | 24.9 | 0.96 (0.77–1.19) | 0.95 (0.76–1.18) |
| 25.0 to <26.5 | 152 | 478,026 | 26.4 | 1.00 (0.79–1.26) | 1.00 (0.79–1.26) |
| 26.5 to <28.0 | 174 | 412,448 | 36.2 | 1.33 (1.06–1.66) | 1.32 (1.05–1.65) |
| 28.0 to <30.0 | 141 | 347,652 | 31.8 | 1.28 (1.01–1.62) | 1.28 (1.01–1.63) |
| 30.0 to <35.0 | 139 | 374,028 | 30.4 | 1.21 (0.95–1.53) | 1.21 (0.95–1.54) |
| ≥35.0 | 52 | 119,191 | 42.8 | 1.53 (1.11–2.11) | 1.54 (1.12–2.14) |
| | | | | | *P* for trend = 0.001 |

[a] Death rates standardized to the CPS-II female population, rate/100,000 person-years.
[b] Adjusted for age at entry and race.
[c] Adjusted for age at entry, race, height, exercise, age at menarche, age at menopause, duration of oral contraceptive use, status and duration of ERT use, and number of full-term pregnancies.

Overall, in a finer stratification of BMI categories, we found no evidence of increased risk of ovarian cancer mortality with increasing BMI among women with BMI <26.50 (Table 2). Ovarian cancer mortality rates were higher among women with BMI ≥26.5 to <35.0 and highest for women with BMI ≥35.0. Compared with women in the reference group, ovarian cancer mortality was 54% higher among the heaviest women (RR, 1.54; 95% CI, 1.12–2.14). A test for trend was statistically significant ($P = 0.001$).

As reported previously in this cohort (2), risk of ovarian cancer mortality was higher among women who ever used postmenopausal estrogens and increased with increasing duration of use among both former and current users at baseline. We further examined whether the association between BMI and ovarian cancer mortality was modified by ever use of postmenopausal estrogens (Table 3). For this analysis, we excluded women who reported using estrogen in cream or by injection exclusively and used WHO categories for BMI. Ovarian cancer mortality rates increased with increasing BMI among "never" estrogen users and were 36% higher among obese women (BMI ≥30) than among women of normal weight BMI <25 ($p$ for trend = 0.001); no increase in risk with increasing BMI was seen in "ever" estrogen users ($p$ for trend = 0.72). The $P$ for interaction was 0.05, based on a multiplicative interaction term for ERT and BMI (modeled continuously as a categorical variable). The RRs specifically for obesity (BMI ≥30), however, were not statistically different among women who had used postmenopausal estrogen and women who had not ($P = 0.10$ for heterogeneity). Chance cannot be ruled out as an explanation for the observed difference in RRs.

Height was positively associated with ovarian cancer mortality (Table 4). Ovarian cancer death rates were lowest among the shortest women (<152 cm tall; RR, 0.72; 95% CI, 0.47–1.10), plateaued at heights between 152 and 171 cm, and increased with increasing height among women 172 cm tall or higher. Compared with women 152–156 cm tall, ovarian cancer mortality rates were 41% higher among women ≥177 cm (RR, 1.41; 95% CI, 0.95–2.09). The test for trend across height categories was statistically significant ($P = 0.01$).

*Table 3* Ovarian cancer mortality by BMI and ever use of ERT, CPS-II, 1982–1998

| | Ever ERT use[a] | |
|---|---|---|
| | Never | Ever, oral |
| BMI <25.0 | | |
| No. of deaths | 462 | 246 |
| Person-years | 1,565,491 | 665,740 |
| Age-standardized rate[b] | 26.07 | 31.46 |
| RR (95% CI)[c] | 1 | 1 |
| BMI 25.0 to <30.0 | | |
| No. of deaths | 273 | 95 |
| Person-years | 733,270 | 250,980 |
| Age-standardized rate[b] | 32.09 | 30.78 |
| RR (95% CI)[c] | 1.20 (1.03–1.39) | 0.99 (0.78–1.26) |
| BMI ≥30.0 | | |
| No. of deaths | 129 | 25 |
| Person-years | 315,962 | 74,365 |
| Age-standardized rate[b] | 36.29 | 29.21 |
| RR (95% CI)[c] | 1.36 (1.12–1.66) | 0.93 (0.62–1.41) |
| | *P* for trend = 0.001 | *P* for trend = 0.72 |
| | *P* for interaction = 0.05 | |

[a] Women who reported using estrogen in cream or injection are excluded.
[b] Death rates standardized to the CPS-II female population, rate/100,000 person-years.
[c] Adjusted for age at entry, race, height, exercise, age at menarche, age at menopause, duration of oral contraceptive use, and number of full-term pregnancies.

We found no evidence that the association of BMI and height with ovarian cancer mortality was significantly modified by previous use of oral contraceptives or any of the other potential confounders included in the multivariate model.

## Discussion

Results from this large prospective study support the hypothesis that postmenopausal obesity is associated with higher death rates from ovarian cancer. Ovarian cancer mortality did not increase steadily throughout the range of lean and normal

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*Table 4* Ovarian cancer mortality by height, CPS-II, 1982–1998

| Height, cm | No. of deaths | No. of person-years | Age-standardized rate[a] | RR (95% CI)[b] | RR (95% CI)[c] |
|---|---|---|---|---|---|
| <152 | 24 | 96,026 | 15.9 | 0.73 (0.48–1.13) | 0.72 (0.47–1.10) |
| 152 to <157 | 162 | 488,247 | 26.1 | 1 | 1 |
| 157 to <162 | 430 | 1,210,093 | 28.6 | 1.10 (0.92–1.32) | 1.12 (0.93–1.34) |
| 162 to <167 | 449 | 1,292,584 | 29.2 | 1.11 (0.93–1.33) | 1.14 (0.95–1.37) |
| 167 to <172 | 305 | 962,754 | 27.9 | 1.04 (0.86–1.27) | 1.07 (0.89–1.30) |
| 172 to <177 | 111 | 308,219 | 33.3 | 1.24 (0.97–1.58) | 1.28 (1.00–1.63) |
| ≥177 | 30 | 76,401 | 37.2 | 1.35 (0.91–2.00) | 1.41 (0.95–2.09) |
| | | | | | *P* for trend = 0.02 |

[a] Death rate standardized to the CPS-II female population, rate/100,000 person-years.
[b] Adjusted for age at entry and race.
[c] Adjusted for age at entry, race, WHO BMI, exercise, age at menarche, age at menopause, duration of oral contraceptive use, status and duration of ERT use, and number of full-term pregnancies.

weight women, however. Higher risk was only observed among overweight and obese women. As we hypothesized, no evidence of increasing risk with increasing BMI was observed among overweight and obese women who ever used postmenopausal estrogen.

The magnitude of the association between BMI and ovarian cancer mortality and the shape of the relationship observed in this study could explain the null results observed in previous studies with smaller numbers of cases or lower cutpoints for the top categories of BMI (16, 21, 24, 25). Furthermore, it is possible that ovarian cancer, similar to breast cancer, may be associated with obesity only among postmenopausal women. Our study examines the relationship between BMI and ovarian cancer mortality among postmenopausal women, whereas previous studies included both pre- and postmenopausal women.

Possible biological explanations for the observed association between BMI and ovarian cancer mortality involve the potential role of estrogen and androgens in ovarian carcinogenesis. Adipose tissue is the primary source of endogenous estrogen after menopause, and circulating levels of estrogen are higher in postmenopausal women who are obese (27–29). Both estradiol and estrone stimulate cell growth in normal and malignant ovarian surface epithelial cell cultures (39). Thus, estrogens from extraglandular sources may promote proliferation and malignant transformation of epithelial ovarian cells (3). A role of estrogen in the etiology of ovarian cancer is supported by the observed increased risk with long-term use of postmenopausal estrogens observed in this cohort (2) and another prospective cohort (26), and the protective effect of breastfeeding, parity, and oral contraceptive use (1) on ovarian cancer risk. In addition, the lack of association between BMI and ovarian cancer observed among women who ever used estrogen therapy may suggest that for ovarian as well as breast cancer (30, 40), there may be a threshold level of estrogen exposure that is biologically important, beyond which higher dosages have negligible effect.

Androgens have been proposed to have a relevant role in the pathogenesis of ovarian cancer (1). High BMI has been associated with increased serum testosterone concentrations among postmenopausal women (27, 41), and testosterone and 5$\alpha$-dihydrotestosterone stimulate growth of malignant and normal cells *in vitro* (39). Prediagnostic serum hormone levels of dehydroepiandrosterone and androstenedione were associated with higher ovarian cancer risk in a prospective study of serum hormone levels and the development of ovarian cancer (42).

Alternatively, risk associated with BMI and height may involve IGF. Obesity, and more specifically abdominal obesity, is related to hyperinsulinemia, and insulin resistance (43), which increases cholesterol levels and IGF-I. IGF-I has been strongly associated with hormone-dependent cancers, such as breast and prostate cancer (44, 45). Epidemiological evidence supporting this hypothesis, however, is limited and inconsistent for ovarian cancer. Higher cholesterol levels were associated with an increased risk of incident ovarian cancer in a prospective study of serum micronutrients and ovarian cancer (42). History of diabetes mellitus, however, did not increase risk of ovarian cancer in several previous studies that assessed this association (46–48). Diabetes reported at study entry did not increase the risk of ovarian cancer in this cohort (data not shown). Height may be a marker of exposure to growth factors during childhood growth. Short stature may reflect caloric restriction during childhood and adolescence. Early caloric restriction is known to correlate with lower stimulation from growth factors such as IGF-I (49). The increased risk associated with height seen in this study, therefore, is consistent with a role of IGF-I or related growth factors in ovarian cancer risk.

Some limitations of the study should be acknowledged:

(*a*) We have no direct measure of central adiposity or of lean body mass. Although BMI is an adequate measure of adiposity in young adults and middle-aged populations (50), it may perform less well in older adults, such as the women included in this cohort. As people age, individuals may lose substantial amounts of lean body mass while maintaining the same weight, thus reducing the validity of BMI as a measure of central adiposity.

(*b*) We used self-reported weight and height at study entry to calculate BMI, both of which are subject to error (51). Although self-reported weight and height are highly correlated with measured weight and height (51), a small, generally systematic error exists: an overestimation of height and an underestimation of weight, especially at higher weights (51).

(*c*) The studied outcome was mortality rather than incidence. The increased risk associated with BMI could reflect a high case-fatality rate among obese women. This possibility seems unlikely, however, because of the low survival rate of ovarian cancer in older women (52) and because obesity has not been related to survival among women with either low malignant potential tumors or invasive tumors (53).

(*d*) We did not have information on histological type of ovarian cancer that could allow us examining histological specificity with obesity. Results from some (8, 15) but not all (17) studies suggest that obesity may be related to the endometrioid form of ovarian cancer in particular.

The main strength of the study is its large size (>1,500 ovarian cancer cases), giving us the opportunity to explore prospectively the association of ovarian cancer mortality with a

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wide range of BMI and height values and the opportunity to adjust for a number of known and hypothesized ovarian cancer risk factors.

In conclusion, results of this large prospective study suggest that overweight and obesity are associated with increased risk of ovarian cancer mortality among women who never used postmenopausal estrogen therapy. Although the observed association is modest, >55% of women aged 25 or older in the United States are overweight or obese (54), reflecting a 47.4% increase in obesity prevalence in adult women between 1991 and 1998 (55). This combined with the high fatality rate of ovarian cancer suggests that effects of obesity on ovarian cancer risk identified in this study have importance for public health.

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