Risk of Ovarian Cancer Associated with BMI Varies by Menopausal Status

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Abstract

Obesity has been linked to increased risk of several malignancies, but the role of obesity in the etiology of ovarian cancer remains unclear. Therefore, a hospital-based case-control study was conducted to investigate the association between body size and risk of ovarian cancer. Participants included 427 women with primary, incident ovarian cancer and 854 cancer-free controls. All participants received medical services at Roswell Park Cancer Institute in Buffalo, NY between 1982 and 1998 and completed a comprehensive epidemiological questionnaire. The instrument included questions regarding height and usual wt prior to survey. Participants were classified as underweight/normal (BMI $\leq$24.9 kg/m^2), overweight (BMI 25.0–29.9 kg/m^2), or obese (BMI $\geq$30.0 kg/m^2). Compared with underweight/normal participants, being overweight (adjusted odds ratio [OR] = 1.02; 95% CI 0.77–1.36) or obese (adjusted OR = 1.17; 95% CI 0.84–1.65) was not significantly associated with an elevated risk of ovarian cancer. After stratification by menopausal status, BMI showed no significant association to ovarian cancer risk among postmenopausal women ($\geq$50 y old). However, among premenopausal women (<50 y old), those classified as obese had a significantly increased risk (adjusted OR = 2.19; 95% CI 1.19–4.04) compared with women classified as normal/underweight. These findings suggest a potential influence of menopausal status on the total endogenous hormonal environment, including estrogens, androgens, and insulin-like growth factors, when considering the association between body size and ovarian cancer risk. In light of the fact that obesity is a modifiable risk factor, further investigation on this topic is warranted. J. Nutr. 136: 2881–2886, 2006.

Introduction

Ovarian cancer is a gynecologic malignancy most frequently diagnosed as late stage disease with 5-y survival rates of ~30% (1). Despite numerous etiologic investigations, only a small number of consistent risk factors for ovarian cancer have been identified, including age, family history of breast or ovarian cancer, and genetic predisposition (i.e., carrying a high risk, germ line tumor suppressor gene mutation such as BRCA1 or BRCA2). These risk factors are largely unmodifiable, with the exception of risk-reducing surgical treatment (2). In contrast, parity and oral contraceptive use are modifiable risk factors that have been shown to confer a reduction in risk (3). Additional putative risk factors, such as body size, have been the subject of numerous studies, but their role in ovarian cancer etiology remains unclear. As proper nutrition and wt reduction are actively promoted as an essential public health goal, increasing attention is being placed on associations between body size and morbidity from gynecological cancers (4,5).

Previous investigations of the relation between body size and the risk of ovarian cancer have produced inconsistent results. A complicating factor in drawing firm conclusions about body size and cancer risk is the highly variable methods in which body size has been assessed, including weight, height, BMI, and waist-to-hip ratio. Several cohort and case-control studies that measured usual body size using BMI or waist-to-hip ratio have shown a significant positive relation to ovarian cancer risk (6–15), whereas other investigations showed no association (16–24) or an inverse association (25). BMI in young adulthood has shown similar inconsistencies, with several epidemiologic studies yielding positive associations (11,12,17–19,26,27) or no association (10,18,22). Recent studies that examined height and ovarian cancer risk have primarily reported positive associations; however, these findings were typically limited to subsets of subjects such as younger age, histological type, or African American ethnicity (8,10,11,17,26). At least 1 study examining height found no association with cancer risk (22) and another found an inverse association (20). Therefore, due to the inconsistencies across previous etiologic studies, a hospital based case-control study was conducted to assess ovarian cancer risk in relation to usual BMI and height, while also considering the role of menopausal status and differences by histological subtype.

Methods

Study population. The study population included women who received medical services at Roswell Park Cancer Institute (RPCI) in Buffalo, New York, between 1982 and 1998, and who agreed to complete a

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0022-3166/06 $8.00

Manuscript received 24 May 2006. Initial review completed 27 June 2006. Revision accepted 27 July 2006.

comprehensive epidemiologic questionnaire. The case group consisted of 427 women with primary epithelial ovarian, peritoneal, or fallopian tube cancer, identified from the RPCI Tumor Registry and Diagnostic Index. Participants with missing information on wt or height were excluded. Median time from diagnosis to participation was 21 d; 71% of cases participated within 6 mo of diagnosis. Women who presented to RPCI concern about possible neoplastic disease, but were not diagnosed with a pathological condition, formed a pool of 5845 possible controls. Control women ($n = 854$) were randomly selected from this pool and frequency matched 2:1 to cases based on age at participation (5-y-age intervals) and residence inside/outside of western New York. Controls were most commonly treated for breast disorders (27%), genitourinary disorders (18%), gastrointestinal disorders (12%), circulatory disorders (6%), metabolic disorders (5%), ill-defined symptoms (4%), skin disorders (3%), musculoskeletal disorders (3%), infectious disorders (3%), and respiratory disorders (3%). For 108 controls (13%), the underlying diagnosis was not available; it is likely these individuals came to RPCI for specialized testing or procedures but received subsequent medical care elsewhere. The RPCI Institutional Review Board approved the conduct of the study.

Questionnaire. All participants completed the Patient Epidemiology Data System (PEDS) questionnaire, which was offered to all new patients as part of the admission process. The PEDS questionnaire was returned by ~50% of patients. The 16-page instrument covered information on anthropometric measures, reproductive and medical histories, family history of cancer, occupational and environmental exposures, diet, and tobacco and alcohol use. Patients reported current body wt, usual body wt, and current height. Usual body wt and current height were used to calculate usual BMI in kg/m^2. Use of usual body wt for calculation of BMI was preferred over current body wt in an effort to account for any recent changes in wt associated with disease status. Usual BMI was then categorized as underweight or normal (≤24.9), overweight (25.0–29.9), or obese (≥30.0). Height in inches was used both as continuous variable and dichotomized based on the sample median [≤64 inches (162.6 cm) and >64 inches]. The lowest categories of BMI and height were used as reference groups in all analyses.

Statistical analyses. All statistical analyses were calculated using SPSS for Windows, version 11.0. Odds ratios (OR) and 95% CI of body size and ovarian cancer risk were computed by unconditional logistic regression in separate models for usual BMI and height. All multivariate regression models were adjusted for the matching variables age (continuous) and residence in western New York (no/yes). Known and suspected risk factors were considered significant confounders if, in addition to their association with both body size and cancer risk, they changed point estimates by at least 10%. The following risk factors were assessed as potential confounders by logistic regression but excluded from the final multivariate models: current marital status (no/yes), annual income ≥$25,000/y (no/yes), non-Hispanic White ethnicity (no/yes), family history of ovarian cancer (no/yes), menses were usually irregular (no/yes), ever pregnant (no/yes), ever had a live birth (no/yes), number of children (continuous), ever had tubal ligation (no/yes), ever used oral contraceptives (no/yes), total years used hormone replacement therapy (continuous), used talc on sanitary napkins or genitals (no/yes), total years smoked cigarettes (continuous), and total alcoholic beverages consumed per wk (continuous). Only years of participation in the study (continuous) was included with the matching variables in the final models. Trend tests to assess for dose-response relations were computed by treating ordinal-level predictors as continuous variables in regression models. Statistical tests at the $P < 0.05$ level were considered statistically significant.

Although data on self-reported menopausal status was available for most participants, ~15% of case women reported the end of menses due to hysterectomy (for cancer treatment or prior to cancer treatment). However, the PEDS questionnaire did not request information on whether or not hysterectomy included oophorectomy. Because of concern about possible misclassification of premenopausal women based on self-report, menopausal status was estimated by using age of 50 y (the median age of natural menopause reported in control women) as the cut-point, with women under age 50 y considered premenopausal and women age 50 y or older considered postmenopausal (28). Menopausal status (based on age) and histological subtype were assessed as possible effect modifiers in multivariate analyses.

Results

Demographic, reproductive, and lifestyle risk factor information were compared by case-control status (**Table 1**). Because of matching, there was no difference between cases and controls on age and residence within western New York. Cases were significantly more likely to be currently married and have an annual income of ≥$25,000. In contrast, controls were significantly more likely to be of non-Hispanic white race, to have been pregnant, had a live birth, or had a tubal ligation. On average, control women reported having significantly more children and longer histories of smoking cigarettes. There were no differences between cases and controls in this sample on risk factors such as family history of ovarian cancer, prior history of irregular menses, or use of oral contraceptives, hormone replacement therapy, talc, or alcohol.

BMI was associated with increased cancer risk among women categorized as premenopausal based on age (**Table 2**). Compared with underweight or normal (BMI ≤24.9) premenopausal women, obese (BMI ≥30.0) premenopausal women showed about a 2-fold increase in risk (adjusted OR = 2.19, 95% CI 1.19–4.04). A significant test for trend ($P < 0.021$) suggested a positive dose-response relation between BMI and cancer risk. Postmenopausal women, however, did not show the same effect, with only a small, nonsignificant decrease in risk among the heaviest women (adjusted OR = 0.88, 95% CI 0.58–1.33; $P = 0.544$. Based on these findings, menopausal status appears to modify the relation between BMI and ovarian cancer risk in this sample of women.

TABLE 1 Descriptive statistics and odds ratios of predictors of ovarian cancer case status among women seen at Roswell Park Cancer Institute, 1982–1998, $n = 1281$[1]

Variable	Cases		Controls		Crude OR	95% CI
	n	%	*n*	%		
Resident of western New York	215	(50.4)	430	(50.4)	1.00	0.79–1.26
Currently married	284	(67.0)	519	(61.1)	1.29	1.01–1.65
Annual income ≥$25K	147	(35.4)	243	(29.0)	1.34	1.04–1.72
Non-Hispanic white	404	(94.6)	844	(98.8)	0.21	0.10–0.44
Family history of ovarian cancer	19	(4.4)	30	(3.5)	1.28	0.72–2.30
Ever pregnant	337	(79.1)	723	(85.5)	0.64	0.48–0.87
Ever had a live birth	319	(76.0)	692	(82.6)	0.67	0.50–0.89
Menses were usually irregular	56	(13.2)	137	(16.6)	0.76	0.55–1.07
Ever had tubal ligation	51	(12.0)	138	(16.4)	0.70	0.46–0.99
Ever used oral contraceptives	137	(32.5)	275	(33.1)	0.98	0.76–1.25
Postmenopausal	287	(67.2)	586	(68.6)	0.94	0.73–1.20
Used talc on sanitary napkins or genitals	171	(44.3)	368	(45.3)	0.96	0.75–1.23
Age, *y*	55.8	±13.7	55.8	±13.8	1.00	0.99–1.01
Study participation year	1989	±4.6	1986	±3.5	1.17	1.13–1.20
Smoked cigarettes, *total y*	23.5	±13.5	26.0	±13.9	0.99	0.97–1.00
Alcoholic beverages, *n/wk*	2.9	±4.7	3.0	±5.1	1.00	0.98–1.03
Children, *n*	2.2	±1.8	2.6	±1.9	0.90	0.84–0.96
HRT use, *total y*	5.0	±6.2	6.6	±7.8	0.97	0.93–1.01

[1] Values are frequencies (percentages) or means ±SD.

TABLE 2 Crude and adjusted odds ratios of ovarian cancer predicted by BMI, among all women and by menopausal status[1]

	Cases	Controls	Crude OR	95% CI	Adjusted OR[2]	95% CI
All Women, *n = 1281*	427 (33.3)	854 (66.7)				
BMI						
≤24.9	229 (53.6)	484 (56.7)	1.0		1.0	
25.0–29.9	116 (27.2)	244 (28.6)	1.01	0.77–1.32	1.02	0.77–1.36
≥30.0	82 (19.2)	126 (14.8)	1.38	1.00–1.89	1.17	0.84–1.65
					$P = 0.40$ for trend	
Premenopausal, *n = 408*						
BMI						
≤24.9	81 (57.9)	181 (67.5)	1.0		1.0	
25.0–29.9	30 (21.4)	58 (21.6)	1.16	0.69–1.93	1.12	0.65–1.92
≥30.0	29 (20.7)	29 (10.8)	2.24	1.25–3.98	2.19	1.19–4.04
					$P = 0.02$ for trend	
Postmenopausal, *n = 873*						
BMI						
≤24.9	148 (51.6)	303 (51.7)	1.0		1.0	
25.0–29.9	86 (30.0)	186 (31.7)	0.95	0.69–1.31	0.97	0.69–1.36
≥30.0	53 (18.5)	97 (16.6)	1.12	0.76–1.65	0.88	0.58–1.33
					$P = 0.56$ for trend	

[1] Values are frequencies (percentages).
[2] Model adjusted for age, geographic area, and year of study participation.

The relation of BMI and cancer risk was also assessed by histological subtype (**Table 3**). Results are suggestive of an increase in risk for obese, premenopausal women with mucinous (adjusted OR = 6.24, 95% CI 1.74–22.41) and endometrioid (adjusted OR = 6.34, 95% CI 6.34–19.90) tumor types. However, it is important to interpret these results with caution, because cell sizes are small, potentially producing unstable risk estimates. Analysis of histological subtypes in postmenopausal women revealed no significant variation from the full sample by cell type.

Because this study employed hospital-based controls, subgroup analysis by disease status of controls was conducted to determine whether risk factors for other disorders were influencing the association between BMI and cancer risk. Controls presenting for breast disease ($n = 226$), genitourinary disease ($n = 156$), digestive disease ($n = 104$), and those with unclassified disease status ($n = 108$) were analyzed separately in regard to BMI and cancer risk. Only those controls with digestive disease showed noticeably different risk estimates, with a nonsignificant decrease in risk associated with overweight BMI ($P = 0.154$). However, after excluding this subset of controls, the association between BMI and cancer risk among obese women increased only slightly (adjusted OR = 2.36, 95% CI 1.23–4.43).

When height (in inches) was used to predict ovarian cancer risk, premenopausal women showed a slight increase in risk, suggestive of a possible association (adjusted OR = 1.05, 95% CI 0.98–1.14). However, the effect of increasing height on ovarian cancer risk was not borne out when height was dichotomized based on the sample median of 64 inches (162.6 cm). Taller premenopausal women with height >64 inches showed a small, nonsignificant ($P = 0.298$) increase in risk (adjusted OR = 1.28, 95% CI 0.83–1.96). For postmenopausal women, height showed no notable relation with cancer risk (data not shown).

Discussion

The results from this hospital-based case-control study indicate that obese, premenopausal women showed an ~2-fold increase in risk of ovarian cancer. Additional analyses pointed to further increase in risk among obese premenopausal women with mucinous and endometrioid histologies. No notable associations between BMI and cancer risk were seen in the postmenopausal women. Overall, evidence for an association between height and ovarian cancer risk was limited to a nonsignificant ($P = 0.298$) increase in risk among taller, premenopausal women. Similar to the results of the current study, several case-control studies (6,11–13,15,23,29) and cohort studies (9,10) have shown that BMI is a positive predictor of ovarian cancer risk, particularly when the role of menopausal status is examined. A population-based case-control study by Kuper and colleagues (23) reported a 57% increase in risk of ovarian cancer that was limited to currently obese, premenopausal women, although the results were not statistically significant. Interestingly, postmenopausal women showed no trend for increasing risk, although those women who were postmenopausal for <10 y showed greater risk relative to women who were postmenopausal for 10 y or more (23), again emphasizing the modifying effect of menopausal status. In contrast to the current study, a report from the Nurses' Health Study cohort found only a small nonsignificant increase in ovarian cancer among premenopausal women who were currently obese ($P < 0.45$ for trend) (19). However, these authors did note a significant 2-fold increase in premenopausal ovarian cancer risk among women who were overweight at age 18 (19).

In addition to menopausal status, consideration of histological subtypes (or the classification of morphological differences across tumors) has been shown to be an important factor when examining ovarian cancer risk. Holschneider and Berek estimate that invasive epithelial ovarian cancer cases are comprised of primarily serous (75–80%), mucinous (10%), and endometrioid (10%) histological subtypes (30). Less common histological subtypes of invasive ovarian cancer include clear cell, Brenner, and undifferentiated carcinoma (30). It has been suggested that mucinous and clear cell subtypes are the most chemoresistent (2), but a more precise relation of histological type and ovarian prognosis is unclear. In terms of etiology, interest in identifying high risk histological subgroups, or tumor types particularly susceptible to a given etiologic risk factor, remains high among researchers. For example, Farrow and colleagues' (15) study of ovarian cancer related to body size found a significant excess in risk among the heaviest, premenopausal women with serous and endometrioid histological subtypes. Other researchers, however, have found the greatest risk among borderline tumors and invasive serous, mucinous, and undifferentiated subtypes (23). A recent pooled analysis of 10 case-control studies concluded that the associations between parity and oral contraceptive use on cancer risk is relatively consistent across histological subtypes (31). In contrast, BMI showed greater heterogeneity in predicting cancer risk across serous, mucinous, and endometrioid histological types (31). The current study also found the highest risk among mucinous and endometrioid types but not among women with serous histology. Taken together, these results suggest the importance of continued examination and search for consistency of potential high-risk histological subgroups for predicting etiology.

The etiology of ovarian cancer is not completely understood, although several complex mechanisms involving ovulation, inflammation, and endogenous hormones may all be involved

TABLE 3 Adjusted odds ratios[1] of ovarian cancer predicted by BMI, by menopausal status and histological type[1,2]

	All, $n_{cases}/n_{controls}$ $_aOR$ (95%CI), $n = 427$	Serous, $n_{cases}/n_{controls}$ $_aOR$ (95%CI), $n = 261$	Mucinous, $n_{cases}/n_{controls}$ $_aOR$ (95%CI), $n = 33$	Endometrioid, $n_{cases}/n_{controls}$ $_aOR$ (95%CI), $n = 54$	Clear cell, $n_{cases}/n_{controls}$ $_aOR$ (95%CI), $n = 28$	Borderline, $n_{cases}/n_{controls}$ $_aOR$ (95%CI), $n = 28$
Premenopausal BMI						
≤24.9	81/181	50/181	8/181	8/181	2/181	12/181
	Ref	Ref	Ref	Ref	Ref	Ref
25.0–29.9	30/58	17/58	1/58	5/58	2/58	4/58
	1.12 (0.65–1.92)	1.02 (0.53–1.94)	0.47 (0.05–4.07)	1.95 (0.59–6.41)	2.23 (0.29–17.17)	1.12 (0.32–3.93)
≥30.0	29/29	11/29	7/29	7/29	1/29	2/29
	2.19 (1.19–4.04)	1.44 (0.65–3.19)	6.24 (1.74–22.41)	6.34 (1.95–19.90)	2.45 (0.19–30.86)	.94 (0.18–4.94)
Postmenopausal BMI						
≤24.9	48/303	96/303	8/303	14/303	14/303	6/303
	Ref	Ref	Ref	Ref	Ref	Ref
25.0–29.9	86/186	50/186	6/186	15/186	6/186	3/186
	0.97 (0.69–1.360)	0.86 (0.57–1.29)	1.03 (0.34–3.13)	1.70 (0.80–3.65)	0.70 (0.26–1.87)	0.86 (0.21–3.54)
≥30.0	53/97	37/97	3/586	5/97	3/97	1/97
	0.88 (0.58–1.33)	0.95 (0.59–1.53)	0.95 (0.24–3.80)	0.96 (0.33–2.80)	0.55 (0.15–2.00)	0.52 (0.06–4.56)

[1] All models adjusted for age, geographic area, and year of study participation.
[2] Values are frequencies.

in ovarian carcinogenesis. The incessant ovulation theory (32,33) considers damage to the epithelial layer of the ovary from uninterrupted ovulation resulting in rapid cellular proliferation a key pathological process. This theory has gained support from numerous epidemiologic investigations that have established parity and use of oral contraceptives, both of which suppress ovulation, as protective factors (33–35). Inflammation has also been suggested as a mechanism for ovarian carcinogenesis (36), because risk factors such as asbestos exposure, talc use, and pelvic inflammatory disease have been associated with increased risk of ovarian cancer, however inconsistently. Additionally, excess body weight has been associated with a subclinical form of chronic inflammation as indicated by increased levels of circulating adipokines (37–39). Perhaps most relevant to the discussion of body size indicators and ovarian cancer risk are the hypotheses focused on the role of the endogenous hormonal environment, including sex steroid hormones and insulin-like growth factors (IGFs) (40). Androgens and IGFs in particular have been suggested to be risk factors, whereas progesterone may be a protective factor (40,41). Finally, although menopausal status plays an important role in estrogen and other sex hormone levels (41), the ultimate influence of menopause on ovarian cancer etiology may differ from that of breast cancer. Higher BMI is an established breast cancer risk factor among postmenopausal women (42) due to greater estrogen metabolism in peripheral adipose tissue. However, previous studies have not found the same consistent influence of menopausal status on body size with increased risk for postmenopausal ovarian cancer, suggesting estrogen may effect ovarian cancer in ways not fully understood at this time (23,41,43).

Although still under debate, body size likely plays a role in determining the endogenous hormonal environment that then may influence ovarian cancer risk. BMI has been shown to be positively associated with sex steroid hormones and IGFs, particularly among postmenopausal women (44). Furthermore, there appears to be a positive correlation between IGFs and androgens but an inverse relation between IGFs and sex–hormone-binding globulin (44), pointing to an important role for IGFs in cancer risk. Elevated IGFs, which may induce cellular proliferation via inhibition of apoptosis (45), have also been shown to be significant, independent predictors of increased ovarian cancer risk (46). Similar to BMI, IGFs vary by stature, with taller individuals generally having higher levels of circulating IGFs (47). As reviewed by Gunnell and colleagues (47), height has been linked to several hormone dependent cancers, including breast and prostate, and can be considered a crude biomarker. However, the nature of adult height as an etiologic factor for ovarian cancer may simply be a proxy measure for a larger, multifactorial human development process dependent on genetic and childhood environmental influences (11).

Several methodological issues should be considered in interpreting these results. The study only enrolled individuals treated at RPCI, a large regional cancer treatment center. Data were collected at RPCI with the PEDS questionnaire over a 16-y period in which the format of the survey remained generally consistent. However, there was a general decline in participation over time due to less aggressive follow-up of nonresponders. Specific participation rates over this period are not known but on average, 50 percent of eligible cases and controls completed the survey. It is difficult to know whether those individuals who failed to complete the instrument differed from participants with respect to body size and we are unable to evaluate the impact of changing participation rates on the present findings. Nonetheless, previous studies that utilized the PEDS database consistently replicated established epidemiological associations for a variety of cancer sites, including ovary (48,49), colon (50), breast (51), prostate (52), and lung (53).

Individuals seen at RPCI were most frequently present with suspicion of neoplastic disease or for specialized screening and diagnostic procedures. Controls were randomly selected from a pool of cancer-free individuals seen at RPCI, yet they are unlikely to be representative of the general population in this geographic region. The use of hospital controls has the potential to decrease recall bias but may introduce selection bias, by including controls with conditions associated with body size or with risk profiles that differ from the general population. Yet, as noted above, the impact of disease status of controls on the current findings appears minimal. The failure of some established risk factors for ovarian cancer (such as oral contraceptive use) to demonstrate an association in these data are due to the

high proportion of controls seen for breast disorders (27%), many of whom are referred to RPCI because of a strong family history of breast and/or ovarian cancer. However, the inclusion of women at increased risk of ovarian cancer would be expected to attenuate the findings. Given the lengthy time frame by which data were collected from hospital patients, the current study included a large sample of ovarian cancer patients with a variety of histological subtypes allowing for exploratory analyses by subgroups. Finally, because data collection with the PEDS questionnaire was completed in 1998, information on more recently identified exposures of interest, such as BMI in early adulthood, was not collected, thereby limiting the ability to assess the role of body size at multiple time points.

In summary, obesity was a significant predictor of increased risk of premenopausal ovarian cancer risk with mucinous and endometrioid types showing the highest risk. Adult height was nonsignificantly associated with small increases in risk. The current study results provide additional evidence for the influence of body size as a modifiable risk factor for ovarian cancer that potentially impacts underlying biological mechanisms, such as androgen and IGFs levels, not directly related to incessant ovulation. Future research including comprehensive information on not just body size, but also histological subtype, is warranted to allow for firmer conclusions about cancer risk among potential high-risk subgroups.

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