Obesity As a Potential Risk Factor for Adenocarcinomas and Squamous Cell Carcinomas of the Uterine Cervix

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BACKGROUND. Hormonal factors may play a more prominent role in cervical adenocarcinoma than squamous cell carcinoma. The authors evaluated whether obesity, which can influence hormone levels, was associated with adenocarcinoma and squamous cell carcinoma.

METHODS. This case–control study included 124 patients with adenocarcinoma, 139 matched patients with squamous cell carcinoma, and 307 matched community control participants. All participants completed interviews and provided cervicovaginal samples for human papillomavirus (HPV) testing. Polytomous logistic regression-generated odds ratios (ORs) and 95% confidence intervals (95% CIs) for self-reported height and weight, body mass index (BMI; kg/m^2), and measured waist-to-hip ratio (WHR) for both histologic types were adjusted and stratified for HPV and other confounders.

RESULTS. Height, weight, BMI, and WHR were positively associated with adenocarcinoma. BMI $\geq$ 30 kg/m^2 (vs. BMI $<$ 25 kg/m^2; OR, 2.1 and 95% CI, 1.1–3.8) and WHR in the highest tertile (vs. the lowest tertile; OR, 1.8 and 95% CI, 0.97–3.3) were associated with adenocarcinoma. Neither height nor weight was found to be associated with squamous cell carcinoma, and associations for BMI $\geq$ 30 kg/m^2 (OR, 1.6) and WHR in the highest tertile (OR, 1.6) were weaker and were not statistically significant. Analyses using only HPV positive controls showed similar associations. The data were adjusted for and stratified by screening, but higher BMI and WHR were associated with higher disease stage at diagnosis, even among recently and frequently screened patients with adenocarcinoma. Thus, residual confounding by screening could not be excluded as an explanation for the associations.

CONCLUSIONS. Obesity and body fat distribution were associated more strongly with adenocarcinoma than with squamous cell carcinoma. Although questions

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about screening remain, obesity may have a particular influence on the risk of glandular cervical carcinoma. ***Cancer* 2003;98:814–21.**
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Obesity is considered an important cause of several malignancies,[1,2] and its association with endogenous hormone levels raises concern regarding its role in hormone dependent carcinomas.[3] Obesity may increase the risk of cervical carcinoma[4–7] and may be especially important for cervical adenocarcinomas, which have been linked to hormonal risk factors[8] and have been reported to be increasing in incidence in recent years.[9,10] Higher body weight and higher body mass index (BMI; kilograms per meters squared [kg/m^2]) were associated positively, but not significantly, with adenocarcinoma in a 1987 case–control study of 40 patients with adenocarcinoma, 418 patients with squamous cell carcinoma, and 801 control participants.[11] A 1988 Italian case–control study that included 39 patients with adenocarcinoma and 409 control participants observed significantly elevated odds ratios (ORs) for patients with BMI 25–29 kg/m^2 and BMI $>$ 30 kg/m^2.[7] However, weight was not associated with adenocarcinoma or squamous cell carcinoma in a 1993 study of 43 patients with adenocarcinoma, 667 patients with squamous cell carcinoma, and 1467 control participants in Latin American countries.[12] In 1996, a case–control study in the U.S. which included 195 participants with adenocarcinoma and 386 control participants noted a significantly elevated OR for $>$ 10 kilograms of weight gain after age 18 years and reported similar, positive associations with high BMI.[6] Some,[13,14] but not all,[15,16] case series reported greater mean weight among patients who had cervical adenocarcinoma compared with patients who had squamous cell carcinoma.

Recognition of the necessary, but not sufficient, causal role of human papillomavirus (HPV) in cervical carcinoma has encouraged epidemiologic studies to focus on *cofactors*: exposures and risk factors that, when present with HPV infection, contribute to the development of carcinoma.[17] The development of sensitive and specific methods for detecting HPV DNA accurately has enabled recent epidemiologic studies to measure HPV directly and to refine the risk associated with cofactors, such as parity[18] and oral contraceptive use.[19] Control for HPV infection generally was limited in earlier studies; therefore, we analyzed obesity as a potential cofactor for cervical adenocarcinoma in a multicenter case–control study that used polymerase chain reaction (PCR)-based HPV testing among patients with cervical adenocarcinoma, patients with cervical squamous cell carcinoma, and control participants.

MATERIALS AND METHODS

Study Population

To summarize the study methods, which are described elsewhere,[20] women ages 18–69 years who were newly diagnosed with in situ or invasive primary adenocarcinoma of the uterine cervix, adenosquamous carcinoma, or other rare histologic types of cervical carcinoma with glandular involvement at 1 of 6 medical centers in the U.S. between 1992 and 1996 were eligible for the adenocarcinoma group. We retrospectively identified women who were diagnosed between January 1992 and June 1994 (the date the study began) and prospectively recruited women who were diagnosed between July 1994 and March 1996. A panel of three pathologists performed a simultaneous microscopic review of adenocarcinomas to provide the study diagnoses for 88% of patients.

Using random-digit dialing, we generated a random sample of telephone numbers within the telephone exchange of each patient with adenocarcinoma, enumerated all adult women in each household, excluded women who reported a hysterectomy, and individually matched healthy control participants with patients in the adenocarcinoma group at a 2:1 ratio based on age ($\pm$ 5 years), race, and geographic region (i.e., telephone exchange).

To address potential referral bias and to evaluate whether risk factors differed according to tumor histology, we included a sample of women who were diagnosed with squamous cell carcinoma. Using identical eligibility criteria, we individually matched women with squamous cell carcinoma to women in the adenocarcinomas group based on clinic, age at diagnosis ($\pm$ 5 years), diagnosis date, and stage of disease at diagnosis (in situ vs. invasive). The analytic group included 124 patients with adenocarcinoma (33 in situ and 91 invasive), 139 patients with squamous cell carcinoma (48 in situ and 91 invasive), and 307 community control participants. Institutional Review Boards at the National Cancer Institute and at each clinical center approved the study.

Interviews

Participants completed personal risk factor interviews with trained staff. Patients with adenocarcinoma and squamous cell carcinoma reported exposures that occurred before a reference date, which was 12 months before their date of diagnosis. Community control participants used the reference date of their index patient in the adenocarcinoma group and reported only exposures before that date.

HPV DNA Testing

After obtaining informed consent, we collected one self-administered and two clinician-administered cervicovaginal samples from study participants. Participants collected self-administered specimens using Dacron swabs stored in 1 mL Specimen Transport Medium (STM; Digene Corporation, Silver Spring, MD). Clinicians collected samples during pelvic examinations using two consecutive Dacron swabs, each stored in 1 mL STM. For patients who were sampled before treatment, patients whose treatment did not include removal of the entire cervix, and community control participants, clinicians collected one specimen from the ectocervix and one specimen from the endocervix. For patients who were sampled after surgical treatment (i.e., who no longer had an intact cervix), clinicians obtained both Dacron swab specimens from the vaginal cuff. For sample collection, control participants visited the clinic from which their index patient in the adenocarcinoma group was recruited. All participants had the option of in-home interviews and sample collections, which included self-administered samples only. Cervical samples were available from 116 of 124 patients (94%) with adenocarcinoma, from 129 of 139 patients (93%) with squamous cell carcinoma, and from 255 of 307 women (83%) in the community control group.

A PCR-based, reverse line-blot detection method[21] that uses the MY09/11 L1 consensus primer system to individually discriminate 27 genotypes determined HPV status, which was grouped according to type[20] after HPV type 16 (HPV-16) status was confirmed using a second set of primers.[22] The 90% agreement between the results of the clinician-administered and self-administered samples[23] allowed us to classify a participant as HPV positive if either the self-administered samples or clinician-administered samples tested positive.

Exposure Assessment

Participants reported their height and weight at the reference date, their weight at age 20 years, their maximum weight after age 20 years and the age at which they reached that weight, their minimum weight after age 20 years and age at which they reached that weight, the number of episodes after age 20 years in which they lost $\geq$ 15 pounds and then gained the weight back, and their predominant pattern of weight gain (around chest or shoulders, waist or stomach, hips and thighs, or equally all over). Trained interviewers measured waist circumference just superior to the iliac crest of the pelvis, which was often at the level of the umbilicus, and hip circumference to include the maximum extension of the buttocks, which usually included underclothing plus a light, loose-fitting garment. We used the average of two measurements to calculate the waist-to-hip ratio (WHR).[24]

Statistical Analysis

We analyzed height, weight, and WHR as tertiles based on the distributions among control participants. We based BMI (in kg/m^2) on the self-reported height and weight. Analyses of BMI used standard definitions for normal weight (< 25 kg/m^2), overweight (25–29 kg/m^2), and obese (≥ 30 kg/m^2).[25] We subtracted the self-reported minimum and maximum weights after age 20 years to generate maximum adult weight change. For presentation, we converted the anthropometry data from U.S. units to metric units.

Because our primary hypothesis focused on a three-level outcome variable (i.e., cervical adenocarcinoma and cervical squamous cell carcinoma vs. control), we used polytomous logistic regression models[26] to generate ORs and 95% confidence intervals (95% CIs) to estimate relative risks associated with anthropometric variables for each histologic type relative to the community control group. We evaluated relevant questionnaire variables (e.g., demographic factors, infertility, menarche, sexual history, menopausal factors, other medical conditions, use of oral contraceptives, family history of cancer, parity and pregnancy characteristics, smoking, and Papanicolaou [Pap] smear screening) as potential confounders. Variables that were associated with both exposure and outcome and that altered the parameter estimates for the anthropometric variables by at least 10% were included parsimoniously in final regression models. Therefore, final models retained age (younger than 30 years, age 30–39 years, age 40–49 years, age 50–59 years, and 60 years and older), HPV status (negative; low-risk types; types HPV-16, HPV-18, HPV-18-like, or other carcinoma-associated types; and unknown), time since last Pap smear ($<$ 3 years before reference date, $\geq$ 3 years before reference date, and unknown), and age at last pregnancy (never pregnant, pregnant before age 35 years, or pregnant at age 35 years and older). Clinic and race/ethnicity (both were matching variables)

TABLE 1
Selected Descriptive Factors for Study Participants

Characteristic	No. of participants (%)		
	Controls	Adenocarcinoma	SCC
Age (yrs)			
< 30	67 (21.8)	27 (21.8)	28 (20.1)
30–39	107 (34.9)	39 (31.5)	52 (37.4)
40–49	83 (27.0)	40 (32.2)	37 (26.6)
50–59	36 (11.7)	6 (4.8)	10 (7.2)
≥ 60	34 (11.1)	12 (9.7)	12 (8.6)
Last Pap smear			
< 3 yrs ago	256 (83.4)	86 (69.4)	89 (64.0)
> 3 yrs ago	27 (8.8)	29 (23.4)	41 (29.5)
Unknown	24 (7.8)	9 (7.3)	9 (6.5)
Age at last pregnancy			
Never pregnant	52 (16.9)	30 (24.2)	19 (13.7)
< 35 yrs	206 (67.1)	74 (59.7)	101 (72.7)
≥ 35 yrs	41 (13.4)	16 (12.9)	13 (9.4)
		Sample collection before treatment?	
HPV			
Not detected	206 (67.1)	Yes, 6 (4.8)	Yes, 12 (8.6)
		No, 52 (41.9)	No, 47 (33.8)
Oncogenic types[a]	36 (11.7)	Yes, 25 (20.2)	Yes, 32 (23.0)
		No, 13 (10.5)	No, 25 (18.0)
Low-risk types[b]	13 (4.2)	Yes, 2 (1.6)	Yes, 1 (0.7)
		No, 18 (14.5)	No, 12 (8.6)
Not tested	52 (16.9)	8 (6.4)	10 (7.2)

SCC: squamous cell carcinoma; Pap: Papanicolaou; HPV: human papillomavirus.
[a] Types 18, 16, 39, 45, 59, 68, 26, 31, 33, 51, 52, 56, 58, and 82.
[b] Types 6, 11, 40, 42, 53, 54, 55, 57, 66, 73, 83, and 84.

were dropped from the models, because they did not influence the results. Among control participants, BMI also was associated positively with a family history of any cancer, the number of live births, age at menarche, the number of sexual partners, menopausal status, and smoking, but additional adjustment for these variables had no effect on the BMI risk estimates. Statistical tests for trends were based on ordinal variables and are presented separately for adenocarcinoma and squamous cell carcinoma. We used the SAS system[27] for all analyses.

RESULTS

We previously reported more detailed demographic characteristics.[20] Table 1 shows the factors that we included in multivariate regression models for this analysis. More control participants than patients had recent Pap smears. The proportion of women whose last pregnancy occurred at age 35 years or older was similar in the 3 groups, but the proportion of women who were never pregnant was greater among the women with adenocarcinoma.

Adenocarcinoma was associated strongly with HPV-18 (OR, 12) and HPV-16 (OR, 5), as described fully elsewhere,[28]and was associated more strongly with HPV-18 (OR, 105) and HPV-16 (OR, 48) when we excluded patients who were sampled after treatment. Squamous cell carcinoma also was associated strongly with HPV-18 (OR, 5) and HPV-16 (OR, 11) and was associated more strongly with HPV-18 (OR, 20) and HPV0-16 (OR, 30) after excluding patients who were sampled after treatment.

For adenocarcinoma, the trend tests for increasing weight ($P = 0.03$), BMI ($P = 0.04$), and WHR ($P = 0.02$) were statistically significant, along with the associations for the highest weight tertile (OR, 1.9) and BMI ≥ 30 kg/m^2 (OR, 2.1) (Table 2). Neither height nor weight was associated with squamous cell carcinoma. The ORs for BMI ≥ 30 kg/m^2 (1.6) and WHR in the highest tertile (1.6) were elevated but were not statistically significant. BMI and WHR were correlated more strongly in the squamous cell carcinoma group (Pearson correlation coefficient, 0.56) compared with the adenocarcinoma group (0.39) and the control group (0.42).

Usual weight-gain patterns (i.e., waist vs. hips vs. other areas) and the number of reported episodes of losing ≥ 6.8 kg (15 pounds) but then gaining it back were not associated with either histologic type. Women in both patient groups reported a greater difference between maximum adult weight (excluding pregnancies) and minimum adult weight compared with women in the control group, but almost all women who reported this weight gain had BMI ≥ 25 kg/m^2 (data not shown).

HPV is considered a necessary cause of cervical carcinoma; therefore, women who are not infected with HPV are not considered at risk of developing cervical carcinoma. Therefore, we repeated the analyses after excluding 206 control participants who had negative HPV results and 52 control participants who did not volunteer a cervicovaginal sample (Table 3). Only 6 control participants with positive HPV results had a BMI ≥ 30; therefore, we collapsed the variables overweight and obese BMI (< 25 kg/m^2 vs. ≥ 25 kg/m^2). For patients with adenocarcinoma, the ORs for BMI ≥ 25 kg/m^2 and WHR in the highest tertile, based on control participants with positive HPV results, were similar to the ORs based on all control participants. For patients with squamous cell carcinoma, the ORs for BMI ≥ 25 kg/m^2 and WHR in the highest tertile were slightly higher when based on control participants with positive HPV results. These ORs were adjusted for age only; further adjustment for screening or for age at last pregnancy produced similar associations but wider confidence intervals. For comparison, the ORs using all control participants for BMI ≥ 25

TABLE 2
Polytomous Regression Associations with Anthropometric Variables: ORs and 95% CIs for 124 Patients with Adenocarcinoma and 139 Patients with SCC Compared with 307 Control Participants

		Adenocarcinoma				Squamous cell carcinoma			
Variable	Control group (%)[a]	%[a]	OR[b]	OR[c]	95% CI	%[a]	OR[b]	OR[c]	95% CI
Height (m)									
≤ 1.60	35	29	1.0	1.0	Ref	40	1.0	1.0	Ref
1.61–1.66	29	28	1.2	1.2	0.68–2.2	22	0.65	0.72	0.41–1.3
≥ 1.67	36	43	1.5	1.4	0.78–2.4	39	0.99	0.94	0.56–1.6
Weight (kg)									
≤ 58.5	31	22	1.0	1.0	Ref	29	1.0	1.0	Ref
58.6–67.9	35	32	1.2	1.1	0.60–2.0	28	0.83	0.75	0.42–1.3
> 68.0	32	46	2.1	1.9	1.1–3.4	42	1.5	1.3	0.73–2.2
BMI (kg/m^2)									
< 25	56	50	1.0	1.0	Ref	54	1.0	1.0	Ref
25–29	28	27	1.2	1.1	0.64–1.9	24	0.96	0.86	0.51–1.5
≥ 30	13	23	2.0	2.1	1.1–3.8	20	1.6	1.6	0.84–2.9
WHR									
≤ 0.78	33	21	1.0	1.0	Ref	23	1.0	1.0	Ref
0.79–0.85	33	33	1.6	1.3	0.70–2.4	30	1.3	0.97	0.54–1.8
> 0.85	33	41	1.9	1.8	0.97–3.3	42	1.8	1.6	0.89–2.8

OR: odds ratio; 95% CI: 95% confidence interval; SCC: squamous cell carcinoma; Ref: reference group; BMI: body mass index (kg/m^2); WHR: waist-to-hip ratio.

[a] Percentages may not total 100% because of rounding or missing data. Height was missing for one control participant; weight was missing for eight control participants and two patients with squamous cell carcinoma. The body mass index was missing for nine control participants and two patients with squamous cell carcinoma, and the waist-to-hip ratio was missing for three control participants, six patients with adenocarcinoma, and seven patients with squamous cell carcinoma.

[b] The odds ratio adjusted for age.

[c] The odds ratio also adjusted for human papillomavirus, months since last Papanicolaou smear, and age at last pregnancy; the 95% confidence interval is for this odds ratio.

kg/m^2 versus BMI < 25 kg/m^2 were 1.4 (95% CI, 0.87–2.2) for the adenocarcinoma group and 1.1 (95% CI, 0.68–1.7) for the squamous cell carcinoma group.

We also repeated analyses among just the patients and control participants in whom HPV was detected. In age-adjusted models, the associations of adenocarcinoma (n = 58 patients) and squamous cell carcinoma (n = 70 patients) were similar to the associations based on all participants for BMI and WHR (data not shown).

Because different body size measurements capture obesity[29] and may have an independent influence on disease risk,[30] we assessed the potential combined contributions of BMI, WHR, and height. Beyond the pattern of elevated ORs displayed in Table 2, no combinations of these variables revealed notable associations with either histologic type.

Analyses according to stage of disease at diagnosis (invasive vs. in situ) revealed stronger associations for invasive carcinomas than for carcinomas in situ. Only 5 patients with adenocarcinoma and 6 patients with squamous cell carcinoma who were diagnosed with carcinoma in situ had BMI ≥ 30 kg/m^2 (vs. BMI < 25 kg/m^2 as the reference category: OR, 1.9; 95% CI, 0.60–6.0 and OR, 0.90; 95% CI, 0.32–2.6, respectively). The corresponding ORs based on invasive adenocarcinoma and invasive squamous cell carcinoma were 2.1 (95%CI, 1.1–4.4) and 1.6 (95%CI, 0.82–3.3), respectively. Only 8 patients with adenocarcinoma and 18 patients with squamous cell carcinoma who were diagnosed with carcinoma in situ had a WHR in the highest tertile (OR, 0.99; 95% CI, 0.35–2.8 and OR, 1.2; 95% CI, 0.54–2.9, respectively). Corresponding ORs based on invasive adenocarcinomas and invasive squamous cell carcinomas were 2.3 (95% CI, 1.1–4.6) and 1.8 (95% CI, 0.87–3.6), respectively. Higher BMI (chi-square P value = 0.03) and higher WHR (P value = 0.03) were associated significantly with invasive adenocarcinoma at diagnosis. Neither BMI nor WHR was associated significantly with stage of squamous cell carcinoma at diagnosis. Only 11 patients (9%) with adenocarcinoma and 18 patients (13%) with squamous cell carcinoma had tumors ≥ Stage II at diagnosis. Within strata of recently screened and annually screened participants, higher BMI was associated positively with both adenocarcinoma and squamous cell carcinoma.

Additional adjustment for menopausal status at the reference date did not change the overall results. However, analyses that were restricted to postmenopausal women (44 control participants, 21 patients with adenocarcinoma, and 22 patients with squamous

TABLE 3
Polytomous Regression Associations with BMI and Waist-to-Hip Ratio: ORs and 95% CIs for All Patients with Adenocarcinoma and SCC Compared with a Control Group of HPV-Positive Control Participants

		All patients			
		Adenocarcinoma		Squamous cell carcinoma	
Variable	No. of HPV-positive control participants[a]	OR	95% CI	OR	95% CI
BMI (kg/m^2)					
< 25	33	1.0	Ref	1.0	Ref
≥ 25	14	2.2	1.0–4.8	1.8	0.84–3.8
WHR					
≤0.78	15	1.0	Ref	1.0	Ref
0.79–0.85	21	0.81	0.34–1.9	0.68	0.29–1.6
> 0.85	12	1.8	0.68–4.5	1.7	0.68–4.3

BMI: body mass index; OR: odds ratio (adjusted for age); 95% CI: 95% Confidence interval; SCC: squamous cell carcinoma, HPV: human papilloma virus; Ref: reference group; WHR: waist-to-hip ratio.
[a] Excludes control participants for whom human papillomavirus status was not known.

cell carcinoma) produced nonsignificant associations with BMI ≥ 25 kg/m^2 for both adenocarcinoma (OR, 1.5; 95% CI, 0.33–6.5) and squamous cell carcinoma (OR, 1.0; 95% CI, 0.21–4.9).

Retrospective patient ascertainment introduced the possibility that some patients had waist and hip circumference measured up to 2.5 years after the date of their diagnosis of cervical carcinoma. A medical records review revealed that only a small number of patients had chemotherapy or radiation treatment that would be expected to induce weight change, and excluding these patients did not produce a notable change in any ORs.

DISCUSSION

We hypothesized, a priori, that high BMI would be a stronger risk factor for cervical adenocarcinoma compared with squamous cell carcinoma. In this study, we observed some positive associations between obesity and cervical carcinoma. Obese women (i.e., BMI ≥ 30 kg/m^2) and overweight women (i.e., BMI ≥ 25 kg/m^2) appeared to be at 2-fold higher risk of cervical adenocarcinoma compared with women who were not overweight or obese. BMI and WHR were associated positively with squamous cell carcinoma in some analyses, but the ORs were less consistent, weaker, and not statistically significant. Analyses that included all community control participants and/or were restricted to control participants who had positive HPV results showed similar associations.

Obesity is considered a marker for increased serum sex hormone levels, because peripheral adipose tissue converts androgen to estrogen, especially in postmenopausal women.[31,32] Our study included primarily premenopausal women, for whom obesity may represent a negligible source of hormone exposure.[33] Nonetheless, associations with BMI or weight may support the hypothesis that cervical adenocarcinoma cofactors resemble endometrial adenocarcinoma risk factors. Obesity is a stronger risk factor for endometrial carcinoma[13] than it appears to be for cervical adenocarcinoma, and not all risk factors for cervical adenocarcinoma in our study[20] behaved as they do for endometrial carcinomas. These potential similarities for some hormonal risk factors for endometrial carcinoma and cervical adenocarcinoma are interesting, but the roles of sex hormones and their correlates in cervical carcinogenesis remain unclear.

BMI was associated positively with both histologic types among recently screened participants and annually screened participants, and residual effects of screening may explain these positive associations for adenocarcinoma. Decreased access to screening or decreased use of screening may contribute to positive associations with high BMI or WHR, because obese women may be less likely to receive recommended Pap smear screening.[34,35] Common clinical practice recognizes that increasing weight or BMI may influence the ease of adequate Pap smear collection, and screening itself may be less effective for cervical adenocarcinoma[36] than for squamous cell carcinoma. Higher stage at diagnosis for patients with adenocarcinoma with higher BMI, even among recently screened and frequently screened patients in our study, may indicate that screening was less intense or otherwise less successful in detecting earlier glandular cervical lesions among women with higher BMI. We had no data with which to evaluate directly the quality of the reported screening. Larger studies with more detailed screening data may be able to shed light on the associations between anthropometry, screening, and adenocarcinoma.

The current study included direct measures of HPV DNA in patients and control participants, but our HPV assessment was not optimal. We could not obtain samples from some control participants or pretreatment samples from all patients, we tested for 27 HPV genotypes (although all major oncogenic types were included), and the resolution of suspected plasmid contamination of some samples required use of a second primer set with lower sensitivity.[20] The rarity of adenocarcinomas necessitated retrospective ascertainment of some patients who underwent prior surgical treatment that removed the infected cervical tissue before it could be sampled. Therefore, we employed several approaches—statistical adjustment,

restriction, and stratification—to account for the necessary but not sufficient causal role of HPV in cervical carcinogenesis. Each approach produced similarly elevated adenocarcinoma ORs for higher levels of height, weight, BMI, and WHR. For squamous cell carcinoma, ORs were highest when they were based on models restricted to control participants who had positive HPV results, but the overall equivocal patterns for squamous cell carcinoma suggest that simple chance may account for the observed results.

There are other potential study limitations. Our panel of three pathologists reviewed histologic slides from potential patients to reduce diagnostic misclassifications of adenocarcinoma, which is a rare and clinically heterogeneous tumor.[37] Control selection methods should have decreased referral bias, but bias due to nonresponse was possible if anthropometry differed for the 21% of eligible patients with adenocarcinoma, the 26% of eligible patients with squamous cell carcinoma, and the 27% of women in the control group who did not participate. The younger mean age of 40 years at diagnosis in both patient groups—approximately 10 years younger than the mean age at diagnosis for most patients in the U.S. with cervical carcinoma[38]—means that, based on age, the results from our group of patients with squamous cell carcinoma may not be generalizable to other women in the U.S. who are diagnosed with squamous cell carcinoma.

The tendency for women who participate in population-based research studies to over-report height and under-report weight[39,40] may misclassify true overweight and obese women as normal weight women in these analyses. With approximately 90% of our study population younger than age 60 years at the time of interview and $< 25\%$ of participants who had a BMI ≥ 30 kg/m^2, severe bias seems unlikely, because those biases particularly affect older and heavier study populations.[39,40] We assume that any differential misclassification bias would operate at the disease level rather than at the histology level and, thus, that bias would be equal for both patients with adenocarcinoma and patients with squamous cell carcinoma.

In the current study, we observed some positive associations between cervical adenocarcinoma and weight, height, BMI, and WHR but found unconvincing associations with squamous cell carcinoma. We cannot rule out residual confounding by screening as an explanation for the increased risks, although obesity may be a more important cofactor for cervical adenocarcinoma than for cervical squamous cell carcinoma. Continued investigation of cofactors for cervical carcinomas of all histologic types can address some of the methodologic, analytic, and mechanistic questions raised by these data.

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