Decreased prevalence of high-risk human papillomavirus infection is associated with obesity

U.S. Jung[1], J.S. Choi[2], J.H. Ko[2], J.H. Lee[3], S.Y. Park[3], S.H. Park[4]

[1]Department of Obstetrics and Gynecology, Konyang University Hospital, Konyang University College of Medicine, Daejon
[2]Department of Obstetrics and Gynecology, Hanyang University College of Medicine, Seoul
[3]Department of Obstetrics and Gynecology, Sungkyunkwan University School of Medicine, Seoul
[4]Dr. Park's Ob & Gyn Clinic, Seoul (Republic of Korea)

Summary

Purpose of investigation: Obesity is correlated with low education, low economic status, and lower rates of Pap smears, which are known as socio-demographic risk factors for cervical cancer. However, the association between obesity and high-risk human papillomavirus (HR-HPV) infection, the necessary cause of cervical cancer, and its related precursors, is not established. *Materials and Methods:* The authors examined the association between obesity and HR-HPV infection in 6,868 patients, who participated in annual health examinations at the Kangbuk Samsung Hospital in Seoul, Korea, from January through December 2007. *Results:* The prevalence of HR-HPV infection was 14.8%. Women infected with HR-HPV had a lower body mass index (BMI), when compared with non-infected women. After adjustment for alcohol intake, cigarette smoking, and marital status, HR-HPV infection was found to be negatively associated with BMI. When the analysis was stratified according to BMI, the risk of HR-HPV infection was significantly lower among those who were overweight (OR = 0.817, 95% CI = 0.680 – 0.982), or obese (OR = 0.688, 95% CI = 0.556 – 0.851), when compared with women with normal weight. *Conclusion:* HR-HPV infection was associated with obesity defined by BMI, with a lower prevalence of infection observed in obese women.

Key words: HPV; Obesity; Risk factor; Prevalence.

Introduction

Since the recognition of high-risk human papillomavirus (HR-HPV) as the causal agent of cervical cancer and its precursor lesions (cervical intraepithelial neoplasia) [1], a substantial amount of epidemiological data has revealed that a higher risk of HR-HPV infection, and progression to precursor lesions and cancer, were significantly associated with younger age, an increased number of sexual partners, and increased frequency of sexual intercourse, smoking, previous exposure to other sexually-transmitted diseases, high parity, contraceptive use, alcohol consumption, immunosuppressive conditions, lower mean income, and unmarried status [2-8]. In contrast, condom use reduced the risk of HPV infection [9].

To the authors' knowledge however, there are no recognizable studies to date addressing the association of HR-HPV infection and obesity. Obesity is a significant contributory factor to the development of gynecological cancer [10]. A strong association between obesity and endometrial cancer was demonstrated [10-12], which is assumed to be mediated by elevated estrogen levels following the aromatization of androstenedione in adipose tissue [10]. Although not all studies on this subject have led to identical results [12], some studies have reported that a significant increase in the risk for cervical cancer was observed in obese women [11]. Notably, obesity was strongly associated with adenocarcinoma, but not with squamous cell carcinoma of the uterine cervix [13].

Predictors of HR-HPV infection may differ from those of cervical cancer, because its development is influenced by many variables [8]. Obesity is correlated with low education and low economic status [14 ,15], which are known as socio-demographic risk factors for cervical cancer [8]. Moreover, obese women are less likely to adhere to physician recommendations for cervical cancer screening [16], which leads to lower rates of Pap smears in obese women [17]. Therefore, the relationship between obesity and HR-HPV infection warrants study.

Materials and Methods

The authors conducted a cross-sectional study of 6,868 patients, who participated in annual health examinations at the Kangbuk Samsung Hospital in Seoul, Korea, from January through December 2007. All subjects provided informed consent prior to participation in the study, which was approved by the ethical committee of the institution. Exclusion criteria included obesity secondary to hypothyroidism or Cushing's disease, severe debilitating diseases, cancer, or loss of more than 10% of normal weight during the previous six months. Women with a history of hysterectomy, and who had a Pap smear for a reason other than routine physical or pregnancy examination, were also excluded from the study.

Anthropometric measurements and blood chemistry

The authors measured the height and weight of every participant in the study. Body mass index (BMI; kg/m^2) was calculated using the measured weight and height. All blood samples were obtained after an overnight fast. The measurements of plasma glucose, cholesterol, triglycerides, and C-reactive protein (CRP) were evaluated using routine clinical chemistry methods. Insulin was measured by radioimmunoassay. Insulin

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Table 1. — *Characteristics of the study subjects according to HR-HPV infection status*.

	HR-HPV infection test negative (n = 5854)	positive (n = 1014)	*p* value[b]
Age (years)	42.54 ± 9.31	42.41 ± 9.37	0.688
BMI (kg/m^2)	22.19 ± 2.97	21.79 ± 2.72	< 0.001
Fasting plasma glucose (mg/dl)	92.57 ± 13.60	92.81 ± 17.02	0.609
Total cholesterol (mg/dl)	184.27 ± 32.66	183.13 ± 32.51	0.305
Triglycerides (mg/dl)	92.88 ± 53.84	93.09 ± 57.63	0.909
HDL-cholesterol (mg/dl)	55.44 ± 11.75	55.83 ± 12.20	0.331
LDL-cholesterol (mg/dl)	104.76 ± 28.59	103.35 ± 28.81	0.146
Fasting plasma insulin (μIU/ml)	9.62 ± 2.93	9.48 ± 2.49	0.095
HOMA-IR	2.22 ± 0.82	2.18 ± 0.73	0.169
CRP (mg/dl)*	0.04 ± 0.39	0.04 ± 0.38	0.893
Hypertension (%)	5.9	5.4	0.570
Diabetes mellitus (%)	1.3	0.9	0.258
Alcohol intake (%)			
Yes	34.7	40.1	0.001
No	65.3	59.9	
Cigarette smoking (%)			
Yes	5.1	7.2	0.006
No	94.9	92.8	
Exercise (%)			
Yes	51.1	49.8	0.442
No	48.9	50.2	
Marital status (%)			
Unmarried	3.3	6.1	< 0.001
Married	90.9	87.4	
Divorced, separated, widowed	5.8	6.5	

*Log transformation values.

resistance was estimated by homeostasis model assessment (HOMA); the HOMA insulin resistance index (HOMA-IR) was calculated using the following formula: fasting plasma glucose (mg/dl) × fasting plasma insulin ([IU/ml] / 405).

Detection of HPV DNA

The authors used the Hybrid Capture II system (Digene, Gaithersburg, MD, USA) for HR-HPV detection, according to the manufacturer's instructions. This technology is a nucleic acid hybridization assay where specimens containing the target DNA hybridize with a specific HPV RNA probe mixture containing probes for carcinogenic HR-HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68. This test was carried out using a luminometer and the results were expressed as relative light units (RLU). Any given sample was classified as positive when the RLU/positive control ratio, calculated as RLU of specimen/mean RLU of three positive controls, was 1 pg/ml or greater.

Statistical analysis

Data were reported as mean ± SD for continuous variables, and as numbers or a percentage for categorical variables. Clinical and biochemical characteristics of HR-HPV-infected and -uninfected women were compared using Student's t-test and chi-square test, when the variables were continuous or categorical, respectively. Because of skewed distributions, CRP levels were logarithmically transformed. Univariate logistic analyses were used to calculate the crude odds ratios (ORs) for potential risk factors associated with HR-HPV infection. Significant variables in univariate analyses were entered into multivariate logistic regression models to calculate adjusted ORs (95% CI).

Table 2. — *Univariate and multivariate odds ratios (ORs) for HR-HPV infection*.

	Crude OR (95% CI)	*p* value	Adjusted OR** (95% CI)	*p* value
BMI (kg/m^2)	0.953 (0.931 – 0.976)	< 0.000	0.954 (0.931 – 0.977)	< 0.000
Alcohol intake*	1.261 (1.100 – 1.446)	0.001	1.198 (1.042 – 1.378)	0.011
Cigarette smoking*	1.446 (1.110 – 1.885)	0.006	1.256 (0.956 – 1.650)	0.102
Marital status				
Married	1		1	
Unmarried	1.919 (1.430 – 2.577)	0.000	1.686 (1.248 – 2.279)	0.001
Divorced, separated, widowed	1.169 (0.890 – 1.536)	0.262	1.266 (0.959 – 1.672)	0.096

*References of risk factor: Never. **ORs were adjusted for all other covariates in the model.

For *post hoc* analysis according to BMI, the subjects were categorized into the following groups, based on Western Pacific Region World Health Organization (WHO) criteria on obesity: "underweight" if the BMI was less than 18.4, "normal" if the BMI was 18.5 to 22.9, "overweight" if the BMI was 23.0 to 24.9, and "obese" if the BMI was over 25.0 [18]. The statistical significance of trends for ORs was assessed by considering the categorical variable as a continuous variable in the logistic model.

All reported *p* values were two-tailed and considered significant when $p < 0.05$. Statistical analyses were performed using SPSS software, version 12.0 (SPSS Inc., Chicago, IL, USA).

Results

The prevalence of HR-HPV infection in the population under study was 14.8%. The characteristics of the study subjects according to HR-HPV infection status are presented in Table 1. Women infected with HR-HPV had a lower BMI and higher prevalence of alcohol intake, smoking, and unmarried status; however, no difference was observed between the two groups regarding the lipid profile and CRP levels.

Age-specific prevalence of HR-HPV infection is shown in Figure 1; the prevalence of HR-HPV infection was not significantly associated with age ($p = 0.903$).

The multivariate logistic regression analysis identified BMI, alcohol intake status, and marital status as independent risk factors for HR-HPV infection (Table 2). In order to investigate the risk for HR-HPV infection associated with obesity, the latter was stratified according to BMI. In comparison to normal-weight women, overweight women had a lower risk of HR-HPV infection (OR = 0.817, 95% CI = 0.680 – 0.982) and obese women also had a lower risk of HR-HPV infection (OR = 0.688, 95% CI = 0.556 – 0.851); however, there was no significant difference in risk for HR-HPV infection between normal weight and underweight women (Table 3).

Discussion

To the best of the authors' knowledge, the study presented here is the first to report an association between

Table 3. — *Univariate and multivariate odds ratios (ORs) for HR-HPV infection according to BMI.*

BMI (kg/m²)	HR-HPV test		Crude OR (95% CI)	*p* value	Adjusted OR* (95% CI)	*p* value
	negative	positive				
18.5 – 22.9	3402 (58.1)	648 (63.9)	1		1	
< 18.5	449 (7.7)	78 (7.7)	0.912 (0.707 – 1.177)	0.479	0.910 (0.705 – 1.175)	0.471
23 – 24.9	1099 (18.8)	170 (16.8)	0.812 (0.677 – 0.974)	0.025	0.817 (0.680 – 0.982)	0.031
≥ 25	904 (15.4)	118 (11.6)	0.685 (0.556 – 0.845)	< 0.001	0.688 (0.556 – 0.851)	0.001
			p for trend < 0.001		*p* for trend < 0.001	

*ORs were adjusted for alcohol intake, cigarette smoking, and marital status.

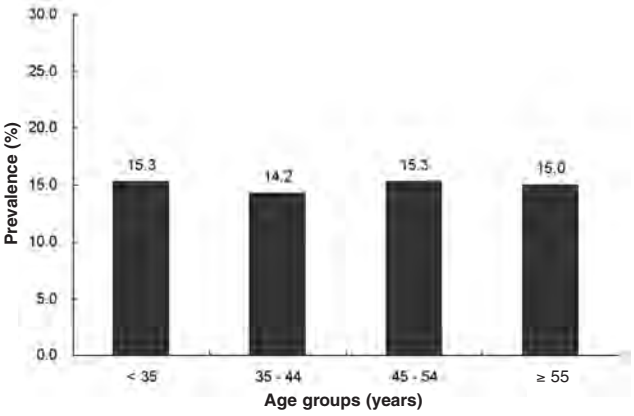

Figure 1. — The prevalence of HR-HPV infection by age of the subject.

obesity and HR-HPV infection in Korean women. It was found that BMI was significantly correlated with HR-HPV infection and that the risk for HR-HPV infection was decreased in accordance with obesity. Overweight status was associated with a 0.817-fold decreased risk for HR-HPV infection and obesity was associated with a 0.688-fold decreased risk for HR-HPV infection, even after adjusting for confounding variables.

The authors had hypothesized, *a priori*, that obese women would have an increased risk for HR-HPV infection. Interestingly, however, the findings in this study suggest the opposite effect and the association detected here cannot be easily explained.

There are several explanations that can be considered. First, obesity may cause changes in sexual behaviors. In men, both overweight and obesity statuses have been identified as risk factors for sexual dysfunction [19] and in women, obesity was also associated with impairment of sexual function, including arousal, lubrication, satisfaction, orgasm, and sexual interest [20-22]. Obese women reported greater impairments of sexual enjoyment, desire, and avoidance of sexual encounters than obese men [23]. Another study reported that moreover, slimmer people of both genders are generally more sexually-attractive, and in healthy women aged 19–40 years, hip size was negatively associated with the frequency of penile-vaginal intercourse [24]. Thus, for these reasons, obese women seem to have lower sexual activity. As sexual activity is the most important primary risk factor for HPV infection, it can be extrapolated that the risk for HR-HPV infection is lower in obese women because of decreased sexual activity.

Another possible explanation of the current findings is a change in immunity. Most HR-HPV infections are subclinical and self-limited [25]; however, a small but medically important fraction of the lesions will progress to cervical cancer [26]. In addition, the prevalence of HR-HPV infection increased, and lesions progressed more rapidly to cancer, among immunosuppressed populations such as those infected with the human immunodeficiency virus (HIV) or renal transplant recipients [2, 3, 25]. These observations suggest an important, albeit currently unknown role of immune responses in the control of HR-HPV infection and progression to cancer.

Cytokines play an important role in the defense against HR-HPV infection, modulating viral replication, and polarizing the immune response to the Th1 or Th2 patterns [27]. Among many cytokines, tumor necrosis factor-α (TNF-α) induces cell-mediated immunity and plays a striking role in viral clearance and inflammatory reactions [28]. TNF-α has specific antiviral effects on HR-HPV through repression of its gene transcription [29]; however, the repression of HR-HPV by TNF-α is lost during malignant conversion [30]. TNF-α is increased in the serum of obese subjects [31]. Moreover, two previous studies found that TNF-α levels were correlated in sera and cervical secretions in fertile and infertile women [32, 33]. In conclusion, the change in immunity in obese women, including changes in serum TNF-α levels, may cause alterations in local cervical immunity, which in turn may lead to a decrease in HR-HPV infection. Other studies have reported that the immune responses may differ between systemic and local infections, at least in terms of cytokine levels [34]; in particular, intralesional TNF-α levels were found to be not associated with HPV-16 infection [35, 36]. In contrast to normal and HPV-16-immortalized keratinocytes, which were sensitive to TNF-α, HPV-18-immortalized keratinocytes were resistant to the inhibitory effects of this cytokine [37]. Therefore, the effect of TNF-α can vary according to HPV type. In addition, other adipocytokines (e.g., leptin) related to obesity may also play a role. Further studies are necessary to clarify this issue.

In the present study, the prevalence of HR-HPV infection was 14.8%, which is similar to that previously reported for Korean [4, 38] and American women [8, 39].

The prevalence of HPV infection was reported to be highest among females below 25 years of age [8, 39] however, in this study the authors did not observe a sig-

nificant difference in HPV infection between age groups. This discrepancy may be explained partly by the low recruitment of women under 25 years of age (n = 26) in this study [40].

Women who consumed alcohol had an increased risk of HR-HPV infection, when compared with never-drinkers. Unmarried women also had an increased risk of HR-HPV infection. These results are in agreement with findings of previous studies [4, 8].

There are several limitations in this study. First, a cross-sectional design was used, which means that causality could not be determined. Individuals infected with multiple pathogens, such as herpes simplex virus, cytomegalovirus, and Helicobacter pylori, have high CRP levels (a marker of inflammation), as well as an increased risk for coronary artery disease [41], and the metabolic syndrome [42]. The phenomenon may be due to the multiple pathogens that induce production of proinflammatory cytokines, which in turn leads to chronic subclinical inflammation and the metabolic syndrome [42]. Polterauer et al. reported that inflammation-induced cytokines may play a role in cervical carcinogenesis, tumor progression, and cancer prognosis [43]. Serum CRP levels can also be used as an additional prognostic parameter in patients with cervical cancer. However, HPV infection is highly-localized to the squamous epithelium, without significant systemic manifestations [25]. The median duration of HPV infection is eight months and about 90% resolve within two years [6]. Although genital infection with HPV is followed by serologic response, a substantial proportion of HPV-infected women fail to seroconvert [8]. In the present study, there was no significant difference in CRP levels between the two groups, and no correlation with the metabolic syndrome was observed (data not shown). Therefore, it is very unlikely that HR-HPV infection acted as the cause of obesity in these women.

Second, the authors observed a relationship between obesity and HR-HPV infection, but obesity is not known as a risk factor for cervical cancer. The results gathered in this study are not sufficient to confirm the influence of the relationship between obesity and HR-HPV on findings of cytology and progression to cancer. These differences may reflect the time interval between infection and development of cancer, as well as the many other variables that influence the development of cancer [8]. Therefore, additional studies are necessary to resolve this issue.

In conclusion, HR-HPV infection was influenced by obesity, with a lower prevalence of infection observed in obese women.

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Address reprint requests to:
J.S. CHOI, M.D., Ph.D.
Director of Gynecologic Oncology
and Gynecologic Minimally Invasive Surgery
Department of Obstetrics and Gynecology
Hanyang University College of Medicine
222 Wangsimni-ro Seongdong-gu
Seoul 133-791 (Republic of Korea)
e-mail: choiyjjy1@hanyang.ac.kr