Research Article

Cancer Epidemiology, Biomarkers & Prevention

Association of Metabolic Syndrome and Human Papillomavirus Infection in Men and Women Residing in the United States

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Abstract

Background: An estimated 33% of adults in the United States have metabolic syndrome (MetS), which has been associated with an increased risk for various cancer types. Theories of synergism among components of MetS that increase cancer risk via chronic inflammation and oxidative stress have been proposed. We hypothesize that men and women with MetS may have compromised immunological response resulting in increased risk for persistent human papillomavirus (HPV) infection. The goal of this study is to determine the association of MetS with HPV types 6, 11, 16, and 18 and to explore variation of these associations by gender using data from a national survey.

Methods: We conducted a retrospective cross-sectional study using data from the National Health and Nutrition Examination Survey.

Results: Thirty-two percent of the population sampled met the criteria for MetS (16% men and 33% women). Nineteen percent tested positive for HPV (6, 11, 16, and 18). Prevalence of HPV infection was estimated at 13% for men and 30% for females. MetS was found to be significantly associated with increased risk of HPV6, 11, 16, or 18 in the entire cohort [RR = 1.24; 95% confidence interval (CI), 1.03–1.48] and in females (RR = 1.26; 95% CI, 1.02–1.56). Although the adjusted risk of HPV+ve status was found to be 21% higher in men with MetS compared with those without, this difference did not attain statistical significance.

Conclusions: We observed a significant association between metabolic syndrome and HPV sero-positivity among the overall population and among females. Although not significant, a similar effect was noted in men. Further prospective studies are needed to better understand this relationship.

Impact: To the best of our knowledge, this is the first study evaluating the impact of metabolic syndrome on HPV positivity in both males and females. *Cancer Epidemiol Biomarkers Prev; 26(8); 1321–7. ©2017 AACR.*

Introduction

Human papillomavirus (HPV) is the most common sexually transmitted infection among Americans (1). It is associated with epithelial cancers such as cervical, penile, vulvar, vaginal, anal, and oropharyngeal. It is also associated with genital warts and other epithelial lesions (2, 3). Approximately half of all cancers that are caused by viruses in humans are attributable to HPV (4). Currently, there are over a 120 known HPV subtypes, 13 of which are considered oncogenic or high-risk HPV (hrHPV); genotypes 16 and 18 are responsible for a majority of HPV-associated cancer cases (4). Nononcogenic types of HPV, such as 6 and 11, are associated with lesions such as condylomata and mild dysplasia (3).

Studies among asymptomatic women estimate the prevalence of HPV infection to range between 2% and 44% with rates varying according to the HPV subtype, testing technique, and populations tested (5). A high proportion of infections with hrHPV will clear over a few years without causing any premalignant lesions (6–8), but in some individuals, the infection persists and leads to premalignant changes. HPV is present in virtually all cases of squamous cell cancer of the cervix. It has therefore been accepted as a necessary but not sufficient factor in the causal pathway of cervical cancer and is linked to over 500,000 cases of cervical cancer per year worldwide (9). Therefore, it is imperative to reduce the risk of HPV infection.

There are some established behavioral factors that increase the risk of developing cervical cancer in the presence of persistent infection with hrHPV; these include tobacco use (10), infection with human immunodeficiency virus (HIV; ref. 11), prolonged use of hormonal contraceptives (11), number of sexual partners, and multiparity (12). Currently specific host and virulence factors that lead to persistent infection versus clearance of the HPV remain largely unknown.

Metabolic syndrome (MetS) is a cluster of risk factors for cardiovascular disease and type 2 diabetes mellitus, which has hyper-insulinemia, atherogenic dyslipidemia, and a proinflammatory state as the underlying characteristic (13). It is estimated that in the United States, 33% of adults have MetS, with a higher prevalence among women, Hispanics, and older adults (14). This syndrome has been associated with an increased risk for various cancer types, namely, cervical (15, 16), prostate (17), colorectal (18), liver (19), and pancreatic cancers (20); furthermore, the

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presence of MetS may increase cancer mortality (21) and morbidity (22). Theories of synergism among the components of MetS that increase cancer risk via chronic inflammation and oxidative stress have been proposed (23).

Two recent studies explored the effect of MetS on HPV infection among women (24, 25). Liu and colleagues found no significant relationship between MetS and HPV infection among females. However, Huang and colleagues report that the presence of MetS increases the risk of HPV infection in females. Both studies were solely focused on females. The gender differences in the risk of HPV infection and MetS have already been established. To our knowledge, the association between MetS and HPV infection in the U.S. population irrespective of gender has not been previously explored. Therefore, we hypothesize that men and women with MetS may have a compromised immunological response resulting in increased risk of HPV infection; thus, the goal of this study is to determine the association of MetS with HPV types 6, 11, 16, and 18 detected in serum and to explore the variation of these associations by gender using data from a national survey.

Materials and Methods

Study population

We conducted a retrospective cross-sectional study using data from the population-based National Health and Nutrition Examination Survey (NHANES; ref. 26). The NHANES is a U.S. National survey conducted annually by the Centers for Diseases Control. This survey uses a stratified, multistage, cluster sampling method to obtain a representative sample of the U.S., civilian, noninstitutionalized population. Data are collected through questionnaires, anthropometric measurements, and body fluids samples. All participants sign informed consent as per the National Center for Health Statistics Research Ethics Review Board (27). We included data from the 2003–2004, 2005–2006, 2007–2008, and 2009–2010 surveys. A total of 4,522 subjects were included for analysis. We excluded subjects with missing data on main outcomes or important covariates and also subjects with reported cervical, rectal, or testicular cancers.

Outcomes assessment

We extracted data on HPV serum antibodies against genotypes 6, 11, 16, and 18. The index laboratory used a competitive Luminex Immunoassay of antibodies to neutralizing epitopes on HPV 6, 11, 16, and 18 L1 virus-like particles. Sero-status cutoff measured in mMU/mL were 20 mMU/mL for HPV6, 16 mMU/mL for HPV11, 20 mMU/mL for HPV16, and 24 mMU/mL for HPV18. Values above these cutoffs were considered positive; otherwise, individuals were considered sero-negative (27). We considered individuals as sero-positive if any one of the four subtypes of HPV was positive.

Exposure assessment

MetS was defined as per the harmonizing criteria for MetS (13) as having the presence of at least three of the following components: increased waist circumference, hypertension, hypertriglyceridemia, hyperglycemia, and low high-density lipoprotein (HDL). Increased waist circumference was defined using the U.S. cutoff, as a waist circumference measurement of $\geq$102 cm and $\geq$88 cm in males and females, respectively (13). Hyperglycemia was defined as either a self-reported diagnosis of diabetes mellitus or prediabetes, taking prescription medication for diabetes, the measurement of fasting glucose serum levels of $\geq$100 mg/dL or glycohemoglobin of >6.5%. Hypertension was defined as either a self-reported diagnosis of hypertension, being told that blood pressure was elevated on two or more separate occasions, taking prescription medication for hypertension, having an average systolic blood pressure reading of $\geq$130 mm Hg or an average diastolic blood pressure reading of $\geq$85 mm Hg. Hypertriglyceridemia was defined as either triglyceride serum levels of $\geq$150 mg/dL or taking prescription for hypertriglyceridemia. Low HDL was defined as serum levels of $\leq$50 mg/dL in women and $\leq$40 mg/dL in men (25).

Covariates assessment

We extracted data on demographic variables as well as known epidemiologic risk factors for cervical cancer. Demographic data included age, gender, body mass index, educational attainment, ethnicity, marital status, and annual household income. Health information included self-reported health status ("would you say your health in general is. . ."), birth control use ("have you ever taken birth control pills for any reason?"), and HIV status (antibody test result). Health behavior variables included history of smoking (previous smoker, current smoker), number of sexual partners in a lifetime ["with how many men (women) have you had vaginal, anal, or oral sex"], and condom use [" in the past 12 months, and about how often have you had (vaginal or anal/vaginal/anal) sex without using a condom?"].

Statistical analysis

As per the NHANES documentation, the data set was appended for the years 2003 to 2010, and sampling weights were applied. Quantitative variables were presented using mean and SD. Categorical variables were presented using frequency and percentage. Data were summarized for the entire cohort and separately by gender. Initially, we determined the probable effect modifiers, which may affect the association between MetS and HPV serum positivity. Our exploration identified sexual partner as an effect modifier for the association between MetS and HPV serum positivity, thus the primary analysis was presented only among female participants with six or less sexual partners. The relationship between considered cofactors with MetS was determined using the design-based Pearson's χ^2 test. Unadjusted associations of considered cofactors with HPV serum positivity were determined using survey generalized linear model (GLM) with log link and Poisson distribution (28). Further, adjusted association of MetS with HPV serum positivity was determined using survey GLM with Poisson distribution and log link. Only the variables that remained significant in the adjusted analysis were kept in the model; otherwise, they were removed from the adjusted analysis. We tested for all possible interaction effects in the regression models before finalizing the adjusted models. The results of unadjusted and adjusted association were summarized using prevalence ratio (PR) along with their 95% confidence interval (CI) and *P* value. The robust standard errors were computed in regression analysis. Analyses were conducted using SAS 9.4 and STATA 13. We used STATA command svy: glm with family = Poisson and link = log for determining associations. The survey design (strata and clustering) and sampling weight were incorporated into all statistical analyses as per the recommendation in NHANES (29). *P* values less than 5% were considered as significant results.

Results

The projected U.S. population size was 111,920,992. Thirty-two percent of the population sampled met the criteria for MetS (16% in men and 33% in women), with 19% testing positive for HPV (6, 11, 16, and 18). The prevalence of HPV infection in men was estimated at 13%, whereas that for females was at 30%. Table 1

Table 1. Characteristics of study participants ($n = 4,522$)

		HPV serum antibodies against 6, 11, 16, or 18 types Positive			HPV serum antibodies against 6, 11, 16, or 18 types Negative		
Characteristics	**Entire cohort (*N* = 4,522)**	**Male (*N* = 2,988)**	**Female (*N* = 1,534)**	**Males and females**	**Male (*N* = 2,988)**	**Female (*N* = 1,534)**	**Males and females**
Age (years): mean (SD, min–max)	38.85 (11.91, 18–59)	41.27 (10.54)	38.83 (12.26)	39.97 (11.53)	37.65 (12.14)	40.90 (11.23)	38.6 (11.98)
Educational level							
Less than high school	1,257 (0.17)	114 (0.14)	146 (0.38)	260 (0.21)	742 (0.86)	255 (0.62)	997 (0.79)
High school/GED	1,155 (0.26)	121 (0.16)	124 (0.33)	245 (0.21)	702 (0.84)	208 (0.67)	910 (0.79)
More than high school	2,107 (0.57)	160 (0.12)	228 (0.26)	388 (0.17)	1,147 (0.88)	572 (0.74)	1,719 (0.83)
Ethnicity							
Mexican American	1,229 (0.12)	72 (0.09)	130 (0.27)	202 (0.15)	689 (0.91)	338 (0.73)	1,027 (0.85)
NH white	2,225 (0.75)	192 (0.13)	202 (0.26)	394 (0.17)	1,289 (0.87)	542 (0.74)	1,831 (0.83)
NH black	1,068 (0.13)	132 (0.19)	166 (0.51)	298 (0.30)	614 (0.81)	156 (0.49)	770 (0.70)
Annual household income							
0–20 K	819 (0.12)	74 (0.15)	125 (0.42)	199 (0.24)	457 (0.85)	163 (0.58)	620 (0.76)
20–45 K	1,352 (0.23)	121 (0.14)	142 (0.31)	263 (0.20)	777 (0.86)	312 (0.69)	1,089 (0.80)
45–75 K	947 (0.25)	86 (0.15)	97 (0.31)	183 (0.20)	553 (0.85)	211 (0.69)	764 (0.80)
75–100 K	589 (0.19)	53 (0.13)	62 (0.26)	115 (0.17)	333 (0.87)	141 (0.74)	474 (0.83)
Unknown	815 (0.21)	62 (0.10)	72 (0.22)	134 (0.14)	472 (0.90)	209 (0.78)	681 (0.86)
Increased waist circumference							
No	2,381 (0.52)	241 (0.13)	153 (0.25)	394 (0.16)	1,633 (0.87)	354 (0.75)	1,987 (0.84)
Yes	2,032 (0.48)	141 (0.14)	335 (0.32)	476 (0.22)	893 (0.86)	663 (0.68)	1,556 (0.78)
Elevated triglycerides							
No	3,145 (0.7)	237 (0.11)	385 (0.31)	622 (0.18)	1,783 (0.89)	740 (0.69)	2,523 (0.82)
Yes	1,361 (0.3)	158 (0.17)	113 (0.27)	271 (0.20)	797 (0.83)	293 (0.73)	1,090 (0.80)
Low HDL							
No	3,143 (0.68)	276 (0.12)	322 (0.28)	598 (0.18)	1,844 (0.88)	701 (0.72)	2,545 (0.82)
Yes	1,378 (0.32)	120 (0.15)	176 (0.32)	296 (0.21)	747 (0.85)	335 (0.68)	1,082 (0.79)
Elevated blood pressure							
No	3,048 (0.66)	216 (0.11)	354 (0.29)	570 (0.17)	1,724 (0.89)	754 (0.71)	2,478 (0.83)
Yes	1,474 (0.34)	180 (0.17)	144 (0.32)	324 (0.21)	868 (0.83)	282 (0.68)	1,150 (0.79)
Elevated blood sugar							
No	2,686 (0.59)	212 (0.13)	338 (0.29)	550 (0.20)	1,407 (0.87)	729 (0.71)	2,136 (0.81)
Yes	1,836 (0.41)	184 (0.13)	160 (0.31)	344 (0.18)	1,185 (0.87)	307 (0.69)	1,492 (0.82)
MetS (3 or more components)							
No	3,149 (0.68)	255 (0.12)	338 (0.28)	593 (0.17)	1,831 (0.88)	725 (0.72)	2,556 (0.83)
Yes	1,373 (0.32)	141 (0.16)	160 (0.33)	301 (0.21)	761 (0.84)	311 (0.67)	1,072 (0.79)
Marital status							
Married/living w partner	2,690 (0.66)	232 (0.13)	261 (0.25)	384 (0.16)	1,448 (0.87)	749 (0.75)	1,859 (0.84)
Widowed/divorced/separated	549 (0.11)	69 (0.21)	100 (0.42)	169 (0.30)	247 (0.79)	133 (0.58)	380 (0.70)
Never married	1,100 (0.21)	86 (0.11)	109 (0.38)	195 (0.18)	768 (0.89)	137 (0.62)	905 (0.82)
Unknown	183 (0.03)	9 (0.06)	28 (0.67)	37 (0.21)	129 (0.94)	17 (0.33)	146 (0.79)
Smoking status							
Current	1,076 (0.24)	155 (0.17)	94 (0.34)	249 (0.21)	675 (0.83)	152 (0.66)	827 (0.79)
Former	734 (0.18)	90 (0.16)	70 (0.32)	160 (0.2)	438 (0.84)	136 (0.68)	574 (0.8)
Never	2,279 (0.53)	135 (0.11)	307 (0.27)	442 (0.18)	1,105 (0.89)	732 (0.73)	1,837 (0.82)
Unknown	433 (0.04)	16 (0.02)	27 (0.63)	43 (0.1)	374 (0.98)	16 (0.37)	390 (0.9)
Condom use							
No	600 (0.12)	47 (0.11)	82 (0.35)	129 (0.19)	325 (0.89)	146 (0.65)	471 (0.81)
Yes	98 (0.02)	14 (0.13)	7 (0.45)	21 (0.17)	69 (0.87)	8 (0.55)	77 (0.83)
Unknown	3,824 (0.86)	335 (0.13)	409 (0.29)	744 (0.19)	2,198 (0.87)	882 (0.71)	3,080 (0.81)
Health condition							
Good	3,559 (0.84)	306 (0.13)	381 (0.29)	687 (0.18)	2,042 (0.87)	830 (0.71)	2,872 (0.82)
Fair	715 (0.12)	58 (0.13)	98 (0.35)	156 (0.21)	381 (0.87)	178 (0.65)	559 (0.79)
Poor	116 (0.02)	15 (0.21)	19 (0.36)	34 (0.27)	54 (0.79)	28 (0.64)	82 (0.73)
Unknown	132 (0.02)	17 (0.09)	N/A	17 (0.09)	115 (0.91)	N/A	115 (0.91)
Birth control							
Yes	1,134 (0.27)	N/A	367 (0.30)	367 (0.30)	N/A	767 (0.70)	767 (0.70)
No	396 (0.07)	N/A	129 (0.28)	129 (0.28)	N/A	267 (0.72)	267 (0.72)
Unknown	2,992 (0.66)	N/A	2 (0.21)	398 (0.13)	N/A	2 (0.79)	2,594 (0.87)
HIV status							
Positive	20 (0)	7 (0.54)	2 (1.00)	9 (0.60)	11 (0.46)	0 (0.00)	11 (0.40)
Negative	3,827 (0.82)	303 (0.12)	438 (0.32)	741 (0.19)	2,241 (0.88)	845 (0.68)	3,086 (0.81)
Unknown	675 (0.18)	86 (0.18)	58 (0.20)	144 (0.19)	340 (0.82)	191 (0.80)	531 (0.81)

Table 2. Unadjusted associations of considered variables with HPV6, 11, 16, or 18

Characteristics	Overall ($N = 4,522$) PR (95% CI)	*P* value	Male ($N = 2,988$) PR (95% CI)	*P* value	Female ($N = 1,534$) PR (95% CI)	*P* value
Metabolic syndrome, yes	1.23 (1.05–1.44)	0.010	1.33 (1.02–1.72)	0.032	1.18 (0.98–1.42)	0.083
Increased waist circumference	1.38 (1.18–1.62)	<0.001	1.08 (0.84–1.38)	0.541	1.28 (1.03–1.59)	0.025
Elevated triglyceride	1.09 (0.93–1.28)	0.293	1.54 (1.24–1.92)	<0.001	0.88 (0.69–1.12)	0.299
Low HDL cholesterol (mg/dL)	1.22 (1.04–1.42)	0.014	1.19 (0.94–1.49)	0.142	1.15 (0.94–1.39)	0.172
Increased blood pressure	1.22 (1.04–1.43)	0.013	1.51 (1.20–1.91)	0.001	1.10 (0.89–1.36)	0.374
Increased blood sugar	0.90 (0.79–1.03)	0.134	1.00 (0.79–1.28)	0.971	1.07 (0.85–1.33)	0.569
Age (years)	1.01 (1.00–1.01)	0.020	1.02 (1.01–1.03)	<0.001	0.99 (0.98–1.00)	0.011
Ethnicity						
NH white (reference)[a]						
Mexican American	0.88 (0.71–1.09)	0.227	0.70 (0.50–0.97)	0.035	1.01 (0.78–1.31)	0.910
NH black	1.76 (1.52–2.04)	<0.001	1.48 (1.20–1.83)	<0.001	1.95 (1.61–2.37)	<0.001
Educational level						
Less than high school (reference)						
High school/GED	0.99 (0.78–1.25)	0.929	1.17 (0.80–1.70)	0.42	0.88 (0.68–1.14)	0.322
More than high school	0.80 (0.65–0.97)	0.028	0.85 (0.61–1.17)	0.309	0.71 (0.56–0.89)	0.004
Annual household income						
0–20 k (reference)						
20–45 K	0.84 (0.69–1.01)	0.065	0.97 (0.76–1.23)	0.791	0.76 (0.61–0.95)	0.016
45–75 K	0.84 (0.65–1.07)	0.148	1.02 (0.77–1.36)	0.867	0.75 (0.56–1.02)	0.063
75–100 K	0.72 (0.53–0.96)	0.026	0.86 (0.58–1.28)	0.462	0.63 (0.46–0.88)	0.007
Unknown	0.58 (0.44–0.77)	<0.001	0.67 (0.43–1.05)	0.081	0.54 (0.39–0.75)	<0.001
Marital status						
Married/living w partner (reference)						
Widowed/divorced/separated	1.73 (1.44–2.08)	<0.001	1.64 (1.24–2.17)	0.001	1.72 (1.35–2.19)	<0.001
Never married	1.02 (0.83–1.26)	0.815	0.86 (0.60–1.23)	0.409	1.56 (1.22–1.98)	<0.001
Unknown	1.21 (0.74–1.99)	0.439	0.46 (0.17–1.30)	0.142	2.71 (1.99–3.69)	<0.001
Smoking status						
Never (reference)						
Current	1.20 (1.01–1.42)	0.044	1.61 (1.20–2.16)	0.002	1.26 (0.93–1.70)	0.128
Former	1.14 (0.94–1.38)	0.166	1.50 (1.06–2.12)	0.022	1.19 (0.91–1.55)	0.206
Unknown	0.59 (0.35–0.98)	0.041	0.22 (0.10–0.48)	<0.001	2.31 (1.64–3.25)	<0.001
Condom use						
Yes (reference)						
No	1.17 (0.65–2.1)	0.603	0.91 (0.45–1.84)	0.779	0.76 (0.33–1.78)	0.525
Unknown	1.12 (0.65–1.94)	0.672	1.07 (0.58–1.98)	0.825	0.64 (0.28–1.44)	0.276
Health condition						
Good[b] (reference)						
Fair	1.16 (0.95–1.41)	0.14	1.02 (0.75–1.40)	0.889	1.22 (0.95–1.56)	0.121
Poor	1.46 (0.97–2.20)	0.068	1.59 (0.94–2.67)	0.083	1.24 (0.67–2.31)	0.488
Unknown	0.51 (0.23–1.15)	0.102	0.72 (0.31–1.65)	0.428	N/A	N/A
Birth control						
No (reference)						
Yes	1.10 (0.86–1.41)	0.447	N/A	N/A	1.10 (0.86–1.41)	0.447
Unknown	0.48 (0.37–0.61)	<0.001	N/A	N/A	0.76 (0.11–5.06)	0.77
HIV status						
Negative (reference)						
Positive	3.21 (2.10–4.91)	<0.001	4.55 (2.57–8.06)	<0.001	N/A	N/A
Unknown	1.01 (0.78–1.32)	0.914	1.52 (1.12–2.06)	0.008	0.62 (0.44–0.89)	0.01

[a]NH, non-Hispanic.
[b]Good = Excellent, very good, and good health conditions.

provides the distribution of considered cofactors by HPV 6, 11, 16, or 18 status for the entire cohort and separately for each gender. Overall, there was a higher proportion of individuals with MetS among people who were positive for HPV genotypes 6, 11, 16, or 18 positive (HPV+ve; 21% vs. 17%, *P* value 0.01). A higher proportion of HPV+ve subjects were Blacks when compared with non-Hispanic whites (30% vs. 17%, *P* value 0.001). In females, a slightly higher but similar trend in the prevalence of HPV+ve status was noticed for ethnicity, elevated triglycerides, low HDL, elevated blood pressure, and presence of MetS compared with males. In addition, a higher prevalence of HPV+ve status was also found in those who reported low income status, had obesity, and fair/poor health conditions for females but not in males. Sixty percent of the HIV-positive subjects were HPV+ve, though the "N" was small for HIV-positive individuals.

Table 2 provides unadjusted associations of cofactors with HPV status for the entire cohort and separately for each gender. MetS, age, ethnicity, marital status, annual household income, smoking status, health status, obesity, and HIV status were found to be associated with HPV+ve status for the entire cohort. These variables except obesity remained significantly associated with HPV+ve status in males. With the exception of smoking status, all the significant variables associated with HPV+ve status for the entire cohort were found to be significant for the female cohort as well. In the unadjusted analysis, MetS was associated with a significant risk of HPV6, 11, 16, or 18 in the overall sample (PR 1.23,

Table 3. Adjusted association of MetS with HPV

Population	PR (95% CI)	*P* value
Entire cohort	1.24 (1.04–1.47)[a]	0.020
Entire cohort	1.22 (1.01–1.47)[b]	0.041
Male cohort	1.23 (0.94–1.60)[c]	0.128
Female cohort	1.27 (1.02–1.57)[d]	0.033

[a]Adjusted for gender, ethnicity, marital status, smoking status, male sexual partner, and HIV status.
[b]Adjusted for age, gender, ethnicity, marital status, smoking status, male sexual partner, and HIV status.
[c]Adjusted for age, ethnicity, marital status, male sexual partner, and HIV status.
[d]Adjusted for age, ethnicity, and marital status.

P value 0.01), and among females (PR 1.33, *P* value 0.032), whereas in males, a trend toward increased risk of HPV+ve status in the presence of MetS was noticed but not statistically significant (PR 1.18, *P* value 0.08).

The adjusted effects of MetS on HPV+ve status for the entire cohort and separately for each gender are reported in Table 3. In the initial adjusted model, all the significant cofactors obtained for MetS and HPV+ve status from the univariate analysis were included. The variables in the adjusted model, which were not statistically significant, were dropped from the final adjusted model. After adjusting for important cofactors, the effects of MetS on HPV+ve status were found to be almost similar for males and females. MetS was found to be significantly associated with increased risk of HPV6, 11, 16, or 18 in the entire cohort (PR = 1.24; 95% CI, 1.03–1.48) and (PR = 1.26; 95% CI, 1.02, 1.56) in females. Although the adjusted risk of HPV+ve status was found to be 21% higher men with MetS compared with those without MetS, this difference did not attain a statistically significant level.

Discussion

Our study reports a 32% prevalence of HPV positivity in the presence of MetS. The prevalence of HPV was much higher in females compared with males in the presence of MetS. We found that the presence of MetS was positively associated with positive antibodies against HPV 6, 11, 16, or 18 genotypes. The adjusted association also supported that MetS increases the risk of HPV positivity to a similar extent in both males and females. The significant association however was present only among females and although positive, was not statistically significant among males.

In contrast to our findings, Liu and colleagues showed that the MetS was not significantly associated with HPV infection in females using the same NHANES database (24). Instead, this study found that fasting adult obese females and those who reported an earlier onset of sexual activity (age <16 years) had significantly lower risk of HPV infection. We theorize that our findings differ with Liu and colleagues' study due to the different definitions of HPV infection. In our study, HPV positivity was based on serum sample results for genotypes HPV 6, 11, 16, or 18, whereas Liu and colleagues' study was based on self-collected vaginal swabs with testing for any of the 37 HPV subtypes. In contrast, a more recent prospective study conducted in China among females showed that MetS increases the risk of HPV infection (25). The adjusted effect size obtained in the Huang and colleagues study was PR 1.25 (95% CI, 1.09–1.46), which is very similar to our study findings PR = 1.26 (95% CI, 1.02–1.56).

Our findings suggest that MetS may play a role in the acquisition of HPV infection. It is possible that this association can be explained by the role that MetS plays in the immune system. Subjects with immunosuppression frequently present with abundant HPV lesions, which indicates that the immune system works to limit the extent of HPV infections (30). Furthermore, it has been seen that HPV infection is associated with increased levels of inflammatory cytokines (31) and increased plasma levels of adipokines and inflammatory markers in older women with persistent HPV infection (32). Previous studies (15, 16) have shown an association between the MetS and cervical cancer, which needs the presence of HPV infection to develop. To our knowledge, there are no other studies assessing the association between MetS and HPV or other HPV-related cancers in males.

In our study, individual components of the MetS were associated with increased sero-positivity for HPV 6, 11, 16, or 18 types, namely, increased waist circumference and blood pressure and decreased HDL. We found that increased waist circumference was positively associated with HPV infection among females but not in males. Although a previous study (Wee and colleagues, 2008) found no association between obesity and HPV prevalence, the difference in findings may be due in part to differences in testing techniques used to establish HPV infection, because Wee and colleagues (33) used vaginal swabs which serve to assess current infection, whereas in our study, we used antibody levels that are more indicative of previous or current exposure to the human papilloma virus.

It has been proposed that chronic inflammation and inflammatory signals initiate in the visceral adipose tissue, which secretes a variety of hormones and cytokines such as IL6 and leptin that lead to the derangements seen in the MetS (34). Elevated blood pressure has been associated with increased risk of cervical cancer (15, 35). Mechanisms through which elevated blood pressure may increase risk for HPV infection include hypertension-induced hypoxia, which in turn promotes angiogenesis through activation of hypoxia-inducible factor-1 (36). The induction of angiogenesis has been described as crucial for the persistence and growth of the HPV lesions (37).

Our findings also shine some light on the prevalence of HPV 6, 11, 16, and 18 in males, which was 16% in this cohort. A previous review reported a prevalence in males of 2.1% for HPV subtypes 6 and 11 and a prevalence of 7.9% for HPV types 16 and 18 which is slightly lower than our cohort (38). We did not assess other risk factors that have been associated with higher HPV prevalence in men such as history of sex with sex workers or homosexual and bisexual status (39). One plausible reason for the lack of association between HPV and the MetS among males in our study is the fact that HPV prevalence is lower in males partly because penile tissues may be less susceptible to infection with HPV (38).

The major limitation of this study is the lack of information as to the timing of the HPV infection; therefore, the association may be an overestimation because serum samples give information about previous but not necessarily current HPV+ve status. HPV is more prevalent immediately after sexual debut, whereas the MetS prevalence increases with age (14). A prospective study with sample collection at multiple points would unveil this association more accurately.

We did not assess the effect of HPV vaccine status on the association between MetS and HPV 6, 11, 16, or 18-antibody positivity. A quadrivalent vaccine, which covers these four genotypes, was introduced in the United States in 2006, and there is

currently insufficient data to asses this. Further studies should explore this effect.

In summary, in this study, we observed a significant association between metabolic syndrome and HPV sero-positivity among the overall population and among females, although not significant a similar effect in men as well. Further prospective studies are needed to better understand this relationship.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: J.C. Molokwu, E. Penaranda, N. Shokar
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Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): J.C. Molokwu, D.S. Lopez, A. Dwivedi, C. Dodoo, N. Shokar
Writing, review, and/or revision of the manuscript: J.C. Molokwu, D.S. Lopez, A. Dwivedi, C. Dodoo, N. Shokar
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): C. Dodoo
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References

1. Satterwhite CL, Torrone E, Meites E, Dunne EF, Mahajan R, Ocfemia MCB, et al. Sexually transmitted infections among US women and men: prevalence and incidence estimates, 2008. Sex Transm Dis 2013; 40:187–93.
2. Bernard H-U, Burk RD, Chen Z, van Doorslaer K, zur Hausen H, de Villiers E-M. Classification of papillomaviruses (PVs) based on 189 PV types and proposal of taxonomic amendments. Virology 2010;401:70–9.
3. Parkin DM, Bray F. The burden of HPV-related cancers. Vaccine 2006;24: S11–25.
4. Li N, Franceschi S, Howell-Jones R, Snijders PJ, Clifford GM. Human papillomavirus type distribution in 30,848 invasive cervical cancers worldwide: variation by geographical region, histological type and year of publication. Int J Cancer 2011;128:927–35.
5. Trottier H, Burchell AN. Epidemiology of mucosal human papillomavirus infection and associated diseases. Public Health Genomics 2009;12: 291–307.
6. Richardson H, Kelsall G, Tellier P, Voyer H, Abrahamowicz M, Ferenczy A, et al. The natural history of type-specific human papillomavirus infections in female university students. Cancer Epidemiol Biomarkers Prev 2003; 12:485–90.
7. Molano M, van den Brule A, Plummer M, Weiderpass E, Posso H, Arslan A, et al. Determinants of clearance of human papillomavirus infections in Colombian women with normal cytology: a population-based, 5-year follow-up study. Am J Epidemiol 2003;158:486–94.
8. Cuzick J, Szarewski A, Cubie H, Hulman G, Kitchener H, Luesley D, et al. Management of women who test positive for high-risk types of human papillomavirus: The HART study. Lancet 2003;362:1871–6.
9. Bosch FX, Lorincz A, Muñoz N, Meijer CJ, Shah KV. The causal relation between human papillomavirus and cervical cancer. J Clin Pathol 2002;55:244–65.
10. Appleby P, Beral V, Berrington de Gonzalez A, Colin D, Franceschi S, Goodill A, et al. Carcinoma of the cervix and tobacco smoking: collaborative reanalysis of individual data on 13,541 women with carcinoma of the cervix and 23,017 women without carcinoma of the cervix from 23 epidemiological studies. Int J Cancer 2006; 118:1481–95.
11. Smith JS, Green J, Berrington de Gonzalez A, Appleby P, Peto J, Plummer M, et al. Cervical cancer and use of hormonal contraceptives: a systematic review. Lancet 2003;361:1159–67.
12. Brinton LA, Hamman RF, Huggins GR, Lehman HF, Levine RS, Mallin K, et al. Sexual and reproductive risk factors for invasive squamous cell cervical cancer. J Natl Cancer Inst 1987;79:23–30.
13. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 2009;120:1640–5.
14. Aguilar M, Bhuket T, Torres S, Liu B, Wong RJ. Prevalence of the metabolic syndrome in the United States, 2003–2012. JAMA 2015;313:1973–4.
15. Ulmer H, Bjørge T, Concin H, Lukanova A, Manjer J, Hallmans G, et al. Metabolic risk factors and cervical cancer in the metabolic syndrome and cancer project (Me-Can). Gynecol Oncol 2012;125:330–5.
16. Penaranda EK, Shokar N, Ortiz M. Relationship between metabolic syndrome and history of cervical cancer among a US National Population. ISRN Oncol 2013;2013:840964.
17. Laukkanen JA, Laaksonen DE, Niskanen L, Pukkala E, Hakkarainen A, Salonen JT. Metabolic syndrome and the risk of prostate cancer in Finnish men: a population-based study. Cancer Epidemiol Biomarkers Prev 2004;13:1646–50.
18. Stocks T, Lukanova A, Johansson M, Rinaldi S, Palmqvist R, Hallmans G, et al. Components of the metabolic syndrome and colorectal cancer risk; a prospective study. Int J Obes 2008;32:304–14.
19. Borena W, Strohmaier S, Lukanova A, Bjørge T, Lindkvist B, Hallmans G, et al. Metabolic risk factors and primary liver cancer in a prospective study of 578,700 adults. Int J Cancer 2012;131:193–200.
20. Johansen D, Stocks T, Jonsson H, Lindkvist B, Björge T, Concin H, et al. Metabolic factors and the risk of pancreatic cancer: a prospective analysis of almost 580,000 men and women in the Metabolic Syndrome and Cancer Project. Cancer Epidemiol Biomarkers Prev 2010;19:2307–17.
21. Zhou J-R, Blackburn GL, Walker WA. Symposium introduction: metabolic syndrome and the onset of cancer. Am J Clin Nutr 2007;86:817S–9S.
22. Ahn HK, Shin JW, Ahn HY, Park CY, Lee NW, Lee JK, et al. Metabolic components and recurrence in early-stage cervical cancer. Tumour Biol 2015;36:2201–7.
23. Cowey S, Hardy RW. The metabolic syndrome: a high-risk state for cancer? Am J Pathol 2006;169:1505–22.
24. Liu SH, Chen HJ, Hsieh TH, Chen JC, Huang YC. Excessive adiposity, metabolic health, and risks for genital human papillomavirus infection in adult women: a population-based cross-sectional study. BMC Obes 2015;2:39.
25. Huang X, Zhao Q, Yang P, Li Y, Yuan H, Wu L, et al. Metabolic syndrome and risk of cervical human papillomavirus incident and persistent infection. Medicine 2016;95:e2905.
26. Centers for Disease Control and Prevention (CDC). National Center for Health Statistics (NCHS). National Health and Nutrition Examination Survey Data. Hyattsville, MD: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, [2005–2006, 2007–2008, 2009–2010]. [cited 2016 Apr 7]. Available from: http://www.cdc.gov/nchs/nhanes.htm
27. National Center for Health Statistics, Centers for Disease Control and Prevention (2010) NCHS Research Ethics Review Board (ERB) Approval. National Center for Health Statistics. [cited 2016 Apr 7]. Available from: http://www.cdc.gov/nchs/nhanes/irba98.htm
28. Dwivedi AK, Mallawaarachchi I, Lee S, Tarwater P. Methods for estimating relative risk in studies of common binary outcomes. J Appl Stat 2014;41: 484–500.
29. Johnson CL, Paulose-Ram R, Ogden CL, Carroll MD, Kruszon-Moran D, Dohrmann SM, et al. National Health and Nutrition Examination Survey: Analytic guidelines, 1999–2010. Hyattsville, MD: National Center for Health Statistics; 2013.

30. Scott M, Nakagawa M, Moscicki A-B. Cell-mediated immune response to human papillomavirus infection. Clin Diagn Lab Immunol 2001;8: 209–20.
31. Kemp TJ, Hildesheim A, García-Piñeres A, Williams MC, Shearer GM, Rodriguez AC, et al. Elevated systemic levels of inflammatory cytokines in older women with persistent cervical human papillomavirus infection. Cancer Epidemiol Biomarkers Prev 2010;19: 1954–9.
32. Baker R, Dauner JG, Rodriguez AC, Williams MC, Kemp TJ, Hildesheim A, et al. Increased plasma levels of adipokines and inflammatory markers in older women with persistent HPV infection. Cytokine 2011;53:282–5.
33. Wee CC, Huang A, Huskey KW, McCarthy EP. Obesity and the likelihood of sexual behavioral risk factors for HPV and cervical cancer. Obesity (Silver Spring) 2008;16:2552–5.
34. Wisse BE. The inflammatory syndrome: the role of adipose tissue cytokines in metabolic disorders linked to obesity. J Am Soc Nephrol 2004;15:2792–800.
35. Ursin G, Pike MC, Preston-Martin S, Peters RK. Sexual, reproductive, and other risk factors for adenocarcinoma of the cervix: results from a population-based case-control study (California, United States). Cancer Causes Control 1996;7:391–401.
36. Bárdos JI, Ashcroft M. Negative and positive regulation of HIF-1: a complex network. Biochim Biophys Acta 2005;1755:107–20.
37. Bodily J, Laimins LA. Persistence of human papillomavirus infection: keys to malignant progression. Trends Microbiol 2011;19:33–9.
38. Partridge JM, Koutsky LA. Genital human papillomavirus infection in men. Lancet Infect Dis 2006;6:21–31.
39. Stone KM, Karem KL, Sternberg MR, McQuillan GM, Poon AD, Unger ER, et al. Seroprevalence of human papillomavirus type 16 infection in the United States. J Infect Dis 2002;186:1396–402.