Gynecologic Oncology Reports 54 (2024) 101465

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

journal homepage: www.elsevier.com/locate/gynor

Association between metabolic syndrome and cervical cancer among women in Southwestern Uganda: A case-control study

Rogers Kajabwangu [a,*], Joseph Ngonzi [a], Jonathan Izudi [b], Joel Bazira [c], Frank Ssedyabane [d], Michael Kanyesigye [e], Raymond Atwine [f], Musa Kayondo [a], Rogers Ankunda [d], Henry Mark Lugobe [a], Stuart Turanzomwe [a], Thomas C. Randall [g], Francis Bajunirwe [b]

[a] Department of Obstetrics and Gynaecology, Faculty of Medicine, Mbarara University of Science and Technology, P.O. Box 1410, Mbarara, Uganda
[b] Department of Community Health, Mbarara University of Science and Technology, P.O. Box 1410, Mbarara, Uganda
[c] Department of Medical Microbiology, Mbarara University of Science and Technology, P.O. Box 1410, Mbarara, Uganda
[d] Department of Medical Laboratory Science, Faculty of Medicine, Mbarara University of Science and Technology, P.O. Box 1410, Mbarara, Uganda
[e] Department of Internal Medicine, Faculty of Medicine, Mbarara University of Science and Technology, P.O. Box 1410, Mbarara, Uganda
[f] Department of Pathology, Faculty of Medicine, Mbarara University of Science and Technology, P.O. Box 1410, Mbarara, Uganda
[g] Department of Obstetrics and Gynecology, Gynecological Oncology Division, Massachusetts General Hospital, Boston, MA, United States

ARTICLE INFO

Keywords:
Cervical cancer
Metabolic
Syndrome
Uganda

ABSTRACT

Objective: To determine the association between MetS and its components with cervical cancer among women in South-western Uganda.

Methods: We conducted an unmatched case-control study on 470 participants in a 1:2 case-to-control ratio among women in southwestern Uganda. We recruited 157 women with cervical cancer as cases and 313 women without cervical cancer as controls at the Mbarara Regional Referral Hospital Cervical Cancer Clinic. We assessed for MetS using the National Cholesterol Education Programme Adult Treatment Panel III (NCEP ATP III) criteria. We used a multivariable binary logistic regression analysis to determine the association between MetS and its components with cervical cancer adjusted for potential confounders. We reported the adjusted odds ratios (aOR) and 95% confidence intervals (CI).

Results: Cases were significantly older than controls: 52.4 ± 13.15 versus 41.9 ± 11.9 respectively, $p < 0.001$. We found MetS was independently associated with cervical cancer (aOR 1.66; 95 % CI 1.07–2.57). Age $\geq$ 50 years (aOR-2.20; 95 % CI 1.35–3.56), HIV infection (aOR 2.51, 95 % CI 1.56–4.05), increasing parity (aOR 1.16, 95 % CI 1.06–1.26), and a lack of formal education (aOR 6.41, 95 % CI, 1.33–30.86) were also associated with cervical cancer. However, none of the components of MetS was associated with cervical cancer.

Conclusion: In Ugandan women, MetS was associated with a higher likelihood of cervical cancer. We, therefore recommend combined screening for MetS and cervical cancer in order to reduce morbidity and mortality from both Mets and cervical cancer.

1. Introduction

Cervical cancer and metabolic syndrome (MetS), a group of risk factors for cardiovascular complications and diabetes mellitus, are both highly prevalent in resource-limited settings (Arbyn et al., 2020; Erasmus et al., 2012). About 500,000 new cases of cervical cancer occur in Sub-Saharan Africa annually (Sung et al., 2021), and nearly 30 % of women in this region now have MetS (Bowo-Ngandji et al., 2023). Literature suggests a potential relationship exists between MetS and cervical cancer (Ulmer et al., 2012; Penaranda et al., 2013).

Chronic infection with high-risk human papillomavirus (HPV) accounts for the majority of cervical cancer cases (Walboomers et al., 1999). Therefore, most cervical cancer control and prevention strategies have focused on eliminating cervical HPV through HPV-based screening and vaccination (Arbyn et al., 2020). Despite this intervention, the global incidence of cervical cancer continues to increase. Globally, cervical cancer cases rose from 471,000 to 604,000 annually, between 2000 and 2020, representing a nearly 30 % increase (Arbyn et al., 2020;

* Corresponding author.
E-mail address: rkajabwangu@must.ac.ug (R. Kajabwangu).

https://doi.org/10.1016/j.gore.2024.101465
Received 4 June 2024; Received in revised form 10 July 2024; Accepted 16 July 2024
Available online 20 July 2024

Sung et al., 2021; Parkin et al., 2001). In low and middle-income countries (LMICs), the steady rise in incidence is partly explained by sub-optimal preventive services (Nakalembe et al., 2020). However, cervical cancer is still a public health challenge even in high-income countries despite efficient preventive services, with cases exceeding the WHO threshold of 4 per 100,000 women years (Arbyn et al., 2020; Siegel et al., 2019). The pathogenesis of cervical cancer is complex. Majority of the HPV infections in women do not progress to invasive cervical cancer (de Sanjose et al., 2010; Nartey et al., 2023). There is also a small percentage of women with cervical who test negative for HPV infection (Fernandes et al., 2022). The complexity suggests that the risk for cervical cancer may be influenced by other factors beyond HPV infection thus necessitating further studies.

MetS is primarily characterized by insulin resistance followed by chronic pro-inflammatory status and oxidative stress resistance (Miranda et al., 2005; Ferriere et al., 2021; Silveira Rossi et al., 2022). Chronic inflammation and oxidative stress facilitate carcinogenesis both directly (Cowey and Hardy, 2006) and indirectly by enabling HPV acquisition and persistence (Huang et al., 2016; Lee et al., 2021; Lee and Lee, 2020). Studies showing the relationship between MetS and cancer of the cervix have been conducted in resource-rich countries so there is a lack of data in low and middle-income countries (Ulmer et al., 2012; Penaranda et al., 2013). Therefore, this study examined the association between MetS and its components on the risk of cervical cancer among women utilizing cervical cancer prevention and treatment services at a tertiary hospital in southwestern Uganda. Evidence from this study will inform screening and control programs for MetS and cancer of the cervix in this region to accelerate the elimination of cervical cancer as a public health problem.

2. Materials and methods

2.1. Study design, setting, and population

We conducted an unmatched case-control study that sampled all women seeking cervical cancer screening and treatment services at the cervical cancer clinic of Mbarara Regional Referral Hospital (MRRH) between April 2022 and August 2023. Cases were women with a new histologically confirmed diagnosis of invasive cervical cancer and controls were all those who screened negative for cervical cancer.

MRRH is a tertiary hospital in Southwestern Uganda serving nearly 4 million people (Uganda Ministry of Health, 2016) across 13 districts. It also provides services to the neighbouring countries namely, Rwanda, Burundi, Tanzania, and the Democratic Republic of Congo. The cervical cancer screening clinic operates 5 days a week, attending to an average of 15 women per day. Health workers at the clinic include several nursing officers, residents, and gynaecologists, all led by a gynaecologic oncologist. The cervical cancer screening tests at the clinic include visual inspection with acetic acid and Lugol's iodine, colposcopy and conventional cytology. Patients with suspicious lesions for cervical cancer undergo cervical biopsy followed by histopathological analysis for definitive diagnosis. On average, 10 women are diagnosed with cervical cancer per month (Kajabwangu et al., 2024). Patients with confirmed cervical cancer are transferred to the Gynaecology ward for clinical staging, and surgical intervention for early-stage cases ($\leq$2A), and those with advanced cancer are referred to the Uganda Cancer Institute at Mulago National Referral Hospital for chemoradiotherapy. There is no routine screening for MetS or any other metabolic risk factor.

The study was approved by the Mbarara University of Science and Technology Research Ethics Committee (MUST-2022–576) and the National Council for Science and Technology (HS3053ES) and Informed consent was obtained from all the study participants.

2.2. Eligibility criteria and sampling

We included all women aged $\geq$ 18 years old, who sought service at the cervical cancer screening clinic of MRRH during the study period. We excluded women who screened positive for premalignant cervical lesions. Cases were selected consecutively while controls were enlisted using the risk-set (incidence density) sampling method (Navidi and Weinhandl, 2002), with a case-to-control ratio of 1:2. The sample size was calculated using OpenEpi (Open-source epidemiologic statistics for public health), Version 3.01 (Dean, 2010), an online sample size calculator. We hypothesized that MetS was associated with cervical cancer. Based on this hypothesis, we computed that 470 participants (157 cases and 313 controls) would be adequate for the study to achieve 80 % statistical power at a 95 % confidence level if 22.8 % of controls had MetS (Ben-Yacov et al., 2020) and participants with MetS were more likely to have cervical cancer than controls with an OR of 1.82 based on findings from a previous study (Penaranda et al., 2013).

2.3. Variables

The outcome variable was cervical cancer (diagnosed histologically) and the primary exposure variable was MetS. The cases and controls were assessed for MetS using the National Cholesterol Education Programme Adult Treatment Panel III (NCEP ATP III) criteria which defines MetS as the presence of three or more of the following criteria (Grundy et al., 2005):

- Central obesity which was defined as waist circumference (WC) > 88 cm.
- Elevated triglycerides ($\geq$150 mg/dl or 1.695 mmol/l).
- Low high-density lipoprotein (<50 mg/dL, equivalent to < 1.295 mmol/l).
- High blood pressure (Systolic blood pressure $\geq$ 130 or Diastolic blood pressure $\geq$ 85 mmHg) or current antihypertensive medication use.
- High fasting blood glucose ($\geq$100 mg/dl or 5.6 mmol/l) or current antihyperglycemic medication use (Grundy et al., 2005).

Additional exposure variables included the individual components of MetS—waist circumference, blood pressure, blood sugar, high-density lipoproteins and triglycerides plus demographic, medical, and reproductive health characteristics.

2.4. Data collection

A pre-tested questionnaire in REDCap was administered by trained research assistants who were nurses at the cervical cancer clinic. The research assistants collected data on demographic, medical, and sexual behaviour: age, educational level, marital status, history of diabetes and hypertension, HIV status, age at first sexual contact, and number of sexual partners in life. Waist circumference was measured to the nearest 0.1 cm using a measuring tape in the horizontal plane midway between the inferior margin of the ribs and the superior border of the iliac crest, the measurement being recorded at minimal respiration. Blood pressure was measured after 5 min of rest, on the left arm in mmHg by the auscultation method using a calibrated sphygmomanometer and a stethoscope with the participant seated on a chair with her back supported, feet on the floor, arm supported, and cubital fossa at heart level. Three readings were measured at a 5-minute interval taking the first and fifth Korotkoff sounds as the systolic and diastolic blood pressure, respectively. The average of the last two systolic and diastolic measurements was taken as the mean systolic blood pressure and diastolic blood pressure, respectively (James et al., 2014). The Fasting blood sugar was measured using a glucometer after at least 8 h of fasting using capillary blood. The blood was obtained using a finger prick.

Blood was then collected for fasting triglycerides (TG) and high-density lipoprotein (HDL) as follows; Four millilitres (4 mL) of venous blood were aseptically drawn from the mid-cubital vein by venepuncture and collected into plain vacutainers. Each specimen was

labelled with a unique identification number and left to clot at room temperature for two hours. Subsequently, the specimens were transported to the laboratory, where centrifugation was performed at 1000 × g for 15 min at 2 ~ 8℃ to separate serum from blood cells. The resultant serum was then carefully transferred into cryovial tubes using a micropipette. Fasting TG and HDL concentrations were measured with a fully automated analyzer (Cobas 6000 Clinical Chemistry Analyzer; Roche Diagnostics International, Rotkreuz, Switzerland). All testing was performed following standard operating procedures.

2.5. Data management and analysis

Study data were collected and managed using REDCap electronic data capture tools hosted at Mbarara University of Science and Technology (Harris et al., 2009; Harris et al., 2019).

We downloaded the data from REDCap into a Microsoft Excel spreadsheet (Microsoft Office Professional Plus 2013, version 15.0.4675.1003, Microsoft Inc, Redmond, Washington, USA) and imported it into Stata version 17 (StataCorp LLC, College Station, Texas, United States) for analysis. We summarized categorical data as frequencies and proportions.

Numerical data were summarised using the mean and the standard deviation if normally distributed and median and interquartile range (IQR) if skewed. We tested differences in the proportions of the outcome variable with categorical data using the Chi-square for large cell counts (≥5) or Fisher's exact test for smaller cell counts (<5). For mean differences with numerical data, we used the student's *t*-test for normally distributed data or the Wilcoxon-rank sum test for skewed numerical data. Bivariate logistic regression was performed to determine the association of metabolic syndrome and its components without adjusting for covariates. Variables with p-value < 0.2 at bivariate analysis and those with biologic plausibility from the literature were considered in multivariable binary unconditional logistic regression to determine the association between metabolic syndrome and its individual components and cervical cancer, adjusted for other covariates. We presented the adjusted odd ratios (aOR) and the 95 % confidence intervals.

3. Results

3.1. Demographic, medical, and reproductive health characteristics of the participants

We enrolled 157 cases and 313 controls. On average, the cases were significantly older than the controls: 52.4 ± 13.15 versus 41.9 ± 11.9 respectively, p < 0.001. Compared to the controls, a higher proportion of the cases had HIV infection, were grand-multiparous, and had had a sexual debut at ≤ 16 years. A higher proportion of controls were single and had attained secondary and tertiary education compared to the cases. We found no statistically significant difference regarding the history of medical conditions (diabetes mellitus and hypertension) and number of sexual partners in life between the cases and controls (Table 1).

Table 1
Demographic, medical, and reproductive health characteristics of the participants.

Characteristic	Level	Cases (n = 157)	Controls (n = 313)	P-value
Age group (years)	<50	65 (41.4)	230 (73.5)	<0.001
	≥50	92 (58.6)	83 (26.5)	
	Mean (SD)	52.4 (13.1)	41.9 (11.9)	<0.001
Highest level of education	None	62 (39.5)	42 (13.4)	<0.001
	Primary	80 (50.9)	185 (59.1)	
	Secondary	13 (8.3)	65 (20.8)	
	Tertiary/ University	2 (1.3)	21 (6.7)	
Marital status	Single	5 (3.2)	9 (2.9)	0.003
	Married	83 (52.9)	213 (68.0)	
	Separated/ divorced	34 (21.6)	57 (18.2)	
	Widowed	35 (22.3)	34 (10.9)	
Parity	0—1	8 (5.1)	37(11.8)	<0.001
	2—4	39(24.8)	134 (42.8)	
	≥5	110 (70.1)	142 (45.4)	
HIV infection	No	94 (59.9)	217 (69.3)	0.041
	Yes	63 (40.1)	96 (30.7)	
Diabetes mellitus	No	151 (96.2)	304 (97.1)	0.580
	Yes	6 (3.8)	9 (2.9)	
Hypertension	No	144 (91.7)	294 (93.9)	0.37
	Yes	13 (8.3)	19 (6.1)	
Age at first sexual intercourse	≥21	22 (14.0)	55 (17.6)	0.002
	17–20	75 (47.8)	187 (59.7)	
	≤16	60 (38.2)	71 (22.7)	
Number of sexual partners in life	1	72 (45.9)	150 (47.9)	0.670
	≥2	85 (54.1)	163 (52.1)	

3.2. Metabolic characteristics of the participants

A higher proportion of the cases had MetS compared to the controls (58 % vs. 42.5 % respectively, p = 0.002). More cases had hypertension and hyperglycaemia compared to the controls. There was no statistically significant difference in the proportion of women with low HDL, hypertriglyceridemia, and central obesity among the cases and controls (Table 2).

3.3. Association between metabolic syndrome and selected co-variates with cervical cancer

In the multivariate analysis (Table 3), MetS, age ≥ 50 years, HIV infection, not having had formal education, and 1-unit increase in parity (0–15) were significantly associated with cervical cancer.

3.4. Association between the individual components of MetS with cervical cancer

In the unadjusted analysis, both hypertension and hyperglycaemia were associated with cervical cancer. Following adjustment for the other individual components of Mets and relevant demographic, medical and reproductive health variables, none of the variables was statistically significant (Table 4).

4. Discussion

We examined the relationship between MetS and its components with cervical cancer among women in Southwestern Uganda. We found that cervical cancer patients were more likely to have metS compared to controls without cervical cancer. Our findings tally with those of Ulmer et al (2012) and Peneranda et al (2013) who also found metabolic syndrome to be associated with cervical cancer among women in Europe and America, respectively (Ulmer et al., 2012; Penaranda et al., 2013).

Table 2
Metabolic characteristics of the participants.

Characteristic	Level	Cases (n = 157)	Control (n = 313)	P-value
Waist circumference	Normal	105 (66.9)	199 (63.6)	0.480
	Central obesity	52 (33.1)	114 (36.4)	
High-density lipoprotein (HDL)	Normal	26 (16.6)	47 (15.0)	0.660
	Low HDL	131 (83.4)	266 (85.0)	
Triglyceride	Normal	122 (77.7)	259 (82.7)	0.190
	Hypertriglyceridemia	35 (22.3)	54 (17.3)	
Blood pressure	Normal	72 (45.9)	189 (60.4)	0.003
	Hypertension	85 (54.1)	124 (39.6)	
Blood glucose	Normal	29 (18.5)	100 (31.9)	0.002
	Hyperglycemia	128 (81.5)	213 (68.1)	
Metabolic Syndrome	Absent	66 (42.0)	180 (57.5)	0.002
	Present	91 (58.0)	133 (42.5)	

Previous studies have reported that MetS increases the risk of breast, colorectal, pancreatic, and endometrial cancers (Katherine Esposito et al., 2012; Akinyemiju et al., 2022). The likely explanation for the association between MetS and cancer of the cervix might be the chronic inflammation and oxidative stress that characterize MetS and facilitate carcinogenesis in cervical cancer either directly or indirectly by facilitating HPV acquisition and persistence (Cowey and Hardy, 2006; Huang et al., 2016; Lee et al., 2021; Lee and Lee, 2020). Additionally, hormonal changes like hyperinsulinemia and hyperestrogenemia resulting from insulin resistance and increased estrogen synthesis in the excess adipose tissue might have a compounding effect (Iyengar et al., 2016; Calle and Kaaks, 2004). In particular, insulin and estrogen are known to induce cellular proliferation and inhibit apoptosis thus promoting tumor development (Kaaks and Lukanova, 2001; LeRoith and Roberts, 2003; Iyengar et al., 2015; Yager and Davidson, 2006). The finding of an association between MetS and cervical cancer is novel in resource-limited settings and contributes to advancing a combined approach in the screening and control of the two morbidities.

Our finding of a lack of association between the individual components of Mets and cervical cancer might imply that the individual components are not sufficient to act as risk factors for cervical cancer but rather they provoke cervical cancer when combined. Our finding is consistent with the results of a study conducted in the United States of America in 2013 (Penaranda et al., 2013). Ulmer et al (2012) reported an association between triglyceridemia and cervical cancer (Ulmer et al., 2012). Their study, however, considered triglycerides as a linear variable contrary to the recommended categorization by NCEP ATP III and also did not adjust for sociodemographic, medical, and reproductive health factors as we did in our study. Another study that found an association between triglycerides and cervical cancer was limited by having included a very small number of cervical cancer cases (Mwangi et al., 2024).

The finding that advanced age (≥55 years of age), lack of formal education, HIV infection, and increasing parity are associated with cervical cancer is not unique as these relationships have been reported in previous studies elsewhere (Paramita et al., 2010; Muñoz et al., 2002; Tekalegn et al., 2022; Franceschi et al., 2009; Stelzle et al., 2021; Bezabih et al., 2015) but not in Uganda. The association of these factors with cervical cancer is likely linked to increased risk of HPV acquisition and persistence in women with advanced age, those without formal education, multiparous women and those living with HIV (Muñoz et al., 2002; Vinodhini et al., 2012; Nang et al., 2023; Tay and Oon, 2014; Smith et al., 2008). Therefore, there is a need to reinforce HPV-based screening, especially in low-resource settings.

The present findings reinforce the existing literature and are important considering that the burden of both MetS and cervical cancer is increasing in sub-Saharan Africa (Isezuo and Ezunu, 2005; Fezeu et al., 2007; WHO I, 2010). Importantly, our findings imply a need to revise the current cervical cancer prevention strategies to integrate screening and treatment for MetS.

Table 3
Logistic regression analysis showing association between MetS and other factors with cervical cancer.

Characteristic	Level	Logistic regression analysis			
		Bivariate		Multivariate	
		COR (95 % CI)	P-Value	AOR (95 % CI)	P-value
Metabolic Syndrome	**Absent**	**1**		**1**	
	Present	**1.87 (1.27–2.75)**	**0.002**	**1.66(1.07–2.57)**	**0.021**
Age category(years)	<50	1		1	
	≥50	3.92 (2.62,5.88)	<0.001	2.20 (1.35,3.56)	<0.001
Education	None	15.50 (3.45,69.6)	<0.001	6.41(1.33,30.86)	0.020
	Primary	4.54 (1.04,19.83)	0.044	2.91(0.63,13.47)	0.171
	Secondary	2.1 (0.43,10.07)	0.354	1.60 (0.32,8.16)	0.565
	Tertiary /University	1		1	
Marital status	Single	1		1	
	Married	0.70 (0.23, 2.154)	0.536	0.4 (0.11,1.47)	0.169
	Separated/divorced	1.07 (0.33,3.47)	0.905	0.52 (0.14,1.96)	0.335
	Widowed	1.85 (0.56,6.60)	0.310	0.42 (0.10,1.63)	0.209
Parity	1-unit increase	1.23 (1.15,1.33)	<0.001	1.16 (1.06,1.26)	0.001
HIV infection	No	1		1	
	Yes	2.00 (1.02,2.26)	0.042	2.51(1.56–4.05)	<0.001
Diabetes mellitus	No	1			
	Yes	1.34 (0.47,3.84)	0.583	1.36 (0.41,4.48)	0.614
Hypertension	No	1			
	Yes	1.9 (0.67,2.91)	0.371	0.58 (0.24–1.36)	0.210
Age at first sexual intercourse (years)	≥21	1		1	
	17–20	1.01 (0.57,1.76)	0.993	0.53 (0.27,1.06)	0.071
	≤16	2.11(1.16,3.86)	0.015	0.88 (0.42,1.84)	0.738
Sexual partners in life	1partner	1		1	
	≥2 partners	1.09 (0.74,1.60)	0.673	1.12 (0.67,1.84)	0.672

1) COR: unadjusted/crude odds ratio; 2) aOR: Adjusted odds ratio.

Table 4
Logistic regression analysis showing the association between the individual components MetS and cervical cancer.

Characteristic	Level	Logistic regression analysis			
		Unadjusted analysis		Adjusted analysis	
		COR (95 % CI)	P-value	AOR (95 % CI)	P-value
Waist circumference	Normal	1		1	
	Central obesity	0.86 (0.58,1.30)	0.480	0.68 (0.42,1.09)	0.112
High-density lipoprotein(HDL)	Normal	1		1	
	Low	0.89 (0.53,1.50)	0.663	1.17 (0.63,2.17)	0.612
Triglyceride	Normal	1		1	
	Hypertriglyceridemia	1.38 (0.85,2.22)	0.189	0.99 (0.56,1.72)	0.966
Blood pressure	Normal	1			
	Hypertension	1.80 (1.22,2.65)	0.003	1.5 (0.96,2.34)	0.076
Blood glucose	Normal	1		1	
	Hyperglycemia	2.07 (1.30,3.32)	0.002	1.62 (0.97,2.71)	0.066

1) COR: unadjusted/crude odds ratio; 2) aOR: Adjusted odds ratio.

Our study has important strengths but some limitations as well. One strength of this study is the use of the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (2005) definition for MetS which utilizes simple clinical assessments and laboratory tests widely available to physicians in different settings hence ensuring replicability (Alberti and Zimmet, 1998; Balkau and Charles, 1999; Grundy, 2002; Zimmet et al., 2005). Cervical cancer in all cases was confirmed histologically and MetS was diagnosed using meticulous clinical assessments and standard laboratory techniques hence minimizing measurement biases. Our study was driven by a hypothesis including the sample size estimation hence the statistical power was adequate to detect statistically significant differences in the population.

However, we did not match the cases and controls by variables like age and HIV infection. Consequently, the cases were older than the controls and more of them had HIV infection compared to the controls. These could have confounded the relationship between the MetS and Cervical cancer. We addressed this by including these variables in the model at multivariate analysis. Additionally, our study could not demonstrate a temporal relationship since we did not have information about the timing of the occurrence of metabolic syndrome in relation to the diagnosis of cervical cancer. This being one of the initial studies to investigate the relationship between MetS and cervical cancer in African women, the findings might provide a benchmark for future studies that might utilize prospective designs in order to ascertain the timing of cervical cancer onset in women with and without MetS. We were also not able to collect data on HPV infection, a major risk factor for HPV infection. These limitations should be considered in the interpretation of results.

5. Conclusions

Our study showed that MetS is a risk factor for cervical cancer among women in Southwestern Uganda. Therefore, there is a need to put in place measures that combine the control, screening, and treatment of MetS and cervical cancer. For example, one option might be to integrate screening for MetS in cervical cancer screening programs or screening for cancer of the cervix at existing diabetes and hypertension clinics. This would contribute to the early diagnosis and treatment of MetS and potentially reduce the morbidity and mortality from cervical cancer.

Availability of data and materials

All data from which this article was generated is available from the corresponding author upon meaningful request.

Funding information

This research project was funded by The Mbarara University Research Capacity Initiative (MURCI) Program funded by the National Institute of Health (NIH) under grant number D43TW011632-01.

CRediT authorship contribution statement

Rogers Kajabwangu: Writing – review & editing, Methodology, Investigation. **Joseph Ngonzi:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **Jonathan Izudi:** Writing – review & editing, Writing – original draft. **Joel Bazira:** Writing – review & editing, Conceptualization. **Frank Ssedyabane:** Writing – review & editing, Writing – original draft, Formal analysis, Conceptualization. **Michael Kanyesigye:** Writing – review & editing, Methodology, Formal analysis. **Raymond Atwine:** Writing – original draft, Methodology. **Musa Kayondo:** Writing – review & editing, Methodology, Conceptualization. **Rogers Ankunda:** Writing – review & editing, Methodology, Investigation. **Henry Mark Lugobe:** Writing – review & editing, Methodology, Conceptualization. **Stuart Turanzomwe:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization. **Thomas C. Randall:** Writing – review & editing, Methodology, Funding acquisition, Conceptualization. **Francis Bajunirwe:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We acknowledge the staff of Mbarara Regional Referral Hospital, especially the cervical cancer screening and prevention clinic. We acknowledge the Mbarara University Research Capacity Initiative (Grant number-D43TW011632-01) for funding the study. We also acknowledge Mark Jacob Siedner for his contribution to the conception of this work and Mwesigye Vincent for his contribution to the data collection process. We acknowledge the research assistants; Alexcer Namuli, Ritah Namugumya, and Joyce Tumwebaze.

References

Akinyemiju, T., Oyekunle, T., Salako, O., Gupta, A., Alatise, O., et al., 2022. Metabolic syndrome and risk of breast cancer by molecular subtype: analysis of the MEND study. Clin. Breast Cancer 22, e463–e472.

Alberti, K.G.M.M., Zimmet, P.Z., 1998. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus. Provisional report of a WHO consultation. Diabet. Med. 15, 539–553.

Arbyn, M., Weiderpass, E., Bruni, L., de Sanjosé, S., Saraiya, M., et al., 2020. Estimates of incidence and mortality of cervical cancer in 2018: a worldwide analysis. Lancet Glob. Health 8, e191–e203.

Balkau, B., Charles, M.-A., 1999. Comment on the provisional report from the WHO consultation. European Group for the Study of Insulin Resistance (EGIR). Diabetic Medicine: a Journal of the British Diabetic Association 16, 442–443.

Ben-Yacov, L., Ainembabazi, P., Stark, A.H., Kizito, S., Bahendeka, S., 2020. Prevalence and sex-specific patterns of metabolic syndrome in rural Uganda. BMJ Nutrition, Prevention & Health 3, 11.

Bezabih, M., Tessema, F., Sengi, H., Deribew, A., 2015. Risk factors associated with invasive cervical carcinoma among women attending Jimma University specialized

hospital, Southwest Ethiopia: a case control study. Ethiopian Journal of Health Sciences 25, 345–352.
Bowo-Ngandji, A., Kenmoe, S., Ebogo-Belobo, J.T., Kenfack-Momo, R., Takuissu, G.R., et al., 2023. Prevalence of the metabolic syndrome in African populations: A systematic review and meta-analysis. PLoS One 18, e0289155.
Calle, E.E., Kaaks, R., 2004. Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. Nat. Rev. Cancer 4, 579–591.
Cowey, S., Hardy, R.W., 2006. The metabolic syndrome: a high-risk state for cancer? Am. J. Pathol. 169, 1505–1522.
de Sanjose, S., Quint, W.G., Alemany, L., Geraets, D.T., Klaustermeier, J.E., et al., 2010. Human papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study. Lancet Oncol. 11, 1048–1056.
Dean, A., 2010. OpenEpi: open source epidemiologic statistics for public health, version 2.3. 1. http://www openepi com.
Erasmus, R.T., Soita, D.J., Hassan, M.S., Blanco-Blanco, E., Vergotine, Z., et al., 2012. High prevalence of diabetes mellitus and metabolic syndrome in a South African coloured population: Baseline data of a study in Bellville, Cape Town. S. Afr. Med. J. 102, 841–844.
Fernandes, A., Viveros-Carreño, D., Hoegl, J., Ávila, M., Pareja, R., 2022. Human papillomavirus-independent cervical cancer. International Journal of Gynecologic. Cancer 32.
Ferriere, A., Santa, P., Garreau, A., Bandopadhyay, P., Blanco, P., et al., 2021. Self-nucleic acid sensing: a novel crucial pathway involved in obesity-mediated metaflammation and metabolic syndrome. Frontiers in Immunology 11, 624256.
Fezeu, L., Balkau, B., Kengne, A.-P., Sobngwi, E., Mbanya, J.-C., 2007. Metabolic syndrome in a sub-Saharan African setting: central obesity may be the key determinant. Atherosclerosis 193, 70–76.
Franceschi, S., Plummer, M., Clifford, G., De Sanjose, S., Bosch, X., et al., 2009. Differences in the risk of cervical cancer and human papillomavirus infection by education level. Br. J. Cancer 101, 865–870.
Grundy, S.M., 2002. Third report of the national cholesterol education program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) final report. Circulation 106, 3143–3421.
Grundy, S.M., Cleeman, J.I., Daniels, S.R., Donato, K.A., Eckel, R.H., et al., 2005. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute scientific statement. Circulation 112, 2735–2752.
Harris, P.A., Taylor, R., Thielke, R., Payne, J., Gonzalez, N., et al., 2009. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. J. Biomed. Inform. 42, 377–381.
Harris, P.A., Taylor, R., Minor, B.L., Elliott, V., Fernandez, M., et al., 2019. The REDCap consortium: building an international community of software platform partners. J. Biomed. Inform. 95, 103208.
Huang, X., Zhao, Q., Yang, P., Li, Y., Yuan, H., et al., 2016. Metabolic syndrome and risk of cervical human papillomavirus incident and persistent infection. Medicine 95.
Isezuo, S., Ezunu, E., 2005. Demographic and clinical correlates of metabolic syndrome in Native African type-2 diabetic patients. J. Natl Med. Assoc. 97, 557.
Iyengar, N.M., Hudis, C.A., Dannenberg, A.J., 2015. Obesity and cancer: local and systemic mechanisms. Annu. Rev. Med. 66, 297–309.
Iyengar, N.M., Gucalp, A., Dannenberg, A.J., Hudis, C.A., 2016. Obesity and cancer mechanisms: tumor microenvironment and inflammation. J. Clin. Oncol. 34, 4270.
James, P.A., Oparil, S., Carter, B.L., Cushman, W.C., Dennison-Himmelfarb, C., et al., 2014. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA 311, 507–520.
Kaaks, R., Lukanova, A., 2001. Energy balance and cancer: the role of insulin and insulin-like growth factor-I. Proc. Nutr. Soc. 60, 91–106.
Kajabwangu, R., Bajunirwe, F., Izudi, J., Bazira, J., Farjardo, Y., et al., 2024. Magnitude and trends in cervical cancer at Mbarara Regional Referral Hospital in South Western Uganda: Retrospective analysis of data from 2017–2022. PLOS Global Public Health 4, e0002848.
Katherine Esposito, M., Chiodini, P., Colao, A., Lenzi, A., Dario Giugliano, M., 2012. Metabolic syndrome and risk of cancer: a systematic review and meta-analysis. Diabetes Care 35, 2402.
Lee, J., Kim, H.S., Kim, K., Bae, D.-S., Kim, B.-G., et al., 2021. Metabolic syndrome and persistent cervical human papillomavirus infection. Gynecol. Oncol. 161, 559–564.
Lee, D.Y., Lee, T.S., 2020. Associations between metabolic syndrome and gynecologic cancer. Obstetrics & Gynecology Science 63, 215.
LeRoith, D., Roberts Jr, C.T., 2003. The insulin-like growth factor system and cancer. Cancer Letters 195, 127–137.
Miranda, P.J., DeFronzo, R.A., Califf, R.M., Guyton, J.R., 2005. Metabolic syndrome: definition, pathophysiology, and mechanisms. Am. Heart J. 149, 33–45.
Muñoz, N., Franceschi, S., Bosetti, C., Moreno, V., Herrero, R., et al., 2002. Role of parity and human papillomavirus in cervical cancer: the IARC multicentric case-control study. Lancet 359, 1093–1101.
Mwangi, G.F., Niyonzima, N., Atwine, R., Tusubira, D., Mugyenyi, G.R., et al., 2024. Dyslipidemia: prevalence and association with precancerous and cancerous lesions of the cervix; a pilot study. Lipids Health Dis. 23, 3.
Nakalembe, M., Makanga, P., Kambugu, A., Laker-Oketta, M., Huchko, M.J., et al., 2020. A public health approach to cervical cancer screening in Africa through community-based self-administered HPV testing and mobile treatment provision. Cancer Med. 9, 8701–8712.
Nang, D.W., Tukirinawe, H., Okello, M., Tayebwa, B., Theophilus, P., et al., 2023. Prevalence of high-risk human papillomavirus infection and associated factors among women of reproductive age attending a rural teaching hospital in western Uganda. BMC Womens Health 23, 1–8.
Nartey, Y., Amo-Antwi, K., Hill, P.C., Dassah, E.T., Asmah, R.H., et al., 2023. Human papillomavirus genotype distribution among women with and without cervical cancer: Implication for vaccination and screening in Ghana. PLoS One 18, e0280437.
Navidi, W., Weinhandl, E., 2002. Risk set sampling for case-crossover designs. Epidemiology: 100-105.
Paramita, S., Soewarto, S., Widodo, M.A.A., Sumitro, S.B., 2010. High parity and hormonal contraception use as risk factors for cervical cancer in East Kalimantan. Medical Journal of Indonesia 19, 268–272.
Parkin, D.M., Bray, F., Devesa, S., 2001. Cancer burden in the year 2000. The global picture. European Journal of Cancer 37, 4–66.
Penaranda, E.K., Shokar, N., Ortiz, M., 2013. Relationship between metabolic syndrome and history of cervical cancer among a US national population. International Scholarly Research Notices 2013.
Siegel, R.L., Miller, K.D., Jemal, A., 2019. Cancer statistics, 2019. CA Cancer J. Clin. 69, 7–34.
Silveira Rossi, J.L., Barbalho, S.M., Reverete de Araujo, R., Bechara, M.D., Sloan, K.P., et al., 2022. Metabolic syndrome and cardiovascular diseases: Going beyond traditional risk factors. Diabetes/metabolism Research and Reviews 38, e3502.
Smith, J.S., Melendy, A., Rana, R.K., Pimenta, J.M., 2008. Age-specific prevalence of infection with human papillomavirus in females: a global review. J. Adolesc. Health 43: S5, e1–e5 e62.
Stelzle, D., Tanaka, L.F., Lee, K.K., Khalil, A.I., Baussano, I., et al., 2021. Estimates of the global burden of cervical cancer associated with HIV. Lancet Glob. Health 9, e161–e169.
Sung, H., Ferlay, J., Siegel, R.L., Laversanne, M., Soerjomataram, I., et al., 2021. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J. Clin. 71, 209–249.
Tay, S.K., Oon, L.L.E., 2014. Prevalence of cervical human papillomavirus infection in healthy women is related to sexual behaviours and educational level: a cross-sectional study. Int. J. STD AIDS 25, 1013–1021.
Tekalegn, Y., Sahiledengle, B., Woldeyohannes, D., Atlaw, D., Degno, S., et al., 2022. High parity is associated with increased risk of cervical cancer: Systematic review and meta-analysis of case–control studies. Womens Health 18, 17455065221075904.
Uganda Ministry of Health, 2016. Mbarara regional referral hospital.
Ulmer, H., Bjørge, T., Concin, H., Lukanova, A., Manjer, J., et al., 2012. Metabolic risk factors and cervical cancer in the metabolic syndrome and cancer project (Me–Can). Gynecol. Oncol. 125, 330–335.
Vinodhini, K., Shanmughapriya, S., Das, B.C., Natarajaseenivasan, K., 2012. Prevalence and risk factors of HPV infection among women from various provinces of the world. Arch. Gynecol. Obstet. 285, 771–777.
Walboomers, J.M., Jacobs, M.V., Manos, M.M., Bosch, F.X., Kummer, J.A., et al., 1999. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J. Pathol. 189, 12–19.
WHO I (2010) WHO/ICO Information Centre on HPV and Cervical Cancer (HPV Information Centre). Human Papillomavirus and Related Cancers in Kenya Summary Report 2010.
Yager, J.D., Davidson, N.E., 2006. Estrogen carcinogenesis in breast cancer. N. Engl. J. Med. 354, 270–282.
Zimmet, P., Magliano, D., Matsuzawa, Y., Alberti, G., Shaw, J., 2005. The metabolic syndrome: a global public health problem and a new definition. J. Atheroscler. Thromb. 12, 295–300.