



Effect of metabolic syndrome and its components on the risk and prognosis of cervical cancer: A literature review

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ABSTRACT

Despite the global implementation of preventive strategies against Human Papilloma Virus (HPV) infection, the incidence of invasive cervical cancer rose by nearly 1.3-fold, from 471,000 annual cases in 2000 to 604,000 cases in 2020. With over 340,000 deaths annually, cervical cancer is the fourth leading cause of cancer mortality in women globally.

There is a need to understand other factors besides HPV such as metabolic syndrome (MetS) that potentially influence the onset and progression of cervical cancer. In this narrative review, we describe evidence showing that Metabolic syndrome (MetS) increases the risk for cervical cancer and worsens its prognosis. Combined screening for MetS and cervical cancer has potential to significantly reduce morbidity and mortality in women with cervical cancer.

1. Introduction

With over half a million new cases every year, cervical cancer is the fourth most common cancer in women globally (Sung, 2021). Nearly 90 % of the global burden of invasive cervical cancer (ICC) is in low and middle-income countries (LMICs) (Torre, et al., 2015) and in these countries, it is the second most common type of cancer in females, with an incidence of 15.7 per 100,000 women (WHO, 2010). Whereas the incidence of ICC continues to rise in LMICs (Jedy-Agba, 2020), high-income countries have reported a 70 % decline in the incidence of the disease over the past 50 years and this is attributed to effective screening and treatment of preinvasive cervical lesions (Quinn, 1999).

Persistent high-risk HPV infection accounts for nearly all cases of ICC (Walboomers, 1999). Therefore, most control and preventive strategies for cervical cancer have focused on eliminating HPV infection of the cervix (Arbyn, 2020). HPV-DNA (Deoxyribonucleic acid) based screening and vaccination against HPV are highly effective and are

recommended by the World Health Organization (WHO) but their implementation remains suboptimal in LMICs (WHO, 2021). Moreover, the full effect of vaccination against HPV is likely to be felt when current vaccine recipients mature to adulthood.

Evidence suggests that HPV is a necessary but not sufficient cause of ICC (Bosch and De Sanjosé, 2003) yet only a small percentage of women who contract HPV infection develop ICC (Elfgren, 2000). There is need to explore other factors that can potentially modify the risk for ICC. HIV and Chlamydia trachomatis, increasing parity, smoking, and long-term use of oral contraceptives have been well-studied as cofactors in ICC causation (Paramita, 2010; Stelzle, 2021; Valasoulis, 2023). Metabolic syndrome (MetS), a group of risk factors for cardiovascular complications and diabetes characterized by insulin resistance and accompanied by a chronic pro-inflammatory status and oxidative stress, has also been identified as one of the risk factors for ICC (Alberti, 2009; Ulmer, 2012). According to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) (2005), MetS is defined as the presence of

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≥ 3 of the following: abdominal obesity which is defined as waist circumference (WC) > 102 cm in men and > 88 cm in women; elevated triglycerides (≥150 mg/dl or 1.695 mmol/l); low high-density lipoprotein < 40 mg/dl (equivalent to < 1.036 mmol/l) in men and < 50 mg/dL (equivalent to < 1.295 mmol/l) in women; high blood pressure (≥130/85 mmHg) or current antihypertensive medication use; and high fasting blood glucose (≥100 mg/dl or 5.6 mmol/l) or current anti-hyperglycemic medication use (Grundy, 2005). MetS is on the rise globally, affecting more than a third of the population in some countries (Ford, 2005). The chronic inflammation and oxidative stress resulting from the metabolic derangements facilitate the persistence of HPV infection, hence promoting carcinogenesis (Cowey and Hardy, 2006; Lee, 2021). Despite multiple studies showing an increased risk of several types of cancer in the presence of MetS (Lee and Lee, 2020), synthesized literature focusing on metabolic syndrome and cervical cancer is scarce. We, therefore, conducted a narrative literature review of evidence regarding the effect of metabolic syndrome and its components on the risk and progression of cervical cancer, with a goal to better guide future investigations and inform public policy.

2. Methods and materials

We performed a literature search on PubMed and Google Scholar and reviewed clinical practice guidelines, position papers by professional societies and organizations, and the reference lists of included articles to identify additional relevant articles. We limited our search to articles published in English until October 2023. We focused on studies that investigated the epidemiology, pathogenesis, incidence and prognosis of cervical cancer and metabolic syndrome (MetS). Our search strategy included the search terms “Metabolic syndrome” and “cancer” either alone or combined using Boolean Operators (“AND” and “OR”), performed by RK and ST. An example of our search strategy on PubMed is as follows: (“uterine cervical neoplasms”[MeSH Terms] OR (“uterine”[All Fields] AND “cervical”[All Fields] AND “neoplasms”[All Fields]) OR “uterine cervical neoplasms”[All Fields] OR (“cervical”[All Fields] AND “cancer”[All Fields]) OR “cervical cancer”[All Fields]) AND (“metabolic syndrome”[MeSH Terms] OR (“metabolic”[All Fields] AND “syndrome”[All Fields]) OR “metabolic syndrome”[All Fields]). We found 63 articles and screened them for relevance. We then searched the references of the retrieved articles by title and abstract for identification of other potential articles. Articles whose abstracts appeared relevant from the first screening were read in full. We were therefore able to find an additional 23 articles.

3. Results

3.1. Epidemiology of ICC and metabolic syndrome

Evidence from epidemiologic, experimental, and clinical studies suggests that MetS may have a role in the onset and progression, and the overall mortality of certain types of cancers. A meta-analysis of cohort studies conducted in the United States, Europe, and Asia reports breast, colorectal, pancreatic, and endometrial cancers as being more incident in women with MetS (Katherine Esposito, 2012). A recent Nigeria study has indicated an increased risk of breast cancer in women with MetS compared to those without MetS (Akinyemiju, 2022). Studies have further shown that the individual components of MetS like obesity, hyperglycemia, and dyslipidemia are associated with cancer in women (Rapp, 2005; Ikeda, 2009; Agnoli, 2014). Except for endometrial cancer (Reeves, 2007), most of the studies have been on non-gynecological cancers, with only a few studies focused on the relationship between MetS and its diagnostic components, and gynecological cancer, especially cervical cancer (Lee and Lee, 2020). Hypertriglyceridemia and hyperglycemia have been associated with a higher risk of ICC (Ulmer, 2012).

While the relationship between the different specific elements of MetS with ICC is fairly well-studied (Ulmer, 2009; Lacey, 2003), the

correlation between the composite MetS and ICC is vaguely understood. In a case-control study conducted by Penaranda *et al* in the United States in 2013, it was found that the likelihood of ICC increased nearly twofold in the presence of MetS (Penaranda, 2013). However, none of the individual components of the MetS showed an association with ICC. A multicenter and multi-year cohort study in Austria, Sweden and Norway showed a 26 % increase in the risk of cervical cancer among women with MetS over an 11 year follow-up period (Ulmer, 2012) and a statistically significant association between the individual components of MetS (obesity, hypertension and hypertriglyceridemia) and ICC. Contrariwise, an Indian study showed no association between metabolic risk factors and cervical cancer (Kedar, 2019).

3.2. Pathophysiology of cervical cancer and metabolic syndrome

In general, MetS increases the risk of cancer through accumulation of reactive oxygen species, excessive production and increased bioavailability of hormones such as estrogen and providing a glucose-rich environment (Cowey and Hardy, 2006).

In specific regard to cervical cancer, these factors facilitate carcinogenesis both directly (Cowey and Hardy, 2006) and indirectly by enabling HPV acquisition and persistence (Huang, 2016).

In women with MetS, the levels of both free and total serum estrogen are increased due to increased estrogen synthesis in the excessive adipose tissue. In addition, the synthesis of sex hormone-binding globulin in the liver significantly decreases thus leading to increased blood concentration of estrogen (Calle and Kaaks, 2004). Estrogen contributes to carcinogenesis by inducing cellular proliferation, inhibiting cell apoptosis, stimulating angiogenesis through vascular endothelial growth factor secretion and causing mutagenic effects through generation of genotoxic metabolites (Yager and Davidson, 2006). Insulin resistance in MetS leads to hyperinsulinemia and hyperglycemia as well as increased freely circulating insulin-like growth factor levels (Iyengar, 2016). The anabolic signals by insulin or insulin growth factor inhibit apoptosis and stimulate cell proliferation hence promoting tumor development (Kaaks and Lukanova, 2001). Furthermore, hyperglycemia leads to activation of I3K, PKCα and Myosin light-chain kinase (MLCK) which promote cell proliferation (Masur, 2011). Hypertriglyceridemia activates reactive oxygen species which cause DNA damage so stimulating cancer cell proliferation and increasing anti-apoptotic capacity (Cowey and Hardy, 2006).

The second mechanism by which MetS increases the risk of ICC, is explained by the effect of MetS on HPV-mediated carcinogenesis. Clinical and epidemiologic evidence indicates that HPV is a necessary factor for ICC causation (Huang, 2016), implying that other factors are only likely to increase the risk of ICC by facilitating HPV-mediated carcinogenesis. Lee *et al* (2020) described an increase in the risk of HPV acquisition in the presence of MetS in a cross-sectional study involving men and women in the United States (Lee and Lee, 2020). Beyond acquisition, MetS has been shown to increase the risk of HPV persistence. An analysis of data on 7682 women who had baseline HPV infection in a study in South Korea showed that MetS increases the risk of HPV persistence by 30 % (Lee, 2021). Lee *et al* (2020) described an increase in the risk of persistence of HPV infection in the presence of MetS (Lee and Lee, 2020). Despite the overwhelming evidence indicating that MetS increases the risk of acquisition and persistence of HPV, Liu *et al* from a study in China reported a lack of an association between MetS and HPV acquisition and/or persistence (Liu, 2015).

The increased risk of HPV acquisition and persistence in MetS can be explained by several pathways. First, the production of estrogen, adipokines, and cytokines creates a state of chronic inflammation (Baker, 2011). Second, MetS poses a state of immune suppression that facilitates the acquisition and persistence of HPV without deterrence from the immune system (Scott *et al.*, 2001). Third, angiogenesis that results from hypertension-induced hypoxia through hypoxia-inducible factor-1 has been proposed as a mechanism by which MetS increases the risk of HPV

infection (Bárdos and Ashcroft, 2005).

3.3. Histological findings of cervical cancer and MetS

ICC is histologically classified into squamous cell carcinoma (SCC), Adenocarcinoma (ADC) and Adenosquamous carcinoma with each accounting for 70 %, 25 % and 5 % of all ICC cases respectively (Park, 2020). Adenocarcinoma is further categorized into various HPV-associated (HPVA) and non-HPV-associated adenocarcinomas (Park, 2020). Although SCC still accounts for majority of the cases of ICC, the rate of adenocarcinoma has been rising at a proportionally higher rate. Obesity and possibly MetS predisposes to adenocarcinoma compared to squamous cell carcinoma (Parazzini and La Vecchia, 1990). In a study conducted by Lacey *et al* among women with a diagnosis of ICC in the United States to determine whether there was a difference in risk factors in regards to tumor histology, findings showed higher odds of adenocarcinoma compared to squamous cell carcinoma in the presence of obesity (Lacey, 2003). In a pooled analysis of data from 8 case-control studies, Castellsague *et al* (2006) found that obesity was strongly associated with adenocarcinoma compared to squamous cell carcinoma (Castellsagué, 2006). Increased estrogen levels as a result of increased production in the excess adipose tissue combined with other viral and host factors, favors adenocarcinoma development (Castellsagué, 2006).

Besides Metabolic risk factors, several other factors predispose to adenocarcinoma compared to squamous cell carcinoma. For instance, although adenocarcinoma and squamous cell carcinoma are each associated with HPV infection, the former is more likely to result from infection with HPV 18 while the latter is linked to HPV16 (Altekruse, 2003). Nulliparity and oral contraceptive use for 5 years or more increase the risk of adenocarcinoma compared to squamous cell carcinoma (Altekruse, 2003). Adenocarcinoma poses a particular clinical challenge compared to squamous cell carcinoma for several reasons. First, adenocarcinoma precursors are hard to detect by conventional screening methods as the initial growth is within the cervical canal (Gunnell, 2007), while squamous cell carcinoma precursors largely develop in the transformation zone which is most commonly on the ectocervix. Adenocarcinoma lesions are therefore easily missed during cytology of brushings from the ectocervix, or with colposcopy and cervical biopsy, since they grow inwards into the endocervical canal (Gien *et al.*, 2010). Adenocarcinoma presents earlier in life compared to squamous cell carcinoma and generally presents at an advanced stage since it is usually detected only after reasonable progression (Galic, 2012; Vinh-Hung, 2007; Liu *et al.*, 2001; Lee, 2006). Adenocarcinoma has a higher metastasis rate to different organs compared to squamous cell carcinoma (Lee, 2011). In both early and late stages of its presentation, adenocarcinoma poses a higher mortality risk relative to squamous cell carcinoma (Galic, 2012).

3.4. The effect of MetS on stage of cervical cancer at presentation remains unknown

Although it is well known that components of MetS worsen stage at diagnosis in cervical cancer patients (Shen, 2023); specific data on the relationship between composite MetS and cervical cancer stage at presentation is scarce.

In most LMICs, the majority of patients present with advanced stage (Grover, 2022), and consequently, mortality rate is very high (Torre, *et al.*, 2015). These patients often seek treatment once they have symptoms of advanced disease, such as vaginal bleeding and abnormal vaginal discharge, among others (Day and Gray, 2012; Mwaka *et al.*, 2013). Even after the onset of symptoms, many patients still take several months to seek care (Rudd, 2017). Stewart *et al* (2018) found that cervical cancer patients from rural areas, those who had high parity, those infected with HIV, those who had no formal education, and those who had had condomless sex were more likely to present with advanced-stage disease (Stewart *et al.*, 2018).

3.5. Effect of MetS on cervical cancer prognosis and clinical outcomes

There has been a general improvement in the prognosis of ICC in both developed and developing countries (Muhamad, 2015). In India for instance, the survival rates for patients with ICC in the first, second, third, fourth and fifth years are 92.5 %, 83.8 %, 78.0 %, 74.7 %, and 72.6 % respectively (Balasubramaniam, 2020). In the same cohort of patients, the 5-year survival rates for patients with ICC in stages I, II, III, and IV were 84.4 %, 80.3 %, 65.9 %, and 37.1 %, respectively (Balasubramaniam, 2020). The 5-year survival rate for cervical cancer in Sub-Saharan Africa is as low as 17 % in some countries (Gondos, 2005). The clinical stage at presentation, lympho-vascular invasion, increasing tumor size, and level of differentiation are some of the factors that influence outcomes in patients with cervical cancer (Baalbergen, 2004).

Although data on the effect of MetS on cervical cancer prognosis are limited, studies conducted on patients with other cancers have found MetS to be associated with increased mortality from the cancers (Ulmer, 2012; Cowey and Hardy, 2006). MetS is known to increase the risk of recurrence and worsen treatment response, with faster invasive progression and death in patients with breast cancer (Muniz *et al.*, 2016; Buono, 2020). The mitogenic, antiapoptotic, and angiogenic effects of excessive insulin secretion—the hallmark of MetS—are postulated to lead to faster cancer progression and mortality (Dong, 2021). The high insulin increases aromatase activity and decreases the production of sex hormone-binding globulin hence increasing estrogen circulation (McTernan *et al.*, 2000). This explains why interventions targeted at preventing and treating MetS such as statins, low-calorie diets together with regular physical exercise improve treatment outcomes among patients with cancer (Dong, 2021).

In specific regard to ICC, obesity, and possibly MetS as a whole, is associated with a high mortality (Calle, 2003). Patients with ICC who do not have MetS are less likely to experience recurrence at two years compared to those with MetS (Ahn, 2015). Even individual components of MetS such as hypertriglyceridemia increase the rate of recurrence at 2 years in patients with ICC (Ahn, 2015). In Korea, one study shows that higher fasting blood sugar levels increase the mortality risk among women with cervical cancer (Jee, 2005). Compared to those with normal Glucose-6-phosphatase catalytic subunit expression, patients with cervical cancer in whom the Glucose-6-phosphatase catalytic subunit (a glycolytic enzyme) is over-expressed are more likely to have metastasis to lymph nodes, late clinical stage at presentation, higher rate of recurrence after treatment, and shortened survival (Zhu, 2022).

4. Conclusion

We highlighted the effect of MetS and its components on the risk and prognosis of ICC from the available literature. Our literature review shows an association between MetS and ICC in a few studies suggesting additional data are needed. Current evidence also demonstrates that MetS worsens prognosis in patients with ICC. Women who screen negative for cervical cancer should be counseled, screened for and treated for MetS in order to reduce on the risk of developing cancer. Screening and treating MetS in women with cervical cancer is likely to increase disease-free survival and reduce mortality.

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CRedit authorship contribution statement

Rogers Kajabwangu: Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization. **Jonathan Izudi:** Writing – review & editing, Methodology. **Joel Bazira:** Writing – review & editing, Conceptualization. **Frank Sedyabane:** Writing – review & editing, Methodology, Conceptualization. **Stuart Turanzomwe:**

Writing – review & editing, Methodology, Investigation. **Abraham Birungi**: Writing – review & editing, Methodology. **Joseph Ngonzi**: Writing – review & editing, Conceptualization. **Francis Bajunirwe**: Writing – review & editing, Methodology, Funding acquisition, Conceptualization. **Thomas C Randall**: Writing – original draft, Investigation, 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.

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