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Metabolic Syndrome and Common Cancers in Nigeria: A Systematic Review between 1999 and 2022

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ABSTRACT: Metabolic syndrome (MetS) and cancers pose significant public health challenges worldwide. However, the exact mechanisms linking MetS to carcinogenesis remain incompletely understood, particularly in the context of Nigeria where information on this association is limited. Consequently, the objective of this paper is to provide a systematic review of metabolic syndrome and common cancers in Nigeria spanning the period 1999 to 2022 by harvesting information and data across academic databases including Google Scholar and PubMed. The focus was on exploring the association of metabolic syndrome with breast, prostate, liver, cervical, ovarian, and endometrial cancers specifically within Nigerian populations. Each constituent of metabolic syndrome was individually investigated alongside each highlighted cancer type (e.g., hypertension and its correlation with liver cancer). Seventeen scholarly articles meeting the inclusion criteria were identified, shedding light on the relationship between metabolic syndrome and various cancers among Nigerians. These studies predominantly reported one or two components of MetS in the context of the specified cancers. Notably, only a singular report discussed the association between MetS and breast cancer within this population. The study highlighted a lack of information regarding the mechanisms linking Metabolic Syndrome (MetS) to carcinogenesis specifically within Nigeria. It suggests the need for further research endeavors aimed at clarifying these mechanisms.

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Cancer ranks as the second leading cause of death globally. In 2015 alone, cancer was responsible for over 8.7 million deaths, with approximately 60% of these fatalities transpiring in low-income countries (GBDCC, 2017). In 2020, Africa recorded over 1 million new cases of cancer and approximately 711,429 deaths attributed to the disease. Projections indicate that Africa may witness well over 2 million new cancer cases and 1.3 million deaths within the next two decades (Sharma *et al*., 2022). Nigeria held the second position in Africa with a cancer incidence rate of 124,815 cases, and it was among the top three countries in terms of cancer mortality. The mortality-to-incidence ratio stood at 0.63 (Sharma *et al*., 2022). Certain risk factors, such as smoking, obesity, and unhealthy lifestyle choices, have been linked to a higher incidence of cancer (GBDCC, 2013; 2017). Factors such as poverty, lack of awareness, insufficient diagnostic and treatment resources have significantly contributed to suboptimal outcomes in cancer management across sub-Saharan Africa (Olaleye and Ekrikpo, 2017). A Nigerian study found that approximately 1.4% of incident cancers were linked to overweight and obesity (Odutola *et al*., 2019). Breast, prostate, cervical, endometrial, ovarian, and liver cancers are prevalent in Nigeria

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(Baba and Hincal, 2016). Metabolic syndrome is characterized by a collection of risk factors associated with cardiovascular disease and type 2 diabetes mellitus (T2DM). These factors include obesity, dysglycemia, high blood pressure, elevated triglyceride levels, and low levels of HDL cholesterol (Esposito *et al*., 2012). A Nigerian study reported a prevalence rate of 33.1% (Fabian *et al*., 2015). A study conducted among university staff across Nigerian geopolitical zones revealed a notable prevalence of Metabolic Syndrome components including hypertension, obesity, and dysglycemia (Joseph-Shehu and Ncama, 2018). Moreover, research conducted in southeastern Nigeria demonstrated a significant prevalence of indicators such as waist-hip ratio, body mass index, and blood pressure (Ulasi *et al*., 2011). A study conducted in the northern region of Nigeria reported a dysglycemia prevalence of 2.5% (Dahiru *et al*., 2008). Metabolic syndrome has been linked to an elevated risk of both cancer incidence and mortality (Esposito *et al*., 2012; Kim *et al*., 2019). Research investigating the correlation between Metabolic Syndrome (MetS) and cancer in Nigeria is limited. However, a report indicates that diabetes mellitus and hypertension often coexist as comorbidities with specific cancers such as breast, cervical, and prostate cancers in Nigeria (Salako *et al*., 2018). These findings imply a potential association between Metabolic Syndrome (MetS) and cancer.

Despite existing studies on Metabolic Syndrome (MetS) and cancer, there remains a lack of comprehensive information regarding their connection within the sub-Saharan African population. Therefore, the objective of this paper is to provide a systematic review of metabolic syndrome and common cancers in Nigeria spanning the period 1999 to 2022

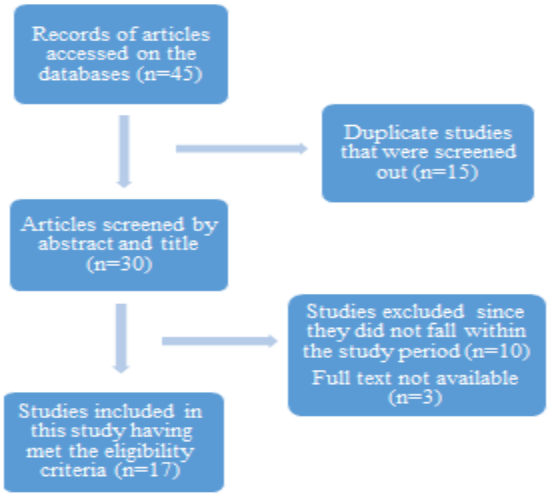

Fig 1: Study selection is shown on the above flow chart

MATERIALS AND METHODS

To investigate the association of metabolic syndrome with breast, prostate, liver, cervical, ovarian, and endometrial cancers in Nigerians, academic databases such as Google Scholar and PubMed were systematically searched from 1999 to 2022. Each component of metabolic syndrome was examined in relation to the aforementioned cancers, for instance, hypertension and its correlation with liver cancer, obesity and breast cancer, and so forth.

RESULTS AND DISCUSSION

A total of 45 articles were identified through searches on Google Scholar (30) and PubMed (15). Of these, 17 studies met the inclusion criteria outlined in Table 1. Among them, 16 were original research articles, while one was a review article. The association of Metabolic Syndrome (MetS) components with various cancers is summarized as follows: Prostate cancer (5 studies), Breast cancer (4 studies), Endometrial cancer (3 studies), Non-alcoholic fatty liver disease (NAFLD) and liver cancer (3 studies), and Ovarian cancer (2 studies). Obesity emerged as the most frequently cited component of MetS across different cancer types. Notably, only one study reported an association between MetS and the risk of breast cancer.

MetS and Breast Cancer: Breast cancer stands as the most prevalent form of cancer among women worldwide, and its incidence rate is on the rise in Africa (Siegel *et al*., 2016; Adeloye *et al*., 2018; Kashyap *et al*., 2022). Research has primarily concentrated on genetic, hormonal, reproductive, and environmental factors, identified as the primary risk elements for breast cancer. However, metabolic factors have not received sufficient attention in studies (Wiseman, 2008; Eden, 2013). At present, there is a scarcity of studies examining the role of Metabolic Syndrome (MetS) in breast carcinogenesis within Nigeria. However, among premenopausal Nigerian women with breast cancer, heightened waist circumference (WC) indicative of visceral obesity has been observed (Ajayi *et al*., 2016). This aligns with the findings of Ogundiran *et al*. (2012) that revealed increased waist circumference (WC) and waist-hip ratio (WHR) among both pre and postmenopausal women diagnosed with breast cancer. Another Nigerian study identified waist-hip ratio (WHR) as a notable predictor of breast cancer (Okobia *et al*., 2006). A notable positive correlation was found between waist-to-height ratio (WHtR), which serves as another indicator of visceral adiposity, and estradiol levels among postmenopausal women diagnosed with breast cancer (Ajayi *et al*.,

2016). Visceral obesity serves as an indicator of dysfunctional adipose tissue, which may lead to insulin resistance and inflammatory responses, potentially triggering carcinogenesis (Despres and Lemieux, 2006).

The role of hypertension in breast carcinogenesis remains subject to debate. However, a Nigerian study involving premenopausal women identified an association between systolic blood pressure and breast cancer. This correlation was attributed to minor visceral adiposity (Ajayi *et al*., 2017).

Table 1: Association of MetS Components with Cancers

S/N	Study Design	Number of Study Participants	Study outcome	Ref
1.	Case-control	169: 85 cases and 84 controls	Increased waist circumference was observed in premenopausal Nigerian women with breast cancer	Ajayi *et al*., (2016)
2.	Longitudinal , case-control	1233 cases and 1101 controls	Elevated waist circumference and waist hip ratio in Nigerian women with breast cancer	Ogundiran *et al*., (2012)
3.	Case-Control	500: 250 cases and 250 controls	Waist: hip ratio predicted breast cancer	Okobia *et al*.,(2006)
4.	Case-control	169: 85 cases and 84 controls	Elevated systolic blood pressure in Nigerian premenopausal women with breast cancer	Ajayi *et al*., (2017)
5.	Case-control	100: 50 cases and 50 controls	Height, weight and waist circumference were associated with the risk of prostate cancer	Agalliu *et al*., (2015)
6.	Case-control	80: 40 cases and 40 controls	Hypertriglyceridaemia increased the risk of prostate cancer	Adedapo *et al*., (2012)
7.	Cases control	100: 50 cases and 50 controls	Elevated serum TG, LDL increased the risk of prostate cancer	Obunwo *et al*., (2016)
8.	Case-control	50: 25 cases and 25 controls	elevated WC, WHR and BMI predicted prostate cancer in a Nigerian study	Arayombo *et al*.,(2019)
9.	Retrospective study	81	Hypertension and T2DM were co-morbidities reported in men with prostate cancer in a Nigerian study.	Oforha and Magnus (2019)
10.	Case-control	336: 168 cases and 168 controls	Association of NAFLD with central obesity and dyslipidaemia	Olusanya *et al*., (2016)
11.	Cross-sectional	80 T2DM Patients	NAFLD increases with increasing BMI and glycated haemoglobin (A1c) in individuals with T2DM	Afolabi *et al*., (2018)
12.	Longitudinal	100 cases of HCC	Hypercholesterolaemia is an important paraneoplastic syndromes of hepatocellular carcinoma in Nigerian patients.	Ndububa *et al*., (1999)
13.	Incidence data from the databases of two population-based cancer registries (PBCRs) in Nigeria (Abuja and Enugu cancer registries)	4336 newly diagnosed cancer cases	Obesity increases ovarian and endometrial cancers' risk	Odutola *et al*., (2012)
14.	Meta-analysis	12 studies comprising 1767 ovarian tumour cases and 229,167 non ovarian tumour cases	Decreased TC and HDL profiles were observed among subjects with Ovarian Tumour in this collection of reports.	Onwuka *et al* (2020)
15.	Retrospective cross-sectional	50	Overweight and obesity increase endometrial cancer	Adekanbi *et al*. (2016)
16.	Retrospective study	5722 Gynaecological cancers	Overweight/Obesity accounted for over 90% of endometrial cancer risk factor	Okunowo *et al*., (2019)
17.	Case-Control	555; 296 cases and 259 controls	MetS was significantly associated with Breast cancer risk	Akinyemiju *et al* (2022)

MetS and Prostate Cancer: Prostate cancer ranks as the second most frequently diagnosed cancer and the sixth leading cause of cancer-related mortality among males (Dabir *et al*., 2012). Prostate cancer exhibits the highest incidence and mortality rates among men of African descent when compared to Asians. In Nigeria specifically, prostate cancer represents the predominant form of male cancer, comprising approximately 11% of all male cancer cases (Delongchamps *et al*., 2006; Ogunbiyi and Shittu OB, 1999; Agalliu *et al*., 2015). While age, family history, and race are recognized as non-modifiable risk factors for prostate cancer, there is speculation regarding the involvement of modifiable factors such as physical activity and diet in its pathogenesis (Xiang *et al*., 2013). Research examining the

relationship between Metabolic Syndrome (MetS) and prostate cancer has yielded conflicting results. However, a Nigerian study found associations between anthropometric indices such as height, weight, and waist circumference (WC) and the risk of prostate cancer (Agalliu *et al*., 2015). In a Nigerian study, it was observed that serum triglyceride levels were notably elevated in prostate cancer patients in comparison to individuals with benign prostate hyperplasia. Additionally, the study suggested that hypertriglyceridemia might contribute to an increased risk of prostate cancer (Adedapo *et al*., 2012). Increased levels of serum triglycerides, low-density lipoprotein (LDL), total cholesterol, and prostate-specific antigen (PSA) are associated with an elevated risk of prostate cancer (Obunwo and Andy-Nwokocha, 2016). Moreover, heightened waist circumference (WC), waist-hip ratio (WHR), and body mass index (BMI) were identified as predictors of prostate cancer in a Nigerian study (Arayombo *et al*., 2019). The notable decrease in anthropometric indices observed among participants with prostate cancer, in contrast to controls, was attributed to cachexia, a condition often associated with the advanced stage of the disease (Agalliu *et al*., 2015).

Hypertension and Type 2 Diabetes Mellitus (T2DM) were identified as co-morbidities among men diagnosed with prostate cancer in a study conducted in Nigeria. (Ofoha and Magnus, 2019). Individuals with Metabolic Syndrome (MetS) and Type 2 Diabetes Mellitus (T2DM) were found to exhibit low testosterone levels, according to reports (Umoh *et al*., 2010; Agbecha and Usoro 2017). The observed low testosterone levels in individuals with Metabolic Syndrome (MetS) and Type 2 Diabetes Mellitus (T2DM) were attributed to impaired glucose uptake by the pituitary gland and gonads, stemming from insulin resistance (Umoh *et al*., 2010). An association was noted between low testosterone levels and Metabolic Syndrome (MetS) among study participants who had both hypertension and Type 2 Diabetes Mellitus (T2DM) (Akinloye *et al*., 2014). In a study involving apparently healthy individuals, waist circumference, which serves as an indicator of insulin resistance, was identified as a predictor of elevated prostate-specific antigen (PSA) levels, a marker indicative of prostate disorders (Muazu *et al*., 2018). Testosterone plays a crucial role in the pathogenesis of prostate cancer, thus prostate cancer management often relies on Androgen Deprivation Therapy (ADT) (Redig and Munshi, 2010). Cardiovascular risk factors like hyperlipidemia and obesity, including elevated body mass index (BMI) and waist circumference (WC), have been documented as potential consequences of Androgen Deprivation Therapy (ADT) in individuals undergoing treatment for prostate cancer (Essien *et al*., 2017).

MetS and Cervical Cancer: Cervical cancer ranks as the second most prevalent cancer among females, and its mortality rate is on the rise in developing nations (Ferlay *et al*., 2010). In Nigeria, approximately one woman succumbs to cervical cancer every hour, with an estimated 10,000 new cases diagnosed annually (Airede *et al*., 2008; Ferlay *et al*., 2010). Over three-quarters of cervical cancer patients are diagnosed at advanced stages, leading to a low survival rate (Toye *et al*., 2017). In certain studies conducted in Nigeria, reasons for patients presenting with advanced stages of cervical cancer at clinics include low awareness of the disease, despite relatively high literacy levels, limited access to early screening services, and the high cost of treatment (Idowu *et al*., 2016; Akinfenwa and Monsur, 2018).

Research indicates a disparity between the high literacy levels and the low awareness of cervical cancer among the population (Nnodu *et al*., 2010; Agida *et al*., 2015; Bisi-Onyemaechi *et al*., 2018). The risk of human papillomavirus (HPV) infection and subsequent cervical cancer is heightened by early age at first sexual exposure, engaging in multiple sexual partnerships, and smoking (Hendricks, 2003). HPV16 and 18 variants contribute to nearly 70% of cervical cancer cases (Orah and Banjo, 2018). While studies investigating the connection between Metabolic Syndrome (MetS) and cervical cancer are scarce in Nigeria, research conducted elsewhere has indicated an elevated risk of cervical cancer among women with hypertriglyceridemia Tulinius *et al*., 1997; Ulmer *et al*., 2012). A Chinese study reported a correlation between Metabolic Syndrome (MetS) and a heightened risk of cervical human papillomavirus (HPV) infection, particularly among obese women (Huang *et al*., 2016). The heightened risk of cervical cancer in women with Metabolic Syndrome (MetS) may be attributed to several factors, including an increased likelihood of human papillomavirus (HPV) incident infection, reduced probability of HPV clearance in infected individuals, and altered prognosis for those with persistent infection (Huang *et al*., 2016).

MetS and Liver Cancer: Liver cancer poses a significant global public health challenge and ranks as the sixth most common cancer worldwide (Akinyemiju *et al*., 2017; Okeke *et al*., 2020). Liver cancer is the second leading cause of cancer-related deaths worldwide, accounting for approximately 810,000 deaths in 2015(Akinyemiju *et al*., 2017; Mak

et al., 2018). In 2012, liver cancer was responsible for around 37,353 deaths in sub-Saharan Africa. By 2030, the mortality rate is projected to rise to 64,525(Ferlay *et al*., 2015). Hepatocellular carcinoma (HCC) is the most prevalent type of liver cancer, constituting approximately 75% to 90% of all liver cancer cases (Center and Jemal, 2011). Hepatocellular carcinoma (HCC) ranks as the fifth most frequently diagnosed cancer among men (Nwokediuko *et al*., 2013). Non-alcoholic fatty liver disease (NAFLD), characterized by hepatic steatosis without excessive alcohol consumption, has been identified as the hepatic manifestation of Metabolic Syndrome (MetS). Additionally, NAFLD is recognized as a significant contributor to the development of hepatocellular carcinoma (HCC) (Takakura *et al*., 2019; Younes and Bugianesi, 2018). According to a Nigerian study, there exists an association between non-alcoholic fatty liver disease (NAFLD) and central obesity as well as dyslipidemia (Olusanya *et al*., 2016). Another study conducted in Nigeria found that the prevalence of non-alcoholic fatty liver disease (NAFLD) rises with increasing body mass index (BMI) and glycated haemoglobin (A1c) levels in individuals with Type 2 Diabetes Mellitus (T2DM). Furthermore, obesity and suboptimal glycemic control were identified as independent predictors of NAFLD (Afolabi *et al*., 2018). The correlation between non-alcoholic fatty liver disease (NAFLD) and Type 2 Diabetes Mellitus (T2DM) can be elucidated by the presence of insulin resistance and hyperinsulinemia, leading to impaired lipid metabolism and accumulation of triglycerides in the liver (Forlani *et al*., 2016). Individuals diagnosed with non-alcoholic fatty liver disease (NAFLD) exhibited a higher prevalence of Metabolic Syndrome (MetS) (Onyekwere *et al*., 2011). It has been reported that chronic hepatitis C infection stimulates insulin resistance, partially through the action of TNF-α. This mechanism may contribute to the development of liver cancer (Agbecha *et al*., 2017). Hypercholesterolemia was identified as a significant paraneoplastic syndrome associated with Hepatocellular Carcinoma (HCC) in Nigerian patients (Ndububa *et al*., 1999)

MetS and Ovarian Cancer: Ovarian cancer ranks as the sixth most common cancer overall and the second most common gynecological cancer in Nigeria (Okunowo and Adaramoye, 2018). Indeed, epithelial ovarian cancer is recognized as the most lethal gynaecological neoplasm (Okunade *et al*., 2020). The challenge of early diagnosis of ovarian cancer persists due to limited understanding of its early stages and the lack of appropriate screening methods. Consequently, patients often present late, which adversely affects prognosis and survival rates (Odutola *et al*., 2019; Zayyan *et al*.,2017; Iyoke *et al*., 2014; Bassey *et al*., 2016). Nigerian patients with ovarian cancer experienced a high recurrence rate, which was linked to insufficient cytoreduction during treatment (Okunade *et al*., 2020). In a study conducted in Nigeria, ovarian cancer ranked second among common cancers associated with obesity and overweight. Approximately 2.6% of 114 cases of ovarian cancer were attributed to overweight and obesity (Odutola *et al*., 2019). In obese women, the activation of ovarian carcinogenesis is believed to occur when leptin binds to its receptor (Odutola *et al*., 2019) Limited data are available regarding the association between ovarian cancer and Metabolic Syndrome (MetS).

MetS and Endometrial cancer: Endometrial cancer ranked as the second most common cancer attributed to overweight and obesity among Nigerian women. The predominant type of endometrial cancer associated with these conditions was type 2 (Odutola *et al*., 2019; Dawodu *et al*., 2019). Among the 44 reported cases of endometrial cancer recorded between 2012 and 2014 by two cancer registries in Nigeria, approximately25% were linked to overweight (Odutola *et al*., 2019). Factors that contribute to an increase in circulating estrogen levels elevate the risk of endometrial cancer. These factors encompass early onset of menstruation, late onset of menopause, prolonged usage of estrogen replacement therapy, and a family history of the disease. Obesity exacerbates this risk through mechanisms involving pro-inflammatory cytokines, dysregulation of insulin and insulin-like growth factor metabolism, and imbalances in estrogen and progesterone levels, leading to the proliferation of endometrial cells (Odutola *et al*., 2019). Hypertension is considered another etiological factor for endometrial cancer. However, in a study involving postmenopausal Nigerian women, no association was found between hypertension and endometrial thickness (Ayodele *et al*., 2006). A study conducted in South Africa revealed associations between endometrial cancer and factors such as overweight, hypertension, and diabetes (Ray *et al*., 2019).

Conclusion: Findings from this study highlight that while certain components of metabolic syndrome were noted in the cases of discussed cancers, the association between metabolic syndrome and breast cancer was the only one reported. This underscores a knowledge gap regarding the role of metabolic syndrome in carcinogenesis, especially among sub-Saharan Africans. Understanding the individual and synergistic mechanisms of metabolic syndrome

components in carcinogenesis is imperative for enhancing cancer prognosis, diagnosis, and management strategies

Declarations
Declaration of Conflict of Interest: The authors declare no conflict of interest

Data Availability Statement: Data are available upon request from the first author or corresponding author or any of the other authors

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