ASSESSMENT OF BLADDER TUMOUR ANTIGEN IN OVARIAN AND CERVICAL CANCER PATIENTS

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ABSTRACT

Background: Bladder cancer is a relatively rare type of cancer that begins in the cells of the bladder, while cervical and ovarian cancers are the most common malignancies of the female genital tract specifically the cervix and ovaries. Cervical and ovarian cancer continues to be a major public health problem affecting middle – aged women, particularly in resource limited countries.

Aim: The research aimed to assess the bladder tumor antigen (BTA) in ovarian and cervical cancer subjects.

Methodology: The BTA was estimated using ELISA method. The results were presented in tables and charts as mean ± SD. Statistical analysis was done using ANOVA and Student's t-test using Statistical Package for Social Sciences (SPSS) version 23. A p-value <0.05 was considered significant.

Results: The result of this study showed that BMI was significantly higher in treated and untreated ovarian and cervical cancer subjects compared with control ($p<0.05$). Furthermore, BTA was significant higher in treated and untreated cervical and ovarian cancer subjects compared with control ($p<0.05$) and significantly lower in treated ovarian and cervical cancer subjects compared to untreated ovarian and cervical cancer subjects respectively ($p<0.05$). In all age groups, BTA was significantly lower in treated ovarian and cervical cancer subjects compared with untreated ovarian and cervical cancer subjects respectively ($p<0.05$).

Conclusion: Cervical and ovarian cancers are risk factors of bladder cancer as BTA level was significant increase in ovarian and cervical subjects compared with healthy control subjects.

Due to its high sensitivity and specificity, BTA can be used in the detection of bladder cancer particularly in women with cervical and ovarian cancer.

Key words: Ovarian cancer, Cervical cancer, Bladder cancer, Bladder tumor antigen

INTRODUCTION

Ovarian cancer is a cancer formed in the ovary which results in abnormal cells that have the ability to invade or spread to other parts of the body (Lengyel, 2020). When this process begins, there may be no or only vague symptoms. Symptoms become more noticeable as the cancer progresses (Ebell *et al.,* 2016). These symptoms may include bloating, pelvic pain, abdominal swelling and loss of appetite among others. Common areas to which the cancer may spread include the lining of the abdomen, lymph nodes, lungs and liver (Yeung, 2015).

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The risk of ovarian cancer increases in women with more ovulation. This includes those who have never had children, those who begin ovulation at a younger age and those who reach menopause at an older age (Momenimovahed *et al.,* 2019). Other risk factors include hormone therapy after menopause, fertility medication and obesity. Factors that decrease risk include hormonal birth control, tubal ligation and breast feeding. About 10% of cases are related to inherited genetic risk; women with mutations in the genes *BRCA1* or *BRCA2* have about a 50% chance of developing the disease. Ovarian carcinoma is the most common type of ovarian cancer, comprising more than 95% of cases. Less common types of ovarian cancers include germ cell tumors and sex cord stromal tumors (Ali *et al.,* 2023).

Cervical cancer is a cancer arising from the cervix. It is due to the abnormal growth of cells that have the ability to invade or spread to other parts of the body (Sarenac and Mikov, 2019). Early on, typically no symptoms are seen. Later symptoms may include abnormal vaginal bleeding, pelvic pain or pain during sexual intercourse. While bleeding after sex may not be serious, it may also indicate the presence of cervical cancer. Worldwide, cervical cancer is both the fourth-most common type of cancer and the fourth-most common cause of death from cancer in women (Sung *et al.,* 2021). Cervical cancer typically develops from precancerous changes over 10 to 20 years. About 90% of cervical cancer cases are squamous cell carcinomas, about 9% are adenocarcinoma and a small number are other types. Diagnosis is typically by cervical screening followed by a biopsy (Zhang *et al.,* 2020).

Bladder cancer is one of the most common urologic malignancies. More than 25% of bladder cancer cases are still muscle-invasive at first diagnosis. Early diagnosis of bladder cancer remains a challenge because it has low sensitivity and specificity (Saginala *et al.,* 2020). In recent years, the use of diagnostic categories for extra genital cytology has increasingly been discussed as an approach to improve the quality of reports. Tumor maker is a biochemical indicator of the presence of tumor. Tumor markers are measurable biochemical tests that are associated with malignancy. These markers are either produced by tumor cells (tumor-derived) or by the body in response to tumor cell (tumor-associated) (Dobruch & Oszczudłowski, 2021).

Bladder Tumour Antigen (BTA) is a human complement factor–H related protein (hCFHrp) which is similar in structure and function to hCFH (Aibara *et al.*, 2021). The hCFH inhibits alternative complement pathway by interacting with complement factor C3 convertase and serving as cofactor for complement factor 1 (Lee and Kim, 2020). This inhibits the formation of membrane attack complex and prevents lysis of cells recognized by host as foreign. Production of hCFHrp by bladder cancer cells may allow the cancer cells to evade the host immunity (Muhammad *et al.*, 2019). The antigen is released into the urine in significant amount in patients with bladder carcinoma (Aibara *et al.*, 2021). Endogenous hCFHrp can leak in urine in patients with haematuria from other urologic diseases and benign urologic diseases (Chokchaichamnankit *et al.,* 2019). Despite significant advances in our understanding of the molecular pathology of bladder cancer, it remains a significant health problem. Furthermore, despite ongoing research on bladder tumor antigens in hospitals and research institutions, no work has been done on the assessment of bladder tumor antigen on ovarian and cervical cancer patients particularly in our study area. Hence, this study was designed to evaluate bladder tumor antigen in cervical and ovarian cancer patients in our study area.

MATERIALS AND METHODS

Study design

This research employed a cross-sectional study design using stratified random sampling technique. Stratification was done by age, family medical history and type of therapy.

Study area

The research was conducted in Ado-Ekiti and its immediate environs. Ado-Ekiti is the capital of Ekiti State, southwestern Nigeria. It lies in the Yoruba Hills, at the intersection of roads from Akure, Ilawe Ekiti, Ilesha, Ila Orangun, and Ikare, and is situated 92 miles (148 km) east of Ibadan.

Sample size

The minimum sample size (N) was calculated by single proportion formula based on 5.32% estimated prevalence of ovarian and cervical cancer. Allowance for error of 0.05 at 95% confidence interval (z). Sample size was calculated using the formular: $N = Z\ p(1-p) / w^2$ (Adeloye *et al*., 2017) N= Z^2 p (1-p) / w^2

Where Z= confidence level at 95, N= minimum sample size, w= allowance for error (0.05), P= estimated prevalence of cancer in Ekiti at 5.32%.

q=1-p=1-0.0532=0.947

N=1.96^2*0.0532*0.947/0.05^2= 77.4

Inclusion criteria

Female subjects aged 20 years and above diagnosed of the ovarian and cervical cancer not undergoing treatment and those that have been receiving treatment within the last eighteen months who gave their consent were included in this study.

Exclusion criteria

Females subject less than 20 years, those with no history of cervical and ovarian cancer, pregnant women, breast-feeding mothers and those who had undergo intervention surgery were excluded from the study.

Sample collection

From each subject, two millimeters (2ml) of venous blood was collected from the cubital fossa using 23G needle and syringe. The blood samples were centrifuged to obtain serum and samples were frozen at −20°C until analysis.

Ethical clearance

Ethical Clearance for this research was obtained from the Ethics and Health Research Committee, College of Medicine and Health Sciences, Afe Babalola University, Ado-Ekiti, Ekiti State. Informed consent was also obtained from each subject who participated in the study before sample collection.

Method of determination of parameters

Body mass Index (BMI) was estimated from the height and body weight measurements using the formula BMI = Weight (kg) / Height (m^2). Height and weight were obtained using a meter gauge and a bathroom scale respectively.

Bladder Tumour Antigen (BTA) was estimated using ELISA kit (Elabsciene Biotechnology Inc. USA) following manufacturer's instructions.

Statistical analysis

Results obtained were subjected to statistical analysis using with SPSS statistical software (version 23.0; IBM-SPSS). All parameters were expressed as mean ±SD. The analysis of variance (ANOVA) was the tool of choice in comparing means. Values were statistically significant at $p<0.05$. Results were presented in tables and charts.

RESULTS

Table 1 shows the mean values of Body Mass Index (BMI) and Bladder Tumour Antigen (BTA) in test subjects with ovarian cancer. The results obtained showed that BMI (kg/m^2) was significantly higher in treated and treatment naive ovarian cancer subjects compared with control ($p<0.05$). There was no significant difference in the BMI of treated ovarian cancer subjects compared with treatment naive ovarian cancer subjects ($p>0.05$). BTA was significantly higher in treated and treatment naive ovarian cancer subjects compared with control ($p<0.05$). Similarly, BTA was significantly lower in treated ovarian cancer subjects compared with treatment naive ovarian cancer subjects ($p<0.05$).

Table 2 shows the mean values of BMI and BTA in test subjects with cervical cancer. The results obtained showed that BMI (kg/m^2) was significantly higher in treated and treatment naive cervical cancer subjects compared with control ($p<0.05$).

There was no significant difference in the BMI of treated cervical cancer subjects compared with untreated cervical cancer subjects ($p>0.05$). BTA (pg/ml) was significant higher in treated and treatment naive cervical cancer subjects compared with control subjects ($p<0.05$). Similarly, BTA was significantly lower in treated cervical cancer subjects compared with treatment naive cervical cancer subjects ($p<0.05$).

Figure 1 shows the BTA levels in treated and treatment naive test subjects in relation to age. BTA level was significantly higher in test subjects aged below 50 years for treated and treatment naive ovarian cancer, below 50 years for treatment naive cervical cancer, above 50 years for treated ovarian cancer and above 50 years for treatment naive cervical cancer compared with control group ($p<0.05$). On the other hand, BTA was significantly lower in test subjects aged below 50 years treated cervical cancer and above 50 years treated cervical cancer in comparison to control group ($p<0.05$). In all age groups, BTA was significantly lower in treated ovarian and cervical cancer subjects compared with treatment naive ovarian and cervical cancer subjects respectively ($p<0.05$).

Figure 2 shows the BTA (pg/ml) level in ovarian cancer subjects with respect to type of treatment. BTA was significantly higher in ovarian cancer subjects not on treatment and ovarian cancer subjects on radiography compared to cancer subjects on chemotherapy ($p<0.05$).

Figure 3 shows the BTA (pg/ml) level in ovarian cancer subjects with respect to type of treatment. BTA was significantly higher in cervical cancer subjects not on treatment and cervical cancer subjects on chemotherapy compared to cervical cancer subjects on radiography ($p<0.05$).

Table 1: Mean values of BMI and BTA in test subjects with ovarian cancer

Variables	Treated Mean ± SD	Treatment naive Mean ± SD	Control Mean ± SD	p-value
BMI (kg/m^2)	26.89 ± 6.12^a	28.89 ± 6.12^a	23.68 ± 3.57^b	0.001
BTA (pg/ml)	49.18 ± 5.50^a	67.83 ± 5.61^b	10.24 ± 5.40^c	0.000

Keys: **BMI**: Body mass index, **BTA**: Bladder tumor antigen

Table 2: Mean values of BMI and BTA in test subjects with cervical cancer

Variables	Treated Mean ± SD	Treatment naive Mean ± SD	Control Mean ± SD	p-value
BMI (kg/m^2)	25.89 ± 6.12^a	27.64 ± 5.44^a	23.68 ± 3.57^b	0.001
BTA (pg/ml)	11.76 ± 7.99^a	40.00 ± 10.90^b	10.24 ± 5.40^c	0.000

Keys: **BMI**: Body mass index, **BTA**: Bladder tumor antigen

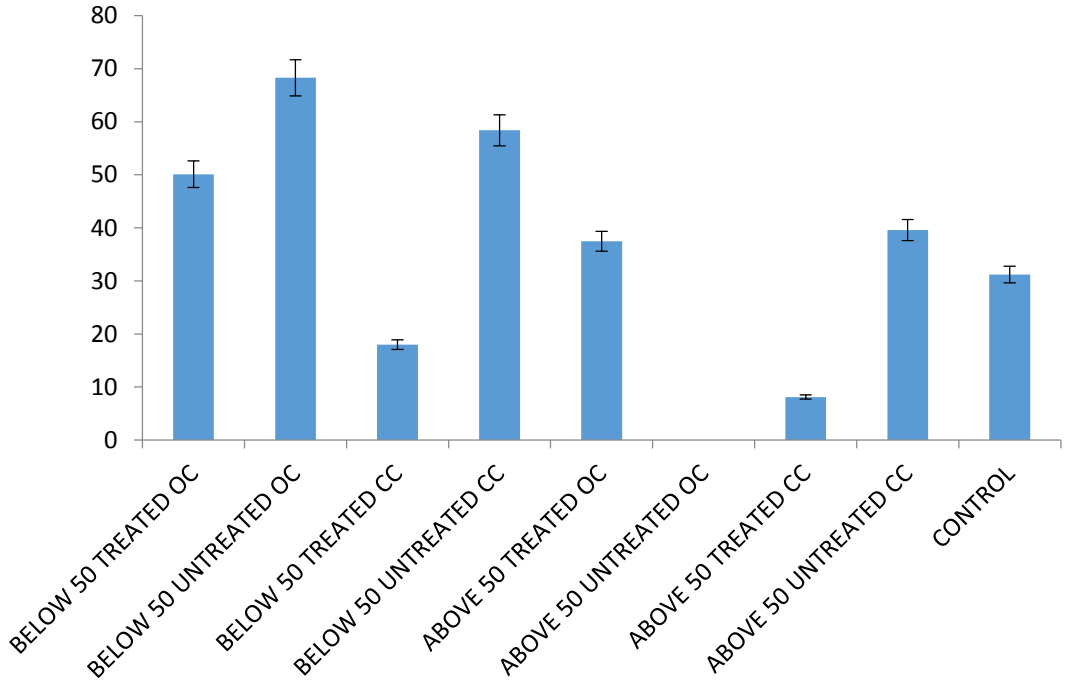

Figure 1: BTA levels in treated and untreated test subjects in relation to age

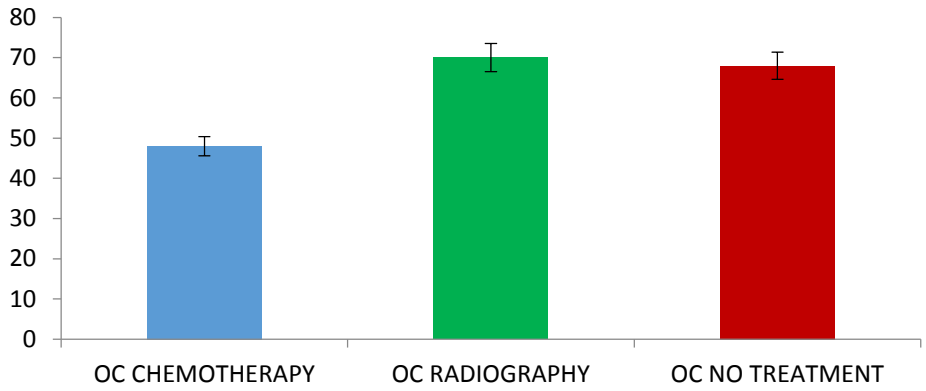

Fig 2: BTA level in ovarian cancer subjects with respect to type of treatment

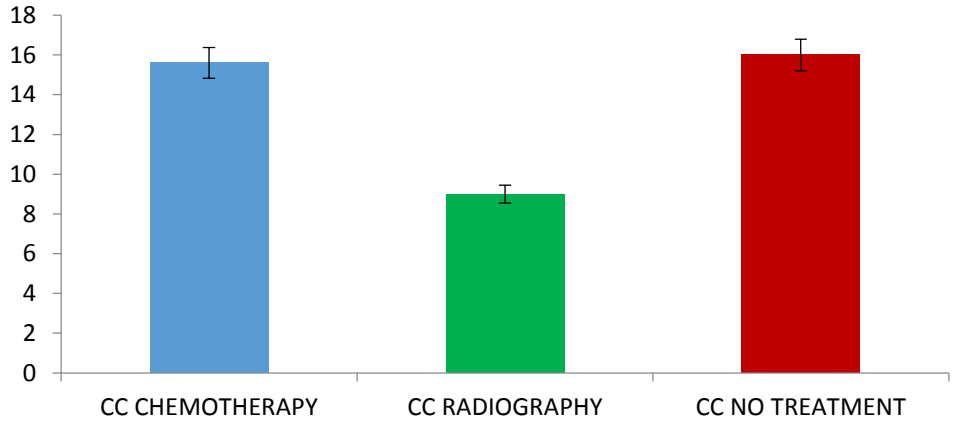

Fig 3: BTA level in cervical cancer subjects with respect to type of treatment
Key: CC – Cervical cancer

DISCUSSION

Cervical cancer continues to be a major public health problem affecting middle-aged women, particularly in resource limited countries. With almost 0.6 million cases and 0.3 million deaths per year, cervical cancer continues to constitute a major public health problem, ranking as the fourth most common cause of cancer incidence and mortality in women worldwide (Arbyn *et al.,* 2020). Ovarian cancer is the most lethal gynaecological malignancy, accounting for 4200 deaths each year (Momenimovahed *et al.,* 2019). Due to lack of specific symptoms and effective screening strategies, almost 60% of women present with advanced disease (stage III and IV) and the 5-year survival rate is less than 30%. In contrast, women presenting with stage I disease have a 5-year survival rate of >90% (Owens *et al.,* 2022). Bladder cancer is the invasion of the basement membrane or lamina propria or deeper by neoplastic cells of urothelial origin (Kaseb and Aeddula, 2022). As Bladder Tumor Antigen (BTA) has been linked to several cancers, this research was designed assess the serum level of BTA in ovarian and cervical cancer subjects.

The result of this study showed that BMI was significantly higher in treated and untreated ovarian and cervical cancer subjects compared with control. The growing cancer epidemic has been linked to the increasing overweight and obesity epidemic. It is well established that obesity is a risk factor for cancer among women (Samman *et al.,* 2022). The report of this study is in agreement with previous authors who reported significant increase in BMI among subjects with cervical, ovarian and breast cancers compared with control subjects (Kumar and Bhasker, 2020; Samman *et al.,* 2022; Loomans-Kropp and Umar, 2023). Increased mortality in obese women could be due to lack of screening with pap smears as one large meta-analysis showed that women with class III (BMI > 40kg/m^2) obesity are approximately 40% less likely to undergo cervical cancer screening, or it may simply be due to a detrimental impact of obesity on treatment outcomes (Jacek *et al.,* 2018). The potential biological mechanism responsible is yet to be fully elucidated and include theories involving increased levels of endogenous hormones and obesity-related chronic low-level inflammation (Motsa *et al.,* 2023).

In this study, BTA was significantly higher in treated and untreated cervical and ovarian cancer subjects compared with control and significantly lower in treated ovarian and cervical cancer subjects compared to untreated ovarian and cervical cancer subjects respectively. No previous study has assessed the detection of BTA in cervical and ovarian cancer subjects. However, in a previous study by Muhammad *et al.* (2019), the highest BTA concentrations were found in patients with adenocarcinoma and squamous-cell carcinoma, whereas the lowest concentrations were found in patients with transitional cell carcinoma. Muhammad et al. (2019) reported that the high level of BTA in their subjects might be due to the de novo invasive and aggressive nature of adenocarcinoma and squamous-cell carcinoma of the bladder. This could also be an explanation to the significantly higher BTA in treated and treatment naive cervical and ovarian cancer subjects reported in this study. The elevated level of BTA in patients with ovarian and cervical cancers could indication that these patients are at risk of developing bladder cancer. Furthermore, BTA was significantly higher in ovarian cancer subjects not on treatment and ovarian cancer subjects on radiography compared to ovarian cancer subjects on chemotherapy. On the other hand, BTA was significantly higher in cervical cancer subjects not on treatment and cervical cancer subjects on chemotherapy compared to cervical cancer subjects on radiography.

Cisplatin-based concurrent chemoradiotherapy remains the mainstay of cervical and ovarian cancer treatment of locally advanced disease and a curative option for early-stage palpable disease (Faye and Alfieri, 2022). Although global efforts at improving access to early detection strategies and human papiloma virus (HPV) vaccination are anticipated to lead to a long-term reduction in the incidence of cervical cancer, in the short term, this will not materialize early enough for present-day patients who present with advanced disease (Kofi *et al.,* 2020). Feasible strategies to improve diagnosis, prognosis and treatment delivery are therefore needed.

CONCLUSION

Cervical and ovarian cancers are risk factors of bladder cancer as BTA level was significantly increased in ovarian and cervical subjects compared with apparently healthy control subjects. The elevated level of BTA in ovarian and cervical cancer subjects could be an indication that these patients are at risk of developing bladder cancer.

RECOMMENDATIONS

Considering the heavy burden of ovarian and cervical cancer on women's health, preventive measures as well as health education and early detection of bladder cancer in high risk women is highly recommended.

Conflict of Interest. None declared

REFRENCES

Aibara, N., Miyata, Y., Araki, K., Sagara, Y., Mitsunari, K., Matsuo, T., Ohba, K., Mochizuki, Y., Sakai, H. and Ohyama, K. (2021). Detection of Novel Urine Markers Using Immune Complexome Analysis in Bladder Cancer Patients: A Preliminary Study. *In Vivo*, **35(4)**: 2073-2080.

Ali, A.T., Al-Ani, O. and Al-Ani, F. (2023). Epidemiology and risk factors for ovarian cancer. *Menopause Review*, **22(2):** 93-104.

Arbyn, M., Weiderpass, E., Bruni, L., de Sanjosé, S., Saraiya, M., Ferlay, J. and Bray, F. (2019). Estimates of incidence and mortality of cervical cancer in 2018: a worldwide analysis. *Lancet Global Health*, **8(2)**: 191-203.

Chokchaichamnankit, D., Watcharatanyatip, K., Subhasitanont, P., Weeraphan, C., Keeratichamroen, S., Sritana, N., Kantathavorn, N., Diskul-Na-Ayudthaya, P., Saharat, K., Chantaraamporn, J., Verathamjamras, C., Phoolcharoen, N., Wiriyaukaradecha, K., Paricharttanakul, N.M., Udomchaiprasertkul, W., Sricharunrat, T., Auewarakul, C., Svasti, J. and Srisomsap, C. (2019). Urinary biomarkers for the diagnosis of cervical cancer by quantitative label-free mass spectrometry analysis. *Oncolology Letter*, **17(6)**: 5453-5468.

Dobruch, J. and Oszczudłowski, M. (2021). Bladder Cancer: Current Challenges and Future Directions. *Medicinal,* 2021; **57(8)**: 749-752.

Ebell, M.H., Culp, M.B. and Radke, T.J. (2016). A systematic review of symptoms for the diagnosis of ovarian cancer. *American journal of preventive medicine*, **50(3)**: 384-394.

Faye, M.D. and Alfieri, J. (2022). Advances in Radiation Oncology for the Treatment of Cervical Cancer. *Current Oncolology*, **29(2)**: 928-944.

Jacek, P.G., Rolf, R., Hannah, R., Radoslav, C., Woopen, H. and Jalid, S. (2018). Impact of Body Mass Index (BMI) on Chemotherapy-associated Toxicity in Ovarian Cancer Patients. A Pooled Analysis of the North-Eastern German Society of Gynecological Oncology (NOGGO) Databank on 1,213 Patients. *Anticancer Research*, **38(4)**: 5853-5858

Kaseb, H. and Aeddula, N.R. (2022). Bladder Cancer. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing, Pp. 63-69.

Kofi, A.K., Frederick, Y., Andrew, D., Kitson-Mills, D., Samuel, Y.O., Joel, Y., Samuel, N.T., Michael, K.A., Kwabena, K.A., Eric, A. and Kofi, A. (2020). Quality of life among cervical cancer patients undergoing radiotherapy. *Pan African Medical Journal*, **35(6):** 125-127.

Kumar, R.V. and Bhasker, S. (2020). Obesity in patients with carcinoma cervix increases the risk of adverse events. *Report of Practical Oncology & Radiotherapy*, **25(2)**: 212-216.

Lee, H.H. and Kim, S.H. (2020). Review of non-invasive urinary biomarkers in bladder cancer. *Translational Cancer Research*, **9(10)**: 6554-6564.

Lengyel, E. (2010). Ovarian cancer development and metastasis. *American Journal of Pathology*, **177(3)**: 1053-1064.

Loomans-Kropp, H.A. and Umar, A. (2023). Analysis of Body Mass Index in Early and Middle Adulthood and Estimated Risk of Gastrointestinal Cancer. *Journal of American Medical Association,* **6(5)**: 231-232.

Momenimovahed, Z., Tiznobaik, A., Taheri, S. and Salehiniya, H. (2019). Ovarian cancer in the world: epidemiology and risk factors. *International Journal of Women's Health*, **11(2)**: 287-299.

Motsa, M.P.S., Estinfort, W. and Phiri, Y.V.A. (2023). Body mass index and cervical cancer screening among women aged 15–69 years in Eswatini: evidence from a population-based survey. *British Medical Council of Public Health*, **23(16)**: 142-148.

Muhammad, A.S., Mungadi, I.A., Darlington, N.N. and Kalayi, G.D. (2019). Effectiveness of bladder tumor antigen quantitative test in the diagnosis of bladder carcinoma in a schistosoma endemic area. *Urolology Annals*, **11(2):** 143-148.

Owens, G.L., Barr, C.E., White, H., Njoku, K. and Crosbie, E.J. (2022). Urinary biomarkers for the detection of ovarian cancer: a systematic review. *Carcinogenesis*, **43(4)**: 311-320.

Saginala, K., Barsouk, A., Aluru, J.S., Rawla, P., Padala, S.A. and Barsouk, A. (2020). Epidemiology of Bladder Cancer. *Medical Sciences*, **8(1)**: 15-19.

Samman, E., Mkuu, R., Zhang, X., Scummings, S. & Burdine, J. (2022). Body Mass Index and Breast and Cervical Cancer Screening. *Women's Health Report*, **3(1):** 508-514.

Sarenac, T. and Mikov, M. (2019). Cervical Cancer, Different Treatments and Importance of Bile Acids as Therapeutic Agents in This Disease. *Frontiers in Pharmacology*, **10(1)**: 484-488.

Sung, H., Ferlay, J., Siegel, R.L., Laversanne, M., Soerjomataram, I., Jemal, A. and Bray, F. (2020). Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA: A Cancer Journal for Clinicians*. **71(3)**: 209–249.

Yeung, T.L., Leung, C.S., Yip, K.P., Yeung, C.L., Wong, S.T. and Mok, S.C. (2015). Cellular and molecular processes in ovarian cancer metastasis. A Review in the Theme: Cell and Molecular Processes in Cancer Metastasis. *American Journal of Physiology & Cell Physiology*, **309(7):** 444-456.

Zhang, S., Xu, H., Zhang, L. and Qiao, Y. (2020). Cervical cancer: Epidemiology, risk factors and screening. *Chinese Journal of Cancer Research*, **32(6)**: 720-728.