



Breast, Ovarian, and Uterine Cancer: Etiology, Pathophysiology, and Management- A Review

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Abstract: The leading cause of morbidity and mortality rate in today's world is cancer. It ranks second in the top 10 list of mortality worldwide. The reproductive system malignancy is one of the main causes of increased mortality that reiterates and threaten women's health and life. breast, ovarian, and uterine cancer has a higher frequency of cases than other gynecological malignancy types. The current review focuses on the epidemiology, etiology and the risk factors associated with the breast, ovarian, and uterine cancer, highlighting the importance of age, gender, time, race, survival rate, mortality rate, and family background. Breast cancer ranks as the first most noxious cancer worldwide and is increasing rapidly in developing countries. Cases reported were most common in women and less in men. The fact is men and women ratio for breast cancer is 135:1 for white and 51:1 for black. Ovarian cancer ranks seventh as the most noxious gynecological malignancy worldwide. Endometrial cancer or uterine cancer ranks sixth as the most widely recognized kind of malignant growth in ladies worldwide. The age factor plays an important role in these cancers. Women aged 45 or above, have a higher chance of acquiring the disease. The public health workers and cancer specialists play an important role in spreading awareness and educating people about the disease and overcoming the disease.

Keywords: Breast , ovarian and uterine cancer, epidemiology, histology, risk factors

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I. INTRODUCTION

Cancer cells arise due to the abnormal division of cells, and the occurrence of breast cancer is due to the uncontrolled growth of cells in any part of the breast, especially in the lobules. There are no distinct signs or symptoms of breast cancer. The only sign is the presence of a lump within the breast. Since there are no distinct signs and symptoms, all women should undergo a screening test to inspect any abnormal growth of the tissue¹. The most popular type of cancer observed among women worldwide was breast cancer, making it a major public health issue. Every year, there is about one lakh cases that surfaces, with almost forty thousand deaths, making this disease one of the most fatal diseases worldwide². Conferring to the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute, the total number of cancer cases in the United States is 14% related to breast cancer in women, and 124.8 breast cancer cases per hundred thousand women reported every year³. During the years 2010-2012, the possibility of acquiring breast cancer was 12.3%. However, the number of cases increased with time and reached to 249,260 breast cancer cases by 2016⁴. The rate of breast cancer in developing countries is much lesser than in developed countries because of late marriages and living style practices in the developed countries⁵. Due to the unavailability of proper resources for patient screening and partially filled reports in underdeveloped countries, the exact number of individuals who have breast cancer remains hidden. Hence there is a slight misinterpretation of the statistical data⁶. Depending upon the stages of breast cancer, as well as the molecular subtypes and histology, the possible treatments involve chemotherapy, surgery, hormone, and radiation therapy. The rate of survival depends on the stages the patients are diagnosed. Early stages of diagnosis have a better chance to survive compared to late stages⁷. The fifth leading cause of death in U.S women is ovarian cancer, and it has a very exiguous survival rate³. The other name given to ovarian cancer is "Silent Killer" as there is delayed incipiency of symptoms, and the growth of the tumor is furtive and hence exhibits no signs during its growth⁸. It has been reported that ovarian cancer patients have a higher risk of anxiety, depression, social dynamic, worries, disturbed sleep and loneliness⁹. However, the only treatment available for the survival of ovarian cancer patients is chemotherapy. Early detection of cancer leads to the maximum survival rate while detection during late stages results in very poor survival chances¹⁰. Uterine cancer, also known as endometrial cancer, originates from the uterus' lining called the endometrium¹¹. The endometrium is a tissue that adapts and keeps varying in its composition due to its interaction with various hormones and demands the necessity of certain molecular and cellular phenomena. Any disturbances in the endometrium regulation can lead to severe complications in women, including infertility, abnormalities in the placenta, miscarriages, and poor implantation¹². In the year 2011, in the U.S, a total of forty-six thousand cases of uterine cancer were recorded and eight thousand deaths⁴. Several risk factors are related to uterine cancer, such as late menopause, early menarche, nulliparity, obesity, and estrogen level changes¹³. Estradiol, androstenedione, and estrone are endogenous hormones that has the maximum effect on increasing the risk for uterine cancer¹⁴. Unimpeded effect of estrogen or continuous exposure of estrogen throughout the life of a woman can lead to high chances of the proliferation of cells in the endometrium, and responsible for error during DNA

replication as well as somatic mutations. Another factor that seems to increase uterine cancer risk is exposure to exogenous estrogen, which includes replacement therapy without progestins¹⁵. This review explains an overview of the risk factors that are associated with each of the cancer cases and the kind of treatment that is recommended based on the cancer type. This review explains the etiology, pathophysiology, management and case report status of the breast, ovarian, and uterine cancers worldwide.

2. BREAST CANCER

Breast cancer is a type of cancer that consists of rapidly proliferating cells with identified biological subtypes. These subtypes are classified into three categories, namely human epidermal growth factor 2 (ERBB2) positive, ERBB2 negative/hormone receptor-positive and triple-negative as well as based on the absence or presence of molecular markers for hormone receptors such as progesterone or estrogen and human epidermal growth factor 2 (ERBB2). The triple-negative breast cancer subtype imposes a larger threat as it can recur post-treatment. However, reports showed that 90% of cancers diagnosed are non – metastatic. Studies showed that 15-20% of the patients were diagnosed with ERBB2 positive subtype, 70% were diagnosed with ERBB2 negative subtype, and 15% were diagnosed with the breast's triple-negative subtype cancer¹⁶. The genes responsible for breast cancer in both women and men are the BRCA 1 and BRCA 2 genes. These genes control the biological activities during DNA replication and repair, thereby increasing the danger of breast cancer. BRCA 1 gene was shown to be responsible for 65% of the women population diagnosed with breast cancer, whereas, BRCA 2 gene was responsible for 45% of the women population to be diagnosed with breast cancer^{17,18}. Observations made from reports from different online databases shows the number of newly diagnosed cases for invasive breast cancer was 268, 600, and ductal carcinoma in situ (DCIS) was 49,000¹⁹.

2.1 RELAPSE OF BREAST CANCER

The relapse of cancer is due to the left-over tumor cells that remain in the host after the initial therapy has been administered to the patient²⁰. Studies on a global scale showed that women who get pregnant at the age of 30 or above possess an increased risk of breast cancer compared to women having kids at an early age of 20-25²¹. The danger of breast cancer increases with age, especially during the premenopausal and postmenopausal stages in life²². Other factors, such as vitamin D deficiency also increases the risk of breast cancer²³. Large populations of women diagnosed with breast cancer were obese women²⁴. The malignancy rate increases if there is a presence of pre-existing tumor cells in and around the breast region. If there is an ancestral background of breast cancer, women within that family have an increased risk of acquiring breast cancer as they are carriers of the genes BRCA 1 and BRCA 2 that give rise to breast cancer²⁵. During the years 2003 and 2011, the frequency of breast cancer increased from 21 to 29 per 100,000 women in China while Australia and the United States remained about 122 and 115 per 100,000 women, respectively (figure 1)^{26,27}. The main cause of the increase in women's mortality rate due to breast cancer is the recurrence of the tumor²⁸. Three main factors influence the tumor recurrence during the tumor surgery: use of volatile anesthetics, surgical stress response, and opioids for

analgesia. These factors hamper the host–defense mechanism resulting in tumor recurrence. Epidemiological studies show that obesity is one of the factors that increase the risk of tumor recurrence²⁹. An assessment was done on young (20–45 years). Older women (>50 years) showed high chances of tumor recurrence because of inadequate treatment in their early stages, when they first began to show signs of tumor

formation. Another factor that resulted in tumor recurrence was the low intensity of the treatment being administered to patients that had low tolerance due to other health conditions, thereby reducing their chance of survival when compared to young women without any additional health conditions³⁰.

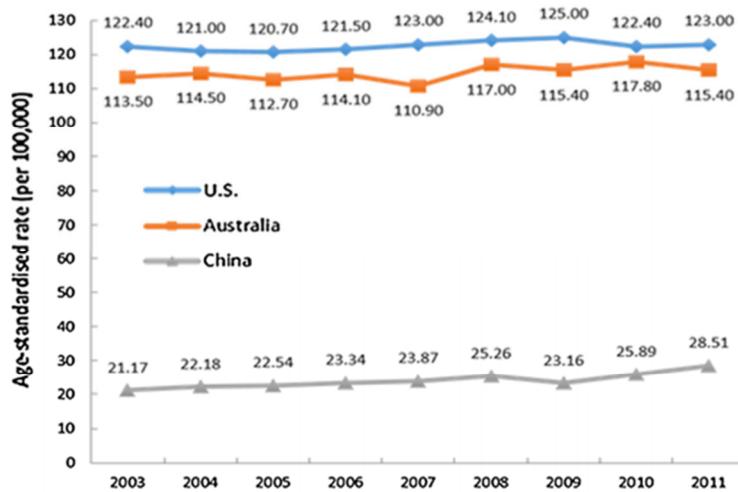


Fig1. The frequency rate of female breast malignant growth in China, Australia, and the United States from 2003 to 2011 [x-axis: year; y-axis: age-standardized rate (per 100,000)]²⁷.

2.2 HISTOLOGY

There are about 21 different histological subtypes of breast cancer, such as ductal carcinoma, lobular carcinoma, mucinous carcinoma, tubular carcinoma, encapsulated papillary carcinoma, etc³¹. Ductal carcinoma is the most common type of carcinoma diagnosed among most women.

A total of 610,350 patients were examined and reported with various histological subtypes of invasive breast cancer between 2006–2016³². A maximum number of patients were diagnosed with ductal carcinoma accounting for almost 82.6 % of the total cohort, and lobular carcinoma, accounting for 78.2%. Other types were also frequent but less as compared to that of ductal and lobular type of carcinoma (Table I)³³.

Table I. Distribution of histological subtypes of breast cancer in women.³³

	Total	Mean RS (Sd)	Node Negative
Overall	610,350	18 (10.8)	493,924 (80.9)
Ductal carcinoma, NOS	504,362	18.4 (11.2)	401,761 (79.7)
Lobular carcinoma, classic type	49,819	16.3 (6.9)	38,783 (77.9)
Lobular carcinoma, other variants	5069	18.2 (9.4)	3980 (78.5)
Invasive carcinoma	25,329	16.4 (8.5)	19,407 (76.6)
Mucinous carcinoma	16,116	14.9 (8.9)	13,902 (86.3)
Papillary carcinoma	4159	11 (13.5)	3422 (82.3)
Tubular carcinoma	3599	14.5 (5.7)	3175 (88.2)
Cribiform carcinoma	1897	12.6 (9.6)	1583 (83.5)

*RS= recurrence score. n=610,350; p<0.0001

2.3 MORTALITY AND SURVIVAL

Breast cancer is a malignant disease and the second dangerous type of cancer in the world. It has about one lakh new cases according to the GLOBOCAN statistics 2018. The diagnosis of the entire female population across the globe has been reported to be 43.3/100,000, while the mortality rate was around 13.0/100,000³⁴. In developed countries, the mortality rates are much higher than that of developing countries because of changes in living style. Breast cancer

was beginning to catch up with a new trend, where women below the age of forty were diagnosed with breast cancer³⁵. Group for Cancer Epidemiology and Registration in Latin Language Countries (GRELL) has reported a growth in the breast cancer rate by 1.2% in the European countries. In 2018 the mortality rate reached up-to 2,883³⁶. Early diagnosis and better treatment increase patients' survival and decrease the mortality rate for breast cancer in high and low-class countries³⁷. In 2010, a total of 4,989 breast cancer patients including 4,885 females and 104 males between the age group

of 19- 78 years were reported from Thailand. Maximum cases were diagnosed with ductal carcinoma, accompanied with lobular carcinoma. The breast cancer's specific rate of

the ten-year crude mortality rate was 3.3 (per 100,000), and the survival rate was with a mean of 57.4 and with a median of 47.5. ³⁸ (Table 2)

Table 2. The survival rate of patients diagnosed with breast cancer³⁸.

Characteristics	Total cases (n= 4,989)	Cases with follow-up (n=1,335)
Age	Mean (SD) 50.4 (SD= 12.9)	50.6 (SD= 12.6)
	Range 21-98	23-93
	<50 years of age 2299 (46.1%)	658 (49.3%)
	≥50 years of age 2689 (53.9%)	677 (50.7%)
Sex	Male 104 (2.1%) Female 4885 (53.9%)	26 (1.9%) 1309 (98.1%)
Morphology	Ductal carcinoma 3096 (62.1%)	1036 (77.6%)
	Lobular carcinoma 585 (11.7%)	81 (6.1%)
	Others NOS 684 (13.7%)	73 (5.5%)
	624 (12.5%)	145 (10.9%)
Grade	I 736 (14.6%)	232 (17.4%)
	II 1348 (27.0%)	511 (38.3%)
	III 248 (4.9%)	86 (6.4%)
	Unknown 2657 (53.3%)	506 (37.9%)

Patients age: n= 2 (<50 and >50 years); p=0.07; Sex: n= 1 (male/female); p=0.32; Morphology: n= 5 (tumor morphology); p=0.02; Grade: n= 4 (tumor grade); p<0.0001

2.4 RISK FACTORS

AGE: The major component that has a massive impact on breast cancer is age³⁹. As the age increases, the occurrence i.e., the incidence rate of breast cancer also increases and reaches a maximum at the menopause stage⁴⁰. Although a large population of older women was diagnosed with breast cancer, they have a slightly higher chance of survival than younger women because younger women diagnosed with breast cancer have an enlarged size of the tumor, thereby resulting in death at a very early age⁴¹.

ETHNICITY: An epidemiological study conducted by Carol E. DeSantis et al. 2019, showed that 56-60% of Hispanic, American Indian/Alaskan Native (AIAN), and non – Hispanic black (black) patients were diagnosed with local stage breast cancer when compared to 64-66% of Asian/ Pacific Islanders (API) and non – Hispanic white (white) patients. 8% of black patients were diagnosed with metastatic breast cancer when compared to 5-6% of patients diagnosed from different races/ethnicities. Black women were the only group of women with high-grade tumors that were 12-42% (>5.0 cm) rather than the low-grade or intermediate-grade tumors⁴².

EARLY MENARCHE AND MENOPAUSE: women starting their menstrual cycle at a very young age had twice the risk of breast cancer. Women who ended their menstrual cycle at a significantly older age (< 50 years) showed an increase in the risk of breast cancer³⁹. An experiment conducted in China, taking a large population of 11,899 women, showed that early menarche increases the risk of breast cancer⁴³. On the contrary, a study done in Italy showed no relationship between the duration of the menstrual cycle and breast cancer⁴⁴.

3. OVARIAN CANCER

Malignancy is the most widely recognized reason for mortality globally and right now is the most well-known obstacle to accomplishing an alluring future in many nations⁴⁵. The ovarian disease is a well-known gynecologic malignancy that ranks third after the cervical and uterine disease⁴⁶. Albeit ovarian disease has a lower pervasiveness in correlation with breast malignant growth, but it is multiple times more deadly¹⁰. It is anticipated that by 2040 the death rate of this disease will rise exponentially⁴⁷. The rate of ovarian disease is increasing globally alongside other malignant diseases. The epidemiological survey on various types of ovarian cancer in different areas can be related to the risk factors that show ovarian cancer⁴⁸. Because of contrasts in diagnosis and therapeutics, the mortality rate of malignant ovarian growth shows a unique design, and the most noteworthy death rates are found in the African population⁴⁹.

3.1 RELAPSE OF OVARIAN CANCER

Epithelial ovarian cancer is a frequent kind of ovarian cancer. Since there are no prominent signs or symptoms, 70% of the cancer diagnosis is done at a late stage⁵⁰. The most common subtype of epithelial ovarian cancer is serous ovarian cancer. Patients who have undergone surgery and platinum-based chemotherapy (a type of chemotherapy to treat ovarian cancer), may suffer from a relapse of the tumor cells within or after six months of their treatment. The serous tumor's recurrence is not detectable at an early stage due to the lack of proper molecular biomarkers⁵¹. To prevent tumor recurrence, platinum-based, and taxane-based adjuvant chemotherapy can be administered after the surgery, thereby reducing the chance of tumor recurrence. Only 75% of the patients showed a positive response, while the rest 25% of the patients showed a relapse of the tumor⁵².

3.2 HISTOLOGY

95% of ovarian malignancies are due to epithelial ovarian cancer (EOC), while 5% of ovarian cancers are due to the non-epithelial type of ovarian cells, including small cell carcinoma, ovarian sarcoma, germ cell, and the sex-cord stromal cancers⁵³.

EOC is classified into five subtypes:

- i. High-grade serous ovarian cancer (HGSOC): it is the most commonly occurring cancer subtype that accounts for 70% of the women population diagnosed with EOC⁵⁴. Although the maximum number of HGSOC is sporadic, 15-20% of the women populations diagnosed with EOC carry a hereditary predisposition of the disease⁵⁵.
- ii. Low-grade serous ovarian cancer (LGSOC): only 10% of the women population are diagnosed with LGSOC⁵⁶.
- iii. Ovarian clear cell carcinoma (OCCC): 25% of the women in Japan have been diagnosed with OCCC, whereas in Europe and North America, only 5 were diagnosed⁵⁷.
- iv. Endometrioid cancer: endometrioid cancer accounts for 10% of EOC. Lynch syndrome, also known as hereditary non-polyposis colorectal cancer, is the leading cause of hereditary colorectal cancer. Women possessing Lynch syndrome show an increased risk of acquiring endometrioid and clear cell ovarian cancer⁵⁸.
- v. Mucinous ovarian cancer is a very rare form of EOC subtype and accounts for 2.4% of ovarian cancer. Some of these cells may arise from tumors that are present on the border line⁵⁹.

3.3 MORTALITY AND SURVIVAL

Ovarian cancer ranks in eighth place due to its high mortality rate in women across the world⁶⁰. Among all EOC patient groups, despite the stages, African American women have a very little survival rate⁶¹. The rate at which ovarian cancer occurs over a period depends on the countries and ethnicities of individuals. In a study conducted in the year 2012, North Europe and the United States were recorded to hold the highest incidence rate, while Japan was reported to have the lowest incidence rate for ovarian cancer⁶². Considering the ethnicity of the groups, the highest frequency of ovarian cancer was seen in Caucasian women (12 per 100,000), followed by Hispanic (10.3 per 100,000), African American (0.4 per 100,000), and Asian women (9.2 per 100,000). However, the death rate in the African community appears to be the highest⁶¹.

3.4 RISK FACTORS

AGE: The epithelial ovarian cancer (EOC) is related to age and occurs mostly in the postmenopausal stage⁵⁰. Women above the age of 65 are more prone to EOC, and due to old age, the chance of survival is meager due to other health complications. Hence, older women cannot get accurate treatment due to a decrease in their tolerance levels to the treatment, thereby resulting in death⁶³.

NUTRITION: A case-control study conducted reported an increase in the EOC with an increased intake of cholesterol. Alternatively, this risk can be controlled by consuming vegetables, B-complex tablets, and vitamin supplements⁶⁴. The consumption of a plant-based diet⁶⁵ can control cancers due to hormones. Ingestion of high concentration of fatty acids increases EOC's risk whereas intake of high

concentrations of calcium, vitamin D and lactose decreases the risk of EOC^{66,67}.

OBESITY: Studies showed obese women had the highest risk of acquiring EOC⁶⁸. Accumulation of fat in the lower torso around the abdominal area increases women's chance to develop EOC. 36% of women that neglected postmenopausal estrogen treatment showed an increased risk in EOC⁶⁹.

4. UTERINE CANCER

Uterine malignancy is one of the highest-level of tumors in women reported from worldwide⁷⁰. Endometrial malignancy emerges from the inward layer (endometrium) of the uterus that leads to 90% of uterine diseases, followed by uterine sarcoma that emerges from the external layer (myometrium) (8%)⁷¹. It is the most widely recognized gynecologic threat in women i.e. it is considered the second most basic gynecologic threat in developing nations after cervical malignancy. North America and Eastern Europe have the most noteworthy rate of corpus uteri disease, and a few areas in Africa show the most minimal rate⁷². According to the data received from the Universal Office for Exploration on Malignancy (GLOBOCAN 2018), corpus uteri malignancy positions are third and fourth in frequency and death rate⁷³.

4.1 RELAPSE OF UTERINE CANCER

Uterine cancer is ranked in the fourth position worldwide, with a yearly estimation of 5,28,000 diagnosed cases and 2,66,000 deaths⁷⁴. Underdeveloped country's reports show the highest mortality rate due to uterine cancer. Therefore, identifying cancer at an early stage leads to an increment of survival rate by 60-80%⁷⁴. According to the International Federation of Gynecology and Obstetrics (FIGO), the relapse rate of uterine cancer ranged between 11-22% in stages IB and IIA, in stages IIB and IVA, it ranged between 28-64%⁷⁵. The tumor cells' recurrence is the lateral pelvic region or the extra pelvic region, or the central pelvic region. A study was conducted on 327 women that showed the recurrence of the tumor. Out of the 327 women, 36.7% showed the recurrence of the tumor in the pelvic region⁷⁶. A study conducted on a group of patients undergoing radiation therapy in the pelvic region in their first set and was found very difficult to continue with further treatments due to longer exposure of the pelvic region to radiation, hence resulting in the relapse of cancer cells. Additional treatment was not effective since the dosage was reduced due to the patient's low tolerance towards the treatment. Therefore, the survival rate was minimal in this group⁷⁷.

4.2 HISTOLOGY

Uterine cancer is divided into 6 subtypes, such as adenocarcinoma, uterine carcinosarcoma, squamous cell carcinoma, small cell carcinoma, transitional carcinoma, and serous carcinoma⁷⁸. The tumor grades of uterine cancer are evaluated into 3 categories⁷⁹:

1. Grade I- consists of 95% or more of the cancer tissues that form glands.
2. Grade II- consists of 50-94% of cancer tissues from glands.
3. Grade III- consists of <50% of cancer tissues that form glands but are quite aggressive⁷⁹.

An experiment conducted on 27,089 women with an average age of 64 showed that 61.3% of the women's population were diagnosed with grade I uterine cancer, whereas 39.7% were diagnosed with grade II uterine cancer. It was observed that 69.4% of the women's population were White women, out of which 64.4% were diagnosed with grade I type of uterine cancer. The grade II type of uterine cancer was exhibited at a higher proportion by 57.6% of Black women, followed by 43.0% in Asian women, 37.7% in Hispanic women, and 35.5% in white women⁸⁰.

4.3 MORTALITY AND SURVIVAL

According to the SEER program, uterine cancer is ranked as the fourth commonly occurring cancer among women, right after breast, lung, and colorectal cancers⁸¹. A study conducted on women, who had undergone hysterectomy-corrected uterine cancer, showed that these women had an increase in their rate of uterine cancer by 1% per year from 2003-2015⁸². Hispanic, Asian and Non-Hispanic Black women showed a rapid increase in the rate of hysterectomy-corrected uterine cancer⁸³. The non-endometrioid subtypes such as serous carcinoma, small cell carcinoma and other subtypes of carcinoma that account for almost 18.3% of all uterine cancer occur at a very high frequency Non-Hispanic Black women thereby reducing their survival rate for about less than 5-years⁸⁴.

4.4 RISK FACTORS

Age- Uterine cancer is age-related. It was observed that older women (60-64 years) were more susceptible to uterine cancer than younger women (45-49 years)⁸⁵.

Surgery- Surgery is one of the most significant factors that increases the risk of uterine cancer. In a study conducted, two categories of women were compared. The first category consisted of women undergoing hysterectomy for fibroids and the other category consisted of women undergoing hysterectomy for genital prolapse. It was observed that women belonging to the first category showed a 29% risk of uterine cancer, whereas women in the second category showed a 0.1% increase in the risk of uterine cancer⁸⁶.

Ethnicity- In a study conducted, taking 229,536 women, approximately 57.2% of Non-Hispanic White women showed an increased risk of uterine cancer when compared to Non-Hispanic Black women (17.1%) because Non-Hispanic Black women had a periodic assessment of uterine fibroids hence keeping them informed about their condition⁸⁷.

5. DIAGNOSIS AND TREATMENTS

Diagnosis of cancer patients is done by first subjecting the patient to a thorough scan of their entire body or a specific part of the body that is reckoned to have a growth of the tumor cells. Patients having signs of breast cancer are subjected to mammogram tests, whereas those patients that show symptoms of ovarian or uterine cancer are subjected to ultrasound tests or magnetic resonance imaging (MRI). Further diagnosis includes a biopsy test that provides a detailed report on the malignancy of the tumor cell. Based on this report, the physician can recommend the appropriate treatment required for the patient⁸⁸. There are different kinds of treatments that are available to treat breast, ovarian and uterine cancer. The most preferred type of breast cancer treatment is Breast Conservation Therapy (BCT). Surgery is

also one of the most suggested treatments by physicians as it reduces the chance for the recurrence of the tumor cells⁸⁹. The type of treatment recommended to patients diagnosed with ovarian cancer over a decade is mostly a combination of surgery followed by chemotherapy. Other treatments also include administering patients with an activated form of Vitamin D3⁹⁰. The most recommended treatment for uterine patients is extrafascial hysterectomy treatment. This treatment is administered only to older women who have no further plans on bearing children. Other treatments that can be employed to treat patients with uterine cancer are concurrent chemotherapy, radical trachelectomy and pelvic lymphadenectomy. Individualized radiotherapy can be recommended to patients to obtain a more promising result⁹¹. Monoclonal antibodies can also be used for the treatment of cancer. Antibodies possess a remarkable capability that can destroy the tumor cells as well as stimulate the immune system of the host to acquire a stronger and deep-rooted effector response. Monoclonal antibody treatments are preferred over other cancer treatments such as chemotherapy because these antibodies have a mixture of multiple mechanisms of action along with target specificity for the tumor cells, making them less toxic and possess a powerful anti-tumor response⁹². The most recommended antibody therapy is IgG. This is because IgG can consort with their associated types thereby giving rise to specialized functions such as complement-dependent cytotoxicity (CDC) and antibody-dependent cellular cytotoxicity (ADCC)⁹³. Tumor cells that are overexpressed or cells that exhibit unique characteristics are killed by using targeted monoclonal antibodies by various processes. When monoclonal antibodies bind to the growth factor receptors of the target cell or stop the ligand binding, the formation for the development and the signal for the survival of the tumor cell is blocked⁹⁴. For the past thirty years, multiple forms of monoclonal antibodies have been designed for the treatment of targeted therapy. Monoclonal antibodies have been proved to be less toxic and more efficient in targeting the tumor cells than other traditional techniques used in cancer treatment⁹⁵.

6. CONCLUSION

Breast cancer is widely recognized in women however rarely reported in men. A matter of fact is men and women ratio for breast malignant growth is 135:1 for white and 51:1 for black. Ovarian malignant growth is a significant reason for death and contributes to 4% of all types of cancer. It has become the most challenging diseases among women and India hold 2nd position after China in case of an ovarian cancer patient. Uterine cancer occurs in women's pelvic region between the bladder and rectum and is the most devastating form of cancer found in women of U.S. Earlier endometrial cancer was lower in black people when compared to white. Public awareness is one of the most important activities for cancer prevention and detection at an early stage. Obesity expands the danger of ovarian malignant growth because of the low progesterone emission bringing about numerous anovulatory cycles. Surprisingly, many cancer cases are reported in virgin women and girls. Early marriage, early delivery, and family history all are important to get the correct root of cancer in an individual life. Precaution and a healthy body can make some difference. In the investigation, 4.2% of uterine malignancy has prompted patients experiencing depression. The study revealed that patients more youthful than 50 years of age had the noteworthy expanding danger of depression. Hormone

Replacement Therapy can be given subsequent to treating the patients of uterine cancer, which is without a doubt the best and the main treatment of menopause estrogen inadequacy manifestations. Awareness spread by the public health and cancer specialists about the disease educates people and the society to fight back against the disease. The need of the hour is to develop effective treatment remedies for the disease which could eventually decrease the rate of mortality.

7. AUTHOR'S CONTRIBUTION STATEMENT

All the authors have contributed significantly to highlight on different types of cancer, to write the manuscript and thoroughly reviewed the manuscript.

8. CONFLICT OF INTEREST

Conflict of interest declared none.

9. REFERENCES

1. Smith RA, Andrews KS, Brooks D, Fedewa SA, Manassaram-Baptiste D, Saslow D, Brawley OW, Wender RC. Cancer screening in the United States, 2017: a review of current American Cancer Society guidelines and current issues in cancer screening. *CA: a cancer journal for clinicians*. 2017 Mar;67(2):100-21.
2. Tao Z, Shi A, Lu C, Song T, Zhang Z, Zhao J. Breast cancer: epidemiology and etiology. *Cell Biochem Biophys*. 2015;72(2):333-8. doi: 10.1007/s12013-014-0459-6, PMID 25543329.
3. Washbrook E. Risk factors and epidemiology of breast cancer. *Women's Health Medicine*. 2006 Jan 1;3(1):8-14.
4. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA Cancer J Clin*. 2016;66(1):7-30. doi: 10.3322/caac.21332, PMID 26742998.
5. World Health Organization. International Agency For Research on Cancer GLOBOCAN 2012: estimated cancer incidence, mortality and prevalence worldwide in 2012 Jun 28.
6. Tsuruta Y, Rogers LQ, Krontiras H, Grizzle WE, Frugé AD, Oster RA, Umphrey HR, Jones LW, Azrad M, Demark-Wahnefried W. Exploring effects of presurgical weight loss among women with stage 0-II breast cancer: protocol for a randomised controlled feasibility trial. *BMJ open*. 2016 Sep 1;6(9):e012320.
7. Anderson BO, Bevers TB, Carlson RW. Clinical Breast Examination and Breast Cancer Screening Guideline. *JAMA* 315 (13): 1403-4, 2016.
8. DeSantis C, Naishadham D, Jemal A. Cancer statistics for African Americans, 2013. *CA Cancer J Clin*. 2013;63(3):151-66. doi: 10.3322/caac.21173, PMID 23386565.
9. Watts S, Prescott P, Mason J, McLeod N, Lewith G. Depression and anxiety in ovarian cancer: A systematic review and meta-analysis of prevalence rates. *BMJ Open*. 2015;5(1):e007618. doi: 10.1136/bmjopen-2015-007618, PMID 26621509.
10. Yoneda A, Lendorf ME, Couchman JR, Multhaup HA. Breast and ovarian cancers: a survey and possible roles for the cell surface heparan sulfate proteoglycans. *J Histochem Cytochem*. 2012;60(1):9-21. doi: 10.1369/0022155411428469, PMID 22205677.
11. Howlader N, AM. No one, M. Krapcho, J. Garshell, N. Neyman, S. F. Altekruse, C. L. Kosary et al. "SEER cancer statistics review, 1975-2010." Bethesda, MD: National Cancer Institute 21 (2013): 12.
12. US Cancer Statistics Working Group. US Cancer Statistics Data Visualizations Tool, based on November 2017 submission data (1999-2015). Bethesda: United States Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute; 2018 [cited Mar 1, 2018]. Available from: <https://www.cdc.gov/cancer/dataviz>.
13. Lambe M, Wu J, Weiderpass E, Hsieh CC. Childbearing at older age and endometrial cancer risk (Sweden). *Cancer Causes Control*. 1999;10(1):43-9. doi: 10.1023/a:1008860615584, PMID 10334641.
14. Shapiro JA, Weiss NS, Beresford SA, Voigt LF. Menopausal hormone use and endometrial cancer, by tumor grade and invasion. *Epidemiology*. 1998;9(1):99-101. doi: 10.1097/00001648-199801000-00020, PMID 9430277.
15. Potischman N, Hoover RN, Brinton LA, Siiteri P, Dorgan JF, Swanson CA, Berman ML, Mortel R, Twiggs LB, Barrett RJ, Wilbanks GD, Persky V, Lurain JR. Case-control study of endogenous steroid hormones and endometrial cancer. *J Natl Cancer Inst*. 1996;88(16):1127-35. doi: 10.1093/jnci/88.16.1127, PMID 8757192.
16. Waks AG, Winer EP. Breast cancer treatment: a review. *JAMA*. 2019;321(3):288-300. doi: 10.1001/jama.2018.19323, PMID 30667505.
17. Antoniou A, Pharoah P. D., Narod S., Risch H. A., Eifjord J. E., Hopper J. L., Pasini B. (2003). Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case series unselected for family history: a combined analysis of 22 studies. *The American Journal of Human Genetics*, 72(5), 1117-1130.
18. Scott CL, Jenkins MA, Southey MC, Davis TA, Leary JA, Easton DF, Phillips KA, Hopper JL. Average age-specific cumulative risk of breast cancer according to type and site of germline mutations in BRCA1 and BRCA2 estimated from multiple-case breast cancer families attending Australian family cancer clinics. *Hum Genet*. 2003;112(5-6):542-51. doi: 10.1007/s00439-003-0908-6, PMID 12601471.
19. Howlader N. No one A.M, Krapcho M, Garshell, J., Miller, D., Altekruse S. F., Kosary C. L. SEER Cancer Statistics Review, 1975-2016. Based on the November 2018 SEER data submission, posted to the SEER website April 2019. Surveillance, Epidemiology, and End Results Program, National Cancer Institute, National Institutes of Health; 2019.
20. Ecker BL, Lee JY, Sterner CJ, Solomon AC, Pant DK, Shen F, Peraza J, Vaught L, Mahendra S, Belka GK, Pan TC, Schmitz KH, Chodosh LA. Impact of obesity on breast cancer recurrence and minimal residual disease. *Breast Cancer Res*. 2019;21(1):41. doi: 10.1186/s13058-018-1087-7, PMID 30867005.
21. Harirchi I, Karbakhsh M, Kashefi A, Momtahen AJ. Breast cancer in Iran: results of a multi-center study. *Asian Pac J Cancer Prev*. 2004;5(1):24-7. PMID 15075000.
22. do Carmo França-Botelho ADC, Ferreira MC, França JL, França EL, Honório-França AC. Breastfeeding and its relationship with reduction of breast cancer: a review. *Asian Pac J Cancer Prev*. 2012;13(11):5327-32. doi: 10.7314/APJCP.2012.13.11.5327, PMID 23317179.

23. Alco G, Igdem S, Dincer M, Ozmen V, Saglam S, Selamoglu D, Erdogan Z, Ordu C, Pilanci KN, Bozdogan A, Yenice S, Tecimer C, Demir G, Koksal G, Okkan S. Vitamin D levels in patients with breast cancer: importance of dressing style. *Asian Pac J Cancer Prev.* 2014;15(3):1357-62. doi: 10.7314/apjcp.2014.15.3.1357, PMID 24606465.

24. Alegre MM, Knowles MH, Robison RA, O'Neill KL. Mechanics behind breast cancer prevention - focus on obesity, exercise and dietary fat. *Asian Pac J Cancer Prev.* 2013;14(4):2207-12. doi: 10.7314/apjcp.2013.14.4.2207, PMID 23725113.

25. Key TJ, Verkasalo PK, Banks E. Epidemiology of breast cancer. *Lancet Oncol.* 2001;2(3):133-40. doi: 10.1016/S1470-2045(00)00254-0, PMID 11902563.

26. Li T, Mello-Thoms C, Brennan PC. Descriptive epidemiology of breast cancer in China: incidence, mortality, survival and prevalence. *Breast cancer research and treatment.* 2016 Oct 1;159(3):395-406.

27. US Cancer Statistics Working Group. (2015). United States cancer statistics: 1999–2012 incidence and mortality web-based report. Atlanta (GA): department of health and human services, centers for disease control and prevention, and national cancer institute.

28. Bergom C, Kelly T, Bedi M, Saeed H, Prior P, Rein LE, Szabo A, Wilson JF, Currey AD, White J. Association of locoregional control with high body mass index in women undergoing breast conservation therapy for early-stage breast cancer. *Int J Radiat Oncol* Biology* Physics.* 2016;96(1):65-71. doi: 10.1016/j.ijrobp.2016.04.020, PMID 27511848.

29. Sessler DI, Pei L, Huang Y, Fleischmann E, Marhofer P, Kurz A, Mayers DB, Meyer-Treschan TA, Grady M, Tan EY, Ayad S, Mascha EJ, Buggy DJ, Breast Cancer Recurrence Collaboration. Recurrence of breast cancer after regional or general anaesthesia: a randomised controlled trial. *Lancet.* 2019;394(10211):1807-15. doi: 10.1016/S0140-6736(19)32313-X, PMID 31645288.

30. Gibreel WO, Day CN, Hoskin TL, Boughey JC, Habermann EB, Hieken TJ. Mastectomy and immediate breast reconstruction for cancer in the elderly: a national cancer data base study. *J Am Coll Surg.* 2017;224(5):895-905. doi: 10.1016/j.jamcollsurg.2016.12.051, PMID 28238934.

31. Dolatkhah R, Somi MH, Jafarabadi MA, Hosseinalifam M, Sepahi S, Belalzadeh M, Nezamdoust M, Dastgiri S. Breast cancer survival and incidence: 10 years Cancer Registry Data in the Northwest, Iran. *Int J Breast Cancer.* 2020;2020:1963814. doi: 10.1155/2020/1963814, PMID 32411480.

32. Fitzmaurice, C., Akinyemiju, T. F., Al Lami, F. H., Alam, T., Alizadeh-Navaei, R., Allen, C., Aremu, O. (2018). Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 29 cancer groups, 1990 to 2016: a systematic analysis for the global burden of disease study. *JAMA oncology.* 4(11), 1553-1568.

33. Tadros AB, Wen HY, Morrow M. Breast cancers of special histologic subtypes are biologically diverse. *Annals of surgical oncology.* 2018 Oct 1;25(11):3158-64.

34. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2018;68(6):394-424. doi: 10.3322/caac.21492, PMID 30207593.

35. Leclère B, Molinié F, Trétarre B, Stracci F, Daubisse-Marliac L, Colonna M, GRELL Working Group. Trends in incidence of breast cancer among women under 40 in seven European countries: a GRELL cooperative study. *Cancer Epidemiol.* 2013;37(5):544-9. doi: 10.1016/j.canep.2013.05.001, PMID 23768969.

36. Cancer Research UK [cited Sep 4 2019]. Available from: <https://www.cancerresearchuk.org/home>.

37. Cardoso F, Loibl S, Pagani O, Graziottin A, Panizza P, Martincich L, Gentilini O, Peccatori F, Fourquet A, Delaloge S, Marotti L, Penault-Llorca F, Kotti-Kitromilidou AM, Rodger A, Harbeck N, European Society of Breast Cancer Specialists. The European Society of Breast Cancer Specialists recommendations for the management of young women with breast cancer. *Eur J Cancer.* 2012;48(18):3355-77. doi: 10.1016/j.ejca.2012.10.004, PMID 23116682.

38. Dolatkhah R, Somi MH, Jafarabadi MA, Hosseinalifam M, Sepahi S, Belalzadeh M, Nezamdoust M, Dastgiri S. Breast Cancer Survival and Incidence: 10 Years Cancer Registry Data in the Northwest, Iran. *International Journal of Breast Cancer.* 2020 May 1;2020.

39. Thakur P, Seam RK, Gupta MK, Gupta M, Sharma M, Fotedar V. Breast cancer risk factor evaluation in a Western Himalayan state: A case-control study and comparison with the Western World. *South Asian J Cancer.* 2017;6(3):106-9. doi: 10.4103/sajc.sajc_157_16, PMID 28975116.

40. Kim Y, Yoo KY, Goodman MT. Differences in incidence, mortality and survival of breast cancer by regions and countries in Asia and contributing factors. *Asian Pac J Cancer Prev.* 2015;16(7):2857-70. doi: 10.7314/apjcp.2015.16.7.2857, PMID 25854374.

41. Assi HA, Khoury KE, Dbouk H, Khalil LE, Mouhieddine TH, El Saghir NS. Epidemiology and prognosis of breast cancer in young women. *J Thorac Dis.* 2013;5 Suppl 1:S2-8. doi: 10.3978/j.issn.2072-1439.2013.05.24, PMID 23819024.

42. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin.* 2019;69(1):7-34. doi: 10.3322/caac.21551, PMID 30620402.

43. Wu MH, Chou YC, Yu JC, Yu CP, Wu CC, Chu CM, Yang T, Lai CH, Hsieh CY, You SL, Chen CJ, Sun CA. Hormonal and body-size factors in relation to breast cancer risk: a prospective study of 11,889 women in a low-incidence area. *Ann Epidemiol.* 2006;16(3):223-9. doi: 10.1016/j.annepidem.2005.02.015, PMID 15996484.

44. Fioretti F, Tavani A, Bosetti C, La Vecchia C, Negri E, Barbone F, Talamini R, Franceschi S. Risk factors for breast cancer in nulliparous women. *Br J Cancer.* 1999;79(11-12):1923-8. doi: 10.1038/sj.bjc.6690306, PMID 10206315.

45. Laamiri FZ, Bouayad A, Hasswane N, Ahid S, Mrabet M, Amina B. Risk factors for breast cancer of different age groups: Moroccan data? *Open J Obstet Gynecol.* 2015;05(2):79-87. doi: 10.4236/ojog.2015.52011.

46. Coburn SB, Bray F, Sherman ME, Trabert B. International patterns and trends in ovarian cancer incidence, overall and by histologic subtype. *Int J Cancer.* 2017;140(11):2451-60. doi: 10.1002/ijc.30676, PMID 28257597.

47. Lowe KA, Chia VM, Taylor A, O'Malley C, Kelsh M, Mohamed M, Mowat FS, Goff B. An international

assessment of ovarian cancer incidence and mortality. *Gynecol Oncol.* 2013;130(1):107-14. doi: 10.1016/j.ygyno.2013.03.026, PMID 23558050.

48. Wang J, Lv H, Xue Z, Wang L, Bai Z. Temporal trends of common female malignances on breast, cervical, and ovarian cancer mortality in Japan, Republic of Korea, and Singapore: application of the age-period-cohort model. *BioMed Res Int.* 2018;2018:5307459. doi: 10.1155/2018/5307459, PMID 29750160.

49. Hunn J, Rodriguez GC. Ovarian cancer: etiology, risk factors, and epidemiology. *Clin Obstet Gynaecol.* 2012;55(1):3-23. doi: 10.1097/GRF.0b013e31824b4611, PMID 22343225.

50. Chornokur G, Amankwah EK, Schildkraut JM, Phelan CM. Global ovarian cancer health disparities. *Gynecol Oncol.* 2013;129(1):258-64. doi: 10.1016/j.ygyno.2012.12.016, PMID 23266352.

51. Fung-Kee-Fung M, Oliver T, Elit L, Oza A, Hirte HW, Bryson P. Optimal chemotherapy treatment for women with recurrent ovarian cancer. *Curr Oncol.* 2007;14(5):195-208. doi: 10.3747/co.2007.148, PMID 17938703.

52. Katsumata N, Yasuda M, Isonishi S, Takahashi F, Michimae H, Kimura E, Aoki D, Jobo T, Kodama S, Terauchi F, Sugiyama T, Ochiai K, Japanese Gynecologic Oncology Group. Long-term results of dose-dense paclitaxel and carboplatin versus conventional paclitaxel and carboplatin for treatment of advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer (JGOG 3016): a randomised, controlled, open-label trial. *Lancet Oncol.* 2013;14(10):1020-6. doi: 10.1016/S1470-2045(13)70363-2, PMID 23948349.

53. Torre LA, Trabert B, DeSantis CE, Miller KD, Samimi G, Runowicz CD, Gaudet MM, Jemal A, Siegel RL. Ovarian cancer statistics, 2018. *CA Cancer J Clin.* 2018;68(4):284-96. doi: 10.3322/caac.21456, PMID 29809280.

54. Prat J. Ovarian carcinomas: five distinct diseases with different origins, genetic alterations, and clinicopathological features. *Virchows Arch.* 2012;460(3):237-49. doi: 10.1007/s00428-012-1203-5, PMID 22322322.

55. Alsop K, Fereday S, Meldrum C, DeFazio A, Emmanuel C, George J, Dobrovic A, Birrer MJ, Webb PM, Stewart C, Friedlander M, Fox S, Bowtell D, Mitchell G. BRCA mutation frequency and patterns of treatment response in BRCA mutation-positive women with ovarian cancer: a report from the Australian Ovarian Cancer Study Group. *J Clin Oncol.* 2012;30(21):2654-63. doi: 10.1200/JCO.2011.39.8545, PMID 22711857.

56. Kaldawy A, Segev Y, Lavie O, Auslender R, Sopik V, Narod SA. Low-grade serous ovarian cancer: a review. *Gynecol Oncol.* 2016;143(2):433-8. doi: 10.1016/j.ygyno.2016.08.320, PMID 27581327.

57. Liu Y, Wang Y, Yao D, Cui D. LncSOX4 serves an oncogenic role in the tumorigenesis of epithelial ovarian cancer by promoting cell proliferation and inhibiting apoptosis. *Mol Med Rep.* 2018;17(6):8282-8. doi: 10.3892/mmr.2018.8892, PMID 29693704.

58. Vierkoetter KR, Ayabe AR, VanDrunen M, Ahn HJ, Shimizu DM, Terada KY. Lynch syndrome in patients with clear cell and endometrioid cancers of the ovary. *Gynecol Oncol.* 2014;135(1):81-4. doi: 10.1016/j.ygyno.2014.07.100, PMID 25093288.

59. Jang JYA, Yanaihara N, Pujade-Lauraine E, Mikami Y, Oda K, Bookman M, Ledermann J, Shimada M, Kiyokawa T, Kim BG, Matsumura N, Kaku T, Kuroda T, Nagayoshi Y, Kawabata A, Iida Y, Kim JW, Quinn M, Okamoto A. Update on rare epithelial ovarian cancers: based on the Rare Ovarian Tumors Young Investigator Conference. *J Gynecol Oncol.* 2017;28(4):e54. doi: 10.3802/jgo.2017.28.e54, PMID 28541641.

60. Momenimovahed Z, Tiznobaik A, Taheri S, Salehiniya H. Ovarian cancer in the world: epidemiology and risk factors. *Int J Womens Health.* 2019;11:287-99. doi: 10.2147/IJWH.S197604, PMID 31118829.

61. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. *CA Cancer J Clin.* 2017;67(1):7-30. doi: 10.3322/caac.21387, PMID 28055103.

62. Holschneider CH, Berek JS. Ovarian cancer: epidemiology, biology, and prognostic factors. In: *Seminars in surgical oncology.* New York: John Wiley & Sons, Inc; 2000, July.

63. Mohammadian M, Ghafari M, Khosravi B, Salehiniya H, Aryaei M, Bakeshei FA, Mohammadian-Hafshejani A. Variations in the incidence and mortality of ovarian cancer and their relationship with the human development index in European Countries in 2012. *Biomed Res Ther.* 2017;4(8):1541-57. doi: 10.15419/bmrat.v4i08.228.

64. Pan SY, Ugnat AM, Mao Y, Wen SW, Johnson KC, Canadian Cancer Registries Epidemiology Research Group. A case-control study of diet and the risk of ovarian cancer. *Cancer Epidemiol Prev Biomark.* 2004;13(9):1521-7.

65. Finn OJ. Human tumor antigens yesterday, today, and tomorrow. *Cancer Immunol Res.* 2017;5(5):347-54. doi: 10.1158/2326-6066.CIR-17-0112, PMID 28465452.

66. McCann SE, Freudenheim JL, Marshall JR, Graham S. Risk of human ovarian cancer is related to dietary intake of selected nutrients, phytochemicals and food groups. *J Nutr.* 2003;133(6):1937-42. doi: 10.1093/jn/133.6.1937, PMID 12771342.

67. Ong, J. S., Cuellar-Partida, G., Lu, Y., Australian Ovarian Cancer Study, Fasching, P. A., Hein, A., Vergote, I. (2016). Association of vitamin D levels and risk of ovarian cancer: a Mendelian randomization study. *International journal of epidemiology*, 45(5), 1619-1630.

68. Bandera EV, Lee VS, Qin B, Rodriguez-Rodriguez L, Powell CB, Kushi LH. Impact of body mass index on ovarian cancer survival varies by stage. *Br J Cancer.* 2017;117(2):282-9. doi: 10.1038/bjc.2017.162, PMID 28588323.

69. Delort L, Kwiatkowski F, Chalabi N, Satih S, Bignon YJ, Bernard-Gallon DJ. Central adiposity as a major risk factor of ovarian cancer. *Anticancer Res.* 2009;29(12):5229-34. PMID 20044641.

70. Forman D, Bray F, Brewster DH, Gombe Mbalawa C, Kohler B, Piñeros M, Ferlay J. Cancer incidence in five continents. *IARC Sci Publ.* 2013;X:164.

71. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin.* 2011;61(2):69-90. doi: 10.3322/caac.20107, PMID 21296855.

72. Alshahrani S, Soliman AS, Hablas A, Ramadan M, Meza JL, Remmenga S, Seifeldein IA, Chamberlain RM. Changes in uterine cancer incidence rates in Egypt.

Obstet Gynecol Int. 2018;2018:3632067. doi: 10.1155/2018/3632067, PMID 30013598.

73. Mohammed AJ, Ghebreyesus TA. Healthy living, well-being and the sustainable development goals. Bulletin of the World Health Organization. 2018 Sep 1;96(9):590.

74. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer*. 2015;136(5):E359-86. doi: 10.1002/ijc.29210, PMID 25220842.

75. Pimple S, Mishra G, Shastri S. Global strategies for cervical cancer prevention. *Curr Opin Obstet Gynecol*. 2016;28(1):4-10. doi: 10.1097/GCO.0000000000000241, PMID 26642063.

76. Quinn MA, Benedet JL, Odicino F, Maisonneuve P, Beller U, Creasman WT, Heintz AP, Ngan HY, Pecorelli S. Carcinoma of the cervix uteri. FIGO 26th annual report on the results of treatment in gynecological cancer. *Int J Gynecol Obstet*. 2006;95(Suppl 1):S43-103. doi: 10.1016/S0020-7292(06)60030-1, PMID 17161167.

77. Zola P, Fuso L, Mazzola S, Piovano E, Perotto S, Gadducci A, Galletto L, Landoni F, Maggino T, Raspagliesi F, Sartori E, Scambia G. Could follow-up different modalities play a role in asymptomatic cervical cancer relapses diagnosis? An Italian multicenter retrospective analysis. *Gynecol Oncol*. 2007;107(1);Suppl 1:S150-4. doi: 10.1016/j.ygyno.2007.07.028, PMID 17868785.

78. Dornhöfer N, Höckel M. New developments in the surgical therapy of cervical carcinoma. *Ann NY Acad Sci*. 2008;1138(1):233-52. doi: 10.1196/annals.1414.029, PMID 18837903.

79. D'Ambrosio V, Vena F, Di Mascio D, Faralli I, Musacchio L, Boccherini C, Brunelli R, Piccioni MG, Benedetti Panici P, Giancotti A. Obstetrical outcomes in women with history of breast cancer: a systematic review and meta-analysis. *Breast Cancer Res Treat*. 2019;178(3):485-92. doi: 10.1007/s10549-019-05408-4, PMID 31451975.

80. Johnson AL, Medina HN, Schlumbercht MP, Reis I, Kobetz EN, Pinheiro PS. The role of histology on endometrial cancer survival disparities in diverse Florida. *PLOS ONE*. 2020;15(7):e0236402. doi: 10.1371/journal.pone.0236402, PMID 32701999.

81. American Cancer Society. American Cancer Society Facts & Figures 2019.

82. Clarke MA, Devesa SS, Harvey SV, Wentzensen N. Hysterectomy-corrected uterine corpus cancer incidence trends and differences in relative survival reveal racial disparities and rising rates of nonendometrioid cancers. *J Clin Oncol*. 2019;37(22):1895-908. doi: 10.1200/JCO.19.00151, PMID 31116674.

83. Cote ML, Alhajj T, Ruterbusch JJ, Bernstein L, Brinton LA, Blot WJ, Chen C, Gass M, Gauvin S, Henderson B, Lee E, Horn-Ross PL, Kolonel LN, Kaunitz A, Liang X, Nicholson WK, Park AB, Petruzzella S, Rebbeck TR, Setiawan VW, Signorello LB, Simon MS, Weiss NS, Wentzensen N, Yang HP, Zeleniuch-Jacquotte A, Olson SH. Risk factors for endometrial cancer in black and white women: a pooled analysis from the epidemiology of endometrial cancer consortium (E2C2). *Cancer Causes Control*. 2015;26(2):287-96. doi: 10.1007/s10552-014-0510-3, PMID 25534916.

84. Setiawan, V. W., Yang, H. P., Pike, M. C., McCann, S. E., Yu, H., Xiang, Y. B., Van Den Brandt, P. A. (2013). Type I and II endometrial cancers: have they different risk factors?. *Journal of Clinical Oncology*, 31(20), 2607.

85. Desai VB, Wright JD, Gross CP, Lin H, Boscoe FP, Hutchison LM, Schwartz PE, Xu X. Prevalence, characteristics, and risk factors of occult uterine cancer in presumed benign hysterectomy. *Am J Obstet Gynecol*. 2019;221(1):39.e1-39.e14. doi: 10.1016/j.ajog.2019.02.051, PMID 30853364.

86. Laughlin-Tommaso SK, Lu D, Thomas L, Diamond MP, Wallace K, Wegienka G, Vines Al, Anchan RM, Wang T, Maxwell GL, Jacoby V, Marsh EE, Spies JB, Nicholson WK, Stewart EA, Myers ER. Short-term quality of life after myomectomy for uterine fibroids from the COMPARE-UF Fibroid Registry. *Am J Obstet Gynecol*. 2020;222(4):345.e1-345.e22. doi: 10.1016/j.ajog.2019.09.052, PMID 31678093.

87. Perkins NJ, Schisterman EF. The inconsistency of "optimal" cutpoints obtained using two criteria based on the receiver operating characteristic curve. *Am J Epidemiol*. 2006;163(7):670-5. doi: 10.1093/aje/kwj063, PMID 16410346.

88. Radovic N, Ivanac G, Divjak E, Biondic I, Bulum A, Brklić B. Evaluation of breast cancer morphology using diffusion-weighted and dynamic contrast-enhanced MRI: intermethod and interobserver agreement. *J Magn Reson Imaging*. 2019;49(5):1381-90. doi: 10.1002/jmri.26332, PMID 30325549.

89. Gilbo. Gilbo P, Potters L, Lee L. Implementation and utilization of hypofractionation for breast cancer. *Adv Radiat Oncol*. 2018 Jul-September;3(3):265-70. doi: 10.1016/j.adro.2018.04.001, PMID 30202795.

90. Jayson GC, Kohn EC, Kitchener HC, Ledermann JA. Ovarian cancer. *Lancet*. 2014;384(9951):1376-88. doi: 10.1016/S0140-6736(13)62146-7, PMID 24767708.

91. Guo H, Guo J, Xie W, Yuan L, Sheng X. The role of vitamin D in ovarian cancer: epidemiology, molecular mechanism and prevention. *J Ovarian Res*. 2018;11(1):71. doi: 10.1186/s13048-018-0443-7, PMID 30157901.

92. National Health Commission Of The People's Republic Of China. Chinese guidelines for diagnosis and treatment of cervical cancer 2018 (English version). *Chin J Cancer Res*. 2019;31(2):295-305. doi: 10.21147/j.issn.1000-9604.2019.02.04, PMID 31156300.

93. Zahavi D, Weiner L. Monoclonal antibodies in cancer therapy. *Antibodies*. 2020;9(3):34. doi: 10.3390/antib9030034, PMID 32698317.

94. Weiner LM, Surana R, Wang S. Monoclonal antibodies: versatile platforms for cancer immunotherapy. *Nat Rev Immunol*. 2010;10(5):317-27. doi: 10.1038/nri2744, PMID 20414205.

95. Patel D, Bassi R, Hooper A, Prewett M, Hicklin DJ, Kang X. Anti-epidermal growth factor receptor monoclonal antibody cetuximab inhibits EGFR/HER-2 heterodimerization and activation. *Int J Oncol*. 2009;34(1):25-32. PMID 19082474.