Somato Publications

Global Research in Gynecology and Obstetrics

Review Article

# Mechanistic Approach to the Pathophysiology and Genes Associated with Uterine Cancer: A Review

**Christopher O. Akintayo[1*]., Oluwatomiwa K. Paimo[2]., Okechukwu O. Ezekpo[3]., Samuel K. Olaniyi[1]., Adesola A. Oniyide[1]., Oluwaseyi E. Adelekan[1]., Adedayo H. Oyebanji[4]., Oghenerukevwe Omeru [5]., Olumide S. Akinsomisoye[6] and Oluwafemi F. Adebayo[7]**

[1]Department of Physiology, College of Medicine and Health Sciences, Afe Babalola University, Ado-Ekiti, 360101, Nigeria

[2]Department of Biochemistry, Faculty of Basic Medical Sciences, College of Medicine, University of Ibadan, Ibadan, Nigeria

[3]Department of Internal Medicine, College of Medicine and Health Sciences, Afe Babalola University, Ado-Ekiti, 360101, Nigeria

[4]Department of Pediatrics, College of Medicine and Health Sciences, Afe Babalola University, Ado-Ekiti, 360101, Nigeria

[5]Department of Human Physiology, Faculty of Basic Medical Sciences, Delta State University, Abraka, Nigeria

[6]Department of Physiological Sciences, Faculty of Basic Medical Sciences, Obafemi Awolowo University, Ile-Ife, Osun State, Nigeria

[7]Department of Human Physiology, Faculty of Basic Medical Sciences, Bingham University, Nigeria

*Address for Correspondence: Christopher O. Akintayo, Department of Physiology, College of Medicine and Health Sciences, Afe Babalola University, Ado-Ekiti, Ekiti State, Nigeria, Tel: +2347032985319; E-mail: tobajoe2001@yahoo.com

Received: 04 April 2021; Accepted: 22 May 2021; Published: 10 June 2021

Citation of this article: Akintayo, CO., Paimo, OK., Ezekpo, OO., Olaniyi, SK., Oniyide, AA., Adelekan, OE., et al. (2021) Mechanistic Approach to the Pathophysiology and Genes Associated with Uterine Cancer: A Review. Global Res Gynecol Obstet, 3(1): 08-24.



**Abstract**

One of the most common causes of cancers of the female reproductive tract is uterine cancer and the rate of spread in both developed and developing countries is alarming, hence, the need for medical intervention. The pathogenesis of uterine cancer/endometrial carcinomas is key as well as the implicated genes in the diagnosis. This review focuses more on the molecular aspect (involving gene expression) in uterine cancer. However, some of the risk factors associated with uterine cancer have been discussed which include, obesity, early menarche, diabetes (Type 2), use of intrauterine device, family history and women who have had breast or ovarian cancer and endometrial hyperplasia in time past. Moreover, early diagnosis and adequate intervention have been proven to be safe in affected individuals (women). Mutation in the genetic makeup leads

to disease onset when not properly corrected. As in the case of endometrial cancer, several mismatched genes have been identified such as MLH1, MSH2, MSH6, deletion of EPCAM found in the family history with Lynch syndrome. PTEN have also been mutated in several patients. However, the diagnosis of endometrial cancer can be done based on clinical, radiological and histo-pathological examination. All three will give a concise and informative description about the progression of endometrial cancer in order to administer proper treatment and progression. The standard evaluation of EC is the radiological examination and histopathological examination involving the pelvic ultrasonography and endometrial biopsy or dilatation and curettage with or without hysteroscopy.

**Keywords:** Uterine cancer, Gene expression, Pathophysiology, Risk factors, Diagnosis, Surgical intervention

## Introduction

The proper genital development in both male and female gives the ability for procreation to occur. Sexual development and maturation are unavoidable and is one of the most important stage involved in human development. The development is closely associated with a coordinate relationship between both the somatic and the germ line cell which involves a complicated dynamic, critical but well-regulated stage, chromosomal recombination and eventual cell development and sexual characteristics features [1]. This review will narrowly focus on the female reproductive system and functions before we then move to the etiology of uterine cancer, epidemiology, pathophysiology, the microscopy and finally the complication associated with uterine cancer.

### The female reproductive organ

The female reproductive system comprises of both the internal and external organ. The internal organ is made of ovaries, uterine tubes, uterus and vagina while the external region include both the perineum and vulvar [2,3]. The external covering generally referred to as vulvar is highly sensitive to touch during sexual pleasure and serve as a protection for urethral and vaginal opening [4]. It is further composed of the mons pubis, the labia majora and minora, the clitoris.

## Internal Female Reproductive Organ

From its name, the internal organs are situated inside the body of the female. It is made up of ovaries, uterine tubes, uterus and vagina. They are found performing different functions in response to specific hormones levels.

### Vagina

Is an elastic muscular part in the female reproductive system that extends from the cervix to the vulva. It is covered by a thin membrane layer called the hymen. The vagina receives the penis during sexual intercourse and ejaculation which is aided by lubrication of the vagina wall. It also serves a major role during child birth, menstrual and urine flow. The vaginal has a regulated acidic environment which helps protect the inflow of infections and bacteria. The imbalance in the pH environment leads to the point of entry for sexual transmitted infections during sexual intercourse. Furthermore, this environment can also be altered by douching, deodorant use amongst several others [2,4,5].

### Uterus

Is found proximal to vagina, behind the bladder and situated in-front of the rectum. This position is held in place by 8 ligaments which is not tightly attached to any part of the skeleton. Menstruation, ovum implantation, fetal development and labor occurs here. The shape and position of the uterus is greatly affected by gravity. Immediately after the first pregnancy there is an increase in the size of the uterus as against its normal size and immediately after menopause the size later reduces. The uterine wall is made of 3 layers; the innermost endometrium layer rich in glands and blood vessels, the middle myometrium layer rich in connective tissues and the otter perimetrium layer found covering the uterus. Anatomically, the uterus can be divided into 3 parts namely; the fundus (the convex portion above the uterine tubes),the body generally referred to the central body and the cervix which opens directly into the vagina [2,5].

### Uterine tubes

Also called the fallopian tube is a muscular J shape structure extending laterally from the uterus and opens towards the ovaries. Each tube measures 7-10 cm long with a diameter of 0. 7cm.Each tube serves as a house for the egg when released from the ovaries and also a transport channel for the egg to the uterus. Anatomically, the fallopian tube is divided into 4 parts namely; Fimbriae which helps in capturing the egg, the funnel shaped Infundibulum on which fimbriae are attached, the Ampulla where fertilization occurs and finally the Isthmus connecting the ampulla to the uterine cavity [5,6].

### Ovaries

Along with other internal organs of the female reproductive system performing specific functions, the ovaries are also found producing eggs also called ova or oocytes. The egg(s) produced is/are transferred and transported by the fallopian tube where fertilization occurs before reaching the uterus. Aside the egg production by the ovaries, it also produces estrogen and progesterone hormones. It is important to note that the sex of the child is determined based on the side where the egg is released hence gravity is important in conception [7]. Each ovary is about 4cm long weighing 2-5 gram, 2cm wide with 1 cm thickness (Figure 1)

## External Female Reproductive Organ

The collective term describing the external reproductive organ is often called Vulvar. The vulvar is an opening or region where the external reproductive organs are found. It is made up of mons pubis, labia majora and minora, clitoris, vestibules and perineum each performing specific functions [2-4,8-10].

### Vulvar

Also called the pudendum is ovoid in shape extending from the wall of the abdomen at the symphysis pubis to the anterior side

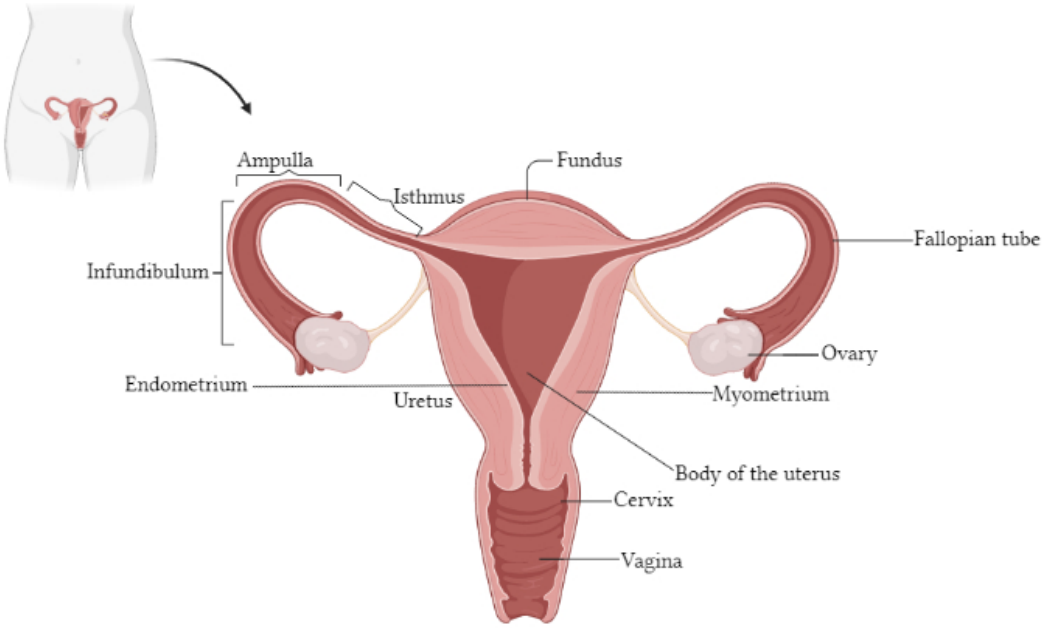


Figure 1: Showing the cross-sectional area of the female internal reproductive organ created by biorender.com.

of the anus. Opening of the thighs exposes the mons pubis, labia majora, minora and the vestibule. Deep within the labia structures are the clitoris and bulb of vestibules which helps in secreting mucus that helps in moistening the vestibules and labia minora. The vulvar performs 3 main functions which are protecting the female reproductive tracts, directing urine flow and finally serving as a sensory tissue during sexual intercourse [11].

**Prepuce**

In the external female reproductive system, we have the foreskin performing similar function as in male. It is found protecting the clitoris serving as the clitoris hood.

**Mon pubis**

This is a fatty tissue found in the female usually covered by the pubic hair. During sexual intercourse, it has a cushioning effect and it is also found protecting the symphysis.

**Labia**

Labia is of two types namely the labia majora and labia minora also referred to as the larger and small lips. Labia major functions primarily to protect vagina opening. It is found covering the labia minora, clitoris amongst others. The anterior part of the labia majora together with connecting skin forms the anterior labial commissure found directly under the mons pubis while the posterior end forms the posterior labial commissure. The posterior commissure together with the anus forms the perineum. Labiocrural fold is found between the labia major and the thigh. Labia minora on the other hand lies just below the labia majora. Labia majora and labia minora is separated by Interlabial sulci. Labia minora is vascular in nature rich in connective tissue giving it its pink color. It is also rich in adipose tissue and highly sensitive. During intercourse, the region is rich in blood supply and becomes edematous. At the anterior side, it meets at the prepuce to surround the clitoris and at the posterior to form frenulum also called fourchette.

**Clitoris**

Similar to penis is highly sensitive to touch during sexual excitement. It is highly rich in blood supply. Corpus cavernous makes up the clitoris. This tissue protrudes to the vulvar exterior forming glans clitoris which is the only visible part of the clitoris.

**Vestibule**

Also called the vulvar vestibule is found enclosed by the minora the posterior end and situated just below the clitoris. Opening in to the vestibule is the urethral and vagina (introitus) opening. Bartholin gland is found in the vaginal opening. It supplies mucus for lubrication during intercourse while Skene gland is found in the urethral opening keeping the opening moist and open for easy passage of urine. It is also believed to possess antimicrobial activity which helps predominantly to prevent urinary tract infection.

Worthy of note is the Hymen also called the maiden head. It is found surrounding the vagina opening. In a virgin it is found tightly enclosing the opening of the vagina. This tightness varies between females. During first sexual intercourse, the hymen tears or appears soft with no tearing while in females with multiple intercourse, it appears as tiny tags of tissues [8].

**Vestibular bulbs**

Related to the clitoris is the vestibular bulbs. It is an erectile tissue originating from the anterior end of the clitoris and extending to the urethra and vagina from the lower leg of the clitoris which ultimately slit up to surround the border of the vagina and urethra. During sexual intercourse, it is filled with blood which in turn exert its pressure on the lower part of the clitoris through the corpus cavernosum.

**Perineum**

This is formed from the anus and the posterior commissure of labia majora. It is made of adipose tissue, muscles and fascia. During childbirth the region becomes torn which in often times requires proper suture (Figure 2).

## Uterine Cancer

There is a rapid growth in the incidence and mortality rate of cancer and this is attributed partly to both social and economic development. Uterine cancer, also called endometrial cancer is the malignancy occurring in the female reproductive system associated with the uterus lining particularly at the endometrium. Most cancerous cells begin at a particular site before spreading and invading other neighboring cells.

It is rated the 7$^{th}$ most common cause of death in Europe. At a

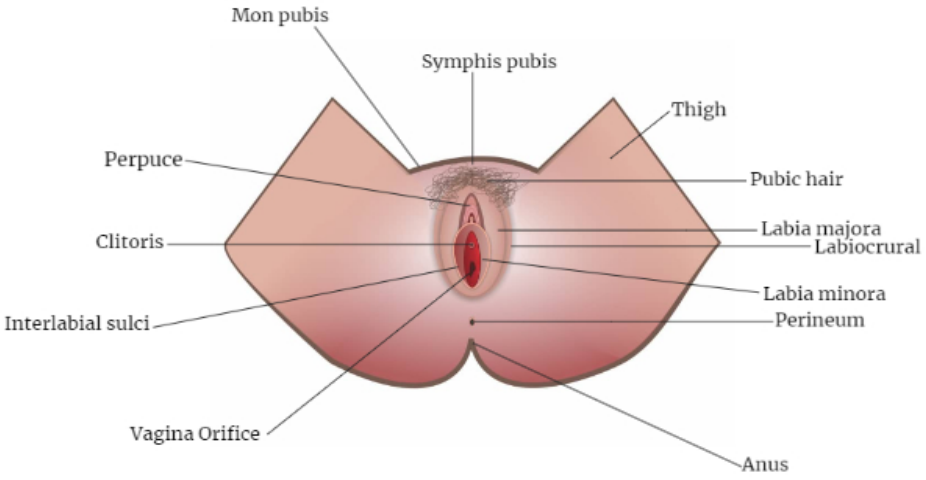


Figure 2: Showing the cross-sectional area of the female external reproductive organ created by biorender.com.

point, the reported survival rate of endometrial cancer had been estimated to be 75% in the United States with an average age of 60 years in women [12,13]. Demographic studies while comparing the risk of developing endometrial cancer among Caucasian women and the African–American women have shown that a lower risk is found in the African American population [14]. while in Europe out of every 100 women selected atleast 1 or 2 persons have the likelihood of developing endometrial cancer [15].

As of today, some risk factors have been associated with the development of endometrial cancer. They include gene alteration, age, family history, prolonged estrogen level, increase in estrone level, obesity, hypertension amongst others. However, some women with this risk factors often times do not have endometrial cancer [13,15]. The use of intrauterine device has also been identified as one of the risk factors of endometrial cancer [16]. Based on the presence and absence of estrogen two types of endometrial cancer have been proposed. The type I estrogen dependent and Type II estrogen independent endometrial cancer. The type I occurs in 85% of patient with the type II occurring in a less percentage. And this is mostly found in obese patient when compared with non-obese patient. Often times, type II is preceded by atypical hyperplasia identified with its site of origin with a decreased invasion to neighboring cells. At the molecular level, Type I often have the mutation of several genes such as B catenin, K-ras, PTEN along with microsatellite instability in contrast to Type II which have the HER2/neu amplification and P53 mutation [17].

## Genetic Mutation

Mutation in the genetic makeup leads to disease onset when not properly corrected. As in the case of endometrial cancer, several mismatched repair genes have been identified such as MLH1, MSH2, MSH6, deletion of EPCAM found in the family history with Lynch syndrome. PTEN have also been mutated in several patients [18,19]. According to Dunlop et al.,1997 MLH1 and MSH2 have a cumulative risk of 42% in endometrial cancer while Aarnio et al. 1999 shows a 60% cumulative risk. Vasen et al.,1996 has demonstrated that mismatched gene MLH1 occurs at 42% with MSH2 having a 62% cumulative risk. Further studies according to Hendriks et al., 2004 has shown the cumulative risk of MLH1, MSH2 and MSH 6 in endometrial cancer to be 27, 40 and 71% respectively [20]. EPCAM deletion on the other hand have been shown to contribute to a lower extent the development of

endometrial cancer when compared with colorectal cancer which can be inferred from the low level of *EPCAM* expression in endometrial cancer progenitor cells [21].

Patient with MLH1, MSH2, MSH6 have the risk of developing endometrial cancer at an average age of 70 with occurrence at 54%, 21% and 16% respectively [13,22,23]. Further findings according to Daphne et al., has shown an alteration in microsatellite instability, alteration in the PI3K,MAPK B-catenin and AR1DIA pathway [24]. Microsatellite instability is identified with increase mutation at the short nucleotide repeat sequence which occurs during DNA replication either due hyper-methylation by a caretaker gene MLH1[25],loss of MSH 2 protein or somatic mutation of MSH6 [26-28]. Other genes also mutated and closely associated with MSI include BRCA, BAX, IGRIIR, TGF-BRII with an incidence risk of 15%, 29-33%, 14-21%, 10-37%respectively [24].

Alteration in the PI3K pathway occurs in more than 80% of endometrial tumor with a dysregulation in PIK3CA and MTOR protein expression. The interplay in the aforementioned pathway further disrupt the signaling cascade mechanism leading to endometrial tumorigenesis progression. Mutation of K-ras also coexist to induce tumorigenesis with increased phosphorylation of MEK1/2, ERK 1/2 and p38MAK [29]. B-catenin an integral pathway in the canonical signal pathway have also been dysregulated with a percent risk of 31-47%. In addition, ARID1A expression have been lost alongside with cyclin E over expression.

## Obesity and Estrogen Level

An obese female have an increase rate of estrogen [15]. In the United states, there have been a rise in the endometrial cancer development with obesity [13,30,31]. Studies have further shown that the risk ratio of disease mortality in obese patient is more striking when compared with non-obese patient with a factor of 6.25 to 2.53 [31,32].

Endometrial proliferation and tumorigenesis are linked with obesity through several mechanisms. Adipokines secreted by the adipose tissue, infiltration by the macrophages and pre adipocytes have been shown to regulate metabolism and modulate chronic inflammation but in the case of obese patient it in turn suppresses the normal insulin signaling leading to insulin resistance, increase in IGF I, hyperglycemia which leads to increase endometrial proliferation. Pro-inflammatory proteins have also been shown to be induced obstructing the normal insulin pathway. In addition, sex hormone binding globulin(SHBG) level in obese patient is reduced leading to an increase or imbalance in the estrogen level [31,33,34]. An unopposed estrogen level binds to its cognate receptor inducing intracellular signaling to modulate the transcription of several proliferative genes. Estrogen has also been discovered to act as a mutagen forming DNA adduct further leading to genomic instability [33].

### Diabetes

As earlier mentioned, an obese patient is identified with an increase in insulin level, insulin-like growth factor and increase glucose concentration. All these taking together increase the ligand binding affinity to its receptor activating the intracellular downstream effects. In this process there is an hyperactivity in the PI3K pathway along with MAPK pathway [31]. Increased activity culminates in increased proliferation and survival of endometrial cancer. This activity is fueled by the loss of PTEN gene. An independent correlation between diabetes and Endometrial cancer have also been documented [35].

### Age

Age have been highlighted as one important risk factor involved in the development of endometrium tumorigenesis. About 15% of women who have attained menopause have a high risk of developing endometrium cancer. Endometrial cancer has also been found in women who are yet to attain menopause a factor contributing to this is obesity [36,37].

Reproductive characteristics also associated with increased risk of developing endometrial cancer include infertility, nulliparity, years of menstruating, late age of attainment of menopause among other factors (Figure 3).

## Signs and Symptoms of Uterine (Endometrium) Cancer

Signs and symptoms of endometrial can be evaluated by the gynecologist or other medical practitioners. Signs include bleeding within periods, pelvic and vaginal bleeding, enlarged uterus after menopause, unexpected weight loss, weakness in the abdomen

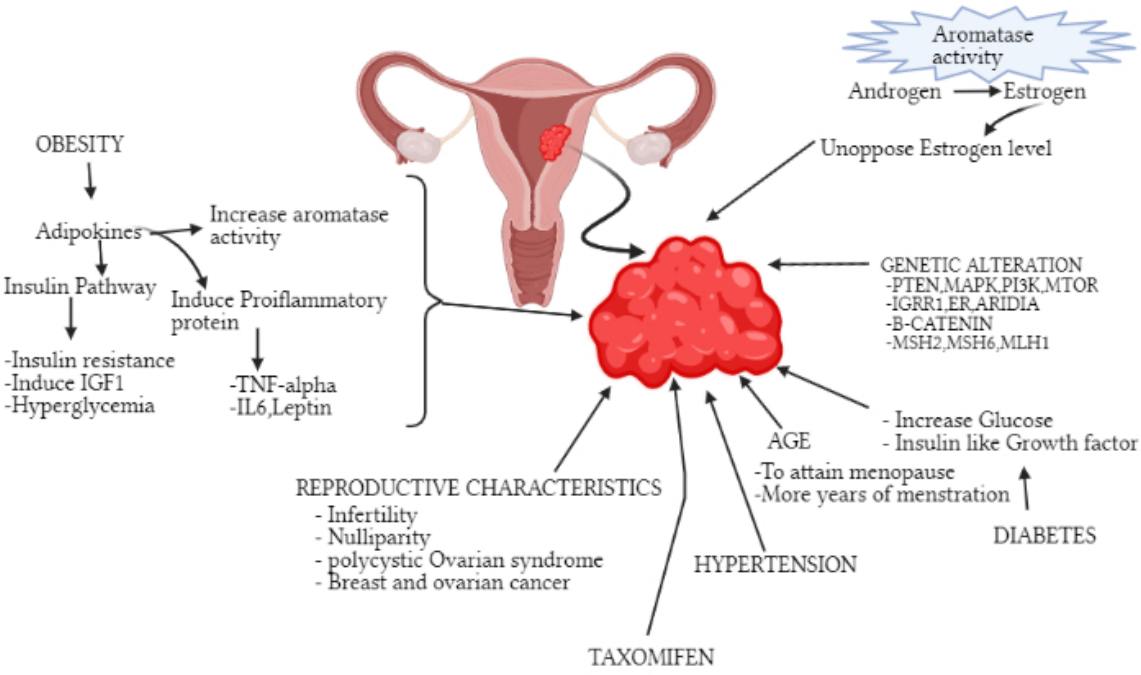


Figure 3: Schematic diagram showing the factors contributing to the development of Endometrial cancer created by biorender.com.

amongst others [38]. According to the Society for Medical Oncology, the diagnosis of endometrial cancer can be done based on clinical, radiological and histo-pathological examination. All three will give a concise and informative description about the progression of endometrial cancer in order to administer proper treatment and progression. The standard evaluation of EC is the radiological examination and histo-pathological examination involving the pelvic ultrasonography and endometrial biopsy or dilatation and curettage with or without hysteroscopy.

In a data review, it has been concluded that 3mm endometrial thickness cut off on transvaginal ultrasonography might exclude the likelihood of developing endometrial cancer in women with postmenopausal bleeding [13,39]. Above all, biopsy remains the gold standard for evaluation. Persistent symptoms often times needs further evaluation for proper prevention and treatment [40,41]. To exclude the occurrence of metastasis diagnostic detection by computed tomography scan, magnetic resonance imaging, Integrated positron emission tomography and computed tomography (PET/CT) scan are necessary. This helps determines the metastatic lymph nodes. The lymph nodes detected in PET/CT scan when compared with MRI and CT has a high sensitivity and possibly high performance detection with 100% sensitivity, 94% specificity and 63% predictive value [13,42,43]. Often times, serum level of CA125 has been investigated also for metastasis [44].

## Pathophysiology of Uterine (Endometrial) Cancer

Endometrial cancer, one of the female reproductive tract malignancy has been diagnosed in about 40,000 women in 2008. of which only 10% is hereditary based leaving 90% sporadic [45].

Several years back amongst women, there have been a major increase in the incidence rate of cancer. In the mid-1970, the incidence rate gradually increased to reach a peak of 30 in the about

1000,000 women [46,47]. In 1980, the incidence and prevalence rates were observed to be 7 and 1.7 respectively when 2,586 asymptomatic women were screened. Although the technique used were costly, the frequency shown were comparative with squamous carcinoma in situ in the cervix of young women. A decrease in the five years survival rate was recorded by the American Society with a 89%-83% decrease in white and 61-52% for African –American population between 1975-1976 and 1979-1984. Thi result can only be attributed to a change in the etiology and risk factors recorded in the past decades [46].

In susceptible women, the risk factors leading to endometrial tumorigenesis needed to be controlled if not prevented completely to improve and contribute to a healthy life. Endometrial cancer can be generally discussed under three majors but overlapping aspect namely; pathogen, histopathology and molecular aspect. As hypothesized by Bokhman in 19883 based on the pathogenic aspect endometrial cancer can be classified into 2 major types namely; the type I estrogen dependent and type II estrogen independent [48,49].

Type I estrogen dependent accounts for the sporadic cause of endometrial cancer in about 70-80 percent of cases. This is associated with unopposed estrogen level, obesity, diabetes amongst other factors. Clinically, they are low grade tumor with favorable prognosis originating from the precursor hyperplasia while the Type II estrogen independent accounts for about 10-20% of endometrial cancer cases. This is hereditary based and the genetic alterations have been used for further classification. Histologically, it appears like clear cells or papillary serous. They have increased spread with poor prognosis [50].

### TYPE I Endometrial cancer

Several genes have been identified with type I estrogen dependent endometrial cancer. Of such genes include PTEN, K-ras, MLH1, MSH2, MSH6, PI3KCA, MSI, ARIDIA and FGFR2 amongst oth-

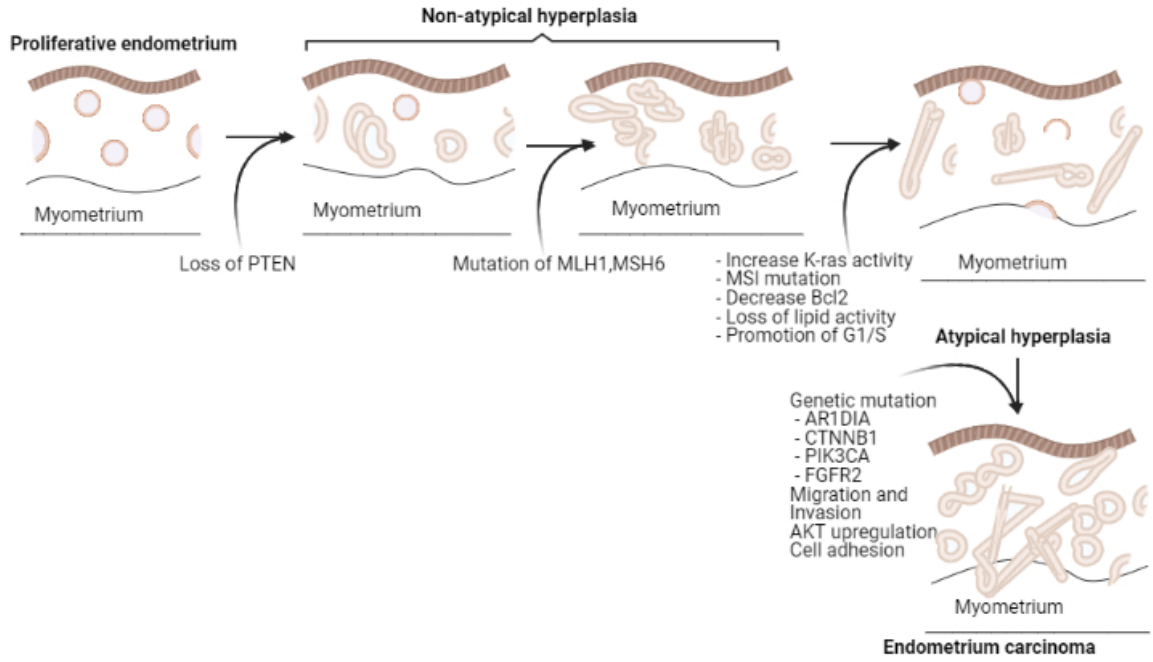


Figure 4: Schematic diagram showing the Type I Endometrial tumorigenesis created by biorender.com.

ers. The interplay in these genes contributes to the disease progression (Figure 4).

PTEN Phosphatase and tens in homolog, a tumor suppressor gene accounts for 83% of type I cancer [51,52]. It is located on chromosome 10q23. In cell cycle regulation it serves as a checkpoint gene at G1/S phase checking the cell's integrity before proceeding to the next phase of the cycle. It works in opposition to PI3KCA to control the action of AKT and its intracellular downstream effect. Mutation of PTEN on both allele leads to the loss of the expression and reverses this mechanism leading to increases cell proliferation and survival, focal cell adhesion, cell migration as well as inhibition of apoptosis [50,53].

Mutation in K-ras at chromosome12 has been reported in about 10-30% of endometrioid cases along with 20% in Microsatellite instability (MSI). K-ras gene an integral part of the RAS/MAPK pathway leads to the amplification of cell proliferation and survival [54,55]. In the early stage of endometrium cancer both MSI and K-ras mutation has been found with MSI targeting genes with repeat sequences. MLHI mutation occurs as a result of hyper-methylation at the CpG Island in the gene promoter region. This methylation maintains heritable repression by controlling DNA accessibility- catenin has also been reported to be mutated in the type I endometrial cancer. The mutation leads to a gain in function in the pathway. 25-38% of patient with type I endometrial cancer have been known to have the B-catenin gene mutated A gain in function of B-catenin gene occurs on chromosome 3p21. This alteration leads to stabilization of the cytoplasmic and nuclear compartment of target genes. Immunohistochemistry assay of type I endometrial cancer has further shown the accumulation of B-catenin when compared with non-endometrioid cases with 31-47% and 0-3% respectively [54,56].

Other mutation also found here include MSH 6 mutation which is relatively uncommon, ARIDIA mutation (AT- rich interacting domain) which contributes to the clinical phenotype by increasing invasion and affecting TGF-B signaling pathway and PIK3CA mutation occurring at chromosome 3q26.3 [57].

**Type II Endometrial cancer**

Also called estrogen independent is hereditary based with several identified mutation which includes P53, FBXW7, CCNE1, PP2R1A, SPOP, HER/neu amongst others. Of all, the commonest mutation is P53. Early in the year 1990, 90% of patient with serous carcinoma have been identified with P53 mutation. This mutation occurs on chromosome 17 [48,54]. With immuno-histochemical staining missense mutation of P53 was discovered serving as a diagnostic tool for testing serous carcinoma. P53 act by inducing apoptosis in damaged cell by inhibiting Rb (retinoblastoma gene) which inturn phosphorylating Cyclin D. In contrast to Type I, it occurs through endometrial atrophy, where invasion to the neighboring cell is absent. Mutated P53 in serous carcinoma leads to continuous propagation of aberrant cell with damaged DNA strand. Mutation of one allele of P53 occurs at the early stage with the other allele mutation occurring at the late phase of the carcinoma [48,50,57]. Mutated P53 leads to P16 a tumor suppressor gene inactivation. This inactivation leads to an uncontrolled cell growth. P16 in activation has been recorded in about 45% of serous carcinomas (Figure 5).

PP2RIA a tumor suppressor gene along with P53 is also one of the major mutation found in Type II endometrial cancer [58]. Along with the hyper-phosphorylation of p70S6K, S6, AKT AND GSK3 beta they promote cell growth by inducing the cell proliferation and survival pathway.17-43% of mutation of PP2RIA have been found in the early stage of serous carcinoma [59,60]. Another tumor suppressor gene, FBXW7 has also been seen in serous carcinoma. FBXW7 forms a complex with SKP1 and CUL 1 to form E3 ubiquitin ligase complex to mediate proteasomal degradation [48].

Other gene alteration in serous carcinoma include TAF1, HER-2/neu and E cadherin, myc, CCNE/Cyclin E and synuclein-y [59,61,62]. The amplification of these genes promotes the proliferation of serous carcinoma. TAF1 mutation have been found in 5-13% of patient with serous carcinoma. A subunit of TFIID transcription complex facilitate RNA polymerase binding to induce transcription of genes.HER-2/neu codes for a tyrosine kinase receptor to facilitate the intracellular signaling cascade. A decrease in E- cadherin with neu amplification leads to a loss in the cell integrity, increase in cell growth and proliferation. Unlike P53, E-cadherin is associated with poor prognosis [48,63].

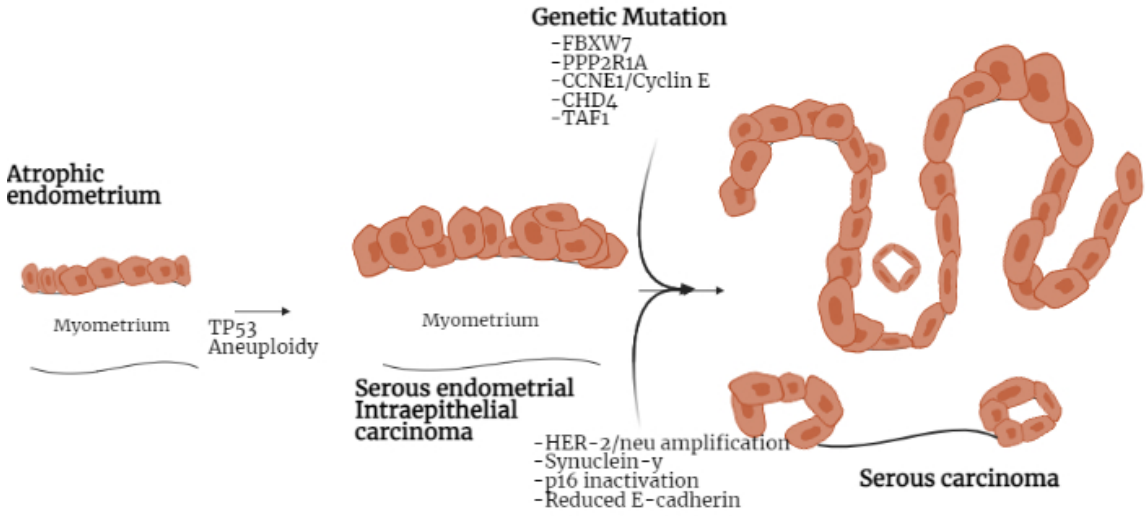


Figure 5: Schematic diagram showing the Type II Serous carcinoma development created by biorender.com.

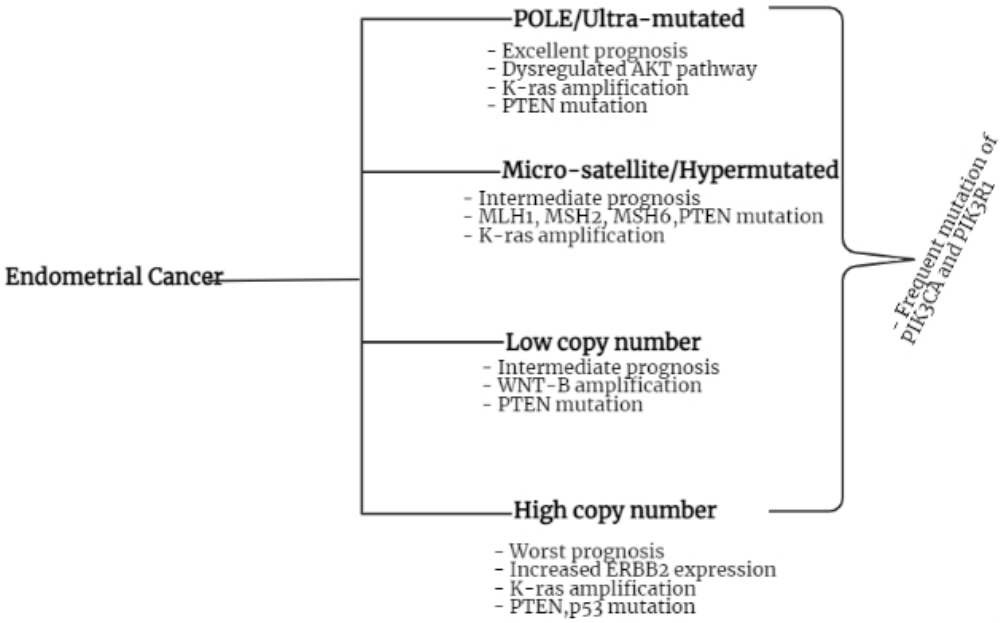


Figure 6: Showing the molecular classification of endometrium cancer development created by biorender.com.

Histopathological analysis has gone a step ahead to show the numerous subtypes of endometrium cancer. They include endometrioid adenocarcinoma, municious carcinoma, serous carcinoma, clear cell carcinoma, squamous carcinoma, undifferentiated carcinoma, and metastatic carcinoma [64]. The most common of all, endometrioid adenocarcinoma is found in about 75-80% of endometrium cancer [65-67]. Endometrioid adenocarcinoma through histopathological grading have been further classified according to FIGO 1988 classification to include villoglandular, secretory, ciliated cells and adenocarcinoma with squamous differentiation. Each subtype have a similar characteristic feature similar to adenocarcinoma with few exception as the case may be (Adapted from FIGO stages-1988 revision. Gynecol Oncol 35:125;1989) [64].

On a final mode of endometrium cancer classification, the molecular aspect of classification provides a distinct feature of the tumor at the molecular level in order for proper prevention and diseases management. Molecular subtype of endometrium cancer includes ultra-muted, hypermutated, endometrioid and serous like with POLE mutated, micro satellite unstable, low copy number and high copy number respectively. Of all, endometrioid remains the most common [48,68].

## Complications Associated with Uterine (Endometrium) Cancer

Complications arising from uterine cancer can occur either due to untreated endometrium cancer or those arising from treatment through surgery. Some of these complications include fertility problem, adhesion and ovarian cyst, surgery complications leading to wound infection, minor bleeding, bruising around the wound ,damage to organs or blood clot in the leg (deep vein thrombosis) or blood clot in the lung(pulmonary embolism), bladder or bowel problems [69]. Some of the complications arriving form treatment through surgery ranges from mild to severe.

### Endometrium and Infertility

Fertility in endometrioid patient is a major complication leading to the less possible chance of getting pregnant. New couples are always on the lookout for the day they will hold their own babies but this is not the case for women with endometriosis. The rate of fecundity per month in women ranges from 0.15-0.2 but this rate decreases as women advances in age. Women with endometriosis have a decrease fecundity rate of 0.02-0.1 leading to a lower chance of conceiving [70-72]. Other factors which have been shown to also contribute to infertility include altered peritoneal, humoral and cell function, distorted pelvic structure, abnormal fertilization and implantation, abnormal endometrial function [72,73]. Research has further demonstrated that about 25-50% of infertile women have endometriosis suggesting a high chance of developing endometrium in women with fertility problem. This estimate is based on histologic finding observed in women undergoing laparoscopy [72,74]. controversial issues arising from the association between infertility and endometriosis was addressed by Jassen and others. In his findings it was discovered that there is an increase in fecundity rate of12% in women with endometriosis when compared with 3.6% found in non-endometrioid patient. This prospective study was in agreement with 2 retrospective study which demonstrated an unexpected fecundity rate in women with endometriosis undergoing insemination [74-77].

Canadian collaborative Group of endometriosis have also shown an increase rate of pregnancy in a randomized trial of laparoscopy with or without treatment [78].

Gruppo italiano per lo studio dell research on the stage I and II endometrium cancer have also shown a 29% chance of fecundity in no treatment group with a 24% rise in the ablation /resection group. This findings have also shown the obvious responsiveness in each patient undergoing therapy in determining the fertility rate [79].

Women with a distorted pelvic structure have been shown to have impairment in the release of egg from the ovaries inhibiting ovum pick up and sperm blockage into the fallopian tube for implantation [80]. Lessey has reported the lack of endometrial integrin expression in the luteal phase of women with endometriosis which helps in implantation. Using rat model with endometriosis Hahn study has also supported that implantation is not possible ultimately leading to infertility [81,82].

Humoral and cellular immunity have also been shown to affect implantation due to increase antibody in the endometrium [73,83].

Increase level of peritoneal have also been reported in women with endometriosis. Increase fluid of prostaglandin, interleukin1, TNF and proteases all impair the fallopian tube, embryo, sperm and oocyte. Prostaglandin may also account for abnormal uterine contraction due to irritation or inflammation [84-86].

**Treatment for infertility**

Treatment administration depends on age, symptoms and fertility. In some cases surgery to remove growth is recommended or medical intervention depending on the stage of endometrium cancer while some other measures combines both [73,87]. In patient who have severe pelvic pain, ablation is recommended [88]. Surgical treatment supported with medical intervention have also been helpful in reducing pain. Effective based therapy for infertility treatment in endometrioid patient include both surgical and reproductive assisted therapy. Such assisted therapy include freezing of eggs, superovulation and intrauterine insemination, in-vitro fertilization and embryo transfer [73,87]. Thanks to IVF, a high fertilization and birth rate has been recorded.

It is important to note that in increasing the chance of getting pregnant it is important to main a good and healthy life style, eating properly a complete diet and engaging in frequent exercise [87]. Pharmaceutical intervention also includes the oral, nasal and injection of estrogen, progesterone and gonadotropin releasing drugs respectively. Of such drugs include danazol, leuprolide, goserelin, progesterone and combined estrogen-progesterine therapy. These drugs helps to control estrogen level production in endometrial tissue and also decrease pituitary production of luteinizing hormone and follicle stimulating hormone [72,89,90].

**Adhesion and ovarian cyst in endometrium**

Adhesion in endometriosis occurs when there is endometrium implant bleeding to neighboring cells leading to the formation of scar tissues [91,92]. This implant are sometimes found in fallopian tubes, ovaries or bladder cutting off blood supply. Just like endometriosis, the adhesion is sometimes accompanied with pains, some women have describes the pain as being painful, stabbing, sharp and intense [91]. Adhesion can also be caused by inflammatory disorder, severe infection or surgery although high risk of developing adhesion occurs from surgery.

Ovarian cyst is of 2 type namely functional and pathogenic cysts. The later arises from endometriosis while the former arises from normal menstrual cycle. Functional cyst can be further divided into follicular cyst or corpus letuem cyst both depending on the release of egg from the fallopian tube or the release of fluid from the corpus letuem leading to fluid buildup. During menstrual cycle the egg is released for implantation and fertilization into the fallopian tube. One there is the release of egg, the remnant of the follicle stimulating hormone corpus leteum helps to release progesterone preparing the uterus lining for pregnancy. This activity is compromised in cyst arising from endometriosis. Implant bleed from endometriosis can be detected by ultrasound. Persistent cyst can be removed by surgery.

**Endometriosis and dyspareunia**

With endometriosis comes severe and intense pain. This pain often time is not time bond. In some women, the pain is amplified through sexual intercourse this is because the penetration pushes tissue growth either behind the vagina or to the lower uterus. Victoria Brooks, a new York based photographer said "with the intense pain, the need for attaining sexual climax is of no relevance [93]. Both quantitative and qualitative measure have been used to further understand the association between pain during intercourse and endometrium cancer.

From the quantitative approach carried out by ferrero et al., while using questionnaires in women with and without endometrium he recorded an increase in the level of dyspareunia with women with endometriosis than those without endometriosis [94,95]. The achieved this with visual analogue scale. Facounnier et al., also went a step further to understand the relationship between the location of endometriosis and pain intensity. It was discovered from his study that 78.8% of women with endometriosis experienced severe pain which was associated with uterosacral ligament. His findings was later affirmed to by porpora et al [96,97]. Vercellini also determined the prevalence and pain intensity to endometriosis stage. Deeppain was also discovered to be associated with vagina endometriosis [98].

Qualitative approach adopted by Denny and Mann [95] while using story telling approach in women with endometrium outpatient

attending clinic, laparoscopy inclusive, he found out that of the 30 patient subjected to the study, 23(86%) experienced dyspareunia with 18(69%) experiencing the pain for several hours after sexual intercourse. The severe pain has been explained to be caused during penetration while the other pain is attributed to a change in position. Further findings have shown the negative effects of endometriosis in active women in that they tend to avoid sex in order to prevent the pain arising from intercourse. This has also led to misunderstanding and arguments between partners.

## Conclusion

It has been revealed in the present review, the genes that are implicated in the pathogenesis and risk factors of endometrial carcinoma (uterine cancer), a particular type of cancer that begins in the uterus, however, most of the endometrial carcinomas (uterine cancer) begin in the endometrial lining of the uterus. Certain risk factors which include among many others are obesity and early menarche. Early diagnosis can be of great advantage in order to prevent metastasis of the endometrial carcinoma. Thus, treatment of uterine cancer is very key to the functionality of the female reproductive system in order to keep to fertility success rate in women. However, surgical intervention include oophorectomy, cervicectomy, lymph node dissection, salpingectomy and hysterectomy respectively.

## References

1. Pask, A. (2016) The reproductive system. Adv Exp Med Biol, 886: 1–12.
2. Olshansky, E. (2014) U n i t t w o.
3. Vaamonde, D., du Plessis, SS., Agarwal, A. (2016) Exercise and human reproduction. Induced fertility disorders and possible therapies. Exerc Hum Reprod Induc Fertil Disord Possible Ther, 1–351.
4. Fahy, K. (2007) Anatomy and Physiology for Midwives by Coad and Dunstall (second ed.), Elsevier, Edinburgh 2005. Women and Birth, 20: 91.
5. Robboy, SJ., Kurita, T., Baskin, L., Cunha, GR. (2017) New insights into human female reproductive tract development. Differentiation, 97: 9–22.
6. Thompson, L. (2019) The Fallopian Tubes (Uterine) - Structure - Function - Vascular Supply.
7. O' neill, T. (2014) How to ensure it's a boy (according to 100-year-old pregnancy guides)
8. Mattson, S., Smith, JE. (2004) Core curriculum for maternal-newborn nursing. St. Louis: Saunders
9. Jing, Y., Run-Qian, L., Hao-Ran, W., Hao-Ran, C., Ya-Bin, L., Yang, G., et al. (2020) Potential influence of COVID-19/ACE2 on the female reproductive system. Molecular Human Reproduction, 26(6): 367-373.
10. Nguyen, J., Duong, H. (2020) Anatomy, Abdomen and Pelvis, Female External GenitaliaStatPearls. StatPearls Publishing
11. The Vulva - Structure - Innervation - TeachMeAnatomy.
12. Siegel, R., Naishadham, D., Jemal, A. (2013) Cancer statistics. CA Cancer J Clin, 63(1): 11–30.
13. Burke, WM., Orr, J., Leitao, M., Salom, E., Gehrig, P., Olawaiye, AB., et al. (2014) Endometrial cancer: A review and current management strategies: Part I SGO Clinical Practice Endometrial Cancer Working Group. Gynecol Oncol, 134(2): 385-392.
14. Oliver, KE., Enewold, LR., Zhu, K., Conrads, TP., Rose, GS., Maxwell, GL., et al. (2011) Racial disparities in histopathologic characteristics of uterine cancer are present in older, not younger blacks in an equal-access environment. Gynecol Oncol, 123(1): 76-81.
15. Society for Medical Oncology (2018) ESMO Patient Guide Series based on the ESMO Clinical Practice Guidelines.
16. Felix, AS., Gaudet, MM., Vecchia C, La., Nagle, CM., (2016) Analysis of the Epidemiology of Endometrial Cancer Consortium, 136(5): 1–26.
17. Ayre, SI., Elit, L. (2014) The epidemiology of endometrial cancer. In: Endometrie432e7tfral Cancer: A Comprehensive Clinical and Translational Update.
18. Kempers, MJE., Kuiper, RP., Ockeloen, CW., Chappuis, PO., Hutter, P., Rahner, N., et al. (2011) Risk of colorectal and endometrial cancers in EPCAM deletion-positive Lynch

syndrome: A cohort study. Lancet Oncol, 12(1): 49-55.

19. Meyer, LA., Broaddus, RR., Lu, KH. (2009) Endometrial cancer and lynch syndrome: Clinical and pathologic considerations. Cancer Control, 16(1): 14–22.

20. Mismatch Repair Defects and Microsatellite Instability (2007)

21. Kempers, MJE., Kuiper, RP., Ockeloen, CW., Chappuis, PO., Hutter, P., Rahner, N., et al. (2011) Risk of colorectal and endometrial cancers in EPCAM deletion-positive Lynch syndrome: A cohort study. Lancet Oncol, 12(1): 49–55.

22. Bonadona, V., Bonaïti, B., Olschwang, S., Grandjouan, S., Huiart, L., Longy, M., et al. (2011) Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in lynch syndrome. JAMA - J Am Med Assoc, 305(22): 2304–2310.

23. Zhou, XP., Kuismanen, S., Nystrom-Lahti, M., Peltomaki, P., Eng, C. (2002) Distinct PTEN mutational spectra in hereditary non-polyposis colon cancer syndrome-related endometrial carcinomas compared to sporadic microsatellite unstable tumors. Hum Mol Genet, 11(4): 445–450.

24. O'Hara, AJ., Bell, DW. (2012) The genomics and genetics of endometrial cancer. Adv Genomics Genet, 2012(2): 33-47.

25. Mutter, GL. (2007) Endometrial Carcinogenesis. In: Molecular Pathology of Gynecologic Cancer. Humana Press, 73–90.

26. Kuismanen, SA., Moisio, AL., Schweizer, P., Truninger, K., Salovaara, R., Arola, J., et al. (2002) Endometrial and colorectal tumors from patients with hereditary nonpolyposis colon cancer display different patterns of microsatellite instability. Am J Pathol, 160(6): 1953–1958.

27. Pijnenborg, JMA., Dam-De Veen, GC., De Haan, J., Van Engeland, M., Groothuis, PG. (2004) Defective mismatch repair and the development of recurrent endometrial carcinoma. Gynecol Oncol, 94(2): 550–559.

28. Simpkins, SB., Bocker, T., Swisher, EM., Mutch, DG., Gersell, DJ., Kovatich, AJ., et al. (1999) MLH1 promoter methylation and gene silencing is the primary cause of microsatellite instability in sporadic endometrial cancers. Hum Mol Genet, 8(4): 661–666.

29. Cheung, LWT., Hennessy, BT., Li, J., Yu, S., Myers, AP., Djordjevic, B., et al. (2011)High frequency of PIK3R1 and PIK3R2 mutations in endometrial cancer elucidates a novel mechanism for regulation of PTEN protein stability. Cancer Discov, 1(2): 170–185.

30. Renehan, A., Tyson, M., Egger, M., Heller, R., Zwahlen, M. (2008) Body-mass Index and Incidence of Cancer: A Systematic Review and Meta-analysis of Prospective Observational Studies. Lancet, 371(9612): 569–578.

31. Onstad, MA., Schmandt, RE., Lu, KH. (2016) Addressing the role of obesity in endometrial cancer risk, prevention, and treatment. Journal of Clinical Oncology. American Society of Clinical Oncology, 34(35): 4225–4230.

32. Calle, EE., Rodriguez, C., Walker-Thurmond, K., Thun, MJ. (2003) Overweight, Obesity, and Mortality from Cancer in a Prospectively Studied Cohort of U.S. Adults. N Engl J Med, 348(17): 1625–1638

33. Park, J., Morley, TS., Kim, M., Clegg, DJ., Scherer, PE. (2014) Obesity and cancer - Mechanisms underlying tumour progression and recurrence. Nat Rev Endocrinol, 10(8): 455–465.

34. Allott, EH., Hursting, SD. (2015) Obesity and cancer: Mechanistic insights from transdisciplinary studies. Endocrine-Related Cancer. BioScientifica Ltd, 22(6): R365–386.

35. Soliman, PT., Wu, D., Tortolero-Luna, G., Schmeler, KM., Slomovitz, BM., Bray, MS., et al. (2006) Association between adiponectin, insulin resistance, and endometrial cancer. Cancer, 106(11): 2376–2381.

36. Gallup, DG., Stock, RJ. (1984) Adenocarcinoma of the endometrium in women 40 years of age or younger. Obstet Gynecol, 64(3): 417–420.

37. Soliman, PT., Oh, JC., Schmeler, KM., Sun, CC., Slomovitz, BM., Gershenson, DM., et al. (2005) Risk factors for young premenopausal women with endometrial cancer. Obstet Gynecol, 105(3): 575–580.

38. Endometrial Cancer Symptoms: 7 Signs of Uterine Cancer Not To Ignore

39. Timmermans, A., Opmeer, BC., Khan, KS., Bachmann, LM., Epstein, E., Clark, TJ., et al. (2010) Endometrial thickness measurement for detecting endometrial cancer in women with postmenopausal bleeding: A systematic review and meta-analysis. Obstetrics and Gynecology. Obstet Gyneco, 116(1): 160–167.

40. Epstein, E., Ramirez, A., Skoog, L., Valentin, L. (2001) Dilatation and curettage fails to detect most focal lesions in the uterine cavity in women with postmenopausal bleeding. Acta Obstet Gynecol Scand, 80(12): 1131–1136.

41. Lee, DO., Jung, MH., Kim, HY. (2011) Prospective comparison of biopsy results from curettage and hysteroscopy in postmenopausal uterine bleeding. J Obstet Gynaecol Res, 37(10): 1423–1426.

42. Signorelli, M., Guerra, L., Buda, A., Picchio, M., Mangili, G., Dell'Anna, T., et al. (2009) Role of the integrated FDG PET/CT in the surgical management of patients with high risk clinical early stage endometrial cancer: Detection of pelvic nodal metastases. Gynecol Oncol, 115(2): 231–235.

43. Kitajima, K., Murakami, K., Yamasaki, E., Kaji, Y., Sugimura, K. (2009) Accuracy of integrated FDG-PET/contrast-enhanced CT in detecting pelvic and paraaortic lymph node metastasis in patients with uterine cancer. Eur Radiol, 19(6): 1529–1536.

44. Hsieh, CH., ChangChien, CC., Lin, H., Huang, EY., Huang, CC., Lan, KC., et al. (2002) Can a preoperative CA 125 level be a criterion for full pelvic lymphadenectomy in surgical staging of endometrial cancer? Gynecol Oncol, 86(1): 28–33.

45. Doll, A., Abal, M., Rigau, M., Monge, M., Gonzalez, M., Demajo, S., et al. (2008) Novel molecular profiles of endometrial cancer-new light through old windows. J Steroid Biochem Mol Biol, 108(3–5): 221–229.

46. Yao, M., Fu, S., Gambone, JC., Berek, S. (1990) Pathophysiology and Management of Endometrial Hyperplasia and Carcinoma, West J Med, 153(1): 50–61.

47. Devesa, SS., Silverman, DT., Young, JLJ., Pollack, ES., Brown, CC., Horm, JW., et al. (1987) Cancer incidence and mortality trends among whites in the United States, 1947-84. J Natl Cancer Inst, 79(4): 701–770.

48. Bell, DW., Ellenson, LH. (2019) Molecular Genetics of Endometrial Carcinoma. Annu Rev Pathol Mech Dis, 14: 339–367.

49. Bokhman, JV. (1983) Two pathogenetic types of endometrial carcinoma. Gynecol Oncol, 15(1): 10–17.

50. Bansal, N., Yendluri, V., Wenham, RM. (2009) The Molecular Biology of Endometrial Cancers and the Implications for Pathogenesis, Classification, and Targeted Therapies. Cancer Control, 16(1): 8-13.

51. Mutter, GL., Lin, MC., Fitzgerald, JT., Kum, JB., Baak, JP., Lees, JA., et al. (2000) Altered PTEN expression as a diagnostic marker for the earliest endometrial precancers. J Natl Cancer Inst, 92(11): 924–930.

52. Mutter, GL., Lin, MC., Fitzgerald, JT., Kum, JB., Baak, JPA., Lees, JA., et al. (2000) Altered PTEN expression as a diagnostic marker for the earliest endometrial precancers. J Natl Cancer Inst, 92(11): 924–931.

53. Maxwell, GL., Risinger, JI., Gumbs, C., Shaw, H., Bentley, RC., Barrett, JC., et al. (1998) Mutation of the PTEN tumor suppressor gene in endometrial hyperplasias. Cancer Res, 58(12): 2500–2503.

54. Lax, SF., Kendall, B., Tashiro, H., Slebos, RJ., Hedrick, L. (2000) The frequency of p53, K-ras mutations, and microsatellite instability differs in uterine endometrioid and serous carcinoma: evidence of distinct molecular genetic pathways. Cancer, 88(4): 814–824.

55. Basil, JB., Goodfellow, PJ., Rader, JS., Mutch, DG., Herzog, TJ. (2000) Clinical significance of microsatellite instability in endometrial carcinoma. Cancer, 89(8): 1758–1764.

56. Saegusa, M., Hashimura, M., Yoshida, T., Okayasu, I. (2001) beta- Catenin mutations and aberrant nuclear expression during endometrial tumorigenesis. Br J Cancer, 84(2): 209–217.

57. Wang, Y., Nicholes, K., Shih, IM. (2020) The Origin and

Pathogenesis of Endometriosis. Annu Rev Pathol Mech Dis,15: 71–95.

58. McConechy, MK., Anglesio, MS., Kalloger, SE., Yang, W., Senz, J., Chow, C., et al. (2011) Subtype-specific mutation of PPP2R1A in endometrial and ovarian carcinomas. J Pathol, 223(5): 567–573.

59. Kuhn, E., Wu, RC., Guan, B., Wu, G., Zhang, J., Wang, Y., et al. (2012) Identification of molecular pathway aberrations in uterine serous carcinoma by genome-wide analyses. J Natl Cancer Inst, 104(19): 1503–1513.

60. Haesen, D., Asbagh, LA., Derua, R., Hubert, A., Schrauwen, S., Hoorne, Y., et al. (2016) Recurrent PPP2R1A mutations in uterine cancer act through a dominant-negative mechanism to promote malignant cell growth. Cancer Res, 76(19): 5719–5731.

61. Morgan, J., Hoekstra, AV., Chapman-Davis, E., Hardt, JL., Kim, JJ., Buttin, BM. (2009) Synuclein-γ (SNCG) may be a novel prognostic biomarker in uterine papillary serous carcinoma. Gynecol Oncol, 114(2): 293–298.

62. Zhang, J., Liu, X-H., Li, C., Wu, XX., Chen, YL., Li, WW., et al. (2020) SNCG promotes the progression and metastasis of high-grade serous ovarian cancer via targeting the PI3K/AKT signaling pathway. Journal of Experimental & Clinical Cancer Research, 39: 79

63. Zhao, S., Choi, M., Overton, JD., Bellone, S., Roque, DM.,, Cocc, E., et al. (2013) Landscape of somatic single-nucleotide and copy-number mutations in uterine serous carcinoma. Proc Natl Acad Sci U S A, 110(8): 2916–2921.

64. Shiozawa, T., Konishi, I. (2004) Pathology of endometrial carcinoma. Nippon rinsho. Japanese journal of clinical medicine, 62: 273–278.

65. Hernandez, E. (1993) Pathological findings and prognosis from uterine malignancy. Current Opinion in Obstetrics and Gynecology, 5: 480–485.

66. Ambros, RA., Kurman, RJ. (1992) Combined assessment of vascular and myometrial invasion as a model to predict prognosis in stage I endometrioid adenocarcinoma of the uterine corpus. Cancer, 69(6): 1424–1431.

67. Fanning, J., Evans, MC., Peters, AJ., Samuel, M., Harmon, ER., Bates, JS. (1989) Endometrial adenocarcinoma histologic subtypes: Clinical and pathologic profile. Gynecol Oncol, 32(3): 288–291.

68. Getz, G., Gabriel, SB., Cibulskis, K., Lander, E., Sivachenko, A., Sougnez, C., et al. (2013) Integrated genomic characterization of endometrial carcinoma, 497(7447): 67–73.

69. Endometriosis - Complications - NHS.

70. Schwartz, D., Mayaux, MJ. (1982) Female Fecundity as a Function of Age. N Engl J Med, 306(7): 404–406.

71. Hughes, EG., Fedorkow, DM., Collins, JA. (1993) A quantitative overview of controlled trials in endometriosis-associated infertility. Fertil Steril, 59(5): 963–970.

72. Schenken, RS. (2009) Infertility Aspects of Endometriosis. Glob Libr Women's Med.

73. Bulletti, C., Coccia, ME., Battistoni, S., Borini, A. (2010) Endometriosis and infertility. J Assist Reprod Genet, 27(8): 441–447.

74. Verkauf, BS. (1987) Incidence, symptoms, and signs of endometriosis in fertile and infertile women. J Fla Med Assoc,74(9): 671–675.

75. Portuondo, JA., Echanojauregui, AD., Herran, C., Alijarte, I. (1983) Early conception in patiens with untreated mild endometriosis. Fertil Steril, 39(1): 22–25.

76. Rodriguez-Escudero, FJ., Neyro, JL., Corcostegui, B., Benito, JA. (1988) Does minimal endometriosis reduce fecundity? Fertil Steril, 50(3): 522–524.

77. Jansen, RPS. (1986) Minimal endometriosis and reduced fecundability: Prospective evidence from an artificial insemination by donor program. Fertil Steril, 46(1): 141–143.

78. Marcoux, S., Maheux, R., Bérubé, S. (1997) Laparoscopic Surgery in Infertile Women with Minimal or Mild Endometriosis. N Engl J Med, 337(4): 217–222.

79. Parazzini, F., Cintio, E Di., Chatenoud, L., Moroni, S., Ardovino, I., Struzziero, E., et al. (1999) Ablation of lesions or no treatment in minimal-mild endometriosis in infertile

women: A randomized trial. Hum Reprod, 14(5): 1332–1334.

80. Schenken, RS., Asch, RH., Williams, RF., Hodgen, GD. (1984) Etiology of infertility in monkeys with endometriosis: Luteinized unruptured follicles, luteal phase defects, pelvic adhesions, and spontaneous abortions. Fertil Steril, 41(1): 122–130.

81. Hahn, DW., Carraher, RP., Foldesy, RG., McGuire, JL. (1986) Experimental evidence for failure to implant as a mechanism of infertility associated with endometriosis. Am J Obstet Gynecol, 155(5): 1109–1113.

82. Lessey, BA., Castelbaum, AJ., Sawin, SW., Buck, CA., Schinnar, R., Bilker, W., et al. (1994) Aberrant integrin expression in the endometrium of women with endometriosis. J Clin Endocrinol Metab, 79(2): 643–649.`

83. Meek, SC., Hodge, DD., Musich, JR. (1988) Autoimmunity in infertile patients with endometriosis. Am J Obstet Gynecol, 158(6 PART 1): 1365–1373.

84. Lebovic, DI., Mueller, MD., Taylor, RN. (2001) Immunobiology of endometriosis. Fertility and Sterility. Fertil Steril, 75(1): 1–10.

85. Halme, J., Becker, S., Haskill, S. (1987) Altered maturation and function of peritoneal macrophages: Possible role in pathogenesis of endometriosis. Am J Obstet Gynecol, 156(4): 783–789.

86. Haney, AF., Muscato, JJ., Weinberg, JB. (1981) Peritoneal fluid cell populations in infertility patients. Fertil Steril, 35(6): 696–698.

87. Getting Pregnant with Endometriosis: Is It Possible? Healthline 2021.

88. Guo, SW. (2009) Recurrence of endometriosis and its control. Hum Reprod Update, 15(4): 441–461.

89. Steingold, KA., Lu, JKH., Judd, HL., Meldrum, DR. (1986) Danazol inhibits steroidogenesis by the human ovary in vivo. Fertil Steril, 45(5): 649–654.

90. Asch, RH., Fernandez, EO., Siler-Khodr, TM., Bartke, A., Pauerstein, CJ. (1980) Mechanism of induction of luteal phase defects by danazol. Am J Obstet Gynecol, 136(7): 932–937.

91. Adhesions | Endometriosis.org .Healthline.April,2021.

92. Endometriosis adhesions: Symptoms, formation, and pictures

93. Endometriosis and Sex: 7 Tips for Relief

94. Ferrero, S., Esposito, F., Abbamonte, LH., Anserini, P., Remorgida, V., Ragni, N. (2005) Quality of sex life in women with endometriosis and deep dyspareunia. Fertil Steril, 83(3): 573–579.

95. Denny, E., Mann, CH. (2007) Endometriosis-associated dyspareunia: The impact on women's lives. J Fam Plan Reprod Heal Care, 33(3): 189–193.

96. Fauconnier, A., Chapron, C., Dubuisson, JB., Vieira, M., Dousset, B., Bréart, G. (2002) Relation between pain symptoms and the anatomic location of deep infiltrating endometriosis. In: Fertility and Sterility. Fertil Steril, 78(4): 719–726.

97. Porpora, MG., Koninckx, PR., Piazze, J., Natili, M., Colagrande, S., Cosmi, EV. (1999) Correlation between endometriosis and pelvic pain. J Am Assoc Gynecol Laparosc, 6(4): 429–434.

98. Vercellini, P. (1997) Endometriosis: What a pain it is. Vol. 15, Seminars in Reproductive Endocrinology. Seminars in Reproductive Endocrinology, 15(3): 251–261.