

Review

A Brief Overview of Oncogenes and Signal Transduction Pathways in Gynecological Cancer

EMMANUEL N. KONTOMANOLIS¹, ANTONIOS KOUTRAS², ZACHARIAS FASOULAKIS², ATHANASIOS SYLLAIOS³, MICHAEL DIAKOSAVVAS², KYVELI ANGELOU², PANAGIOTIS SYMEONIDIS⁴, ATHINA A. SAMARA⁵, VASILIOS PERGIALIOTIS², NIKOLAOS GARMPISS³, DIMITRIOS SCHIZAS³, ATHANASIOS PAGKALOS⁶, ATHANASIOS CHIONIS⁷, GEORGIOS DASKALAKIS² and THOMAS NTOUNIS²

¹Department of Obstetrics and Gynecology, Democritus University of Thrace, Alexandroupolis, Greece;

²1st Department of Obstetrics and Gynecology, National and Kapodistrian University of Athens, General Hospital of Athens 'ALEXANDRA', Athens, Greece;

³1st Department of Surgery, National and Kapodistrian University of Athens, Laikon General Hospital, Athens, Greece;

⁴University General Hospital of Alexandroupolis, Alexandroupolis, Greece;

⁵Department of Surgery, University Hospital of Larissa, Larissa, Greece;

⁶Department of Obstetrics and Gynecology, General Hospital of Xanthi, Xanthi, Greece;

⁷Department of Obstetrics and Gynecology, Laiko General Hospital of Athens, Athens, Greece

Abstract. *Gynecological cancer is the cancer that originates in the female reproductive system. According to the anatomical location of the cancer, it is distinguished into cervical, uterine, vaginal, ovarian, and vulvar cancer. Oncogenes and tumor catalytic genes play a key role in the genesis and development of gynecological cancer. This article presents the signaling pathways and expression of oncogenes that take place in the carcinogenesis of the female reproductive system.*

Lately, cancer has become one of the deadliest diseases in the world (1). World widely, the World Health Organization's statistics indicate an increase of 18,1 million new cases and 9,6 million deaths from cancer (1). Additionally, by the year 2040, the percentage of people developing cancer will be augmented

by 60% and the percentage of cancer deaths will rise up to 70% (1). Scientists define gynecological cancer as a cancer that develops in the female reproductive system (2, 3).

Gynecological cancer, depending on its exact anatomical position, can be divided into the following categories: 1) Cervical cancer. This type of cancer begins in the tissues of the cervix (4). 2) Ovarian cancer, which begins in the ovaries of the female reproductive system. In 2012, ovarian cancer was the seventh most common cancer and the 8th most common cause of cancer death among the female population worldwide (3). 3) Uterine cancer. This cancer begins in the uterus of the female reproductive system (5). 4) Vaginal cancer that starts in the vagina of the female reproductive system (6). 5) Vulvar cancer. This cancer begins in the vulva of the female reproductive system, which is the outer part of the female genitals (7).

This article is freely accessible online.

Correspondence to: Athanasios Syllaios, MD, MSc, PhDc, 1st Department of Surgery, National and Kapodistrian University of Athens, Laikon General Hospital, Agiou Thoma Str. 17, 11527, Athens, Greece. Tel: +30 6972374280, e-mail: nh_reas@hotmail.com

Key Words: Oncogenes, gynecological cancer, signal transduction, gynecological cancer, molecular biology, review.

©2022 International Institute of Anticancer Research
www.iiar-anticancer.org

Oncogenes and Signal Transduction in Gynecological Cancer of Internal Genitalia

Oncogenes and signal transduction. In recent years, scientific research has shown that all stages of carcinogenesis are determined by a series of alterations in a substantially limited class of cellular genes known as oncogenes, tumor suppressor genes, and microRNAs (8). An oncogene is defined as the gene whose function is activated during the process of carcinogenesis (9).

This activation takes place in the following ways: 1) Point mutations, which activate an enzyme, 2) deficiencies that remove negative regulatory regions from proteins, and 3) increased expression, due to disruption of promoter expression or the presence of multiple copies of the gene (“amplification”) (10).

An alteration in a single allele that leads to oncogene activation, is sufficient to allow cancer to either start or progress and is considered to be the predominant mechanism of carcinogenesis. A proto-oncogene is the inactivated form of an oncogene. The proto-oncogene is essentially a normal gene, often with important functions in controlling cellular signals for cell proliferation, differentiation, motility, or cell survival (10). Signal transduction is the mechanism by which a signal is transmitted from the cellular surface to a cell’s nucleus. Many of the transmissions sent throughout the body, *e.g.*, *via* growth factors or neurotransmitters, rely on receptors on cell surfaces. Once activated, the receptors forward the signals to the nucleus *via* signal transduction pathways (10). Regarding gynecological cancer and its various types, a different set of oncogenes have been studied, which are considered to be actively involved in its development and metastasis.

Cervical Cancer

Cutaneous carcinoma is the first in frequency (70-80%) followed by adenocarcinoma (10-25%). Adenocarcinoma is the one with the worst prognosis. As for the other histological types of cervical cancer, they are found in very limited percentages, such as small cell carcinoma, which occurs in less than 1% (11). Depending on the degree of differentiation, tumors are subdivided into well (Grade I), intermediate (Grade II), and poor (Grade III) differentiation, and the depth of filtration seems to play a major role. If the filtration depth is less than one-centimeter, five-year survival rate is estimated to be approximately 90%, while if it is greater than one centimeter, it is estimated to be below 80% (12). In 2020, this cancer was the fourth most frequently diagnosed cancer among women worldwide and the fourth leading cause of cancer death (13). According to World Health Organization statistics, in 2018, the number of women diagnosed with cervical cancer worldwide reached 570,000, while the number of deaths from this type of cancer in the same year was 311,000 (14).

Cervical cancer is most often diagnosed in women between the ages of 35 and 44, with the median age of diagnosis being 50 years of age. Older women do not seem to realize that the risk of cervical cancer persists as they get older. More than 20% of cervical cancers are found in women over the age of 65, while only 6% of cases involve women older than 85 years. However, this cancer appears to occur rarely in women who had undergone regular screening for cervical cancer before the age of 65 years (15).

The most important causative agent for the development of cervical cancer is considered to be the human papillomavirus (HPV) (16). Cervical cancer develops by cervical intraepithelial neoplasia (CIN), caused by HPV (17). Cervical cancer risk factors include: 1) Early age of first sexual intercourse. Women who had their first sexual intercourse before reaching the age of 18, seems to have doubled the risk (18); 2) Immunosuppression, such as seen in women infected with the human immunodeficiency virus (HIV) (19); 3) Large number of sexual partners (20); 4) Existence of a high-risk sexual partners; 5) History of infection with sexually transmitted diseases (21); 6) Active or passive smoking (22); 7) Usage of oral contraceptives (23); 8) Pregnancy and childbirth at a young age (18); 9) Large number of deliveries (24); 10) Racial characteristics (25); 11) Individual history of either vulvar or vaginal intraepithelial lesion or cancer (26); 12) HPV infection (27); 13) Low socio-economic status (28).

Usually, the diagnosis is made during a preventive screening with a Pap test, followed by cytological examination colposcopy and biopsy of the cervix (29). The clinical profile of women with cervical cancer depends directly on the extent and exact anatomical location of the lesion. In early stages, the patient is usually asymptomatic and the diagnosis may occur randomly (30). Symptoms in advanced stages of the disease include: 1) Posterior sternal pain (31); 2) increased vaginal secretions (6); 3) a foul-smelling vaginal secretion (32); 4) Vaginal bleeding (either spontaneously or after sexual intercourse) (33); 5) inguinal lymph nodes enlargement (34); 6) Weakness - fatigue – exhaustion; 7) Anemia; 8) Weight loss (35); 9) Ureteral obstruction; leading to oliguria or anuria in advanced stages of the disease (36).

The management of cervical cancer depends on the stage and extent of the disease. Treatment options include chemotherapy, radiotherapy and surgery (cone resection, radical cervical resection, hysterectomy - partial, radical or modified) (37). In developing countries, where Pap smear availability is limited, cervical cancer is the second leading cause of morbidity and cancer death among women compared to developed countries. It is estimated that if screening for cervical cancer was performed in accordance with international recommendations, the prevalence of this disease could be reduced to >4 per 100,000 cases per year (27).

Oncogenes and signal transduction in cervical cancer (Figure 1). According to Voutsadakis, the process of gene amplification is the most common mechanism of activating oncogenes with the 3q chromosome arm amplification being the most common trigger for the onset of cervical cancer (38). A less dangerous course is realized when *PIK3CA* alterations induce molecular lesions with a better disease-free survival. These alterations are characterized as mutations and amplifications, which must be taken seriously into consideration. Concerning this aspect,

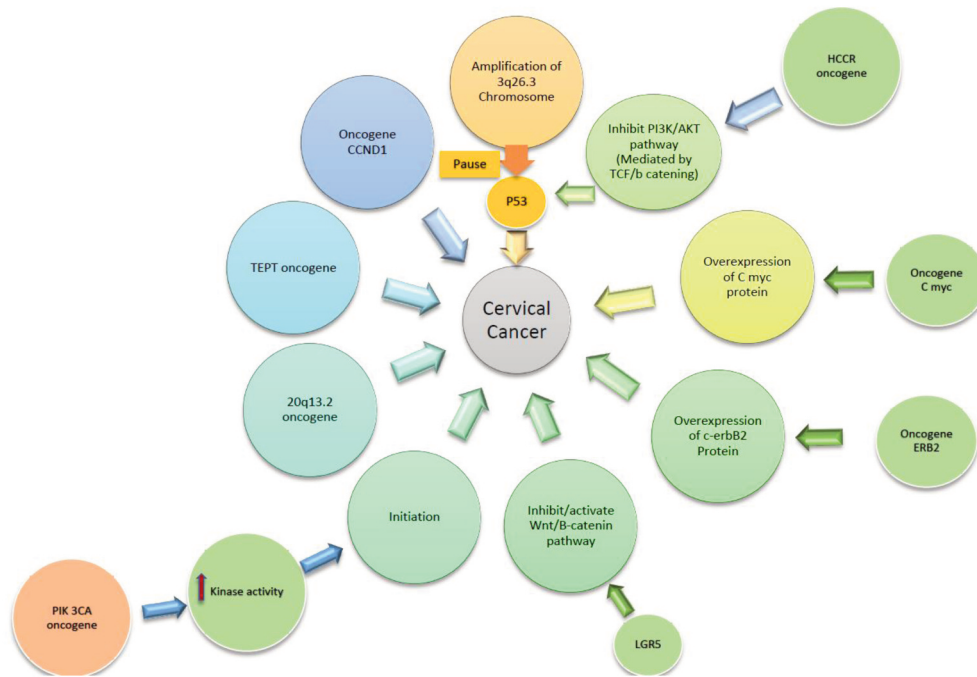


Figure 1. Signal transduction and cervical cancer.

DDR- and MSI- associated genes are associated with higher tumor gene mutation burden (TMB) in *PIK3CA* mutant cancers. *TP53* mutations are being paused by 3q26-amplified cancers. In another study, they sought to elucidate the possible role of the *PIK3CA* oncogene in the mechanism of cervical carcinogenesis using 55 samples of cervical cancer (39). The results showed:

- About 85% of the research samples were infected with HPV.
- Amplification of the 3q26.3 chromosome was found in the majority of samples of gynecological cancer tissues of the cervix.
- An increased number of *PIK3CA* copies (detected by competitive PCR) were detected in the cancer samples and this was associated with high kinase activity (39).

Researchers concluded that *PIK3CA* is one of the oncogenes responsible for cervical carcinogenesis (39). According to Yu-Li and Wang (2015), another oncogene responsible for initiating cervical carcinogenesis is *HCCR*. This oncogene is involved in the development of cervical cancer, by inhibiting the function of the tumor suppressor gene *TP53*. The pathway that signals *HCCR* expression is *PI3K/Akt*, modulated by *TCF/β-catenin* (40). Zhang *et al.* (41) examined 84 tumors of the cervix and came to the following conclusions:

- 77% of the samples were infected with HPV.
- The *PIK3CA* oncogene appeared amplified by 43% on the samples.

- There were other amplified oncogenes in the samples, such as: *TERT* at a rate of 33%, 20q13.2 at a rate of 30%, *C-MYC* at a rate of 25%, and *CCND1* at a rate of 12%.
- Increased expression of c-erbB2 and c-myc proteins was observed in tumors with the corresponding gene amplification.
- Most amplified oncogenes were found mainly in tumors that were infected with HPV (mainly *TERT* and *C-MYC* oncogenes) (41).

Riou *et al.* have long argued that cervical cancer causes various lesions of the *HRAS* gene and this was observed in 36% of the samples (42). According to Pinion *et al.*, cervical cancer cells have over-amplification of the following oncogenes: *Ha-RAS*, *ERB-2* and *C-MYC* (43). Finally, another oncogene that has been implicated in the development of cervical cancer is *LGR5*, which functions by inhibiting or activating the *Wnt/β-catenin* pathway in cervical cancer cells (44).

Ovarian Cancer

Malignant ovarian tumors are epithelial in 90% of the cases. Epithelial tumors may show various degrees of histological differentiation and are considered to be aggressive (45). In recent years, knowledge about the histological origin of ovarian cancer has changed dramatically. The disease was initially thought to originate from the ovarian epithelial cell

lining, but in the light of new evidence, it seems that ovarian cancers originate from other structures (including the fallopian tube and endometrium) (46). These new data are important for both prevention and detection of cancer. They should also be taken into account when conducting clinical trials and experimental studies, especially with regard to the search for new diagnostic markers and new therapeutic targets (46).

According to the latest data, ovarian cancer, although it is not the most common gynecological cancer, it has high rate of mortality (47). In 2012, 239,000 new cases of ovarian cancer were diagnosed worldwide, leading to 152,000 deaths. Ovarian cancer is the 7th most common cancer in women worldwide and ranks 5th in prevalence in developed countries (48). The exact cause of ovarian cancer has not yet been scientifically established, but there are some factors that have been well known to be implicated in increasing the risk (47). These factors include: 1) A positive medical family history of ovarian cancer, breast cancer and /or colorectal cancer (without polyps); 2) Age over 50 years; 3) HPV infection; 4) Smoking; 5) Sedentary life; 6) Obesity; and 7) Endometriosis (47).

In the early stages of the disease, women usually show complete absence of clinical signs and symptoms (47). The diagnosis is based on hereditary and personal history, clinical examination, abdominal and/or vaginal ultrasound (depending on the estimated size of the tumor), possibly the color Doppler, and plasma CA 125 levels (49). In advanced stages symptoms may appear, including:

A possible palpable mass during a typical gynecological examination; 2) Constipation; 3) Feeling of bloating; 4) Dizziness - nausea - vomiting; 5) Weakness, fatigue and exhaustion; 6) Anorexia and weight loss; 7) Anemia; 8) Swelling of the lower extremities; 9) elevated core body temperature (50).

Therapeutic approaches include chemotherapy and surgery (depending on the extent of the disease) (51).

Oncogenes and signal transduction in ovarian cancer (Figure 2). The oncogene HER-2/neu appears to be potentiated in ovarian and breast cancer, at a rate of 25% to 30% in both cases, and is associated with poor prognosis (52). HER-2/neu over-expression is induced by adenovirus type 5 early region 1A (E1A) gene product by repressing HER-2/neu promoter activity. Furthermore, the tumorigenesis of ovarian cancer cells is initialized by the suppression of HER-2/neu.

In addition, there is evidence that the same oncogene may appear amplified in other types of cancer, such as endometrial, gastric, and salivary gland cancers (54). The HER-2/neu proto-oncogene encodes a 185 kDa transmembrane receptor protein with endogenous tyrosine kinase activity, which acts as an epidermal growth factor (53).

According to Berchuck *et al.*, mutation and amplification of the p53 repressor gene is observed in at least half of the cases of ovarian cancer (55). It has also been shown that the

amplification of the HER-2/neu and c Myc oncogenes is also common (54). Bellacosa *et al.* confirmed that potentiation of the *AKT2* oncogene is observed in several cases of ovarian cancer. This oncogene encodes a serine-threonine kinase protein (55). Another study identified p85a as an oncogene that is amplified in ovarian cancer (56).

Amplification of the *c-Myc* oncogene was observed in approximately 33% of ovarian cancers in a study by Baker *et al.* and their finding was confirmed by Sasano and Garrett in 1992 (57, 58).

Increased degree of nuclear atypia and mitotic count is linked with the presence of *c-Myc* amplification. Decisive prognostic factors in human ovarian cancer constitute the nuclear grade and the mitotic index. High mitotic count is linked with *c-Myc* amplification, while the progression from Go to G1 phase of the cell cycle is determined by a factor modulating c-myc.

Another oncogene whose amplification has been shown to be involved in the development of ovarian cancer is PIK3CA, which encodes the p110 α catalytic subunit of phosphatidylinositol 3-kinase (PI3-kinase) (59). Finally, a group of researchers tried to correlate the enhancement of the GIP2 oncogene expression, with the development of ovarian cancer, but did not find a significant correlation (60).

Uterine Cancer

Rarely, cancer of the uterine body comes from histological elements other than the endometrium. There are two types of uterine cancer:

Type 1. This type is more frequently found and accounts for 80% of endometrial cancers. It is related to postmenopausal and concurrently obese women.

Type 2. This type is associated with a poor prognosis, and it usually refers to younger women with a slimmer body type (5).

According to 2018 statistics, endometrial cancer is the 6th most common cancer among the female population worldwide, while in relation to the total population it is ranked in the 15th place (61). Factors, either exogenous or endogenous, that increase uterine exposure to estrogen are associated with increased risk of endometrial adenocarcinoma development (62). Another risk factor that triples the risk of endometrial cancer is polycystic ovarian syndrome (63). Other factors include: 1) Early menarche; 2) Delayed menopause; 3) neglected women (the risk for them is up to twice as high); 4) Exogenous administration of estrogen; 5) Treatment for breast cancer with tamoxifen (risk increases up to twice); 6) Thyroid disease; 7) Elevated body mass index; 8) Advanced age; 9) Diabetes mellitus; 10) Lynch syndrome; 11) HPV infection; 12) Positive medical family history of endometrial, ovarian, colon or breast cancer (64).

Early endometrial cancer diagnosis leads to more positive outcomes. The most common initial symptom is postmenopausal

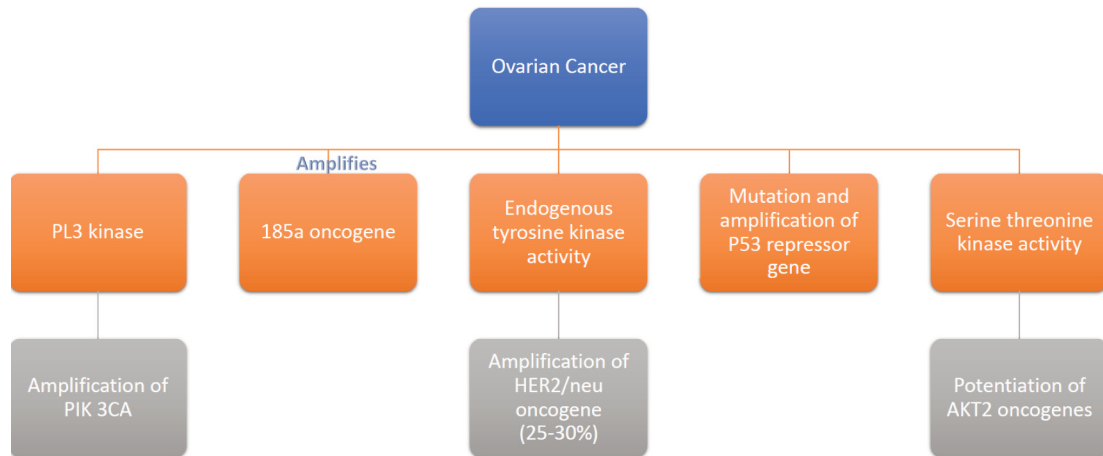


Figure 2. Signal transduction in ovarian cancer.

hemorrhage or spotting, although may also occur in reproductive ages (65). The diagnosis is confirmed by obtaining endometrial biopsy after dilation and curettage or uterine ablation (65). Other symptoms that may appear include: 1) Low hematocrit; 2) Weakness - fatigue – exhaustion; 3) Abdominal - pelvic pain (65).

Surgery is defined as treatment for endometrial cancer, and the surgical technique is determined by the stage of the disease at the time of diagnosis (65).

Oncogenes and signal transduction in uterine cancer (Figure 3). According to Liu *et al.*: 1) Enhancement of the AKT pathway is associated with the development of uterine cancer. 2) Down-regulation of (m6A) mRNA methylation plays an important role in uterine cancer development and 70% of uterine cancer cells show reduction in m6A methylation. 3) Decrease in m6 A methylation led to lower expression of the negative AKT regulator PHLPP2 and higher expression of the positive AKT regulator mTORC2. In conclusion, reduced m6A mRNA methylation acts as an oncogenic mechanism in endometrial cancer development, while m6A methylation has a regulatory effect on AKT signaling (66). METTL4 mutation or downregulated expression of METTL3, a component of the methyltransferase complex, defines reductions in m6A methylation in about 70% of endometrial tumors. The induction of the AKT pathway leads to changes in proliferation and tumorigenicity of endometrial cancer cells. Down-regulation of the expression of the negative AKT regulator PHLPP2 and upregulation of the expression of the positive AKT regulator mTORC2 are mediated by reductions in m6A methylation. These results and the identification of m6A methylation as a defining factor of AKT signaling indicate that m6A mRNA methylation is an oncogenic mechanism in endometrial cancer.

Giannakis *et al.* conducted two prospective cohort studies, which concluded that E3 ubiquitin - RNF43 protein ligase negatively regulates the Wnt signaling pathway and therefore, plays a role not only in ovarian, but also in colon, pancreas, and breast carcinogenesis (67).

Jiang *et al.* demonstrated that PRMT6 is regulated in uterine cancer and exhibits oncogenic activity by activating the AKT/mTOR pathway. In fact, there is increased expression of this oncogene in the cancerous tissues of the uterus and is correlated to disease progression and metastasis development (68). Another proto-oncogene that has been shown to play an important role in the development of uterine cancer is c-FMS, which encodes for the colony stimulating factor receptor (CSF) (69). Finally, according to Lin *et al.*, deregulation of the UBE2S enzyme can accelerate the growth of uterine tumor. This enzyme exerts an oncogenic activity and induces the amplification of c-Myc and Cyclin D1 by activating the SOX6/ β -Catenin signaling (70).

Vaginal Cancer

Vaginal cancer is mainly due to epidermal carcinoma (90% of cases) and adenocarcinoma (5% of cases). Other rarer types are melanoma (2% of cases), sarcoma (2% of cases) and wart carcinoma (1% of cases) (71). This type of gynecological cancer is not so common (1-2% of gynecological cancers) and is usually a metastasis from another primary site. Older women in menopause have a higher risk of developing the disease than younger women with childbearing potential (72). The exact cause of vaginal cancer has not been determined yet. There are various theories about the origin of this cancer but none is fully scientifically substantiated (72). The following factors have

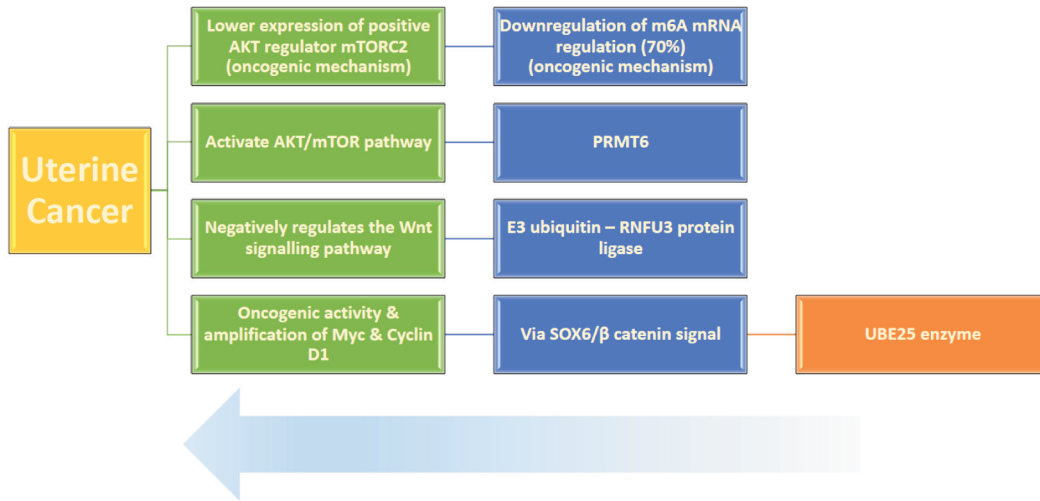


Figure 3. Signal transduction in uterine cancer.

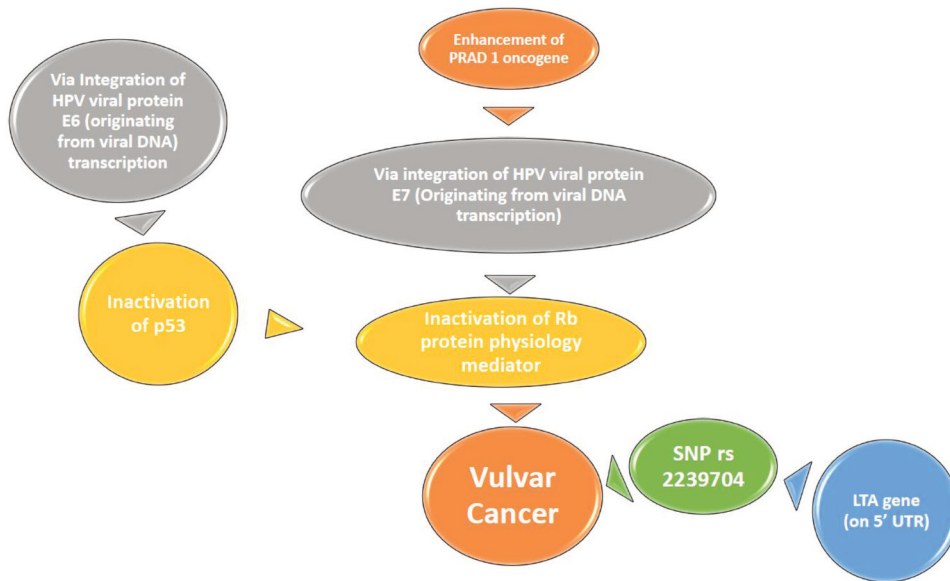


Figure 4. Signal transduction in vulvar cancer.

been implicated: 1) Multiple sexual partners; 2) Young age during the first sexual intercourse; 3) Smoking; 4) Excessive alcohol consumption; 5) HPV infection (73).

The initial diagnosis is based on a careful examination of the vagina and cytological smears, while the final diagnosis is made by biopsy (72). In the early stages, the disease is asymptomatic and thus difficult to detect. In more advanced stages symptoms may appear such as: 1) Vaginal bleeding; 2) Bleeding or pain during sexual intercourse; 3) Bad smelling vaginal secretions; 4) Increased vaginal secretions;

5) Intense vaginal itching that does not subside; 6) Urinary discomfort (72).

The main treatment options for vaginal cancer are radiation therapy, surgery, and chemotherapy if metastases are present (74).

Vulvar Cancer

About 90% is due to epidermal carcinoma, while the rest is due to wart carcinoma, melanoma, basal cell carcinoma or sarcoma

(75). Vulvar cancer belongs to the category of rare gynecological cancers as it represents 4% of gynecological tumors (75). The pathogenesis of vulvar cancer refers to dysplasia that usually arises from the HPV or from vulvar dermatitis, such as sclerosis of the vulva (75). Risk factors include: 1) Smoking; 2) Positive personal medical history of sexually transmitted diseases; 3) Immunosuppression; 4) Increased body weight; 5) Diabetes mellitus; 6) Hypertension (76).

For the diagnosis of vulvar cancer, it is necessary to perform a biopsy. Other additional examinations that are usually performed include pelvic magnetic tomography, abdominal CT scan (disease staging), groin ultrasound (lymph nodes evaluation) and various blood tests (75). The main symptom of the disease is itching of the vulva, which very often becomes very persistent and unbearable. Other symptoms are: 1) Genital pain; 2) Vulvar swelling; 3) Increased secretions with possible presence of blood; 4) Superficial inguinal lymph node swelling; 5) Difficulty urinating and / or defecating; 6) Weakness - fatigue (75).

In case of early-stage diagnosis, a radical local resection can be performed without lymph node dissection. Unfortunately, vulvar cancer in most cases is diagnosed usually at advanced stage. The surgical techniques applied in these cases depend on the respective stage of the disease. A radical “butterfly” type vasectomy is usually performed with lymph node dissection (removal of the perineum, anus, and rectum may be required) or radical resection. In addition, the patient may need to undergo a cycle of radiation and/or chemotherapy (71).

Oncogenes and signal transduction in vulvar cancer (Figure 4). Research has shown that in vulvar cancer there is amplification of the *PRADI* oncogene. This oncogene has also been shown to be amplified in cases of cervical cancer (77). *PRADZ* (*CYCLIN D1*) protein encoded by this tumor suppressor gene, physiologically regulates the inactivation of retinoblastoma protein. The E6 and E7 viral proteins are being transcribed following integration of the viral DNA into human genome. Concerning E7 proteins, they interact with the retinoblastoma protein, while E6 proteins interact with the product of the p53 tumor suppressor gene. As a result, there is a deactivation of retinoblastoma and p53 proteins. Retinoblastoma or p53 mutations appear in some cervical cancers and tumor suppressor genes.

Bodelon *et al.* confirmed that mutation in a gene as well as HPV infection play an important role in the development of vulvar cancer. The authors found that SNP rs2239704, found in the 5' UTR of the *LTA* gene, is significantly associated with carcinogenesis in both vulvar and cervical tissues (78).

Conclusion

This review of the literature indicates that in recent years there has been a lot of research on the genetic contribution to the

development of gynecological cancer. Several signaling pathways and oncogenes have been implicated in the development, growth, and metastasis of gynecological cancer.

Conflicts of Interest

The Authors declare that they have no competing interests in relation to this work.

Authors' Contributions

S.D, G.N, C.A, K.NE and S.P; Contributed to conception and design. K.NE, N.T, F.Z, AK and P.A.; were responsible for overall supervision. SA, S.AA, D.M and K.A; Drafted the manuscript, which was revised by K.NE. All Authors read and approved the final manuscript.

References

- 1 A tool that predicts the future cancer incidence and mortality burden worldwide from the current estimates in 2018 up until 2040, 2018. France, WHO - World Health Organization. Available at: <https://gco.iarc.fr/tomorrow/en>
- 2 Grywalska E, Sobstyl M, Putowski L and Roliński J: Current possibilities of gynecologic cancer treatment with the use of immune checkpoint inhibitors. *Int J Mol Sci* 20(19): 4705, 2019. PMID: 31547532. DOI: 10.3390/ijms20194705
- 3 What is gynecologic cancer? CDC - Centers for Disease Control and Prevention, 2019. Available at: https://www.cdc.gov/cancer/gynecologic/basic_info/what-is-gynecologic-cancer.htm [Last accessed on August 16, 2021]
- 4 Key Statistics for Cervical Cancer, 2016. American Cancer Society. Available at: <https://www.cancer.org/cancer/cervical-cancer/about/key-statistics.html> [Last accessed on January 12, 2021]
- 5 Faizan U and Muppidi V: Uterine cancer. 2021. PMID: 32965984.
- 6 Kaltenecker B and Tikaria R: Vaginal Cancer. In: StatPearls (Internet). Treasure Island, FL, USA, StatPearls Publishing, 2021. Available at: <https://www.ncbi.nlm.nih.gov/books/NBK559126/> [Last accessed on July 19, 2021]
- 7 Capria A, Tahir N and Fatehi M: Vulva Cancer. In: StatPearls (Internet). Treasure Island, FL, USA, StatPearls Publishing, 2021. Available at: <https://www.ncbi.nlm.nih.gov/books/NBK567798/> [Last accessed on June 26, 2021]
- 8 Ahmad J, Hasnain SE, Siddiqui MA, Ahamed M, Musarrat J and Al-Khedhairi AA: MicroRNA in carcinogenesis & cancer diagnostics: a new paradigm. *Indian J Med Res* 137(4): 680-694, 2013. PMID: 23703335.
- 9 Proto-Oncogenes and Tumor-Suppressor Genes Lodish H, Berk A and Zipursky SL: Proto-Oncogenes and Tumor-Suppressor Genes. In: *Molecular Cell Biology*, 4th edition. W.H. Freeman (ed.). New York, Section 24.2, 2000. Available at: <https://www.scirp.org/%28S%28351jmbntvnsjt1aadkposzje%29%29/reference/referencespapers.aspx?referenceid=1312254> [Last accessed on October 20, 2014]
- 10 Kontomanolis EN, Koutras A, Syllaios A, Schizas D, Mastoraki A, Garpis N, Diakosavvas M, Angelou K, Tsatsaris G, Pagkalos A, Ntounis T and Fasoulakis Z: Role of oncogenes and

- tumor-suppressor genes in carcinogenesis: a review. *Anticancer Res* 40(11): 6009-6015, 2020. PMID: 33109539. DOI: 10.21873/anticancer.14622
- 11 Burd EM: Human papillomavirus and cervical cancer. *Clin Microbiol Rev* 16(1): 1-17, 2003. PMID: 12525422. DOI: 10.1128/CMR.16.1.1-17.2003
 - 12 Matsuo K, Mandelbaum RS, Machida H, Purushotham S, Grubbs BH, Roman LD and Wright JD: Association of tumor differentiation grade and survival of women with squamous cell carcinoma of the uterine cervix. *J Gynecol Oncol* 29(6): e91, 2018. PMID: 30207099. DOI: 10.3802/jgo.2018.29.e91
 - 13 Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A and Bray F: Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 71(3): 209-249, 2021. PMID: 33538338. DOI: 10.3322/caac.21660
 - 14 Arbyn M, Weiderpass E, Bruni L, de Sanjosé S, Saraiya M, Ferlay J and Bray F: Estimates of incidence and mortality of cervical cancer in 2018: a worldwide analysis. *Lancet Glob Health* 8(2): e191-e203, 2020. PMID: 31812369. DOI: 10.1016/S2214-109X(19)30482-6
 - 15 Castañón A, Landy R, Cuzick J and Sasieni P: Cervical screening at age 50-64 years and the risk of cervical cancer at age 65 years and older: population-based case control study. *PLoS Med* 11(1): e1001585, 2014. PMID: 24453946. DOI: 10.1371/journal.pmed.1001585
 - 16 Biswas A: Human papillomavirus (HPV) and cervical cancer. *J Indian Med Assoc* 98(2): 53-55, 2000. PMID: 11016151.
 - 17 Cox JT: Epidemiology of cervical intraepithelial neoplasia: the role of human papillomavirus. *Baillieres Clin Obstet Gynaecol* 9(1): 1-37, 1995. PMID: 7600720. DOI: 10.1016/s0950-3552(05)80357-8
 - 18 Louie KS, de Sanjose S, Diaz M, Castellsagué X, Herrero R, Meijer CJ, Shah K, Franceschi S, Muñoz N, Bosch FX and International Agency for Research on Cancer Multicenter Cervical Cancer Study Group: Early age at first sexual intercourse and early pregnancy are risk factors for cervical cancer in developing countries. *Br J Cancer* 100(7): 1191-1197, 2009. PMID: 19277042. DOI: 10.1038/sj.bjc.6604974
 - 19 Ghebre RG, Grover S, Xu MJ, Chuang LT and Simonds H: Cervical cancer control in HIV-infected women: Past, present and future. *Gynecol Oncol Rep* 21: 101-108, 2017. PMID: 28819634. DOI: 10.1016/j.gore.2017.07.009
 - 20 Finocchiaro-Kessler S, Wexler C, Maloba M, Mabachi N, Ndikum-Moffor F and Bukusi E: Cervical cancer prevention and treatment research in Africa: a systematic review from a public health perspective. *BMC Womens Health* 16: 29, 2016. PMID: 27259656. DOI: 10.1186/s12905-016-0306-6
 - 21 Frazier EL, Sutton MY, Tie Y, McNaghten AD, Blair JM and Skarbinski J: Screening for cervical cancer and sexually transmitted diseases among HIV-infected women. *J Womens Health (Larchmt)* 25(2): 124-132, 2016. PMID: 26447835. DOI: 10.1089/jwh.2015.5368
 - 22 Min KJ, Lee JK, So KA and Kim MK: Association between passive smoking and the risk of cervical intraepithelial neoplasia 1 in Korean women. *J Epidemiol* 28(1): 48-53, 2018. PMID: 29093300. DOI: 10.2188/jea.JE20160118
 - 23 Asthana S, Busa V and Labani S: Oral contraceptives use and risk of cervical cancer-A systematic review & meta-analysis. *Eur J Obstet Gynecol Reprod Biol* 247: 163-175, 2020. PMID: 32114321. DOI: 10.1016/j.ejogrb.2020.02.014
 - 24 Hinkula M, Pukkala E, Kyyrönen P, Laukkanen P, Koskela P, Paaavonen J, Lehtinen M and Kauppila A: A population-based study on the risk of cervical cancer and cervical intraepithelial neoplasia among grand multiparous women in Finland. *Br J Cancer* 90(5): 1025-1029, 2004. PMID: 14997202. DOI: 10.1038/sj.bjc.6601650
 - 25 Pratte MA, Griffin A, Ogazi C, Yurasevecz S, Blanks CA, McCooley L and Kaufman JS: Racial/ethnic disparities in cervical cancer screening services among contractors of the connecticut breast and cervical cancer early detection program. *Health Equity* 2(1): 30-36, 2018. PMID: 29696243. DOI: 10.1089/heq.2017.0038
 - 26 Buchanan TR, Zamorano AS, Massad LS, Liu J, Thaker PH, Powell MA, Mutch DG and Kuroki LM: Risk of cervical and vaginal dysplasia after surgery for vulvar intraepithelial neoplasia or cancer: A 6 year follow-up study. *Gynecol Oncol* 155(1): 88-92, 2019. PMID: 31375270. DOI: 10.1016/j.ygyno.2019.07.017
 - 27 Zhang S, Xu H, Zhang L and Qiao Y: Cervical cancer: Epidemiology, risk factors and screening. *Chin J Cancer Res* 32(6): 720-728, 2020. PMID: 33446995. DOI: 10.21147/j.issn.1000-9604.2020.06.05
 - 28 Akinyemiju T, Ogunsina K, Sakhuja S, Ogbhodo V and Braithwaite D: Life-course socioeconomic status and breast and cervical cancer screening: analysis of the WHO's Study on Global Ageing and Adult Health (SAGE). *BMJ Open* 6(11): e012753, 2016. PMID: 27881528. DOI: 10.1136/bmjopen-2016-012753
 - 29 Mishra GA, Pimple SA and Shastri SS: An overview of prevention and early detection of cervical cancers. *Indian J Med Paediatr Oncol* 32(3): 125-132, 2011. PMID: 22557777. DOI: 10.4103/0971-5851.92808
 - 30 Petignat P and Roy M: Diagnosis and management of cervical cancer. *BMJ* 335(7623): 765-768, 2007. PMID: 17932207. DOI: 10.1136/bmj.39337.615197.80
 - 31 Kim YJ, Munsell MF, Park JC, Meyer LA, Sun CC, Brown AJ, Bodurka DC, Williams JL, Chase DM, Bruera E and Ramondetta LM: Retrospective review of symptoms and palliative care interventions in women with advanced cervical cancer. *Gynecol Oncol* 139(3): 553-558, 2015. PMID: 26432043. DOI: 10.1016/j.ygyno.2015.09.079
 - 32 Aziz N and Yousfani S: Pattern of presentation of cervical carcinoma at Nuclear Institute of Medicine and Radiotherapy, Pakistan. *Pak J Med Sci* 29(3): 814-817, 2013. PMID: 24353634.
 - 33 Gyenwali D, Pariyar J and Onta SR: Factors associated with late diagnosis of cervical cancer in Nepal. *Asian Pac J Cancer Prev* 14(7): 4373-4377, 2013. PMID: 23992006. DOI: 10.7314/apjcp.2013.14.7.4373
 - 34 Toita T, Nakano M, Higashi M, Sakumoto K and Kanazawa K: Prognostic value of cervical size and pelvic lymph node status assessed by computed tomography for patients with uterine cervical cancer treated by radical radiation therapy. *Int J Radiat Oncol Biol Phys* 33(4): 843-849, 1995. PMID: 7591892. DOI: 10.1016/0360-3016(95)00204-5
 - 35 Cull A, Cowie VJ, Farquharson DI, Livingstone JR, Smart GE and Elton RA: Early stage cervical cancer: psychosocial and sexual outcomes of treatment. *Br J Cancer* 68(6): 1216-1220, 1993. PMID: 8260376. DOI: 10.1038/bjc.1993.507
 - 36 Patel K, Foster NR, Kumar A, Grudem M, Longenbach S, Bakkum-Gomez J, Haddock M, Dowdy S and Jatoi A: Hydrometaphrosis in patients with cervical cancer: an assessment of morbidity and survival. *Support Care Cancer* 23(5): 1303-1309, 2015. PMID: 25339620. DOI: 10.1007/s00520-014-2482-y

- 37 PDQ Adult Treatment Editorial Board: Cervical cancer treatment (PDQ®): Health professional version. 2021. PMID: 26389493.
- 38 Voutsadakis IA: 3q26 amplifications in cervical squamous carcinomas. *Curr Oncol* 28(4): 2868-2880, 2021. PMID: 34436017. DOI: 10.3390/curroncol28040251
- 39 Ma YY, Wei SJ, Lin YC, Lung JC, Chang TC, Whang-Peng J, Liu JM, Yang DM, Yang WK and Shen CY: PIK3CA as an oncogene in cervical cancer. *Oncogene* 19(23): 2739-2744, 2000. PMID: 10851074. DOI: 10.1038/sj.onc.1203597
- 40 Li XY and Wang X: The role of human cervical cancer oncogene in cancer progression. *Int J Clin Exp Med* 8(6): 8363-8368, 2015. PMID: 26309489.
- 41 Zhang A, Mánér S, Betz R, Angström T, Stendahl U, Bergman F, Zetterberg A and Wallin KL: Genetic alterations in cervical carcinomas: frequent low-level amplifications of oncogenes are associated with human papillomavirus infection. *Int J Cancer* 101(5): 427-433, 2002. PMID: 12216070. DOI: 10.1002/ijc.10627
- 42 Riou G, Sheng ZM, Zhou D, Lusinchi A, Le Doussal V and Barrois M: [c-myc and c-Ha-ras proto-oncogenes in cervical cancer: prognostic value]. *Bull Cancer* 77(4): 341-347, 1990. PMID: 2191730.
- 43 Pinion SB, Kennedy JH, Miller RW and MacLean AB: Oncogene expression in cervical intraepithelial neoplasia and invasive cancer of cervix. *Lancet* 337(8745): 819-820, 1991. PMID: 1672915. DOI: 10.1016/0140-6736(91)92518-7
- 44 Chen Q, Cao HZ and Zheng PS: LGR5 promotes the proliferation and tumor formation of cervical cancer cells through the Wnt/ β -catenin signaling pathway. *Oncotarget* 5(19): 9092-9105, 2014. PMID: 25193857. DOI: 10.18632/oncotarget.2377
- 45 Cho KR and Shih IeM: Ovarian cancer. *Annu Rev Pathol* 4: 287-313, 2009. PMID: 18842102. DOI: 10.1146/annurev.pathol.4.110807.092246
- 46 Kurman RJ and Shih IeM: The origin and pathogenesis of epithelial ovarian cancer: a proposed unifying theory. *Am J Surg Pathol* 34(3): 433-443, 2010. PMID: 20154587. DOI: 10.1097/PAS.0b013e3181cf3d79
- 47 Momenimovahed Z, Tiznobaik A, Taheri S and Salehiniya H: Ovarian cancer in the world: epidemiology and risk factors. *Int J Womens Health* 11: 287-299, 2019. PMID: 31118829. DOI: 10.2147/IJWH.S197604
- 48 Reid BM, Permut JB and Sellers TA: Epidemiology of ovarian cancer: a review. *Cancer Biol Med* 14(1): 9-32, 2017. PMID: 28443200. DOI: 10.20892/j.issn.2095-3941.2016.0084
- 49 Rauh-Hain JA, Krivak TC, Del Carmen MG and Olawaiye AB: Ovarian cancer screening and early detection in the general population. *Rev Obstet Gynecol* 4(1): 15-21, 2011. PMID: 21629494.
- 50 Suh-Burgmann EJ and Alavi M: Detection of early stage ovarian cancer in a large community cohort. *Cancer Med* 8(16): 7133-7140, 2019. PMID: 31568690. DOI: 10.1002/cam4.2522
- 51 Cortez AJ, Tudrej P, Kujawa KA and Lisowska KM: Advances in ovarian cancer therapy. *Cancer Chemother Pharmacol* 81(1): 17-38, 2018. PMID: 29249039. DOI: 10.1007/s00280-017-3501-8
- 52 Cirisano FD and Karlan BY: The role of the HER-2/neu oncogene in gynecologic cancers. *J Soc Gynecol Investig* 3(3): 99-105, 1996. PMID: 8796816.
- 53 Moasser MM: The oncogene HER2: its signaling and transforming functions and its role in human cancer pathogenesis. *Oncogene* 26(45): 6469-6487, 2007. PMID: 17471238. DOI: 10.1038/sj.onc.1210477
- 54 Berchuck A, Kohler MF and Bast RC Jr: Oncogenes in ovarian cancer. *Hematol Oncol Clin North Am* 6(4): 813-827, 1992. PMID: 1500387.
- 55 Bellacosa A, de Feo D, Godwin AK, Bell DW, Cheng JQ, Altomare DA, Wan M, Dubeau L, Scambia G, Masciullo V, Ferrandina G, Benedetti Panici P, Mancuso S, Neri G and Testa JR: Molecular alterations of the AKT2 oncogene in ovarian and breast carcinomas. *Int J Cancer* 64(4): 280-285, 1995. PMID: 7657393. DOI: 10.1002/ijc.2910640412
- 56 Rao L, Mak VCY, Zhou Y, Zhang D, Li X, Fung CCY, Sharma R, Gu C, Lu Y, Tipoe GL, Cheung ANY, Mills GB and Cheung LWT: p85 β regulates autophagic degradation of AXL to activate oncogenic signaling. *Nat Commun* 11(1): 2291, 2020. PMID: 32385243. DOI: 10.1038/s41467-020-16061-7
- 57 Baker VV, Borst MP, Dixon D, Hatch KD, Shingleton HM and Miller D: c-myc amplification in ovarian cancer. *Gynecol Oncol* 38(3): 340-342, 1990. PMID: 2227545. DOI: 10.1016/0090-8258(90)90069-w
- 58 Sasano H and Garrett CT: Oncogenes in gynecological tumors. *Curr Top Pathol* 85: 357-372, 1992. PMID: 1628518. DOI: 10.1007/978-3-642-75941-3_12
- 59 Chalhoub N and Baker SJ: PTEN and the PI3-kinase pathway in cancer. *Annu Rev Pathol* 4: 127-150, 2009. PMID: 18767981. DOI: 10.1146/annurev.pathol.4.110807.092311
- 60 Park JT, Shih IeM and Wang TL: Identification of Pbx1, a potential oncogene, as a Notch3 target gene in ovarian cancer. *Cancer Res* 68(21): 8852-8860, 2008. PMID: 18974129. DOI: 10.1158/0008-5472.CAN-08-0517
- 61 Zhang S, Gong TT, Liu FH, Jiang YT, Sun H, Ma XX, Zhao YH and Wu QJ: Global, Regional, and National Burden of endometrial cancer, 1990-2017: Results from the Global Burden of Disease Study, 2017. *Front Oncol* 9: 1440, 2019. PMID: 31921687. DOI: 10.3389/fonc.2019.01440
- 62 Brown SB and Hankinson SE: Endogenous estrogens and the risk of breast, endometrial, and ovarian cancers. *Steroids* 99(Pt A): 8-10, 2015. PMID: 25555473. DOI: 10.1016/j.steroids.2014.12.013
- 63 Dumesic DA and Lobo RA: Cancer risk and PCOS. *Steroids* 78(8): 782-785, 2013. PMID: 23624028. DOI: 10.1016/j.steroids.2013.04.004
- 64 Raglan O, Kalliala I, Markozannes G, Cividini S, Gunter MJ, Nautiyal J, Gabra H, Paraskeva E, Martin-Hirsch P, Tsilidis KK and Kyrgiou M: Risk factors for endometrial cancer: An umbrella review of the literature. *Int J Cancer* 145(7): 1719-1730, 2019. PMID: 30387875. DOI: 10.1002/ijc.31961
- 65 Clarke MA, Long BJ, Del Mar Morillo A, Arbyn M, Bakkum-Gamez JN and Wentzensen N: Association of endometrial cancer risk with postmenopausal bleeding in women: a systematic review and meta-analysis. *JAMA Intern Med* 178(9): 1210-1222, 2018. PMID: 30083701. DOI: 10.1001/jamainternmed.2018.2820
- 66 Liu J, Eckert MA, Harada BT, Liu SM, Lu Z, Yu K, Tienda SM, Chryplewicz A, Zhu AC, Yang Y, Huang JT, Chen SM, Xu ZG, Leng XH, Yu XC, Cao J, Zhang Z, Liu J, Lengyel E and He C: m⁶A mRNA methylation regulates AKT activity to promote the proliferation and tumorigenicity of endometrial cancer. *Nat Cell Biol* 20(9): 1074-1083, 2018. PMID: 30154548. DOI: 10.1038/s41556-018-0174-4
- 67 Giannakis M, Hodis E, Jasmine Mu X, Yamauchi M, Rosenbluh J, Cibulskis K, Saksena G, Lawrence MS, Qian ZR, Nishihara R, Van Allen EM, Hahn WC, Gabriel SB, Lander ES, Getz G, Ogino S, Fuchs CS and Garraway LA: RNF43 is frequently mutated in

- colorectal and endometrial cancers. *Nat Genet* 46(12): 1264-1266, 2014. PMID: 25344691. DOI: 10.1038/ng.3127
- 68 Jiang N, Li QL, Pan W, Li J, Zhang MF, Cao T, Su SG and Shen H: PRMT6 promotes endometrial cancer *via* AKT/mTOR signaling and indicates poor prognosis. *Int J Biochem Cell Biol* 120: 105681, 2020. PMID: 31884111. DOI: 10.1016/j.biocel.2019.105681
- 69 Leiserowitz GS, Harris SA, Subramaniam M, Keeney GL, Podratz KC and Spelsberg TC: The proto-oncogene *c-fms* is overexpressed in endometrial cancer. *Gynecol Oncol* 49(2): 190-196, 1993. PMID: 8504987. DOI: 10.1006/gyno.1993.1106
- 70 Lin M, Lei T, Zheng J, Chen S, Du L and Xie H: UBE2S mediates tumor progression *via* SOX6/ β -Catenin signaling in endometrial cancer. *Int J Biochem Cell Biol* 109: 17-22, 2019. PMID: 30690078. DOI: 10.1016/j.biocel.2019.01.014
- 71 PDQ Adult Treatment Editorial Board: Vaginal cancer treatment (PDQ®): Health professional version. 2021. PMID: 26389242.
- 72 Rajaram S, Maheshwari A and Srivastava A: Staging for vaginal cancer. *Best Pract Res Clin Obstet Gynaecol* 29(6): 822-832, 2015. PMID: 25847318. DOI: 10.1016/j.bpobgyn.2015.01.006
- 73 Goodman A: Primary vaginal cancer. *Surg Oncol Clin N Am* 7(2): 347-361, 1998. PMID: 9537981.
- 74 Rajaram S and Gupta B: Management of vulvar cancer. *Rev Recent Clin Trials* 10(4): 282-288, 2015. PMID: 26411953. DOI: 10.2174/1574887110666150923112723
- 75 Rogers LJ and Cuello MA: Cancer of the vulva. *Int J Gynaecol Obstet* 143(Suppl 2): 4-13, 2018. PMID: 30306583. DOI: 10.1002/ijgo.12609
- 76 Koh WJ, Greer BE, Abu-Rustum NR, Campos SM, Cho KR, Chon HS, Chu C, Cohn D, Crispens MA, Dizon DS, Dorigo O, Eifel PJ, Fisher CM, Frederick P, Gaffney DK, Han E, Higgins S, Huh WK, Lurain JR 3rd, Mariani A, Mutch D, Nagel C, Nekhlyudov L, Fader AN, Remmenga SW, Reynolds RK, Tillmanns T, Ueda S, Valea FA, Wyse E, Yashar CM, McMillian N and Scavone J: Vulvar cancer, version 1.2017, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw* 15(1): 92-120, 2017. PMID: 28040721. DOI: 10.6004/jnccn.2017.0008
- 77 Kurzrock R, Ku S and Talpaz M: Abnormalities in the PRAD1 (CYCLIN D1/BCL-1) oncogene are frequent in cervical and vulvar squamous cell carcinoma cell lines. *Cancer* 75(2): 584-590, 1995. PMID: 7812927. DOI: 10.1002/1097-0142(19950115)75:2<584::aid-cnrcr2820750223>3.0.co;2-p
- 78 Bodelon C, Madeleine MM, Johnson LG, Du Q, Galloway DA, Malkki M, Petersdorf EW and Schwartz SM: Genetic variation in the TLR and NF- κ B pathways and cervical and vulvar cancer risk: a population-based case-control study. *Int J Cancer* 134(2): 437-444, 2014. PMID: 23824834. DOI: 10.1002/ijc.28364

Received November 4, 2021

Revised December 30, 2021

Accepted January 5, 2022