

# Genome-wide analysis of gynecologic cancer: The Cancer Genome Atlas in ovarian and endometrial cancer (Review)

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**Abstract.** Cancer typically develops due to genetic abnormalities, but a single gene abnormality cannot completely account for the onset of cancer. The Cancer Genome Atlas (CGA) project was conducted for the cross-sectional genome-wide analysis of numerous genetic abnormalities in various types of cancer. This approach has facilitated the identification of novel AT-rich interaction domain 1A gene mutations in ovarian clear cell carcinoma, frequent tumor protein 53 (*TP53*) gene mutations in high-grade ovarian serous carcinoma, and Kirsten rat sarcoma and B-rapidly accelerated fibrosarcoma proto-oncogene, serine/threonine kinase gene mutations in low-grade ovarian serous carcinoma. Genome-wide analysis of endometrial cancers has led to the establishment of four subgroups: Polymerase ultramutated, microsatellite instability hypermutated, genome copy-number low and genome copy-number high. These results may facilitate the improvement of the prediction of patient prognosis and therapeutic sensitivity in various types of gynecologic cancer. The enhanced use of currently available therapeutic agents and the development of novel drugs may be facilitated by the novel classification of ovarian cancer based on *TP53* mutations, the efficacy of poly (ADP-ribose) polymerase inhibitors for tumors with breast cancer 1/2 mutations and the effect of phosphoinositide-3-kinase (PI3K)/mammalian target of rapamycin inhibitors for tumors with mutations in the PI3K/protein kinase B signaling pathway. Important results have been revealed by genome-wide analyses; however, the pathogenic underlying mechanisms of gynecologic cancer will require further studies and multilateral evaluation using epigenetic, transcriptomic and proteomic analyses, in addition to genomic analysis.

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## 1. Introduction

In the early 20th century, chromosomal abnormalities were considered to cause carcinogenesis (1). The subsequent identification of various oncogenes and tumor-suppressor genes demonstrated that cancer develops due to genetic abnormalities (2,3); however, single-gene abnormalities are insufficient to explain the malignant transformation of all types of cancer, which are hypothesized to require a combination of numerous genetic abnormalities (4). To investigate the underlying mechanisms of cancer development, a human genome-wide analysis study was proposed in 1986, and the Human Genome Project was conducted from 1990 to 2003 (5). Genome-wide analyses of various types of cancer have subsequently increased due to the widespread use of next-generation sequencers (6).

Genome-wide analyses have revealed that B-rapidly accelerated fibrosarcoma proto-oncogene, serine/threonine kinase (*BRAF*) and phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit  $\alpha$  (*PIK3CA*) are frequently expressed in melanoma and rectal cancer, respectively (7,8), and that epidermal growth factor receptor genetic abnormalities may occur in lung cancers (9-11). The Cancer Genome Atlas (CGA) project was conducted in the USA and has collected data on 12 types of cancer (cervical cancer, cholangiocarcinoma, esophageal carcinoma, liver hepatocellular carcinoma, mesothelioma, pancreatic ductal adenocarcinoma, paraganglioma and pheochromocytoma, sarcoma, testicular germ cell cancer, thymoma, uterine carcinosarcoma and uveal melanoma) since 2006 till 2012. The objective of the CGA was to conduct comprehensive analyses of complete genomes for various

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types of cancer and to compare them with normal human genomes, with the aim of identifying the presence of genetic abnormalities in each type of cancer (12). The CGA aims to conduct further analyses in other types of cancer in order to determine characteristic and common genetic abnormalities among various types of cancer (13).

Data from the tumor genomes of several hundred patients with ovarian cancer, brain tumors or squamous cell lung cancer, and comparative data from normal genomes, have been analyzed in the CGA (14-16). These results were published in 2009, and formed the basis for the Pan-Cancer Analysis Project, which began in 2012 (17). In that study on 5,074 patients, the exomes of 12 types of cancer were analyzed, including bladder urothelial carcinoma, breast and colon cancers, head and neck squamous cell carcinoma, renal clear cell carcinoma, acute myeloid leukemia, lung adenocarcinoma, squamous cell lung cancer, and ovarian, rectal and endometrial cancer (17). Comprehensive genome-wide analysis was used to identify common or independent molecular characteristics among these types of cancer (18). Regarding gynecologic cancers, all exomes of ovarian clear cell carcinoma were analyzed in 2010, and the results of the genomic analyses of ovarian serous carcinoma and endometrial cancer were published in 2011 and 2013, respectively (19,20).

## 2. Genomic analysis in ovarian clear cell carcinoma

Ovarian clear cell carcinoma accounts for 8.4% of all ovarian cancers worldwide (21). Mutations in the *PIK3CA* gene were identified to occur in ~33% of cases of ovarian clear cell carcinoma (22). Tan *et al* identified protein kinase B 2 (*AKT2*) gene amplifications in certain clear cell carcinomas, and demonstrated its involvement in patient prognosis (23). The CGA identified a number of frequent mutations in the AT-rich interactive domain 1A (*ARID1A*) gene, which is located on chromosome 1q36 and encodes Brahma/SWI2-related gene 1-associated factor 250 (24). The transcription product of the *ARID1A* gene is a component of the SWItch/sucrose non-fermentable chromatin remodeling complex (25), which alters the nucleosomal structure and regulates DNA-binding proteins in an adenosine triphosphate-dependent manner (26). Therefore, abnormalities in these complexes may cause abnormalities in DNA transcription, replication and repair, and may result in the malignant transformation of cells. Abnormalities in this specific component protein have been frequently identified in patients with ovarian clear cell carcinoma, particularly at International Federation of Gynecology and Obstetrics stages III and IV, and in patients with high cancer antigen 125 expression levels (27).

In order to examine the messenger RNA (mRNA) expression pattern in clear cell carcinoma, ~400 gene groups with differential expression profiles specific to clear cell carcinoma were selected, and the signature of ovarian clear cell carcinoma was identified (28). Mutations in hepatocyte nuclear factor-1 $\beta$  (29) and *ARID1A* (24) are currently considered to be important for occurrence of clear cell carcinoma, and numerous genes that are associated with the ovarian clear cell carcinoma signature are involved in stress response, glucose metabolism and coagulation, which are three key signaling pathways in clear cell carcinoma (30). Numerous

patients with clear cell adenocarcinoma originally present with endometriosis, which suggests that the microenvironment in endometriosis includes signaling factors that may be involved in the development of this type of cancer (28). In a typical case of endometriosis, high levels of free iron are observed, which may generate reactive oxygen species (31). In addition, the oxidative stress levels are high, and cell dysfunction and DNA damage are common (31). Stress response genes are often highly expressed in patients with clear cell adenocarcinoma who originally had endometriosis, which indicates that the stress response signaling pathway may be involved in the development of clear cell carcinoma from endometriosis (28).

## 3. Genomic analysis in ovarian high-grade serous carcinoma

Serous carcinoma accounts for ~52.4% of all cases of ovarian cancer (21), and >90% of serous carcinomas are highly malignant (19). In a genomic analysis of 489 patients with high-grade serous ovarian cancer (HGSOC) published in 2011 (21), the CGA demonstrated that the *tumor protein 53 (TP53)* gene was mutated at a rate of ~96%, and genetic abnormalities were identified in 87% of *TP53*-associated signaling molecules, including the *TP53* gene-related forkhead box protein M1 (*FOXM1*) gene (19). In normal non-cancerous cells, *TP53* inactivates *FOXM1* in the presence of DNA damage (32). Therefore, *TP53* mutations induce an increase in *FOXM1* expression and subsequent abnormal signaling (33). Three isoforms of *FOXM1*, *FOXM1c*, *FOXM1b* and *FOXM1s*, are involved in cell proliferation and DNA repair (34,35), and the effects of *TP53* genetic mutations on these signaling molecules have been hypothesized to cause malignant transformation in cells (36).

Brachova *et al* identified numerous types of functionally significant *TP53* mutations, and classified these mutations into four types, as follows: Oncomorphic, loss of function, unclassified and wild type (37). Oncomorphic mutations in endometrial cancer and HGSOC were detected in ~21.2% of high-grade serous carcinomas, and these cases were associated with poorer progression-free survival (PFS), higher risk of recurrence (~60%) and greater resistance to platinum-based drugs, as compared with the other three groups (37). However, unclassified *TP53* mutations account for ~59.1% of cases of high-grade serous carcinomas (38), and the numerous effects of these mutations have yet to be elucidated.

In serous ovarian cancer, the incidence of mutation is also frequent (~22%) for the breast cancer 1/2 (*BRCA1/2*) gene (39). *BRCA* is involved in homologous recombination and thus, mutations in this gene may cause defects in DNA repair mechanisms (40). Abnormal homologous recombination has been identified in ~50% of cells with *BRCA* mutations (41). Mutations in *BRCA2*-interacting transcriptional repressor (*EMSY*; 8%), phosphatase and tensin homolog (*PTEN*; 7%), *RAD51* paralog C (3%) and Fanconi anemia complementation group D2 (5%) have also been identified in various serous carcinomas (19).

A DNA copy number analysis was also performed in the CGA, as chromosomal instability is a characteristic of high-grade serous carcinoma (42). High-grade serous

carcinoma has more changes in DNA copy number than other tissue types of epithelial ovarian cancer (43). DNA copy number abnormalities in HGSOC include amplification of the v-myc avian myelocytomatosis viral oncogene homolog (*MYC*) and cyclin E1 (*CCNE1*) genes, as well as *BRCA* defects, a number of which are considered to be involved in patient prognosis (44). The CGA analysis identified complex DNA copy number abnormalities in >1/2 of the patients involved (19), with chromosomal regions including *CCNE1*, *MYC* and *MDS1* and EVI1 complex locus protein EVI1 being highly amplified in >20% of tumors (45). Five specific amplified genes were identified, including the activated C-kinase receptor zinc finger MYND-type containing 8, the p53 target gene interferon regulatory factor 2 binding protein 2, the DNA-binding protein inhibitor inhibitor of differentiation 4, the embryonic development gene paired box 8 and the telomerase catalytic subunit telomerase reverse transcriptase (*TERT*) (19).

The results of the analysis described above indicate that >20 gene abnormalities may occur in high-grade serous adenocarcinoma, and that these are often identified in certain signaling molecules, including retinoblastoma, PI3K/AKT, neurogenic locus notch homolog and FOXM1 (46).

#### 4. Genomic analysis in ovarian low-grade serous carcinoma

An analysis of low-grade serous carcinoma was performed in 2012 (47). Somatic mutations in Kirsten rat sarcoma (*KRAS*) and *BRAF* have been identified in low-grade serous carcinoma at an incidence of ~65% (48). *BRAF* mutations may occur in patients without concurrent *KRAS* mutations, in various types of cancer, which suggests that *KRAS* and *BRAF* have complementary functions in the activation of the mitogen-activated protein kinase (MAPK) signaling pathway (49). The CGA aimed to identify novel gene abnormalities, but only *KRAS* and *BRAF* mutations were revealed in cases of low-grade serous carcinoma (50). In cases of high-grade serous carcinoma, abnormalities were identified in the PI3K/AKT signaling molecules, whereas abnormalities in the *KRAS/BRAF* signaling molecules were present in low-grade serous carcinoma (51). Therefore, genetic abnormality in cell growth regulators may induce malignant transformation in high- and low-grade serous carcinomas, but the effect of abnormalities in the underlying signaling pathways may vary.

#### 5. Genomic analysis in endometrial cancer

Endometrioid carcinoma accounts for ~84% of endometrial cancers (21), and estrogen stimulation is an established risk factor (52). Both serous carcinoma and clear cell carcinoma are estrogen-independent endometrial cancers of type II (53). In 2013, the CGA published a comprehensive genomic analysis of 373 patients with these two types of endometrial cancer (54), and a novel classification of endometrial cancers was proposed based on genomic alterations, in contrast to the conventional classification system based on tissue type and estrogen stimulation (55). The novel classification system is based on polymerase  $\epsilon$  (*POLE*) gene abnormalities, microsatellite

instability (MSI) and chromosomal copy number, and includes four subgroups, as follows: *POLE* ultramutated, MSI hypermutated, genome copy-number low and genome copy-number high (Fig. 1).

Patients included in the *POLE* ultramutated subgroup are positive for *POLE* gene abnormalities, but negative for MSI. Patients in this subgroup have a good disease-free survival rate and, therefore, a favorable prognosis. Patients included in the MSI hypermutated subgroup are MSI-positive and also have frequent gene mutations. The genome copy-number low subgroup is MSI-negative and has a low frequency of DNA copy number abnormalities. The copy-number high subgroup has a *TP53* gene mutation rate of >90%, and includes a number of patients with serous adenocarcinoma (Table I) (56-58).

*ARID1A* mutations have been observed to occur in >40% of subjects in the other three subgroups, and mutations in *KRAS* and *PTEN* are also common in these three subgroups. Mutation of the PI3K pathway-related phosphatidylinositol-3-kinase regulatory subunit 1 gene occurs at a high frequency in all four subgroups. Mutations in other types of cancer often involve the components of the receptor tyrosine kinase (RTK)/RAS/PI3K signaling pathway; however, mutations in endometrial cancer are typically associated with the RTK/RAS/ $\beta$ -catenin (CTTNB1) and PI3K signaling pathways, with mutation rates differing among the four subgroups. Therefore, *KRAS* and fibroblast growth factor receptor 2 (*FGFR2*) mutations are common in the MSI subgroup;  $\beta$ -catenin, SRY-box 17 and *FGFR2* mutations frequently occur in the genome copy-number low subgroup; and Erb-B2 receptor tyrosine kinase 2 gene amplifications and F-box and WD repeat domain containing  $\beta$ 7 (*FBXW7*) mutations occur in the genome copy-number high subgroup (59).

Among uterine serous carcinoma, somatic mutations in *TP53*, *PIK3CA* and *FBXW7* were identified (57). Gene amplification of *CCNE1* was identified in 50% of cases (60). Amplification increases the *CCNE1* expression levels, whereas *FBXW7*-mediated ubiquitination of *CCNE1* reduces its expression levels (61). Therefore, the mutation or amplification of these genes causes certain abnormalities in the cell cycle that may result in carcinogenesis (62).

Ring finger protein 43 (*RNF43*) mutations are common in pancreatic cystic neoplasms and are also observed in endometrial cancer (60). *RNF43* encodes an E3 ubiquitin ligase, and negatively regulates Wnt signaling (63). The genomes of 248 subjects with endometrial cancer from the CGA were identified to have *RNF43* mutations at a rate of 18.1% (63). *RNF43* mutations increase Wnt signaling, which increases cell proliferation and causes carcinogenesis (64). *RNF43* mutations are frequently identified in MSI-positive tumors, and these mutations are present in ~50.7% of subjects with endometrial cancer with MSI (65). *CTNNB1*, *MYC* and *CCND1* are also involved in the activation of Wnt signaling, and the overexpression of these genes decreases overall survival in patients with endometrial cancer (66).

A recent CGA analysis demonstrated high expression levels of *TERT* and cleft lip and palate transmembrane protein 1-like protein in endometrial cancer (67). *TERT* is highly expressed in DNA copy number-stable cancers, including thyroid carcinoma (68), and in endometrial cancer with a low genome copy number (69).

Table I. Frequency of gene mutations in endometrial cancer, as determined by genome-wide analysis (revised from reference 57 for *TP53*, *KRAS*, *PI3K*, *FBXW7/CCNE1* and *PTEN*; and 58 for *ARID1A* and *PTEN*).

Gene name	<i>POLE</i> ultramutated, %	MSI hypermuted, %	Copy-number low, %	Copy-number high, %	Serous carcinoma, %
<i>ARID1A</i>	>70	>30	>40	<10	6.0
<i>TP53</i>	>30	<10	<10	90	90.0
<i>KRAS</i>	>50	>30	>10	<10	4.4
<i>PI3K</i>	>70	>50	>50	>40	50.0
<i>FBXW7/CCNE1</i>	>80	<10	<10	>20	50.0
<i>PTEN</i>	>90	>80	>70	<10	17.0

*POLE*, polymerase  $\epsilon$ ; MSI, microsatellite instability; *ARID1A*, AT-rich interactive domain 1A; *TP53*, tumor protein 53; *KRAS*, Kirsten rat sarcoma; *PI3K*, phosphoinositide-3-kinase; *FBXW7*, F-Box and WD repeat domain containing 7; *CCNE1*, cyclin E1; *PTEN*, phosphatase and tensin homolog.

Table II. Frequency of gene mutations in ovarian cancer by tissue type (revised from reference 22 for *PI3K3*; 25 for *ARID1A*; 39 for *BRCA*; 50 for *KRAS*; and 71 and 93 for *TP53*).

Gene name	HGSC, %	CCC, %
<i>ARID1A</i>	0	57.0
<i>TP53</i>	96	52.0
<i>BRCA</i>	22	6.3
<i>KRAS</i>	0	14.0
<i>PI3K3</i>	<10	33.0

*ARID1A*, AT-rich interactive domain 1A; *TP53*, tumor protein 53; *KRAS*, Kirsten rat sarcoma; *PI3K*, phosphoinositide-3-kinase; *BRCA*, breast cancer; HGSC, high-grade serous carcinoma; CCC, clear cell carcinoma.

## 6. Classification of ovarian cancer based on genome-wide analysis and clinical application

Analyses of ovarian and endometrial cancers reveal common gene abnormalities, despite tumor development in various tissues, whereas gene abnormalities may differ in certain types of cancer that develop in the same tissues (Tables I and II) (70). In ovarian cancer, *TP53* mutations occur in 96% of high-grade serous adenocarcinoma cases (71). HGSOC has a poor prognosis (63), which previously led to the proposal to classify ovarian cancer according to the type of gene mutation, rather than the tissue type (71). In the proposed classification, type I includes low-grade serous adenocarcinoma, low-grade endometrioid carcinoma, clear cell carcinoma and serous carcinoma, which have infrequent *TP53* mutations, while type II includes high-grade serous carcinoma, undifferentiated cancer and carcinosarcoma, which have frequent *TP53* mutations (72). The classification according to the frequency of *TP53* mutations facilitates screening and therapy (73), and may allow the development of personalized treatments.

Previous studies have proposed that HGSOC develops in the fallopian tube (44,74). The fallopian tube tissues in patients with ovarian cancer have been revealed to contain

*BRCA* mutation-positive carcinoma *in situ*, which is referred to as serous tubal intraepithelial carcinoma (STIC) (75). STIC has frequent *TP53* mutations (44,74), which suggests that the engraftment of STIC cells from the fallopian tube on to the ovarian surface may induce the development of ovarian cancer.

## 7. Clinical application of the results from genomic analysis

Novel treatments targeting specific gene abnormalities have been developed based on the CGA results. In a previous study, 6-12 cycles of platinum-based adjuvant chemotherapy were administered following tumor debulking in 60 patients with ovarian clear cell adenocarcinoma and 17 patients with high-grade serous adenocarcinoma (27). An evaluation of prognosis and *ARID1A* expression levels demonstrated that the PFS in the *ARID1A*-negative group was significantly shorter, as compared with that in the *ARID1A*-positive group ( $P < 0.01$ ), indicating a resistance to platinum-based chemotherapy in the absence of *ARID1A* (27). Therefore, the results of genome-wide analysis revealed the mechanisms underlying the variation in chemoresistance among these patients. Current chemotherapeutic strategies for ovarian cancer are determined based on the disease stage; however, conventional chemotherapy may be disadvantageous for certain patients, and treatment may be more effectively selected based on the presence of specific gene mutations.

Poly (ADP-ribose) polymerase (PARP) inhibitors for *BRCA1/2* are currently being developed as novel anticancer drugs targeting tumors with gene abnormalities (76). PARP is activated following DNA damage, and repairs single-stranded DNA by polymerization of adenosine diphosphate-ribose residues (77). In the absence of DNA repair by PARP, double-stranded DNA is repaired by *BRCA1/2* (78). In tumors with *BRCA1/2* mutations, the use of PARP inhibitors eliminates all DNA repair mechanisms, inducing an antitumor effect via the promotion of cell death (79,80). The CGA identified numerous *BRCA1/2* mutations in HGSOC, and olaparib, a PARP inhibitor, has been examined in a phase II clinical trial in patients with this disease (81). Trials using a combination of current chemotherapeutic agents for ovarian cancer and olaparib are also in progress (82,83).

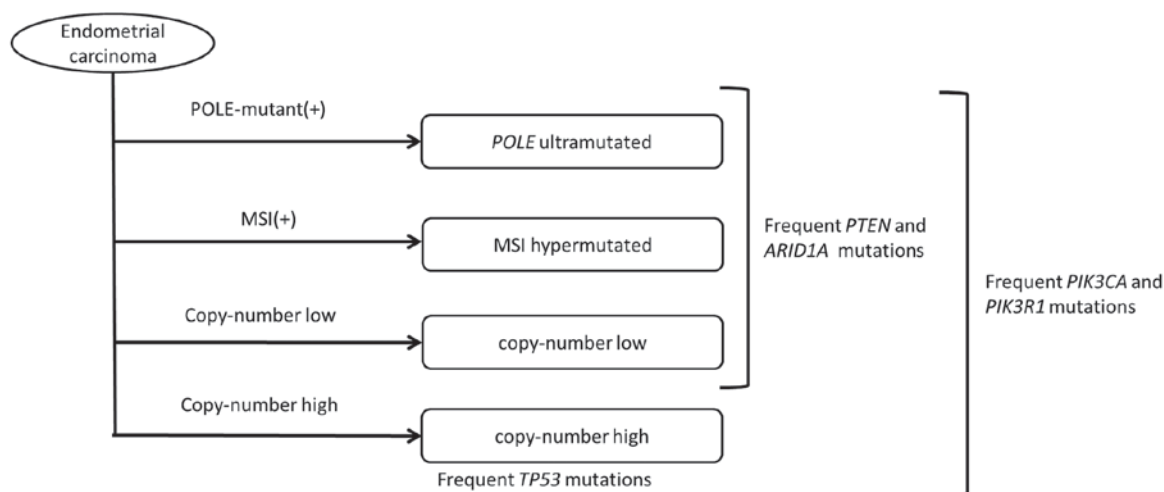


Figure 1. Classification and characteristics of endometrial cancer, as determined by genome-wide analysis. The novel classification of endometrial cancer is based on *POLE* gene abnormalities, MSI and chromosomal copy number. *POLE* gene-positive subjects are classified into the *POLE* ultramutated group and MSI-positive subjects are classified into the MSI hypermutated group. Those patients with a low or high chromosomal copy number are classified into the copy-number low and high groups, respectively. *POLE*, polymerase  $\epsilon$ ; MSI, microsatellite instability; *TP53*, tumor protein 53; *PTEN*, phosphatase and tensin homolog; *ARID1A*, AT-rich interactive domain 1A; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit  $\alpha$ ; *PIK3R1*, phosphatidylinositol-3-kinase regulatory subunit 1.

Thus, the treatment of ovarian cancer may improve due to the enhanced understanding of the genetic abnormalities involved in this disease.

PI3K/mechanistic target of rapamycin (mTOR) inhibition may be effective for the treatment of HGSOC and endometrial cancer with mutations in the PI3K/AKT signaling pathway. mTOR is a serine/threonine kinase that regulates cell proliferation (84). Certain gene mutations increase mTOR expression levels, resulting in abnormal cell proliferation (84). Hypoxia-inducible factor 1 $\alpha$  is located downstream of mTOR, and is involved in angiogenesis; thus, mTOR overexpression enhances cell proliferation and *vasa vasorum* neovascularization (85-87). Anticancer drugs targeting mTOR include everolimus, an mTOR inhibitor used to treat renal cell carcinoma (88). Gene analysis of ovarian cancer tissues revealed mTOR mutations, therefore suggesting the effectiveness of mTOR inhibitors in ovarian cancer (88-90). In mice with subcutaneously implanted human ovarian clear cell carcinoma cells, the tumor size was halved following treatment with everolimus, Taxol<sup>®</sup> and cisplatin (86). When everolimus was administered alone, the tumor size did not decrease, but cellular apoptosis was observed (86).

As previously described, DNA copy number abnormalities occur at a high rate in type II HGSOC, with amplification of  $\geq 22$  oncogenes (19). Therefore, specific gene abnormalities are present in numerous signaling pathways in high-grade serous adenocarcinoma (91). A molecular-targeted drug may only inhibit one signaling pathway and thus, conventional chemotherapy may be required to obtain a good therapeutic effect (92). Trials of novel drugs that are able to simultaneously inhibit PI3K and mTOR have also been conducted (93,94). These include a phase I study on the use of DS-7423 for the treatment of ovarian cancer and a phase I study on the use of NVP-BEZ235 for the treatment of endometrial cancer, in which, the efficacy of NVP-BEZ235 was compared with that of everolimus (94).

Ovarian low-grade serous carcinoma also has poor sensitivity to standard chemotherapy (95,96). In this disease, KRAS and BRAF are important in the MAPK signaling pathways, and the MAPK kinase inhibitor selumetinib has an antitumor effect (97,98). A phase II study demonstrated a response rate of 15.4%, a disease progression-control rate of 80.8% and a median PFS of 11.0 months (98). In contrast to HGSOC, the low-grade type of serous ovarian carcinoma has relatively lower DNA copy number, and the underlying mechanism of carcinogenesis may depend on a single signaling pathway (99). Therefore, the efficacy of specific molecular-targeted drugs is consistent with the CGA analysis.

## 8. Conclusion

CGA analyses of gene mutations have provided novel classifications and the foundation for therapy selection based on gene abnormalities. Epigenetic mutations include those in microRNAs (miRNAs or miRs) (100-102), which are small RNA molecules containing  $\sim 22$  nucleotides that induce gene silencing (102,103). In gynecologic cancers, the downregulation of specific miRNAs, including miR-30c and miR-152, is involved in the onset of cancer (104,105). These miRNAs downregulate the expression of certain oncogenes, including discoidin domain receptor and latent transforming growth factor- $\beta$  binding protein-4; therefore, decreased expression of these miRNAs results in tumorigenesis (106). Further analyses of epigenetic changes, including those associated with miRNAs, are required for comparison with the analyses of gene mutations.

The causes of gene mutations also require further evaluation. The CGA results indicate that the apolipoprotein B mRNA editing enzyme catalytic polypeptide-like 3B (APOBEC3B) is a cause of certain gene mutations (107-109), with a C-T base substitution rate identified to be more frequent than other substitutions in numerous types of cancer,

including bladder and lung cancer (110). APOBEC3B is overexpressed in cancer cells with frequent C-T base substitutions, which suggests that APOBEC3B may be associated with genome mutations (108).

The genome-wide analyses in the CGA project have detected common abnormalities in various types of cancer (109). However, only 12 types of cancer have been analyzed to date, and the CGA aims to analyze a further 50 types of cancer through extended data collection (109). Genome-wide analyses were initially intended to determine the mechanisms underlying the development of cancer; however, the pathogenic mechanisms have yet to be elucidated, despite the important information previously obtained on gene abnormalities (17). Epigenetic data, including those for miRNAs, and proteomic analyses have revealed that carcinogenesis depends on numerous other factors in addition to gene abnormalities (110). These results indicate that further understanding of the pathogenic mechanisms underlying cancer will require numerous genomic, epigenetic, transcriptomic and proteomic studies, including current genome, miRNA expression, DNA methylation and reverse-phase protein array analyses.

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