DOI: https://doi.org/10.53350/pjmhs020241861

REVIEW ARTICLE

DNA Methylation: A Key Player in Ovarian Serous Adenocarcinoma: A Review

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ABSTRACT

Ovarian cancer, particularly serous adenocarcinoma, in women, is the most significant cause of cancer-related death, with its progression strongly linked to epigenetic modifications, notably DNA methylation. Epigenetic biomarkers, especially changes in DNA methylation patterns, have significant prognostic value in cancer, aiding in risk assessment and the development of therapeutic strategies. Two major epigenetic alterations are commonly seen: global DNA hypomethylation, which can activate oncogenes, and CpG island hypermethylation, which silences tumour suppressor genes. Understanding these epigenetic mechanisms not only deepens knowledge of ovarian cancer's molecular basis but also opens avenues for more accurate early detection, personalized treatment, and preventive measures.

Keywords: DNA methylation, Serous adenocarcinoma, Ovarian cancer, Epigenetic, hypermethylation,

INTRODUCTION

Ovarian cancer, a global killer disease, is often overlooked due to lack of symptoms, leading to poor prognosis in late stages. It accounts for over 50% of female genital cancer deaths. Serous adenocarcinoma (SAC) a subtype of ovarian carcinoma (OC) is one of the leading gynaecological cancers, the cause of death among women, even though it only represents 3% of all cancers affecting women[1]. More than half of all OC deaths occur in postmenopausal women aged 55-74, indicating that hormonal variables may play a role. Because of the lack of obvious symptoms in the early stages, approximately 70%of cases of this subtype are detected after the cancer has progressed to the late stages, resulting in decreased survival rates[2]. While early detection could potentially increase five-year survival rates to as high as 92%, the actual survival rate remains between 15–45%[3]. The key therapeutic problems are the lack of early diagnostic indicators and the emergence of medication resistance after chemotherapy. Ovarian epithelial carcinoma (OEC) is themost frequently diagnosed form of ovarian cancer is ovarian which displays a variety of histopathological variations, with serous ovarian carcinoma (SOC) being the common subtype[4]. Although the OECs are sporadic, about 5–10% are inherited, often linked to BRCA1 and BRCA2 mutations, which compromise DNA repair and genomic stability. Despite significant research, genetic factors alone do not fully account for ovarian cancer's complexity. As genetic changes are largely irreversible, the reversibility of epigenetic alterations presents new opportunities for prevention and treatment. It accounts for 90% of cases and is diagnosed in advanced stages, with only 30% of patients surviving five years or longer[5].

DNA methylation, histone modifications, and non-coding RNA interactions are all examples of epigenetic processes that alter gene expression without changing the genome. These modifications are crucial in cancer progression, contributing to drug resistance[6].The unique DNA methylation patterns observed in various subtypes of ovarian cancer suggest distinct pathways of tumour development, influenced by genetic predisposition, environmental factors, and somatic lineage[7]. These epigenetic signatures offer promising biomarkers for improving cancer detection, classification, and individualized treatment.

DNA methylation plays a vital role in cancer: Methylation in these areas, particularly gene promoters, often inhibits gene activity. In cancer, two kinds of DNA methylation alterations are commonly observed: hypomethylation and CpG island hypermethylation[8]. Hypomethylation can cause genomic instability and the activation of oncogenes, resulting in uncontrolled cell proliferation. Conversely, hypermethylation silences tumour suppressor genes, reducing their ability to regulate DNA repair, cell division, and programmed cell death[9]. These aberrant methylation patterns play a vital role in cancer development, leading to tumour formation, progression, metastasis, and treatment resistance. Because DNA methylation is reversible, so it represents a possible therapeutic target. DNA methyltransferase inhibitors, such as azacitidine and decitabine, are being studied for their ability to reactivate silenced tumour suppressor genes and limit tumour development[10]. Furthermore, different methylation patterns in cancer cells may serve as biomarkers for diagnosis, prognosis, and personalised therapy regimens. Understanding the significance of DNA methylation in cancer is critical for early identification and focused treatment.

Methylation events linked to ovarian tumorigenesis: A general reduction in heterochromatin DNA methylation, resulting in oncogene demethylation, and specific CpG island hypermethylation linked with tumour suppressor gene promoters are the common epigenetic processes associated with ovarian carcinoma. This abnormal methylation reduces gene expression, resulting in the loss of tumour suppressor gene (TSG) activity[11]. This causes unregulated cell division, metastasis, apoptosis, and angiogenesis, all of which promote tumour growth. A substantial number of TSGs are hypermethylated in ovarian cancer. The BRCA1 gene is important in ovarian cancer, as it influences both hereditary and spontaneous forms of the illness. Non-somatic mutations may cause hypermethylation of the gene promoter in patients with sporadic ovarian cancer. Heterozygosity loss, linked to BRCA1 deficiency in ovarian cancers is due to the aberrant methylation of the gene promoter[12]. Stage II and III ovarian tumours have high BRCA1 promoter methylation rates. However, methylation of BRCA1 has not been observed in hereditary instances of the disease or women with germ-line BRCA1 mutations. In ovarian cancer, BRCA2 has a distinct methylation profile, with methylated CpGs in the BRCA2 promoter being missing or present at extremely low levels in the DNA of the tumour in comparison to the normal tissues[13].

Ovarian cancer patients frequently have hypermethylation of some traditional tumour suppressor genes (TSGs), such as DNA mismatch repair (MMR) involved in TSGs. MMR molecular process that corrects replication faults, resulting in more spontaneous somatic mutations[14]. Germline mutations in genes such as hMLH1, hMSH2, MGMT, and MSH6 often produce defective MMR, with hypermethylation in 10-30% of ovarian malignancies and hMLH1 promoter methylation in 56% of platinum-based chemotherapy-resistant patients.Methylation of hMSH2 promoters is as high as 57% in ovarian tumours, which is associated with lymphatic metastasis.RAS association domain family protein 1a (RASSF1A) and OPCML are the commonly methylated genes in OC. E-

Received on 08-02-2024
Accepted on 15-05-2024

cadherin, a transmembrane glycoprotein, is methylated in OC patients[15].

Homeobox (HOX) gene methylation has been investigated in OC patients, with aberrant expression of certain genes associated with the disease. The HOXA9 and HOXAD11 genes methylation status might beimportant diagnostic and prognostic indications[16]. In ovarian cancer, hypermethylation suppresses different cancer formation pathways, whereas global and selective hypomethylation of overexpressed protein-expressed genes plays a significant role.LINE-1 segments reduced methylation is linked to high grade, advanced stage, and worse prognosis[17]. Oncogenes such as CLDN4, MAL, and BORIS influence treatment resistance and disease prognosis. In advanced ovarian carcinoma with drug-acquired chemoresistance, there is an increase in ABCG2 multidrug transporter and TUBB3 genes, indicating taxane resistance[18].

Genetic features of ovarian cancer and the events of DNA methylation: High-grade serous ovarian carcinoma (HGSC) is frequently related to mutations in the TP53 gene and alterations in DNA repair mechanisms, particularly in the homologous recombination pathway, involving genes like BRCA1 and BRCA2. In contrast, endometrioid and clear-cell ovarian cancers often exhibit mutations in the ARID1A, PIK3CA, and CTNNB1 genes[19]. Low-grade serous ovarian carcinoma typically features mutations in KRAS and BRAF. Global DNA hypomethylation has been seen in HGSC, as has promoter hypermethylation of tumour suppressor genes such as BRCA1[20]. Endometrioid and clear cell subtypes often display hypermethylation of genes involved in cellular differentiation and DNA repair. Because of these methylation patterns lead to gene silence, which promotes tumour growth. The different methylation landscapes seen across ovarian cancer subtypes highlight the complicated interaction between genetic abnormalities and epigenetic alterations that contribute to disease development[21].

DNA Hypermethylation Dynamics in Ovarian Serous Adenocarcinoma: The significant factor in the development of ovarian cancer is hypermethylation, as it contributes to gene silencing, especially in tumour suppressor genes. This modification occurs in promoter regions of key regulatory genes, leading to reduced expression and disruption of normal cellular processes[22]. Hypermethylation patterns vary between ovarian cancer subtypes, reflecting their unique molecular signatures. These methylation alterations, often reversible, present potential targets for therapeutic interventions aimed at reactivating silenced genes and restoring normal cellular function. DNA methylation, particularly hypermethylation of CpG islands, is crucial in gene function regulation and serves as an epigenetic marker for cancer diagnosis, classification, and prognosis. CpG islands are typically protected from methylation in normal cells, but in cancer, they often become hypermethylated, leading to the silencing of tumour suppressor and DNA repair genes[23].

DNA hypermethylation represents a key mechanism driving tumour development by inactivating critical tumour suppressor genes in ovarian serous adenocarcinoma. This process occurs when methyl groups are added to CpG islands, regions rich in cytosine and guanine, located within gene promoters. As a result, the methylation blocks the binding of transcription factors, effectively silencing gene expression[24]. Tumor suppressor genes, such as BRCA1, are involved in DNA repair, RASSF1A, which regulates cell cycle control, and p16, a key regulator of cell cycle progression, are frequently targeted by hypermethylation in this cancer subtype[25]. When these genes are silenced, the regulatory mechanisms they control are disrupted, allowing for unchecked cell growth, impaired DNA repair, and resistance to apoptosis, all of which contribute to the progression of the cancer[26].

Epigenetic changesare not only crucial in the early stages of tumour formation but also play a role in the aggressiveness and poor outcomes associated with ovarian serous adenocarcinoma. Patients with higher levels of hypermethylation in these key genes often exhibit resistance to standard treatments like platinum-based chemotherapy, as the loss of DNA repair mechanisms makes the cancer more adaptable[27]. Understanding the dynamics of DNA hypermethylation in ovarian serous adenocarcinoma could pave the way for targeted therapies aimed at reversing these epigenetic changes, potentially restoring the function of silenced genes and improving treatment outcomes[28].

DNA HypomethylationDynamics in OvarianSerous Adenocarcinoma: This process involves the loss of methyl groups from CpG sites, leading to the deregulation of gene expression in the serous ovarian adenocarcinoma. Unlike hypermethylation, which silences tumour suppressor genes, hypomethylation often results in the activation of oncogenes and repetitive elements within the genome. The reduction in methylation can reactivate normally silenced retrotransposons and enhance the expression of genes that drive unchecked cell growth and invasion. Hypomethylation commonly impacts regions of heterochromatin, destabilizing the genome and contributing to chromosomal abnormalities such as translocations, amplifications, and deletions. This increased genomic instability accelerates the accumulation of genetic changes that promote tumour progression. The hypomethylation may activate genes involved in metastasis, further contributing to the aggressive behaviour of ovarian serous adenocarcinoma**[29].**

These epigenetic events often occur along with other genetic mutations, such as those in TP53, and are linked to poorer outcomes and treatment resistance[30]. The literatureon DNA hypomethylation dynamics in ovarian serous adenocarcinoma highlights its potential as both a biomarker for disease progression and a target for therapeutic intervention. Focusing on medicines that repair aberrant hypomethylation patterns has the potential to reduce tumour aggressiveness and improve patient responses to current medications[31].

Scientific findings on DNA methylation patterns in ovarian serous adenocarcinoma: High-Grade Serous Carcinoma (HGSC) carcinomas vary from other ovarian carcinomas in that they have modest hypermethylation levels. Studies utilising illuminate and human methylation 27k Bead chips revealed that genes such as AMT, CCL21, REB25, and SPARCL1 are often hypermethylated in HGS carcinomas[32]. However, there is no agreement on which genes are hypermethylated, indicating that hypermethylation in HGS carcinomas occurs randomly and may not play a critical role in tumour development. Furthermore, investigations on known tumour suppressor genes and CpG sites show little overlap and conflicting frequency estimates of DNA hypermethylation. No clustering analyses using DNA methylation data have produced persistent groups that differentiate carcinomas based on biological and clinical features[33].

The study discovered that HGSC is more closely connected to fallopian tube epithelium (FTE) as compared to the ovarian surface epithelium (OSE), independent of sample size, genomic location, CpGs, CpG islands, promoters, genes, DMR, or methylation analysis technique. This link was maintained by CpG island enhancers and coasts, emphasising the significance of tissue-specific CpG island shore differential methylation and the role of enhancers in driving tissue specification[34]. LGS ovarian carcinomas have a distinct appearance and are more mutated than HGS carcinomas. RAS pathway genemutations such as KRAS, BRAF, NRAS, and PTEN are associated with it. These chromosomally stable tumours develop from benign or borderline phases, starting with serous borderline tumours (SBTs) and progressing to invasive LGS ovarian carcinomas[35].

Studies have shown that SBT/LGS carcinomas evolve differently from HG carcinomas, with BRAF/KRAS/ERBB2 mutations and, in rare cases, TP53 alterations. HGS carcinomas are aggressive, with little BRAF/KRAS/ERBB2 mutations but a high prevalence of TP53 mutations. HGS carcinomas have greater levels of chromosomal instability[36]. DNA methylation profiling studies on LGS, SBT, and HGS ovarian tumours revealed that AATK, HOXA9, WNT5A, MAPK4, and GFI1 are hypermethylated in LGS compared to SBTs, while DBC1, GPATC3, TUBB3,

HDAC6, and TSG101 are hypomethylated[37]. More research with larger sample sizes and genome-wide methylation data is required to demonstrate the reproducibility of these trends.

Table 1: Summary of serous ovarian adenocarcinoma

Serous	Highgrade (grade º 2)	Lowgrade	Literature Citation
Possible sites	Ovarian surface epithelium, Fallopian tube	Ovarian surface epithelium, inclusion cysts, serous borderline ovarian tumours	38
DNA methylation patterns			
Global pattern	Histologically no major role in the patterns of global DNA hypomethylation (39)		
Hypomethylation	Hypomethylation is correlated with increasing grade and stage(40).		
Hypermethylation of CGIs	1%	0%	
Gene patterns			
Genes frequently hypomethylated	SLC6A8, BGN, TIMP1, WEE1, and NCL	TUBB3, TSG101, HDAC6, DBC1 and GPATC3	12,40
Genes frequently hypermethylated	RAB25, AMT, CCL21, SPARCL1; GFAP, TAL1, IPF1, AREG, HOXA9 ; ALDH1A3, AMT, LONRF2, NPDC1, SLC16A5; OPCML, DLEC1, BRCA1, CDKN2A, SFN	MAPK4, HOXA9, AATK, WNT5A, GFI1; NF3	41
Genetic features			
Global patterns	Chromosomal instability; mutations relatively infrequent	Chromosomally stable	(42)
Germline Altered Genes	BRCA1, BRCA2, RAD51C		(43)
Somatically Altered Genes	BRCA1, TP53, CSMD3, CDK12, NF1,BRCA2, FAT3,GABRA6, RB1	Ras pathway: KRAS, NRAS, BRAF, PTEN, ERBB2,	(43, 44)

Correlation between DNA methylation and chemotherapy resistance in the treatment of ovarian carcinoma: DNA methylation contributes to chemotherapy resistance in OC, which is treated mostly with platinum (carboplatin) and taxane (paclitaxel). Carboplatin promotes apoptosis by integrating into DNA, resulting in adducts and mismatch repair. Taxanes stabilise tubulin, which results in apoptosis and cell cycle arrest[45].

The majority of patients relapse owing to medication resistance, which may be caused by mutations or modifications such as DNA hypermethylation/hypomethylation. Early on, it was discovered that various subtypes of EOC have distinct genetic and epigenetic characteristics. However, previous investigations on DNA methylation have not taken into account the relationship between DNA methylation and therapeutic response. Many studies cover all subtypes, whereas others do not. Some research focuses on HGS, Clear Cell carcinoma, and ovarian endometroid adenocarcinoma[46].

Future studies should concentrate on histotypes for in-depth studies. In vitro DNA methylation studies have revealed that treatment efficacy is influenced by gene methylation status, and resistance to common chemotherapy choices can aid in assessing methylation and results[47].

DNA methylation patterns as biomarkers in high-grade serous ovarian carcinoma: DNA methylation pattern modification in several genes shows promise as a potential biomarker for all sorts of malignancies, including HGS ovarian carcinoma (HGSOC), which grows quickly and is identified late. HGSOC,the most common kind is the deadliest gynecologic carcinoma, accounting for 70% of all ovarian cancer cases[19,48]. Accurate identification of early-stage HGSOC, ideally pre-invasive, is expected to increase survival rates. Despite the low incidence of ovarian cancer, HGS Ca responds to surgical cytoreduction and chemotherapy in over 70% of patients. However, the response rate for advanced ovarian cancer is less than 20 percent. Up to 90% of stage I patients can be healed. Round-up pelvic examinations are insensitive, with only 20% of cases detected at stage I[49]. CA125, the best-known serum EOC biomarker, is utilised to quantify post-operative risk, although it lacks sensitivity and specificity for population-based screening. Combining prognostic biomarkers for enhanced screening is critical. A greater knowledge of EOC molecular aetiology will likely contribute to the development of novel biomarkers for the early diagnosis of HGS carcinomas[50]. More study on DNA methylation signatures in cancer formation, progression, risk assessment, and treatments is required for this specific tumour type.Researchers have found eight tumour suppressor genes that are heavily methylated in epithelial ovarian cancer (EOC) (HGSOC). These genes are: HOXA9, SFN GATA4, GATA5, HSULF1, CDH1, DLEC1, and RASSF1A. BRCA1 was also chosen, though in HGSOC it is not known to be heavily methylated. The genes in main HGS Ca were methylated in varying degrees, with HOXA9 methylation occurring in 95% of instances. Except SFN, in benign OES most genes are seldom methylated. DLEC1 methylation was linked to recurrence, regardless of inadequate surgical debulking. Methylation status, when paired with EN1 and HOXA9, distinguishes benign OSE from HGS ca with 98.8% sensitivity and 91.7% specificity[51].

Future research is planned to produce more sensitive and specific DNA methylation indicators for HGS CA. Genome-wide DNA methylation approach is proposed to do new cancer classification. However, research on DNA methylation in HGS carcinoma is sparse, making it difficult to develop an independent and comprehensive profile for determining the predictive significance of DNA methylation-based biomarkers in HGS malignancies.

DNA Methylation as a Prognostic or risk assessment marker in Serous ovarian cancers: DNA methylation changes are recognized as potential markers of tumour progression, particularly in ovarian cancer. However, there are still no effective DNA methylation-based epigenetic signatures for HGS cancers. A study analyzed methylation sites related to prognosis and identified four methylation subgroups with different prognoses. These subgroups had diverse biological characteristics, raising the need for cautious classification due to the heterogeneity of HGS cancers[52]. A prognostic prediction model for HGS carcinoma was established using multivariate Cox analysis, which was validated to establish its reliability. This model provides valuable information on the biological characteristics, prognosis, and therapeutic options for HGS ovarian carcinoma[53]. Different histological subtypes of ovarian cancers harbour distinct DNA methylation profiles, reinforcing the need to treat different subtypes of ovarian carcinoma as separate entities. For Serous subtypes, widespread DNA hypermethylation is observed in low malignant potentialtumours, while significant DNA hypomethylation is only seen in HGS CA grade 3. Currently, information regarding DNA methylation of HGS carcinoma is limited to the appointed methylation sites between HGSOC and normal epithelial tissue and between primary and recurrent carcinoma[54]. A Four-cluster system is identified in previous TCGA studies, but this classification system was formatted based on multiple data integrations (DNA methylation, mRNA, and miRNA expression). TGA-based data studies reveal differentially methylated genes in the MAPK signalling pathway, which plays a crucial role in gene expression, cell growth, and survival[55]. However, few researchers have focused on the interaction between MAPK signalling pathway proteins and methylation alterations.

DNA Methylationin HGS Ovarian Carcinoma as a therapeutic option: New therapeutic methods, such as DNA methyltransferase inhibitors (DNMT inhibitors), can reverse hypermethylation in tumour suppressor genes, reactivating their activity and increasing cancer cell susceptibility to conventional therapies. DNMT inhibitors are being studied in conjunction with other therapies to prevent drug resistance in HGSOC, such as reactivating genes involved in homologous recombination repair, especially in tumours with mutations[56].

The methylation profiling data classified HGS into four groups. Methylation levels of all subtypesare linked toa variety of molecular features[22].

a. Group C1Showed association of cg13055001 (PPP1CA), cg12493906 (MMP26), and cg03848675(FOXF2), hypomethylation. Thesubgroup C1hypomethylation loci were closely linked to tumour metastasis, so C1 was termed as the metastasis subgroup. In this subgroup targeted therapy that prevents metastasis may be more effective than the other subgroups.Matrix metalloproteases (MMPs) play an important role in cancer metastasis. The immunostaining intensity of MMP-26 immunostainingshows an increasedintensity with the stage ofovarian cancer, which means MMP-26 has a vital role in ovarian cancer biological behaviour. In gastric carcinogenesis,FOXF2 is a known tumour suppressor. Researchers report that FOXC2 in basal-like breast carcinoma suppress epithelial-mesenchymal transition and causes multidrug resistance. It also promotes bone metastasis. By regulating the miR-182-5p/FOXF2 axis,lncRNA ADAMTS9-AS2 decreases tumour progression in ovarian carcinoma[57,58].
b. Group C2 subtype showed relative hypomethylation of the following which were annotated as MCF2L2 (cg27239157), HSPB6 (cg24673765), and IGF2 (cg13791131, cg25574024), and respectively and has the best prognosis.MCF2L2is the most important markercontributing to polycystic ovary syndrome. Future studies are needed to see ifthis subtype is related to metabolic disordersand the usageof metabolic drugs in this subgroup will be valuable[59].
c. Group C3 hypermethylation associated with cg03848675, which was opposite to the one in C1, and cg14290451(RPL10A) hypomethylation is seen in this group. Via the insulin signalling pathway, RpL10A stimulates cellular proliferation[60].
d. Group C4 is the poorest prognostic group and showshypermethylation of 54 methylation loci. Tumour suppressor genes hypermethylation means a more aggressive phenotype. Therefore, C4 is categorized as the hypermethylation subtype, suggesting that preclinically demethylation agents can be tested for this group[61]. It is important to understand the reasons for these unique subtypes and correlate the relationship between different subtypes and their sensitivity level to specific targeted therapy. Therapeutic intervention to reverse a pattern identified in a cluster can lead to adverse effects so all precautions must be taken into consideration. Survival outcome, residual carcinoma, and lymphatic spread, all were greatly different in the four subgroups. In the hypermethylation subtype,the frequency of residual tumours was higher as compared to the other subtypes. This means that neoadjuvant chemotherapy in the hypermethylation group will help to improve the treatmentquality and reducerecurrent lesions.

CONCLUSION

DNA methylation has the potential to serve as a cancer diagnostic, but its application in clinical decision-making is relatively recent. Only a few methylation indicators are employed in clinical decision-making, such as methylation of DNA repair genes to differentiate colorectal cancer. Although DNA methylation is implicated in the course of colorectal cancer (OC), the majority of observed alterations have not been verified by independent research. To find satisfactory OC markers, new genome-wide techniques and screening methodologies are required. Future discovery research should include both benign and malignant samples, and various carcinogenesis stage subgroups, including individuals who are chemo-responsive or resistant. Precision therapy driven by biomarkers has the potential to enhance treatment and survival rates, turning OC into a chronic illness with a good quality of life. Genome-wide research that results in a better knowledge of the disease's aetiology might lead to a cure for OC.

Conflict of interest statement: All authors declare no conflict of Interest

Author's contribution: N.A

Acknowledgements: N.A.
Funding: There is no funding source.

Data Availability: N.A

Ethics Statement: N.A

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This article may be cited as: Tanvir I, Rahman ASA: DNA Methylation: A Key Player in Ovarian Serous Adenocarcinoma: A Review. Pak J Med Health Sci, 2024; 18(6):3-7.