Review Article

CHEK2, MCM3 and MSH6 may have a Potential Role as Molecular Markers of Screening in the Detection of Cervical Premalignant and Malignant Lesions: A Scoping Review

Gulfishan Zameer[1], Maham Javed[2*], Saima Zaki[3], Bushra Nisar[4], Saba Khaliq[5], Nadia Naseem[2]

ABSTRACT

Lesions of the uterine cervix, including neoplasia, are the foremost cause of female deaths worldwide. Cervical malignancy ranks as the third most common gynecological malignancy globally, with an increasing prevalence reported in Asia each year. Early detection through cytology-based screening makes it one of the most preventable forms of malignancy. This review was planned to investigate the potential role of CHEK2, MCM3, and MSH6 in detecting cervical lesions. Therefore, a scoping review involved searching for published articles on databases such as PubMed, MEDLINE, EMBASE, and the Cochrane Library. According to the searched literature, several genes contribute to cervical cancer occurrence. The CHEK2 gene acts as a tumour suppressor by regulating the cell cycle pathway. At the same time, the loss of function of MSH6 leads to high rates of mutations in microsatellites, thereby deactivating the mismatch repair pathway. Moreover, the MCM3 gene's helicase activity in cell cycle regulation is overexpressed in various malignant tissues and cancer cell types. Tumor microsatellite instability (MSI) indicates the loss of mismatch repair function, which is seen in cervical cancer and reported in many other tumors. Expression of these genes may be associated with the "abnormality of the epithelial cell" term in the Bethesda system for classifying cervical lesions on cytology, ranging from atypical squamous cells to low-grade and high-grade dysplasia, which can potentially lead to invasive squamous cell carcinoma linked to transient HPV infection. Due to the scarcity of local data regarding the role of these genes in cervical malignancy, further research is crucial.

KEYWORDS: Liquid-based cytology, Pap smear, Cervical cancer, CHEK2, MSH6, MCM3, HPV.

INTRODUCTION

Cervical cancer is a growing female malignancy throughout the world, especially in developing countries[1]. Gynecological cancers, particularly cervical cancer, significantly impact women's quality of life and contribute to the global healthcare burden. As reported by Globocan 2022, cervical cancer is the fourth most common cancer in terms of incidence and the eighth most common malignancy in terms of mortality among women worldwide [2]. In Asia, it is the third most typical kind of malignancy in females. It is one of the foremost causes of death associated with cancer in women from low- and middle-income countries[3]. The National Cancer Registry of Pakistan's comprehensive report for 2015-2019 analysed 269,707 cases of cancer. Among these, cervical cancer accounted for 4.17% of female cancers, making it the fourth most common cancer in women during that period [4]. The high death rate in Pakistan is a result of the fact that more than 70% of cervical cancer patients present with the disease in a very advanced stage [5].

Globally well-documented data is present regarding the association between Human Papillomavirus (HPV) and cervical cancer. Still, unfortunately, data from Pakistan remains scarce due to the absence of organised cervical screening programs [6]. Persistent infections by high-risk HPV type raise the risk of developing cervical cancer[7] In high-income countries, cervical cancer rates have declined due to comprehensive screening programs and vaccination against high-risk HPV. However, such initiatives are largely absent in many low-income developing nations, including Pakistan. Several studies in Pakistan have shown a significant association between high-risk HPV, especially types HPV 16 and HPV 18, with cervical cancer, similar to global trends[8]. Unsanitary living conditions, early sexual experience, multiparity, sexually immoral, and HPV infection are among the common risk factors for cervical cancer[9].

[1]*M.Phil Scholar Cytotechnology, University of Health Sciences, Lahore, Pakistan*
[2]*Department of Histopathology, University of Health Sciences, Lahore, Pakistan*
[3]*Department of Obstetrics & Gynecology, Jinnah Hospital, Lahore, Pakistan*
[4]*Department of Pathology, Children's Hospital and Institute of Child Health, Lahore, Pakistan*
[5]*Institute of Allied Health Sciences, University of Health Sciences, Lahore, Pakistan*
Correspondence: *mahamjaved77@gmail.com*

doi: 10.22442/jlumhs.2025.01200
Received: 11-10-2024 *Revised: 17-01-2025*
Accepted: 03-02-2025 *Published Online: 30-04-2025*

Lack of education, history of STIs, recurrent genital warts, use of contraceptives, chronic excessive smoking, and lack of screening practices are other possible etiological factors for carcinoma of the cervix[10]. The government and non-governmental organisations are working together to provide free HPV vaccines, with support from international philanthropists.

Although cervical carcinoma is a grave malignancy, it is still considered one of the most preventable carcinomas through vaccination against the HPV or regular Pap smear testing in females for screening of premalignant lesions [11]. The Bethesda System is a current method for reporting cervical cytology, which was last updated in 2015. The descriptive categories include Negative for intraepithelial lesion or malignancy (NILM), Abnormalities of epithelial cells (such as squamous or glandular cells), or other cells. There are four types of abnormal squamous cells. Atypical squamous cells (ASCs), High-Grade Squamous Intraepithelial Lesion that cannot be excluded (ASC-H), Low-grade squamous intraepithelial lesions or (LSIL), High-grade squamous intraepithelial lesions (HSL), Squamous cell invasive cancer. (**Table I**)[12]

In developed countries, routine cytology screening programs have led to a decrease in both the incidence and mortality rates of cervical cancer. The most efficient strategy for both preventing and detecting cervical cancer is the conventional Pap smear[13]. Other advanced methods include the LBC system, in which ThinPrep has overcome many of the deficiencies of the traditional Pap test[14]. Monolayers of cells, less ineffective smears, quicker and more efficient techniques, the removal of blood, the utilisation of residual cell suspension for HPV DNA and immunohistochemistry assays, a more precise interpretation, and the removal of mucous and inflammatory cells from smears are all advantages of LBC over conventional pap testing[15]. Additionally, cell block preparation using a variety of techniques on residual cytological material is an established method that provides the advantage of valuable diagnostic evidence, including the preservation of nuclear and cytoplasmic characteristics, preservation of architecture, and the presence of tissue fragments that cannot be obtained by cytology alone, thereby increasing diagnostic sensitivity[16].

Several molecular markers, including genes involved in DNA damage response and repair, have been implicated in the development and progression of cervical cancer. Specifically, **CHEK2, MCM3,** and **MSH6** are of particular interest.

Checkpoint kinase 2 (CHEK2) and cervical cancer

The CHEK2 gene-encoded protein is a cell cycle regulator and a tumour suppressor gene[17]. This protein is activated in response to DNA damage to prevent entry into the mitotic phase. It is located at the chromosome 22q at 12.1[18]. DNA damage activates the Serine/threonine-protein kinase pathway in the cell cycle control pathway. Mutations in suppressor genes cause alterations that disrupt the cell's ability to control and repair DNA. These genetic mutations accumulate within the cell and remain "latent," only manifesting under favorable conditions, such as exposure to certain environmental factors (e.g., HPV) or genetic predispositions[19]. Subsets of numerous human malignancies, including lymphomas, ovarian, breast, lung, vulvar, colon, and osteosarcomas, have been found to harbour somatic CHEK2 gene

Table I:
2014 Bethesda System for Cervical Cytology

Patient ID	**Age**	
Specimen Type		
Conventional pap smear, Liquid-based cytology, or any other preparation		
Specimen Adequacy		
Unsatisfactory for evaluation	Specimen with more than 75% of cells obscured by inflammation and bacteria is unsatisfactory (assuming no abnormal cells are present).	
Satisfactory for evaluation	Adequate number of squamous cells (at least 30 well-preserved cells were considered adequate)	
General Categorisation		
NILM	Cellular changes associated with Human Papilloma Virus (HPV) Other non-neoplastic findings including reactive cellular changes associated with: a) Inflammation b) Radiation c) Others	
Other	Endometrial cells in a woman ≥45 years of age	
Epithelial cell Abnormalities	ASC-US, ASC-H, LSIL, HSIL	
Epithelial cell Abnormalities		
Squamous Cell Abnormalities	ASC-US	
	ASC-H	
	LSIL	Encompassing HPV / mild dysplasia / CIN I
	HSIL	Encompassing moderate and severe dysplasia / CIN 2 / CIN 3 / CIS With features suspicious for invasion (if invasion suspected)
	SCC	
	Atypical endocervical cells NOS	
	Atypical endometrial cells NOS	
	Atypical Glandular Cell	
	Atypical endocervical cells, favor neoplastic	
	Atypical glandular cells, favor neoplastic	
	Endocervical adenocarcinoma in situ (AIS)	
	Adenocarcinoma	
	Endocervical	
	Endometrial	
	Extrauterine	

mutations[20]. It is also reported to be altered in cervical carcinoma patients[21]. Intracellular HPV is an additional biological factor that can facilitate the further penetration of an existing DNA mutation into infected cells[22].

MutS homolog 6 (MSH6) and cervical cancer

The MSH gene, located on chromosome 2p16.3, encodes the DNA mismatch repair protein MSH, a member of the MutS family of proteins. In the chromatin remodelling and DNA methylation pathway, MSH6 is a DNA mismatch repair protein[23]. Mismatches are frequently caused by errors in DNA replication, genetic recombination, and other chemical and biological processes[24]. Because failing to identify and repair these mismatches results in MSI and a higher rate of spontaneous mutation (leading to a mutated phenotype), it is crucial for cells to do so. 24 Tumorous MSI, characterises the loss of MMR function, and the cervical tumour exhibits loss of MSH2 and MSH6 protein expression[25]. as well as in tumors of the ureter and colon[21]. Cervical cancer's tumorigenesis has also been linked to the MMR defect inherent in MSI and loss of MMR protein expression[26].

Minichromosome maintenance 3 (MCM3) and cervical cancer

MCM3 exhibits helicase activity during the cell cycle, which is crucial in regulating replication timing. Overexpression of MCM3 has been observed in various cancerous tissues and carcinoma cell lines[27], with a typical pattern of MCM-positive cells dispersed on the surface of the neoplastic and precancerous epithelium, as shown by immunostaining[28]. The advanced tumor stage and the presence of metastases are adversely linked with the MCM3 expression level. Particularly, there is a considerable difference in MCM3 expression between stage 1 and stage 3 cervical cancer patients. There is growing evidence that MCM, more so than p16 and p63, can be utilised as a biomarker to determine the malignancy of cervical lesions. Good survival and prognosis are correlated with high expression of MCM2, MCM3, MCM5, and MCM7 [29].

Despite significant research on the molecular pathogenesis of cervical cancer, there remains a lack of consensus on the use of CHEK2, MCM3, and MSH6 as consistent biomarkers for early detection, screening, or prognostic evaluation of cervical lesions. Data on the molecular pathogenesis of cervical cancer in Pakistan is indeed limited and sparse, which is a significant challenge for understanding the disease more deeply and improving preventive measures. Therefore, this review was planned to delve deeply into the use of **CHEK2, MCM3,** and **MSH6** as reliable biomarkers for timely detection and screening, highlighting their value in improving diagnostic accuracy and outcomes for women at risk of cervical malignancy.

METHODOLOGY

A scoping review methodology was designed to analyse published work by searching prestigious online databases, including PubMed, EMBASE, EBSCOhost, Scopus, and Web of Science, for articles published between 2004 and 2024, adhering to the PRISMA guidelines.

Guidelines (**Table II**). Three reviewers searched the literature for relevant articles. Keywords include PAP smear, tumorigenesis, CHEK2, MSH6, MCM3, HPV, Cervical Cancer and their variations.

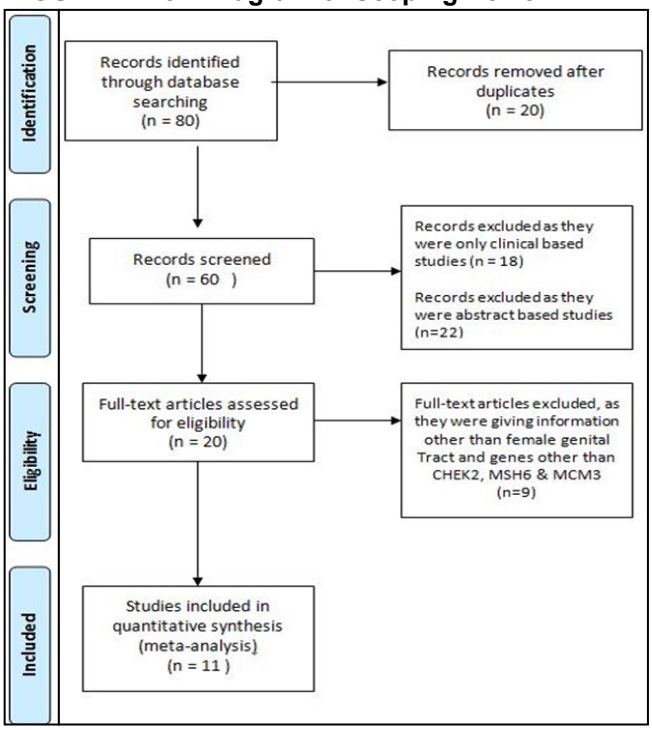
Hospital and clinic-based studies with cytological and histopathological analyses conducted by pathologists up to 2024 and studies consisting of females of child-bearing age (18-45 years) who underwent cervical brush or cervical tissue biopsies of these lesions and presented with clinical evidence of recurrent cervical infections or suspected cervical intraepithelial lesions were included. Moreover, research papers consisting of original articles and systematic reviews that explored the potential tumorogenic role of CHEK2, MSH6, and MCM3 in cervical carcinogenesis were included. However, case reports, case series, editorials, opinions, and studies focused solely on clinical features, as well as those available only in abstract form, were excluded from this study. Moreover, pregnant females and patients using intra-uterine conceptive devices were excluded.

Data Extraction

A total of 80 articles were retrieved from various databases, with 20 identified as duplicates. The titles and abstracts of the remaining articles were screened, resulting in the exclusion of 18 studies focused solely on clinical aspects and 22 studies that were abstract-only publications, leaving 20 articles for further evaluation. Of these, nine full-text articles were excluded as they investigated genes unrelated to cervical cancer tumorigenesis or were published in languages other than English. Finally, 11 articles were included in the review. Various details were extracted from the shortlisted studies, including the first author's name, publication year, the area where the study was conducted, its duration, sample size, patient demographics (gender and age), study design, and the authors' ultimate conclusions related to the gene. The results were mapped and presented using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) [30] (Figure I)

Quality Assessment: Joanna Briggs Institute (JBI) Critical Appraisal Tool[31] was used to assess the quality of 11 articles. All of the included studies were of good quality and were included in this study. Two reviewers (S.K. and N.N.) read the final selected 11 articles and evaluated them using the PRISMA-ScR and JBI critical appraisal checklists for systematic reviews and meta-analysis.

FIGURE I: Flow Diagram of Scoping Review



REVIEW AND DISCUSSION

Recent developments in cancer research elucidate the intricate interactions among genes, proteins, and viruses that play a role in the development and progression of various malignancies. This review examines several studies that illuminate the altered expression of specific genes and proteins, including CHEK2, MCM3, and MSH6, and their potential applications in cancer diagnosis, prognosis, and treatment.

One area of focus is on improving the accuracy of cancer detection. Zheng J 2015[38] explored the potential of MCM2, a protein, as a biomarker for identifying precancerous lesions in the cervix. This study concluded that combining the MCM2 expression with the standard HPV detection significantly improved the accuracy of identifying lesions. This study presents a comprehensive analysis utilising multiple markers, providing a more reliable diagnosis. A study by Ha S-A et al.[27] investigated the potential role of MCM3 as a diagnostic marker for various cancers. This research suggested that detecting MCM3 levels within tumors could be a valuable tool for assessing the presence and potentially the type of cancer. Moreover, Yu S et al.[28] explored the role of MCM

Table II: Role of CHEK2, MCM3 and MSH6 in various malignancies given by different authors over the years (2004 – 2024)

Author	Place of Study	Publication year	Study Duration	Study Design	Sample size	Gender	Conclusion
Guo et al.[32]	China	2024	2012-2014	Descriptive cross-sectional	**118**	Female	This study investigated the mechanism by which the DNA mismatch repair (MMR) system regulates the expression of PD-L1 in cervical cancer through DNA methyltransferase (DNMTs). PD-L1 is universally expressed on the surface of cervical cancer (CC) cells, and this expression is further elevated in cells exhibiting deficient mismatch repair (dMMR) status. In cervical cancer, defects in the mismatch repair (MMR) system are linked to the demethylation of the promoter region of the PD -L1 gene, contributing to its increased expression.
Kazanci et al. [33]	Brazil	2024	July 2015 - August 2022	Descriptive cross-sectional	1673	Females	The detection of pathogenic variations, including recurrent mutations in the CHEK2 gene in the endometrium and the ATM gene in the ovary, corroborated the diagnosis of synchronous endometrial and ovarian cancer, with genetic alterations linked to endometrioid-type tumors.
Ozdemir et al. [34]	Turkey	2024	2018-2021	Cohort study	1707 with high-risk cancer predisposition	Females & males-	Germline pathogenic variants in CHEK2 have been reported to be associated with an increased risk of breast cancer, cervical cancer, thyroid cancer, and kidney cancer. Three main CHEK2 PVs (p.Thr476Met, p.Arg137Gln, and c.592+3A>T) were more highly present in the study cohort than in the non-cancer group.
Addante et al[35]	Italy	2024	2023-2024	-	373	Females	Immunohistochemistry (IHC) for MMR proteins (such as MLH1, MSH2, MSH6, and PMS2) has become the preferred diagnostic method for identifying microsatellite instability (MSI) worldwide. MMR/MSI and POLE testing are vital for the accurate histo-molecular classification of Endometrial carcinoma.
Wu et al[36]	China	2021	-	-	-	Females	Upregulation of MCM2 and CHEK1 plays a key role in cervical cancer progression and is associated with worse prognosis.

Ma et al[37]	China	2021	-		304	Females	MCM3 was found to be more highly expressed in cervical cancer than in normal cervical tissues. The results suggest that MCM3, PRIM2 and MCM6 could be helpful in the early detection of cervical cancer and serve as prognostic indicators.
Yu et al. [28]	China	2020	-	Cohort study	1441	Females	MCM proteins are often overexpressed in various cancers and can be utilised for both diagnostic and prognostic purposes. These proteins contribute to cancer progression and are potential therapeutic targets by influencing protein modifications.
Zheng et al. [38]	China	2015	2011-2012	Descriptive Cross-sectional	183	Females	Detecting cervical lesions with ICC for MCM2 was found to be more effective than using HPV typing alone. Combining these two approaches could significantly improve diagnostic sensitivity and specificity.
Banaszkiewicz et al [22]	Poland	2013	-	Descriptive Cross-sectional	131	Females-16 Males-115	The presence of CHEK2 gene mutations or the CYP1B1 gene 355T/T polymorphism, along with oncogenic HPV types, is significantly associated with the histological grades of malignancy in urinary bladder carcinoma.
Antill et al. [26]	USA, Canada, Australia	2015	1997-2012	Descriptive Cross-sectional	14931	Females-7119 Males-7812	The development of cervical cancer in individuals with MMR gene mutations is associated with recognised tumorigenic pathways that are affected by the carcinogenic processes driven by HPV exposure.
Ha S-A et al. [27]	Korea	2004	-	Experimental	110	Females, Males	Measuring MCM3 expression levels will improve the diagnostic assessment of various human cancers, as MCM3 is involved in several types of carcinogenesis.

CHEK2= Checkpoint Kinase 2, CYP1B1= cytochrome P450 1B1, HPV= Human Papillomavirus, ICC=Immunocytochemistry, MCM3= Minichromosome maintenance complex component 3, MMR= DNA mismatch repair, DEGs = Differentially Expressed Genes, ISPPs= In Silico Pathogenicity Predictors.

proteins in cancer more deeply. According to the study, MCM proteins are frequently found in high levels within many cancers and act as valuable markers for both diagnosis and prognosis. Measuring MCM protein levels can not only aid in identifying cancer but also potentially predict its course of progression.

Furthermore, it was concluded that MCM3 is integral to the development of various cancers, making it a potential target for future therapeutic interventions. This opens exciting avenues for developing drugs specifically designed to target MCM3 function or production, potentially leading to novel cancer treatments. A recent study by Ma H et al.[37] has also emphasised the potential involvement of increased levels of MCM3 in cervical cancer tissues as compared to normal cervical tissues, suggesting its possible role in the development of cervical cancer. This study concluded that MCM3, PRIM2 and MCM6 could serve as valuable biomarkers for the early detection of cervical cancer. These genes may also serve as prognostic indicators, helping to predict the likely course or outcome of the disease in patients. By focusing on MCM3, therapies could potentially be developed to specifically target cancer cells with high expression of this gene, providing a more targeted and practical approach to treatment. A recent study explored by Addante F et al.[35] explained the role of immunohistochemistry (IHC) in diagnosing microsatellite instability (MSI), a condition often associated with certain types of cancer, including those linked to Lynch syndrome.

Immunohistochemistry for MMR proteins—including MLH1, MSH2, MSH6, and PMS2 has become the gold standard diagnostic tool for identifying MSI. A loss of expression of any of these proteins suggests that the tumor has defective MMR, which can indicate Lynch syndrome. This hereditary disorder increases the risk of several cancers, including colorectal, endometrial, and ovarian cancer. This information emphasises the importance of identifying MSI in cancer diagnosis and monitoring, as it can provide insight into the underlying genetic causes, including Lynch syndrome, and guide treatment decisions.

The CHEK2 gene plays a crucial role in the DNA damage response pathway, maintaining genomic stability by halting the cell cycle to allow DNA repair or triggering apoptosis in cells with irreparable damage. Its dysfunction has implications for various cancers, including cervical lesions. While CHEK2 mutations are well-documented in various cancers, including breast, prostate, and colon cancers, their specific role in cervical lesions is less clearly defined. A study by Banaszkiewicz M et al. [22] examined the concomitance of oncogenic HPV types, CHEK2 gene mutations, and CYP1B1 polymorphism and found a statistically significant relationship between the presence of HPV infection, CHEK2 gene mutations, or CYP1B1 polymorphism and the histological grade of tumour malignancy. This suggests that CHEK2 mutations, in

conjunction with HPV infection, may influence the progression of cervical lesions. A recent study by Kazanci F et al.[33] analysed the genetic alterations in tumors using a homologous recombination deficiency gene panel in patients with synchronous endometrial ovarian cancer who had been followed for over five years. Pathogenic genetic variations were frequently observed in two critical DNA repair genes: CHEK2 in the endometrium and ATM in the ovary. The high prevalence of these mutations in this study underscores their importance in understanding and diagnosing this rare and complex condition. A recent study by Ozdemir O et al.[34] explored the range of CHEK2 gene variants in individuals from Turkey who may be at risk for cancer development due to genetic predisposition or a family history of hereditary cancer. The research highlighted that specific genetic variants, or variant allele frequencies, in the Turkish population differ from those seen in Northern European populations, suggesting regional genetic differences that could influence cancer risk. CHEK2 variants were found to be more prevalent in the cancer group than in the non-cancer group, indicating a potential link between these variants and cancer susceptibility. This approach aimed to improve the precision of genetic assessments and clinical decisions related to cancer risk.

Different studies have highlighted the role of CHEK2 in tumors other than cervical cancer. Gąsior-Perczak D et al. [39] studied the role of CHEK2 in papillary thyroid cancer (PTC). Their study suggested that high levels of CHEK2 and p53 expression within tumors might indicate a more aggressive form of PTC. Similarly, a study by Kuhlen M et al.[40] investigated a rare case of undifferentiated embryonal sarcoma of the liver (UESL) with double genetic mutations in the CHEK2 and TP53 genes. This dual mutation mechanism suggested that TP53 plays a central role in tumour initiation. At the same time, the loss of CHEK2 enhances the tumour's ability to survive and grow, highlighting the complex interplay between these genetic changes in the development of various tumours. This suggested that the germline TP53 pathogenic variant acts as a driver of tumorigenesis in this case and supports a complex interaction between the germline TP53 and CHEK2 pathogenic variants.

The interplay between genes and viruses also affects cervical cancer development. Antill YC et al.[26] explored the role of Mismatch Repair (MMR) genes in DNA repair and their interaction with human papillomavirus (HPV). The study revealed that individuals with mutations in MMR genes are at an increased risk of developing cervical cancer when exposed to high-risk HPV types. These specific HPV strains activate pathways in the body that can promote cancer formation. Consequently, a compromised DNA repair mechanism due to MMR mutations, combined with HPV exposure, creates a favorable environment for the activation of cancer-associated pathways. This research underscored the importance of HPV vaccination, particularly in individuals with a familial predisposition to genetic mutations that elevate cancer risk.

The MSH6 gene encodes a protein integral to the DNA mismatch repair (MMR) system, which maintains genomic stability by correcting replication errors. MSH6 plays a crucial role in maintaining DNA integrity, and its mutations are linked to an elevated risk of cervical cancer. Ongoing research continues to elucidate its role in tumour progression and the response to treatment. Wu B 2021[36] examined the role of MCMs and their related genes in cervical cancer. In this study, the mRNA expression of various MCMs was analysed using the Oncomine database in patients with cervical cancer. The mRNA and protein expression of MCMs increased in tumor tissue. Overexpression of MCM2/3/4/5/6/7/8/10 was found to be significantly associated with clinical cancer stage. This study concluded that by identifying these genes and pathways, there would be a deeper insight into the molecular mechanisms that underlie the onset and progression of cervical cancer.

Mutations in MSH6 can lead to Lynch syndrome, a hereditary condition associated with an elevated risk of various cancers, including colorectal, endometrial, thyroid, lung and bladder cancers. Tous C et al. [41] have suggested the potential role of MSH6 in the development of Medullary Thyroid Carcinoma (MTC). Beyond Lynch syndrome, mutations in MSH6 have also been identified as pathogenic (disease-causing) in a variety of other cancers, including lung, pancreatic, and breast cancer. This highlights the broader role of MSH6 in maintaining genetic stability and preventing tumorigenesis across different tissue types. Similarly, He N et al.[42] explored the role of **MSH6** in bladder cancer, focusing on its impact on diagnosis, prognosis, and potential link to immune responses. The study highlighted MSH6 as a critical factor influencing the immune system's interaction with cancer, potentially affecting tumour behaviour and the body's response to it. It emphasised the value of identifying novel prognostic biomarkers, such as MSH6, which could enhance diagnostic accuracy, improve prognostic assessments, and inform treatment strategies for bladder cancer and other malignancies. The association between MSH6 mutations and an increased risk of cervical cancer, particularly in individuals with Lynch syndrome, further emphasises the importance of genetic counseling and regular screening for at-risk populations. Insights into the role of MSH6 in cervical carcinogenesis could also guide therapeutic approaches, such as immunotherapies targeting the PD-1/PD-L1 pathway.

Hence, this review was aimed to understand the intricate interplay between genes, proteins, and viruses in cancer development. By elucidating these

complex pathways, researchers are advancing the development of more effective diagnostic tools, identifying novel therapeutic targets, and creating personalised treatment strategies across various cancers.

CONCLUSION

The differential expression of genes related to cervical lesions may help identify and monitor the biological course of the malignancy. Literature supports the significance of many gene panels in assessing tumour risk as well as its progression. Numerous tumors, including carcinoma of the cervix, have dysregulated this gene expression. Thus, establishing, validating, and enhancing a panel of molecular markers that predict pre-neoplasia and neoplasia in cervical samples with inconclusive biological behaviour based on morphology is the need of the hour. Subsequently, early diagnosis and timely management of such lesions may reduce the burden of morbidity and mortality related to cervical neoplasia in females.

Conflict of Interest: The authors have no conflict of interest to declare

Financial Disclosure/Grant Approval: This research did not receive specific funding from any financially supporting body.

Data Sharing Statement: The corresponding author can provide the data proving the findings of this study on request. Privacy or ethical restrictions bound us from sharing the data publically.

AUTHOR CONTRIBUTION

Zameer G: Conception, manuscript drafting, literature search and interpretation of data.
Javed M: Drafting of manuscript, literature search and interpretation of data, critical input
Zaki S: Data collection and interpretation, critical intellectual input.
Nisar B: Data collection and interpretation, critical intellectual input.
Khaliq S: Data collection and interpretation, critical intellectual input.
Naseem N: Conception of study, critical intellectual input and approval of final draft for publication.

REFERENCES

1. Mutombo Baleka A. Cervical cancer control and prevention strategies in a low-resource setting: University of Antwerp; 2019.
2. Cervical Cancer: Estimated cancer incidence, mortality, and prevalence worldwide in 2022 [Internet]. Available from: https://gco.iarc.who.int/ media/globocan/factsheets/ populations/900-world -fact-sheet.pdf. Last cited on [12 Dec 2024].
3. Aoki ES, Yin R, Li K, Bhatla N, Singhal S, Ocviyanti D et al. National screening programs for cervical cancer in Asian countries. J Gynecol Oncol. 2020; 31(3): 1-9. doi: 10.3802/ jgo.2020. 31.e55.
4. Ikram A, Khadim MT, Sohaib M, Uddin H, Badar F, Masood AI, Khattak ZI et al. National Cancer Registry of Pakistan: First Comprehensive Report of Cancer Statistics 2015-2019. J Coll Physicians Surg Pak. 2023; 33(6): 625-32. doi: 10.29271/ jcpsp.2023.06.625.
5. Reports SKCR. Cervical Cancer Awareness Month 2021. Available from: https:// shaukatkhanumorgpk/about-us/blog/cervical-cancer-2021/.
6. Pervez S, Jabbar AA, Haider G, Qureshi MA, Ashraf S, Lateef F et al. Karachi Cancer Registry (KCR): consolidated data of 5 years 2017-2021. J Coll Physcians Surg Pak. 2023;1:01. doi: 10.29271/jcpsp.2023.05.560.
7. Chan CK, Aimagambetova G, Ukybassova T, Kongrtay K, Azizan A. Human papillomavirus infection and cervical cancer: epidemiology, screening, and vaccination -review of current perspectives. Ann Oncol. 2019; 2019: 1-11. doi: 10.1155/2019/3257939.
8. Ikram A, Pervez S, Khadim MT, Sohaib M, Uddin H, Badar F et al. National cancer registry of Pakistan: first comprehensive report of cancer statistics 2015-2019. J Coll Physicians Surg Pak. 2023; 33(6): 625-32.
9. Al Niyazee A, Abedalrahman SK, Saleh L. Prevalence of cytological abnormality of cervical Papanicolaou smear. Middle East J Fam Med. 2019; 7(10): 16-21. doi: 10.5742/MEWFM.2019. 93687.
10. Kashyap N, Krishnan N, Kaur S, Ghai S. Risk Factors of Cervical Cancer: A Case-Control Study. Asia Pac J Oncol Nurs. 2019; 6(3): 308-14. doi: 10.4103/apjon.apjon_73_18.
11. Hirani S, Khan S, Akram S, Virji SN, Shaikh PA, Naeem E et al. Knowledge, awareness, and practices of cervical cancer, its risk factors, screening, and prevention among women in Karachi, Pakistan. Eur J Cancer Prev. 2021; 30 (1): 97-102. doi: 10.1097/CEJ.0000000000000 590.
12. Nayar R, Wilbur DC. The Pap Test and Bethesda 2014. Acta Cytologica. 2015; 59(2): 121-132. doi: 10.1159/000381842.
13. Pankaj S, Nazneen S, Kumari S, Kumari A, Kumari A, Kumari J et al. Comparison of conventional Pap smear and liquid-based cytology: a study of cervical cancer screening at a tertiary care center in Bihar. Indian J Cancer. 2018; 55(1): 80-3. doi: 10.4103/ijc.IJC_352_17.
14. Varsegi GM, Shidham V. Cell block preparation from cytology specimen with predominance of individually scattered cells. J Vis Exp. 2009; 29: 1-8. doi: 10.3791/1316.

15. Singh U, Anjum, Qureshi S, Negi N, Singh N, Goel M et al. Comparative study between liquid-based cytology & conventional Pap smear for cytological follow up of treated patients of cancer cervix. Indian J Med Res. 2018; 147(3): 263-7.
16. Khan S, Omar T, Michelow P. Effectiveness of the cell block technique in diagnostic cytopathology. J Cytol. 2012; 29(3): 177-82. doi: 10.4103/ijmr. IJMR_1290_16.
17. Luo L, Gao W, Wang J, Wang D, Peng X, Jia Z et al. Study on the Mechanism of Cell Cycle Checkpoint Kinase 2 (CHEK2) Gene Dysfunction in Chemotherapeutic Drug Resistance of Triple Negative Breast Cancer Cells. Med Sci Monit. 2018; 24: 1-8. doi: 10.4103/0970-9371.101167.
18. Brooks K, Holman M, Steding C, Tucker M. A founder CHEK2 pathogenic variant in association with kidney cancer. Cancer Genet. 2022; 262: 40-2. doi: 10.1016/j.cancergen. 2021.12.007.
19. Motoyama N, Naka K. DNA damage tumor suppressor genes and genomic instability. Curr Opin Genet Dev. 2004; 14(1): 11-6. doi: 10.1016/j. gde.2003.12.003.
20. Sharifi MJ, Zaker F, Nasiri N, Yaghmaie M. Epigenetic changes in FOXO3 and CHEK2 genes and their correlation with clinicopathological findings in myelodysplastic syndromes. Hematol Oncol Stem Cell Ther. 2020; 13(4): 214-9. doi: 10.1016/j.hemonc.2019. 11.004.
21. Consortium APG. AACR Project GENIE: powering precision medicine through an international consortium. Cancer Discov. 2017; 7(8): 818-831. doi: 10.1158/2159-8290.CD-17-0151.
22. Banaszkiewicz M, Constantinou M, Pietrusiński M, Kępczyński L, Jędrzejczyk A, Rożniecki M et al. Concomitance of oncogenic HPV types, CHEK2 gene mutations, and CYP1B1 gene polymorphism as an increased risk factor for malignancy. Cent European J Urol. 2013; 66(1): 23-9. doi: 10.5173/ ceju.2013.01.art7.
23. Liu J, Zheng B, Li Y, Yuan Y, Xing C. Genetic Polymorphisms of DNA Repair Pathways in Sporadic Colorectal Carcinogenesis. J Cancer. 2019; 10(6): 1-17. doi: 10.7150/jca. 28406.
24. Modrich P, Lahue R. Mismatch repair in replication fidelity, genetic recombination, and Cancer Biology. Ann Rev Biochem. 1996; 65(1): 101-33. doi: 10.1146/annurev. bi.65.070196.000 533.
25. Mendoza RP, Haidary T, Gabutan E, Zhou YY, Bukhari Z, Connelly C et al. Mixed and nonvaccine high risk HPV types are associated with higher mortality in Black women with cervical cancer. Sci Rep. 2021; 11(1): 1-14. doi: 10.1038/ s41598-021-93485-1.
26. Antill YC, Dowty JG, Win AK, Thompson T, Walsh MD, Cummings MC et al. Lynch syndrome and cervical cancer. Int J Cancer. 2015; 137(11): 2757 -61. doi: 10.1002/ijc.29547.
27. Ha S-A, Shin SM, Namkoong H, Lee H, Cho GW, Hur SY et al. Cancer-associated expression of minichromosome maintenance 3 gene in several human cancers and its involvement in tumorigenesis. Clin Cancer Res. 2004; 10(24): 8386-95. doi: 10.1158/1078-0432.CCR-04-1029.
28. Yu S, Wang G, Shi Y, Xu H, Zheng Y, Chen Y. MCMs in Cancer: Prognostic Potential and Mechanisms. Anal Cell Pathol. 2020; 2020: 1-11. doi: 10.1155/2020/3750294.
29. Wu B, Xi S. Bioinformatics analysis of the transcriptional expression of minichromosome maintenance proteins as potential indicators of survival in patients with cervical cancer. BMC Cancer. 2021; 21(1): 1-17. doi: 10.1186/s12885-021-08674-y.
30. McGowan J, Straus S, Moher D, Langlois EV, O'Brien KK, Horsley T et al. Reporting scoping reviews-PRISMA ScR extension. J Clin Epidemiol. 2020; 123(177): e9. doi: 10.1016/ j.jclinepi.2020. 03.016.
31. Buccheri RK SC. Critical appraisal tools and reporting guidelines for evidence□based practice. Worldviews on Evidence□Based Nursing. Critical Appraisal Tools and Reporting Guidelines for Evidence-Based Practice. 2017; 14(6): 463-472. doi: 10.1111/wvn.12258.
32. Guo F LR, Kong W, Anwar M, Feng Y. DNA mismatch repair system regulates the expression of PD-L1 through DNMTs in cervical cancer. Cancer Cell Int. 2024; 24(1): 25-41. doi: 10.1186/ s12935-024-03214-7.
33. Kazanci F, Çelik ZY, Polat M, Karademir F, Erdem O, Şahin Fİ et al. Homologous recombination deficiency gene panel analysis results in synchronous endometrial and ovarian cancers. Rev Assoc Med Bras. 2024; 70(10): e20240534. doi: 10.1590/1806-9282.20240534.
34. Ozdemir O, Bychkovsky BL, Unal B, Onder G, Amanvermez U, Aydin E et al. Molecular and In Silico Analysis of the CHEK2 Gene in Individuals with High Risk of Cancer Predisposition from Türkiye. Cancers. 2024; 16(22): 3876. doi: 10.3390/cancers16223876.
35. Addante F, d'Amati A, Santoro A, Angelico G, Inzani F, Arciuolo D et al. Mismatch Repair Deficiency as a Predictive and Prognostic Biomarker in Endometrial Cancer: A Review on Immunohistochemistry Staining Patterns and Clinical Implications. Int J Mol Sci. 2024; 25(2): 1056. doi: 10.3390/ijms25021056.
36. Wu B, Xi S. Bioinformatics analysis of differentially expressed genes and pathways in the development of cervical cancer. BMC Cancer. 2021;21(1):733. doi:10.1186/s12885-021-08412-4.

37. Ma H, Liu Z, Li H, Guo X, Guo S, Qu P et al. Bioinformatics analysis reveals MCM3 as an important prognostic marker in cervical cancer. Computational and mathematical methods in medicine. 2021; 2021(1): 8494260. doi: 10.1155/2021/8494260.
38. Zheng J. Diagnostic value of MCM2 immunocytochemical staining in cervical lesions and its relationship with HPV infection. Int J Clin Exp Pathol. 2015; 8(1): 875-80.
39. Gąsior-Perczak D, Kowalik A, Kopczyński J, Macek P, Niemyska K, Walczyk A et al. Relationship between the Expression of CHK2 and p53 in Tumor Tissue and the Course of Papillary Thyroid Cancer in Patients with CHEK2 Germline Mutations. Cancers. 2024; 16(4): 815. doi: 10.3390/cancers16040815.
40. Kuhlen M ST, Dintner S, Stadler N, Hofmann TG, Schmutz M, Claus R et al. Double heterozygous pathogenic variants in TP53 and CHEK2 in boy with undifferentiated embryonal sarcoma of the liver. Int J Mol Sci. 2024; 25(21): 11489-96. doi: 10.3390/ijms252111489.
41. Tous C, Muñoz-Redondo C, Bravo-Gil N, Gavilan A, Fernández RM, Antiñolo J et al. Identification of Novel Candidate Genes for Familial Thyroid Cancer by Whole Exome Sequencing. Int J Mol Sci. 2023; 24(9): 7843. doi: 10.3390/ijms24097843.
42. He N, Bao LR, Fu ZI, Gao WN, Wang JY, Chen LG. MSH6 as a prognostic biomarker in bladder cancer and its correlation with immunity. 2024. doi: 10.21203/rs.3.rs-4930584/v1.