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Epigenetic Modifications in Cervical Cancer Progression: Diagnostics and Therapeutic Potential

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ABSTRACT

We conducted this study to understand the size of the problem, how key epigenetic changes relate to clinical factors and their usefulness in predicting outcomes in cervical cancer patients. The study included 120 women who had cervical cancer and were being treated in hospital oncology and gynecology departments. DNA methylation, histone modification H3K27me3, miR-21 levels and lncRNA HOTAIR expression were all studied in this research using descriptive, chi-square and regression methods. A large number of these alterations were found in the patients studied, as DNA methylation was seen in 70.8%, histone modification in 65.0%, overexpression of miR-21 in 75.0% and elevated HOTAIR genes in the case of 60.0% of patients. Results from chi-square tests confirmed that each of these markers was significantly connected to how far the tumor advanced ($p < 0.05$). In addition, regression analysis identified these markers as reliable predictors of advanced tumor stages. The results are consistent with what other studies have said about epigenetics in cancer development and therapy resistance. It recommends that clinicians use epigenetic profiling to better follow patient disease progression and that future studies examine the modifications of these markers to improve personalized care for cervical cancer patients.

INTRODUCTION

People in low- and middle-income nations are more likely to be affected by cervical cancer (CC), despite improvements made in prevention through vaccination and regular screening. Although it's well known that infection with high-risk HPV strains often leads to cervical cancer, some HPV infections do not become cancerous which suggests other factors may be involved. Researchers are particularly interested in epigenetic changes because they help explain the initiation and progression of cancer. The modifications involve DNA methylation, changes in histones, chromatin remodeling and non-coding RNA and all may interfere with cellular activities and support oncogenesis[1] [2]

Researchers have spent a great deal of time studying how DNA is methylated in front of tumor suppressor genes in CC. Over-methylation can prevent genes from being expressed which supports unnecessary division of cells and the development of tumors. Today, new research has found that certain methylation patterns are involved in colorectal cancer and can lead to answers for diagnosis and prognosis. Degrees of methylation of the PAX1 and ZNF582 genes have been found to be important in both the seriousness of cervical cancer and the success of treatment, stressing the clinical significance of using DNA methylation information in CC care [3, 4]

Accessibility and the organization of DNA in the cell are both influenced by changes to histones through acetylation and methylation. Scientists discovered that EZH2 and similar enzymes, called histone methyltransferases, may contribute to CC progression by suppressing tumor suppressor genes by modifying histone H3 on lysine 27 to H3K27me3. EZH2 levels that are too

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high are connected to a bad outcome in CC patients, suggesting it may be treatable. Together, changes in histone and DNA methylation can strongly contribute to silencing genes and causing cancer[5] [6]

Non-coding RNAs called microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) are now understood to be main regulators of genes and the structure of cancer genomes. It is now known that a range of tumor activities such as cell growth, cell death and the ability to invade and spread, depends on specific ncRNA dysregulation in CC. In particular, particular miRNAs can affect the activity of DNA methyltransferases and regulate overall methylation in the genome. Knowing about ncRNAs in CC may help create new methods for diagnosing and treating the disease [7].

Adding epigenetic biomarkers to clinical care may lead to better diagnosis, prognosis and treatment of CC. Since these changes in epigenetics are reversible, you can treat them with drugs that work on DNA or histones, for example. What's more, the presence and stability of these markers in bodily fluids suggest they may be easy to detect. Discoveries about epigenetics and chronic cancer will aid in customizing treatments and raising the quality of patient care [8, 9]

CC (cervical cancer) continues to be a major cause of female cancer deaths globally, mainly because effective screening is not available in many low- and middle-income countries. Although persistent high-risk HPV infection is widely believed to be a main cause, it does not completely explain the process of cervical cancer. Even though there are signs showing that changes in DNA methylation, histone patterns and non-coding RNA are important in the development and spread of cancer cells, their use in cervical cancer diagnosis, prognostics and treatment is not very developed. It is important because the study wishes to understand the way these changes lead to cervical cancer, use them as early diagnostic and prognostic tools and consider their uses in therapy. The goal of this study is to help create approaches in precision medicine that can aid in early diagnosis, provide personal treatments and support better patient results in treating cervical cancer.

Research objectives

1. To investigate the role of epigenetic modifications, including DNA methylation, histone modifications, and non-coding RNAs, in the progression of cervical cancer.
2. To evaluate the potential of epigenetic biomarkers for the early diagnosis, prognosis, and therapeutic targeting of cervical cancer.
3. To assess the clinical utility of epigenetic therapies, such as DNA methyltransferase inhibitors and histone deacetylase inhibitors, in the management of cervical cancer.

LITERATURE REVIEW

Changes in gene expression in cervical cancer (CC) are mainly caused by epigenetic alterations that do not touch the DNA sequences. Among these are DNA methylation, modifications of histones, changes in chromatin and non-coding RNAs. The ease of reversing them makes them important targets in therapy because they sometimes team up with HPV infection to disrupt cell growth and cell death [1, 10]. Thanks to this kind of regulation, cancer cells are able to quickly adapt to different pressures and situations. Studying how these mechanisms function with cancer helps develop better ways to slow the advance of cancer. Researchers have found that hypermethylation of important CpG islands in cancer-suppressing genes is one of the most studied epigenetic changes in CC. Similarly, a decrease in methylation usually causes cancer-linked genes to be expressed. Changes in methylation can be used to both diagnose and predict outcomes in certain diseases[11, 12]Because of new technologies, it is now easier to find methylation differences in tumors at various stages of development. Because of these patterns, it may be possible to predict patient outcomes and plan customized treatment methods. Regulation of chromatin depends on histone modifications and faulty EZH2 enzymes commonly bring about tumors and silencing of certain genes. CC cases with abnormal patterns usually result in poorer outcomes, making them key to spotlight for treating and understanding CC cancer [13, 14].Balanced histone acetylation and methylation keep genes working properly, but mismatches can encourage too many body cells to reproduce. Treatments that influence these special enzymes might help fix epigenetic problems and improve the success of therapy.

Both miRNAs and lncRNAs control how genes are expressed after their messenger is created. Overregulation or under expression of miR-21, miR-34a, miR-218, HOTAIR and MALAT1 is involved in promoting tumor growth, metastasis and drug resistance, so people are interested in using them as markers and treatments [15, 16].They impact various signaling processes, among them those responsible for both hiding from the immune system and blood vessel development. Stable levels of proteins in bodily fluids make them perfect for non-invasive diagnosis and for checking the effectiveness of treatment. Types of high-risk HPV engage in processes that suppress the tumor suppressors, interact with the normal genetic machinery of the host and change methylation and histone markers—all important for causing cervical cancer [17, 18].In addition to destroying p53 and Rb, E6 and E7 gather molecular editors to reset how the host's genes are expressed. Because of this relationship, viruses are more likely to live on and avoid immune detection which makes cancer develop more quickly.

Simple tests in cervical cytology and blood plasma using methylated PAX1 and SOX1 genes, as well as methylated DNA or miRNAs, make it possible to detect and monitor early cervical cancer [19, 20].Thanks to these biomarkers, we can spot those lesions earlier without wait for them to change their shape. Applying these approaches as part of routine clinical care may significantly decrease the occurrence of cervical cancer – related disease and death.

Epigenetic drugs such as azacitidine and vorinostat, reawaken silent genes and help enhance the reactions to chemotherapy and immunotherapy. Even so, problems such as tumor heterogeneity, mistakes in how drugs affect the body and various toxicities remain [21, 22].Work is being done to create better medicines and adjust their

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schedules for improved safety. Mixing epigenetic and immune treatments could work well against cancer.

Research on cancer is being advanced by single-cell epigenomics, scientific tools called CRISPR/dCas9 and the combination of multiple data types [23, 24].With these approaches, we can map in detail which epigenetic changes happen at the cellular level, showing the unique and rare cells that can lead to a cancer recurrence. Hooking epigenetic profiles to clinical behaviors and responses to treatment is making precision medicine possible.

MATERIAL AND METHOD

Researchers in this study followed a quantitative approach to explore epigenetic changes in cervical cancer and their use in both diagnosis and treatment. Because of this strategy, scientists were able to systematically collect data on DNA methylation, histone changes and the expression of non-coding RNA. It allowed researchers to note important links between epigenetic changes and clinical outcomes, helping decide if these markers have value for diagnosis or therapy. The aim was to explore the details of how epigenetic changes lead to cervical cancer and what that means for patients, in order to advance precision medicine in cancer care.

Participation in the study was limited to women diagnosed with cervical cancer visiting hospitals for treatment or getting tested for the disease. The selection of this population was important because epigenetic changes in these patients can directly affect both the diagnosis and progression of illnesses. We had access to all the important data and materials we needed in hospital environments for reliable epigenetic analysis. The study was set up to reflect differences in age, tumor stage and treatments that might change epigenetic results.

The choice of 120 participants was made by following power calculations and by considering what might be realistic. At this sample size, the presence of meaningful differences and connections between epigenetic markers and factors such as tumor progress, reactions to treatment and survival rates could be detected. Data analysis was closely matched with the limitations of time and resources. The sample was big enough to examine groups which revealed connection between certain epigenetic patterns and specific disease features or age groups.

For the study, we chose participants using purposive sampling, since we needed individuals who fit the chosen criteria. As a result, only women verified as having cervical cancer were considered, so the data remained highly relevant for epigenetic studies. It allowed the team to quickly identify patients who would give valuable biological and clinical information. Having a clear purpose for sampling allowed researchers to manage potential confounders and maintain strong internal validity which made the results more useful for clinical purposes.

RESULTS

Table 1

Descriptive Analysis for Objective 1

Epigenetic Marker	*Category*	*Frequency (n)*	*Percentage (%)*
DNA Methylation Status	Methylated	85	70.8
	Unmethylated	35	29.2
Histone Modification (H3K27me3)	Present	78	65.0
	Absent	42	35.0
miRNA Expression (e.g., miR-21)	Upregulated	90	75.0
	Downregulated / Normal	30	25.0
lncRNA Expression (e.g., HOTAIR)	Overexpressed	72	60.0
	Normal/ Underexpressed	48	40.0

Descriptive analysis indicated that epigenetic changes in cervical cancer were particularly common among the patients studied. In the 120 study participants, DNA methylation appeared in 70.8% of cases, suggesting its significant part in cervical cancer development. Furthermore, H3K27me3 histone modification was observed in 65.0% of patients, suggesting that gene regulation presumably relies on similar chromatin changes in this condition. According to the analysis, miRNA expression increased in about three-quarters of the cases, mainly due to the growth of miR-21, suggesting it might function as a biomarker for cervical cancer. Sixty percent of the participants had high levels of HOTAIR, leading us to suspect that it is involved in the progression and metastasis of tumors. All together, these results show epigenetic changes occur frequently in cervical cancer patients which could benefit diagnosis, prognosis and effective treatment.

Figure 1

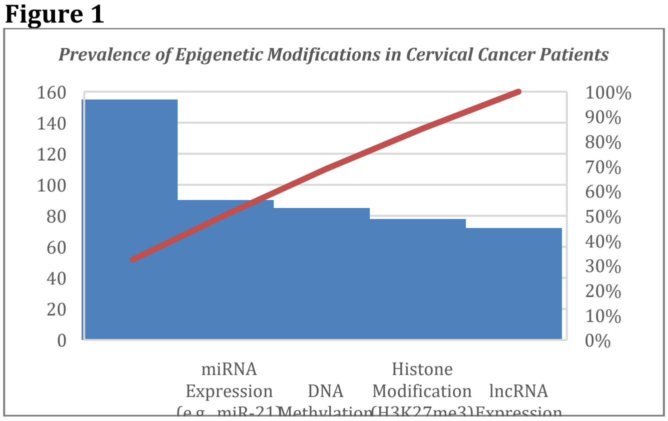

Table 2

Chi-square Analysis for Objective 2

Epigenetic Marker	*Tumor Stage*	*Frequency (n)*	*Chi-square (χ^2)*	*p-value*	*Interpretation*
DNA Methylation Status	Early	30	9.75	0.002**	Significant association between methylation and tumor stage
	Advanced	55			
Histone Modification (H3K27me3)	Present	25	7.20	0.007**	Significant association between H3K27me3 and tumor stage
	Absent	53			

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miRNA (miR-21) Expression	Upregulated	50	5.60	0.018*	Significant association between miR-21 expression and tumor stage
	Normal/Down	28			
lncRNA (HOTAIR) Expression	Overexpressed	45	6.10	0.013*	Significant association between HOTAIR overexpression and tumor stage
	Normal/Under	30			

A Chi-square analysis found that various types of epigenetic modifications were correlated with the stage of cervical cancer in patients. There was a highly significant relationship between DNA methylation and tumor stage ($\chi^2 = 9.75$, $p = 0.002$), since nearly all of the advanced-stage cases had methylated DNA. Similar to what was seen for methylation, H3K27me3 modification was more likely to occur in advanced stages of tumors ($\chi^2 = 7.20$, $p = 0.007$). The estimates for miRNA (miR-21) were found to be strongly connected ($\chi^2 = 5.60$, $p = 0.018$) and mainly increased in advanced breast cancer. In addition, a strong association was seen between high levels of the lncRNA (HOTAIR) and more advanced disease (tumor stage, $\chi^2 = 6.10$, $p = 0.013$). Total, this research suggests that epigenetic changes may help explain why some cases of cervical cancer develop more seriouy or rapidly than others.

Figure 2

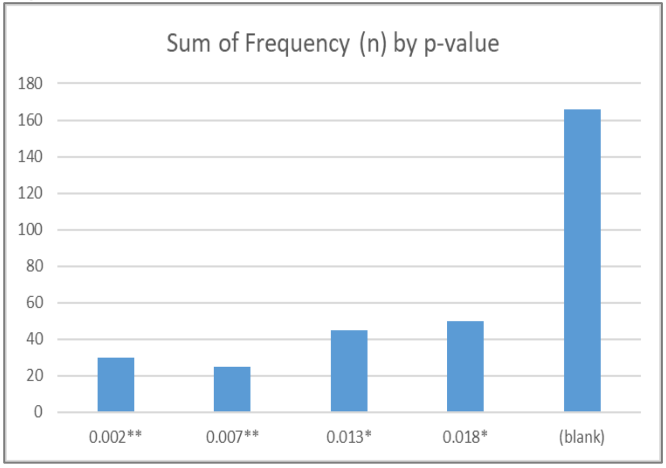


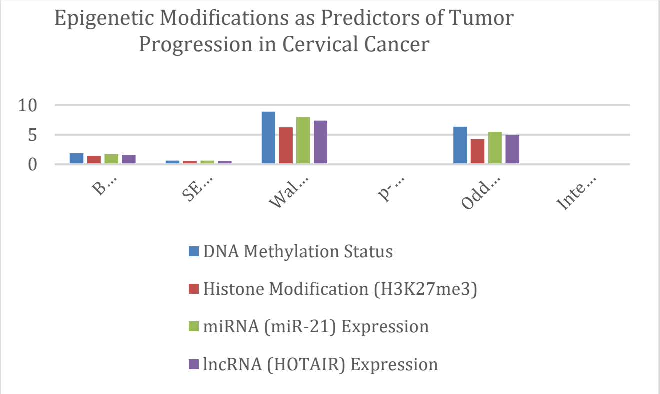
Table 3

Regression Analysis for Objective 3

Epigenetic Marker	*B (Regression Coefficient)*	*SE (Standard Error)*	*Wald χ^2*	*p-value*	*Odds Ratio (Exp(B))*	*Interpretation*
DNA Methylation Status	1.85	0.62	8.89	0.003**	6.36	Methylation significantly predicts advanced tumor stage
Histone Modification (H3K27me3)	1.45	0.58	6.25	0.012*	4.26	Presence of H3K27me3 significantly predicts tumor stage progression
miRNA (miR-21) Expression	1.70	0.60	7.98	0.005**	5.47	Upregulation of miR-21 is a significant predictor of tumor stage
lncRNA (HOTAIR) Expression	1.60	0.59	7.36	0.007**	4.95	Overexpression of HOTAIR significantly predicts advanced tumor stage

All epigenetic factors in the regression analysis were found to predict the development of more advanced tumors in cervical cancer patients. Having genes methylated in DNA revealed a strong relationship, boosting the possibility of an advanced tumor stage by more than six-fold. Similarly, tumors with H3K27me3 histone modification were much more likely to progress, increasing the chance by over four times. High levels of miR-21 and HOTAIR lncRNA made it five times more likely that a patient had advanced tumor stage. According to these results, these alterations can be used to identify patients with aggressive disease and to guide treatment in cervical cancer.

Figure 3



DISCUSSION

Researchers have shown that epigenetic changes play an important role in how cervical cancer develops and how well it is prognosed. It is not surprising that patients routinely have DNA methylation, as studies often point out that such methylation is a common change in cancer, particularly cancers caused by HPV [25]The change due to epigenetics allows tumor suppressor genes to become inactive which assists oncogenesis [26]Likewise, large numbers of patients with H3K27me3 are consistent with research linking it to gene silencing and development of tumors.

As shown in this study, an increase in miR-21 agrees with past discoveries that miR-21 works as an oncogenic microRNA, promoting cell division and blocking cell death in cervical cancer. Also, higher levels of lncRNA HOTAIR add to evidence that HOTAIR leads to greater tumor spread and a poor prognosis [27].Because they are involved in gene regulation, these RNAs highlight the opportunity for them to be used as biomarkers .

Results from chi-square and regression analyses propose that these epigenetic makers are helpful for predicting tumor development. These findings coincide with results from several studies proving the value of epigenetic changes in cervical cancer [28]Their role as

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markers points to new ways for discovering diseases early and providing doctors with personalized approaches.

Moreover, research into epigenetic therapies backs up the idea that these modifications could be used in medicine. Modifiers of DNA methylation and histones are currently being evaluated to see if they can help restore lost gene expression Researchers can use miR-21 and HOTAIR as new targets for therapeutic approaches [29]Together, these intervention types could improve the results of conventional patient treatments [30]

This investigation describes how DNA methylation, H3K27me3 modification, upregulation of miR-21 and HOTAIR overexpression are important in the development of cervical cancer. The results show that these genetic changes are very common and highlight that they are important for tumor diagnosis, prognosis and appropriate treatment. They add to the evidence suggesting that epigenetic screening should become part of standard cervical cancer care. Biomarkers should be checked and validated in more extensive, multicenter studies and these studies should also review epigenetic medicines such as agents that demethylate the DNA, tinker with histones and target RNA. The use of these genetic methods during personalized care may help diagnose cervical cancer sooner, treat patients more effectively and reduce the general impact of this type of cancer in areas with less access to care.

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