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Use of DNA Methylation in Cancer Therapy

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Authors' contributions

This work was carried out in collaboration between both authors. Author AA designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors AA and CB managed the analyses of the study. Author CB managed the literature searches. Both authors read and approved the final manuscript.

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ABSTRACT

The aim of this paper is the review the factors that determine cancer progression which would help in the treatment and diagnosis of the disease. Cancer is a leading life-threatening disease and despite the recent technological advancement, there is still a poor survival rate in cancer patients because of inadequate diagnosis and poor prognosis of cancer.

Keywords: Cancer; hypomethylation; hypermethylation; genes; tumor suppressor genes; epigenetic; receptor ligands; chemotherapy; DNA transferases; chromosomal arrangements; tumor suppressor; biomarker; hormone therapy; chromatin structure.

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1. INTRODUCTION

WHO statistics stated that the major types of cancer leading to overall cancer death per year are lung cancer (1.3 million), stomach cancer (1 million), liver cancer (662,000 deaths), colon cancer (655,000 deaths) and breast (502,000 deaths) [1]. Which the mortality from cancer is projected to continue rising, by 1.4 million dying in 2030. Also, more than 70% of all cancer deaths occur in low and middle-income countries whereas the resources available for prevention, diagnosis, and treatment of cancer are restricted and do not exist hereby over 40% of all cancers could be prevented by early detection and treated early [2].

Cancer is a multistage disease, and the onset and progression are associated with a complex array of epigenetic alterations which affect the cellular signalling and leads to a formation of a tumour and malignancy [3].

Cancer is hereby one of the highest causes of death in the world today be one of the most common cause of death in the United States [4]. Hereby Cancer is a leading life-threatening disease and despite the recent technological advancement, there is still poor survival rate in cancer patients because of inadequate diagnosis and poor prognosis of cancer [3,5]. The conventional methods used in the diagnosis of cancer include magnetic resonance imaging, ultrasound and biopsy which are not efficient for early-stage cancer detection because these methods depend on the tumour phenotypic properties [6].

Hereby the early detection and monitoring of the advancement or remission of cancer are of great importance in oncological medicine today and several shows early detection of cancer increases the odds of patient survival [7]. For high-risk patients, those with a genetic predisposition to cancer or those who have already been diagnosed and treated for the disease, periodic monitoring for early detection of recurring cancer is vital to long-term survival rates in patients [8].

2. RESEARCH METHODOLOGY

2.1 Review Centric

This includes a comprehensive literature review of the factors that determine the progression of cancer in human and how they progress in the human body and factors that would help inadequate diagnosis and treatment of the disease.

2.2 Research Process

This review paper shows how cancer can factors that determines the development of cancer namely; DNA methylation, hypomethylation, genes and hypermethylation and how they can serve as an indication of the disease. DNA methylation is a heritable epigenetic mark involving the covalent transfer of a methyl group to the C-5 position of the cytosine ring of DNA by DNA methyltransferases (DNMTs) [9]. Epigenetics involves genetic control by factors other than an individual's DNA sequence. Epigenetic changes can switch genes on or off and determine which proteins are transcribed [10]. This paper provides information in proper diagnosis and treatment of cancer hereby reducing the number of people that die through lack of early cancer diagnosis hereby it would contribute largely to the healthcare industry.

3. CANCER

The steady nature of epigenetic silencing result to the hypothesis that it found a viable mechanism of inactivating tumour-suppressor genes in cancer [11]. Epigenetic gene silencing refers to nonmutational gene inactivation that can be faithfully propagated from precursor cells to clones of daughter cells. The addition of methyl groups to cytosine residues in CpG dinucleotides in DNA is a biochemical modification that meets this requirement [12]. Deviating gene regulation by epigenetic mechanism can be as a result of a pathological process such as cancer [13].

Cancer growth is produced from many different genetic or epigenetic changes that can lead to the activation of oncogenes and the inactivation of tumour suppressor genes [14].

DNA hypomethylation was the initial epigenetic abnormality recognized in human tumours [15]. Cancer-associated DNA hypomethylation sounds a note of caution in the current development of cancer therapies aimed at decreasing DNA methylation in a non-targeted manner [16].

Cancer cells alter the epigenetic equilibrium of normal cells [17]. Cancer is a disease that begins with epigenetic alterations and a genetic complex array disturbs cellular signalling. Therefore, it results in tumour formation [18].

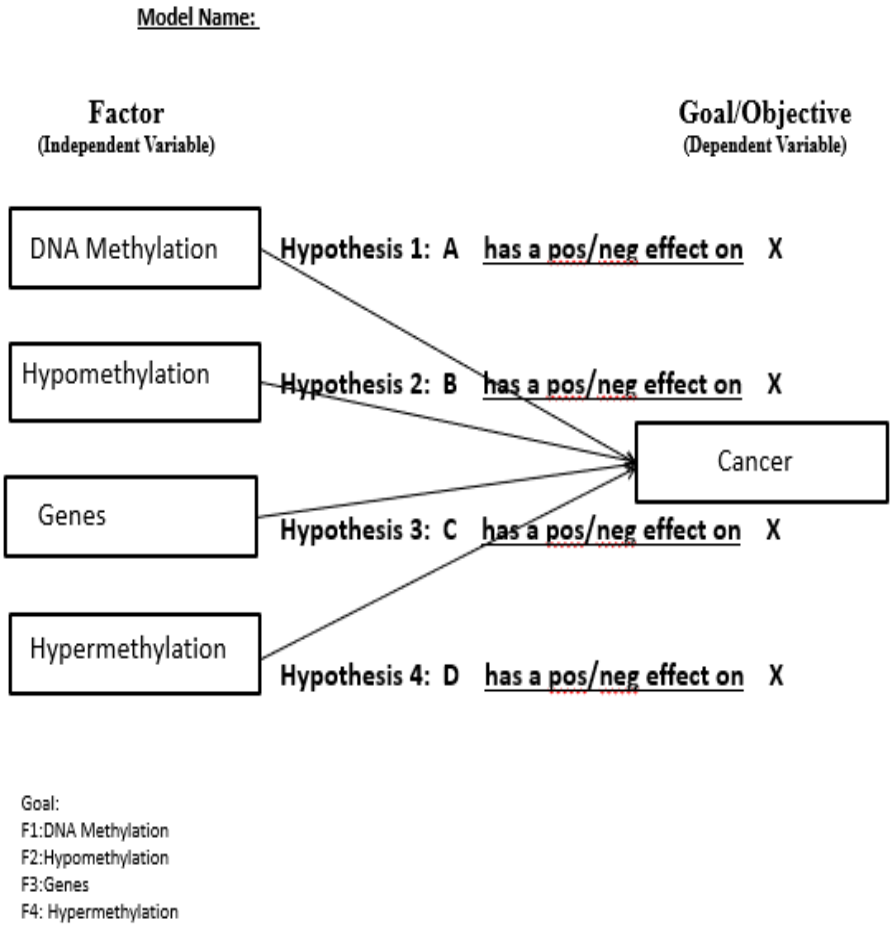

Fig. 1. The scientific method of DNA methylation in cancer therapy

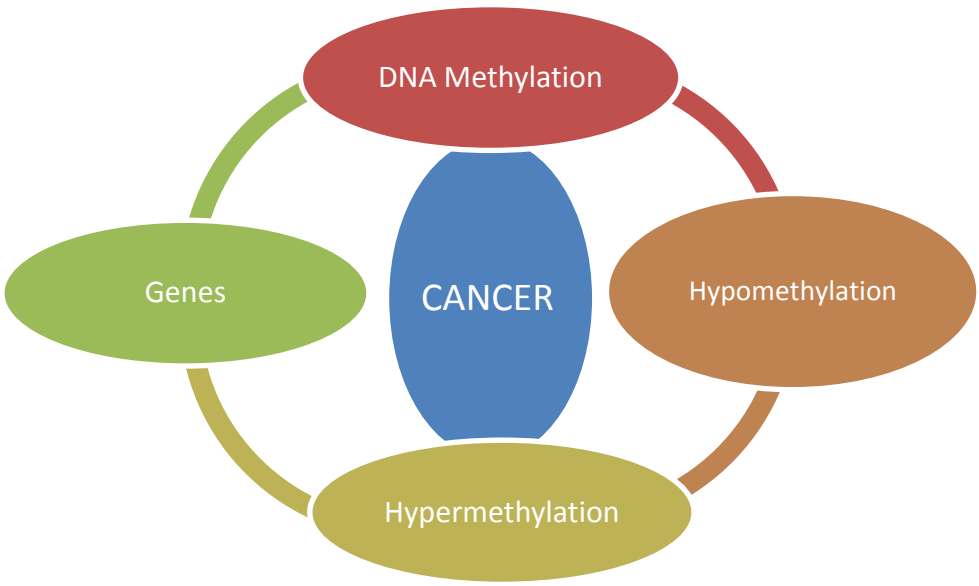

Fig. 2. Showing the interaction between cancer and its four variables

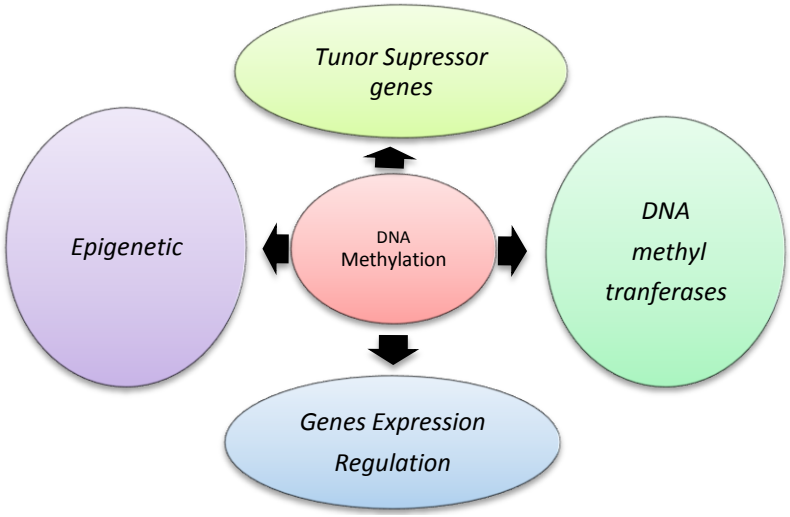

Fig. 3. Showing the relationship between DNA methylation and its four factors

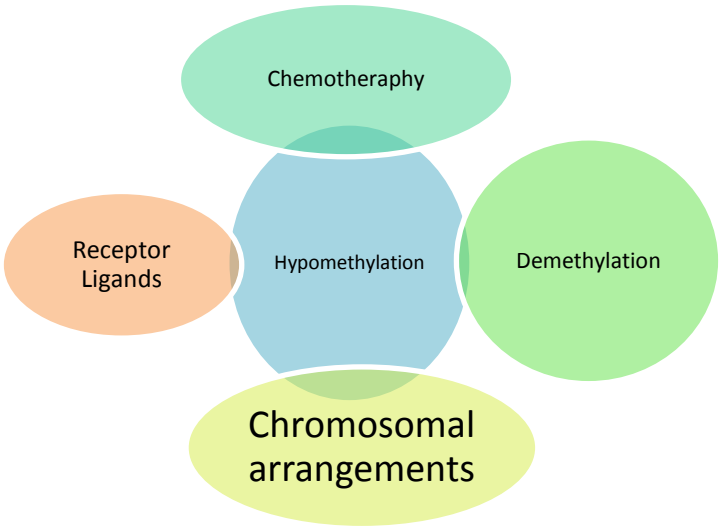

Fig. 3a. The variable affecting hypomethylation

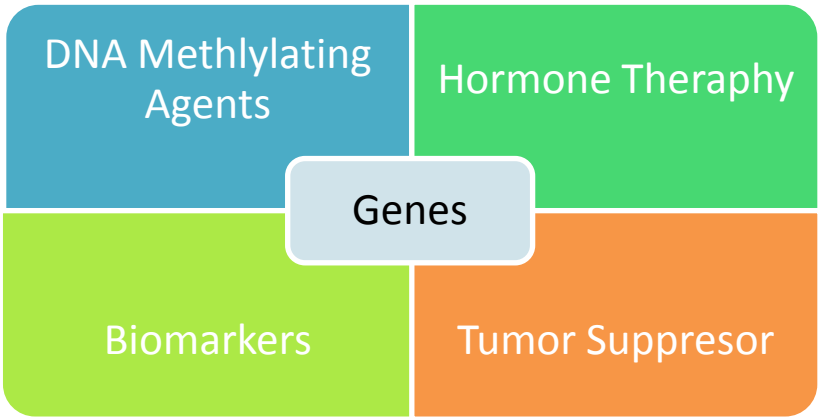

Fig. 4. Factors depending on genes

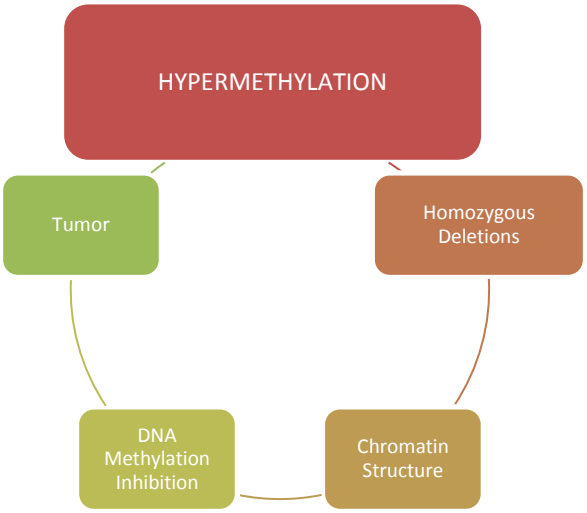

Fig. 5. Figure showing the progressive activity of hypermethylation

3.1 DNA Methylation

DNA methylation plays a major role in the structure of chromatin, epigenetic silencing, suppressing the activity of endogenous parasitic sequences, and a process normally reserved for special situations such as the inactive X-chromosome and imprinted genes [19].

Reducing methylation prevents the formation of cancer under specific circumstances hereby it provides evidence for a pathogenic role of increased DNA methylation in cancer [20].

Irregular patterns and dysregulation of DNA methylation lead to steady, heritable transcriptional silencing the gene that is associated with tumorigenesis [21].

The interaction between transcriptional silencing of tumour suppressor genes and DNA methylation in human cancer as observed in experimental inhibition of DNA methylation with 5-aza-2′-deoxycytidine [22].

3.1.1 Epigenetic

Epigenetic events as a significant function in cancer progression and the development of cancer [18]. The mutations occur in oncogenes leads to function gain while the deletion and mutation associated with tumour suppressor genes cause inactivation of negative regulators [23]. In cancer, epigenetic silencing through methylation occurs at least as frequently as mutations or deletions and leads to aberrant silencing of normal tumour-suppressor function [24].

3.1.2 DNA methyltransferases

DNA methylation is a heritable epigenetic mark involving the covalent transfer of a methyl group to the C-5 position of the cytosine ring of DNA by DNA methyltransferases (DNMTs) [9]. The addition of methyl groups to the family of enzymes is called DNA methyltransferases. The Chromatin structure in the vicinity of gene promoters affects transcriptional activity and DNA methylation [18].

DNA recombinant Dnmt3a and Dnmt3b proteins methyl- methyltransferases as the same biochemical properties CpG dinucleotides synthetic and both genes are expressed at high levels in Embryonic stem cells [25].

3.1.3 Tumour suppressor genes

Tumour suppressors have loss of function is rate-limiting for a specific step in multi-stage [26]. Several tumour suppressor genes are hypermethylated in numerous cancer which includes hematopoietic malignancies [18]. The Somatic mutations that affect the prevalence and tumour rate progression in sporadic human neoplasia fail to be linked to inherited cancer syndromes or cancer predisposition [26].

3.1.4 Gene expression regulation

Gene expression regulation an important factor of molecular biology and other new mechanisms enables us to categorize the gene expression profiles and patterns at a phenomenological level [27]. This has led to the finding that DNA methylation involved in silencing gene

expression [28]. The early regulated genes show sequence similarity to the small interfering Ribonucleic Acid (siRNA), impossible transcripts the sequence level similarity were silenced [29].

3.2 Hypomethylation

Hypomethylation as a vital role in the development of a tumour and the inhibitors of the process is functional for the resting potential of cancer therapy [30]. Hypomethylation can affect the silencing pathways like the cell cycle control, apoptosis, angiogenesis and invasion and they also silence oncogenes in cancer by DNA methylation [31]. Hypomethylation changes an organized way involving genome and also gene-specific demethylation [32]. The effects of hypomethylation therapy are the effects on cellular physiology which can be taken therapeutically [33]. A therapeutic ratio for hypomethylation therapy is related to the tumours that depend on gene silencing for their phenotype than normal adult cells [34]. Dietary deficiency of selenium leads to global hypomethylation of liver and colon DNA [35].

3.2.1 Receptor ligands

The mammalian ligands that bind to the EGF receptor include EGF, transforming growth factor-α (TGFα), heparin-binding EGF-like growth factor (HB-EGF) [36]. The mammalian ligands that bind the betacellulin, amphiregulin, epiregulin, and epigen [37].

3.2.2 Chemotherapy

Chemotherapy resistance is the obstacle to effective anti-cancer treatments which results in worsen and progress to tumours [38]. Chemotherapy for advanced non-small cell lung cancer is not effective [39]. The hypomethylating agents, for example, azacytidine and decitabine gives traces of long-term disease control without needed to achieve complete remission and can represent a reasonable alternative to in-depth chemotherapy [40].

3.2.3 Demethylation

DNA synthesis in the presence of drugs gives rise full double-stranded DNA demethylation while decitabine and azacitidine and leads to methylation and they may differ in various respects [18]. DNA methylation patterns are created during the development by a combination of methylation and demethylation event [41]. The centre of methylation results in a combination of methylated paternal DNA and undermethylated maternal although they lead to highly dynamic and its opposing demethylation methylation processes in parental genomes [42].

3.2.4 Chromosomal arrangements

Chromosomal rearrangements effects on fitness are greatly different. The rearrangements cause reduction of gene flow more by suppressing recombination and it extends the effects of linked genes isolation than by reducing fitness [43]. The Multiple classes of gene rearrangements in cancer explain the common role for chromosomal rearrangements in common epithelial cancers [44]. The Abnormal miRNA expression has had a lot of attention which includes the understanding of the roles of miRNAs in modulating cancer development.

3.3 Genes

The stable nature of epigenetic silencing leads to a feasible method of inactivating tumour-suppressor genes in cancer [45]. The plethora of genes and pathways affected by DNA methylation makes this specific therapeutic target also remarkably nonspecific in its effects [46]. The major quantity for methylation in human DNA occurs a late part of DNA that do not encode the gene [20]. Hypermethylation of CpG-rich promoter stimulates the local histone code which results in cellular camouflage mechanism that sequesters gene promoters from the transcription factors [47]. Gene expression pattern is DNA- binding transcription factors that make use of genes for transcriptional activation [48].

3.3.1 Tumour suppressor

The tumour suppressor is inactivated by chromatin structure modifications in the absence of DNA methyltransferases and it suggests that the methylation of p16 in cancer cells follows inactivation of chromatin [14]. The activation of chromatin of tumour suppressors occurs in the absence of DNA methyltransferase [49]. The p53 tumour suppressor is at cellular pathways recognizes the DNA damage and improper mitogenic stimulation and cellular stress [50].

3.3.2 Biomarkers

The gene's product is silenced by DNA methylation and it is used as biomarkers of response to chemotherapy or hormone therapy [17]. Biomarker genes increase the efficiency of the prediction of cancer [8]. Analytical techniques that assess oxidative DNA damage at the level of base or sugar are susceptible to technical difficulties, the expression of genes, a biological response to DNA damage holds a sensitive in biomarker [51].

3.3.3 Hormone therapy

Hormone therapy failure is genes that are overexpressed and they are essential for that tumour recognition [52]. An essential duty of sterol and steroid synthesis in tumour progression doesn't dependent of exogenous androgen and transduction pathways activation that may have direct effects on signalling hereby it leads to the activation other survival pathways [53]. Hormone therapy resistance is associated with different expression a particular set of genes which reflect potential mechanisms of reactivation [54].

3.3.4 DNA demethylating agents

Demethylating agents like 5-aza-cytidine and 5-aza-2deoxycytidine inhibit DNA methyltransferases hereby it causes global hypomethylation [55]. The demethylating effect of 5-aza-2-deoxycytidine affects all human cancer cell lines and new inhibitors of DNA methylation are introducing [17]. The demethylation of a CpG-island-associated gene (*RAR*β*2*) and growth prevents cancer cells. DNA methylated agents restore the expression of the hypermethylated gene in cancer cells and reduce the xenograft tumour growth [56].

3.4 Hypermethylation

The silenced genes and hypermethylated are hMLH1 and O6-MGMT and they encode DNA repair proteins [57]. Cancer-associated localized hypermethylation is used for CpG islands, DNA sequences of about 1–2 kb that are (C+G)-rich. Biologic effect of the loss of gene function by promoter and coding-region mutation is triggered by hypermethylation [58]. Modified genes by promoter hypermethylation have definitive tumour-suppressor function [59]. The role of genes in carcinogenesis of cancer-linked hypermethylation of transcription control regions is understandable because of the consequent transcriptional silencing of genes vital for the prevention of cancer [60].

3.4.1 Homozygous deletions

Homozygous deletion is silenced when the tumour suppressor genes that exist have used an integrative genomic approach [61]. Homozygous deletion of the gene has acquired in both cell lines and primary cancer cells [61].

3.4.2 Chromatin structure

Chromatin structure plays an important role in gene expression and its consequence [53]. *C*hromatin structure modifications like chromatin-binding proteins and histone deacetylation affect the local chromatin structure, gene transcription and DNA methylation [18]. The Chromatin in cooperated with methylated DNA conjoins with, refractory to nuclease, hypoacetylated histones and transcriptionally silent [62].

3.4.3 Tumour

Epigenetic silencing by methylation leads to abnormal silencing of normal tumour suppressor function [18]. The biallelic loss leads to the inactivation of coding tumour suppressor genes which is implicated in the development of a tumour and progression [61]. Methylation-associated tumour silencing of the suppressor genes is the molecular hallmark of human cancer [61].

3.4.4 DNA methylation inhibition

The DNA methylation inhibition of tumour suppressor gene promoters contributes greatly to the inhibition of some cancers [62]. DNA methylation inhibition focuses on the inheritance, generation, and biological significance of genomic methylation patterns in mammal development. [48]. DNA methylation inhibits the gene expression in part through histone deacetylation, HDAC inhibitors and has been used to activate expression from methylated genes [63].

4. RESULTS AND DISCUSSION

Despite the consistent discovery of new drugs for cancer treatment, there is a need for progress in new technology for its diagnosis. The high demand of effective methods for rapid analysis of cellular alterations to detect cancer at its onset that would improve the treatment and prognosis strategies and also to reduce the mortality rate caused by this disease [64].

Table 1. Showing the other factors that are important in cancer

	Other factors	Importance in Cancer
1.	Epigenetic Modification	"The main epigenetic modification of DNA methylation in human beings is methylation of the cytosine located within the dinucleotide CpG. [17] p. 351."
2.	Gene Expression	" The tight relation of DNA methylation, chromatin structure and gene expression plays an important role in gene expression and chromatin structure [41] p. 299."
3.	DNA	"This loss of DNA methylation was in individual genes in is suggested as a mechanism of regulation of gene expression [65] p. 1235."
4.	Homozygous Sequence	"Analysis of *MTS1* in pancreatic carcinomas shows the homozygous deletions and sequence changes in hypermethylation [1] p. 502."
5.	Transcriptional Activity	"The Chromatin structure in the vicinity of gene promoters also affects the hypermethylation and transcriptional activity. Which are regulated by nucleosome spacing and histone acetylases, which affect access to transcriptional factors [18] p. 107."
6.	Tissue origin	"The particular genes that are hypermethylated in tumour cells are strongly particular to the tissue origin of a tumour [66] p.3225."
7.	Chromosome	"The multiple tumour suppressor genes are located on the chromosome has recently been implicated as a candidate tumour suppressor gene in many different types of a tumour [67] p. 57."
8.	Gene product	"The gene's product that is silenced by DNA methylation can serve as biomarkers of response to chemotherapy or hormone therapy [66] p. 3225"
9.	Methylation	"The products of genes that are silenced by DNA methylation can be used as biomarkers of response to chemotherapy or hormone therapy [66] p. 351."

DNA hypermethylation is an essential diagnostic and prognostic tool [16]. DNA hypomethylation analysis is also very important in cancer detection and management [20]. Hypomethylation of repeated or single-copy DNA sequences as an interaction with the progression of this disease [68-70]. The bioactive ingredient is very important in human health and diseases like cancer. The dietary components like genistein, selenium as a great influence on DNA methylation hereby altering the gene expression profile and cancer inhibition [13].

Several studies have shown notable decreases in the DNA methylation levels with tumour grade, progressing tumour stage, tumour grade and poor prognosis [70,71]. DNA hypomethylation in cancer is associated with hypomethylation of a DNA repeats [5,72]. In some cancer types, the DNA hypomethylation is seen as an early measure of tumorigenesis [4,68,73]. DNA hypomethylation is very essential in of cancer-associated DNA hypomethylation which gives a safety note in the current development of cancer therapies which is aimed at decreasing DNA methylation in a non-targeted manner.

Cancer linked DNA hypomethylation is unlikely to suffice for carcinogenesis. The role of cancer-linked genomic hypomethylation to tumorigenesis or tumour progression while suppressing CpG methylation as a beneficial effect in cancer treatment which assists in tumour progression from residual cancer cells [16].

One of the major challenges in the diagnosis and treatment of cancer is the high degree of complexity of the cancer cell in which a single biomarker is involved in multiple cellular processes, therefore there is need to understand the molecular alterations that underlie cancer progression [2].

Genomic and proteomic profiling aids the discovery of new cancer-specific biomarkers hereby multiple detections of several biomarkers is needed for the proper diagnosis of particular cancer [2].

This study offers comprehensive research on the role of genes, hypomethylation, hypermethylation and DNA methylation on the influence of cancer biology and its susceptibility on human epigenome to its effects. Also, it provides a better understanding of their effects on the development of cancer which would facilitate drug discovery and new approaches to cancer therapeutic strategies.

4.1 Contribution and New Insight

A lot of research has been carried out to determine the cause of cancer progression in the human body. There is a need to get an adequate method for the early detection of cancer which would enhance the treatment of this disease.

This paper as researched on key factors that determine the cancer development and progression in the body. These factors disrupt the body process and metabolism hereby causing a change in the biological process in the body. Also, mutations and environmental factors can lead to the development and progression of this disease [66]. Also, there is an abrupt change in the trends in the rate of the development of early detection of cancer and treatment [74].

5. CONCLUSION

With the increase in cancer related mortality, the current technique used in cancer techniques include ionizing or non-ionizing radiological methods which includes x-ray, MRI, computed tomography which they do not have sufficient sensitivity for the screening or diagnosis off theses disease hereby new research and tools are needed for effective diagnosis hereby it would give provide a lot of molecular profiles that would make extensive and effective diagnosis of this disease hereby reducing the amount of mortality in human.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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