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Diagnostic utility of epigenetics in breast cancer – A review

Showkat Ahmad Bhat[a], Sabhiya Majid[b,*], Hilal Ahmad Wani[a], Samia Rashid[c]

[a] Department of Biochemistry, Government Medical College, Srinagar, Jammu & Kashmir, India
[b] Department of Biochemistry, Government Medical College, Srinagar, Jammu & Kashmir, India
[c] Government Medical College, Srinagar, Jammu & Kashmir, India

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ABSTRACT

Epigenetic alterations are clearly involved in cancer initiation and progression as recent epigenetic studies of genomic DNA, histone modifications and micro-RNA alterations suggest that these are playing an important role in the incidence of breast cancer. Epigenetic information has recently gained the attention of researchers because epigenetic modification of the genome in breast cancer is still an evolving area for researchers. Several active compounds present in foods, poisons, drugs, and industrial chemicals may as a result of epigenetic mechanisms increase or decrease the risk of breast cancer. Epigenetic regulation is critical in normal growth and development and closely conditions the transcriptional potential of genes. Epigenetic mechanisms convey genomic adaption to an environment thereby ultimately contributing towards given phenotype. In addition to the use of epigenetic alterations as a means of screening, epigenetic alterations in a tumor or adjacent tissues or peripheral blood may also help clinicians in determining prognosis and treatment of breast cancer. As we understand specific epigenetic alterations contributing to breast tumorigenesis and prognosis, these discoveries will lead to significant advances for breast cancer treatment, like in therapeutics that target methylation and histone modifications in breast cancer and the newer versions of the drugs are likely to play an important role in future clinical treatment.

1. Introduction

Breasts are external symbols of beauty and womanhood in females. Sadly, breast cancer is responsible for the death of millions of women worldwide every year [1, 2]. Carcinogenesis is a multi-step process and results mainly from the direct changes in sequence of the genome. There are a number of genetic alterations involved in carcinogenesis and it is very difficult and time consuming to detect these changes in specific individual cancers. For this reason there are new methods to study the relationship between the changes in genome and cancer development. Among researchers epigenetic modifications has recently gained the interest because these modifications are believed to be early events in carcinogenesis and these alterations can be useful as a good source for early detection, prognosis and targeted therapy of cancer [3]. Breast cancer is one of the frequently diagnosed cancers among women with the well-known hereditary and familial tendency. Besides, breast cancer has well-established precursor lesions indicating an increased risk of cancer, such as moderate to severe atypical hyperplasia [4]. Breast cancer has remained a main clinical challenge due to its poor prognosis, limited treatment options, relatively resistance to chemotherapy / radiotherapy and late diagnosis of the disease [5]. Since the epigenetic alteration occurs early in cancer development and also even in normal tissues which surrounds the tumor. Finding of exact epigenetic changes may help in early diagnosis of breast cancer as well as the determination of prognosis and response to treatment.

2. Epigenetic modifications

Epigenetic modifications are newly discovered issue and are still a developing area in the genomic research. The major epigenetic modifications in cancer encompass changes in DNA methylation, post-translational modifications of histones and micro-RNA. These are the main epigenetic modifications which interfere with expression of the genes and have been discussed as players in the development and progression of breast cancer. Some epigenetic changes and possible mechanisms by which they promote tumorigenesis in different cancers are shown in Table 1.

2.1. Methylation

Methylation of genomic DNA is the most widely studied epigenetic modification and is described as covalent binding of a methyl group to cytosine-guanosine (CpG) dinucleotides by enzyme DNA methyl transferases located on genome. CpG dinucleotides are usually located near

* Corresponding author.
E-mail addresses: biochemistrygmcsrinagar@gmail.com (S. Majid), hilalbiochm2007@gmail.com (H.A. Wani).

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Table 1
Epigenetic changes and possible mechanisms by which they promote tumorigenesis.

Epigenetic change	Mechanism	Biological consequence
DNA hypomethylation	Activation of the cellular oncogenes	Increased proliferation and growth advantage
	Activation of the transposable element	Genomic instability and transcriptional noise
DNA hypermethylation	De novo hypermethylation of CpG islands within gene promoters leading to silencing of tumour suppressors and cancer-associated genes	Genomic, chromosomal instability and increased proliferation, growth advantage
Histone acetylation	Gain of function	Activation of the tumour promoting genes
	Loss of function	Defects in DNA repair and checkpoints
Histone deacetylation	Silencing of the tumour suppressor genes	Genomic instability and increased proliferation
Histone methylation	Loss of heritable patterns of the gene expression (cellular memory)	Genomic instability, growth advantage
miRNAs	50% of genes encoded by miRNAs are located at sites called fragile sites	Chromosomal rearrangements at these cites associated with cancer occurrence
	miRNAs are seemingly deregulated which may be caused by transcriptional deregulation, epigenetic alterations as well as problems in miRNA biogenesis pathways	These mechanisms can either work alone or together in order to deregulate miRNAs. The mutation in any given miRNA of a somatic cell can lead to tumorigenesis and if are present in the germ line cells it may be precursor to cancer.

the promoter regions of genes as clusters of large repetitive sequences like that of satellite sequences or centromeric repeats [6]. These CpG islands are normally unmethylated and in this status, the transcription factors can easily bind to the promoter regions of the related genes and activate these genes. In contrast these repetitive genomic sequences are sometimes heavily methylated and it is thought by this property they are playing an important role by silencing specific genes during evolution as well as endoparasitic and retroviral transposons [7]. In cancer cells the hypermethylation occurs at the promoter regions of the tumor suppressor genes which inactivate these genes by deregulation and some important cellular networks such as cell cycle control, DNA repair, apoptosis, cell adhesion, and migration are negatively affected [8, 9].

2.2. Methylation imbalance in cancer cells

Typical CpG islands are unmethylated and are most commonly found in 5′ regulatory (promoter) regions of many “housekeeping” genes which are essential for normal cell functions [10]. In breast cancer and in some other disease states the hypermethylation of CpG islands results from over activity of DNA methyltransferases (DNMTs) as these DNMTs are the main mediators of the DNA methylation by catalyzing the transfer of a methyl group from S-adenosyl-L-methionine (SAM) onto the carbon on the 5′ position of CpG dinucleotides. In humans, the primary DNMTs are DNMT1, DNMT3a and DNMT3b. DNMT1 is most abundant as it functions to maintain the methylation pattern but while the other DNMTs serve as the mediators of de novo methylation [11, 12]. The consequence of hypermethylation of the CpG islands is reversible silencing of tumor suppressor genes but hypermethylation-induced gene silencing is heritable that is inherited by subsequent generations of the cells undergoing mitotic divisions [13, 14]. Methylation is also known to activate the human telomerase reverse transcriptase (hTERT) gene which promotes the cell immortality in some cancer cells. DNA methylation at CpG islands of the promoter regions generates long-term gene silencing which makes the majority of chromatin inaccessible for transcription [15, 16]. Although unmethylated CpG islands of the gene promoter regions mark sites where genes can be expressed and non CpG sequences at non-promoter regions nearly associated with transcription start sites may be important for tissue specific dynamical de novo methylation [17, 18]. The methylation of such non-CpG sites has been implicated in somatic cell reprogramming which may be occur in response to the environment and gene interactions which can promote the development of breast and other cancers [16]. DNA methylation in future may serve as a marker of breast tumor cell lineage, thereby reflecting the cell type from which a cancer originates and perhaps explaining the correlations of histological heterogeneity and prognosis of breast cancers with the DNA methylation profiles in them [19].

Past and present research studies showed that methylation of various genes such as *cyclin D2, retinoic acid receptor beta (RARβ), Twist, glutathione S-transferase P1 (GSTP1), p16, p14, Ras-associated domain family member 1A (RASSF1A)*, and *death-associated protein kinase (DAPK)* were reported in ductal lavage fluid and nipple aspirate of breast cancer patients [20, 21]. Besides, detection of methylated DNA in plasma/serum of breast cancer patients is more convenient compared to detection of specific mutations for the breast cancer in whole genome. In addition to this, the detection rate of breast cancer patients increased when a combination of different markers was utilized in the previous studies and the sensitivity for the detection of breast cancer cells increased from 43 to 71% using a panel of markers compared to cytology [22]. However, comparison between breast cancer patients and healthy subjects has not been evaluated thoroughly even some studies like *BRACA1, BRACA2* gene methylation within case control studies [3, 23–25]. On the other hand, methylation of some specific genes was reported to be related to the prognosis in breast cancer as methylation of *RASSF1A* and *APC* in the serum samples correlated with poor prognosis in breast cancer patients [26]. The expression of *ACADL, SFRP2, UAP1L1, UGT3A1, ITR* and *RECK* gene is reported to be significantly correlated with the methylation and relapse-free survival and the *RECK* gene is prominent because of its association with the worst cancer prognosis [27–29].

2.3. Histone modifications

Histone proteins are backbone of the genomic DNA and play significant function in the translation of genotype to phenotype. The post-translational modifications of the histones determine translational activity in the genome. Acetylation, methylation, phosphorylation, sumoylation, and ubiquitination are histone modifications which determine the functioning of genome as these histone modifications are catalyzed by several enzymes: Histone acetyltransferases (HATs), histone deacetylases (HDACs), histone methyltransferases (HMTs), and histone demethylases (HDMs) [30]. Histone modifications which activate or deactivate genes depend up on the residue of the histone to be modified as trimethylation of lysine 4 on histone H3 (H3K4me3) activates gene transcription but on lysine 9 (H3K9me3) and lysine 27 (H3K27me3) suppress gene transcription [31]. Histone acetylation at the lysine residues positioned at gene promoter regions may activate the genes by relaxing and opening the chromatin, thereby providing access to the DNA by transcriptional enzymes and other factors [12]. The type of modification and the affected amino acid on histones determine the DNA-histone interaction and also the transcriptional activity of genome. Even though the histone modifications have been less studied as compared to DNA methylation, both of these epigenetic modifications interact with each other in the regulation of the gene expression in cancer cells [32].

An increasing number of the histone modifications and related enzymes, have been found which are deregulated in breast cancer as histone H4K16ac and its responsible enzyme Acetyltransferase hMOF were found to be significantly reduced in the primary breast carcinomas and medulloblastomas [33]. Enhancer of zeste homolog 2EZH2 is a histone-lysine N-methyltransferase enzyme encoded by *EZH2* gene, a subunit of the polycomb-repressive complex 2PRC2 and catalyzes the trimethylation of histone H3 on Lys 27 (H3K27). It is amplified and overexpressed in breast cancer [34]. PYGO2 interacts with histone-modifying enzymatic complexes, specifically in the MLL2 histone methyltransferase (HMT) and STAGA histone acetyltransferase (HAT) complexes, to help their interaction with the β-catenin and to augment Wnt1-induced, TCF/LEF-dependent transcriptional activation in breast cancer cells [35]. Reduction of the H3K9 trimethyl demethylase JMJD2B being an integral component of the H3K4-specific methyltransferases and the mixed-lineage leukemia (MLL) 2 complex, impairs the estrogen-induced G(1)/S transition of cell cycle in vitro and inhibits the breast tumorigenesis in vivo [36]. Past results reveals that Histone Lysine Demethylase (LSD1) is downregulated in the breast carcinomas and its expression level is negatively correlated with that of the TGFβ1 which inhibits invasion of the breast cancer cells in vitro and suppresses breast cancer metastatic potential in vivo [37].

2.4. MicroRNAs (miRNAs)

The epigenetic modifications are not restricted to CpG methylation and post-translational changes of the histones, but also include the regulation by microRNAs (miRNAs). The most recently discovered molecules in the field of epigenetics are small regulatory RNAs known as MicroRNAs (miRNAs). The small miRNAs, single-stranded RNA molecules, are having 20–22 nucleotides and are complementary to the untranslated regions of mRNAs. These miRNA molecules play a key role in gene silencing by binding to the mRNAs and results in either the translational inhibition or mRNA degradation. The change in miRNA number and distribution on genome leads to the modulations in gene expression [38]. The hypermethylation of promoter regions of genes coding for miRNAs downregulates the synthesis of miRNAs and results in decreased number of miRNAs which may activate the expression of oncogenes [39]. Downregulation of the miRNAs have been detected in various cancers including breast cancer and is frequently related to worse prognosis and on the other hand the deregulated miRNAs could be used as tumor biomarkers or as the anti-cancer drug targets making early diagnosis or better treatment options for cancer [40].

MiRNAs play a key function in many cellular processes such as cellular growth, differentiation and apoptosis [41, 40] but they also contribute to the development and progression of cancer as there was aberrant expression of miRNAs as has been seen in breast cancer [41, 42]. For example the increased expression of miR-21 is associated with advanced stages of breast cancer and the upregulation of miR-155 correlates with the metastasis and poor prognosis in breast cancer. In addition, miRNA-497 impacts the cell growth and the invasion by targeting cyclin E1 in breast cancer [43, 44].

3. Epigenetic alterations as tumor microenvironment in breast cancer

Breast cancer is considered to be promoted by the tumor microenvironment and predominantly by interactions between the epithelial cancer cells and the cancer associated with fibroblasts [45]. Indeed, cancer associated with stroma including fibroblasts can synthesize various growth factors or cytokines that promote cell proliferation and metastasis in triple negative breast cancer [46]. As an instance, the EMT process is critical for the tumor progression and metastasis which is driven by epigenetic changes, depends on the multiple signals received from nearby environment, including TGF-b, which induce the expression of EMT-TFs, such as Snail, Twist and ZEB1, leading to the repressed expression of E-cadherin [47, 48].

In addition, the breast cancer microenvironment might become a new tool for diagnosis and treatment of breast cancer [49] e.g., fibroblasts themselves express the specific markers such as α-smooth muscle actin (a-SMA) or type-I collagen that could help in detection of cancer [46, 50]. Epigenome of the immune T cells surrounding tumors may also help to define prognosis and to predict the response to therapy [51, 52].

4. Role of epigenetics as diagnostic and prognostic biomarker in cancer

The early diagnosis of breast cancer absolutely prolongs survival so there is requirement of specific markers for early diagnosis, but the available markers are not specific enough for this purpose. The markers related to the epigenetic changes in cancer may become more useful for the early diagnosis because these epigenetic changes occur even before the cancer is developed [53, 54]. Presently researchers aim to discover a combination of specific epigenetic markers to develop “epigenetic signatures” which are specific to cancer. These Epigenetic changes/patterns can act as potential diagnostic and prognostic markers for cancer diagnosis as per some recent research work that is also summarized in Table 2 [55].

The body fluids such as nipple aspirate and ductal lavage fluid in breast may be better sources than serum for sample collection in the breast cancer. The assessment upon the molecular mechanisms underlying during the development and progression of breast cancer and the genetic mutations have been an evident cause that has long been well-known [56]. Though epigenetic modification mechanisms are now becoming recognized as significant factors in the development of breast and other cancers. Mechanism of epigenetics coordinate biological processes such as X-chromosome inactivation, position effect variegation, genomic imprinting, RNA interference, and reprogramming of genome during the differentiation and development leading to gene silencing and other process which can lead to cancer [57]. The defects in any of these functions may cause human disorders including breast cancer. The epigenetic malfunctions are manifested through aberrant methylation and acetylation of the genes and histone proteins involved in normal tissue development to activate or silence gene expression [58]. Consequently, abnormal tissue differentiation and growth may result from the loss of crucial cell adhesion proteins and over excitation of estrogen receptor pathways in breast cancer and migration of abnormal cells gets increased [59, 60]. The occurrences of such epigenetic processes suggests that every person should be aware or there should be awareness camps in whole population about balanced diet, which are known to be protective and supportive while avoiding or limiting exposures to the known risk factors for breast cancers.

4.1. Epigenetics as diagnostic and prognostic biomarkers for breast cancer

In the recent past years there are several studies which have referred the potential use of epigenetics as diagnostic and prognostic or predictive tools in breast cancer [64, 93, 94]. Hocque et al. studied the aberrant methylation of *APC, GSTP1, RASSF1A* and *RARb2* gene in the serum samples of patients with breast cancer and revealed that methylation of at least one of these four genes of interest were detected in the plasma of cancer cases with a sensitivity of sixty two percent and a specificity of eighty seven percent [95]. After few years later, the same research team showed that three genes APC, CDH1 and CTNNB1 are directly involved in the early stages of breast cancer progression and the analysis of their methylation in breast cancer samples allowed distinguishing between normal and pathologic samples with a specificity of seventy five percent and a sensitivity of sixty seven percent [96]. Moreover, a very recent study on breast cancer samples demonstrated that 14-3-3 Sigma gene was hypermethylated in breast cancer tumor samples [97]. Thus, epigenetic patterns such as DNA methylation in

Table 2
Epigenetic changes/patterns as potential diagnostic and prognostic markers in cancer.

Epigenetic marker	Reference
Histone modifications	
H3K9ac, H3K9me3, H4K16ac (tissue)	[61]
H4K20me1, H4K20me2 (tissue)	[62]
H3K4me2, H3K18ac (tissue)	[63]
H3K27me3 (plasma)	[64]
H3K18ac, H4K12ac, H3K4me2, H4K20me3, H4R3me2, H4K16ac (tissue)	[65]
H3K9me3, H4K20me3 (plasma)	[66]
H3K9me3 (tissue)	[67]
H3K27me3 (serum)	[68]
H3K18ac, H4R3me2,H3K27me3 (tissue)	[69]
H3K9me1 (tissue)	[70]
H3K4me3 (tissue)	[71]
DNA methylation	
Analysis of methylation patterns of 45 DNA fragments using methylation-sensitive arbitrarily primed-PCR (MS-AP-PCR) screening	[72]
Analysis of 1184 unselected CpG islands in 98 primary human tumours using restriction landmark genomic scanning (RLGS)	[73]
Methylation analysis of 1104 CpG islands using CpG island arrays (differential methylation hybridization, DMH)	[74]
Methylation of CpG island of 9 genes identified by MS-RDA	[75]
Methylation of MGMT	[76]
Methylation of DAPK	[77]
Methylation of RASSF1 and/or APC in serum DNA	[78]
Methylation analysis (MSP) of 12 cancer-associated genes	[79]
Methylation analysis (MSP) of 8 genes in 105 specimens of NSCLC representing all stages of cancer	[80]
Methylation analysis of 9 genes (by QM-MSP) on ductal lavage cells from women undergoing mastectomy	[81]
Methylation of 4 GATA genes	[82]
Methylation of 7 fragments derived from screening of methylated CpGs (by MS-RDA)	[83]
MiRNA	
miR-20a, miR-106b and miR-221 (plasma, qRT-PCR)	[84]
miR-486 and miR-451 (plasma, miRNA microarray and qRT-PCR)	[85]
miR-17-5p miR-106b, miR-106a, miR-21, and let-7a (plasma qRT-PCR)	[86]
miR-221, miR-376c and miR-744 (serum, TaqMan low-density array and TaqMan qRT-PCR)	[87]
miR-378 (serum miRNA microarray and real-time qRT-PCR)	[88]
miR-196a (serum, Quantitative RT-PCR_	[89]
miR-223, miR-21 and miR-218 (tissue, qRT-PCR)	[90]
miR-17-5p, miR-21, miR-106a, miR-106b and let-7a (tissue, qRT-PCR)	[91]
miR-195-5p let-7a, MiRNA- 199a-3p (tissue, real-time qRT-PCR)	[92]

tumor or even in plasma may represent useful tools for early detection of BC [98]. Yan et al. confirmed during their study that the hypermethylation of CpG islands is related with histological grade in breast tumors and more precisely an increasing number of the methylated CpG islands correlated to decreased differentiation of BC cells. [99]. Recently, the concept of B CIMP (Breast CpG Islands Methylator Phenotype) has emerged as fang et al. showed during their study that the absence of the methylator phenotype (B-CIMP-) within CpG islands in promoters of specific genes is associated with the high metastatic risk, describing a new classification with the breast cancer being B-CIMP1 or B-CIMP2 [100, 101]. These latter results which were obtained in the breast cancer cell lines have been confirmed more recently in vivo with a level of aberrant DNA-methylation found higher in the late stage than in early stage of breast cancer regarding consistent candidate genes [102]. Dedeurwaerder et al. have suggested that the cell type of source as well as the alterations linked with the tumor progression contribute to the DNA methylation pattern in breast cancer [19]. Some research studies have shown that the methylation of the promoter region of tumor suppressor genes can be detected in the blood stream of patients and can be linked to their prognosis. Indeed, the presence of methylated BRCA1 and/or p16 DNA in serum has been independently associated with poor outcome [3, 60, 103]. The recent meta-analysis suggested also that methylation of BRCA1 is significantly correlated with a poor overall survival in breast cancer [104]. Interestingly, Yu et al. have recently studied EMT in circulating tumor cells from breast cancer patients and they concluded that patients having CTCs expressing a majority of epithelial transcripts (E1) presented with a less aggressive form of breast cancer (ER/ PR1) while patients with the CTCs expressing a majority of mesenchymal transcript (M1) presented with a more aggressive type of BC (such as TNBC) [105]. Epigenetic events may act indirectly as prognostic biomarkers through their capability to influence EMT also this might have therapeutic consequences since the M1 phenotype found in breast cancer patients could lead to consider combination therapies. All in all, strong evidences suggest that an epigenetic signature could differentiate prognosis in breast cancer and that studies of peripheral blood DNA or of CTCs might become useful tools to predict the prognosis of breast cancer in the future [106, 107].

4.2. Epigenetic modifications as predictive biomarkers for BC

Epigenetic biomarkers have the potential to significantly improve the clinical practice by enabling risk stratification, early diagnosis, and rising therapeutics. Although, the use of epigenetic biomarkers has several potential pitfalls to be aware of, including the multifactorial etiology of diseases, chemical influences, acquired drug resistance and practical considerations. It is necessary to consider these possible limitations before epigenetic biomarkers are routinely adapted into clinical practice, treatment and diagnosis to prevent potential harms to patients [108]. First example of the ER-positive breast cancer can benefit from anti-estrogen therapy. In fact excessive activation of the estrogen signaling is known to lead ER-positive breast cancer and representing about seventy percent of breast cancer [109]. Although about thirty to forty percent of the ER-positive cancer patients at the time of diagnosis become ER-negative and resistant to anti-estrogen treatment in the course of the disease which is mostly by the phenomenon due to epigenetic mechanisms [110, 111]. In addition the DNA hypermethylation occurs in forty-one percent of cases when the anti-estrogen resistance is acquired [112]. The activated, normal ER dimerizes, translocates into the nucleus and activates estrogen-regulated genes, leading to the proliferation and differentiation. The Tamoxifen medication is the most used anti-estrogen which binds to ER-α and blocks its dimerization and activation and prevents breast cancer in women and in men [113, 114]. ESR1 is a gene that codes for estrogen receptor α (ER-α). Its methylation seems to predict response to anti-estrogen therapy in breast cancer patients [114, 113]. Martinez-Galan et al. have demonstrated in a recent study, that methylation of the ESR1 gene in peripheral blood significantly correlated with the non-expression of estrogen receptor (ER) in excised tumors meaning that the DNA methylation of ESR1 in serum might become a predictive biomarker in response to anti-estrogen treatment [111]. In one other recent study there was identified a different mechanism of resistance to the tamoxifen due to RNAi, related to downregulation of cyclin-dependent kinase (CDK10) in the ER-α positive breast cancer early relapsing under the tamoxifen treatment, and is associated with methylation of the CDK-10 promoter region [115]. Therefore, the methylation of the cyclin-dependent kinase-1 gene may also serve as a predictive biomarker for determining response to endocrine therapy. One another example of the possible use of epigenetic alterations to predict the patient's response towards the treatment is provided by the study of BRCA genes [116–118]. The BRCA deficiency can impair the capability of the cancer cells to repair the DNA cross-link's caused by chemotherapy as with platinum derivatives. Therefore; based on experimentations led on BC cell lines, Olafur et al. have suggested that BRCA1 hypermethylation could also become a predictor response element to platinum based chemotherapy in breast cancer [119]. Micro-RNAs may also turn into the predictors of response to the treatment; as recently Kolacinska et al. have showed that in triple-negative breast Cancer (TNBC) core biopsies sampled before preoperative

chemotherapy, a high expression of miR-200b-3p, miR-190a and miR-512-5p is linked with a better response to chemotherapy and increased the feasibility of the breast conserving surgery [120]. Recently Nicholas et al. identified a 6-miRNA signature which can differentiate between high-risk women who do and do not develop breast cancer over a median follow-up of 8.7 years. The accessibility and stability of the circulating miRNAs, has the potential to significantly improve breast cancer risk prediction by identifying the women at greatest risk who can be offered aggressive screening, prevention and clinical trials [121, 122].

5. The future prospects of epigenetics in cancer

One of the biggest advantages of using epigenetics for therapeutic reasons would be because it can target multiple genes involved in a similar pathway. The researchers are fighting that by targeting epigenetic markers that inhibit the normal functioning of the cell cycle, they are able to knock these proteins out to restore the regular functioning of cell cycle. However, with a lot of the recent information on epigenetics, there is evidence of promise in the future for cancer prevention, prognoses, and therapeutics. There is still much work to be done in this field, but progress is being made daily to understand how these modifications can cause tumor and how these can be applied to prevent cancer. Not only epigenetic markers having the potential to serve as diagnostic and prognostic biomarkers but they are also being considered as biomarkers for predicting the response to therapy in several malignancies. In addition they can also identify the clinical and pathological stage of the disease. Furthermore, these modifications can predict risk of progression, relapse, and metastasis, and help to evaluate possible clinical scenarios in relation to the therapy response. The clinical validity of these epigenetic modifications should be determined using large independent cohorts in multi-centric studies, in combination with the use of more robust platforms, more appropriate and accurate bio-computational and advanced statistical software.

6. Conclusion

Epigenetic alterations are clearly involved in cancer initiation and progression and as newer genome-wide methods are focusing on identifying many genes whose regulation is epigenetically altered in cancer, recent epigenetic studies on genomic DNA, histone modifications and micro-RNA alterations demonstrated that these epigenetic alterations are playing an important role in incidence of breast cancer. In addition to the use of epigenetic alterations as a means of screening, epigenetic alterations in a tumor or adjacent tissues or peripheral blood may also help clinicians in determining prognosis and treatment in breast cancer patients. As we understand specific epigenetic alterations contributing to breast tumorigenesis and prognosis, these discoveries will lead to significant advances for breast cancer treatment, like in therapeutics that target methylation and histone modifications in breast cancer. The newer versions of these drugs are likely to play an important role in future clinical treatment.

Disclosure of potential conflicts of interest

Authors declare that they have no conflict of interests.

Author's contribution

All the authors have contributed equally. All authors read and approved the final manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ctarc.2019.100125.

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