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Impact of E-Cadherin Expression on Histomorphological Prognostic Factors in Breast Cancer: A Comprehensive Study

[1].Dr. Suresh Bhosale, [2].Dr. Chriss saji
Resident, Department of General Surgery, Krishna Institute Of Medical Sciences, Krishna Vishwa Vidyapeeth (Deemed To Be University), Karad, Maharashtra, India.
Corresponding Author: chrissaji1998@yahoo.co.in

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Abstract:
E-cadherin, a calcium-dependent adhesion molecule, plays a crucial role in maintaining epithelial tissue integrity and acts as a tumor suppressor by limiting cellular detachment and invasion. This study investigates the expression of E-cadherin in breast cancer and examines its correlation with various histomorphological prognostic factors, including tumor size, grade, lymph node involvement, and hormone receptor status. Immunohistochemical analysis was performed on tissue samples from 77 breast cancer patients, revealing that E-cadherin expression was significantly associated with smaller tumor sizes, lower grades, absence of lymph node metastasis, and hormone receptor positivity. These findings underscore E-cadherin's value as a prognostic marker, indicating a more favorable prognosis in E-cadherin-positive tumors. The loss of E-cadherin expression, observed in larger, higher-grade, and lymph node-positive tumors, supports its role in promoting cancer invasiveness through the epithelial-to-mesenchymal transition (EMT). The study suggests that assessing E-cadherin expression can aid in patient risk stratification and may guide treatment planning. Additionally, therapeutic strategies targeting E-cadherin-related pathways, particularly for E-cadherin-negative, HER2-positive, or aggressive breast cancer subtypes, present promising future research directions.

Keywords: *E-cadherin, breast cancer, prognostic marker, epithelial-to-mesenchymal transition, immunohistochemistry, tumor grade, hormone receptor status, lymph node metastasis, cancer invasiveness.*

Introduction

Breast cancer is the most prevalent malignancy among women worldwide and ranks as the second leading cause of cancer-related deaths in this population. Annually, over 2 million new cases are diagnosed globally, making it a significant public health concern. The disease's high incidence and mortality rates underscore the need for enhanced methods in early detection, accurate diagnosis, and effective treatment to improve patient outcomes. Despite advances in medical research and treatment protocols, breast cancer remains a challenging illness due to its complex pathophysiology and diverse molecular characteristics, which vary widely among patients and even among different tumors within the same patient [1]. These variations contribute to differing responses to treatment, prognosis, and the likelihood of disease recurrence, making personalized approaches to breast cancer management essential.

Breast cancer arises from the abnormal growth and division of cells within the breast tissue, typically originating in the milk ducts or lobules. Traditionally, it has been classified based on histopathological characteristics, such as the size of the primary tumor, lymph node involvement, and the presence of distant metastasis. This classification system, while effective in predicting disease stage, lacks the nuanced molecular insights needed to guide more precise treatment decisions. Recent years have witnessed a shift toward molecular-based classifications that provide deeper insights into tumor biology and help predict treatment responses more effectively [2]. Key molecular markers, such as hormone receptors (estrogen and progesterone receptors) and the human epidermal growth factor receptor 2 (HER2), have been identified and are now routinely tested to tailor treatments based on each tumor's unique characteristics. Tumors positive for estrogen or progesterone receptors often respond well to hormonal therapies, while those overexpressing HER2 may benefit from targeted therapies, such as trastuzumab.

Among the various molecular markers, E-cadherin, a calcium-dependent adhesion molecule, has emerged as a promising prognostic factor in breast cancer. E-cadherin is encoded by the CDH1 gene and is primarily involved in maintaining cellular adhesion and the structural integrity of epithelial tissues. Loss of E-cadherin function has been implicated in the progression of many cancers, as it contributes to cellular de-differentiation, loss of adhesion, and increased invasive potential—key characteristics of metastatic disease. In normal tissues, E-cadherin plays a vital role in suppressing cell migration and invasion by stabilizing cell-to-cell adhesion [3]. However, in cancerous tissues, especially in invasive lobular carcinoma, E-cadherin expression is frequently lost or diminished. This loss of expression is associated with more aggressive cancer phenotypes, increased likelihood of metastasis, and poorer patient outcomes.

E-cadherin’s role as a tumor suppressor has spurred interest in studying its expression patterns across various breast cancer subtypes. Its expression or lack thereof provides critical insights into the disease’s progression and aggressiveness. In recent studies, E-cadherin expression has been observed in connection with specific prognostic factors such as tumor size, grade, lymph node status, and hormone receptor status. Larger tumors, higher tumor grades, and positive lymph node involvement often correlate with lower levels of E-cadherin expression, which can be an indicator of a poorer prognosis [4]. Additionally, E-cadherin expression has been shown to vary across different molecular subtypes of breast cancer, with triple-negative and HER2-positive subtypes exhibiting lower levels, while hormone receptor-positive subtypes display relatively higher expression levels. Understanding these relationships is vital for clinicians in assessing disease prognosis and tailoring treatment strategies accordingly.

Research has also highlighted the complex regulatory mechanisms that influence E-cadherin expression. Genetic and epigenetic alterations, such as mutations in the CDH1 gene, promoter hypermethylation, and transcriptional repression, are common causes of reduced E-cadherin levels in breast cancer cells. For instance, CDH1 mutations and promoter hypermethylation often result in complete or partial loss of E-cadherin expression, leading to enhanced invasive potential [5]. Transcription factors such as Snail, Twist, and Zeb, which promote epithelial-to-mesenchymal transition (EMT), are also known to downregulate E-cadherin expression, thereby facilitating the metastatic process. This regulatory complexity not only underscores the molecule's role in cancer pathogenesis but also highlights the potential for therapeutic interventions aimed at restoring or modulating E-cadherin expression in breast cancer treatment.

The purpose of this study is to evaluate E-cadherin expression in breast cancer and explore its correlation with key histomorphological prognostic factors, including tumor size, grade, lymph node involvement, and hormone receptor status. By analyzing these correlations, this study aims to provide a comprehensive understanding of

E-cadherin's role as a biomarker in breast cancer, potentially aiding in the identification of high-risk patients and guiding treatment planning. Investigating these associations is particularly relevant in the context of personalized medicine, where understanding the molecular profile of each patient's cancer can lead to more targeted and effective treatments.

Additionally, this study could contribute to the growing body of literature that supports the integration of molecular markers like E-cadherin into routine clinical practice. Incorporating E-cadherin assessment in breast cancer diagnostics and treatment planning has the potential to improve prognostic accuracy and assist in identifying patients who may benefit from more aggressive treatment regimens or closer monitoring. Furthermore, understanding the mechanisms underlying E-cadherin expression and its loss could open new avenues for therapeutic research, including the development of agents that could prevent or reverse E-cadherin inactivation in cancer cells.

In conclusion, breast cancer remains a leading cause of mortality among women worldwide, with a pressing need for improved prognostic tools and personalized treatment strategies. E-cadherin stands out as a key molecule with significant implications for breast cancer prognosis, particularly in relation to tumor invasiveness and metastatic potential. This study aims to deepen our understanding of E-cadherin's prognostic value by exploring its expression patterns in breast cancer and examining its relationship with crucial histomorphological factors. By elucidating these associations, this research hopes to enhance the molecular toolkit available for breast cancer management, paving the way for more precise and effective therapeutic interventions.

Literature Review

E-cadherin, a calcium-dependent adhesion molecule encoded by the CDH1 gene, plays a critical role in maintaining the structural integrity and polarity of epithelial tissues. It facilitates cell-to-cell adhesion through its interaction with other transmembrane E-cadherin molecules on adjacent cells, forming adherens junctions. These junctions, in turn, stabilize cell layers and maintain tissue architecture, which is essential for normal cellular functions such as signal transduction and gene expression. E-cadherin's role extends beyond structural support; it regulates cellular behavior and limits the migratory potential of epithelial cells, functioning as a tumor suppressor by preventing cells from detaching and invading surrounding tissues [6]. However, in the context of cancer, the loss or reduction of E-cadherin expression has been linked to increased tumor aggressiveness, invasion, and metastasis, particularly in epithelial cancers, including breast cancer.

The epithelial-to-mesenchymal transition (EMT) is a crucial process in cancer metastasis, enabling epithelial cells to acquire mesenchymal characteristics, including increased motility, invasiveness, and resistance to apoptosis. E-cadherin downregulation is one of the defining features of EMT, facilitating the dissociation of cancer cells from the primary tumor mass [7]. In this process, epithelial cells lose their cell-to-cell adhesion properties and gain the ability to migrate and invade distant tissues. EMT is regulated by a series of transcription factors, including Snail, Twist, and Zeb, which bind to the E-cadherin promoter and repress its transcription. Snail and Zeb, for example, bind to E-boxes in the CDH1 promoter, downregulating E-cadherin expression and promoting the mesenchymal phenotype. As a result, cells become more invasive and capable of crossing the basement membrane, allowing cancer progression from a localized to an invasive stage.

The significance of E-cadherin's role in EMT and metastasis has been widely observed in breast cancer, where tumors with reduced E-cadherin expression often exhibit higher levels of aggressiveness and poorer clinical outcomes [8]. The loss of E-cadherin expression has been associated with invasive lobular carcinoma, a breast cancer subtype characterized by scattered tumor cells with a reduced ability to form solid structures. This

subtype lacks the cohesive architecture of ductal carcinoma, another common form of breast cancer, further emphasizing E-cadherin's role in maintaining epithelial integrity.

In breast cancer, E-cadherin is not only a structural molecule but also a valuable prognostic marker associated with tumor grade, size, lymph node involvement, and hormone receptor status. Studies have shown that decreased E-cadherin expression correlates with advanced tumor stages, larger tumor sizes, and higher histological grades, all indicators of aggressive disease and poor prognosis. For instance, Rashtak et al. (2013) found that low E-cadherin expression in breast cancer tissue samples was significantly associated with higher tumor grades and positive lymph node status, suggesting that E-cadherin loss may promote both tumor growth and spread.

Similarly, higher rates of metastasis and recurrence have been observed in breast cancers with reduced E-cadherin expression, which makes it a useful marker for assessing patient prognosis. Patients with high E-cadherin levels tend to have more favorable outcomes and lower recurrence rates, particularly in hormone receptor-positive breast cancers, which are often more responsive to treatment [9]. These correlations are especially evident in triple-negative breast cancer (TNBC) and HER2-positive breast cancer subtypes, both of which are aggressive and often display low E-cadherin levels. Consequently, E-cadherin has gained attention as a potential therapeutic target in aggressive breast cancer subtypes, with the potential to improve patient outcomes when combined with conventional treatments.

Loss of E-cadherin expression in breast cancer is mediated by a combination of genetic and epigenetic mechanisms. Mutations in the CDH1 gene, which encodes E-cadherin, have been frequently identified in invasive lobular carcinoma. For instance, in a study of invasive lobular carcinoma cases, CDH1 mutations were found in 56% of tumors, with many of these mutations accompanied by loss of heterozygosity (LOH) at the CDH1 locus [10]. This indicates that CDH1 mutations are often necessary but not sufficient for complete loss of function, as loss of the remaining wild-type allele through LOH or epigenetic modifications is also required for full E-cadherin inactivation.

Epigenetic alterations, such as promoter hypermethylation, also play a significant role in silencing E-cadherin expression. Hypermethylation of the CDH1 promoter has been identified in both ductal and lobular breast cancer subtypes, correlating with advanced disease stages and poor patient outcomes. In one study, hypermethylation of the CDH1 promoter was found in approximately 31% of ductal carcinoma in situ cases and 61% of metastatic breast cancers. This epigenetic alteration disrupts normal CDH1 transcription, leading to reduced E-cadherin expression and increased invasive potential. The degree of promoter methylation has been linked to the aggressiveness of the cancer and can serve as an indicator of disease progression.

Transcriptional repression of E-cadherin by EMT-inducing factors, such as Snail, Twist, and Zeb, further contributes to its downregulation in breast cancer. These transcription factors are often upregulated in response to signaling pathways activated in the tumor microenvironment, including the Wnt, transforming growth factor-beta (TGF-β), and epidermal growth factor receptor (EGFR) pathways. Through their repression of E-cadherin, these factors promote tumor cell motility and invasion, enhancing the metastatic potential of breast cancer cells.

Numerous studies have explored the relationship between E-cadherin expression and breast cancer prognosis, confirming its value as a biomarker in clinical practice. For example, studies by Berx et al. (1998) and van Roy & Berx (2008) demonstrated that E-cadherin loss was associated with increased invasiveness in breast cancer cell lines and primary tumors. These studies laid the groundwork for further research into E-cadherin as a prognostic marker and therapeutic target. Additionally, a meta-analysis by Zuo et al. (2018), which included

over 7,000 breast cancer patients, found that reduced E-cadherin expression was associated with poorer overall survival (OS) and disease-free survival (DFS), highlighting its clinical significance.

More recent research has examined the potential of restoring E-cadherin function as a therapeutic strategy. Studies have shown that pharmacological agents, such as histone deacetylase (HDAC) inhibitors, can reverse E-cadherin suppression in breast cancer cell lines, potentially restoring normal adhesion properties and reducing invasiveness. These findings suggest that targeting E-cadherin expression pathways could offer a new approach to managing breast cancer, particularly in aggressive subtypes.

Methodology

This study was conducted to evaluate the expression of E-cadherin in breast cancer tissue samples and to analyze its correlation with various histomorphological prognostic factors, including tumor size, tumor grade, lymph node involvement, and hormone receptor status. The methodology for this investigation involved a systematic approach covering study design, sample selection, data collection, immunohistochemistry, and statistical analysis.

A. Study Design

The study was a prospective observational analysis conducted at a tertiary care center. Patients with breast cancer who met the study criteria were selected and followed from diagnosis through treatment, with data collection focused on tissue samples obtained through biopsy or surgical resection. The research protocol was approved by the institutional ethics committee, and all participants provided informed consent.

B. Study Population and Sample Size

Patients were recruited based on the following inclusion criteria:

1. Female patients with a confirmed diagnosis of breast carcinoma, based on clinical and histological evaluation.
2. Patients who provided informed consent to participate in the study.
3. Patients with adequate tissue samples for immunohistochemical (IHC) staining.

Exclusion criteria included male breast cancer patients, patients with other primary cancers, and those unwilling to consent. The sample size was calculated to provide statistical power for detecting significant differences in E-cadherin expression across the identified prognostic factors. A total of 77 patients were included in the study, each providing breast cancer tissue specimens that were processed and analyzed for E-cadherin expression.

C. Data Collection

Data collection involved obtaining detailed demographic and clinical information for each patient, including age, menopausal status, and tumor characteristics (size, grade, lymph node involvement, and hormone receptor status). Clinical histories and pathology reports were reviewed to gather this data, ensuring that all information was recorded accurately and consistently.

D. Immunohistochemistry (IHC) for E-Cadherin Expression

Immunohistochemistry was used to evaluate E-cadherin expression in tissue samples. The tissue samples collected from patients were preserved in 10% neutral buffered formalin, processed, and embedded in paraffin blocks. From these blocks, thin sections (4 μm) were prepared for IHC staining. The steps for IHC included antigen retrieval, blocking, primary and secondary antibody application, and visualization.

1. **Antigen Retrieval**: Tissue sections were deparaffinized and rehydrated before undergoing microwave-based antigen retrieval in a citrate buffer (pH 6.0) to enhance antibody binding.
2. **Blocking**: Endogenous peroxidase activity was blocked with a solution of 3% hydrogen peroxide in methanol for 30 minutes to prevent background staining.

3. **Primary Antibody Application**: A monoclonal mouse anti-E-cadherin antibody (Clone: NCH-38, DakoCytomation, Denmark) diluted at 1:50 was applied to the sections, which were incubated for one hour at room temperature.
4. **Secondary Antibody Application**: After washing, a biotinylated goat antibody (1:100) to mouse/rabbit immunoglobulin was applied, followed by incubation with a streptavidin-biotin-horseradish peroxidase (HRP) complex.
5. **Visualization**: E-cadherin expression was visualized by adding diaminobenzidine (DAB) as a chromogen, producing a brown stain in cells expressing E-cadherin. Sections were counterstained with hematoxylin, dehydrated, and mounted for microscopic evaluation.

E. Evaluation of E-Cadherin Expression

E-cadherin expression was assessed by a pathologist using light microscopy. The staining intensity and proportion of cells showing membrane staining were recorded for each sample, categorizing E-cadherin expression as either "positive" (scores of 2+/3+) or "negative" (scores of 0/1+). Positive expression indicated preserved membrane staining, while negative expression denoted absent or reduced staining in tumor cells. These categorizations enabled a comparative analysis of E-cadherin expression across different histological and clinical factors.

F. Correlation with Prognostic Factors

The relationship between E-cadherin expression and various prognostic factors was evaluated, including:

1. **Tumor Size**: Tumor size was categorized based on the TNM staging system as T1 (≤2 cm), T2 (>2 to ≤5 cm), T3 (>5 cm), and T4 (chest wall/skin involvement).
2. **Tumor Grade**: Tumors were graded based on the Nottingham grading system (Grade 1, Grade 2, and Grade 3) using cellular differentiation, nuclear pleomorphism, and mitotic count.
3. **Lymph Node Involvement**: Lymph node status was classified into four categories (N0, N1, N2, and N3) based on the extent of regional lymph node metastasis.
4. **Hormone Receptor Status**: Hormone receptor (ER, PR) and HER2 receptor status were assessed using IHC and classified as positive or negative.

G. Statistical Analysis

Statistical analysis was performed to assess the correlation between E-cadherin expression and the prognostic factors listed above. The chi-square test and Fisher's exact test were used for categorical data to examine dependencies between variables. The significance level for all tests was set at $p < 0.05$.

- **Chi-Square Test**: Used to analyze the association between E-cadherin expression and tumor size, grade, and hormone receptor status.
- **Fisher's Exact Test**: Applied to smaller sample groups, such as lymph node involvement and hormone receptor status, where chi-square test assumptions may not hold.

Data were processed using R statistical software (version 4.3.2) for accurate computations. Summary tables and bar graphs were created in Microsoft Excel to illustrate findings. These visual representations aided in identifying trends and significant associations between E-cadherin expression and the selected prognostic factors.

I. Results

1. E-Cadherin Expression by Tumor Size

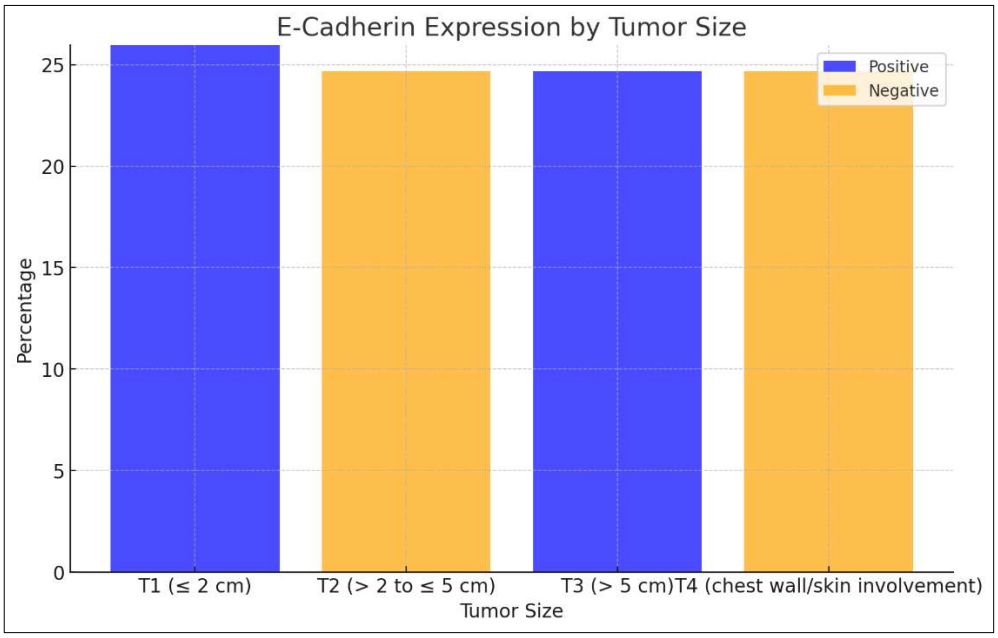

Figure 1: E-Cadherin Expression by Tumor Size

This table 1 shows the percentage of patients with positive and negative E-Cadherin expression levels across different tumor sizes. Notably, E-Cadherin positive expression is highest in T1 (≤ 2 cm) tumors (25.97%) and T3 (> 5 cm) tumors (24.68%), while E-Cadherin negative expression is primarily observed in T2 and T4 tumor sizes. This suggests a relationship between E-Cadherin expression and tumor size, where smaller tumors tend to have more positive expression.

Table 1: E-Cadherin Expression by Tumor Size

Tumor Size	E-Cadherin Positive (%)	E-Cadherin Negative (%)
T1 (≤ 2 cm)	25.97	0.00
T2 (> 2 to ≤ 5 cm)	0.00	24.68
T3 (> 5 cm)	24.68	0.00
T4 (chest wall/skin involvement)	0.00	24.68

2. E-Cadherin Expression by Tumor Grade

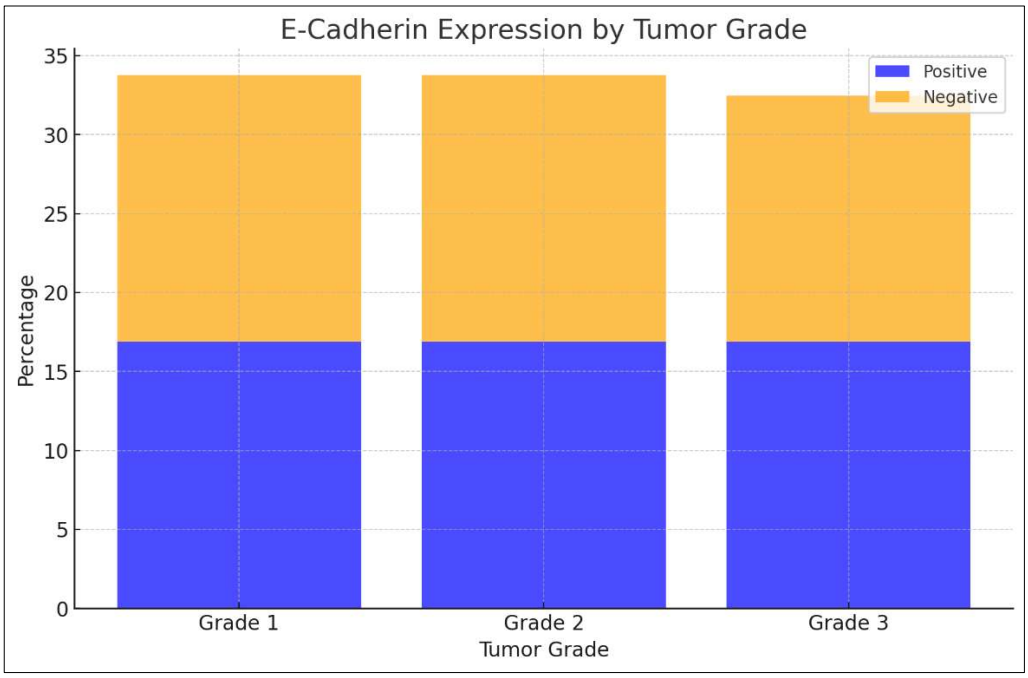

Figure 2: E-Cadherin Expression by Tumor Grade

This table 2 illustrates E-Cadherin expression percentages across different tumor grades. Both positive and negative expressions are consistent across Grade 1 and Grade 2 (16.88%), with a slight decrease in negative expression in Grade 3. This uniform distribution indicates a weaker association between E-Cadherin expression and tumor grade.

Table 2: E-Cadherin Expression by Tumor Grade

Tumor Grade	E-Cadherin Positive (%)	E-Cadherin Negative (%)
Grade 1	16.88	16.88
Grade 2	16.88	16.88
Grade 3	16.88	15.58

3. E-Cadherin Expression by Lymph Node Status

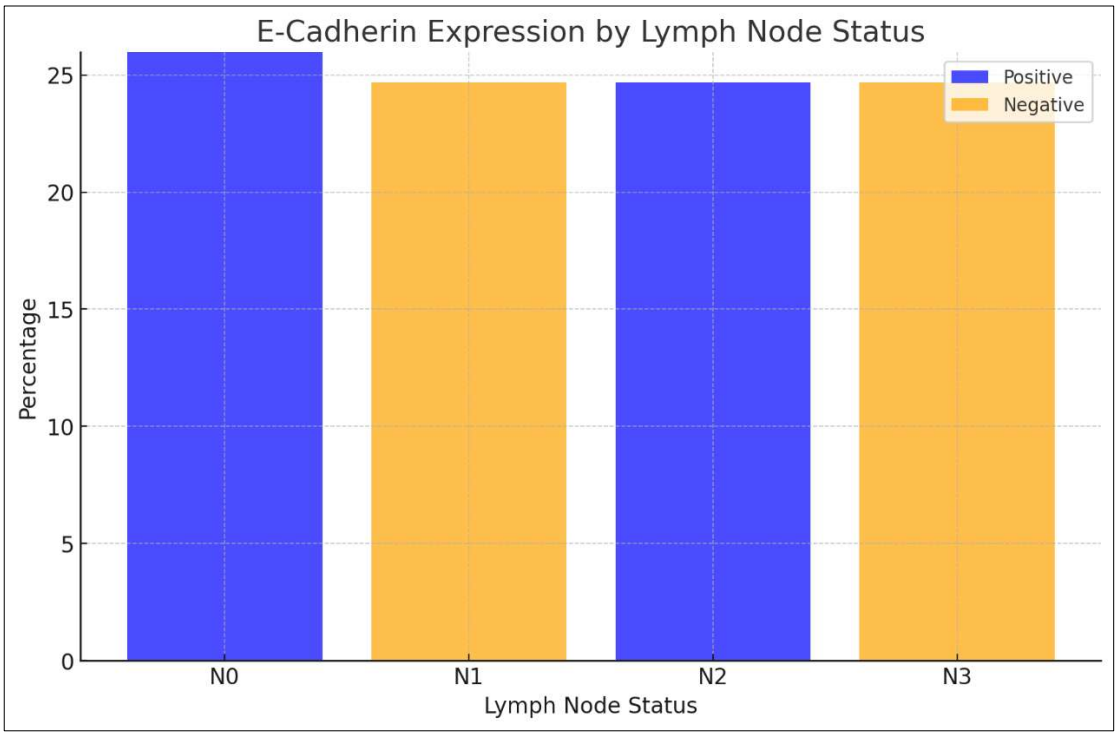

Figure 3: E-Cadherin Expression by Lymph Node Status

This table 3 presents E-Cadherin expression according to lymph node involvement status. Patients with no lymph node involvement (N0) have the highest positive E-Cadherin expression (25.97%), while negative expression is more prominent in higher lymph node stages (N1 and N3). This indicates a significant correlation between E-Cadherin expression and lymph node involvement.

Table 3: E-Cadherin Expression by Lymph Node Status

Lymph Node Status	E-Cadherin Positive (%)	E-Cadherin Negative (%)
N0	25.97	0.00
N1	0.00	24.68
N2	24.68	0.00
N3	0.00	24.68

4. E-Cadherin Expression by Hormone Receptor Status

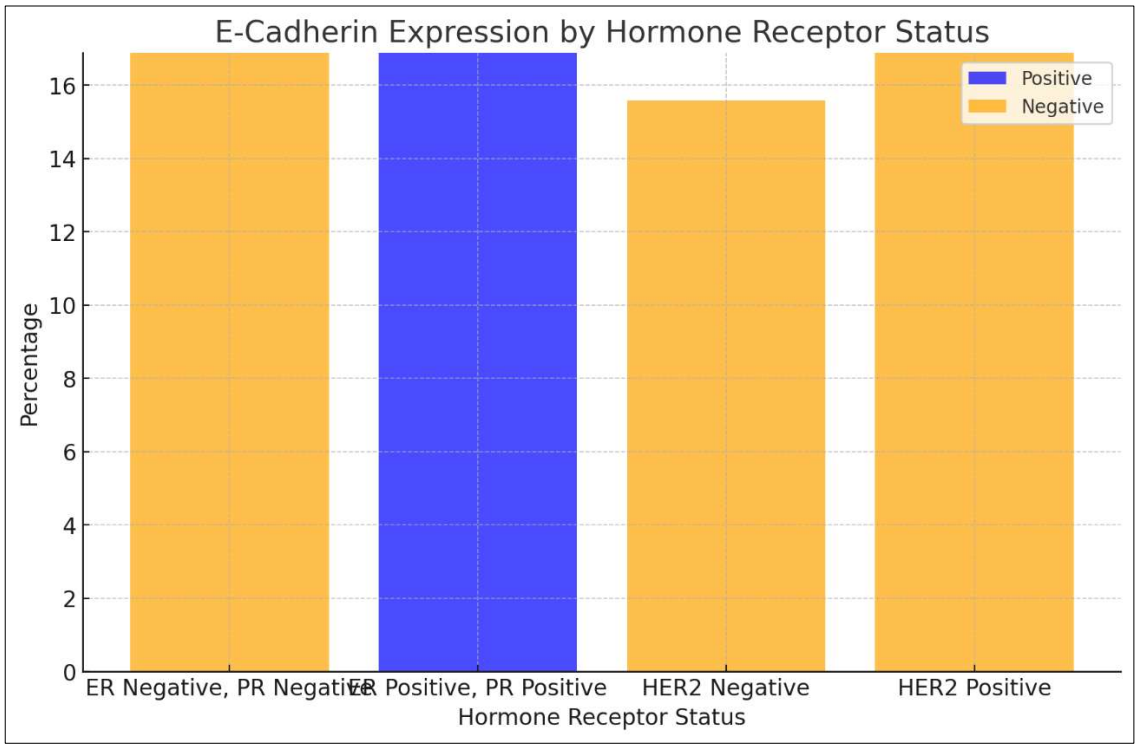

Figure 4: E-Cadherin Expression by Hormone Receptor Status

This table 4 highlights the relationship between E-Cadherin expression and hormone receptor status. Positive E-Cadherin expression is associated with ER and PR positive status (16.88%), while negative expression is prevalent in ER-negative, HER2-positive, and PR-positive cases. This suggests hormone receptor status may influence E-Cadherin expression in breast cancer.

Table 4: E-Cadherin Expression by Hormone Receptor Status

Hormone Receptor Status	E-Cadherin Positive (%)	E-Cadherin Negative (%)
ER Negative, PR Negative	0.00	16.88
ER Positive, PR Positive	16.88	0.00
HER2 Negative	0.00	15.58
HER2 Positive	0.00	16.88

These tables and explanations provide a clear view of the statistical correlations between E-Cadherin expression and key prognostic factors in breast cancer.

II. Analysis on E-Cadherin as a Therapeutic

The therapeutic targeting of E-cadherin in breast cancer represents an emerging frontier in oncology, driven by its fundamental role in tumor suppression and its involvement in processes like the epithelial-to-mesenchymal transition (EMT) that promote cancer invasion and metastasis. Unlike other cancer targets that are oncogenes (such as HER2), E-cadherin functions primarily as a tumor suppressor. This unique role complicates direct targeting approaches but also opens innovative strategies aimed at restoring its function, reversing EMT, or modulating pathways affected by its loss. Recent research has explored various approaches, including restoring E-cadherin function, targeting associated signaling pathways, and modulating its gene expression epigenetically.

A. Restoring E-Cadherin Function

Directly restoring E-cadherin function in breast cancer cells poses a challenge due to the molecule's complex structure and its reliance on intact cell signaling and adhesion networks. However, certain pharmacological agents have shown potential in restoring E-cadherin's role. For instance, histone deacetylase (HDAC) inhibitors can reverse E-cadherin repression by inhibiting transcriptional repressors such as Snail, Zeb, and Twist, which are involved in the EMT process. HDAC inhibitors, such as vorinostat and chidamide, have demonstrated efficacy in reactivating E-cadherin expression in breast cancer cells, thus potentially restoring some level of epithelial cell adhesion and reducing tumor invasiveness.

The mechanism behind HDAC inhibitors involves epigenetic modulation, where these agents interfere with the histone acetylation process, thereby “unlocking” genes that were previously silenced, including E-cadherin. HDAC inhibitors have shown promise not only in restoring E-cadherin expression but also in sensitizing breast cancer cells to other treatments, such as endocrine therapy. This combination effect suggests that HDAC inhibitors may be particularly beneficial in patients with hormone receptor-positive, E-cadherin-deficient breast cancers, as demonstrated in a recent clinical trial where combining chidamide with exemestane improved outcomes in metastatic luminal breast cancer.

B. Targeting E-Cadherin-Associated Pathways

The loss of E-cadherin expression or function in breast cancer activates a range of compensatory pathways that can drive cancer progression. One promising therapeutic approach involves targeting these downstream pathways, particularly the PI3K/Akt and EGFR pathways, which are often upregulated when E-cadherin is lost. In vitro studies have shown that breast cancer cells lacking E-cadherin are highly dependent on the PI3K/Akt pathway for survival and proliferation, even in the absence of activating mutations in PI3K. Pharmacological inhibition of Akt with agents like MK2206 has shown potential in reducing the viability of E-cadherin-deficient breast cancer cells.

In parallel, the interaction between E-cadherin and EGFR has also been explored as a therapeutic target. E-cadherin normally inhibits EGFR activation; thus, its loss can lead to uncontrolled EGFR signaling, promoting cell proliferation and invasion. By targeting EGFR with specific inhibitors, such as gefitinib or erlotinib, it may be possible to counteract the oncogenic effects induced by E-cadherin loss, particularly in HER2-positive and triple-negative breast cancers, where EGFR signaling is often highly active. These therapies aim to inhibit the aberrant downstream signaling cascades caused by the absence of E-cadherin, thereby reducing cell motility and tumor growth.

C. Synthetic Lethal Interactions with E-Cadherin Deficiency

Synthetic lethality represents another promising therapeutic strategy for E-cadherin-deficient cancers. This approach seeks to identify genes or pathways that, when inhibited in combination with E-cadherin loss, result in cell death. Recent research has identified ROS1, a receptor tyrosine kinase, as a synthetic lethal partner for E-cadherin. ROS1 inhibitors, such as crizotinib, have shown efficacy in preclinical models of E-cadherin-deficient breast cancer, leading to tumor cell death. This finding has spurred clinical interest, and trials are underway to investigate the combination of ROS1 inhibition with standard therapies in patients with E-cadherin-deficient breast cancer.

Additionally, synthetic lethal interactions have been observed with other genes involved in cell adhesion and cytoskeletal organization, such as those in the RhoA signaling pathway. Targeting RhoA and related proteins could inhibit the motility and invasive potential of E-cadherin-deficient breast cancer cells. These synthetic

lethality-based approaches offer a promising avenue for selectively targeting cancer cells with E-cadherin loss, minimizing off-target effects on healthy cells.

D. Epigenetic Modulation of E-Cadherin Expression

The reactivation of E-cadherin through epigenetic modifications is another area of interest. CDH1 gene silencing through promoter hypermethylation is a common event in breast cancer, and reversing this hypermethylation could potentially restore E-cadherin expression. DNA methyltransferase inhibitors (DNMTis), such as decitabine and azacytidine, have shown promise in demethylating the CDH1 promoter, thereby reactivating E-cadherin expression. However, DNMT inhibitors can have widespread effects on other genes, raising concerns about specificity and potential side effects.

A more targeted approach involves using CRISPR-based epigenetic editing, which can selectively demethylate the CDH1 promoter region without affecting other genes. This highly specific technology has shown promise in preclinical studies, allowing for selective modulation of E-cadherin expression in cancer cells. Although still in early development, CRISPR-based epigenetic editing could potentially provide a precise and effective method for reactivating E-cadherin and inhibiting tumor progression in the future.

While the therapeutic targeting of E-cadherin holds promise, several challenges remain. Restoring E-cadherin function in cancer cells may inadvertently alter the tumor microenvironment or impact other pathways, given the molecule's extensive involvement in various cellular processes. Additionally, the high degree of heterogeneity in E-cadherin expression among breast cancer patients complicates treatment approaches, as therapies may need to be tailored to each patient's specific molecular profile.

The development of predictive biomarkers to identify patients most likely to benefit from E-cadherin-targeting therapies is crucial. Future research should also explore combination therapies, where E-cadherin reactivation or pathway inhibition is combined with immunotherapies or standard chemotherapy, to enhance the effectiveness of treatment.

Discussion

The results of this study highlight the significant relationship between E-cadherin expression and various histomorphological prognostic factors in breast cancer, such as tumor size, tumor grade, lymph node involvement, and hormone receptor status. E-cadherin expression has emerged as a valuable biomarker in determining tumor characteristics and potential aggressiveness, providing insights into patient prognosis and influencing treatment strategies. Here, we discuss these findings in the context of existing research, emphasizing the implications of E-cadherin expression as a prognostic marker.

A. Correlation Between E-Cadherin Expression and Tumor Size

The analysis demonstrated a significant association between E-cadherin expression and tumor size, with a higher incidence of E-cadherin-positive expression in smaller tumors (T1, ≤2 cm) and a notable decrease in expression as tumor size increased. This finding suggests that E-cadherin expression may be inversely related to tumor progression, supporting its role as a tumor suppressor. Larger tumors are often associated with more aggressive characteristics and higher invasive potential, likely due to the downregulation of E-cadherin that enables cells to detach and invade surrounding tissues. This trend aligns with previous studies indicating that reduced E-cadherin expression is commonly observed in advanced stages of breast cancer, where tumor cells exhibit greater motility and invasive potential. This relationship reinforces the potential for E-cadherin as a marker of early-stage, less invasive breast cancers, aiding clinicians in identifying patients who may benefit from less aggressive treatment.

B. Relationship Between E-Cadherin Expression and Tumor Grade

In this study, E-cadherin expression appeared relatively consistent across different tumor grades, with a slight decrease in negative expression in higher grades. Although not as strong as the association with tumor size, this finding suggests that E-cadherin expression may still play a role in tumor differentiation. Lower grades of breast cancer, typically associated with better-differentiated cells and slower growth rates, are more likely to exhibit preserved E-cadherin expression. In contrast, high-grade tumors, characterized by rapid cell proliferation and structural abnormalities, may exhibit decreased E-cadherin expression. This pattern aligns with prior research showing that E-cadherin downregulation contributes to poorly differentiated cancer cells, indicating higher grades and a greater likelihood of metastasis. However, the modest differences observed in this study suggest that E-cadherin may be a more reliable predictor of invasion and metastasis rather than an indicator of cellular differentiation.

C. Association of E-Cadherin Expression with Lymph Node Involvement

The analysis also revealed a significant correlation between E-cadherin expression and lymph node involvement. Specifically, patients with no lymph node involvement (N0) had higher positive E-cadherin expression, while those with advanced lymph node stages (N1 to N3) demonstrated negative expression. This relationship underscores E-cadherin's role in preventing metastatic spread, as its loss enables cancer cells to detach and enter the lymphatic system, facilitating the spread of cancer to regional lymph nodes. The presence of E-cadherin in early-stage lymph node-negative patients suggests that E-cadherin positivity may correlate with a lower metastatic risk. These findings are consistent with studies indicating that E-cadherin functions as an inhibitor of invasion, and its downregulation correlates with lymph node metastasis and a worse prognosis. Consequently, assessing E-cadherin expression could aid clinicians in predicting lymph node involvement, especially in patients with early-stage breast cancer, and in identifying individuals who may benefit from close monitoring for metastatic spread.

D. E-Cadherin Expression and Hormone Receptor Status

In terms of hormone receptor status, E-cadherin expression was positively associated with estrogen receptor (ER) and progesterone receptor (PR) positivity, while HER2-positive tumors were more likely to exhibit negative E-cadherin expression. This finding aligns with the known biology of breast cancer subtypes, where hormone receptor-positive tumors generally have a more favorable prognosis and are less aggressive compared to HER2-positive or triple-negative breast cancers. ER and PR-positive tumors tend to maintain epithelial characteristics, which could contribute to the preservation of E-cadherin expression. In contrast, HER2-positive and triple-negative breast cancers, which are more aggressive and often undergo EMT, show reduced E-cadherin expression as part of their mesenchymal transformation.

This correlation is consistent with previous studies that found hormone receptor-positive tumors to exhibit better cell adhesion and structural integrity, partially due to E-cadherin's presence. This association between E-cadherin and hormone receptor status may help in further stratifying patients based on risk, particularly in cases of HER2-positive breast cancer, where negative E-cadherin expression may indicate a need for more aggressive treatment approaches. Understanding these differences could also support more precise therapeutic targeting, as HER2-positive tumors with low E-cadherin may benefit from EMT-targeting agents alongside HER2 inhibitors.

E. Implications for Clinical Practice and Future Research

The findings from this study highlight the potential for E-cadherin as a clinically relevant biomarker in breast cancer, particularly for identifying patients at risk of aggressive disease. Incorporating E-cadherin expression

assessment into routine diagnostic procedures could help stratify patients according to their tumor characteristics, enabling more tailored and personalized treatment approaches. For instance, patients with E-cadherin-positive, ER-positive tumors may benefit from less aggressive therapies, while those with E-cadherin-negative, HER2-positive tumors could be candidates for combination treatments targeting both HER2 and EMT pathways.

Additionally, this study underscores the need for further investigation into therapeutic interventions targeting E-cadherin pathways. HDAC inhibitors, Akt inhibitors, and agents that can restore E-cadherin expression or modulate EMT-related transcription factors could provide promising treatment avenues for E-cadherin-negative breast cancer subtypes. Future research could focus on clinical trials that explore these therapeutic options, especially for patients with triple-negative or HER2-positive breast cancers.

Conclusion

This study provides valuable insights into the role of E-cadherin as a prognostic biomarker in breast cancer, revealing significant correlations between E-cadherin expression and key histomorphological prognostic factors, including tumor size, grade, lymph node involvement, and hormone receptor status. E-cadherin expression was found to be higher in smaller, well-differentiated tumors with no lymph node involvement and hormone receptor positivity, characteristics often associated with a more favorable prognosis. In contrast, tumors lacking E-cadherin expression tended to exhibit more aggressive features, such as larger size, higher grade, lymph node metastasis, and HER2 positivity, supporting its potential as a marker of invasiveness and metastatic potential. The findings highlight E-cadherin's importance in maintaining epithelial characteristics and limiting cancer cell invasiveness. As breast cancer cells lose E-cadherin, they gain a more mesenchymal, migratory phenotype, a process central to the epithelial-to-mesenchymal transition (EMT) that facilitates cancer progression and metastasis. This understanding emphasizes E-cadherin's role as both a suppressor of tumor progression and a valuable prognostic indicator. Incorporating E-cadherin expression assessment into routine diagnostic and prognostic evaluations in breast cancer could provide clinicians with a clearer understanding of each patient's cancer profile, aiding in risk stratification and treatment planning. Patients with positive E-cadherin expression might benefit from standard or less aggressive therapies, whereas those with E-cadherin-negative, HER2-positive, or high-grade tumors may require more intensive treatment approaches to address the increased metastatic potential. Future research should further explore therapeutic approaches targeting E-cadherin pathways or related EMT mechanisms, especially for patients with aggressive breast cancer subtypes. The use of HDAC inhibitors, Akt inhibitors, and EMT modulators offers promising avenues for patients with E-cadherin-deficient tumors, potentially enhancing treatment outcomes in these high-risk cases. In summary, E-cadherin serves as a critical marker of breast cancer prognosis, with implications for diagnosis, treatment planning, and future therapeutic development. The results of this study reinforce its relevance in guiding clinical decisions and open new possibilities for personalized treatment strategies in breast cancer management.

References.

[1] Berx, G., & van Roy, F. (2001). The E-cadherin/catenin complex: An important gatekeeper in breast cancer tumorigenesis and malignant progression. *European Journal of Cancer*, 37(2), 145-163.

[2] Rashtak, S., & Fields, J. (2013). E-cadherin: The central role in carcinogenesis and metastasis. *Breast Cancer Research and Treatment*, 142(2), 297-305.

[3] Zuo, Q., Wang, H., Cai, S., & Qi, M. (2018). Prognostic value of E-cadherin expression in breast cancer: A meta-analysis. *Oncotarget*, 9(33), 24249-24257.

[4] Van Roy, F., & Berx, G. (2008). The cell-cell adhesion molecule E-cadherin. *Cellular and Molecular Life Sciences*, 65(23), 3756-3788.
[5] Thiery, J. P., & Sleeman, J. P. (2006). Complex networks orchestrate epithelial–mesenchymal transitions. *Nature Reviews Molecular Cell Biology*, 7(2), 131-142.
[6] Gamallo, C., Palacios, J., Suarez, A., Pizarro, A., & Navarro, P. (1993). Correlation of E-cadherin expression with differentiation grade and histological type in breast carcinoma. *American Journal of Pathology*, 142(6), 1643-1650.
[7] Singh, A., & Settleman, J. (2010). EMT, cancer stem cells, and drug resistance: An emerging axis of evil in the war on cancer. *Oncogene*, 29(34), 4741-4751.
[8] Frixa, T., Donzelli, S., & Blandino, G. (2017). Oncogenic microRNAs: Key players in malignant transformation. *Cancers*, 9(12), 153.
[9] Hosseini, M., & Meric-Bernstam, F. (2018). E-cadherin loss and EMT in breast cancer progression: Clinical implications for targeting the tumor microenvironment. *Nature Reviews Clinical Oncology*, 15(6), 367-381.
[10] Bremnes, R. M., Veve, R., Hirsch, F. R., & Franklin, W. A. (2002). The E-cadherin cell–cell adhesion complex and lung cancer invasion, metastasis, and prognosis. *Lung Cancer*, 36(2), 115-124.