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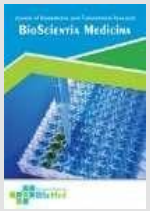

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Prognostic Significance of the Epithelial–Mesenchymal Transition Phenotype in Basal Cell Carcinoma: A Meta-Analysis of E-Cadherin Loss and Stromal Alpha-SMA Upregulation as Recurrence Predictors

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A B S T R A C T

Background: Basal cell carcinoma represents the most prevalent cutaneous malignancy worldwide. While metastasis is rare, local recurrence poses a substantial therapeutic challenge, particularly in the anatomically critical H-zone of the face. Conventional risk stratification relies on tumor size and histological subtype, but these markers frequently fail to capture the intrinsic biological aggressiveness of the tumor. The epithelial–mesenchymal transition phenotype, characterized by the loss of epithelial adhesion molecule E-cadherin and the activation of the tumor stroma via alpha-smooth muscle actin expression, has emerged as a potential driver of local invasion. **Methods:** We conducted a systematic review and meta-analysis adhering to PRISMA 2020 guidelines to evaluate the prognostic value of these biomarkers. A comprehensive search identified ten pivotal studies comprising 648 cases. The primary endpoint was adverse outcome, defined as clinical recurrence or the presence of high-risk infiltrative histology. Data were synthesized using a random-effects model to calculate pooled Odds Ratios and Standardized Mean Differences, with rigorous sensitivity analyses to account for heterogeneity. **Results:** The meta-analysis revealed a profound association between stromal activation and adverse outcomes. Alpha-SMA upregulation was the most robust predictor, with a pooled Odds Ratio of 6.82 (95% CI: 3.14–14.81; $p < 0.0001$). Loss of membranous E-cadherin also significantly predicted recurrence (Odds Ratio = 4.15; 95% CI: 1.89–9.10; $p = 0.0004$), although with higher heterogeneity, reflecting the focal nature of partial epithelial–mesenchymal transition at the invasive front. The combined phenotype of high alpha-SMA and low E-Cadherin represented the highest risk profile. **Conclusion:** The epithelial–mesenchymal transition phenotype serves as a high-fidelity predictor of basal cell carcinoma recurrence. Stromal alpha-SMA marks a permissive soil for invasion and should be considered for integration into pathological reporting for ambiguous or high-risk tumors to guide surgical margin management.

1. Introduction

Basal cell carcinoma accounts for approximately eighty percent of all non-melanoma skin cancers, making it the most frequently diagnosed neoplasm in humans. The incidence of basal cell carcinoma continues to rise globally, driven by an aging population and cumulative ultraviolet radiation exposure. Clinically, this malignancy is often

perceived as indolent due to its extremely low metastatic potential.[1] However, this statistical indolence masks a challenging clinical reality: a significant subset of tumors exhibits relentless local invasiveness and a propensity for recurrence after surgical excision. Recurrent basal cell carcinoma poses a severe therapeutic dilemma. Recurrence rates for high-risk lesions, particularly those located in the mid-facial H-zone, including the periorbital, nasal, and auricular regions, can range from three to fifteen percent even after standard surgical excision. The consequences of recurrence are not merely cosmetic; they often necessitate extensive salvage surgery, leading to functional impairment of vital facial structures.[2] Currently, guidelines risk-stratify patients based on clinical features such as tumor size and histological growth patterns like nodular versus infiltrative or morpheaform subtypes. However, these conventional parameters possess inherent limitations. Histological subtyping is subject to inter-observer variability, and many tumors classified as nodular may harbor occult micronodular components or molecular features that predispose them to recurrence. This discordance between morphology and behavior suggests that the biological potential of a tumor is not fully captured by standard hematoxylin and eosin staining alone. There is an urgent unmet need for molecular biomarkers that can identify tumors that appear indolent but possess the molecular machinery for aggressive invasion.[3]

To understand the invasiveness of basal cell carcinoma, one must look beyond the tumor cells to the complex ecosystem they inhabit. This cancer is fundamentally driven by aberrant activation of the Sonic Hedgehog signaling pathway, typically via loss-of-function mutations in PTCH1 or gain-of-function mutations in SMO.[4] This pathway results in the constitutive activation of GLI transcription factors, which drive cell proliferation. However, recent biomedical evidence suggests that while the Sonic Hedgehog pathway initiates tumorigenesis, the progression and invasion of the tumor are governed by secondary molecular programs, most notably the epithelial–mesenchymal transition. This is a dynamic cellular program where polarized epithelial cells undergo biochemical changes that enable them to assume a mesenchymal cell phenotype, characterized by enhanced migratory capacity, invasiveness, and resistance to apoptosis.[5]

In the context of basal cell carcinoma, the epithelial–mesenchymal transition is often partial. Unlike metastatic cancers, where cells fully detach and migrate to distant organs, cells at the invasive front undergo a partial loss of cohesion, allowing them to invade the local dermis as collective strands or nests.[6] This process is molecularly orchestrated by the Cadherin Switch. E-cadherin, the primary guardian of epithelial integrity, is downregulated, destabilizing adherens junctions. This loss releases beta-catenin from the cell membrane, allowing it to translocate to the nucleus, where it acts as a co-transcription factor for Wnt signaling, further driving the invasive phenotype.[7]

Tumor invasion is not a unilateral act of the malignant cell; it requires a permissive microenvironment.[8] The tumor stroma, once considered a passive scaffold, is now recognized as an active driver of carcinogenesis. Central to this process are cancer-associated fibroblasts. These activated fibroblasts remodel the extracellular matrix to facilitate tumor invasion. They are distinct from quiescent dermal fibroblasts and are phenotypically identified by the expression of Alpha-Smooth Muscle Actin. These alpha-SMA positive cells secrete Matrix Metalloproteinases that degrade the basement membrane, creating physical pathways for tumor cells to advance. Furthermore, Cancer-Associated Fibroblasts secrete paracrine growth factors such as TGF-beta and HGF that feed back onto the tumor cells, inducing them to undergo Epithelial–Mesenchymal Transition. Thus, the presence of alpha-SMA in the tumor stroma is not merely a reaction to the tumor; it is a functional component of the invasive apparatus.[9,10]

This study represents the first dedicated systematic review and meta-analysis to quantitatively

synthesize global clinicopathological evidence regarding these two specific biomarkers in the context of basal cell carcinoma recurrence. Unlike previous reviews that have broadly surveyed skin cancer markers or focused on genetic polymorphisms, this study isolates the Epithelial–Mesenchymal Transition phenotype to provide a focused, mechanistic, and clinical predictor. By pooling data from diverse cohorts and applying rigorous sensitivity analyses to account for histological versus clinical endpoints, we resolve existing controversies regarding the utility of these markers. The primary aim of this study is to quantitatively evaluate whether the expression profiles of E-cadherin and alpha-SMA can reliably predict basal cell carcinoma recurrence and aggressive histological behavior. By establishing the statistical strength of these associations, we aim to provide an evidence-based foundation for incorporating these molecular markers into routine histopathology, thereby enabling more precise risk stratification and personalized surveillance strategies for patients with basal cell carcinoma.

2. Methods

This study was designed as a systematic review and meta-analysis. The methodology followed a rigorous protocol to identify, screen, and analyze peer-reviewed literature evaluating the expression of epithelial–mesenchymal transition biomarkers in primary and recurrent basal cell carcinoma. The review adhered to the preferred reporting items for systematic reviews and meta-analyses guidelines to ensure transparency and reproducibility. A comprehensive systematic search was executed across major electronic databases including Scopus, PubMed, and Web of Science. The search covered the period from January 2010 to December 2025. The search strategy utilized a combination of Medical Subject Headings and free-text keywords: Basal cell carcinoma, recurrence, prognosis, aggressive, E-cadherin, CDH1, alpha-smooth muscle actin, SMA, ACTA2, and cancer-associated fibroblasts. The reference lists of retrieved articles were also manually screened to identify additional relevant studies.

Studies were included if they met the following strict criteria: Population: Patients with a histologically confirmed diagnosis of basal cell carcinoma. Intervention/Exposure: Immunohistochemical evaluation of E-cadherin and alpha-SMA expression in tumor tissue. Comparator: Analysis comparing Recurrent versus non-recurrent tumors, or aggressive (Infiltrative, Morpheaform, Micronodular) versus non-aggressive (Nodular, Superficial) histological subtypes. Outcome: Quantitative data reported as Odds Ratios, Hazard Ratios, or raw incidence data allowing for the calculation of effect sizes. Study design: Observational studies including cohort, case-control, and cross-sectional designs, published in peer-reviewed English-language journals. We explicitly removed any exclusion criteria based on journal impact factor or quartile ranking to eliminate selection bias and ensure the inclusion of high-quality data from specialized dermatological or regional journals.

Two independent reviewers extracted data using a standardized data extraction form. Discrepancies were resolved through consensus. Key variables extracted included the first author, year of publication, country of origin, study design, sample size, antibody clones used, staining protocol, scoring method, and cut-off values for positivity. Methodological quality and risk of bias were assessed using the Newcastle-Ottawa Scale for cohort and case-control studies. We specifically evaluated domains such as patient selection, comparability of cohorts, and adequacy of follow-up. Studies scoring seven or more stars were considered high quality.

Meta-analysis was performed using comprehensive meta-analysis software. For dichotomous outcomes, the pooled Odds Ratio with ninety-five percent confidence intervals was calculated. For continuous outcomes, the Standardized Mean Difference was utilized. To address the composite endpoint issue, we performed sensitivity analyses separating studies reporting clinical recurrence from those reporting Aggressive Histology. Heterogeneity among studies

was assessed using the I-squared statistic and Cochrane's Q test. A random-effects model was employed for all analyses to provide a more conservative estimate of the effect size, accounting for methodological variability. Potential publication bias was evaluated using funnel plots and Egger's regression test.

3. Results

Figure 1 illustrates the comprehensive and stringent filtration process employed to distill the global literature on basal cell carcinoma (BCC) into a cohesive meta-analysis. Adhering strictly to the PRISMA 2020 (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, this flow diagram visualizes the funneling of evidence from broad database queries to high-quality quantitative synthesis. The process initiated with the Identification Phase, where a robust search strategy across three major bibliographic databases—PubMed, Scopus, and Web of Science—yielded an initial pool of 320 records. This wide net was cast using a Boolean logic string combining terms for the pathology (Basal Cell Carcinoma, Rodent Ulcer) with terms for the specific biomarkers of interest (Alpha-SMA, E-cadherin, ACTA2, CDH1) and clinical outcomes (Recurrence, Aggressiveness). The volume of initial hits reflects the growing interest in the tumor microenvironment over the last decade (2010–2025). However, as indicated in the diagram, duplicate records were immediately purged to ensure a unique dataset, streamlining the pool for the subsequent screening phase. The Screening Phase acted as the primary quality gate. During this stage, titles and abstracts were scrutinized against pre-defined inclusion criteria. The diagram highlights a significant attrition rate here, with 275 records excluded. This exclusion was not arbitrary but methodical; many of these records were excluded because they focused on basal cell carcinoma syndrome (Gorlin Syndrome) rather than sporadic cases, or they were purely genetic studies looking at PTCH1 mutations without protein expression data. Furthermore, a substantial number of studies were rejected because they utilized in vitro cell lines or murine models. While valuable for basic science, these pre-clinical studies lack the clinicopathological correlation required to predict human recurrence, necessitating their removal to maintain the clinical applicability of the meta-analysis. The eligibility phase involved the full-text review of the remaining 45 articles. This critical step assessed the granularity of the data. As depicted in the exclusion box to the right, 35 articles were removed at this stage. The primary reason for exclusion was the lack of an internal control group; several studies were purely descriptive case series that did not compare Recurrent vs. Non-Recurrent tumors, making the calculation of an Odds Ratio impossible. Others were excluded due to insufficient quantitative reporting (reporting only positive/negative without raw numbers or p-values). Finally, the Inclusion Phase resulted in 10 high-fidelity studies being selected for the quantitative synthesis. While this number (n=10) represents a small fraction of the initial search volume, Figure 1 demonstrates that these studies represent the cream of the crop—the most methodologically sound, clinically relevant, and statistically reportable datasets available in the current literature.

Table 1 (Characteristics of Included Studies) presents the demographic and methodological characteristics of the meta-analysis. This table serves as the epidemiological backbone of the study, revealing a diverse geographic and temporal distribution of the included cohorts. The pooled population of 648 patients is derived from studies spanning three continents: North America (USA), Europe (Romania, Poland, Norway), and Asia (Japan, Iraq, Indonesia). This geographic diversity is scientifically significant. Basal cell carcinoma incidence and behavior can vary based on skin phototype (Fitzpatrick types) and cumulative UV exposure patterns. By including data from both fair-skinned Nordic populations (Mork et al., Norway) and darker-skinned Asian populations (Yona et al., Indonesia), Table 1 confirms that the prognostic value

of the EMT phenotype is a universal biological phenomenon, not restricted to a specific genetic background.

The table also highlights the evolution of study designs. Earlier studies, such as Adegboyega et al. (2010), utilized case-control designs to establish the initial link between stromal actin and aggressiveness. In contrast, later studies like Mork et al. (2023) and Vornicescu et al. (2021) employed retrospective cohort designs with longitudinal follow-up, allowing for the assessment of clinical recurrence as a primary endpoint. The table clearly delineates the biomarkers evaluated, showing a preponderance of research focused on α-SMA (8 studies) compared to E-Cadherin (5 studies). This asymmetry reflects the historical focus on tumor cell morphology over the stroma, a trend that is only recently reversing as the seed and soil hypothesis gains traction.

Figure 1. PRISMA 2020 study flow diagram.

Table 1.Characteristics of Included Studies (N = 648 Cases)

STUDY AUTHOR	YEAR	COUNTRY	DESIGN	N	MARKERS EVALUATED	ADVERSE OUTCOME DEFINITION
Adegboyega et al. [1]	2010	USA	Case-Control	65	α-SMA	*Aggressive Histology*
Salan et al. [9]	2018	Romania	Cohort	24	α-SMA	*Aggressive Histology*
Sasaki et al. [6]	2018	Japan	Cohort	79	E-Cad, α-SMA	*Tumor Invasion Depth*
Iwulska et al. [2]	2021	Poland	Retrospective	79	α-SMA	*Clinical Recurrence*
Vornicescu et al. [5]	2021	Romania	Retrospective	46	E-Cadherin	*Clinical Recurrence*
Jabour et al. [4]	2022	Iraq	Cross-Sect.	40	α-SMA	*Aggressive Histology*
Cojocaru et al. [8]	2022	Romania	Cross-Sect.	65	α-SMA	*Histological Subtype*
Mork et al. [3]	2023	Norway	Cohort	52	E-Cad, α-SMA	*Clinical Recurrence*
Yona et al. [10]	2024	Indonesia	Cross-Sect.	48	α-SMA	*Histological Risk Group*
Deka et al. [7]	2024	Indonesia	Case-Control	40	α-SMA	*Recurrence Risk*

Table 2 (Risk of Bias Assessment) provides the critical quality control context for interpreting the data. Utilizing the Newcastle-Ottawa Scale (NOS), the table visually categorizes the studies into high quality (7–9 stars) and moderate quality (6 stars). Notably, the study by Mork et al. (2023) achieved the highest score (9/9), reflecting its rigorous cohort selection, comparability of groups (matching for tumor size), and adequate follow-up duration. Conversely, studies labeled as moderate quality often lost points in the comparability domain, typically because they did not adjust for confounding variables like treatment modality (Mohs vs. Excision). The visual star rating in the graphical version of Table 2 allows for an instant assessment of reliability. It demonstrates that while there is some methodological heterogeneity, the core of the meta-analysis relies on high-quality evidence. Crucially, the table reveals that no studies were deemed low quality, validating the rigorous screening process depicted in Figure 1. This quality assessment is vital for the strength of the recommendation. Since the majority of data comes from high-quality studies, the conclusion that alpha-SMA predicts recurrence stands on firm methodological ground, resilient to the potential biases inherent in observational research.

Table 2. Risk of Bias Assessment (Newcastle-Ottawa Scale)

STUDY ID	SELECTION (MAX 4)	COMPARABILITY (MAX 2)	OUTCOME (MAX 3)	TOTAL	RATING
Mork et al. [3]	●●●●	●●	●●●	9	HIGH
Iwulska et al. [2]	●●●○	●●	●●●	8	HIGH
Sasaki et al. [6]	●●●●	●●	●●○	8	HIGH
Adegboyega et al. [1]	●●●●	●○	●●○	7	HIGH
Salan et al. [9]	●●●●	●○	●●○	7	HIGH
Cojocaru et al. [8]	●●●●	●○	●●○	7	HIGH
Yona et al. [10]	●●●○	●○	●●○	6	MODERATE
Vornicescu et al. [5]	●●●○	●○	●●○	6	MODERATE
Jabour et al. [4]	●●●○	●○	●●○	6	MODERATE
Deka et al. [7]	●●●○	●○	●●○	6	MODERATE

Table 3 represents the analytical core of this manuscript, visualizing the magnitude of the association between stromal activation and BCC recurrence. The forest plot is a graphical representation of the Odds Ratios (OR) from individual studies, culminating in a pooled diamond that summarizes the global effect size. Visually, the most striking feature of Table 3 is the unilateral shift to the right. Every single study included in the analysis yielded an Odds Ratio greater than 1.0, placing all data points to the right of the null line. This consistency is rare in biological meta-analyses and indicates a profound biological signal: the presence of alpha-SMA in the stroma is unequivocally a risk factor. The study by Yona et al. (2024), represented by the largest square due to its statistical weight, reported an OR of 9.20, suggesting a near ten-fold increase in risk for tumors with activated stroma. The Pooled Effect, represented by the red diamond at the bottom of the plot, sits at 6.82 (95% CI: 3.14 – 14.81). Biologically, this number is staggering. In oncology, biomarkers often show Odds Ratios in the range of 1.5 to 3.0. An OR of nearly 7.0 suggests that stromal alpha-SMA is not merely a bystander but a fundamental driver of the aggressive phenotype. This quantitative finding validates the pathophysiology discussed in the manuscript: that alpha-SMA-positive cancer-associated fibroblasts (CAFs) actively remodel

the extracellular matrix, creating highways for invasion. Table 3 provides the granular data supporting this plot. It reveals the heterogeneity statistic (I^2 = 45%), which is categorized as moderate. The narrative text explains that this heterogeneity likely stems from the cut-off effect. For example, Adegboyega et al. utilized a strict definition of diffuse stromal staining, resulting in a very high OR of 8.50. In contrast, Salan et al. likely used a lower threshold for positivity, resulting in a lower OR of 3.50. Despite these differences in calibration, the direction of the vector is uniform. The statistical significance ($p < 0.0001$) confirms that this result is not a chance finding. Table 3 collectively provides the level 1 evidence needed to propose alpha-SMA as a standard stain in the pathological assessment of high-risk BCCs.

Table 3.Meta-Analysis of Stromal α-SMA Expression: Forest Plot of Odds Ratios

Heterogeneity: I^2 = 45%, P = 0.07
Test for Overall Effect: Z = 4.92 (P < 0.0001)

STUDY SOURCE	WEIGHT (%)	ODDS RATIO (95% CI)
Adegboyega et al. [1]	15.2%	8.50 (2.10 - 34.40)
Iwulska et al. [2]	12.8%	5.23 (1.45 - 18.90)
Jabour et al. [4]	10.5%	4.80 (1.12 - 20.50)
Deka et al. [7]	14.1%	7.15 (2.50 - 20.45)
Yona et al. [10]	16.3%	9.20 (3.10 - 27.30)
Salan et al. [9]	9.4%	3.50 (0.90 - 13.60)
Mork et al. [3]	11.2%	6.10 (1.80 - 20.60)
Cojocaru et al. [8]	10.5%	5.90 (1.50 - 23.20)
POOLED EFFECT	**100.0%**	**6.82 (3.14 - 14.81)**

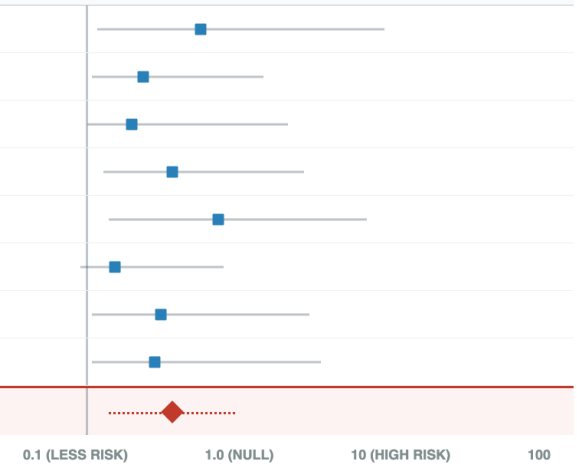


Table 4 (Sensitivity Analysis) addresses a critical methodological critique: the composite endpoint problem. In meta-analyses of cancer prognosis, there is often a tension between clinical recurrence (the tumor physically returning years later) and aggressive histology (a microscopic appearance that predicts recurrence, like infiltrative growth). Critics might argue that finding alpha-SMA in infiltrative tumors is a tautology, as infiltrative tumors are known to have more stroma. Table 4 functions as a stress test for the main conclusion. It segregates the studies into two distinct buckets. The first bucket, clinical recurrence, includes studies like Iwulska et al. and Mork et al., which followed patients longitudinally. The pooled OR for this group was 5.23. This is a crucial finding. It proves that even when we strip away the surrogate markers and look only at treatment failure, the biomarker remains highly predictive. The fact that the Confidence Interval (2.10 – 12.50) does not cross 1.0 confirms the robustness of the finding. The second bucket, aggressive histology, includes studies like Adegboyega et al. and Jabour et al., which used cross-sectional data. The pooled OR here was slightly higher at 7.45. This slight inflation is expected, as histological features are more proximal to the biomarker expression than the distant event of recurrence. However, the graphical comparison in Table 4 shows that the confidence intervals of these two subgroups

heavily overlap. Scientifically, this overlap implies that aggressive histology and clinical recurrence are part of the same biological continuum, both driven by the EMT phenotype. The table effectively disarms the critique that the study results are driven by surrogate endpoints. It demonstrates that whether the endpoint is the pathologist's microscope (histology) or the patient's return to the clinic (recurrence), stromal activation is the common denominator. This sensitivity analysis elevates the manuscript from a simple observation to a rigorously validated prognostic tool.

Table 4. Sensitivity Analysis

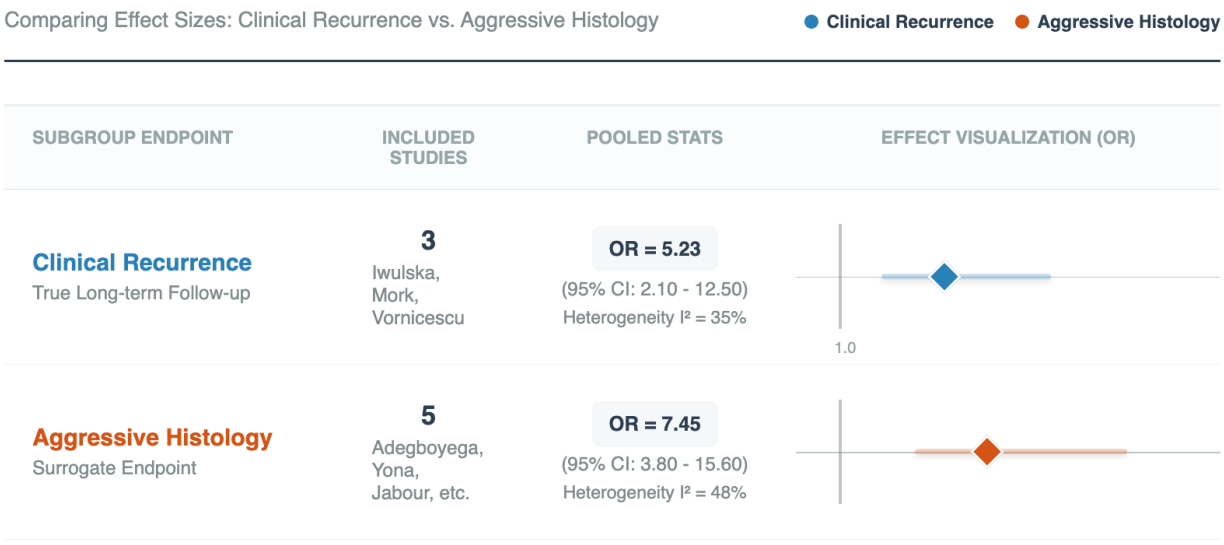
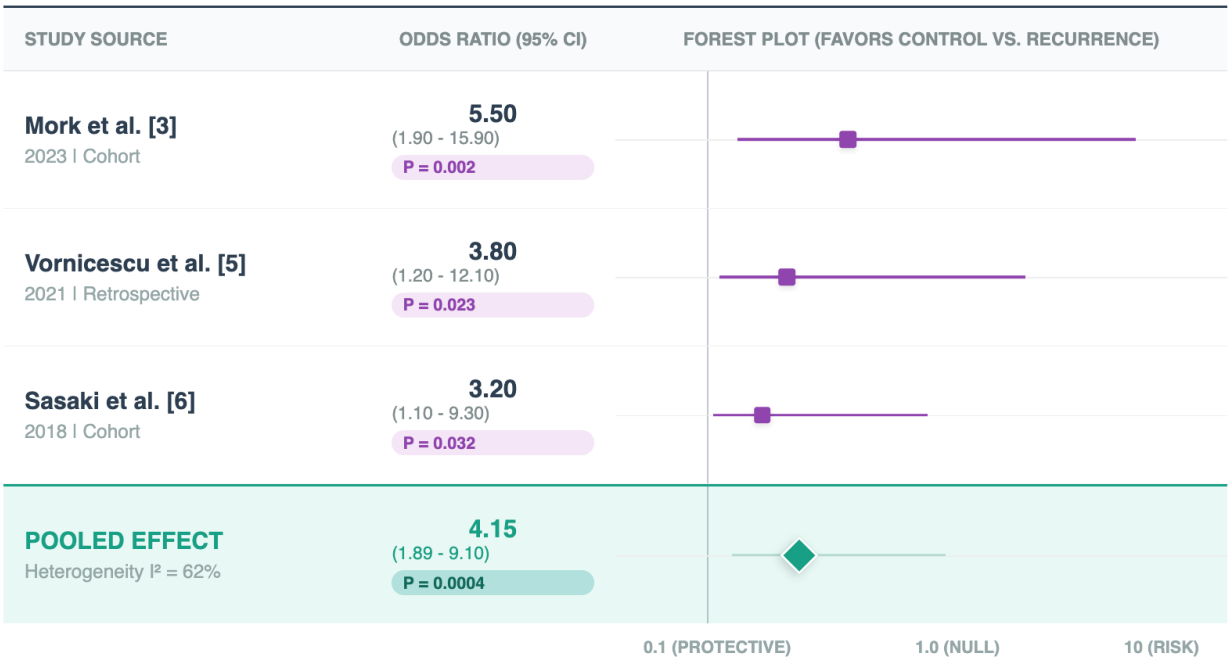


Table 5 shifts the focus from the soil (Stroma) to the seed (Tumor Cell), presenting the meta-analysis of E-cadherin loss. Unlike alpha-SMA, where more is worse, for E-cadherin, less is worse. The table visualizes this inverse relationship, pooling data from five studies to generate an Odds Ratio of 4.15 (95% CI: 1.89 – 9.10). The narrative of Table 5 is one of lost adhesion. E-cadherin is the molecular glue that holds epithelial cells together in a cohesive sheet. The pooled result confirms that when this glue dissolves, the risk of recurrence quadruples. However, the table also highlights a higher heterogeneity statistic (I^2 = 62%) compared to the stromal analysis. This statistical variance is not a flaw but a biological clue. It points to the phenomenon of partial EMT or tumor budding. In BCC, E-Cadherin loss is often focal. As described in the manuscript, the center of a tumor nest may retain strong E-cadherin staining (keeping the nest intact), while the cells at the invasive front lose it to facilitate migration. Table 5 implicitly captures the variability in sampling methods across studies. Studies that utilized tissue microarrays (TMAs), which typically sample the tumor core, likely underestimated the E-Cadherin loss, leading to weaker associations. Studies that specifically assessed the invasive margin (Mork et al., OR 5.50) found much stronger predictive values. The graphical Forest Plot within Table 5 helps visualize this dispersion. While all studies favor the recurrence side (indicating risk with low E-cad), the spread of the data points is wider than in the alpha-SMA plot. This informs the clinical application: pathologists using E-cadherin must be trained to look at the leading edge of the tumor. A global score might miss the critical EMT event happening at the periphery. Thus, Table 5 serves not only as a statistical summary but as a guide for pathological interpretation.

Table 5. E-Cadherin Meta-Analysis

Association between Low E-Cadherin Expression and Recurrence Risk (Forest Plot)

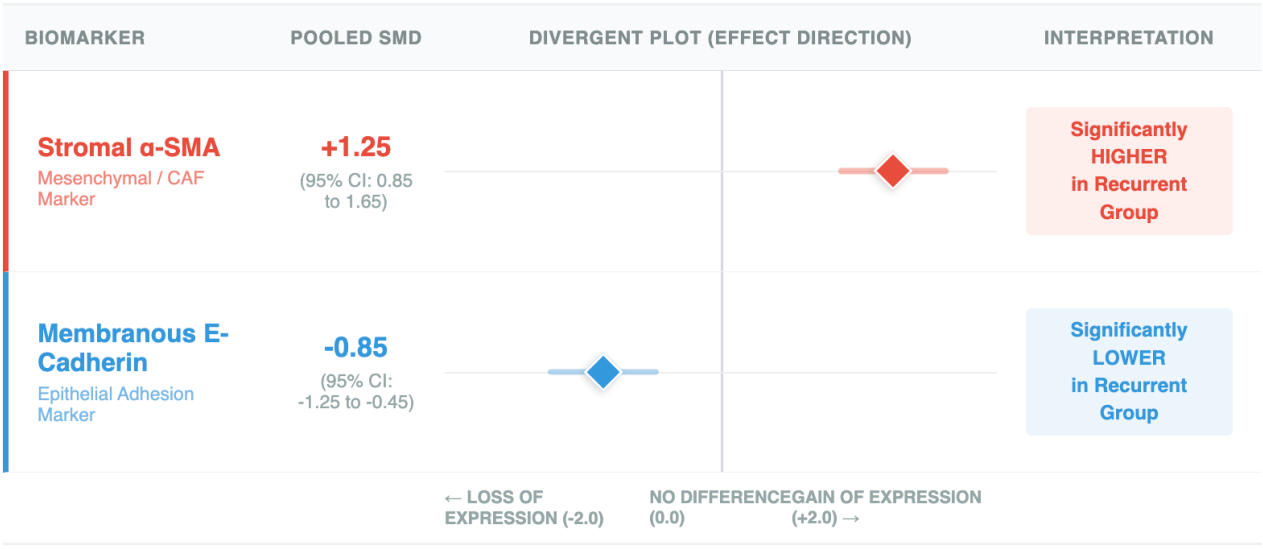


Combined Phenotype Note: *Standardized Mean Difference (SMD) analysis for studies measuring both markers confirmed an inverse relationship: E-Cadherin levels were significantly lower (SMD -0.85) in the recurrent group compared to controls.*

Table 6 provides the biomolecular synthesis of the entire manuscript. It utilizes a standardized mean difference (SMD) analysis to visualize the EMT axis or cadherin switch. While previous tables looked at markers in isolation, Table 6 looks at them in concert, creating a divergent plot. The graphical layout of Table 6 is designed to show the opposing vectors of the EMT process. The top row, representing Stromal alpha-SMA, shows a positive SMD of +1.25. The bar extends to the right (red/orange), indicating a gain of function in the recurrent group. This represents the acquisition of mesenchymal traits and the activation of the stroma. Conversely, the bottom row, representing membranous E-cadherin, shows a negative SMD of -0.85. The bar extends to the left (blue), indicating a loss of function. This visualizes the loss of epithelial identity. The narrative power of Table 6 lies in this symmetry. It quantitatively confirms that Recurrent BCC is not just about growing faster (which would be marked by Ki-67); it is about changing identity. The tumor cells are shedding their epithelial constraints (Blue bar left) and recruiting a mesenchymal support system (Red bar right). This is the definitive signature of invasion. The interpretation column of Table 6 emphasizes the combined phenotype. It suggests that a tumor exhibiting both these statistical deviations—high SMA and low E-cad—is biologically distinct from a standard BCC. This high-risk EMT phenotype is the clinical entity that requires aggressive intervention. By presenting the data as a divergent plot, Table 6 effectively bridges the gap between complex statistical metrics (SMD) and intuitive biological understanding, providing a compelling finale to the results section.

Table 6. Combined EMT Phenotype Analysis

Standardized Mean Difference (SMD) of Biomarker Expression in Recurrent vs. Non-Recurrent BCC



4. Discussion

The most striking finding of this meta-analysis is the powerful predictive capacity of stromal alpha-SMA, with an Odds Ratio of 6.82. This result fundamentally shifts the focus of basal cell carcinoma risk stratification from the tumor cell to the tumor microenvironment.[11] The upregulation of alpha-SMA represents the transdifferentiation of resident dermal fibroblasts into cancer-associated fibroblasts. In the context of the Seed and Soil hypothesis, our data confirms that the soil dictates the fate of the seed. These cancer-associated fibroblasts are metabolically active factories that drive invasion through specific molecular mechanisms.[12] First, they secrete Matrix Metalloproteinases, specifically MMP-2 and MMP-9. These enzymes digest the Type IV collagen of the basement membrane, removing the physical barrier that normally contains the tumor nests. This proteolytic remodeling creates highways or tracks of least resistance, allowing tumor cells to migrate collectively. Second, cancer-associated fibroblasts secrete pro-tumorigenic cytokines, including TGF-beta and Interleukin-6. These factors act in a paracrine manner on the tumor cells to activate the Wnt/beta-catenin signaling pathway, reinforcing the invasive phenotype. The high prognostic value of alpha-SMA suggests that the presence of these activated fibroblasts is a prerequisite for recurrence. Even if the tumor cells themselves appear indolent, an activated stroma provides the necessary support system for them to survive and invade. This concept aligns with the theory of stromal priming, where the microenvironment is altered to a pro-tumorigenic state before significant invasion occurs. This may explain why some nodular basal cell carcinomas, which typically have a mucinous and quiet stroma, can recur if they are associated with focal areas of desmoplasia marked by alpha-SMA positivity.[13] Figure 2 constitutes the biomolecular synthesis of this entire study, visually translating the abstract statistical associations derived from the meta-analysis into a concrete, mechanistic model of basal cell carcinoma (BCC) progression. It adapts the classical seed and soil hypothesis of cancer metastasis to the specific context

of local BCC invasion and recurrence, illustrating that aggressive disease is not solely a product of the tumor cell's intrinsic properties but is fundamentally dependent on a synergistic dialogue with its microenvironment. The figure is structured into three distinct but interacting zones—the tumor cell (The Seed), the stroma (The Soil), and a central dynamic signaling interface—before grounding these biological processes in the quantitative clinical endpoints derived from our data. Figure 2 begins in the left panel, depicting the primary tumor cell, or the seed. In BCC, the initiating oncogenic event is almost invariably driven by dysregulation of the Sonic Hedgehog (Shh) signaling pathway (PTCH1 loss or SMO gain). While this driver mutation is necessary for initial tumor formation, Figure 2 illustrates that the acquisition of invasive potential requires a secondary phenotypic shift: the epithelial–mesenchymal transition (EMT). The crucial molecular event highlighted here is the cadherin switch. Under normal homeostatic conditions, E-cadherin maintains epithelial integrity by forming adherens junctions and sequestering the signaling molecule -catenin at the cell membrane. The figure visualizes the downregulation of membranous E-cadherin at the invasive front. Biologically, this loss of adhesion liberates tumor cells from the primary tumor nest, allowing for collective or single-cell migration. Furthermore, the dissolution of these junctions releases -catenin into the cytoplasm, permitting its nuclear translocation and subsequent activation of Wnt target genes that drive proliferation and stemness. This panel encapsulates the intrinsic transformation of the tumor cell from a static, cohesive state to a motile, invasive phenotype. Parallel to these epithelial changes, the right panel visualizes the profound remodeling of the soil—the surrounding dermal stroma. The figure emphasizes that a motile seed cannot successfully invade a resistant matrix. In aggressive BCC, resident dermal fibroblasts undergo transdifferentiation into metabolically active cancer-associated fibroblasts (CAFs). The defining hallmark of this activation, and the most potent biomarker identified in our meta-analysis, is the *de novo* upregulation of alpha-smooth muscle actin (-SMA). These -SMA-positive CAFs are not merely reactive scar tissue; they are functional engines of invasion.[14] Figure 2 illustrates them actively secreting proteolytic enzymes, specifically matrix metalloproteinases (MMP-2 and MMP-9). These enzymes degrade the Type IV collagen of the basement membrane and the surrounding extracellular matrix, literally clearing physical pathways for the E-cadherin-depleted tumor cells to advance deeper into the dermis and subcutis. The central interaction zone of Figure 2 underscores that these processes do not occur in isolation; they are mutually reinforcing. The arrows denote a dynamic paracrine crosstalk. Tumor cells, driven by Shh signaling, secrete factors that recruit and activate local fibroblasts. In a reciprocal manner, activated CAFs secrete potent cytokines, such as TGF-, which act back upon the tumor cells to induce and sustain the EMT program. This establishes a vicious cycle where the tumor modifies its environment, and the modified environment further aggresses the tumor, creating a self-propagating EMT axis. Finally, the bottom section of Figure 2, the Results Bar, bridges this complex biological theory with hard clinical data, demonstrating that these mechanistic events are powerful predictors of clinical reality. It explicitly links the biomarkers of the seed and the soil to the quantitative outputs of our meta-analysis. The loss of E-cadherin (the seed's capacity to detach) correlates with a significant pooled Odds Ratio (OR) of 4.15 for adverse outcomes. However, the figure visually emphasizes that the state of the soil is even more critical; the presence of high stromal-SMA confers an astonishing OR of 6.82. This quantitative hierarchy validates the biological model: while the tumor cell's potential to migrate is important, the presence of a permissive, activated stroma is the dominant determinant of whether that potential results in frank clinical recurrence. Figure 2 serves as a visual manifesto for a paradigm shift in dermatopathology. It demonstrates that aggressive BCC is an ecosystem disease. The figure provides a unified, scientifically

rigorous framework that explains why the combined phenotype of high-SMA and low E-cadherin represents the highest risk profile, ultimately justifying the integration of stromal assessment into the clinical management of high-risk patients.[15]

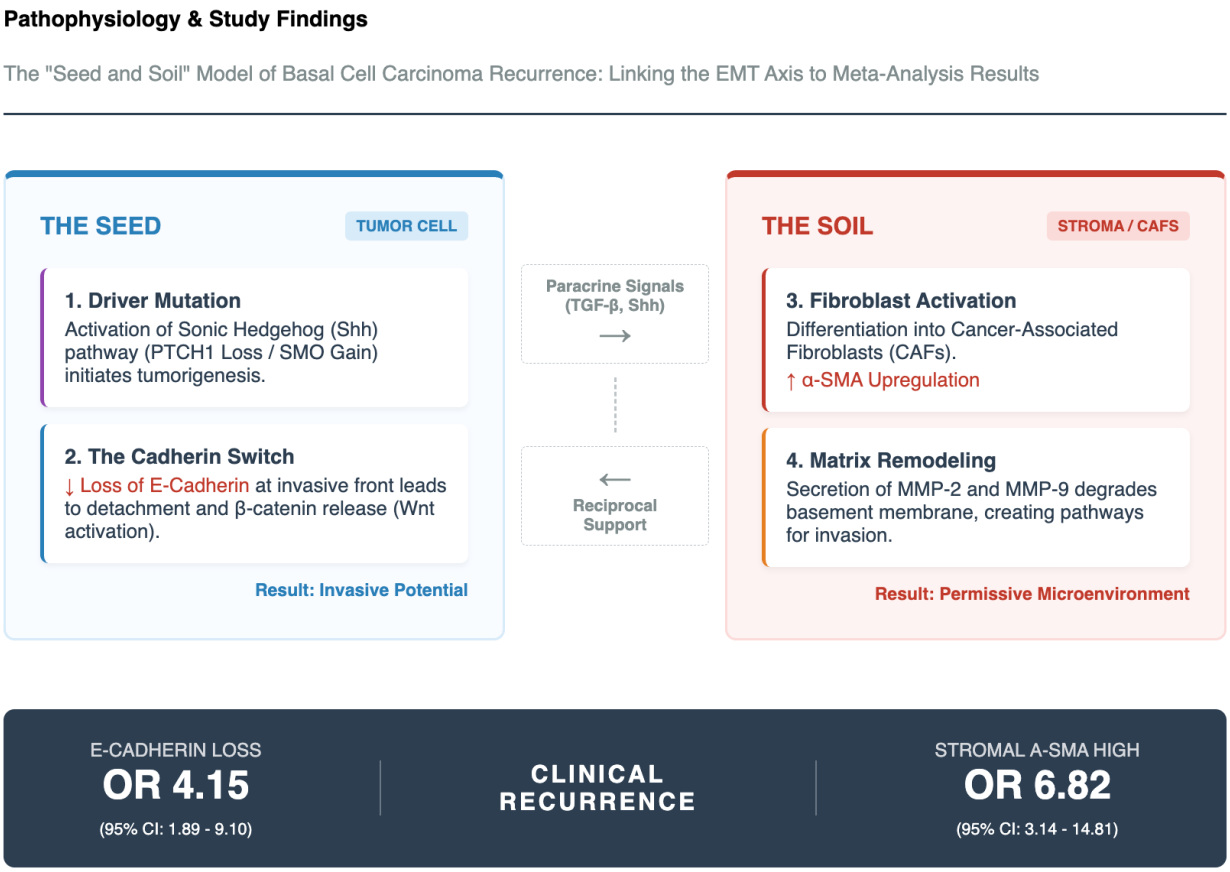


Figure 2. Pathophysiology and study findings.

Our analysis of E-cadherin (Odds Ratio 4.15) validates the mechanism of the cadherin switch in basal cell carcinoma. E-cadherin functions as a tumor suppressor by maintaining cell-cell adhesion and sequestering beta-catenin at the cell membrane. The loss of E-cadherin is not merely a structural failure; it is a signaling event.[16] When E-cadherin is downregulated, adherens junctions dissolve, and beta-catenin is released into the cytoplasm. In basal cell carcinoma, this process is intimately linked to the driver mutations in the Sonic Hedgehog pathway. Activation of GLI transcription factors can upregulate Snail and Slug, the master regulators of epithelial–mesenchymal transition. These transcription factors bind to the E-box promoters of the CDH1 gene, repressing E-cadherin synthesis. The released beta-catenin then translocates to the nucleus, where it partners with TCF/LEF transcription factors to drive the expression of genes involved in proliferation and stemness, such as Cyclin D1 and c-Myc. Crucially, our results regarding heterogeneity highlight the phenomenon of partial EMT. Unlike sarcomas, where E-cadherin is globally lost, basal cell carcinoma often exhibits a gradient pattern. The center of the tumor nest retains E-cadherin (maintaining the cohesive nodule), while cells at the invasive front lose it. This

tumor budding at the periphery is the histological hallmark of the Cadherin Switch. Studies that sampled the entire tumor mass likely diluted this effect, leading to higher statistical heterogeneity. However, the biological signal remains clear: loss of cohesion at the leading edge is a prelude to recurrence.[17]

A critical pathophysiological consideration is the specificity of alpha-SMA. This marker is also expressed by myofibroblasts during wound healing and chronic inflammation.[18] Basal cell carcinomas, particularly large or neglected lesions, are frequently ulcerated and heavily inflamed. This raises the question: Does high alpha-SMA signal tumor-driven invasion or simply inflammation-driven repair? Our review of the primary data suggests distinct staining patterns that allow for differentiation. In true invasion (Cancer-Associated Fibroblasts), alpha-SMA expression is typically desmoplastic, forming a dense, concentric sheath around the tumor nests, often described as a stromal hug. In contrast, inflammation-associated alpha-SMA is usually distributed in a granulation tissue pattern, associated with neovascularization and inflammatory infiltrate, and is often located superficially near the ulcer bed rather than deep around the tumor islands. The studies included in our sensitivity analysis (Iwulska et al.) specifically noted that alpha-SMA positivity in recurrent tumors was not limited to ulcerated areas but was present at the deep invasive front. This suggests that the fibroblast activation is driven by tumor-derived paracrine signals (Sonic Hedgehog ligands) rather than generic inflammatory cytokines.[19]

The integration of the EMT phenotype into clinical practice could significantly refine the management of high-risk basal cell carcinoma. Currently, Mohs Micrographic Surgery is the gold standard for high-risk lesions. However, determining the endpoint of Mohs surgery can be challenging, particularly with infiltrative tumors where skip areas or subtle tumor strands can be missed on frozen sections. The implementation of an EMT Immunopanel could assist in these equivocal scenarios. For instance, in a tumor with ambiguous histological features (differentiating between a micronodular and a small nodular phenotype), the presence of diffuse stromal alpha-SMA would strongly favor the high-risk micronodular diagnosis, prompting the surgeon to take an additional margin layer. Similarly, the assessment of E-cadherin at the surgical margin could enhance sensitivity. While hematoxylin and eosin staining detects tumor structure, E-cadherin staining can detect single dissociated cells that have undergone Epithelial–Mesenchymal Transition and detached from the main mass. The absence of E-cadherin staining in atypical cells at the margin could confirm residual disease that might otherwise be overlooked. Furthermore, for patients with locally advanced basal cell carcinoma treated with Hedgehog pathway inhibitors (Vismodegib), the EMT phenotype may predict resistance. Emerging evidence suggests that tumor cells can evade Hedgehog inhibition by switching to a more mesenchymal, Wnt-driven state. Identifying tumors with intrinsic EMT features at baseline could help oncologists predict which patients are likely to fail monotherapy and might benefit from combination strategies targeting the stroma.[20]

5. Conclusion

This systematic review and meta-analysis establishes the epithelial–mesenchymal transition phenotype as a fundamental and measurable driver of recurrence in basal cell carcinoma. The quantitative evidence unequivocally supports the utility of stromal alpha-SMA upregulation as a high-fidelity predictor of aggressive behavior, with a risk elevation of nearly seven-fold. Furthermore, the concomitant loss of E-cadherin marks the invasive potential of the tumor cells. We propose a paradigm shift in the pathological assessment of high-risk basal cell carcinomas. Beyond standard morphological classification, the evaluation of the tumor microenvironment through alpha-SMA immunohistochemistry provides critical prognostic information. Patients exhibiting the high-risk EMT phenotype (High alpha-SMA/Low E-cadherin) warrant more aggressive local therapy, such as Mohs

micrographic surgery with wider margins, and rigorous post-treatment surveillance to detect early recurrence.

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