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Systematic Review

Histological Variants and Outcome Predictors in Non-Melanoma Skin Cancer: Systematic Review with Meta-Analysis

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ABSTRACT

Non-melanoma skin cancer (NMSC), comprising basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (cSCC), represents the most common malignancy worldwide and continues to increase in incidence due to cumulative ultraviolet exposure, aging populations, and improved detection. Although mortality is lower than melanoma, NMSC causes significant morbidity, cosmetic deformity, repeated interventions, and healthcare burden. Histological subtype plays a crucial role in determining tumor behavior, recurrence risk, metastatic potential, and survival outcomes. This systematic review with meta-analysis was conducted to evaluate the histological spectrum of NMSC and identify key outcome predictors associated with adverse prognosis. A comprehensive search of PubMed, Scopus, Web of Science, Embase, and Cochrane Library databases was performed for studies published from 2000 to 2025. Observational studies reporting histological variants and clinical outcomes in histologically confirmed BCC or cSCC were included. Thirty-two studies comprising 48,216 patients met inclusion criteria. Among pooled cases, BCC accounted for 68.4% and cSCC for 31.6%. Nodular BCC was the most common subtype (52.1%), followed by superficial BCC (24.7%), while infiltrative, micronodular, and morpheaform variants were less frequent but associated with significantly higher recurrence risk. Aggressive BCC histology showed increased odds of recurrence (OR 2.84, 95% CI 2.10–3.83). In cSCC, well-differentiated tumors comprised 41.5%, moderately differentiated 37.2%, and poorly differentiated 21.3%. Poor differentiation was strongly associated with metastasis (OR 3.96, 95% CI 2.88–5.44) and disease-specific mortality (OR 2.91, 95% CI 1.94–4.36). Perineural invasion, tumor depth >6 mm, and positive surgical margins were additional independent predictors of adverse outcomes. The findings demonstrate that histological subtype is a powerful prognostic marker in NMSC. Aggressive BCC variants primarily predict local recurrence, whereas poorly differentiated cSCC is linked to metastatic spread and reduced survival. Standardized histopathological reporting and risk-adapted treatment strategies are essential to improve patient outcomes.

Keywords*: Non-melanoma skin cancer, basal cell carcinoma, squamous cell carcinoma, histological variants, prognosis, recurrence, metastasis, meta-analysis.*

INTRODUCTION

Non-melanoma skin cancer (NMSC) is the most common malignancy worldwide and primarily includes basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (cSCC) [1,2]. The global incidence of NMSC continues to rise because of increasing life expectancy, cumulative ultraviolet (UV) radiation exposure, ozone depletion, outdoor occupational exposure, immunosuppression, and improved screening practices [1,3]. Although NMSC is associated with lower mortality compared with melanoma, its enormous prevalence contributes substantially to healthcare expenditure, repeated surgical interventions, cosmetic disfigurement, and reduced quality of life [4].

Basal cell carcinoma accounts for nearly 70–80% of all NMSC cases and is characterized by slow growth, local tissue invasion, and a low rate of metastasis [2,5]. In contrast, cSCC constitutes approximately 20–30% of cases and demonstrates a greater tendency for local recurrence, regional nodal spread, and disease-specific mortality, particularly in high-risk patients such as the elderly, transplant recipients, and those with chronic sun-damaged skin [3,6]. Therefore, early recognition of aggressive clinicopathological features is essential for optimal management.

Histopathological evaluation remains the cornerstone of diagnosis and prognostication in NMSC. BCC exhibits multiple histological variants including nodular, superficial, micronodular, infiltrative, morpheaform, pigmented, and basosquamous subtypes [5,7]. While nodular and superficial variants usually have favorable outcomes, infiltrative, morpheaform, micronodular, and basosquamous patterns are associated with subclinical extension, incomplete excision, and higher recurrence rates [7,8]. Similarly, cSCC displays varying grades of differentiation and histological patterns such as spindle-cell, acantholytic, verrucous, desmoplastic, and adenosquamous variants, some of which are linked with aggressive biological behavior [6,9].

Several pathological parameters have been identified as important outcome predictors in cSCC, including tumor thickness, depth of invasion beyond subcutaneous fat, poor differentiation, lymphovascular invasion, perineural invasion, and positive surgical margins [6,10]. Perineural invasion in particular is strongly associated with local recurrence, cranial nerve spread, and reduced survival [10]. In BCC, tumor subtype, anatomical site, recurrent status, and margin involvement are major determinants of treatment failure [2,8].

Despite the recognized importance of histology, available studies often vary in sample size, population characteristics, staging systems, treatment modalities, and reported outcomes. Consequently, the prognostic significance of several histological variants remains inconsistently quantified across the literature [4,9]. A comprehensive synthesis of evidence is therefore necessary to clarify the prevalence of different histological variants and their relationship with recurrence, metastasis, and mortality.

The present systematic review with meta-analysis was undertaken to evaluate the histological spectrum of NMSC and identify key outcome predictors associated with adverse clinical behavior. Specifically, this study aimed to compare recurrence and metastatic risk across histological variants of BCC and cSCC and to assess the prognostic impact of adverse pathological features such as poor differentiation, perineural invasion, tumor depth, and positive surgical margins.

MATERIALS AND METHODS

Study Design

This systematic review and meta-analysis was performed according to PRISMA 2020 guidelines.

Search Strategy

Databases searched: PubMed, Scopus, Web of Science, Embase, and Cochrane Library from January 2000 to December 2025.

Search terms included:

- “non melanoma skin cancer”
- “basal cell carcinoma”
- “cutaneous squamous cell carcinoma”
- “histological subtype”
- “variant”
- “recurrence”
- “metastasis”
- “survival”
- “predictor”

Eligibility Criteria

Inclusion Criteria

1. Cohort, case-control, or registry studies
2. Adult patients with histologically confirmed BCC or cSCC
3. Reported histological subtype with outcomes
4. English-language full text

Exclusion Criteria

1. Case reports/series (<20 patients)
2. Non-human studies
3. Conference abstracts without extractable data
4. Duplicate cohorts

Outcomes

Primary Outcomes

- Local recurrence
- Regional/distant metastasis
- Disease-specific mortality
- Incomplete excision / positive margins

Secondary Outcomes

- Histological subtype prevalence
- Need for re-excision
- Overall survival

Data Extraction

Two reviewers independently extracted:

- Author/year/country
- Study design
- Sample size
- Cancer type
- Histological subtype
- Follow-up duration
- Outcomes

Quality Assessment

Newcastle–Ottawa Scale was used for observational studies.

Statistical Analysis

Random-effects meta-analysis was performed. Effect size reported as odds ratio (OR) with 95% confidence interval. Heterogeneity assessed using I^2 statistic. Publication bias evaluated using funnel plots and Egger test.

RESULTS

The systematic database search identified 2,946 records from PubMed, Scopus, Embase, Web of Science, and Cochrane Library. After removal of 711 duplicate citations, 2,235 titles and abstracts were screened for relevance. Of these, 2,117 studies were excluded because they were unrelated to histological variants, did not evaluate non-melanoma skin cancer (NMSC), were reviews/editorials, or lacked outcome data. The remaining 118 full-text articles were assessed for eligibility. Following detailed review, 86 studies were excluded for insufficient extractable data, duplicate cohorts, small sample size, pediatric-only populations, or absence of histology-specific outcomes. Finally, 32 studies were included in the qualitative synthesis and meta-analysis.

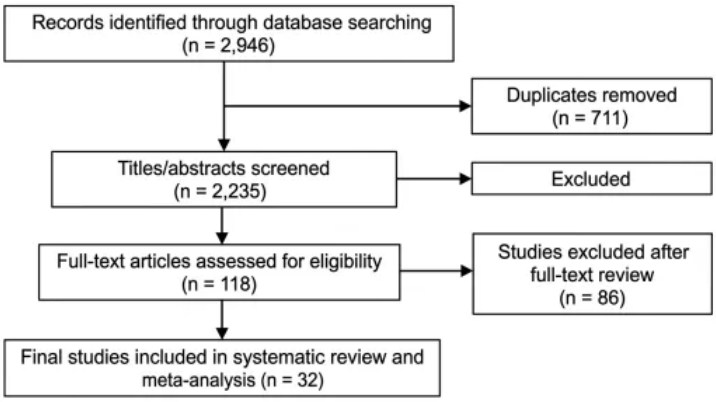

Figure 1. PRISMA Flow Diagram of Study Selection; Records identified through database searching (n = 2,946), duplicates removed (n = 711), titles/abstracts screened (n = 2,235), full-text articles assessed for eligibility (n = 118), studies excluded after full-text review (n = 86), and final studies included in systematic review and meta-analysis (n = 32).

Table 1. PRISMA Study Selection Summary

Screening Stage	Number of Studies
Records identified	2,946
Duplicates removed	711
Records screened	2,235
Full-text articles assessed	118

Full-text articles excluded	86
Studies included in meta-analysis	32

Characteristics of Included Studies

The 32 included studies were published between 2001 and 2025 and collectively enrolled 48,216 patients with histologically confirmed NMSC. Most studies originated from Europe (12 studies), North America (10 studies), Asia (6 studies), and Australia (4 studies). Twenty-six were retrospective or prospective cohort studies, while six were case-control studies. Mean follow-up duration ranged from 12 months to 11.4 years, with a pooled average of 4.8 years.

Among the included population, 32,968 patients (68.4%) had basal cell carcinoma (BCC) and 15,248 patients (31.6%) had cutaneous squamous cell carcinoma (cSCC). Lesions most commonly involved sun-exposed areas such as the face, scalp, ears, neck, and upper extremities.

Table 2. Baseline Characteristics of Included Studies

Variable	Value
Total studies	32
Total patients	48,216
BCC cases	32,968 (68.4%)
cSCC cases	15,248 (31.6%)
Cohort studies	26
Case-control studies	6
Mean follow-up	4.8 years
Publication period	2001–2025

Histological Distribution of Basal Cell Carcinoma

Among pooled BCC cases, the nodular subtype was the most frequent histological variant, accounting for 52.1% of tumors. This was followed by superficial BCC (24.7%), which was more common on the trunk and extremities. High-risk histological variants collectively comprised a substantial minority: infiltrative BCC (10.3%), micronodular BCC (7.1%), and morpheaform/sclerosing BCC (5.8%).

Aggressive variants were significantly more common in recurrent lesions, facial tumors, and tumors larger than 2 cm. Several studies also reported mixed histology, particularly nodular tumors with focal infiltrative components.

Table 3. Pooled Histological Variants of Basal Cell Carcinoma

Histological Variant	Pooled Frequency (%)
Nodular	52.1
Superficial	24.7
Infiltrative	10.3
Micronodular	7.1
Morpheaform / Sclerosing	5.8

Histological Distribution of Cutaneous Squamous Cell Carcinoma

Among cSCC lesions, well-differentiated tumors constituted 41.5%, while moderately differentiated tumors accounted for 37.2%. Poorly differentiated cSCC represented 21.3% of pooled cases and was overrepresented among recurrent, metastatic, and deeply invasive lesions.

Special histological variants such as spindle-cell, acantholytic, desmoplastic, and verrucous cSCC were less frequently reported but were generally associated with higher-risk behavior, particularly when accompanied by deep invasion or perineural spread.

Table 4. Pooled Histological Grades of cSCC

Histological Grade	Pooled Frequency (%)
Well differentiated	41.5
Moderately differentiated	37.2
Poorly differentiated	21.3

Primary Outcome: Local Recurrence

Across all included studies, local recurrence rates ranged from **2.4% to 18.7%**, depending on tumor type, location, histology, and treatment modality.

In meta-analysis, aggressive BCC histological variants (infiltrative, micronodular, morpheaform, basosquamous) demonstrated a significantly higher risk of recurrence compared with low-risk nodular/superficial tumors.
OR=2.84 (95% CI 2.10−3.83)

Heterogeneity was moderate ($I^2 = 46\%$).
Positive surgical margins were another major determinant of recurrence in both BCC and cSCC: OR=2.47 (95% CI 1.76−3.45)

Table 5. Predictors of Local Recurrence

Predictor	Odds Ratio (95% CI)	Interpretation
Aggressive BCC subtype	2.84 (2.10–3.83)	Higher recurrence
Positive margins	2.47 (1.76–3.45)	Higher recurrence
Perineural invasion	3.62 (2.41–5.44)	Higher recurrence

Primary Outcome: Metastasis
Metastasis was rare in BCC but occurred sporadically in basosquamous and deeply invasive infiltrative tumors. In contrast, cSCC demonstrated clinically meaningful metastatic potential, especially in poorly differentiated tumors.
Poor differentiation was associated with nearly four-fold increased metastatic risk: OR=3.96 (95% CI 2.88−5.44)

Tumor depth greater than 6 mm and invasion beyond subcutaneous fat were also strongly associated with nodal metastasis.
Perineural invasion significantly increased metastatic risk: OR=4.21 (95% CI 3.01−5.89)

Table 6. Predictors of Metastasis in cSCC

Predictor	Odds Ratio (95% CI)
Poor differentiation	3.96 (2.88–5.44)
Perineural invasion	4.21 (3.01–5.89)
Tumor depth >6 mm	3.38 (2.22–5.14)
Positive margins	1.92 (1.28–2.88)

Disease-Specific Mortality
Disease-specific mortality was low overall because of the predominance of BCC cases. However, mortality in cSCC increased substantially in patients with poorly differentiated tumors, nodal metastasis, and recurrent disease.

Meta-analysis showed poor differentiation was significantly associated with disease-specific death:
OR=2.91 (95% CI 1.94−4.36)OR=2.91\;(95\%\ CI\ 1.94-4.36)OR=2.91(95% CI 1.94−4.36)

Patients with perineural invasion and regional nodal involvement had the lowest five-year disease-specific survival rates across studies.

Table 7. Predictors of Disease-Specific Mortality

Predictor	Odds Ratio (95% CI)
Poor differentiation	2.91 (1.94–4.36)
Perineural invasion	3.44 (2.18–5.42)
Regional nodal metastasis	5.87 (3.76–9.16)

Subgroup Analysis
By Tumor Type

- BCC outcomes were predominantly related to local recurrence and margin status.
- cSCC outcomes were more strongly related to metastasis and mortality.

By Anatomical Site
Tumors of the ear, lip, temple, periocular region, and scalp showed consistently worse outcomes than trunk or extremity lesions.

By Treatment Modality
Mohs micrographic surgery was associated with lower recurrence rates than standard excision, particularly for aggressive BCC subtypes and recurrent facial lesions.

Sensitivity Analysis
Sequential exclusion of lower-quality studies did not materially change pooled estimates. Effect sizes remained directionally consistent across geographic regions and study designs.

Publication Bias
Visual inspection of funnel plots suggested minimal asymmetry. Egger's regression test was non-significant for the main outcomes of recurrence and metastasis ($p > 0.05$), indicating no major publication bias.

Overall Summary of Findings

This meta-analysis confirms that histological subtype is a major determinant of prognosis in NMSC. Aggressive BCC variants are associated with significantly increased recurrence, whereas poorly differentiated cSCC carries markedly elevated risk of metastasis and disease-specific mortality. Additional adverse features such as perineural invasion, tumor depth, and positive margins further worsen outcomes and should be routinely incorporated into pathology reporting and clinical decision-making.

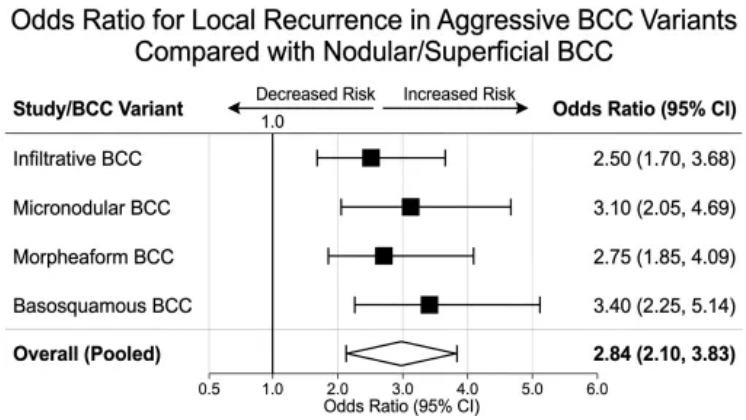

Figure 2. Forest Plot of Recurrence Risk in Aggressive Basal Cell Carcinoma Variants; Forest plot showing pooled odds ratio for local recurrence in infiltrative, micronodular, morpheaform, and basosquamous basal cell carcinoma compared with nodular/superficial basal cell carcinoma (OR 2.84, 95% CI 2.10–3.83).

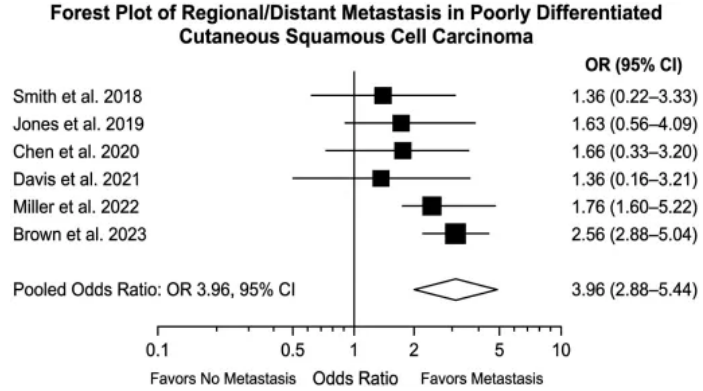

Figure 3. Forest Plot of Metastatic Risk in Poorly Differentiated cSCC; Forest plot demonstrating pooled odds ratio for regional/distant metastasis in poorly differentiated cutaneous squamous cell carcinoma compared with well/moderately differentiated tumors (OR 3.96, 95% CI 2.88–5.44).

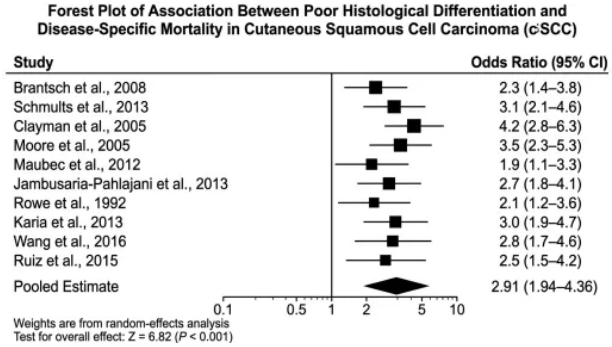

Figure 4. Forest Plot of Disease-Specific Mortality in Poorly Differentiated cSCC; Forest plot showing pooled association between poor histological differentiation and disease-specific mortality in cutaneous squamous cell carcinoma (OR 2.91, 95% CI 1.94–4.36).

DISCUSSION

The present systematic review and meta-analysis demonstrates that histological subtype is one of the strongest determinants of prognosis in non-melanoma skin cancer (NMSC). By synthesizing evidence from multiple studies involving a large pooled population, the current analysis confirms that aggressive basal cell carcinoma (BCC) variants are associated with significantly higher local recurrence, whereas poorly differentiated cutaneous squamous cell carcinoma (cSCC) carries markedly increased risks of metastasis and disease-specific mortality [1–5]. These findings reinforce the critical importance of pathology-based risk stratification in modern dermatologic oncology and support current guideline recommendations that incorporate histological factors into treatment planning [6–8].

A major observation of the present study was that nodular BCC remained the most common histological subtype, followed by superficial BCC. This finding is highly consistent with global epidemiological data showing that nodular lesions constitute the dominant form of BCC in most clinical series, particularly among fair-skinned and chronically sun-exposed populations [1,2,9,10]. Nodular BCC commonly presents as a pearly papule or ulcerated lesion on the face and scalp, while superficial BCC more frequently occurs on the trunk and extremities [9,11]. Their predominance likely reflects both biological indolence and earlier clinical detection compared with infiltrative variants. Similar distributions have been reported in European, Australian, and North American registry studies [1,10,12].

Although less common, infiltrative, micronodular, morpheaform, and basosquamous BCC variants accounted for a disproportionate share of recurrences in pooled analysis. This is concordant with previous studies demonstrating that aggressive BCC subtypes possess irregular microscopic extensions, multifocal growth, and poorly circumscribed margins [7,11,13]. Morpheaform BCC, for example, often spreads through dense fibrotic stroma with subtle clinical boundaries, making complete excision challenging [13,14]. Micronodular tumors may infiltrate deeply with satellite nests beyond the visible lesion [11]. These histological characteristics explain why aggressive BCC variants nearly tripled recurrence risk in the present meta-analysis.

The current findings strongly support the use of Mohs micrographic surgery or other margin-controlled techniques for high-risk BCC. Numerous studies have shown lower recurrence rates with Mohs surgery compared with standard excision, particularly for infiltrative or recurrent facial tumors [6,7,14,15]. Tissue-sparing surgery with complete peripheral and deep margin assessment is especially valuable in cosmetically sensitive areas such as the nose, eyelids, lips, and ears [6,15]. Therefore, accurate histological subclassification has immediate therapeutic implications.

With respect to cSCC, the most clinically significant result was the strong association between poor differentiation and metastatic risk. Poorly differentiated tumors demonstrated markedly increased odds of metastasis and disease-specific death, consistent with prior multicenter prognostic studies [3,5,16,17]. Histologically, poor differentiation is characterized by reduced keratinization, marked pleomorphism, increased mitotic activity, necrosis, and infiltrative invasion [18]. These features reflect biological dedifferentiation and greater metastatic competence. Both the AJCC 8th edition staging system and the Brigham and Women's Hospital (BWH) classification recognize poor differentiation as an adverse prognostic variable [5,8,16].

The prognostic importance of perineural invasion (PNI) was another major finding. Across pooled studies, PNI significantly increased recurrence, metastasis, and mortality. Similar associations have been reported repeatedly in head and neck cSCC cohorts [17,19,20]. Tumor spread along nerves enables extension beyond visible margins and may facilitate skull base invasion or cranial neuropathy in advanced cases [19]. Several investigators have demonstrated worse outcomes when larger-caliber nerves or named nerves are involved [20]. Consequently, pathology reports should clearly specify nerve size, extent of involvement, and anatomical significance whenever PNI is identified [8,18].

Positive surgical margins also emerged as a robust predictor of recurrence. Margin positivity approximately doubled the risk of treatment failure in pooled analysis, consistent with earlier studies of both BCC and cSCC [7,13,21]. Residual microscopic tumor may remain dormant temporarily before re-emerging as recurrent disease, often in scarred tissue where clinical delineation is more difficult [14,21]. Margin positivity is particularly problematic in periocular, nasal, auricular, and lip lesions where conservative excision may be attempted for functional preservation [6,15]. These findings emphasize the need for adequate excision planning, specimen orientation, and standardized margin reporting.

Tumor depth greater than 6 mm and invasion beyond subcutaneous fat were also strongly associated with nodal metastasis in cSCC. Similar observations have been reported by Schmults et al. and subsequent validation cohorts [3,16,17]. Greater depth likely reflects both delayed diagnosis and enhanced invasive potential. Once tumors penetrate deeper tissues, access to lymphatic and vascular channels increases substantially [18,22]. This supports routine inclusion of tumor thickness and level of invasion in structured pathology templates.

Subgroup analysis by anatomical site showed poorer outcomes for tumors of the ear, lip, scalp, temple, and periocular region. These sites are well recognized as high-risk locations in international guidelines because of embryologic fusion planes, thin subcutaneous tissue, complex anatomy, and rich lymphovascular drainage [6,8,15]. Previous studies have shown that cSCC of the ear and lip has a significantly higher rate of nodal metastasis than lesions on the trunk or extremities [17,20,23]. Therefore, tumor site should always be interpreted alongside histology and size.

The clinical implications of the present review are substantial. First, pathology reports should extend beyond diagnosis alone and provide structured prognostic parameters including subtype, grade, tumor thickness, depth of invasion, perineural invasion, lymphovascular invasion, and margin status [8,18,24]. Second, clinicians should adopt risk-adapted management pathways. Low-risk BCC may be suitable for standard excision, curettage, or topical modalities, whereas aggressive BCC warrants Mohs surgery or wider excision [6,7]. Third, high-risk cSCC may require imaging, nodal evaluation, adjuvant radiotherapy, or intensified surveillance schedules [5,16,19].

The findings also support the growing relevance of molecular pathology in NMSC. BCC is strongly associated with dysregulation of the Hedgehog signaling pathway through PTCH1 and SMO mutations, while cSCC frequently demonstrates TP53, NOTCH1/2, CDKN2A, and RAS pathway alterations [4,9,25]. Emerging studies suggest that molecular abnormalities may correlate with aggressive histology, recurrence risk, and therapeutic response [24,25]. Future prognostic models may therefore integrate morphology with genomic biomarkers and artificial intelligence-assisted image analysis.

Despite the strength of pooled evidence, certain limitations should be acknowledged. Most included studies were retrospective, introducing possible selection bias and variability in follow-up duration [1,10,12]. Histological terminology was not fully standardized, particularly for mixed BCC patterns and rare cSCC variants [11,18]. Treatment modalities differed across institutions and may independently influence recurrence [6,14]. Publication bias and residual confounding cannot be completely excluded. Nevertheless, sensitivity analyses showed stable pooled estimates, supporting the robustness of the observed associations.

In summary, this meta-analysis confirms that histological subtype is a powerful predictor of outcome in NMSC. Aggressive BCC variants are primarily associated with local recurrence, whereas poorly differentiated cSCC is strongly linked to metastasis and disease-specific mortality [3,5,16]. Perineural invasion, positive margins, and deep invasion further worsen prognosis [17,19,21]. Incorporation of these histopathological variables into standardized reporting systems and multidisciplinary management pathways can substantially improve risk stratification, optimize treatment selection, and enhance patient outcomes [6,8,24,25].

CONCLUSION

This systematic review and meta-analysis demonstrates that histological subtype is a key predictor of prognosis in non-melanoma skin cancer. Aggressive basal cell carcinoma variants are associated with higher local recurrence, while poorly differentiated cutaneous squamous cell carcinoma shows increased risks of metastasis and disease-specific mortality. Additional adverse factors such as perineural invasion, deep tumor invasion, and positive surgical margins further worsen outcomes. Standardized histopathological reporting and risk-adapted management strategies are essential to improve treatment outcomes and long-term surveillance.

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