# Advances in recurrence and malignant transformation of sinonasal inverted papillomas (Review)

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**Abstract.** Sinonasal inverted papilloma (SIP) is a benign tumor of the nasal cavity and sinus. SIP is characterized by aggressive malignant transformation and a high rate of recurrence. Inadequate removal of the tumor during surgery is one of the most significant contributors to SIP recurrence. A growing body of evidence suggests that molecular alteration in SIP, including human papilloma virus infections, single nucleotide polymorphisms of key genes, deregulation of signaling pathways and immunological changes, may lead to SIP occurrence and malignant transformation. However, the extent to which these molecular mechanisms contribute to SIP pathology and transformation remains unclear due to limited research. Further studies are warranted to elucidate the primary dependent factors that contribute to SIP etiology. The present article reviewed risk factors of progression and recurrence of SIP, including outdoor and industrial occupational exposure, smoking, septal deviation, SIP location, recurrent cases, stage of SIP-associated squamous cell carcinoma and choice of surgical method.

**Contents**



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## 1. Introduction

Sinonasal inverted papilloma (SIP) is a benign tumor which originates from the sinonasal Schneiderian mucosa and accounts for 0.5 to 4% of all nasal and sinus neoplasm (1). Pathologically, SIP epithelium inverts into submucosal stroma, which is distinguished from other types of nasal papilloma. Unlike other benign tumors, SIP exhibits remarkable aggressive behaviors, including invasiveness, recurrence and malignant transformation (~10%) (2). Therefore, SIP can spread into the sparanasal sinus, orbit, and cranial base, which can lead to poor prognosis for SIP patients (2).

To date, the treatment for SIP includes surgery and surgery combined with radiotherapy for SIP-associated squamous cell carcinoma (SIP/SCC). Currently, the majority of surgeons prefer endoscopic methods to traditional external approaches, due to similar success rates, less trauma and no facial scars. However, the common view is that SIP recurrence is due to inadequate removal during the first surgery (2-4). Therefore, preoperative evaluation as well as postoperative follow up is very important.

## 2. Clinical risk factors for SIP recurrence

Understanding clinical risk factors is critical for preventing the recurrence of SIP. Similar to other head and neck tumors, smoking has been identified as a risk factor of SIP recurrence in two previous studies (containing 132 and 162 SIP patients, respectively) (5,6). Outdoor and industrial occupations may be another potential environmental risk factor, particularly exposure to organic solvents, including diethylnitrosamine (7-9). These factors include smoking history, smoking amount, and occupation environment (5-9). Recently, Nomura *et al* (10) found that the SIP-affected area was significantly associated with the concave side of the septal deviation. Considering that the high wall shear stress of high-velocity airflow in this location, the study may suggest a causative role of human papilloma virus (HPV) and chemicals in the occurrence of sinonasal papilloma due to the traumatic effects caused by airflow (10). However, whether nasal septal construction should be performed following SIP surgery remains to be determined.

In the majority of head and neck tumors, the clinical stage is associated with recurrence and poor prognosis (11). The clinical stage of SIP has been defined using the Krouse staging

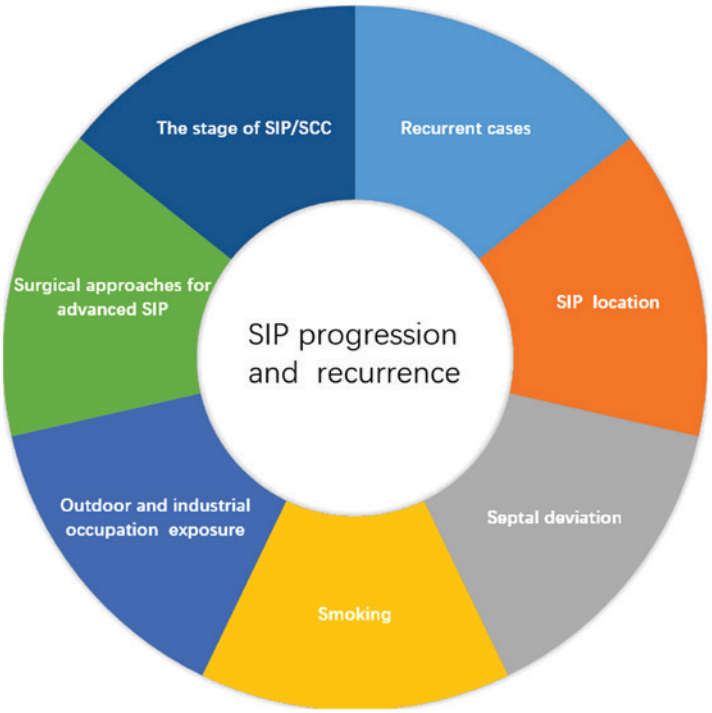


Figure 1. Clinical risk factors of progression and recurrence of SIP. These factors may involve smoking, outdoor and industrial occupational exposure, septal deviation, SIP location, recurrent cases, stage of SIP-associated squamous cell carcinoma and choice of surgical method for advanced SIP. SIP, sinonasal inverted papilloma.

system (12), the Furuta staging system (13), the Cannady staging system (14) and the Han staging system (15). The Krouse staging system is currently the most widely used (16). While certain authors have emphasized the role of SIP stage system on SIP recurrence (17,18), it is not clear whether clinical stage is associated with SIP recurrence. An association between Krouse stage system and recurrence of SIP was not identified in a recent study involving 156 SIP patients (19). In a multicenter study involving 578 SIP patients, three stage systems (the Krouse staging system, the Furuta staging system and the Cannady staging system) did not associate with SIP recurrence rates (2). This study also suggested that patients with advanced stage of SIP who underwent single endoscopic surgery presented a higher recurrence rate. Furthermore, the study also found that SIP involving the frontal sinus or maxillary sinus was associated with higher recurrence rates (2). Consistently, in 57 patients with SIP based within the sphenoid sinus, a multi-institutional retrospective study revealed that the attachment site of SIP over the optic nerve and carotid artery correlated with a 14.6% rate of recurrence (20). Our previous study conducted by the present authors did not show the correlation between Han staging systems and recurrence rates of SIP in 89 SIP cases, but indicated that there is a statistically higher recurrence rate (27.3%) in patients who underwent secondary surgery (21). Consistent with this study, a recent study reported a 50% SIP recurrence rate following secondary surgery compared with a 12% rate following primary resection (18). However, this study did not classify the SIP as benign or SIP/SCC. Recently, two studies, involving 87 and 32 SIP/SCC patients, suggested that advanced American Joint Committee on Cancer (AJCC) stages and therapeutic methods may be risk factors for poor prognosis (22,23). To the best of our knowledge, these are the largest series of SIP/SCC cases reported to date. Collectively, these studies proposed that smoking, chemical exposure, septal deviation, SIP location, secondary surgery and AJCC stage of SIP/SCC may be clinical risk factors for progression and recurrence of SIP. Notably, the AJCC stage of SIP/SCC may contribute to treatment selection (Fig. 1) (22,23).

The choice of surgical methods may be another potential risk factor for SIP recurrence. Although endoscopic sinus surgery (ESS) has been considered the treatment of choice for the majority of SIP cases, surgical decisions should take into account the extent, volume, and lesion location (24). A study of 212 SIP patients demonstrated that SIP lesions with an extensive involvement of the frontal sinus and/or supraorbital cell may require a combined approach (25). In addition, the Korean multicenter study suggested that surgeons should consider combined approaches to reduce recurrence for advanced SIP [Krouse staging system: T3 stage (12); Furuta staging system: T3-A stage (13); Cannady staging system: group B (14)], particularly for novice surgeons (2). Although certain authors propose that SIP involving attachment sites within the maxillary sinus require a endoscopic-external combined technique (1,26), emerging evidence suggests that novel tailored ESS techniques (endoscopic modified medial maxillectomy, and transnasal endoscopic anterior and medial maxillectomy) allow enhanced visualization and preserve important structures, including the inferior turbinate and nasolacrimal duct (27-29). However, other authors proposed that the endoscopic-external combined approach remains essential for recurrent maxillary SIP (30). Therefore, a multicenter study or large meta-analysis is required to determine the most significant factors affecting progression and recurrence of SIP.

Table I. Collision between SIP and other patterns of tumor/disease.

| Pathologic collision | Treatment | References |
|---|---|---|
| SIP and esthesioneuroblastoma | Surgery, adjuvant concomitant chemoradiation | (48) |
| NK/T-cell lymphoma (nasal type) and SIP | Surgery, chemotherapy | (49) |
| Unilateral SIP and angiofibroma | Surgery | (50) |
| SIP and MFSS | Surgery, postoperative adjuvant radiotherapy and subsequent chemotherapy | (51) |
| SIP and fungal ball | Surgery | (52) |

SIP, sinonasal inverted papilloma; MFSS, monophasic fibrous synovial sarcoma; NK, natural killer.

In summary, the location of SIP, secondary surgery, AJCC stage of SIP/SCC and the choice of surgical method for advanced SIP directly contribute to incomplete or inadequate removal of tumors. Therefore, incomplete or inadequate removal is a direct cause of recurrence. SIP location, secondary surgery, AJCC stage of SIP/SCC, and surgical approaches for advanced SIP are the direct risk factors of SIP recurrence.

## 3. Clinical prevention for the recurrence of SIP

The management of risk factors of SIP recurrence involves precise identification of the SIP attachment site, anatomical anomalies in sinonasal regions, careful planning of surgical procedures and a well-planned postoperative follow-up (19). The use of computed tomography (CT) and magnetic resonance imaging (MRI) is critical for preoperative prediction of SIP attachment sites and differentiation (31,32). Radical ablation of SIP attachment sites is crucial for the first surgical resection. Therefore, imaging is important in preoperative prediction of SIP attachment sites.

Since the majority of recurrence is localized to the same site as the primary tumor, the accurate preoperative prediction of SIP attachment sites is crucial for the first surgical resection (3). Notably, SIPs with an origin in close proximity to vital structures, including the optic nerve and carotid artery, may be associated with higher rates of recurrence (20), which may be a factor for consideration when choosing the surgical approach.

Prior reports have suggested that focal osteitis within the SIP tissue may be a predictor of SIP origin (31). While the mechanisms underlying the origin of SIP-induced osteitis remains to be determined, certain studies report that the SIP attachment site provides blood supply to the large bulky tumor volume, which leads to hypervascularization of the attachment site (31). Hypervascularization within the origin site may cause bone growth (31), driven by bone morphogenetic protein 4 expressed by SIP cells (33) or cytokines released due to inflammation (34). Bhalla *et al* (34) found that the predictive value of osteitis was 95% via CT scan, and similar results were also reported by Yousuf *et al* (35). Lee *et al* (31) evaluated 55 lesions associated with focal hyperostosis using CT images and revealed that the location of hyperostosis coincided with the actual tumor attachment sites in 49 (89.1%) of all the lesions. Notably, Lee *et al* (31) suggested that areas of cone-shaped hyperostosis matched with the SIP origin rather than plaque-like hyperostosis.

Accurate tumor mapping is likely to be challenging due to inadequate differentiation of the tumor from pathological inflammation (36) and squamous cell carcinoma (32). MRI may have an advantage in differentiating soft tissue. MRI is able to identify inflammation more clearly and is also able to identify tumor margin, tumor extent (32) and convoluted cerebriform pattern (CCP), which is considered a valuable SIP characteristic (37). Wang *et al* (38) have demonstrated that there were significant differences between SIP and malignancy in T2 homogeneity, CCP and other MRI parameters. The authors concluded that non-enhanced and static combined with dynamic contrast-enhanced MRI facilitates the identification of SIP and malignant tumors (38). Another study demonstrated the diagnostic value of tumor blood flow obtained by pseudocontinuous arterial spin labeling is able to effectively differentiate between SCC, non-aggressive SIP and aggressive SIP using a 3.0-T MRI (39). Nakamaru *et al* (40) analyzed 10 consecutive patients with SIP and diagnosis in these patients was confirmed by histological assessment. The study indicated that MRI indicated greater specificity compared with CT scan and suggested that a combination of preoperative CT and MRI may able to provide more useful information compared with using either CT or MRI alone (40).

Currently, there are no distinct clinical signs and symptoms that differentiate SIP and malignant transformation of SIP (2,32). The diagnosis of SIP malignant transformation is based on the observation of synchronous transformation, which appears at the same time as papilloma, and metachronous transformation, which appears at the site of a previous papilloma (41).

Furthermore, preoperative histological examination is difficult and ineffective to differentiate SIP and malignant transformation of SIP (22). Several investigators have suggested that CT/MRI may be ineffective in distinguishing SIP from SCC (42), while others have reported that bone invasion may be a differentiating feature of synchronous malignant transformation of SIP on CT scan (43). Therefore, recent studies introduced fluorine-18-fluorodeoxyglucose (18F-FDG) positron emission tomography (PET) /CT for the identification of SIP, which depends on the extent of FDG uptake by different tissues though glycolysis (44). Allegra *et al* (42) analyzed 12 patients (7 with primary diagnosis of SIP and 5 with suspected recurrence of SIP) using 18FDG-PET/CT for the diagnosis of SIP with a sensitivity and specificity rate of 100% (42). Similarly, a 2015 study containing 27 patients

Table II. Putative factors underlying mechanisms leading to SIP malignant transformation.

| Materials | Methods | Putative factors | References |
|---|---|---|---|
| Tissue samples | IHC | p53, p63 | (80) |
| Tissue samples | IHC | FSCN1 | (87) |
| Tissue samples | IHC | Ki-67, PCNA | (65) |
| Tissue samples | IHC, TMA | p16, p53 | (80) |
| Tissue samples | IHC | p21, p16, p63 | (79) |
| Tissue samples, venous blood samples | IHC | MT2A-5A/G (rs28366003) | (85) |
| Tissue samples | IHC, western blotting, fluorescence microscopy | Reduced expression of TFPI-2 | (86) |
| Tissue samples | IHC, FISH | SOX-2 | (88) |
| Tissue samples | IHC, PCR | DSG-3 | (92) |
| Tissue samples | IHC, gene chip analysis, PCR | CTSS, stefin A | (94) |
| Tissue samples | IHC, TMA | COX-2 | (96,97) |
| Tissue samples | IHC, RT-qPCR | DLEC1 | (98) |
| Tissue samples | IHC | PTEN, HIF-1α | (74) |
| Tissue samples | IHC | IQGAP1 | (99) |
| Tissue samples | IHC | E-cadherin, β-catenin | (95) |
| Tissue samples | IHC | Wnt pathways (β-catenin, cyclin D1 and Dvl-1) | (82) |
| Tissue samples | PCR, IHC | MSX2, topoII α | (89,90) |
| Tissue samples | IHC | TopoII-α, Ki-67 | (84) |
| Tissue samples | IHC, PCR | HPV integration, pRb | (100) |
| Tissue samples | TMA, DIPS-PCR | HPV, EGFR | (78) |
| Tissue samples | IHC | Survivin, PCNA | (83) |
| Tissue samples | IHC | Smac, survivin | (93) |
| Tissue samples | IHC | MMP-2, HPV-16/18 | (76) |
| Tissue samples | IHC | OPN, MSX2 | (91) |
| Tissue samples, peripheral blood | Flow cytometry, Boyden chamber assay, IHC, Luminex analyzer | Treg cells | (101) |
| Tissue samples, SIP/SCC cell lines | Ion AmpliSeq cancer hotspot panel, Sanger sequencing, western blotting, proliferation assay | EGFR mutations | (77) |

COX-2, cyclooxygenase-2; CTSS, cathepsin S; DIPS-PCR, detection of integrated papillomavirus sequences by ligation-mediated-polymerase chain reaction; DLEC1, deleted in lung and esophageal cancer protein 1; DSG-3, desmoglein-3; Dvl-1; Segment polarity protein dishevelled homolog DVL-1; EGFR, epidermal growth factor receptor; FSCN1, fascin; HIF-1α, hypoxia-inducible factor 1-α; HPV, human papilloma virus; IHC, immunohistochemistry; IQGAP1, IQ motif containing GTPase activating protein 1; RT-qPCR, reverse transcription-quantitative polymerase chain reaction; MSX-2, homeobox protein MSX-2; MT2A; metallothionein-2A; PCNA; proliferating cell nuclear antigen reverse transcription; qPCR, quantitative polymerase chain reaction; pRb, retinoblastoma protein; PTEN, phosphatidylinositol 3,4,5-trisphosphate 3-phosphatase and dual-specificity protein phosphatase; MMP-2, matrix metallopeptidase-2; OPN, osteopontin; SIP/SCC, sinonasal inverted papilloma-associated squamous cell carcinoma; SOX-2, sex determining region Y-box 2; TMA, tissue microarray; Treg, regulatory T cells; Smac, second mitochondria-derived activator of caspase; TFPI-2, tissue factor pathway inhibitor 2; topoII-α, topoisomerase II α.

demonstrated that 18FDG-PET/CT is able to distinguish polyposis, SIP and SCC by distinct standardized uptake value ($SUV_{max}$) values (45). Shojaku *et al* (46) confirmed that higher SIP $SUV_{max}$ values may indicate the probability of an associated malignancy, even when preoperative biopsy indicates a benign papilloma. By contrast, another study containing 8 patients reported a wide discrepancy between MRI and PET/CT findings (47). Taken together, these studies suggest that preoperative SIP imaging should involve a combination of CT, MRI and PET/CT.

Histologically, the most common malignancy associated with SIP is SCC. However, growing evidence has demonstrated a pathologic collision exists between SIP and other tumors. Karam *et al* (48) reported a case with a pathologic collision of SIP with esthesioneuroblastoma. The tumor was resected; however the postoperative surgical margin was positive, and neck lymph nodes were metastatic. Therefore the patient was treated with adjuvant concomitant chemoradiation, and evidence of tumor recurrence was not detected in the 42-month follow-up (48). In another study, a patient with nasal type natural killer/T-cell

Table III. Putative factors underlying mechanisms leading to SIP occurrence and recurrence.

| Materials | Methods | Putative factors | References |
|---|---|---|---|
| Tissue samples | IHC | PLUNC | (65) |
| Tissue samples | IHC | CK14, Ki-67 | (66) |
| Tissue samples | IHC | Survivin, Bcl-2 | (67) |
| Tissue samples | IHC, ELISA, PCR | OPN, VEGF | (68) |
| Tissue samples | IHC | FSCN1, MVD | (69) |
| Tissue samples | - | CCAAT enhancer binding proteins | (71) |
| Tissue samples | IHC | COX-2 | (72) |
| Tissue samples | IHC, RT-PCR, western blot | AMOT | (73) |
| Tissue samples | IHC | MVD | (70) |
| Tissue samples | IHC | PTEN, HIF-1α | (74) |
| Tissue samples | IHC, PCR | HPV, STMN1 | (75) |

AMOT, angiomotin; Bcl-2, B-cell lymphoma 2; CK14, keratin, type I cytoskeletal 14; COX-2, cyclooxygenase-2; ELISA, enzyme-linked immunosorbent assay; FSCN1, fascin; HIF-1α, hypoxia-inducible factor 1-α; HPV, human papilloma virus; IHC, immunohistochemistry; MVD, mean vessel density; OPN, osteopontin; PLUNC, palate, lung, and nasal epithelium clone protein; PTEN, phosphatidylinositol 3,4,5-trisphosphate 3-phosphatase and dual-specificity protein phosphatase; RT-PCR, reverse transcription polymerase chain reaction; STMN1, stathmin1; VEGF, vascular endothelial growth factor.

lymphoma and SIP, received surgery with postoperative chemotherapy. Tumor recurrence was not observed in the subsequent 10-month follow-up (49). Shahrjerdi *et al* (50) reported a case of co-existing unilateral SIP and angiofibroma. The nasal mass was treated by radical surgical resection, and the 3-month follow-up indicated that the patient was asymptomatic with no signs of cancer recurrence (50). Additionally, a patient with SIP and accompanying monophasic fibrous synovial sarcoma in the sphenoid sinus was also reported (49). The treatment for this case involved surgery, postoperative adjuvant radiotherapy and subsequent chemotherapy. There were no signs of recurrence following the 50-month follow-up (51). Furthermore, SIP with fungal ball in the maxillary sinus has also been reported (52). SIP accompanied with a malignancy of a different pathology is extremely rare, which may lead to pretherapeutic misdiagnosis (51) and an increased risk of recurrence potentially due to a lack of therapeutic regimen such as surgical margin, dose and cycles of radiotherapy, selection of chemotherapeutic agent, and lack of evidence-based analysis of in large well-controlled studies (Table I).

Apart from histological variations of SIP, exceptional clinical cases should also be emphasized. It has been reported that SIP may spread to the middle ear and temporal bone. The spread of SIP may be mediated either due to migration via the eustachian tube or due to embryological migration of the Schneiderian mucosa into the middle ear (53,54). Garcia *et al* (55) reported that SIP/SCC in the maxillary sinus may extend to the mouth as an early symptom. Furthermore, as a common unilateral nasal occurrence, a case with a bilateral SIP involving both sides of frontal sinus was reported in Keskin *et al* (56). Sharma *et al* (57) reported a patient with a history of multiple locations, who presented with recurrent SIP with a pathologically benign large mass on the left side of the upper neck. Additionally, another study reported that SIP/SCC is associated with neck metastasis (58). These cases demonstrate that SIP may origin from multiple sites and therefore should not be ignored. Preoperative examinations should include a complete head and neck assessment.

A number of studies suggest that the length follow-up for SIP was usually >3 years (2,16). Unfortunately, it is difficult to distinguish inflammation from SIP recurrence using nasal endoscopy (19,59). MRI and PET/CT may be recommended for post-surgery follow-up. In addition to imaging techniques, the serum level of squamous cell carcinoma antigen may also be used as a molecular marker for the recurrence of SIP (59,60).

## 4. Potential mechanisms underlying the recurrence and malignant transformation of SIP

A literature search on PubMed (https://www.ncbi.nlm.nih.gov/pubmed/) was performed using the following key words: 'Inverted papilloma'; 'sinonasal inverted papilloma'; 'inverted papilloma malignant transformation'; 'inverted papilloma recurrence'; and 'inverted papilloma malignant'. The search found that a majority of the clinical literature focused on diagnosis, surgery and prognosis. The majority of the studies were retrospective analyses. A number of studies focused on surgical methods and were published in prominent otorhinolaryngology journals in 2015 and 2016 (61-64). Notably, there were a limited number of experimental studies. To the best of our knowledge, the present study is the first to clearly identify the clinical etiology and problems concerning SIP malignancy and recurrence.

The mechanisms leading to the occurrence, recurrence and malignant transformation of SIP remain a matter of debate. To date, many studies have aimed to resolve this issue (Tables II and III). Putative aberrant mediators that may participate in the recurrence of SIP include palate, lung, and nasal epithelium clone protein (65), keratin, type I cytoskeletal 14 (66), Ki-67 (66), survivin (67), B-cell lymphoma 2 (67), osteopontin (OPN) (68), vascular endothelial growth factor (68), fascin (69), mean vessel density (69,70),

CCAAT enhancer binding proteins (71), cyclooxygenase-2 (COX-2) (72), angiomotin (73), phosphatidylinositol 3,4,5-trisphosphate 3-phosphatase and dual-specificity protein phosphatase (PTEN) (74), hypoxia-inducible factor 1-α (HIF-1α) (74), HPV infection and stathmin (75).

Malignant transformation of SIP may be associated with the following factors: HPV 16/18 infection (76), epidermal growth factor receptor (EGFR) 1 (77,78); cell cycle proteins [p21 (79); p16 (79,80); p53 (80,81); p63 (79,81); p27; cyclin D1 (82); proliferating cell nuclear antigen reverse transcription (65,83); Ki-67 (65,84); metallothionein-2-5A/G (reference single nucleotide polymorphisms cluster ID, 28366003) (85); TFPI-2 (86); fascin (87); matrix metallopeptidase-2 (76); sex determining region Y-box 2 (88); topoisomerase II-α (84,89,90); OPN (91); homeobox protein MSX-2 (89-91); desmoglein 3 (92); survivin (83,93); cathepsin S (94); stefin A (94); E-cadherin (95); β-catenin (82,95); COX-2 (96,97); deleted in lung and esophageal cancer protein 1 (98); IQ motif containing GTPase activating protein 1 (99); Smac (93); PTEN (74); HIF-1α (74); Dvl-1 (82); retinoblastoma protein (100); and regulatory T cells (101). However, there were several key limitations in these studies. The materials and methods used were simple (1). The majority of literature analyzed primary resected SIP tissue samples and performed immunohistochemistry as a common method. However, accurate research on molecular biological mechanisms requires comprehensive materials and methods. For instance, the establishment of SIP cell lines and animal models is necessary for research on SIP (2). The major dependent factors of SIP. The basement of target therapy is that tumor cells depended on a core factor for their progression. Starska *et al* (85) emphasized EGFR mutations as a regulator of SIP to SIP/SCC. Variations in the EGFR gene have been identified as a key factor that are associated with poor prognosis in head and neck squamous cell carcinoma (102). It is likely that EGFR may be a target for SIP treatment; however further studies are required to confirm this hypothesis.

## 5. Conclusion

In summary, the clinical risk factors of SIP progression and recurrence include smoking, outdoor and industrial occupational exposure, septal deviation, SIP location, recurrent cases, stage of SIP/SCC and choice of surgical method for advanced SIP. The best preventative measure for SIP recurrence is the complete removal of the tumor during the first surgery and a comprehensive follow-up. Additionally, further studies are required to elucidate the molecular mechanisms underlying the recurrence and malignant transformation of SIP.

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