

Expression pattern of CK7, CK20, CDX-2, and villin in intestinal-type sinonasal adenocarcinoma

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Background: Intestinal-type sinonasal adenocarcinoma (ITAC) is an uncommon neoplasm, which resembles adenocarcinoma of the gastrointestinal tract. ITAC occurs sporadically or in association with occupational exposure to hardwood dust and other agents.

Aims: To investigate the phenotype and possible pathogenetic mechanisms of primary sinonasal and nasopharyngeal adenocarcinomas by staining for cytokeratin 7 (CK7), CK20, CDX-2, and villin.

Methods: Twelve sporadic sinonasal and nasopharyngeal adenocarcinomas were stained with monoclonal antibodies to CK7, CK20, CDX-2, and villin. The ITACs were classified as papillary, colonic, solid, mixed, or mucinous types.

Results: The diagnosis of ITAC was confirmed in 10 cases: five were colonic type and five were papillary. One was a sinonasal papillary low grade adenocarcinoma, and one a papillary nasopharyngeal adenocarcinoma, and these tumours were CK7 positive, but CK20, CDX-2, and villin negative. All ITACs were positive for CK20, CDX-2, and villin, and six were CK7 positive. One ITAC had a focus of intestinal metaplasia away from the invasive carcinoma.

Conclusions: Sinonasal ITACs have a distinctive phenotype, with all cases expressing CK20, CDX-2, and villin. Most ITACs also express CK7, although a proportion of tumours are CK7 negative. ITAC seems to be preceded by intestinal metaplasia of the respiratory mucosa, which is accompanied by a switch to an intestinal phenotype. Although ITACs are morphologically similar, differences in cytokeratin expression patterns suggest two distinct types. The expression pattern of CK7, CK20, CDX-2, and villin positive may be useful in separating these tumours from other non-ITAC adenocarcinomas of the sinonasal tract and nasopharynx.

Intestinal-type adenocarcinomas (ITACs) of the nasal cavity and paranasal sinuses are uncommon tumours that occur sporadically or are associated with occupational exposure to hardwood and leather dusts, nickel, and possibly smoking.^{1–2} ITACs are clinically aggressive and generally present at an advanced stage, with an overall mortality of approximately 53%.² Histopathological grading appears to be a significant prognostic indicator.^{1–3} The morphological appearance of these tumours is variable and may resemble normal small intestinal mucosa, villous adenomas, conventional colorectal adenocarcinomas, mucinous adenocarcinomas, and signet ring cell carcinomas.^{1–4} The similarities between ITAC and intestinal adenocarcinoma extend beyond the light microscopic level to ultrastructural and immunohistochemical characteristics.^{4–6} Several studies have attempted to determine whether immunohistochemical markers could be useful in distinguishing sinonasal ITACs from metastatic colorectal adenocarcinomas, and from other non-ITAC sinonasal adenocarcinomas.^{6–8}

To gain further insight into the phenotype and possible pathogenetic mechanisms of sinonasal ITACs, we investigated the expression of keratin 7 (CK7), CK20, the intestinal cytoskeletal protein villin, and the homeobox gene product CDX-2 in a group of sporadic sinonasal and nasopharyngeal adenocarcinomas. The differential expression of CK7 and CK20 has been useful in determining the site of origin of many adenocarcinomas.^{9–10} Given that most (78%) adenocarcinomas of the upper gastrointestinal tract coexpress CK7 and CK20, and most colorectal adenocarcinomas are CK20 positive,^{9–10} we hypothesise that the CK7/CK20 staining pattern in ITAC will reflect differentiation toward intestinal staining profiles, rather than the usual CK7+/CK20– phenotype seen in normal upper respiratory mucosa.

CDX-2 is an intestine specific transcription factor product of the CDX-2 homeobox gene. This gene is involved at one of the earliest stages of intestinal differentiation and plays an essential role in the proliferation and differentiation of intestinal epithelial cells.¹¹ CDX-2 expression is lineage specific and has been found in normal colonic and small intestinal mucosa, Barrett's metaplasia and adenocarcinomas,^{12–13} gastric intestinal metaplasia and intestinal-type adenocarcinomas,^{14–15} and colorectal adenocarcinomas.¹⁶ Because the Schneiderian mucosa is of ectodermal origin and normally shows no evidence of intestinal differentiation, ITAC probably originates from intestinal metaplasia induced by hardwood dust, leather dust, and other unknown agents. The molecular mechanisms involved in metaplastic transformation of terminally differentiated epithelium to a phenotypically different epithelium are largely unknown; however, the intestinal phenotype of ITACs suggests that the CDX-2 gene is activated, so that these tumours should show consistent nuclear expression of the CDX-2 protein.

“To gain further insight into the phenotype and possible pathogenetic mechanisms of sinonasal intestinal-type sinonasal adenocarcinomas, we investigated the expression of keratin 7 (CK7), CK20, the intestinal cytoskeletal protein villin, and the homeobox gene product CDX-2”

Villin is a cytoskeletal protein required for the formation of brush border microvilli in the normal small intestine, colon,

Abbreviations: CK, cytokeratin; ITAC, intestinal-type sinonasal adenocarcinoma; LGSA, low grade sinonasal papillary adenocarcinoma

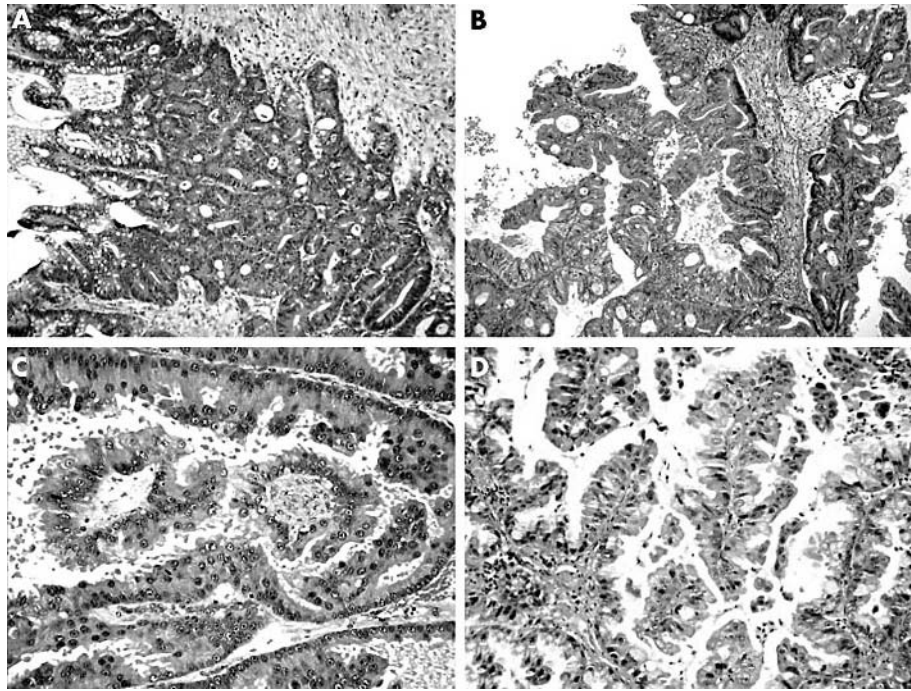


Figure 1 (A) Intestinal-type sinonasal adenocarcinoma (ITAC) colonic type with cribriform architecture; (B) ITAC papillary type showing a predominant population of tall columnar cells; (C) papillary low grade sinonasal adenocarcinoma composed of papillae lined by tall columnar cells with round nuclei containing small nucleoli and vesicular chromatin; (D) papillary adenocarcinoma of the nasopharynx showing thin papillae lined by cells with nuclear pleomorphism. Mucous cells were common in this tumour.

pancreatic ducts, biliary system, and proximal renal convoluted tubules. The restricted tissue expression of villin is conserved during neoplastic processes and an apical or brush border pattern of villin expression is seen in all gastrointestinal adenocarcinomas, even when their organised brush

border structure is lost.¹⁷ Villin is also abundantly expressed in Barrett's metaplasia and oesophageal adenocarcinoma.¹² Villin expression in ITAC has not been studied as yet, but we also hypothesise that it should be uniformly positive in ITACs.

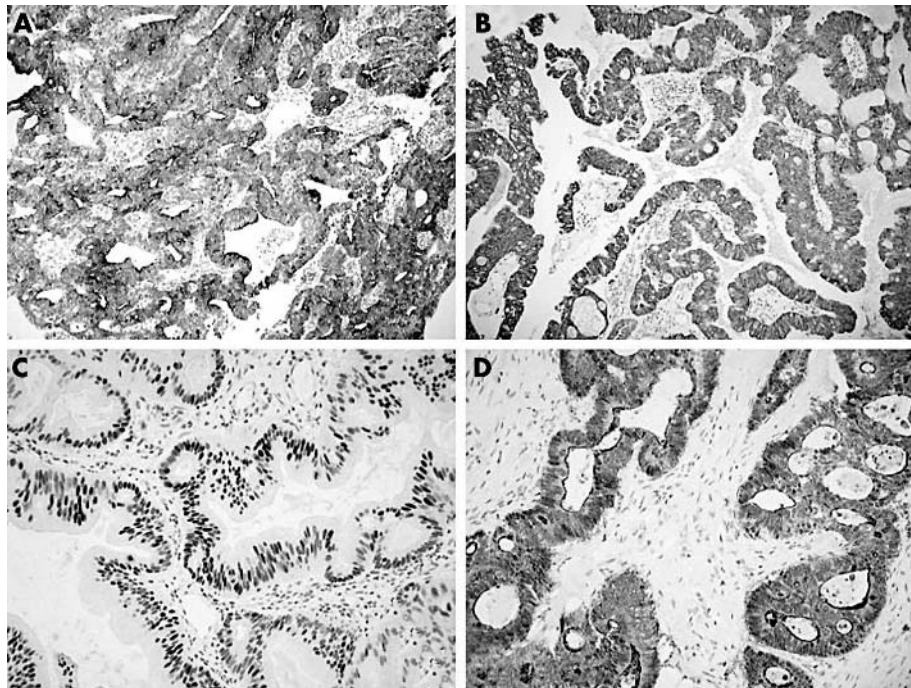


Figure 2 (A) Intestinal-type sinonasal adenocarcinoma (ITAC) colonic type with diffuse and strong expression of cytokeratin 7 (CK7); ITAC papillary type strongly positive for CK20; (C) characteristic nuclear staining for CDX-2 in sinonasal ITAC; strong apical immunoreactivity for villin in sinonasal ITAC.

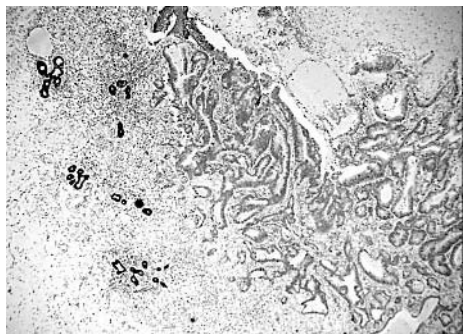


Figure 3 Example of sinonasal intestinal-type sinonasal adenocarcinoma negative for cytokeratin 7. Note the staining by residual seromucous glands.

MATERIALS AND METHODS

Twelve cases of primary non-salivary gland-type adenocarcinoma of the sinonasal tract and nasopharynx were retrieved from surgical pathology files on the basis of an original pathological diagnosis of ITAC or non-salivary gland adenocarcinoma. Original haematoxylin and eosin stained slides were reviewed by two of the authors (MK and BP-O). A representative, formalin fixed, paraffin wax embedded block was selected for immunohistochemical studies using the antibodies listed in table 1. Villin and CDX-2 immunostains were performed manually with overnight incubation with the primary antibodies. Staining was completed using the ultrastreptavidin–horseradish peroxidase detection system (ID Labs Biotechnology, London, Ontario, Canada) and colour development was performed using the NovaRed substrate kit (Vector Laboratories, Burlingame, California, USA). Staining for CK7 and CK20 was performed in a Ventana BenchMark system (Ventana Medical Systems Inc, Tucson, Arizona, USA). The immunohistochemical stains were evaluated semiquantitatively and scored as: –, 0–5% positive cells; 1+, > 5–25% positive cells; 2+, > 25–50% positive cells; and 3+, > 50% positive cells. CDX-2 was regarded as positive if there was distinctive nuclear staining. Tumours with brush border membranous staining for villin were considered positive. All the tumours in which the diagnosis of ITAC was confirmed were subsequently subtyped, as described by Barnes,² as papillary, colonic, solid, mixed, or mucinous types. Special attention was placed on the identification of Paneth cells and goblet cells. All tumours were investigated for the presence of squamous and intestinal metaplasia.

RESULTS

Clinical findings

Ten patients were male and two were female. None of the patients had a known history of occupational exposure to hardwood dust. The age at presentation ranged from 21 to 87 years (mean, 63). Five tumours arose in the ethmoid sinus, three in the maxillary sinus, two in the nasal cavity, one in the sphenoid sinus, and one in the nasopharynx.

Morphological findings and immunohistochemistry

Table 2 shows the pathological types and immunohistochemical results. Five cases were classified as colonic type (fig 1A), five were papillary (fig 1B), and one was mixed, showing papillary architecture with abundant extracellular mucin production. One case was a low grade sinonasal papillary adenocarcinoma (LGSA) (fig 1C) and an additional case was a papillary nasopharyngeal adenocarcinoma (fig 1D). The cases classified as ITAC showed a variable cellular appearance and were composed of a mixture of tall columnar absorptive

cells, atypical stratified cylindrical cells similar to the cells seen in conventional colorectal adenocarcinomas, goblet cells, and large round to polygonal non-descriptive epithelial cells. Paneth cells were seen in four cases and neuroendocrine cells with infranuclear cytoplasmic granules were readily seen in three. Of the tumours designated as ITAC, six were positive for CK7, CK20, CDX-2, and villin (fig 2). Four cases were negative for CK7 (fig 3), and positive for CK20, villin, and CDX-2. In summary, all tumours classified as ITACs were CK20 positive, villin positive, and CDX-2 positive, and six of 10 coexpressed CK7 and CK20. No differences in immunophenotype were seen between the papillary and colonic subtypes, or between those tumours with Paneth cells and those without. The papillary nasopharyngeal adenocarcinoma showed a distinctly different phenotype, and was positive for CK7 but negative for CK20, villin, and CDX-2. The non-ITAC LGSA was also CK7 positive and completely negative for CK20, villin, and CDX-2. The adjacent normal respiratory epithelium was positive for CK7, and negative for CK20, villin, and CDX-2.

Squamous metaplasia was identified in non-neoplastic mucosa in one patient. Intestinal metaplasia was present in one case (fig 4A). This focus of intestinal metaplasia was found 2 mm from carcinoma in situ and involved glandular epithelium. The metaplastic focus comprised atypical cylindrical epithelium and goblet cells, closely resembling a tubular adenoma of the colon. The metaplastic focus partially involved seromucous glands and was covered by morphologically normal surface ciliated respiratory epithelium. The focus of intestinal metaplasia was negative for CK7 and positive for CK20, CDX-2, and villin (fig 4B–D). The neighbouring non-metaplastic glandular and surface epithelia retained their CK7 positive phenotype, with lack of expression of CK20, CDX-2, and villin. The invasive adenocarcinoma associated with this area of metaplasia showed a similar phenotype.

DISCUSSION

We investigated the expression of CK7, CK20, CDX-2, and villin in 10 cases of ITAC, one LGSA, and a papillary adenocarcinoma of the nasopharynx. We found that all 10 cases of ITAC were positive for CK20 with six also coexpressing CK7. Furthermore, all 10 cases were also positive for CDX-2 and villin, demonstrating a distinctive intestinal phenotype. These results are in agreement with a small number of previous studies that investigated the expression of CK7 and CK20 in ITACs.^{7 8 18 19} Krane *et al* reported the coexpression of CK7 and CK20 in five cases of ITAC.¹⁸ Bashir *et al* also reported positive staining for CK7 and CK20 in three of their four cases of ITAC.⁷ The only case in the series by Bashir *et al* lacking CK20 staining was a colloid carcinoma, which incidentally was positive for CK7.⁷ Whether this tumour is indeed an example of ITAC is arguable because no additional stains such as CDX-2 and villin were performed. In a larger study, 15 ITACs reported by Franchi *et al* were also positive for both CK7 and CK20.¹⁹ Unlike these early reports, Choi *et al* found that some ITACs lack expression of CK7.⁸ These investigators found that all their seven cases of ITAC were positive for CK20; however, four lacked CK7 staining.⁸ Our results and the published literature show that all ITACs are consistently positive for CK20, and that most cases coexpress CK7 and CK20; however, we also confirmed the findings of Choi and colleagues⁸ that a smaller but significant proportion of ITACs possess a CK7–/CK20+ phenotype. Choi *et al* have suggested that coexpression of CK7 and CK20 results from a more rapid metaplastic transformation from respiratory epithelium to intestinal-type epithelium, whereas a longer transition time may allow time for the first set of cytokeratin

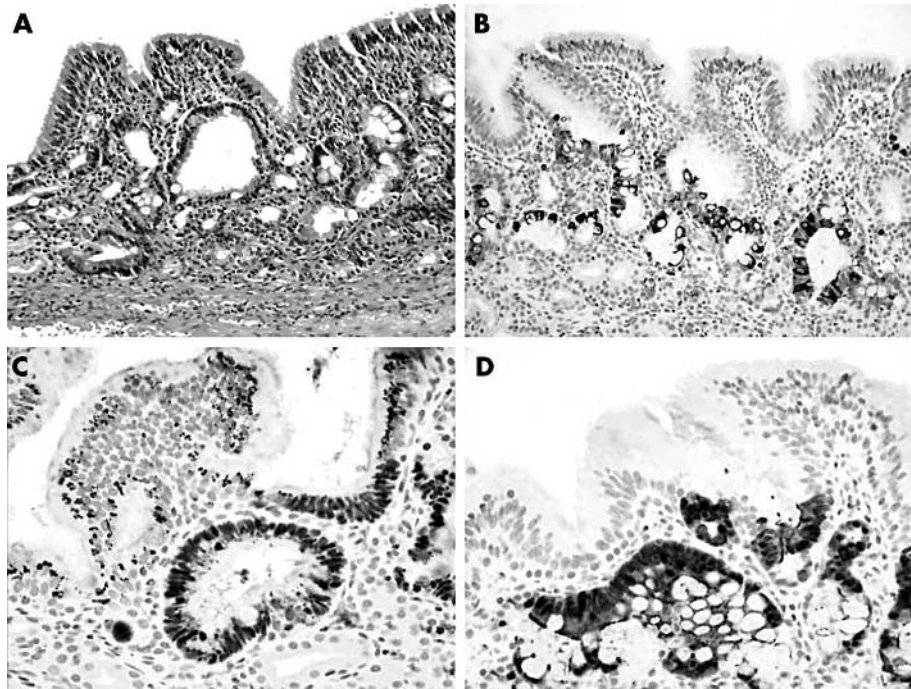


Figure 4 (A) Intestinal metaplasia of the nasal mucosa with columnar and goblet cells predominantly involving seromucous glands; (B) expression of cytokeratin 20 (CK20) by goblet cells in nasal mucosa with intestinal metaplasia; (C) strong nuclear expression of CDX-2 by metaplastic cells—note the lack of staining in the adjacent respiratory epithelium; (D) villin expression in intestinal metaplasia of the seromucous glands. The surface respiratory epithelium is negative.

genes to disappear and leave a solely CK20 positive profile.⁸ Thus, based on cytokeratin profiles, our results suggest that two divergent subsets of ITAC exist—one shows an expression profile similar to colorectal adenocarcinoma and the other resembles other upper gastrointestinal tract tumours. These findings may be useful for identifying differences in behaviour between the two groups, although a larger study with follow up is needed to determine this.

“Based on cytokeratin profiles, our results suggest that two divergent subsets of intestinal-type sinonasal adenocarcinoma exist—one shows an expression profile similar to colorectal adenocarcinoma and the other resembles other upper gastrointestinal tract tumours”

CDX-2 is a transcription factor product of the CDX-2 homeobox gene. This gene is one of the earliest genes involved in intestinal differentiation and plays an essential role in the proliferation and differentiation of intestinal epithelial cells.¹¹ CDX-2 expression is largely but not absolutely confined to adenocarcinomas of the gastrointestinal and pancreaticobiliary tracts.¹⁶ CDX-2 expression in

tumours outside of the gastrointestinal tract includes mucinous adenocarcinomas of the ovary and adenocarcinomas of the urinary bladder.¹⁶ To the best of our knowledge, only one other study to date has investigated CDX-2 expression in sinonasal ITACs.¹⁹ Franchi *et al* demonstrated nuclear expression of CDX-2 in 15 cases of ITAC.¹⁹ Five tumours showed focal staining (5–10% of tumour cells), whereas the remainder showed diffuse positivity in > 50% of the tumour cells. CDX-2 staining was not present in normal respiratory mucosa or seromucous glands. In our study, using a similar antibody, we detected strong and diffuse nuclear expression of CDX-2 in nine of 10 cases. Only one case showed expression in 25–50% of the cells. As noted by Franchi *et al*, we found no CDX-2 staining in normal respiratory mucosa or seromucous glands.¹⁹

Villin is a cytoskeletal protein required for the formation of brush border microvilli in normal small intestine, colon, pancreatic ducts, biliary system, and proximal renal convoluted tubules. Villin expression is conserved in all gastrointestinal adenocarcinomas including colonic, gastric, pancreaticobiliary, and Barrett’s oesophagus and adenocarcinomas.^{12–17} These tumours show a characteristic apical or brush border pattern of expression. Villin expression in ITAC

Table 1 Panel of antibodies used

Antigen	Source	Clone	Dilution	Digestion
CK7	DakoCytomation, Glostrup, Denmark	OV-TL 12/30	1/2000	Proteinase
CK20	DakoCytomation	K ₂₀ .8	1/100	Proteinase
Villin	Novocastra, Newcastle upon Tyne, UK	CWWB1	1/100	Citrate, pH 6.0
CDX-2	BioGenex, San Ramon, California, USA	CDX2-88	1/100	Citrate, pH 6.0

Table 2 Histological types and immunohistochemical profile

Case	Histology	CK7	CK20	Villin	CDX-2
1	Colonic, grade 3	Negative	3+	3+	3+
2	Papillary, grade 3	Negative	3+	3+	3+
3	Mixed (papillary with mucinous component), grade 3	Negative	3+	3+	3+
4	Colonic grade 2	Negative	1+	3+	3+
5	Papillary, grade 2	1+	3+	3+	3+
6	Papillary, grade 2	1+	3+	3+	3+
7	Colonic, grade 2	1+	3+	3+	3+
8	Colonic, grade 2	2+	3+	3+	3+
9	Papillary, grade 2	3+	2+	3+	2+
10	Colonic, grade 2	3+	3+	3+	3+
11	Papillary nasopharyngeal adenocarcinoma	3+	Negative	Negative	Negative
12	Sinonasal papillary low grade adenocarcinoma	3+	Negative	Negative	Negative

CK, cytokeratin.

had not been previously studied. In keeping with the distinctive intestinal appearance of ITAC, all of our patients showed strong apical staining for villin. Similar to CDX-2, no staining for villin was seen in normal mucosa or seromucous glands.

The differential diagnosis of ITAC includes LGSA,^{20, 21} primary adenocarcinomas of the nasopharynx,²² and metastatic intestinal adenocarcinomas.²³ In general, low grade sinonasal adenocarcinomas show tubulocystic or papillary patterns and are composed of a single layer of eosinophilic cuboidal or columnar cells. These tumours must be properly distinguished from ITAC because they have a much less aggressive clinical course and better prognosis.^{20, 21} The distinction between typical ITAC and LGSA is based on the higher grade of most ITACs and their predominant cell population of cylindrical cells and goblet cells. However, this distinction can be difficult in low grade papillary ITACs. Our case of papillary nasopharyngeal adenocarcinoma was also difficult to distinguish from papillary ITAC because it contained a large number of mucous cells. However, the CK7 and CK20 profile and the expression of CDX-2 and villin were useful in distinguishing ITAC from these two non-ITAC adenocarcinomas. Both non-ITAC sinonasal and nasopharyngeal adenocarcinomas retained the CK7+/CK20-/CDX-2-/villin- phenotype of surface respiratory epithelium and seromucous glands. These results are mostly similar to the experience reported by Bashir and colleagues⁷ and Choi *et al*,⁸

who found that most ITACs were positive for CK20, with a small proportion coexpressing CK7 and CK20, whereas all non-ITACs were always negative for CK20 and positive for CK7.

Other than the two cases presented in our report, there is no previously published experience with CDX-2 and villin in non-ITAC sinonasal adenocarcinomas, but the consistent expression of these two antigens in adenocarcinomas of the gastrointestinal tract suggest that they are helpful in separating ITAC from other non-ITAC sinonasal and nasopharyngeal adenocarcinomas. Given the similarities between ITAC and colorectal adenocarcinoma, the expression of CK20, CDX-2, and villin does not seem to be useful for distinguishing primary ITAC from metastatic intestinal adenocarcinoma. The coexpression of CK7 and CK20 largely excludes a metastasis from a colorectal adenocarcinoma, but will not necessarily exclude metastases from gastric, oesophageal, or pancreaticobiliary primaries.^{8, 19}

The identification of precursor lesions of ITAC is not only academically intriguing but also clinically important because it may allow early detection and surgical intervention in patients at increased risk as a result of occupational exposure. However, the identification of these putative preinvasive lesions has remained elusive and controversial. Several studies have reported an increased incidence of squamous metaplasia in woodworkers,²⁴ whereas others have described goblet cell hyperplasia, cuboidal metaplasia,²⁵ and cuboidal metaplasia with dysplasia.²⁶ Kleinsasser and colleagues^{27, 28} argue that ITACs arise de novo from "intraepithelial mucous glands" on the surface ciliated epithelium. The identification of a specific immunophenotype for ITAC may help in the identification of its precursor lesions. Choi *et al* found intestinal metaplasia in surface respiratory epithelium in four of their seven cases of ITAC.⁸ These metaplastic foci were accompanied by conversion from CK7 positivity to CK20 positivity. In our series, we also found a case with a focus of intestinal metaplasia. The metaplastic focus showed a phenotype (CK7-/CK20+/CDX-2+/villin+) similar to the invasive carcinoma, whereas the non-neoplastic mucosa retained its CK7+/CK20-/CDX-2-/villin- phenotype. Our observations and the results reported by Choi and colleagues⁸ suggest that the development of ITACs is preceded by intestinal metaplasia, with conversion from a normal CK7+/CK20-/CDX-2-/villin- phenotype to an abnormal CK7-/CK20+/CDX-2+/villin- intestinal phenotype. None of the previous studies describing the presence of cuboidal metaplasia and dysplasia in woodworkers investigated the immunophenotype of these putative preneoplastic lesions; however, the use of this group of antibodies may provide a better definition of these lesions and clarify their relation to ITAC. There is experimental evidence derived from studies in oesophageal keratinocytes with chronic acid exposure and

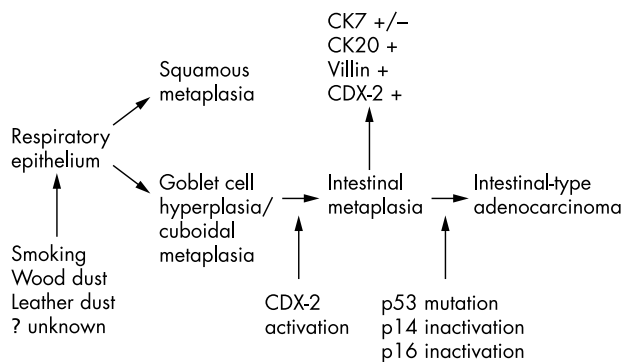


Figure 5 Hypothetical pathogenesis of intestinal-type sinonasal adenocarcinoma (ITAC). Exposure to hardwood and leather dusts, smoking, and other unknown agents induces metaplasia in the respiratory mucosa. In most cases, the respiratory mucosa undergoes squamous metaplasia. In other cases, the respiratory mucosa undergoes goblet cell hyperplasia or cuboidal metaplasia. CDX-2 activation may induce and maintain intestinal metaplasia with the acquisition of a full intestinal phenotype. Additional genetic events such as p53 mutations and p14 and p16 inactivation may be necessary for the development of invasive ITAC.

Take home messages

- Sinonasal intestinal-type sinonasal adenocarcinomas (ITACs) have a distinctive immunophenotype—all cases express CK20, CDX-2, and villin
- Most ITACs also express CK7, although a small but significant proportion do not
- It appears that ITAC is preceded by intestinal metaplasia of the respiratory mucosa, which is accompanied by a phenotypic switch to an intestinal phenotype
- The expression of CK7, CK20, CDX-2, and villin is useful in separating these tumours from other non-ITAC adenocarcinomas of the sinonasal tract and nasopharynx

gastric intestinal metaplasia that CDX-2 becomes activated,^{13 14 29 30} and possibly plays a crucial role in the development and maintenance of an intestinal phenotype. Additional genetic events such as p53 mutations, and p14 and p16 inactivation may be necessary for the development of invasive adenocarcinoma.³¹ Based on a review of the literature, we propose a hypothetical model of the pathogenesis of ITAC (fig 5). Further investigation of the possible role of certain genes and their products, such as CDX-2 and MUC2, in the mucosa of woodworkers seems warranted.

“Our observations suggest that the development of intestinal-type sinonasal adenocarcinoma is preceded by intestinal metaplasia, with conversion from a normal CK7+/CK20–/CDX-2–/villin– phenotype to an abnormal CK7–/CK20+/CDX-2+/villin– intestinal phenotype”

Sinonasal ITACs show a distinctive phenotype, with all cases expressing CK20, CDX-2, and villin. Most ITACs also express CK7; however, there is a small but significant proportion of tumours that lack staining for CK7. ITAC seems to be preceded by intestinal metaplasia of the respiratory mucosa, which is accompanied by a phenotypic switch to an intestinal phenotype. The expression of CK7, CK20, CDX-2, and villin is useful in separating these tumours from other non-ITAC adenocarcinomas of the sinonasal tract and nasopharynx.

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