

## REVIEW

## HPV infections in benign and malignant sinonasal lesions

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*J Clin Pathol* 2003;56:174–181

This review updates the evidence that the human papillomavirus (HPV) is involved in the development of benign and malignant sinonasal lesions. Since the early 1980s, when evidence was provided on the possible involvement of HPV in the aetiology of both benign respiratory papillomas and squamous cell carcinomas, a substantial number of studies have explored this issue. To date, 33.3% of sinonasal papillomas and 21.7% of sinonasal carcinomas analysed have been shown to be positive for HPV. Many elements of the data parallel the observations made in HPV lesions at other mucosal sites, such as malignant transformation and frequent recurrence after radical treatment; the fact that low risk HPV types 6 and 11 are usually confined to benign lesions, whereas the reverse is true for the oncogenic HPV types 16 and 18; and the presence of squamo-columnar junctions and squamous cell metaplasia in the sinonasal system. The discrepancies reported by several studies might result in part from technical reasons, but it is also possible that sinonasal lesions have a heterogeneous aetiology (HPV related and non-related) and/or that some novel (yet unidentified) HPV types exist in these lesions, which are detected by some studies but not by others.

evidence supporting a causal role for HPV in the development of benign papillomas and squamous cell carcinomas of the nasal mucosa and paranasal sinuses, evidence which is discussed in more detail in my recent textbook.<sup>1</sup>

**MUCOSA OF THE NASAL CAVITY AND PARANASAL SINUSES**

The mucosal lining of the nasal cavity and paranasal sinuses is made up of pseudostratified ciliated columnar epithelium, with a prominent secretory component. This mucous membrane (also called schneiderian membrane) is derived from both the neuroectoderm of the olfactory placode and from the nasopharyngeal mucosa of endodermal origin.<sup>2</sup> Such a divergent origin probably explains the very different histological appearance of benign papillomas at this site.<sup>1,12–14</sup> Because of their identical histology and biological behaviour (in the nasal mucosa and sinuses), in addition to their frequently multifocal appearance and spread throughout the sinus system (even to the pharynx, middle ear, and mastoid), all papillomas in this region are known collectively as sinonasal papillomas.<sup>1,12–17</sup>

**SINONASAL PAPILOMAS**

Papillomas of the nasal mucosa have been recognised since 1854, when first described with the name inverted papilloma.<sup>18,19</sup> The interesting early history of nasal papillomas (polyps) was reviewed in 1935 by Kramer *et al*, who were the first to make the important distinction between true papillomas and inflammatory polyps.<sup>20</sup> Since that time, the literature on nasal papillomas has expanded rapidly.<sup>1,3,12,21</sup> Until 1998, approximately 1700 nasal papillomas had been reported, of which 1300 were reported during the past 20 years.<sup>1,22–24</sup>

Despite this, however, the pathogenesis and aetiology of nasal papillomas had not been studied intensely until recently.<sup>1,2,12–17,25</sup> The earlier confusion about their pathogenesis is reflected by the highly divergent nomenclature used to describe these lesions.<sup>12,21,26</sup> A distinction into three different morphological types of sinonasal papillomas, namely—(1) exophytic (everted) squamous cell papilloma, (2) inverted papilloma, and (3) cylindric cell papilloma—seems justified, and may have implications for the aetiology,

The respiratory tract comprises several distinct anatomical sections including the nasal cavity, paranasal sinuses, nasopharynx, oropharynx, hypopharynx, larynx, trachea, and bronchi. The epithelial lining in the major part of the respiratory tract is composed of respiratory epithelium (columnar cells), whereas stratified squamous epithelium covers the mucosa of the pharynx and a part of the larynx.<sup>1</sup> This coexistence of two different epithelia creates squamo-columnar junctions (SCJs) at multiple sites in the respiratory tract, entities that are thought to be a prerequisite for the spread of human papillomavirus (HPV) infections in this region.<sup>1–9</sup> Because of this divergent histology of the mucosal lining, a wide variety of both benign and malignant tumours arises in the respiratory tract.<sup>2–6,10</sup> Since the early 1980s when the first evidence was provided on the possible involvement of HPV in the aetiology of both benign respiratory papillomas and squamous cell carcinomas (SCCs), a rapidly growing interest in the tumours of this region has resulted in the accumulation of a substantial number of papers exploring such evidence.<sup>2,9,11</sup> My present review updates the

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Accepted for publication  
11 October 2002

pathogenesis, recurrence, and malignant transformation of these lesions.<sup>1 12 21</sup>

### Epidemiology

For simplicity, sinonasal papillomas are discussed collectively in this section, despite the differences in their clinical presentation and behaviour, as recently reviewed.<sup>1 2 4 5</sup> Overall, sinonasal papilloma is a rare disease. Based on extensive series, the annual incidence of sinonasal papillomas seems to be in the order of 0.6/10<sup>5</sup> in defined geographical regions.<sup>24</sup> Data from the studies reported between 1972 and 1992, based on 1325 cases, indicate that men are more frequently affected than women, with a male to female ratio of 3 : 1.<sup>25</sup> The mean age of the patients was 53 years, but the disease can also occur in children.<sup>27</sup>

“Based on a meta-analysis of the reports covering 1972 to 1992, the overall recurrence rate is substantial—32%—with a variation from 0% to 100%”

There are two characteristic features in the natural history of sinonasal papillomas, those of the inverted type in particular: (1) the tendency to recurrence even after radical treatment, and (2) a substantial potential for malignant transformation,<sup>2 4 11 21 25 28</sup> convincingly demonstrated in practically all series reported since the recognition of sinonasal papillomas as a disease entity (reviewed in Syrjänen<sup>1</sup>). Based on a meta-analysis of the reports covering 1972 to 1992, the overall recurrence rate is substantial—32%—with a variation from 0% to 100%.<sup>25 28</sup> This high recurrence rate as such clearly suggests an infectious aetiology of these papillomas, with a clinical behaviour closely resembling that of recurrent respiratory papillomatosis and genital condylomas.<sup>1 6 10</sup> This fact was already emphasised in our primary report, where the possible involvement of HPV in sinonasal papillomas was suggested for the first time.<sup>29</sup>

Another characteristic feature of sinonasal papillomas is their considerable malignant potential, extensively documented in numerous reports during several decades, and discussed in more detail later.<sup>1 2 4 6 25 30 31</sup>

### Clinical features

On clinical examination, nasal papillomas are usually large and bulky, presenting with a deep red to grey colour and prominent vascularity.<sup>32</sup> As the name implies, sinonasal papillomas can affect the mucosa of the entire paranasal sinus system, including the maxillary, sphenoid, and ethmoid sinuses.<sup>1 2 6</sup> Extension to the pharynx, external ear, and mastoid has been reported occasionally.<sup>1 15 17</sup> In larger series, papillomas are bilateral in about 8% of cases.<sup>1</sup> In addition, true multicentricity appears to be substantial, with figures ranging from 4.5%<sup>33</sup> up to 20%<sup>14 16 34</sup> having been reported. It should be emphasised that such a multicentric presentation is one of the key features of HPV lesions at other mucosal sites—for example, the larynx, the lower genital tract, and peri-anal region.<sup>1–10</sup> The question is: are these multiple lesions truly multicentric in origin or do they result from dissemination from a single original lesion? Probably both of these scenarios are true, because dissemination into the nasopharynx, middle, and even external ear as a result of surgical manipulation of sinonasal papillomas was recently reported.<sup>35</sup>

### Morphology

#### Exophytic (everted) squamous cell papilloma

The light microscopic appearance of these exophytic lesions is identical to squamous cell papillomas (SCPs) at other mucosal sites.<sup>1 4 6 21</sup> Depending on tumour localisation, the squamous epithelium may range from immature (basal type) to fully keratinised epithelium, particularly in the nasal vestibulum. Regularly, small fragments or zones of respiratory epithelium

are found intermingled between the squamous epithelium. Such an abrupt change from columnar to squamous epithelium is analogous to the SCJ in the transformation zone of the uterine cervix.<sup>1 6 9 10</sup> Probably, the same process of squamous metaplasia is operative in the nasal mucosa also.<sup>1 2 12</sup> In my experience, and that of others, these exophytic SCPs exhibit areas of dysplasia in a considerable proportion (approximately 10–15%) of cases.<sup>29 36 37</sup>

#### Inverted papilloma

As the name implies, inverted papilloma (IP) is characterised by an endophytic growth pattern, and this morphological variant is by far the most frequent of all sinonasal papillomas.<sup>12 21 24 36</sup> IP is usually a unilateral lesion with its origin in the lateral wall of the nose, ethmoid sinus, or maxillary antrum. IP is not a real papilloma, but rather a polypoid change of the mucosa, where metaplastic squamous epithelium gradually replaces the respiratory epithelium on the surface of these polypoid masses and the glandular ducts within these polyps.<sup>12 21 29</sup> The residual respiratory epithelium usually remains intermingled with the metaplastic squamous epithelium, creating numerous SCJs in the three dimensional array of these extensive lesions.<sup>38–41</sup> In addition to such abrupt junctions, small microcystic spaces regularly remain within the squamous epithelium, as an indication of the progressing squamous metaplasia.

Of importance in this morphological variety is its distinction from a low grade SCC. Low grade SCC can cause serious differential diagnostic problems with IP, especially when well differentiated.<sup>12 21 38 41–44</sup> Indeed, malignant transformation or concomitant presence of SCC are prone to occur in IPs, in contrast to exophytic SCPs, where such an occurrence is extremely rare. Needless to say, such a distinction of benign IP from SCC is of major clinical importance.<sup>12 21</sup>

#### Cylindric cell papilloma

The concept of the third morphological variant, a cylindric cell papilloma (CCP), was introduced in 1971 by Hyams, based on the analysis of a large series of such cases.<sup>33</sup> This third morphological variant is now generally recognised as an entity of its own, distinct from SCC and IP.<sup>1 2</sup> CCP is characterised by slender papillary projections of the nasal-type mucosa, with extensive branching to the second or even third degree. The epithelium covering the outgrowths is columnar, but can also be of the oncocytic type. Because of the tangential sections of this three dimensional growth, the epithelium may give rise to a glandular appearance in some areas of the papilloma. As in IPs, microcysts are also regularly encountered within the covering epithelium.<sup>12 21</sup> Malignant transformation has been reported occasionally in association with CCPs, but it seems to be far less common than with IPs.<sup>33 42 45 46</sup>

## EVIDENCE FOR HPV INVOLVEMENT IN SINONASAL PAPILOMAS

### Expression of HPV structural proteins

Despite the extensive number of studies published on sinonasal papillomas since their first description in 1854,<sup>1 6</sup> only a few studies investigated the possible aetiological factors of this tumour until the early 1980s.<sup>47</sup> Then, prompted by the recently established association of HPV with benign and malignant genital lesions and laryngeal SCPs, in addition to the emerging evidence on the involvement of HPV in other squamous cell lesions of the aerodigestive tract,<sup>9 10</sup> I examined a nasal SCP for evidence of HPV antigen expression using immunohistochemistry (IHC).<sup>29</sup> In this primary report, morphological similarities between sinonasal SCPs and established HPV lesions (exophytic condylomas) were emphasised, and indeed, the expression of HPV structural antigens was confirmed by IHC.

**Table 1** Detection of HPV DNA in sinonasal papillomas and carcinomas

Type of lesion	Technique	No. of cases	HPV type detected							Total (%) HPV+	First author (ref)	Year
			6	6/11	11	16	16/18	18	Other			
SCP	IH	1								100	Syrjänen <sup>29</sup>	1983
IP	ISH	14	1		5	5*				79	Syrjänen <sup>37</sup>	1987
SCC	ISH	3				3				100		
IP	SB	2			2					100	Respler <sup>48</sup>	1987
IP	ISH	21			11					52	Weber <sup>49</sup>	1988
IP	SB	2				1				50	Bradsmā <sup>50</sup>	1989
IP	ISH	7	3			1				57	Brandwein <sup>51</sup>	1989
SCP	SB	1							HPV57a	100	de Villiers <sup>52</sup>	1989
VV	ISH	2							HPV2	100	Furuta <sup>53</sup>	1989
IP	ISH	26†			3	1				16		
IP	IH, ISH	21								62	Siivonen <sup>32</sup>	1989
IP	PCR	ND								ND	Bryan <sup>54</sup>	1990
IP	ISH	26†			3	1				16	Furuta <sup>55</sup>	1990
SCC	ISH	40				4		1		12.5		
IP	SB	7	1							14	Ishibashi <sup>56</sup>	1990
IP	DB	1								4	Vonka <sup>57</sup>	1990
IP	DB, ISH	26			3					12	Furuta <sup>58</sup>	1991
SCC	DB, ISH	2				1				50		
SCC	PCR	8	1							12	Judd <sup>59</sup>	1991
IP	PCR	12								0		
SCP	PCR	7			3					43		
IP	ISH	9	8							89	Fu <sup>60</sup>	1992
IP	ISH	15	6							40	McLachlin <sup>61</sup>	1992
SCP	PCR	5	3							60		
IP	PCR	29	2		5					24	Kashima <sup>62</sup>	1992
SCP	PCR	26	3		1					15		
SCC	PCR	24					1			4		
SCC	PCR	49				6		1		14	Furuta <sup>63</sup>	1992
IP	DB, SB	3						1		0	Ogura <sup>64</sup>	1992
SCP	DB, SB	2			1					50		
SCC, SCP	ISH, PCR	35	1							3	Sarkar <sup>65</sup>	1992
IP	ISH, PCR	14		3						21.4	Buchwald <sup>66</sup>	1993
IP	SB, PCR	8							1, ND	12.5	Gilain <sup>67</sup>	1993
SCC	PCR	3				1				33	Tyan <sup>68</sup>	1993
SCC, SCP	ISH, PCR	22								86	Wu <sup>69</sup>	1993
IP, SCC	PCR	29		14		19§			57b‡	69	Arndt <sup>70</sup>	1994
NP	PCR	30								0	Becker <sup>71</sup>	1994
IP	SB	17	1		1			3		29	Nakano <sup>72</sup>	1994
IP	ISH	26								0	Tang <sup>73</sup>	1994
SCP	ISH	7		6						86		
IP	PCR	32							ND	63	Beck <sup>74</sup>	1995
IP	PCR	32	12		6	1	1			63	Beck <sup>75</sup>	1995
SCC	PCR	7				3	1			57		
IP	ISH, PCR	52		3						6	Buchwald <sup>42</sup>	1995
SCP	ISH, PCR	16		11						69	Buchwald <sup>76</sup>	1995
CCP	ISH, PCR	5								0		
SCC	ISH, PCR	5		1			1			40		
IP	PCR	14								0	Hosone <sup>77</sup>	1995
IP	PCR	20							9, ND	45	MacDonald <sup>78</sup>	1995
IP	SB	1							57	100	Ogura <sup>79</sup>	1995
IP, SCP	ISH, PCR	28	3		3	1				25	Gaffey <sup>80</sup>	1996
IP, SCP	SB, PCR	12							5, ND	42	Ogura <sup>81</sup>	1996
IP	PCR	40	5	7	5					42.5	Shen <sup>82</sup>	1996
SCC	PCR	14			3					21		
IP	PCR	21		6				1		33	Bernaer <sup>83</sup>	1997
SCP, IP	PCR, ISH	24¶		1				1		100	Buchwald <sup>84</sup>	1997
SCC	PCR	9				3				33	Caruana <sup>85</sup>	1997
IP	PCR	15	1		1	4				40		
IP	PCR	38			30	18		2		79	Zhou <sup>86</sup>	1997
IP	PCR	1	1							100	Harris <sup>87</sup>	1998
IP	PCR	1**					1			100	Jones <sup>88</sup>	1998
SCC	PCR	19				3				16	Mineta <sup>89</sup>	1998
IP	PCR	30							ND	20	Mirza <sup>90</sup>	1998
SCP	P	13							ND	ND	Franzman <sup>91</sup>	1998
IP		12							ND	ND		
SCC		5							ND	ND		
IP	PCR	36	1	2						9	Hwang <sup>92</sup>	1998
IP+SCC	PCR	6				2				33		
IP	PCR	10				4				40	Kassim <sup>93</sup>	1998
IP	PCR	36							ND	58	Wang <sup>94</sup>	1998
IP+SCC	PCR	16							ND	69		
VC	PCR	13								0	Orvidas <sup>95</sup>	1999
SCP	PCR	27						2		7.4	Saegusa <sup>96</sup>	1999
IP	PCR	28						6		36		
SCC	PCR	32						9		28		
IP	ISH	1		1						100	Luceno <sup>97</sup>	1999
SCP	ISH, PCR	5			2					40	Kraff <sup>98</sup>	2000

**Table 1** continued

Type of lesion	Technique	No. of cases	HPV type detected							HPV+	Total (%) First author (ref)	Year
			6	6/11	11	16	16/18	18	Other			
Type of lesion	Technique	No. of cases	HPV type detected							Total (%) HPV+	First author (ref)	Year
			6	6/11	11	16	16/18	18	Other			
IP+SCC	ISH, PCR	34(4)	1		1					6		2001
CCP	ISH, PCR	4								0		
IP	IH	57								9	Delank <sup>99</sup>	2000
SCC	ISH, PCR	14		3			2			36	Suarez <sup>100</sup>	2000
SCC	PCR	35							ND	20	Buchwald <sup>101</sup>	2001
IP	PCR	20							ND	80	Schwerer <sup>102</sup>	2001
SCC	PCR	5								40		

\*Double infection with HPV-11 and HPV-16 in 3 cases; †same cases in Furata and colleagues<sup>53-55</sup>; ‡19 cases HPV-57b positive; §double infection with HPV-6/11 and HPV-16 in 13 cases; ¶both underwent malignant transformation; \*\*extended to eustachian tube. CCP, cylindric cell papilloma; DB, dot blot hybridisation; IH, immunohistochemistry; IP, inverted papilloma; ISH, in situ hybridisation; ND, not clearly defined; NP, nasal polyp; PCR, polymerase chain reaction; SB, southern blot hybridisation; SCC, squamous cell carcinoma; SCP, squamous cell papilloma; VC, verrucous carcinoma; VV, verruca vulgaris of nasal vestibulum.

### Detection of HPV DNA

These observations prompted our further interest in these lesions, and led to the collection of a series of similar lesions, including 14 benign sinonasal papillomas and three SCCs. These were subjected to HPV DNA analysis using in situ hybridisation (ISH).<sup>37</sup> Not unexpectedly, seven of the 14 papillomas expressed HPV antigens, and 11 were HPV DNA positive: one for HPV-6, five for HPV-11, two for HPV-16, and three for both HPV-11 and HPV-16. All SCCs proved to contain HPV-16 DNA. Importantly, these observations in the first series of sinonasal lesions ever analysed for HPV suggested that benign papillomas are preferentially (but not exclusively) associated with the low risk HPV types 6 and 11, whereas their malignant counterparts are exclusively positive for HPV-16 DNA.<sup>37</sup>

"The low risk human papillomavirus types 6 and 11 are by far the two most frequent viral types detected in benign lesions"

Following these two reports, HPV research was extended to an entirely new field when other groups started analysing their sinonasal tumours for HPV. In less than 10 years (until the completion of the chapter in our textbook in early 1998<sup>1</sup>) this had resulted in a total of 41 studies, where HPV DNA was analysed in benign and malignant sinonasal tumours. By that time, a total of 714 sinonasal papillomas had been analysed, using various hybridisation techniques; dot blot, ISH, Southern blot, and the polymerase chain reaction (PCR). Table 1 summarises these studies.<sup>32 37 42 48-62 64-67 69-87</sup> Of these 714 papillomas, HPV DNA has been detected in 260 cases (a detection rate of 36.4%). The low risk HPV types 6 and 11 are by far the two most frequent viral types detected in these benign lesions. A few cases have been shown to contain HPV-16 or HPV-18 DNA.<sup>51 70 75 80 85 86</sup> Most HPV positive cases are of the IP type and, to date, HPV has not been detected in CCP.

Since the completion of the monograph,<sup>1 9</sup> a series of studies appeared between 1998 and 2002, and are now included in table 1.<sup>88 90-94 96-99 102</sup> These recent studies contribute substantially to the total number of sinonasal papillomas analysed for HPV until the autumn of 2002, by adding 327 new cases (table 1). Of these newly reported cases, 87 (26.6%) were shown to contain HPV DNA. As before, the detection rates are subject to wide variation, from 0% to 100%. The effect of the different technology used for the analysis of HPV DNA will be dealt with later. The appearance of so many recent studies reflects a significantly increased interest in these lesions among HPV researchers.<sup>1 6 103</sup> Taken together, the current literature now contains 1041 sinonasal papillomas subjected to HPV detection with different hybridisation methods or PCR, and HPV DNA has been reported in 347 (33.3%) of these cases.

### SINONASAL CARCINOMA

#### Epidemiology

Cancer of the nasal cavity and paranasal sinuses is a rare disease.<sup>26</sup> For example, according to the data from the Finnish Cancer Registry, the age adjusted incidence rates are 0.3/100 000 and 0.6/100 000 for women and men, respectively.<sup>104</sup> Thus, men are more often affected than women. SCC is by far the most frequent malignant tumour of this region. Unfortunately, no such figures are available globally because GLOBOCAN or other IARC data bases do not report sinonasal carcinomas as a separate entity.<sup>105</sup>

During the past few years, several different agents have been implicated as risk factors for these malignancies.<sup>106-113</sup> Among the foremost of these factors, cigarette smoking and different occupational exposures (for example, working in the nickel and wood industries) have been listed. However, a detailed discussion of all these data and special subtypes of sinonasal carcinomas falls outside the remit of this review.

#### Evidence for HPV involvement in sinonasal carcinomas

The increased interest in these malignancies parallels the research activity focused on their benign counterparts since the 1980s, when evidence on the possible involvement of HPV was first provided.<sup>29 32 37 48-50</sup> The evidence on HPV as a potential aetiological agent in sinonasal cancer is derived from two major lines of research, namely: (1) the reports on malignant transformation of benign (HPV associated) papillomas, and (2) direct detection of HPV DNA in sinonasal carcinomas by hybridisation assays and PCR (table 1).

#### Malignant transformation of sinonasal papillomas

For a detailed discussion of the voluminous literature on malignant transformation of sinonasal papillomas, the reader is referred to recent comprehensive reviews.<sup>25 30 31 114 115</sup> When considering the papilloma-carcinoma sequence, it is important to make a distinction between: (1) those cases where an invasive disease has succeeded a pre-existing benign papilloma (metachronous), and (2) those cases where SCC is detected concomitantly with a papilloma (synchronous),<sup>30</sup> which is not always possible.

"The question arises as to whether the aetiological agent responsible for these papillomas persists in the mucosa after treatment and continues to exert its oncogenic effects on the target cells, resulting in frequent tumour recurrence and eventually malignant transition"

Based on a total number of 1325 reported cases, the rate of metachronous malignancy was 3%, varying within relatively

narrow limits (0–16%).<sup>25</sup> However, in the same material, the detection rate of a synchronous malignancy varies with a much wider range, from 0% to 100%, with a mean rate of 8%.<sup>25 30 31 114 115</sup> Together with this malignant potential, the observed tendency for recurrence after treatment also has important implications for the treatment and follow up of patients, which is frequently problematical.<sup>25 116–119</sup> Clearly, the question arises as to whether the aetiological agent responsible for these papillomas persists in the mucosa after treatment and continues to exert its oncogenic effects on the target cells, resulting in frequent tumour recurrence and eventually malignant transition.<sup>1 4–6</sup> This type of behaviour neatly fits with the known characteristics of tumour viruses, such as HPV. Indeed, HPV DNA has recently been detected in the normal mucosa of the nasal cavity, substantiating this view.<sup>120–122</sup>

### Detection of HPV DNA in sinonasal carcinomas

The discoveries made in the genital tract since the late 1970s, where HPV was shown to be associated with benign condylomas, flat lesions, and precancerous and cancer lesions,<sup>9–11</sup> has led us to explore the involvement of HPV at other mucosal sites,<sup>9 10</sup> including the sinonasal system.<sup>29 37</sup> Evidence on the involvement of HPV was immediately obtained in benign sinonasal papillomas,<sup>29</sup> and a few years later also in sinonasal SCCs.<sup>37</sup>

These early observations have prompted a series of studies from different laboratories, where HPV DNA has been searched for in sinonasal lesions (table 1). Most of the studies published so far have assessed benign sinonasal papillomas only. Until 1998,<sup>1</sup> a total of 14 studies where SCCs were also included were identified.<sup>37 55 58 59 62 63 65 67–69 75 76 82 85</sup> Unfortunately, in some of these reports the exact characterisation of the material is lacking, making the counting of the total cases somewhat uncertain. However, at least 173 SCCs were included in these analyses, using different hybridisation methods and PCR. HPV DNA was detected in 31 of 173 sinonasal carcinomas, giving an overall detection rate of 17.9%. Not unexpectedly, HPV-16 seems to be the single most frequent HPV type, followed by HPV-18. In a few cases, HPV-6 or HPV-11 were found in SCCs.<sup>59 76 82</sup>

Since 1998, several reports have been published in which a substantial number of additional sinonasal carcinomas have been analysed for HPV DNA.<sup>89 91 92 94 98 100–102</sup> Unfortunately, in some of these studies, the same problem of counting the exact numbers of cases is encountered. However, at least 149 new SCC cases could be calculated, of which 39 (26.2%) were shown to contain HPV DNA (table 1). These new reports make the total number of sinonasal carcinomas analysed for HPV up to 322, and the number of HPV positive cases up to 70, giving an HPV prevalence of 21.7%.

As with the detection of HPV at other mucosal sites, the reports are not concordant and unanimous in the detection of HPV DNA in these lesions. This is well illustrated by the divergent detection rates reported in the different studies cited in table 1. There is no doubt that at least some of these discrepant results must be attributed to the different technologies (with divergent sensitivity and specificity) used in HPV detection. A detailed discussion about these technological issues in HPV detection falls outside the scope of this review, however, and the reader is referred to a recent monograph.<sup>9</sup>

### CONCLUSIONS

The current evidence linking HPV to at least a proportion of benign sinonasal papillomas is convincing. Based on the analysis of over 1000 such lesions, HPV-6 and HPV-11 seem to be present in one third (33.3%) of these tumours. This detection rate is higher than reported for most other extragenital papillomas, except for those of the larynx and bronchus.<sup>4 6 9 10</sup> This association applies to sinonasal SCPs and IPs, but the data are still too scanty for the CCPs, which have not yet been

shown to be HPV positive. Apart from the direct evidence on HPV DNA detection, there are great similarities to established HPV lesions elsewhere, favouring the viral aetiology of these sinonasal lesions. These include: (1) the morphological similarities to other established HPV lesions; (2) the multicentricity of the disease; (3) the spread by dissemination into the entire paranasal sinus system, ear, and even orbit; (4) the tendency for recurrence after a radical treatment; and (5) the substantial potential for malignant progression. In addition, the expression of the HPV transforming oncogenes E6 and E7 was recently demonstrated in sinonasal papillomas.<sup>123</sup> Furthermore, no evidence for the involvement of other viruses, such as Epstein-Barr virus, has been obtained in sinonasal papillomas.<sup>124</sup> Taken together, these data strongly implicate HPVs as aetiological factors in a substantial proportion of sinonasal papillomas.<sup>1 4 6 9 85 124 125</sup> Whether important differences exist in the aetiology of the different morphological variants of these papillomas (SCP, IP, and CCP) remains to be established by additional studies correlating lesion morphology with the detection of HPV DNA.

The data concerning the causal role of HPV in sinonasal squamous cell carcinogenesis still need further confirmation. There are, however, many elements in these data that parallel the observations made in well established and in emerging HPV lesions.<sup>9 10</sup> Briefly, (1) there are well defined benign and malignant squamous cell lesions in this area, which bears an analogy to all known HPV lesions at other mucosal sites; (2) malignant transformation and frequent recurrence after radical treatment of the benign papillomas is a well documented salient feature of these lesions; (3) low risk HPV types 6 and 11 are typically confined to benign lesions and are very rare in malignant ones, whereas the reverse is true for the oncogenic HPV types 16 and 18; (4) the overall detection rate of these oncogenic HPV types (21.7%) in all studied sinonasal carcinomas (n = 322) is almost equal to their prevalence in malignant squamous cell lesions at other non-genital sites, such as the oral cavity, larynx, oesophagus, bronchus, conjunctiva, and skin<sup>9 10</sup>; (5) SCJs and squamous cell metaplasia similar to those found in the uterine cervix are also encountered in the sinonasal system, and these are considered to be a prerequisite for HPV to gain access to its target cells.<sup>9</sup>

“Sinonasal squamous cell carcinoma (SCC) should be categorised as an emerging human papillomavirus lesion, which shares many similarities with SCCs at other anatomical regions, for which more evidence is available today”

However, it is equally clear that the number of analysed cases (n = 322) is still far too small to confirm the causal association of HPV with sinonasal carcinomas. Thus, at the present stage, the evidence linking HPV to sinonasal carcinoma must be considered, at best, only suggestive. Based on the same arguments that are applicable to the benign sinonasal papillomas (which SCCs seem to be closely related to) I think that sinonasal SCC should be categorised as an emerging HPV lesion, which shares many similarities with SCCs at other anatomical regions, for which more evidence is available today.<sup>9</sup> The literature on these tumours is accumulating rapidly, however, as shown by the increasing number of reports on the detection of HPV during the past two to three years (table 1). Similarly, the studies on molecular mechanisms involved in sinonasal carcinogenesis have begun to emerge only recently.<sup>96 102 126–132</sup>

It is to be anticipated that the more widespread application of sensitive nested PCR techniques will disclose HPV DNA in a higher proportion of cases, and possibly new as yet unidentified HPV types will be found in sinonasal carcinomas in the future.<sup>52 79 81 133</sup> However, as now seems to be the case with oesophageal cancer and HPV (where there is divergent

### Take home messages

- A substantial number of studies have reported evidence on the involvement of human papillomavirus (HPV) in sinonasal papillomas and carcinomas
- To date, 1041 sinonasal papillomas have been analysed for HPV and 347 (33.3%) cases have been positive, whereas 322 sinonasal carcinomas have been analysed and 70 (21.7%) have been positive
- There are many parallels with HPV lesions at other mucosal sites: (1) there are well defined benign and malignant squamous cell lesions at this site; (2) malignant transformation and frequent recurrence can occur after radical treatment of benign papillomas; (3) low risk HPV types are confined to benign lesions, whereas the reverse is true for the oncogenic HPV types; (4) the overall detection rate of HPV is higher or equal to that seen in the benign and malignant HPV lesions at other non-genital sites; (5) squamo-columnar junctions and squamous cell metaplasia, which are thought to be a prerequisite for HPV oncogenesis, are present
- Reported discrepancies might result from: (1) technical reasons (differences in the sensitivity and specificity of HPV detection assays); (2) possible heterogeneous aetiology of sinonasal lesions (HPV related and non-related); and (3) the possibility that some novel yet unidentified HPV types exist in these lesions, which can be detected by some techniques but not others
- Sinonasal squamous cell carcinoma (SCC) should be categorised as an emerging HPV lesion, which shares many similarities with SCCs at other anatomical regions, for which more evidence is available today

aetiology in low and high risk regions),<sup>2 4 6 134</sup> it is possible that the aetiology of sinonasal papillomas and carcinomas may be heterogeneous; that is, HPV related and non-related lesions exist. This would explain the recent discrepant results reported by laboratories using almost identical and sensitive HPV detection techniques, which precludes technical reasons as the prime suspect for this discrepancy.

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*J Clin Pathol* 2003 56: 174-181

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