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Aetiological parallel between tonsillar and anogenital squamous-cell carcinomas

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Patients with human papillomavirus (HPV)-associated anogenital cancers had a 4.3-fold increased risk of tonsillar squamous-cell carcinoma. These cancer types also have histopathological and molecular biological similarities. Thus HPV may be aetiological important in tonsillar carcinogenesis.

Similarities between mucosal linings at anogenital and oral sites make plausible a role for human papillomaviruses (HPV) in oral carcinogenesis. HPV are found in most anogenital squamous-cell carcinomas (SCC), but usually in less than 20% of oral cancers. Tonsillar SCC, however, is more likely than other oral cancers to be HPV positive.¹ We studied patients with HPV-associated anogenital SCC to test the hypothesis that these patients are at increased risk of tonsillar SCC.

Using Surveillance, Epidemiology, and End Results data from 1973 to 1994, we identified 72 066 individuals whose first cancer was an HPV-associated anogenital SCC (or cervical SCC in situ) and 422 023 with invasive HPV-unrelated first cancers of the colon, stomach, or breast (table 1). Person-years were counted from 1 month after the initial diagnosis until a diagnosis of one of the studied invasive SCC (tonsillar, other oral, cervical, vulvar/vaginal, or anal), death, or Jan 1, 1995, whichever came first. Population incidence rates for these SCC were calculated for strata of sex, race, and 5-year age and calendar periods. The expected number of a particular SCC was calculated as the sum of stratum-specific products of person-years and population incidence. Ratios of observed-to-expected SCC served as measures of relative risk. We compared relative risks of tonsillar SCC and of other oral SCC after anogenital SCC.²

Among patients with anogenital SCC, risks of SCCs at other anogenital sites were high (209 observed, relative risk 3.6 [95% CI 3.1-4.1]; table 2). The risk of tonsillar SCC was similarly increased. All three cases of tonsillar SCC after anal SCC were in men (relative risk 12.0 [2.4-35.1]).

Other oral SCC also occurred in excess, though the relative risk (2.3 [1.7-3.0]) was significantly lower than that for tonsillar SCC ($p=0.013$, one-sided). Among patients with HPV-unrelated cancers, relative risks were close to 1.0, although slightly low for cervical SCC.

This study suggests a strong link between tonsillar and anogenital SCC. HPV may be a common aetiological factor. Tobacco, a major risk factor for oral cancers, is also linked aetiological to anogenital SCC and may have contributed to the association. However, the finding that the relative risk was significantly higher for tonsillar SCC than for other oral SCC supports a role for HPV in the aetiology of tonsillar SCC. Although based on small numbers, the highest relative risk for tonsillar SCC was in patients with anal SCC, a cancer common among homosexual men. All three tonsillar cancers after anal SCC were in unmarried or divorced men. Unprotected orogenital sex with an infected partner may result in transmission of HPV to the oral cavity. There are no specific published data on sexual behaviours of patients with tonsillar cancer, but one study suggested an association between active oral sex and risk of oral cancer positive for HPV-16 DNA, of which tonsillar SCC was the most common type.³ The role of the immune system in tonsillar carcinogenesis is unknown. Other HPV-associated cancers occur in excess among patients with HIV infection and AIDS and among patients with transplantation-related immunosuppression. Tonsillar SCC has been reported in young transplant patients.⁴ The increasing incidence of tonsillar SCC in young US men, but not women (unpublished) may reflect an association with HIV-related immunosuppression.

The tonsillar crypt epithelium, believed to favour the capture and processing of antigens, may facilitate viral access to basal mucosal cells. This idea accords with the suggestion that HPV-associated tonsillar SCCs originate from the crypts, whereas HPV-unrelated SCC emerge from the tonsillar surface.⁵

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Initial cancer	ICD-O2 code topography + histology	Number of patients	Median age (years)	Person-years of follow-up
HPV-associated anogenital SCC				
Cervical SCC	C530-C539 + 80503-80763	18 586	50	120 535
Cervical SCC in situ	C530-C539 + 80502-80762	46 093	31	341 713
Vulvar/vaginal SCC	C510-C529 + 80503-80763	4155	70	21 907
Anal SCC*	C209-C218 + 80503-80763, 80943, 81203-80243	3232	63	16 522
Total		72 066		500 677
HPV-unrelated cancer				
Colon cancer*	C180-C189 + any	145 994	71	668 614
Stomach cancer*	C160-C169 + any	37 104	69	78 915
Breast cancer (women)	C500-C509 + any	238 925	62	1 490 875
Total		422 023		2 238 404

ICD-O2=International Classification of Diseases for Oncology, 2nd edn, 1990.

*Proportions of women were 66%, 53%, and 39% among patients with initial anal SCC, colon cancer, and stomach cancer, respectively.

Table 1: Cohorts of patients followed up for tonsillar SCC, other oral SCC, and anogenital SCC after initial HPV-associated and HPV-unrelated cancers, SEER 1973-94

Initial cancer	Second cancer*									
	Tonsillar SCC		Other oral SCC		Cervical SCC		Vulvar/vaginal SCC		Anal SCC	
	O/E	RR (95% CI)	O/E	RR (95% CI)	O/E	RR (95% CI)	O/E	RR (95% CI)	O/E	RR (95% CI)
HPV-associated anogenital SCC										
Cervical SCC	9/1.7	5.2 (2.4-10.0)	19/9.0	2.0 (1.3-3.3)	54/4.8	11.2 (8.4-14.7)	10/2.5	4.0 (1.9-7.3)
Cervical SCC (in-situ)	7/2.0	3.5 (1.4-7.3)	17/9.6	1.8 (1.0-2.8)	52/36.8	1.4 (1.1-1.9)	53/5.4	9.8 (7.3-12.8)	14/3.0	4.7 (2.6-8.0)
Vulvar/vaginal SCC	1/0.4	2.5 (0-13.7)	9/2.8	3.3 (1.5-6.2)	9/3.0	3.0 (1.4-5.8)	8/0.8	10.4 (4.5-20.5)
Anal SCC	3/0.5	6.1 (1.2-17.9)	10/2.7	3.7 (1.8-6.9)	1/1.5	0.7 (0-3.6)	8/0.8	9.6 (4.1-18.9)
Total	20/4.6	4.3 (2.7-6.7)	55/24.1	2.3 (1.7-3.0)	62/41.3	1.5 (1.2-1.9)	115/11.0	10.5 (8.6-12.5)	32/6.3	5.1 (3.5-7.2)
HPV-unrelated cancers										
Colon cancer	17/22.8	0.7 (0.4-1.2)	149/135.1	1.1 (0.9-1.3)	45/49.0	0.9 (0.7-1.2)	35/34.6	1.0 (0.7-1.4)	29/20.2	1.4 (1.0-2.1)
Stomach cancer	3/3.0	1.0 (0.2-2.9)	15/16.4	0.9 (0.5-1.5)	2/5.2	0.4 (0-1.4)	6/2.9	2.1 (0.8-4.5)	3/2.0	1.5 (0.3-4.3)
Breast cancer (women)	26/28.7	0.9 (0.6-1.3)	189/171.2	1.1 (1.0-1.3)	144/196.1	0.7 (0.6-0.9)	79/97.8	0.8 (0.6-1.0)	42/48.2	0.9 (0.6-1.2)
Total	46/54.5	0.8 (0.6-1.1)	353/322.7	1.1 (1.0-1.2)	191/250.3	0.8 (0.7-0.9)	120/135.3	0.9 (0.7-1.1)	74/70.4	1.1 (0.8-1.3)

O=observed; E=expected; RR=relative risk.

*ICD-O2 codes used to define observed and expected oral cancers comprise C090-C099 + 80503-80763, 80943, 81203-81243 (tonsillar SCC) and C019-C069, C100-C109 + 80503-80763, 80943, 81203-81243 (other oral SCC). Observed and expected invasive cervical, vulvar/vaginal, and anal SCC meet the topography and histology criteria for corresponding cohorts in table 1.

Table 2: Tonsillar SCC, other oral SCC, and anogenital SCC after initial HPV-associated cervical, vulvar/vaginal, and anal SCC and HPV-unrelated cancers of colon, stomach, and breast, SEER 1973-94

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Clopidogrel and membranous nephropathy

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Membranous nephropathy with nephrotic syndrome occurred in a patient with anterior myocardial infarction 2 months after the start of clopidogrel treatment. Sensitisation by prior treatment with ticlopidine is discussed.

The thienopyridine derivatives ticlopidine and clopidogrel are specific and potent inhibitors of platelet aggregation that are metabolised in the liver into active substances.¹ The CAPRIE study showed that clopidogrel is superior to aspirin in patients with ischaemic risk,² and clopidogrel was subsequently approved in many countries for secondary prevention of myocardial infarction and ischaemic stroke in patients with symptomatic atherosclerotic vascular disease. Severe adverse events have been associated with ticlopidine therapy: acute renal failure^{3,4} and acute interstitial nephritis⁵ have been reported. The occurrence of severe side-effects is thought to be lower with clopidogrel than with ticlopidine.

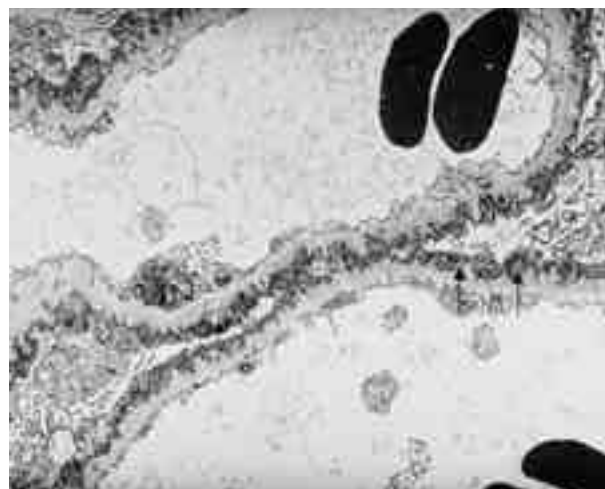
We report a 46-year-old man who had an anterior myocardial infarction in March, 1997. After streptokinase lysis, stenosis of the right coronary artery was detected by coronary angiography. 4 days later, percutaneous transluminal angioplasty of this stenosis was carried out, and a multilink stent was positioned. 500 mg/day ticlopidine and 100 mg/day aspirin were subsequently given for 4 weeks; a β -blocker (initially metoprolol and thereafter sotalol) and pravastatin were added. Owing to gastrointestinal complaints, all other medications with the exception of sotalol were withdrawn. 16 months later, clopidogrel was given for a period of 63 days. 2 months after the start of medication, calf oedema was observed, which subsequently increased and led to withdrawal of the therapy.

At this time, the patient's bodyweight was 88 kg. He presented with proteinuria of 11.5 g/day (non-selective,

glomerular). Serum protein was about 45 g/L with an albumin fraction of 20 g/L. The creatinine clearance was 106 mL/min per 1.73 m² and serum creatinine was 79.56 μ mol/L. Antinuclear antibodies, antineutrophil cytoplasmic antibodies, glomerular basement membrane antibodies, and direct Coombs' test were all negative. The IgE concentration was raised at 140 U/mL. The differential blood count did not show any abnormalities. Serum cholesterol was 12.93 mmol/L.

Ultrasonography of the kidneys and the other upper abdominal organs did not show any abnormalities. There was no indication of a tumour or an infection, and the chest radiograph was normal. Histological investigation of a kidney-puncture led to the diagnosis of a stage II membranous nephropathy without glomerular or tubulointerstitial scarring (figure). In the follow-up period, proteinuria of more than 10 g/day persisted despite use of 100 mg/day prednisolone with gradual dose reduction over 4 weeks. In addition, piretanide, nadroparin, pantoprazole, and, starting at day 30 of treatment, 5 mg/day ramipril, were also given. Bodyweight was constant, and the oedema not very pronounced. Blood pressure was about 140/90 mm Hg.

Membranous nephropathy is the major cause of nephrotic syndrome in adults, and, in 62-86% of cases, it is idiopathic. Drugs are the most frequent cause of secondary forms. The manifestation of nephrotic syndrome 2 months after the start of clopidogrel treatment in the case described here may



Glomerular-capillary walls with electron-dense subepithelial deposits, partially surrounded by basement-membrane material. Transmission electron micrograph, magnification \times 8900.