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Prospective seroepidemiological evidence that human papillomavirus type 16 infection is a risk factor for oesophageal squamous cell carcinoma

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The genome of the major type of human papillomavirus that is associated with anogenital cancer, HPV16, is occasionally found in non-genital cancers, such as oesophageal cancer and various cancers of the head and neck,[1] but it is not clear whether human papillomavirus infection is a measurable risk factor for these cancers. Since seropositivity for HPV16 capsids has documented specificity for HPV16 infection,[2] serological testing can provide information on whether HPV16 infection is a risk factor for disease development. Previously we found that HPV16 capsid seropositivity was a risk factor for both cervical and anal cancers at odds ratios of 9·5 and 30·4 respectively.[3] Therefore we designed a prospective study to assess whether HPV16 infection is also a risk factor for oesophageal or head and neck cancers.

Subjects, methods, and results

During 1968-72 the mobile clinic of the Social Insurance Institution of Finland collected serum samples from 39 268 subjects resident in most parts of Finland.[4] Registry linkage with the nationwide Finnish Cancer Registry identified 165 cases of head and neck cancers that had occurred in the cohort up to 1991. For each patient with cancer, two controls (free of any cancer at baseline) were selected, matched for sex, age, and municipality. In 134/165 matched sets the ages were exactly matched. The maximum age discrepancy (in 4/165 sets) was seven years. The matching for municipality also resulted in a matching for time of sample collection. Detection of IgG against HPV16 capsids was performed by standard enzyme linked immunosorbent assay (ELISA).[3] Relative risks, estimated as odds ratios, were calculated using conditional logistic regression of non-dissociable matched sets.

At a preassigned cut off level (0·180 absorbence units; relative to internal standards the same as previously used[3]) 39/492 serum samples were positive to HPV16 capsids. The proportions seropositive were similar in the subjects who acquired head and neck cancer and the controls. However, 7/29 subjects who acquired squamous cell carcinoma of the oesophagus and 8/39 subjects who developed any oesophageal cancer were HPV16 seropositive compared with only 2/78 matched controls ($P < 0·001$; table). Calculation of odds ratios for two alternative, arbitrarily assigned cut off levels (0·150 and 0·200) resulted in similar or identical odds ratios. HPV16 seropositivity was not significantly related to age, sex, time lag until diagnosis of disease, or smoking status.

Relative risk of developing head and neck cancers among HPV16 seropositive subjects

Primary site of cancer	No positive for HPV16/total No of cases	% Of positive cases	Odds ratio (95% confidence interval)	Smoking adjusted odds ratio (95% confidence interval)
Oesophagus	8/39	21	14·6 (1·8 to 117)	13·1 (1·6 to 108)
Larynx	1/37	3	0·2 (0·0 to 1·6)	0·2 (0·0 to 2·0)
Lip, tongue, salivary	4/60	7	0·7 (0·2 to 2·2)	0·6 (0·2 to 2·1)
Other oral	1/29	3	0·6 (0·1 to 7·4)	0·4 (0·0 to 7·1)

Comment

The major risk factors for oesophageal cancer (smoking, alcohol consumption, low socioeconomic status, nutritional deficiencies, certain chemical agents) have not fully explained the geographical variation of the disease.[1] In some cultural settings smoking and drinking habits and socioeconomic status are associated with sexual behaviour and thus also with HPV16 infection.[5]

The risk associated with HPV16 is, however, unlikely to be a secondary association since (*a*) adjustment for smoking habits did not affect the HPV16 related risk (table), (*b*) the risk of cancer associated with HPV16 was considerably higher than the risk associated with these other risk factors, and (*c*) as assessed in a comparable Swedish cohort, HPV16 seropositivity was only weakly associated with alcohol consumption (maximum odds ratio at any exposure level: 2·0 (1·1 to 3·8)) and, as in this cohort, not associated with smoking regardless of exposure level (J D and I Kallings, unpublished). Epidemiological studies of possible interactions between HPV16 seropositivity and other risk factors might be important in elucidating the cause of oesophageal cancer.

Whereas cervical human papillomavirus infection is a sexually transmitted disease,[5] the mode whereby the virus infects the oesophagus is unclear. Human papillomavirus of types 6 and 11 can be transmitted at birth and cause juvenile respiratory papillomatosis, whereas oral condyloma in adults can be contracted by oral/genital sex. Future studies will need to clarify the frequency and duration of oesophageal human papillomavirus infection as well as the mode of transmission. It will also be interesting to determine to what extent exposure to human papillomavirus differs between populations at high or low risk for oesophageal cancer.

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