
EDITORIAL

Establishment of an Association Between a Virus and a Human Cancer

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Proving a causal relationship between a putative cancer virus and a human cancer is no easy task. The difficulty comes in trying to apply the criteria of infectious disease causation in instances complicated by the long latent period between viral infection and the onset of cancer, the low prevalence of the cancer among infected individuals, and the scientific and logistical problems involved in developing, implementing, and evaluating prevention programs through primary vaccination.

In table 1 we have listed several putative human cancer viruses and the cancers with which they are associated, the strength of the association, and the preconditions as determined by the available epidemiologic data. The strongest evidence for a direct cause-and-effect association is between hepatitis B virus (HBV) and hepatocellular carcinoma. The prospective study by Beasley et al. (1) so firmly established the likelihood of a causal association that large-scale vaccine prevention trials are now under way. The association between human T-cell lymphotropic virus type 1 (HTLV-I) and T-cell lymphomas in southern Japan is similarly strong and points toward a direct cause-and-effect relationship. In both instances, the geographical distribution of the prevalence of virus infection and the incidence of cancer closely approximates.

Epstein-Barr virus (EBV) is an almost universal human infection, although the age at first infection varies considerably worldwide. Generally, EBV infection occurs earliest where populations are most dense. The relationship between EBV and Burkitt's lymphoma (BL) has been the subject of much study. Unlike the situation with HBV and HTLV-I, EBV infection alone is probably insufficient to cause BL. Instead, the role of EBV appears to be opportunistic, effective only in conjunction with a congenital or an acquired immunodeficiency state. In Africa this immunodeficiency state is induced by chronic malaria, which eventually leads to the loss of normal immunologic control of EBV-infected B cells. A growing body of evidence indicates that the association between other, histologically similar, high-grade lymphomas and human immunodeficiency virus (HIV) has the same pathogenesis. In this case, immunodeficiency induced by HIV

allows uncontrolled proliferation of EBV-infected B lymphocytes.

The relationship between EBV and nasopharyngeal carcinoma (NPC) is more obscure. Although EBV is associated with virtually 100% of these cancers, the high concentration of NPC among certain populations, such as the southern Chinese, is not explained by the distribution of the virus. A strong association has been established between ingestion of Cantonese-style salted fish and NPC, and the prevalence of this exposure is compatible with the distribution of NPC (2). The overall evidence suggests that for this tumor EBV is merely a passenger virus. The coexistence of EBV and NPC may not occur because EBV is required in the carcinogenic process; rather the association may happen as a consequence of the proliferation of cells that normally harbor the virus. The relationship between herpes simplex type 2 virus (HSV-2) and cervical cancer is likewise uncertain. A prospective study by Vonka et al. (3) failed to show a relationship between risk of progression to cervical neoplasia and antibody to HSV-2.

The association between human papillomavirus (HPV) and cervical cancer has only recently been established through the pioneering work of Zur Hausen and Schneider (4). HPV types 16 and 18 have been reported with a high frequency (average, about 60%–70%) in invasive squamous cell carcinomas of the cervix (5). Types 6 and 11 have been found less commonly in invasive cancer but in about 10%–30% of in situ cervical lesions. The frequency of HPV infection in noncancerous cervical epithelial cells has been more difficult to establish. The usual method of obtaining "control" cells is by cervical scraping, which yields a variable number of intact cells. The laboratory assays for virus identification involve in situ hybridization, and large surveys are performed on filter paper disks, often without a mechanism to indicate whether epithelial cells are even present. Not surprisingly, therefore, prevalence surveys performed in this way of HPV infection from patients without cervical cancer have produced estimates ranging from 0% to 45.0% (5).

By analogy with the association between HBV and liver cancer and HTLV-I and T-cell lymphoma, if HPV is causally related to cervical cancer, one might expect a geographic correspondence between the prevalence of HPV infection and the risk of cervical cancer. Such analyses produce unexpected results and raise doubts about the etiologic significance of this association. For example, a comparison of HPV prevalence rates in Greenland and Denmark (the former has cervical cancer rates 5.7 times higher than the latter) demonstrates higher HPV 16/18 infection rates in Denmark (13.0%) than in Greenland (8.8%) (6).

The article by Villa et al. in this issue of the journal attempts to shed light on the significance of this association by comparing HPV prevalence rates among groups of Brazilian women with differing risks of cervical cancer. The prevalence rate of HPV 16/18 infection in these Brazilian women

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Table 1. Human cancer viruses and cancers with which they are associated, strength of association, and necessary preconditions


Virus	Cancer	Strength of epidemiologic association	Required precondition
HBV	Hepatocellular carcinoma	Strong	None
HTLV-1	T-cell lymphoma	Strong	None
EBV	BL	Strong	Chronic malaria
EBV	High-grade lymphoma	Strong	HIV
HPV	Cervical cancer	?Consistent	?None
EBV	NPC	Inconsistent	—
HSV-2	Cervical cancer	Inconsistent	—

ranges from 2.0% in São Paulo, where the age-adjusted incidence rate of cervical cancer is 35.1 new cases per 100,000 women per year, to 5.9% in Recife, where the corresponding rate is 96.5. Although the prevalence rates seem to correlate well with cervical cancer incidence on this highly limited geographic basis, they are low by comparison with studies published elsewhere in populations where cervical cancer rates are likely to be equally high. Thus, Reeves et al. (7) reported a prevalence rate for HPV 16/18 infection of 45.0% in Panama, where the cervical cancer rate is presumably similar to that in Brazil. Villa et al. report further that HPV 16/18 prevalence rates do not vary as much as expected with the prevalence of established cervical cancer risk factors.

Although there is a growing body of evidence that the association between HPV and cervical cancer is causal, these important inconsistencies in the epidemiologic data must be resolved. In particular, there is a need to determine whether such inconsistencies are explained in total or in part by the insensitivity of available laboratory assays or by the technical problems associated with their use.

References

- (1) BEASLEY RP, LIN CC, HWANG LU: Hepatocellular carcinoma and hepatitis B virus: A prospective study of 22,707 men in Taiwan. *Lancet* 2:1129-1133, 1981
- (2) YU MC, HO JHC, LAI SH, ET AL: Cantonese-style salted fish as a cause of nasopharyngeal carcinoma: Report of a case-control study in Hong Kong. *Cancer Res* 46:956-961, 1986
- (3) VONKA V, KAŇKA J, HIRSCH I, ET AL: Prospective study on the relationship between cervical neoplasia and herpes simplex type-2 virus. II. Herpes simplex type-2 antibody presence in sera taken at enrollment. *Int J Cancer* 33:61-66, 1984
- (4) ZUR HAUSEN H, SCHNEIDER A: The role of papillomaviruses in human anogenital cancer. In *The Papovaviridae*, vol 2. The Papillomaviruses (Salzmann NP, Howley PM, eds). New York: Plenum Press, 1987, p 245
- (5) MUNOZ N, BOSCH X, KALDOR JM: Does human papillomavirus cause cervical cancer? The state of the epidemiological evidence. *Br J Cancer* 57:1-5, 1988
- (6) KJAER SK, DE VILLIERS EM, HAUGAARD BJ, ET AL: Human papillomavirus, herpes simplex virus and cervical cancer incidence in Greenland and Denmark. A population-based cross-sectional study. *Int J Cancer* 41:518-524, 1988
- (7) REEVES WC, CAUSSY D, BRINTON LA, ET AL: Case-control study of human papillomaviruses and cervical cancer in Latin America. *Int J Cancer* 40:450-454, 1987




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Apr 4, 2005 - The association between human immunodeficiency virus (HIV) DNA load and immunologic parameters was cess of therapy in hemophilic patients (6) and of the level of more frequently reported unprotected homosexual behavior. (P . HUMAN IMMUNODEFICIENCY VIRUS 1 - BioMedSearch.Â The association between infectious agents and a number of cancers has been documented elsewhere (Weiss, 1984; ZurHausen, 1991). In South Africa about a third of the female and a sixth of the male cancers are thought to be infective in origin (Sitas et al, 1996).