

This Week's Citation Classic

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Rawls W E, Tompkins W A F & Melnick J L. The association of herpesvirus type 2 and carcinoma of the uterine cervix. *Amer. J. Epidemiol.* 89:547-54, 1969.
[Dept. Virology and Epidemiology, Baylor Univ. Coll. Med., Houston, TX]

A method was developed to distinguish type 2 from type 1 herpesvirus antibodies in patients. Type 2 antibodies were detected in 78 percent of patients with cervical carcinoma, but in only 22 percent of matched control healthy women or women with other types of cancer. Type 1 antibodies begin to appear in the normal population soon after birth and by early adulthood almost all are infected. In contrast, type 2 antibodies do not appear until adolescence and the start of sexual relations, indicating venereal spread. [The SC][®] indicates that this paper has been cited in over 270 publications since 1969.]

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"In the early 1960s, the department of virology and epidemiology at Baylor College of Medicine had begun a study of cervical cancer. Epidemiological studies had left little doubt that coitus was a prerequisite for the development of carcinoma of the cervix. The disease was virtually nonexistent among women of celibate religious orders. A higher incidence of the disease had been correlated with early intercourse, early marriage, multiple marriages, and multiple sexual partners. Pivotal among these variables was that of early intercourse. This suggested that the agent was maintained in the population primarily by venereal spread and that susceptibility to infection decreased with age or the susceptibility to the oncogenic effect of the agent was greatest in younger women. In either case, a venereally transmitted virus

with oncogenic potential might then be a common viral agent.

"This led us to test smegma samples from young males for the presence of a transmissible venereal agent. Of the 220 samples tested, four yielded a previously unrecognized member of the herpesvirus group, now known as herpes simplex virus type 2 (HSV2), from work independently carried out by Dowdle, Nahmias, and their co-workers¹ in Atlanta and by us in Houston. We developed methods for determining antibodies to the type 2 virus and carried out the study reported in this paper, which showed that women with cervical cancer had been commonly infected with the newly recognized HSV2. Again, similar results were found independently at Emory University.²

"We believe this paper is cited frequently because it opened new avenues for investigating the role of viruses and cancer. The study bridged the gap often found between the clinic and the laboratory. New methods were developed and applied to an epidemiological problem; this resulted in focusing attention on a newly recognized herpesvirus as a potential cause of cervical cancer. It also pointed the way to a resolution of the problem: if the agent could be controlled, the disease should vanish. International efforts are now under way to develop effective chemotherapeutic drugs and viral vaccines; the results are promising in both directions.^{3,4}

"In our paper we suggested that herpesvirus type 2 might also play a role in vulvar carcinoma. Recent evidence has supported this view. In the US, concomitant increases have occurred in prevalence of genital herpes infections and of vulvar carcinoma, especially in women under 40 years of age. In similar fashion to cervical cancer victims, these patients have type 2 antibodies in their blood and type 2 antigens that bind to DNA in their cancer cells.⁵ With this new evidence that herpesvirus type 2 is associated with genital cancers, it is hoped that efforts will be intensified to control the virus infection and thus the cancer."

1. Dowdle W R, Nahmias A J, Harwell R W & Pauls F P. Association of antigenic type of herpesvirus hominis with site of viral recovery. *J. Immunology* 99:974-80, 1967. (Cited 235 times.)
2. Nahmias A J, Josey W E, Naib Z M, Luce C F & Guest B. Antibodies to herpesvirus hominis types 1 and 2 in humans. II. Women with cervical cancer. *Amer. J. Epidemiol.* 91:547-52, 1970. (Cited 220 times.)
3. Nahmias A J, Dowdle W R & Schinazi R F, eds. *The human herpesviruses. an interdisciplinary perspective.* New York: Elsevier, 1981. 721 p.
4. Myers M W, Glasgow L A & Glasco C J. Summary of a workshop on antiviral agents for genital herpesvirus infections. *J. Infect. Dis.* 145:774-82, 1982.
5. Kaufman R H, Dreesman G R, Burek J, Korhonen M O, Matson D O, Melnick J L, Powell K L, Purifoy D J M, Courtney R J & Adam E. Herpesvirus-induced antigens in squamous-cell carcinoma in situ of the vulva. *N. Engl. J. Med.* 305:483-8, 1981.