Persistently high loads of human papillomavirus 16 over time were associated with an increased risk for cervical cancer

Ylitalo N, Sørensen P, Josefsson AM, et al. ***Consistent high viral load of human papillomavirus 16 and risk of cervical carcinoma in situ: a nested case-control study****. Lancet 2000 Jun 24;**355**:2194–8.*

QUESTION: In women with a first normal cervical smear, what is the temporal relation between human papillomavirus (HPV)-16 infection and cervical carcinoma in situ (CIS)?

Design
Nested case control study of 146 889 women screened from 1969 to 1995.

Setting
Uppsala County, Sweden.

Participants
Women who were < 50 years of age at entry (time of first registered smear); were born in Sweden; and had ≥1 cervical smear, a normal first smear, and smears containing β actin. The case group consisted of women who had CIS (n = 478; 2081 smears). For each woman with CIS, 5 women in the control group were matched by date of first registered smear and age. Eligible women in the control group were randomly selected from each set of 5 women (n = 604; 1754 smears); they had no history of CIS or invasive cervical carcinoma or hysterectomy before the date of diagnosis for the corresponding woman in the case group.

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Assessment of risk factors
All smears taken after entry were analysed for HPV-16 by using quantitative polymerase chain reaction (5′-exonuclease [Taqman] method). The technician who analysed the smears was blinded to case control status. The level of β actin was also assessed.

Main outcome measure
Women with CIS were identified by the National Cancer Registry, and their histological samples were reassessed to confirm the diagnosis.

Main results
871 (42%) smears from women with CIS and 117 (7%) smears from women in the control group were positive for HPV-16. The estimated cumulative risk for CIS increased with time since first smear, up to 22.7% (95% CI 12.4% to 31.8%) in women with high viral loads (HPV-16 threshold cycle [C_t] < 39.6) and 6.6% (CI 1.7% to 11.2%) in women with medium viral loads (HPV-16 C_t ≤45.6 to ≥39.6) after 15 years. The mean incubation period from first confirmed HPV infection to detection of CIS was > 17 years for women with a high viral load and > 19 years for women with a medium viral load. The risk for CIS increased with increasing viral load (table).

Conclusion
In women with a normal first cervical smear, consistently high human papillomavirus 16 loads over the long term were associated with an increased risk for cervical carcinoma in situ.

Adjusted odds ratios for associations between cervical carcinoma in situ and human papillomavirus (HPV) 16 load at different years before diagnosis (adjusted for levels of β actin)

Years before diagnosis	Low viral load	Medium viral load	High viral load
1	3.1 (0.9 to 10.1)*	10.3 (2.4 to 43.5)	43.1 (8.0 to 233.3)
5	2.3 (0.7 to 7.9)*	9.1 (2.6 to 31.5)	31.4 (5.7 to 173.1)
≥9	1.7 (0.4 to 6.9)*	5.7 (1.1 to 30.5)	33.3 (4.7 to 236.8)

*Not significant.

COMMENTARY—*continued from previous page*

In the US, most women who develop cervical cancer have never had a Papanicolaou (Pap) smear, have not had a Pap smear within 5 years of diagnosis, or did not have appropriate follow up of an abnormal smear.[5] The problems of screening coverage and adequate follow up of abnormal test results will probably not be solved by advances in HPV technology. Further prospective studies of women with high risk HPV viral load (multiple types) are needed using tests with potential commercial application. Women with both positive and negative results will need to be followed over time to determine whether HPV testing can be used to triage accurately enough to permit longer intervals between tests for women with negative test results. Given the long period between a high HPV viral load test and development of abnormal cells for which effective treatment is available, loss to follow up will probably remain a substantial problem.

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