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Letter

Study results and related evidence do not support use of HPV16 L1 DRH1 antibodies as a cancer screening test

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In their recent article, Weiland et al. suggest that an assay measuring HPV16 L1 DRH1 antibodies could be used for early detection of HPV-driven cancers. We believe it is unethical to recommend this assay to patients as a screening test, because its harms would outweigh any (unproven) benefit in avoiding cancer mortality [1]. Since HPV-related oropharyngeal cancer is rare, 99% of positive tests would be false-positives with the assay characteristics as stated by the authors (Table 1, Scenario 1). Using a more realistic specificity estimate, this percentage increases to 99.8% (Scenario 2).

However, due to methodological flaws, we believe that the true sensitivity and specificity of the assay are lower than presented in the study. Testing appears to have been done in separate batches for cancer cases and healthy controls without blinding, leaving results vulnerable to bias from batch effects. The cases and controls lack a common source population, but were pooled for AUC analyses which also omitted groups with undesirable results post-hoc. No details are provided regarding the healthy controls, whose demographic and health characteristics could affect the specificity estimate. Details are also lacking for laboratory methods, assay reproducibility, and validity as compared with standard assays. No pre-diagnostic sera were analyzed to address early detection [2-5], and for cancer recurrence, claims for utility were based on a single patient. Formal statistical comparisons are lacking and many confidence intervals are omitted.

The authors report 27% seroprevalence of HPV16 L1 DRH1 antibodies in young women, and all vaccinated individuals in the study

Table 1
Estimated impact of oropharyngeal cancer incidence rate, HPV attributable fraction, and marker specificity on assay positive predictive value, and screening characteristics, not considering time (re-calculated from Kreimer et al., Cancer 2018).

	A[a] Annual OPC Incidence rate	B[a] HPV16 attributable fraction	C[b] Marker sensitivity	D[b] Marker specificity	E[c] Detected HPV16-driven OPC cases per 100,000 screened	F[d] Expected false-positive screens per 100,000 screened	G[e] Estimated PPV	H[e] Number needed to screen to detect 1 case
Scenario 1	10/100,000	50%	95%	99.5%	5	495	1.0%	20,000
Scenario 2	10/100,000	50%	95%	97.7%	5	2345	0.2%	20,000

AF, attributable fraction; HPV, Human Papillomavirus; OPC, oropharyngeal cancer; PPV, positive predictive value.
[a] based on published literature.
[b] based on Weiland et al.; sensitivity and specificity (Scenario 1) according to abstract; specificity (Scenario 2) calculated as (22 women and 3 men seropositive) / 1064 blood donors.
[c] calculated as Column A * Column B * Column C * 100,000.
[d] calculated as (1 - Column D) * 100,000 - Column E.
[e] calculated as Column E / ((100,000 - Column E) * (1 - Column D))
[f] calculated as 100,000 / Column E.

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were strongly seropositive. This shows that seropositivity reflects not only tumor-related antibodies, but also natural infection and vaccine-induced antibodies. Therefore, the assay could not be used to detect cancer or cancer recurrence in vaccinated individuals, or among people with unknown vaccination status.

Declaration of Competing Interest

For completeness, JPK and TW serve on advisory boards for MSD (Merck) Sharp & Dohme.

However, all authors declare no competing interest.

Achnowledgment

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References

[1] Kreimer AR, Shiels MS, Fakhry C, et al. Screening for human papillomavirus-driven oropharyngeal cancer: considerations for feasibility and strategies for research. Cancer 2018;124(9):1859–66. doi: 10.1002/cncr.31256.

[2] Kreimer AR, Johansson M, Waterboer T, et al. Evaluation of human papillomavirus antibodies and risk of subsequent head and neck cancer. J Clin Oncol 2013;31(21):2708–15. doi: 10.1200/JCO.2012.47.2738.

[3] Kreimer AR, Ferreiro-Iglesias A, Nygard M, et al. Timing of HPV16-E6 antibody seroconversion before OPSCC: findings from the HPVC3 consortium. Ann Oncol 2019;30(8):1335–43. doi: 10.1093/annonc/mdz138.

[4] Kreimer AR, Brennan P, Lang Kuhs KA, et al. Human papillomavirus antibodies and future risk of anogenital cancer: a nested case-control study in the European prospective investigation into cancer and nutrition study. J Clin Oncol 2015;33(8):877–84. doi: 10.1200/JCO.2014.57.8435.

[5] Kreimer AR, Johansson M, Yanik EL, et al. Kinetics of the human papillomavirus Type 16 E6 antibody response prior to oropharyngeal cancer. J Natl Cancer Inst 2017;109(8):djx005. doi: 10.1093/jnci/djx005.