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Commentary

Potential role of naturally acquired immunity against HPV in the control of HPV related diseases

Tian Tian^a, Leiwen Fu^a, Yi-Fan Lin^a, Huachun Zou^{a,b,*}^a School of Public Health (Shenzhen), Sun Yat-sen University, Shenzhen, PR China^b Kirby Institute, University of New South Wales, Sydney, Australia

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Human papillomavirus (HPV) infection has been identified as one of the most common sexually transmitted infections. Most HPV infections appear to be transient and asymptomatic, but persistent infections will cause genital warts, cervical cancer, and other diseases, resulting in severe disease burden. [1] Existing studies have confirmed the almost perfect type-specific efficacy of available HPV vaccines in baseline uninfected populations, and the protection is thought to be largely antibody mediated.

Although prophylactic HPV vaccines are expected to solve this public health problem at its root, questions about best practices for implementation remain, especially in the circumstance of the insufficient supply of vaccines. In order to find an optimal vaccination strategy in controlling the HPV epidemic, abundant infectious disease modellings have been established to predict HPV transmission dynamics (dynamic mathematical models) and determine the cost benefit (cost-effectiveness analysis). In spite of the depth of understanding of HPV and cervical cancer natural history, several key parameters about the extent and duration of naturally acquired immunity after infection, remain indecisive. Because of the uncertainty around these parameters, decision models often involve sensitivity analyses in assumptions about natural immunity, the prediction value from the models is highly sensitive to these assumptions.[2] Therefore, it is crucial to determine the extent of HPV natural immunity to accurately model the effectiveness of different vaccination strategies.

Humoral immune response is thought to be critical mechanism for preventing HPV infection.[3] Several assays have been developed to detect antibody responses to HPV infection, which include pseudovirion-based neutralization assay (PBNA), the com-

petitive Luminex immunoassay (cLIA), and the virus-like particle-based enzyme-linked immunosorbent assay (VLP-ELISA). Each assay measures an overlapping but distinct subset of HPV VLP antibodies. The PBNA measures total amount of functional neutralizing HPV antibodies, which is considered to be the gold standard for assessing protective immunity. However, the PBNA is highly labor intensive and does not discriminate different antibody isotypes and subclasses. The cLIA measures antibodies directed against one dominant neutralizing epitope, which may result in an underestimate of the total neutralizing activity of HPV antibodies. And on the other hand, the dominant neutralizing monoclonal antibody is not easy to be acquired. The ELISA measures both neutralizing and non-neutralizing antibodies binding with the coating L1 VLP, [4,5] at the same time, it has the potential for nonspecific cross-reactivity with other agents which might lead to misclassification. Several studies have proved that naturally acquired HPV antibodies are partly protective, with approximately 35% decreased risk of subsequent infections.[6,7] However, the immunity indicator used in these studies has mostly been binding IgG antibodies, and one-time detection of HPV was used as the endpoint which is less specific than the persistent infection endpoint. Limited work has been carried out to determine the protective effect against HPV based on the functional neutralizing antibody, in a large cohort with longer follow-up time.

Yao and colleagues reported the naturally acquired antibodies to HPV-16/18 are associated with some reduced risk of subsequent homologous type infections in Chinese women aged 18-45 years with a follow-up period of up to 66 months [8]. These findings were based on neutralizing antibodies measured by PBNA and IgG antibodies measured by VLP-ELISA simultaneously. Compared with seronegative women, the seropositivity of HPV-16/18 neutralizing antibodies significantly reduced the risk of subsequent 6-month persistent infection by 84% (HR, 0.16; 95%CI, 0.04-0.65), while the seropositivity of IgG antibodies slightly lowered the risk by 34%

* Corresponding author. School of Public Health (Shenzhen), Sun Yat-sen University, Shenzhen, Guangdong, PR China

E-mail addresses: zouhuachun@mail.sysu.edu.cn, hzou@kirby.unsw.edu.au (H. Zou).

(HR, 0.66; 95%CI, 0.40-1.09). However, protective immune effect significantly increased with raising the cut-off value to the median IgG antibodies level, as 62% (HR, 0.38; 95%CI, 0.18- 0.83).

From the practical viewpoint, the highlight of the study was its assessment of natural immunity conferred with the more specific functional neutralizing antibodies measured by PBNA, which showed substantially stronger protective effect than IgG antibodies. This study provided more objective parameter for the evaluation of vaccine cost-effectiveness and for further optimizing HPV vaccination strategies, especially designing the target population of catch-up programmes. This is of great significance to achieving the global strategic goal of eliminating cervical cancer by 2030 put forth by the WHO, given the insufficient supply of HPV vaccines in many settings.

As indicated by Yao et al., there is potential imbalance that seropositive women have a higher behavioural risk of HPV exposure than seronegative women, thus the protective effect of natural immunity observed in this study might even be underestimated. It's reasonable to argue that the protection conferred by natural immunity might be similar to those by vaccine induced immunity, although natural immunity has much lower antibody titers. Thus, it would be feasible to allocate more resources to explore the one-shot vaccination programmes.

The protective effect based on IgG antibodies was lower than those on neutralizing antibodies, urging caution in setting the cutoff value for functional analysis when using IgG antibodies as the immunity indicator. Although IgG measured by ELISA is less specific than neutralizing antibody by PBNA assay, IgG is more exercisable in large population. The natural immunity is highly protective against subsequent homologous HPV infection, however, the duration of natural immunity remains unclear. In China, seroprevalence of HPV-16 and/or -18 neutralizing antibodies in 27-45 years old middle-aged women are only slightly higher than 18-26 years old young women (17.2% vs 14.8%), and there is another HPV infection peak in middle-aged women [9]. The longitudinal patterns of antibody titers and duration of protection conferred by natural infection should be further studied.

Author contributions

HZ conceived study design and was responsible for funding acquisition. TT, LF and YL drafted the manuscript with HZ critically reviewing the manuscript.

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Declaration of Competing Interest

Authors declare no conflict of interest

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