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Effects of exogenous estrogen & progesterone on the natural history of the human papillomavirus: Implications for vaccine induced immunogenicity & long-term efficacy

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Background:

Cervical cancer, the 2nd most common cancer among women worldwide, is caused by persistent infection with the human papillomavirus (HPV). Recently, a prophylactic subunit vaccine utilizing empty viral capsids known as virus like particles (VLP) has been shown to be highly immunogenic and effective in preventing viral infection, persistence and development of neoplastic lesions. Cancer development, however, requires both the presence of HPV as well as other environmental co-factors. Prolonged exposure to exogenous female reproductive hormones, estrogen and progesterone, administered in the form of combined oral contraception (COC) increases the risk of cervical cancer and HPV 16 viral persistence. These hormones are immunomodulators in human experimental models of autoimmunity, but have never been assessed in the context of either the natural history of HPV or vaccine induced immunogenicity. Long-term use of COC could potentially diminish vaccine immunogenicity over time leading to viral breakthrough and decreased efficacy.

Study design/methods:

A multi-disciplinary study was performed to assess the role of estrogen and progesterone on HPV natural history and vaccine immunogenicity. This study consisted of 1) a population-based analysis of the association of COC use on HPV prevalence, incidence and duration in cohort of 1250 long-term hormonal contraception users from Thailand and 2) a laboratory-based study utilizing peripheral blood mononuclear cells (PBMCs) collected from normal healthy donors (n=8) to characterize immune responses to HPV type 16 VLPs and assess the effects of hormones on these responses.

Results:

Population-based sub-study:

Increased duration of COC use was directly associated with an increased risk of prevalent HPV 16 infection, in a dose-dependent fashion. In addition, increasing time since last use (i.e. recency) among current non-COC users was independently associated with an attenuation of risk in a similar dose-response relationship. Currently COC use is being assessed in relation to HPV incidence and persistence.

Laboratory-based sub-study:

Exposure of human PBMCs to HPV 16 VLPs caused a significant upregulation of overall lymphoproliferation as well as production of pro-inflammatory cytokines, including IL-6, IL-8, IL-1 β , TNF- α , as well as T-cell associated cytokines, including IL-2, IFN- γ , and IL-5, as compared with media controls. Differential induction of these markers in the context of hormonal treatment is currently being evaluated.

Conclusions & Implications:

Increased duration of COC use is positively associated HPV prevalence while increased recency is negatively associated with prevalence independent of sexual behavior, a relationship which seemed to be restricted to HPV16 infection. In addition, HPV 16 VLP is broadly immunostimulatory in normal healthy donors with unknown HPV 16 exposure status. These preliminary data suggest a potential role of COC in altering the natural history of HPV which may have direct effect on long-term vaccine efficacy.