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A population-based case–control study of genetic variation in cytokine genes associated with risk of cervical and vulvar cancers

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HIGHLIGHTS

- Immunogenetic variation may contribute to HPV clearance or progression.
- T-helper pathway variants may impact risk of HPV-related cancers.
- We report novel associations between Th17 genes and cervical and vulvar cancers.

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ABSTRACT

Objective. Persistent infection with oncogenic human papillomavirus (HPV) is known to be the necessary cause of cervical cancer and a majority of vulvar cancers. Persistent HPV infections must evade host immune responses, including cytokines released by activated T-helper (Th) cells. In this study, we investigated the risk of cervical and vulvar cancers associated with common genetic variations in 560 tagging single-nucleotide polymorphisms (SNPs) in candidate cytokine genes.

Methods. The study included 399 invasive squamous cell carcinomas (SCCs) and 502 in situ or invasive adenocarcinomas (AC) of the cervix; 357 in situ or invasive vulvar SCC; and 1109 controls from the Seattle-area case–control studies of HPV-related cancers. Logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) using a log additive model, with adjustment for multiple testing.

Results. Statistically significant risks were observed for HPV16-containing SCC of the cervix with the variant allele rs879576 in *IL17RA* and rs2229094 in *TNF* [OR, 95% CI and multiple-testing corrected p: 1.91 (1.30–2.79), p = 0.018 and 0.61 (0.45–0.83), p = 0.02, respectively]. We also observed significantly increased risk of HPV-positive vulvar cancers associated with variant alleles in *CSF2* (rs25882 and rs27438, 26–28% increased risk) and *IL-12B* (rs2569254 and rs3181225, 40–41% increased risk) genes.

Conclusions. We found that variation in several Th-cytokine genes is significantly associated with cervical and vulvar cancer risk. The strong association between these HPV-related cancers and common variation in cytokine genes in the Th1 and Th17 pathways may be important for development of new therapies.

1. Introduction

Although the burden of carcinoma of the cervix has decreased considerably in countries with wide-spread screening, it remains the third most commonly occurring cancer and fourth most common cause of cancer deaths among women worldwide [1]. Persistent infection with oncogenic human papillomavirus (HPV) has been established as the necessary cause for the development of cervical cancer and a large proportion of HPV-related cancers at other anogenital sites, including vulvar cancer [2]. In contrast with the overall decreased incidence of cervical cancer, there has been a steady rise in the incidence of cervical adenocarcinoma (AC) and squamous cell carcinoma (SCC) of the vulva [3,4]. HPV infections alone are not sufficient for neoplastic progression to these cancers, as transient HPV infections are extremely common in the general population and relatively few women infected with HPV progress to cancer [5,6]. The mechanism of clearance of transient infections is complex: it involves HPV antigen presentation to CD4 and CD8 T cells, leading to activated T cells that proliferate into armed effector T

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cells [7]. In the small group of women who progress from HPV persistent infection to HPV-related cancer, HPV evades detection mainly through activation of the adaptive immune system [8].

Evidence of the role of adaptive immunity comes from studies that assess T-cells generated in response to HPV infection and lesion development [9,10]. Those studies suggest that T helper (Th) cells are necessary for the production of HPV-specific antibody response and in aiding the development of cytotoxic T lymphocytes. Th responses that result in predominantly Th1-type cytokines favor HPV clearance (Fig. 1), whereas activation and terminal differentiation of Th2 cells lead to higher levels of circulating pro-inflammatory cytokines and fewer HPV-specific T-cell responses [9,10]. Th17 cells are induced by TGFB and produce IL-17-related pro-inflammatory cytokines that act to suppress HPV response [11].

Further evidence of the role of immunity in HPV-related cancers comes from natural history studies, which demonstrated that most young women clear the virus within 1–2 years of infection [12]. In contrast, however, a high burden of HPV-related cancers has been observed in several immunosuppressed populations, suggesting that cancer is more likely to develop among individuals with compromised adaptive immune responses [13]. HPV-associated malignancies occur in excess among patients with HIV and AIDS, probably due to reduced HPV clearance among HIV/AIDS patients with low CD4 T-helper cell counts [13]. Incidence of HPV-related cancers is also greatly increased following solid organ transplantation, and these risks increase with length of time on immune suppression [14]. In a rare genetic disease, individuals with WHIM syndrome (OMIM #193670) have mutations in a chemokine receptor, CXCR4, which leads to impaired chemotaxis of leukocytes and inability to clear HPV infections [15]. These studies suggest that the adaptive immune responses are critical to HPV progression to cancer.

In prior publications involving single genes (or a group of genes) within immune response pathways, our research group has found several statistically significant associations with cervical cancer subtypes [16–19]. In this paper, we conducted a comprehensive analysis of genes within the three primary immune response pathways: Th1, Th2 and Th17, and their association with SCC of the cervix, AC of the cervix and vulvar cancers. We focused on subsets, such as HPV16 positive squamous cell and adenocarcinoma of the cervix to determine if HPV16, the most prevalent cause of cervical cancer, was associated with the candidate genes across histologic types. We investigated whether genetic polymorphisms in cytokine genes involved in adaptive immunity, specifically genes important in the Th1, Th2 and Th17 immune response pathway, are associated with cervical and vulvar cancer risk in a population-based case–control study in western Washington state, in the northwest US.

2. Methods

2.1. Study population and data collection

The present analysis utilized data from participants within a large population-based case–control study aimed at understanding the role of host and environmental factors in anogenital cancers. The

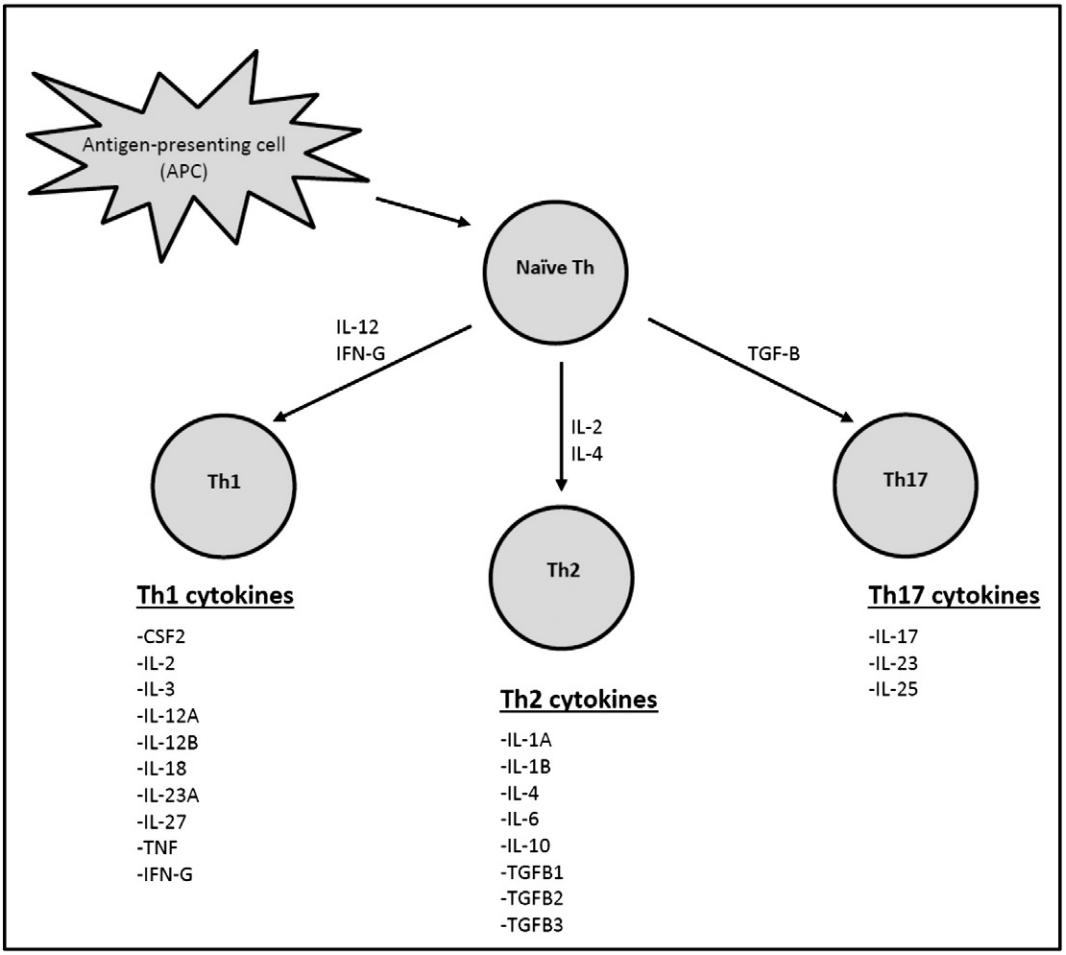

Fig. 1. Cytokines comprising the Th1, Th2 and Th17 immune pathways. Naïve T-cells may react to interferon-gamma (IFN-G) or interleukin (IL)-12 to differentiate into Th1 cells that clear intracellular pathogens including viruses, or they may respond to IL-4 and IL-2 to evolve into Th2 cells that promote humoral immunity; or transforming growth factor-beta (TGF-β) and IL-6 to promote a Th17 response [Ref: Zhu e. al.; Cell Research (2010) 20:4–12.].