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Human leukocyte antigens and other genetic factors in cervical neoplasia

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High-risk human papillomavirus (hrHPV) infection is the major risk factor for cervical cancer (CxCa). The role of genetic susceptibility in the disease has been suggested, but the existing data lack consistency. Although, several human leukocyte antigen (HLA) markers have been postulated to be risk factors to CxCa development, whether or not HLA type determines also regional susceptibility to persistent HPV infection and CxCa incidence is known. Additionally, validation or replication of postulated CxCa-susceptibility genes warrants further investigation. To understand the mentioned issues the present research work was performed by comprising two different approaches: (i) an ecological study to understand whether there is a possible genetic susceptibility to CxCa at a community level in Finland and (ii) a nested case-control study to evaluate candidate genes involve in the susceptibility of CxCa. In the first approach, a systematic review of literature identified following HLA to be associated with CxCa: A11 (odds ratio [OR]=1.4, 95% confidence interval [CI]: 1.1–2.0); B7 (OR=1.5, 95% CI:1.1–2.0); B15 (OR=0.6, 95% CI:0.4–0.8); DR2 (OR=1.2, 95% CI:1.1–1.4) and DR6 (OR=0.6, 95% CI:0.5–0.8). In the Caucasian population, HLA-B7 and DR6, and DR2 and B15 antigens showed at least borderline associations. In view of a bone marrow donor registry at the Finnish Red Cross and the Finnish Cancer Registry, geographic distribution maps of index HLA frequencies and CxCa incidence in the fertile-aged Finnish population ware created. Increased incidence of CxCa was found in a region of western coastal Finland, where frequency of two CxCa susceptibility genes (HLADR2 and B7) was increased, and frequency of one CxCa resistance gene (HLA-B15) was decreased. Geographic overlap of susceptibility and missing of those protected HLA genes with increased incidence of CxCa may partially explain a genetic component in the disease observed in Finland, however individual-level studies are need to confirm this hypothesis.

Beside of the ecological study in the Finnish population, a nested case-control study on 973 CxCa cases and 1763 matched controls, from two Swedish population-based cohorts to examine the association of common genetic variants with CxCa risk. HLA-DRB1 alleles and 24 other polymorphisms in 14 genes were selected on the basis of reported association or mechanistic plausibility with an HPV infection or cervical cancer development. Genotyping was conducted using multiplex PCR and Luminex technology. A significant association of CxCa with various polymorphisms was observed: rs1800797 in the IL-6 gene (OR=0.88, 95% CI: 0.79-0.99); rs1041981 in the LTA gene (OR=0.87, 95% CI: 0.78-0.98), and rs9344 in the CCND1 gene (OR=1.14, 95% CI: 1.02-1.27), for those individuals carrying the rare allele. Additionally, the alleles 0401 and 1501 of the HLA class II DRB1 locus were associated with an increased risk (OR=1.23, 95% CI: 1.04-1.45 and OR=1.29 95% CI: 1.11-1.50, respectively), and allele 1301 was associated with decreased risk (OR=0.59, 95% CI: 0.47-0.73). The effects of CCND1 and the HLA*DRB1 alleles were independent of the effect of smoking. We did not find any association of risk with polymorphisms in genes related to the innate immune system. In conclusion, our study provides evidence for genetic susceptibility to CxCa due to variations in genes involved in the immune system and in cell cycle.