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The role of the high-risk human papillomavirus intratype variants in the development of cervical cancer worlwide

Project coordinator : **Gary Clifford**
International Agency Research on Cancer
ice@iarc.fr

Identifying which human papillomavirus (HPV) infections are self-limiting from the minority which are destined to progress to cancer remains an important focus of cervical cancer research and prevention, especially in the era of HPV-based screening. The most important known determinant for progression to cervical cancer is the HPV type involved, namely the presence of HPV16 or 18. However, intratype sequence variations or "variants" are increasingly suspected to have differential oncogenic potential.

Variants of HPV16 and 18, the two most common types in cancer worldwide, fall into distinct phylogenetic trees with branches that segregate geographically and with major human ethnic groups. American and European studies have reported that non-European HPV16 variants confer higher risk for high-grade cervical lesions (CIN3) and cancer in comparison to the predomiant European lineage, although this finding has not been observed in world regions where Asian and/or African variants dominate.
To add to this picture, recent data show that the outcome of infection with a given HPV16 or 18 variant is worse in a host of the same ethnic origin as the phylogenetic branch of the virus. Much less is known about the phylogeny and clinical relevance of high-risk HPV type variants other than HPV16 and 18.

In this proposal, we intend to compare the potential of different high-risk HPV variants to cause cervical cancer in geographically and ethnically diverse populations, exploiting a large international biological resource. Over the last decade, the Infection and Cancer Epidemiology Group at IARC has co-ordinated population-based HPV prevalence surveys and cervical cancer case series in more than 20 different areas across 4 continents (Clifford et al, Lancet, 2005).
Cervical samples from >2,000 cancer cases and >20,000 women without cancer (controls) are held by IARC, from nine regions in Asia (Shanxi, China; Shenyang, China; Shenzhen, China, Mongolia, India, Nepal, Pakistan, Thailand and Korea), three regions in Africa (Algeria, Nigeria and Guinea), two regions from South America (Argentina and Chile), and three regions from Europe (Poland, Spain and Georgia). Such a broad representation constitutes an important gain in study power over previous studies, both for the study of non-European lineages of HPV16 and HPV18 (including novel isolates from populations unrepresented in current phylogenetic classifications), and for study of HPV types that are more frequent in cervical cancer outside Europe and the Americas e.g. HPV45 in Africa, HPV 58 in Asia. Furthermore, the exploitation of large population surveys provides appropriately large numbers of HPV-positive women without cancer to serve as controls. No new sample collection or genotyping is required as all samples have already been tested for more than 35 HPV types. This resource currently includes 1264 cases and 598 controls positive for HPV16, 324 and 198 positive for HPV18, and 595 and 1204 positive for types 31, 33, 35, 45, 52, or 58.

We propose to describe worldwide sequence variation for these seven high-risk HPV types, with particular attention to variation in the E6 oncogene, with the aim to be able to characterise the oncogenic potential of different variants. We will also determine whether the oncogenic risk-profile of high-risk HPV variants varies according to the

ethnic/geographic origin of the host, and/or the histological type of cancer. Lastly we expect to establish a rich DNA resource on which to base future studies of viral-host immunogenetic interactions.