PREFACE
Human papillomavirus (HPV) infection is an important public health problem affecting both women and men. Genital HPV infections, which are predominantly sexually transmitted, are responsible for a range of benign, premalignant and malignant diseases in both sexes. In women, the most important complication of persistent infection with high-risk types of HPV (hrHPV) is cervical cancer. Furthermore, female genital HPV infection can lead to the development of anal, vulvar, vaginal and oropharyngeal cancer. For decades, women have been the primary focus of HPV research. However, given the mode of transmission, men play a crucial role in the spread of the virus. In addition, the burden of HPV-related disease in men, such as oropharyngeal cancer, anal cancer and penile cancer, is increasingly acknowledged.

This thesis addresses two relevant questions in HPV research.

How can we improve the triage of high-risk HPV-positive women in cervical cancer screening?

The introduction of organized cervical cancer screening programs has led to a drastic reduction in cervical cancer incidence and mortality. Yet, globally, cervical cancer is still diagnosed in 528,000 women each year, of whom 266,000 die as a result of the disease. Improvement of these figures requires change at various levels, such as an increase in the availability of prophylactic HPV vaccination and the implementation of screening in developing countries. Moreover, it requires improvement of tests and algorithms used in cervical cancer screening. Until recently, cervical cancer screening was primarily based on the cytological evaluation of cervical scrapes, which is a subjective method with a limited sensitivity and reproducibility. An abundance of randomized controlled trials has shown that testing for hrHPV provides a superior protection against cervical high-grade premalignant lesions and cervical cancer compared to cytology. For this reason, hrHPV-testing has recently replaced cytology as a primary screening tool in several nationwide screening programs, and many countries will follow this example in the near future. However, as most women who test hrHPV-positive clear the virus spontaneously and do not develop cervical cancer, referral of all hrHPV-positive women to a gynecologist for colposcopy would induce significant over-treatment, leading to obstetric complications and unnecessary costs. Therefore, it is of great importance to find a feasible triage strategy, which effectively identifies only those hrHPV-positive women with cervical premalignant lesions with a high short-term progression risk to cancer, as these women are in need of direct treatment. The first part of this thesis describes the clinical evaluation of several molecular candidate markers for detection of high-grade cervical premalignant disease among hrHPV-positive women.

What is the prevalence and clinical relevance of the presence of HPV in semen?

Although the presence of HPV has been described in several parts of the male genital tract, little is known about the exact mechanisms behind the sexual transmission of HPV. Previous
studies have shown that semen can contain HPV\textsuperscript{30}, but very few have addressed the possible source of seminal HPV presence or the relation of HPV presence in semen with HPV infections of the penile epithelium. Furthermore, an important question is whether the presence of HPV is clinically relevant in terms of fertility. Previous small studies have led to fierce conclusions on the necessity of standardized HPV-testing on semen in the screening of subfertile couples and in settings of assisted reproduction.\textsuperscript{31} The second part of this thesis adds evidence to this discussion by exploring the relationship between seminal HPV presence and penile HPV infections, and by addressing the relation of HPV presence in semen and parameters of semen quality.
REFERENCES


