PREVENTION OF CERVICAL CANCER IN THE NETHERLANDS. STUDIES ON CYTOLOGY AND HPV INFECTIONS

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SUMMARY

Cervical cancer prevention by cytology screening has been possible since the middle of the 20th century. In the Netherlands, organized screening was introduced nationwide in 1988. However, a new evaluation of the screening modality used is called for by the possibilities of high-risk human papillomavirus-based screening. In this thesis, cervical cancer epidemiology, cervical cancer screening and human papillomavirus infections are described. The first part of the thesis deals with the epidemiology of cervical cancer and human papillomavirus infections. In the second part, aspects of the causal relation between these entities are addressed. Integration of both approaches will result in an advice for the Dutch screening programme.

We have performed two ecological studies on cervical cancer incidence, as described in **CHAPTER 3**. Here, we confirmed that cervical cancer is a relatively rare disease in the Netherlands. Still, during the last decade, the incidence rate has decreased continuously. This decrease seems to be a decrease in the incidence of squamous cell carcinoma of the cervix only, while the incidence of adenocarcinoma of the cervix has remained stable (3.1). These findings seem to confirm that the cytological detection of squamous precursor lesions is superior than the cytological detection of precursor lesions of adenocarcinoma by cervical cancer screening. Stratified for age, the main decrease in incidence has occurred in women aged 60-74 years suggesting the influence of participation in the screening programme on cervical cancer incidence. A rising trend in incidence of adenocarcinoma may be present in women aged 15-44 years, again suggesting a decreased efficiency of screening compared of adenocarcinoma to squamous (precursor) lesions (3.2).

Thus, cervical cancer incidence has decreased in the Netherlands, and its decrease in incidence coincides with the introduction of cervical cancer screening by exfoliative cytology of the cervix (the Pap smear). In **CHAPTER 4**, we describe the cervical cytology coding classification used in the Netherlands and the effect of changes effectuated therein in order to better select women with cervical lesions from the general population screened while reducing the number of referrals for low-grade abnormalities. We have evaluated the CISOE-A scoring system for the diagnosis of cervical lesions used in the Netherlands in a cross-sectional study of one geographically defined region of the Netherlands. We found that the introduction of the CISOE-A classification in 1996 has led to a decrease in the number of women diagnosed with abnormalities, while the detection of high-grade lesions was not affected. This indicates that the cytological screening programme increased its efficacy.

Since high-risk types of the human papillomavirus cause cervical cancer, we have sought to establish whether certain high-risk types confer a preferential risk for the development of cervical cancer compared to the other high-risk types in **CHAPTER 5**. Cross-sectionally obtained data of women with normal cytology and a positive high-risk HPV test in the POBASCAM trial was compared to data of cases with (invasive)

cervical cancer obtained retrospectively (5.1). High-risk HPV types HPV16 and HPV18 occurred with the highest frequency in all carcinoma subtypes studied compared to the other high-risk types. HPV16 conferred a preferential risk for squamous cell carcinoma, and less for adenocarcinoma (in situ). HPV 18 on the other hand, conferred the highest risk for adenocarcinoma (*in situ*), and conferred a lesser risk for squamous cell carcinoma. After correction for high-prevalence types, HPV45 conferred a preferential risk for adenocarcinoma as well. Subsequently, we compared cases with (invasive) squamous cell carcinoma with cases of cervical intra-epithelial neoplasia grade 2 and 3 (CIN2/3) (5.1). In this study of exclusively squamous lesions, HPV16 was associated with both high-grade lesions and squamous cell carcinoma. HPV18 conferred a high risk of squamous cell carcinoma compared to high-grade lesions. This indicates that the contribution of HPV18 to the burden of cervical cancer may be underestimated in studies using CIN2/3 as intermediate endpoint for invasive cervical cancer.

A useful cervical cancer screening test selects participants with (a high risk of) disease from a larger population of women without disease participating in screening. Therefore, in order to implement high-risk HPV testing in the Dutch screening programme, we evaluate the addition of high-risk HPV testing to cervical cancer screening in **CHAPTER 6**. We evaluated whether a type-specific HPV test better identifies women at risk for cervical precancer than cytology (6.1). We performed a prospective study with retrospective retrieval of case material in order to evaluate this question. Women who were diagnosed with high-grade lesions in spite of adherence to the screening programme often harbored HPV infections in the normal smear taken in the screening round preceding the diagnosis of a high-grade lesion. In addition, the high-risk HPV harbouring smears previously diagnosed as normal were more often upgraded after revision than normal smears without high-risk HPV. Thus, the use of high-risk HPV testing to select smears for rescreening would facilitate early diagnosis of high-grade lesions. In 6.2, we evaluated a risk stratification in a randomized controlled trial, the POBASCAM trial, to better identify women at risk for cervical disease. Women with high-grade cervical lesions were better identified by adding a second cytology test after 6 months follow-up to the baseline cytology and HPV test than were identified by testing at intake only. Especially in the groups of women with a positive HPV test and BMD or normal cytology at intake, a subset of women with a high risk of cervical precancer could be identified by a high-grade cytology result at the repeat test. When extra high-risk types HPV16 and HPV18 were analyzed separately from the other high-risk HPV types, baseline testing for HPV16 and/or HPV18 identified a subgroup with extra high-risk for the presence of high-grade CIN lesions at short-term follow-up, while, conversely, the group with negligible risk consisted of women with a negative high-risk HPV test. These data confirm that the high-risk HPV test offers a unique possibility in the screening programme to select women at risk for precancer and thus enables a better risk

stratification than cytology only as currently employed in cervical cancer screening in the Netherlands.

In the general discussion (**CHAPTER 7**), the main findings of this thesis are considered in the context of current scientific knowledge and ongoing research in the field of cervical cancer screening. We conclude that the addition of high-risk HPV to the cervical cancer screening programme will result in an increased detection of high-grade lesions and cervical cancer in screening participants. A type-specific high-risk HPV test may further aid in the selection of women with the highest risk of cervical cancer.