Modeling the effects of cervical cancer prevention in the Netherlands

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2015

document version
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1 | General Introduction

CERVICAL CANCER

Epidemiology of cervical cancer

Cervical cancer was ranked 4th among newly diagnosed cancers in women worldwide in 2012.[1] Over 527,000 women were diagnosed with cervical cancer and it was the primary cause of death for 265,000 women.[1] Mortality rates vary across countries and are highest in low income countries without established screening programs. In the Netherlands, a country with an established cervical screening program, yearly around 700 cervical cancers are diagnosed.[2] Although cervical cancer can often be treated successfully if detected at an early stage, approximately one third of all women diagnosed with cervical cancer in the Netherlands will not survive up to 5 years after diagnosis.[2]

Natural history of cervical cancer

Cervical cancer is a cancer from the mucosa of the transformation zone of the cervix and can be classified into a few histological subtypes. Squamous cell carcinoma is the most common one and accounted for 74% of all diagnosed cervical cancers in the Netherlands in 2012.[2] Adenocarcinoma is the second most common type and accounted for 19% of all cervical cancer cases in the Netherlands in 2012.

Precursor lesions

It is generally assumed that cervical cancer is a slowly growing cancer and the early stages may be free of symptoms. Cervical squamous cell carcinoma develops through premalignant precursor lesions, called cervical intraepithelial neoplasia (CIN) which are graded into mild (CIN1), moderate (CIN2) or severe (CIN3). Grading of the precursor lesions depends on the extent of replacement of the epithelial lining by atypical cells, with the highest grade denoting total replacement of the epithelium with atypical cells. It is known that not all precancerous lesions will eventually progress to cervical cancer if left untreated; they can regress, persist or progress.[3, 4] The higher the CIN grade, the higher the chance of progression to cervical cancer. The progression risk of CIN2 and CIN3 is thought to be over 20%[3] and therefore these high-grade lesions are treated upon detection, preferably by a large loop excision of the transformation zone (LLETZ) also known as loop electrosurgical excision procedure (LEEP). There is not yet a reliable method to distinguish between progressing or non-progressing CIN2/3[5] and therefore a considerable number of women will receive unnecessary treatment after diagnosis of CIN2/3. This is considered a problem because overtreatment causes unnecessary anxiety in women, an increase in cervical morbidity such as cervical insufficiency and preterm birth, and induces healthcare costs. The progressing potential of CIN1 is considered low and therefore the Dutch guidelines advise not to treat these lesions but to follow a "wait-and-see policy".[6]

Human papillomavirus infection

In the 1950's it was noted that cervical cancer was very rare in women that lived a celibate life (e.g., nuns) and in women of ethnic groups where male circumcision was very common.[7, 8] The etiology of cervical cancer was unknown, but it was believed that men played a key role.[8] In 1977 professor Harald zur Hausen hypothesized the role of the sexually transmittable human papillomavirus (HPV) in the development of cervical cancer.[9] A couple of years later, in 1983/84, he and co-workers in his lab were able to isolate HPV16 and HPV18 in cervical cancer. Zur Hausen noted the preferential association of these two HPV types with malignant cervical tumors and observed HPV16 in 7 out of 10 cervical dysplasias.[10] Zur Hausen was awarded the Nobel prize in physiology or medicine in 2008 for his discovery of the role of HPV in cervical cancer. He shared this prize with Françoise Barré-Sinoussi and Luc Montagnier who discovered human immunodeficiency virus (HIV).

HPV is a sexually transmitted virus, which is highly transmittable and very common in the general population. Approximately 80% of the population has been infected at least once in their lifetime with a high-risk HPV type.[11] Both men and women can be infected with HPV and develop anogenital cancers: cervical, vulvar, and vaginal carcinomas in women, penile carcinomas in men, and anal carcinomas in both. In addition, HPV infection is a major etiologic factor for oropharyngeal cancers.[12]

Over 150 HPV types are known of which more than 40 types infect the mucosal epithelium of the genital tract.[13] Based on phylogeny and epidemiological criteria these mucosal papillomavirus types can be divided into low-risk types (lrHPV) that can cause ano-genital warts, and high-risk types (hrHPV) that are associated with cancer. Persistent infection with a high-risk HPV type is the necessary cause of cervical cancer.[14] For HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59 there has been sufficient evidence for their oncogenic potential and these 12 types are defined by the WHO as being hrHPV (IARC class 1). HPV types 26, 53, 66, 67, 68, 70, 73 and 82 are considered agents with limited evidence in humans for their oncogenic potential.[15]

HrHPV prevalence in women is dependent on age.[16] The highest prevalence of around 25% is observed in women under the age of 25 years.[17] In accordance with a declining trend in hrHPV incidence,[18] the hrHPV prevalence levels off to around 3% at age 50 years. The hrHPV prevalence among men shows a different picture; it remains fairly constant with a minor increased prevalence at younger ages.[19] HPV16 is the most prevalent type in squamous cell carcinomas (55%),[20] and therefore considered the most oncogenic HPV type. In adenocarcinomas HPV18, HPV 16 and HPV 45 are the most prevalent types in decreasing order.[21]

Viral life cycle

It is thought that HPV can access basal cells from the cervical epithelium through microabrasions. HPV virions infect epithelial stem cells that are located in the basal epithelial layer.[22, 23] In normal viral life-cycle the replication of the virus is dependent on the differentiation program of the infected squamous epithelium with viral replication taking place in differentiated, non-dividing cells. The viral proteins E1 and E2 are both functionally involved in replication of the

viral genome. For viral replication the virus makes use of the host cell DNA replication machinery in the differentiated epithelial cell. Normally this replication machinery in the differentiated epithelial cell is not active, but early viral proteins in particular E7 can activate this machinery. New viral particles are formed and released from terminally differentiated cells. This process is called *productive HPV infection*.

*I*n case of a *transforming HPV infection* the viral oncogenes E6 and E7 show an improperly increased expression in the proliferating fraction of the squamous epithelium. E6 binds with tumor suppressor gene product p53 and prevents cells from undergoing p53 mediated apoptosis and cell cycle arrest. E7 binds with the protein encoded by the retinoblastoma protein (pRb) tumor suppressor gene, thereby disturbing the G1/S checkpoint and continuously triggering transition to S-phase by activating the E2F transcription factor family members. The continuous overexpression of E6 and E7 in proliferating basal cells of the epithelium results in genetic instability leading to additional (epi)genetic alterations in the cellular genome. Via the precursor stages CIN grade 1, CIN grade 2 and CIN grade 3 the HPV infection ultimately results into invasive cervical cancer.

HPV clearance and CIN lesions

The immune response to HPV after infection is weak compared with other viral infections; there is little tissue destruction that is associated with HPV infection.[22] However, most infections clear within 12 months. Approximately 20% of the incident infections turn into a productive infection.[5] Only few of these infections become transforming infections leading to genetic instability and additional epigenetic changes. These result into morphological epithelial changes, leading to the most advanced lesion CIN3. The duration from HPV infection to CIN2/3 development is thought to be relatively short (3-5 years).[24, 25] The process of further progression is not yet well understood, but is usually accompanied by genomic loss and integration of the virus in the cellular genome.

HPV DNA detection methods

To assess whether someone is currently infected with HPV, one can test for the presence of HPV DNA in cervical smears, vaginal/cervical self-samples and biopsies of cervical tissues. Most HPV assays target HPV DNA of 13-15 hrHPV types by polymerase chain reaction (PCR) using consensus and/or type specific primers from the L1 and/or the E6/E7 region. If the interest is to detect any sign of an HPV infection, an HPV assay with high analytical sensitivity is preferred. However, a positive test result from an analytical HPV test does not necessarily imply a clinically relevant infection (i.e., an infection that is associated with a CIN lesion) it could also indicate a transient HPV infection (clinically irrelevant). Only HPV infections that are informative for the presence of CIN2/3 or cancer are of interest in clinical settings. Guidelines for clinical validation of candidate HPV tests have been published before.[26]

Serological detection methods

The presence of IgG antibodies to viral antigens in serum is generally considered a well-defined marker of past infection or vaccination. The natural antibody response to HPV is weak; HPV

causes little tissue destruction and little viraemia since only epithelial cells are affected.[27, 28] Not everyone shows a detectable antibody response after an HPV infection and antibody concentration may wane over time.[29, 30] Note that most serological assays detect IgG antibodies and that seropositivity (presence of IgG antibodies) is considered a marker of past HPV infection but not a correlate of immune protection.[31] Several serological assays have been developed of which the pseudovirion-based neutralization assay (PBNA) is considered the gold standard as it measures the amount of neutralizing HPV antibodies. This test is labor intensive and complicated and therefore not suitable for large sero-epidemiological studies. In this thesis, the VLP-MIA is used as an alternative. This assay measures HPV type-specific IgG serum antibodies against L1 virus like particles and has been validated against the PBNA.[32]

CERVICAL CANCER PREVENTION

Secondary prevention of cervical cancer

The Pap test

Georgios Papanicolaou discovered in 1928 that cervical cancer could be identified by means of a cervical smear.[33, 34] The smear could be visually inspected under the microscope for abnormal cells and if present, women were referred to the gynecologist. This procedure is nowadays known as the Pap-test. This test is noninvasive and cheap compared to a biopsy, and it was for a long time the only available method to detect cervical cancer. In the 1950's, it was discovered that cervical cancer was preceded by precancerous lesions which could also be detected by this Pap test. Cervical cancer now had the potential to become a preventable disease but organized screening was not yet feasible due to the lack of trained cytologists at that time.[8]

National screening program

Several countries started to train cytologists and to develop national screening programs. In the Netherlands, screening started with a pilot study in 1976 in three experimental regions. This was soon followed by the development of local and regional invitational screening programs and by performing opportunistic screening.[35, 36] The nationwide screening program started in 1989 for women aged 35 to 54 years at a 3-yearly interval. Evaluation of this program pointed towards a suboptimal performing program in terms of organization and costs and therefore it was restructured in 1996 into its current format; 5-yearly screening for women aged 30 to 60 years.[37] The organized screening program has high coverage with per-round attendance rates around 70% of the target population in the Netherlands.

Although in the Netherlands cervical cancer mortality has been decreasing since 1960 (before organized screening was implemented), organized screening is likely responsible for the acceleration in the decline.[38] The mortality rates decreased from 7.0 per 100,000 woman years in 1970

to 2.0 in 2007, and the cervical cancer incidence decreased from 9.1 per 100,000 woman years in 1989 to 7.9 in 2007.[39]

Revision of the screening program for cervical cancer

Adding high-risk HPV (hrHPV) DNA testing to cytology has the potential to increase the effectiveness of cervical screening because it has a better sensitivity for CIN2+ detection and a better negative predictive value compared with cytology alone. Several randomized controlled trials have confirmed that hrHPV DNA based screening resulted in earlier detection of high-grade lesions. A combined analysis of these trials showed that the hrHPV DNA test has a better negative predictive value for cervical cancer than cytology.[40-43] However, the specificity of hrHPV screening is 2.5-4% lower compared with cytology, which could possibly lead to over referral for colposcopy and overtreatment of otherwise regressive lesions. To overcome this problem, triage of hrHPV-positive women by cytology at baseline and repeat cytology after 6 months is at present the most accepted management strategy.[44]

The Netherlands will be the first country in the world to adapt their organized cytology based screening program and to replace the Pap-test by the hrHPV DNA test as the primary screening instrument, starting in 2016.[45] In the new program, women are invited every 5 years from age 30 to 60 years to have a cervical smear taken by their general practitioner (GP). This smear is first tested for hrHPV DNA and in case of a positive hrHPV test, cytology triage testing at baseline (on the same smear material) and after 6 months will be carried out. If cytology is abnormal, women will be referred to the gynecologist. To limit the burden of screening and to control costs, the screening interval will be extended from 5 to 10 years for women who test hrHPV-negative at age 40 or 50 years. For hrHPV-positive women with a negative cytology triage test, the 5-year invitation scheme will be preserved. In addition to these changes, women who do not attend screening at the GP can request a self-sampling device to test for the presence of hrHPV at home. In case of a positive hrHPV test, women will be advised to visit their GP for making a cytology triage smear. These women will have the same follow-up procedure as mentioned earlier.

Primary prevention of cervical cancer

HPV vaccination

Much effort has been put into the development of a vaccine for primary prevention after the discovery that isolated L1 and L2 proteins of the HPV capsule folded automatically into virus like particles. Starting in 2006, two prophylactic vaccines have been registered by the European Medicines Agency (EMA); a bivalent vaccine that protects against HPV16 and HPV18 (Cervarix, by GSK), and a quadrivalent vaccine that also includes the low-risk types HPV6 and HPV11 (Gardasil, by Merck). Both vaccines are approved for girls above age 9 years and Gardasil is also approved for boys above this age. These vaccines were soon after registration included in the national immunization programs of many Western countries. The vaccines have not shown an effect

on pre-existing HPV infections[46] and are probably most effective in those who are HPV naïve. Therefore, vaccination is preferably administered prior to sexual debut.

The Netherlands included a three-dose schedule of bivalent HPV16/18 vaccination for 12-year-old girls in 2010 after a catch-up campaign for 13 to 16-year-old-girls in 2009. In December 2013, the EMA licensed a two-dose schedule for both HPV vaccines, and this has been adopted by the Dutch national immunization program from March 2014 onward.[47] So far, uptake of HPV vaccination has been relatively low compared with the uptake of other vaccines that are offered via the national immunization program; uptake of a 3-dose HPV vaccination schedule was 58% in 2013.[48]

Efficacy and effectiveness of HPV vaccination

The efficacy of HPV vaccination has been studied in several randomized controlled trials (RCT) conducted in women aged 15-25 years and the results are promising.[49-51] These trials use surrogate endpoints for assessing the vaccine efficacy (e.g., CIN2 or CIN3) as the time from HPV infection to cancer is long and it will take several decades before the clinical efficacy can be evaluated.

Interpretation of HPV vaccine efficacy depends on the characteristics of the cohort under study (e.g., the number of received vaccine doses, sexual history and evidence of previous HPV exposure). We summarize the efficacy rates on the endpoints CIN2 and CIN3 of the two HPV vaccines in Table 1. Note that besides protection against the vaccine-types, both vaccines also have shown to provide cross-protection against non-vaccine HPV types (Table 2) but the duration of cross-protection is uncertain.

Table 1. Vaccine efficacy rates of HPV16/18 related endpoints of the bivalent HPV vaccine in the PATRICIA trial (adapted from Lehtinen et al.[51]) and of the quadrivalent vaccine in the FUTURE I/II trial (adapted from Munoz et al.[63]) after 4 years of follow-up by cohort definition.

PATRICIA trial (bivalent vaccine)	% efficacy (95% CI)	FUTURE I/II trial (quadrivalent vaccine)	% efficacy (95% CI)
TVC-naïve		Unrestricted susceptible	
CIN2+	99.0 (94.2-100)	CIN2	100 (91.4-100)
CIN3+	100 (85.5-100)	CIN3	100 (90.5-100)
TVC		ITT	
CIN2+	60.7 (49.6-69.5)	CIN2	53.0 (38.2-64.5)
CIN3+	45.7 (22.9-62.2)	CIN3	43.5 (27.3-56.2)

CIN: cervical intraepithelial neoplasia; TVC: total vaccinated cohort; ITT: intention-to-treat.
The TVC/ITT cohorts comprised all women who received at least one vaccine dose.
The TVC-naïve and unrestricted susceptible cohorts comprised women with no evidence of oncogenic HPV infection at baseline.

Table 2. Cross-type protection against 6-month persistent infection in women that had no evidence of oncogenic HPV infection at baseline (adapted from Malagon et al.[64])

	% efficacy (95% CI)	
	PATRICIA trial (bivalent vaccine)	FUTURE I/II trial (quadrivalent vaccine)
HPV31	77.1 (67.2, 84.4)	46.2 (15.3, 66.4)
HPV33	43.1 (19.3, 60.2)	28.7 (-45.1, 65.8)
HPV45	79.0 (61.3, 89.4)	7.8 (-67.0, 49.3)
HPV52	18.9 (3.2, 32.2)	18.4 (-20.6, 45.0)
HPV58	-6.2 (-44.0, 21.6)	5.5 (-54.3, 42.2)

The first results of population-based vaccine effectiveness have just appeared. Australia, the first country to implement nationwide HPV vaccination, reported a vaccine effectiveness of 86% (95% CI: 71-93) against prevalence of HPV types 6, 11, 16 and 18 combined for fully vaccinated women compared with unvaccinated women.[52]

Monitoring the effects of HPV vaccination

Together with the advice to introduce vaccination against HPV16/18 in the national immunization program, the Dutch Health Council strongly recommended careful monitoring of the vaccine efficacy, its safety, and the duration of protection in the vaccinated population.[53] Next to the direct protection afforded by vaccination, also indirect effects are expected in the unvaccinated women and men, and these should be monitored as well. Indirect protection of unvaccinated individuals arises when their sexual partners (or partners thereof) have received vaccination, thus shielding them from infection. The reduced infection risk is called the herd effect of vaccination.[54-56] As a result, the incidence of cervical cancer and precancerous lesions in unvaccinated women may reduce throughout the next century,[57] but the effects on infection related endpoints (HPV DNA prevalence or seroprevalence) are expected sooner. In the Netherlands, several studies are currently carried out for monitoring the direct and indirect effects of HPV vaccination. These include the longitudinal follow-up of a partly vaccinated cohort of young girls,[58] repeated cross-sectional HPV DNA prevalence and seroprevalence studies in high-risk populations,[59] and repeated cross-sectional serological surveys in the general population.[60, 61]

THIS THESIS

Modeling the effects of prevention measures

Experimental research provides the strongest evidence that an intervention has the desired effect on the outcome of interest. Randomized controlled trials are considered one of the most valid methods for generating scientific evidence. However, such trials cannot always inform public health decision makers for example if the long-term consequences of an intervention measure

cannot be observed. Mathematical models are an alternative for answering questions when empirical data are lacking and also provide a framework for synthesizing multiple data sources.

The impact of an intervention measure can be studied by a counterfactual analysis using mathematical models. These analyses compare the outcome of interest (e.g., cervical cancer incidence) if the intervention measure (e.g., HPV vaccination) is or is not implemented within the same population. In addition, these models provide information on timing of the predicted effects, which may be useful input for the organization of monitoring programs (e.g., how many years after vaccination can we expect a reduction in the cervical cancer incidence? In which age groups do we expect this decrease?).

Both primary and secondary cervical cancer prevention have interesting questions that require modeling studies for answers. In the first part of this thesis we will study the effects of the new Dutch hrHPV-based screening program on the cervical cancer risk. In the second part, we will study the expected herd effects of HPV vaccination on HPV16 infection outcomes in the Netherlands.

Part 1: Effects of hrHPV screening on the cervical cancer risk

To predict the impact of prevention programs on the incidence of cervical cancer, knowledge of the natural history is required. In **Chapter 2** we study the duration from CIN2/3 to cervical cancer. Longitudinal data on the progression of CIN2/3 are not available as it would be unethical to leave women with CIN2/3 untreated once detected. We developed a statistical model for estimating the time distribution between CIN2/3 and cancer using national registry data on the age-specific occurrence of CIN2/3 and cervical cancer in the Netherlands. In addition, we estimated separate durations for HPV16-positive and HPV16-negative CIN2/3.

Although the benefit of the hrHPV DNA test as screening instrument has been confirmed in RCT's, a screening interval extension from 5 to 10 years has not been part of these studies. The effect of the hrHPV DNA test was studied in the setting of 5-yearly screening and therefore women were censored for progression to cancer at the moment of CIN2/3 detection. As it is not possible to infer the safety of an interval extension from these empirical studies, we used mathematical modeling as an alternative. We study the effects of the new Dutch screening program on the cervical cancer risk for women HPV-negative at age 30 to 50 years in **Chapter 3**. Per 5-year age cohort, we simulated the natural history of cervical disease for 1,000,000 women and estimated the number of cancers averted under the old and the new screening program.

Part 2: Effects of HPV vaccination on markers of HPV16 infection

The infection dynamics of the HPV vaccine-types are expected to change after the implementation of HPV vaccination. These changes should be monitored and serological surveys may be a useful means. A benchmark of the pre-vaccine situation is required in order to study the change in seroprevalence after vaccination. Because the serological response after infection with HPV is in general weak, methods that assess the seroprevalence based on a cut-off value will lead to a misclassification bias. In **Chapter 4**, we developed a statistical model to estimate the pre-vaccine

HPV16 seroprevalence without prior classification of seropositive individuals and we assessed whether the serological response differs between men and women. Because the serological response after an HPV infection is poorly understood and the signal induced by the multiplex assay is noisy, we assessed in **Chapter 5** whether a bivariate analysis of the natural antibody response to HPV16 and HPV18 can aid in interpreting serological data. This analysis enables studying the association between the antibody concentrations of HPV16 and HPV18, and in the seropositivity of HPV16 and HPV18.

Changes in the HPV16 DNA prevalence and seroprevalence on the short term may be informative of the ultimate reduction of the cervical cancer incidence due to vaccination. In **Chapter 6** we use an HPV16 transmission model to study how vaccination changes the infection risk in the unvaccinated population (both men and women), and how the HPV16 prevalence and seroprevalence figures will change over time. Monitoring the changes of these cross-sectional outcomes could inform on the ultimate impact of HPV vaccination.

A summarizing discussion of the results presented in this thesis and recommendations for future research are given in **Chapter 7**.

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