Screening in low resource settings, towards a world without cervical cancer

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Chapter 7

Summary and general discussion

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Cervical cancer is a major public health problem, especially in low- and middle-income countries where the health care infrastructure often prohibits successful implementation of organized screening programs due to lack of financial support, professional human resources, and laboratory services (1-4). Indonesia is a low-income country with high rates of cervical cancer, with limited organized screening programs especially in low resource settings (5, 6).

In this thesis several aspects of cervical cancer in Indonesia have been studied: starting with a description of the prevalent HPV types in Indonesia in a hospital-based population and in a population-based setting (**chapter 2 and 3**). An alternative way of cervical cancer screening in a single visit approach has been set up in low resource areas in Indonesia and is described in **chapter 4**: "See and Treat" using visual inspection with 3-5% acetic acid (VIA) and treatment with cryotherapy. Furthermore, we investigated the HPV types persisting after cryotherapy (**chapter 5**). In the last chapter we assessed the performance of an objective tool for cervical cancer screening; screening with an optoelectronic device **(chapter 6)**. Below, the results obtained, and the main conclusions are discussed and put in perspective for future implications.

Human papilloma Virus (HPV)

HPV 16 and 18 are responsible for 70% of the cervical cancers worldwide, overall HPV 16 causes 50% of the cervical cancers and HPV 18 20% (7-9). HPV prevalence, age-specific prevalence, and type of distribution differ substantially between populations (10-13). This underlines the importance to know the prevalent types of HPV in a country to estimate the impact of future HPV vaccination programmes.

In Indonesia, HPV 18 has a greater role in cervical cancer than in other parts of the world; HPV 18 was found as frequent as HPV 16 in cervical cancer (14) or even more frequently than HPV 16 (9, 15). We investigated the prevalent HPV types in healthy Indonesian women, described in a hospital-based case control study in **chapter 2** and described in a population-based study in **chapter 3**.

A total of 74 cervical carcinoma cases and 209 control women, recruited from the gynecological outpatient clinic of in the University Hospital Rumah sakit Cipto Mangunkusumo in Jakarta, were included. HPV was detected in 95.9% of the cases and in 25.4% of the controls and we calculated an OR for HPV infection of 69.5 for HPV prevalence in the cases. The high prevalence of HPV, found in our hospital-based control was in agreement with the high estimated incidence rate of cervical cancer in Indonesia (6, 16, 17). In our study population the detection rate of HPV 16 and HPV 18 in the case group were comparable, which we also found in the control group. These two findings suggest that the oncogenic potentials of HPV 16 and HPV

18 in Indonesia are similar. We supposed that the high incidence of HPV 18 in the control group compared to the world incidence of HPV 18, will be related to the high prevalence of HPV 18 in the general Indonesian population (**chapter 2**).

Based on the findings from this case-control study, we investigated the age-specific prevalence of HPV types among women in the Indonesian population and possible risk factors of HPV positivity, described in **chapter 3.**

Of 20.834 women 2686 random age stratified samples were taken and HPV was tested. In this population-based study, 91.2% of the women had never been screened before. The overall HPV prevalence was 11.4%, age-standardized to the world standard population 11.6%.
We found that in Indonesia HPV 16 and 18 are equally common in the general population, as they are in cervical cancer as described before. We also found that HPV 52 was the most prevalent type. In Indonesia different age-specific prevalence patterns were seen overall high in Jakarta and in Tasikmalaya and declining with age in Bali.

In the risk calculations, HPV positivity was found to be associated with a history of more than one sexual partner (OR 1.81 95% CI 1.31-2.51), as expected (this thesis), (1, 18-20). A small group of divorced women in Tasikmalaya and women with high daily income in Bali were associated with HPV positivity, which could also reflect sexual behavior **(chapter 3)**. Significant risk factors for cervical cancer in addition to HPV infection were young age at first intercourse, having a history of more than one sexual partner and high parity **(chapter 2).**

Screening and treatment

The need for secondary prevention programs remains as long as HPV vaccines are not yet available to all women in the world and do not yet provide a 100% coverage of all HPV types. Moreover, surveillance and management of women who haven't been vaccinated before the onset of sexual activity, is still needed.

Because of the high incidence rates in low- and middle-income countries, it is of major importance that the screening methods chosen are highly efficient, cost-effective and feasible in local circumstances. Screening using visual inspection with acetic acid (VIA) and treatment using cryotherapy have shown to meet these requirements and have shown to reduce incidence and mortality due to cervical cancer (21-28).

Based on these findings we set up the See and Treat project for cervical cancer screening described in **Chapter 4.**

To be effective in reducing incidence and mortality rates, screening programmes should focus on the target population. The target population for cervical (pre-) cancer are women aged 30-49 in whom the highest incidence in of (pre-)malignant lesions

are found (29-32). When financial resources are limited, focus on the target population should be intensified.

As our study describes a pilot project, the target population was 30-49 years old but was open to all women interested to participate. Our study population reinforces the importance of the target population as the highest prevalence of women with a positive VIA screening test was found in the high-risk group of women aged 30–49, accounting for 70.7% of positive cases.

The overall positive predictive value of VIA for histological diagnosis of ≥ CIN I and ≥ CIN II was 58.7% and 29.3%, respectively. The approximate specificity was 98.1%, and the detection rate for ≥ CIN I was 2.6% **(chapter 2)**. Our study gives insight in the use of VIA in the field conditions and its routine performance in health services in Indonesia. Our rates are comparable to population-based VIA screening programs in other high incidence areas as Tanzania (VIA positivity 3.8%), Bangladesh (4.8%) and Angola (6.6%) (33-35). The use of VIA and cryotherapy performed well in the described single-visit approach, and the acceptance of the procedure was high.

A major aspect in screening programmes is awareness: women have to be informed about cervical cancer, about the importance of screening, and about symptoms that could reveal cervical lesions. When these awareness programmes are adjusted to the culture of the population screened, the information will be more accepted by its public and will have more impact (36-38). To avoid unnecessary stigmatization, it is important to underline the fact that cervical cancer is a rare complication of a highly prevalent high-risk HPV type infection because of a failing immune system rather than a sexual transmitted disease as 85% of all women will be infected with HPV sometime during their lifetime (39).

Collaboration with existing health institutions is of major importance. In the See and Treat project, collaboration was set up with the Indonesian family welfare movement (Pembinaan Kesehahteraan Keluarga PKK), the Indonesian cancer foundation (Yayasan Kanker Indonesia YKI), and the University hospitals (Rumah sakit Cipto Manungkosumo in Jakarta Java and Rumah Sakit Sanglah in Den Pasar Bali).

This collaboration succeeded in reaching the target population, i.e., high-risk women who had limited access to health-care facilities and lived in low-resource settings **(chapter 4)**. When screening programmes are implemented in already existing health structures, the potential of sustainability increases. When the implementation succeeds on low scale it is easier to scale-up (40).

Screening with the optoelectronic device (Truscreen) is another alternative to conventional cytology screening. This device utilizes optical and electrical technology, it has the advantage of producing an immediate result, it is objective, requires low training efforts and does not need laboratory equipment. We assessed its performance in a perfectly regulated tertiary hospital setting and compared the results to liquid-based cytology and HPV testing. Truscreen demonstrated

comparable sensitivity to high quality cytology, and sensitivity and specificity approaching HPV DNA testing **(chapter 6)**. The device showed promising results in a hospital setting and should now be further tested in population based cervical cancer screening settings. A review based on Chinese studies showed a moderately good diagnostic accuracy (41), a Mexican study showed low sensitivity but high specificity (42). Truscreen can potentially become an important tool in the prevention of cervical cancer, particularly in low- and middle-income countries with resource-limited see and treat screening settings as results are directly available.

More screening tests and techniques are being used and developed. HPV DNA self-sampling is upcoming and has been reported to be of patient preference because of privacy and ease (43). Self-samples are accurate and it's an effective way to reach under screened women (44). Molecular tests, dual staining on cytological slides and more advanced visual inspection tests based on artificial intelligence or machine learning platforms are under research.

Cryotherapy

Excisional methods of treatment (LEEP/LLETZ) are very effective and standard of care in developed countries, and overall LEEP has a higher overall cure rate compared to cryotherapy (96.4% compared to 88.3% respectively, p=0.026) (45). The treatment is less suitable for See and Treat approaches in low- and middle-income countries as it is a multistep treatment procedure that requires electricity, anesthetics, and it is associated with higher complications rates due to post treatment bleeding and infection. It also carries an increased risk of preterm delivery (46-48).

The WHO guideline recommends to use cryotherapy in resource restrained settings (and LEEP when the lesions are not eligible for cryotherapy) (49),(50). Cryotherapy is a widely used treatment in a single visit approach setting during cervical cancer screening. It has proven to be safe, effective, easy to use, cheap and readily available in low resource areas (51-53). Treatment of premalignant lesions using thermal ablation has been evaluated as alternative to cryotherapy and shows comparable or better performance (54). Thermal ablation is a battery-powered, hand-held device, not requiring any gas which makes its usage in low resource settings easier. Immunomodulators and therapeutic vaccines might be future options to treat premalignant lesions but are now still in research setting.

The use of VIA and cryotherapy in the single-visit approach in low resource settings in Indonesia as described in **chapter 4**, performed well, and the acceptance of the therapy was high. There were no major side effects reported, although we might not have been fully informed as follow-up rates are limited. However, these findings are consistent with earlier performed studies on the safety, acceptability and feasibility of cryotherapy, where side effects were found to be rare (55, 56).

The overall positive predictive value of VIA for histological diagnosis of ≥ CIN I and ≥ CIN II was 58.7% and 29.3%, respectively, with consequent overtreatment rates of 41.3% and 70.7%, respectively (**chapter 4**). Although these overtreatment rates are high, we think these are acceptable as the morbidity associated with cryotherapy is very low and the overall benefit of treatment in reducing the risk of cervical cancer in high incidence areas is significant. In a large randomized trial in India, the intervention group (screening with VIA and treatment with cryotherapy if eligible) had a significant 25% reduction in cervical cancer mortality (HR 0.65 (0.47-0.89) compared to the control group after 7 years of follow up (57).

Only 47.4% of the initial population that received cryotherapy came for follow-up screening despite several attempts to retrieve them all. These low follow up rates underline the importance of the single visit approach in low- and middle-income countries (**chapter 4**).

Although many HPV infections are cleared spontaneously within 2 years (39, 58), we can conclude that cryotherapy does increase the HPV clearance rate **(chapter 5)**. Six months after cryotherapy we found an 80.3% clearance rate for type specific HPV infections. The most common persisting HPV types after cryotherapy were HPV 51, HPV 18, HPV16 and HPV 52.

HPV types 16, 31, 33, 35, 52, and 58 are phylogenetically related and grouped as clade a-9, while HPV types 18, 39, 45, 59, and 68 are phylogenetically related and grouped as clade a-7. The clades show differences in preferences with respect to the site of infection. The clade a-9 genotypes are more associated with squamous cell carcinomas (SCC), the clade a-7 genotypes are more commonly associated with adenocarcinomas (ADC) (59-63). Although most HPV types in these clades can lead to both ADC and SCC, the difference in association may be caused by a greater tropism for infection and/or a better ability to “neoplastically” transform the glandular tissue or squamous cell tissue (60, 62). As some HPV types are more associated with squamous cell tissue and others are more associated with glandular cell tissue, there might be a difference in persistence after cryotherapy.

We didn't find any difference in the risk of persistence between the HPV types that are associated with glandular cells (clade a-7) compared to those associated with squamous cells (clade a-9) **(chapter 5).** Consequently, it seems that the risk of undertreatment by cryotherapy of HPV clade a-7 infections because of the deeper location in the cervix, is relatively small. Probably part of the explanation lies with the cascade of immunological responses that cryotherapy induces.

The risk of HPV persistence after cryotherapy was significantly higher for low-risk HPV types compared to high-risk HPV types **(chapter 5)**. A possible explanation for the observed higher risk of persistence in low-risk HPV types is that after destroying the squamous columnar junction (SCJ) with cryotherapy, the high-risk HPV types will be cleared, and relatively more low-risk HPV types remain in the vagina and can be detected (64).

Cryotherapy is associated with a significant reduction in newly detected high-risk HPV infections. In a South African study, testing HPV after cryotherapy, women were 55% (95% CI 0.28–0.71) less likely to have a newly detected high-risk HPV infection compared to women in the no-treatment control group (65). Besides the immunological response induced by cryotherapy, infecting the SCJ after cryotherapy might be more difficult as the new SCJ migrates deeper into the endocervix.

Future, towards a world without cervical cancer

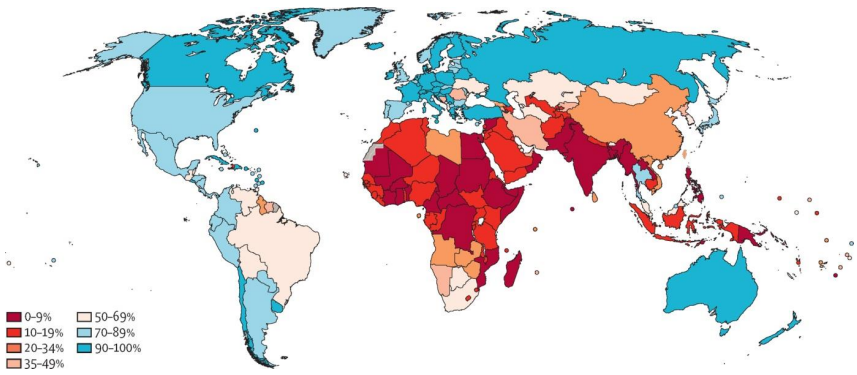
If prevention and screening programs are not implemented in low- and middle-income countries, more than 44 million women will be diagnosed with cervical cancer in the next 50 years (66).

In 2018 the WHO called for action to eliminate cervical cancer, by adopting the global strategy of cervical cancer as a public health problem to accelerate its elimination (67). It is the first time in history that a cancer has been named a public health problem. The points of actions are worldwide and at primary, secondary and tertiary level. The way to achieve this goal, eliminating cervical cancer, is referred to as 'the 90-70-90 targets' and should be accomplished by 2030. The first goal is that 90% of the girls should be fully vaccinated with an HPV vaccine by the age of 15. The second goal that 70% of the woman should be screened with a high-performance test at the age of 35 and again at the age of 45. And the third goal is that 90% of the identified premalignant lesions should be treated and 90% of the invasive cancer should be managed accordingly (67).

If these goals are achieved, it's possible to reduce in mortality from cervical cancer in low- and middle-income countries by the year 2030 by one third. If the strategy is implemented successfully worldwide, by the year 2130 more than 62 million women's lives will be saved which would reduce the mortality from cervical cancer by 99%. By then, cervical cancer will be a rare disease with an incidence of ≤ 4 per 100.000 women (66, 68).

Around 70% and 84% of cervical cancers can be prevented by Cervarix and Gardasil HPV vaccines (first generation), and about 90% of cervical cancers using Gardasil 9 (66). By 2017, globally 107 countries (37%) had introduced HPV vaccination in their national immunization program for girls, and 11 countries (6%) also for boys. However, by 2021, only 15% of the girls in the world are yet fully protected (69). To ensure long-term sustainability, HPV vaccine supply and access is of utmost importance. Gavi, the vaccine alliance plays an important role in assisting low- and middle- income countries setting up vaccination program (70).

In 65% of the countries worldwide screening program are in place, in 40% these are population-based, in 18% they reach the cover target of at least 70% (71). The estimated worldwide coverage of women screened at least once in their lifetime between the age of 30-49 years is 36%, which means 2 in 3 women aged 30-49 years have never been screened before, see the figure below for the worldwide distribution (72). In low resource settings premalignant lesions are mostly treated with cryotherapy, but thermal ablation is an upcoming modality. Facilities to treat more extensive premalignant lesions and cancers should be in place. Now, in 90% of the high-income countries, and in 15% of the middle- low- income countries have cancer surgery, radiation and chemotherapy facilities (WHO).



Ever in lifetime cervical cancer screening coverage in women aged 30-49 years in 2019 by country. Adapted from Bruni et al Lancet 2022 (72)

The recommendation of the WHO regarding see and treat strategies in low resource settings, used to be screening with VIA and treatment using cryotherapy, as we did in the screening project in Indonesia. Now is has been proven that the impact on incidence and mortality is even higher using HPV DNA testing followed by treatment, and the strategy recommended by the WHO has now been adjusted to HPV DNA screening (73-78).

If resources are sufficient, all positive HPV tests can be followed by a triage test (VIA, colposcopy, cytology, HPV16/18 analysis, p16/Ki67 dual staining) before treatment to reduce the amount of overtreatment (49). When resources are insufficient for a triage test, HPV testing alone followed by treatment may achieve greater health benefits (79, 80).

In resource-constrained settings, where screening with HPV DNA tests is not feasible, screening with VIA followed by treatment is still suggested (73). When the infrastructure for VIA screening has been set up, it can be easily changed into HPV screening when the resources would improve (81). The WHO has displayed 7

strategies for screening and treatment, as it remains of outmost importance that the strategy chosen is feasible in the local circumstances.

Overall, pilot projects to set up awareness, screening, treatment, call- and recall-systems, give insight in the possibilities and difficulties of local circumstances. Once the set up in the pilot project is optimized, implementation on national level is the ultimate goal in cervical cancer screening.

Organized population based screening program linked to feasible and affordable treatment for all stages of disease together with high HPV vaccination coverage, will be key towards a world without cervical cancer.

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