The ideal cervical cancer screening recommendation for Belgium, an industrialized country in Europe

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Summary

Cervical cancer should be a historical disease, why are we not succeeding! The prophylactic vaccination will reduce cervical cancer by almost 80 % in Belgium. Cervical cancer screening should therefore remain in order to prevent the remaining 20%. The current used Pap cytology test misses 50% of all clinically significant precancers and cancers at the time of testing. The test should remain but the analysis should be altered. The screening should be modified based on our knowledge of human papillomavirus (HPV) as causal factor. Instead of looking for a cell abnormality, one should look for the presence of HPV. Then depending on the test, only two to ten percent of all relevant lesions are missed. The introduction of the vaccination should lead to the re-introduction of the screening based on HPV. This will not only lead to a considerable reduction in morbidity and mortality, allow longer screening intervals, but it will also be more cost-effective. More for less should be the driving force in cervical cancer screening if we want to be successful.

Key words: Cervical cancer screening; Cytology; HPV; Pap triage of HPV positive; Mortality; Sensitivity; History; Vaccination.

Introduction

The most recent cancer report in Belgium was published in 2011 and showed that in 2008, 643 women were diagnosed with cervical cancer at a mean age of 54 years and that 186 died of this disease. The crude incidence and mortality rates (n/100.000) are respectively 11.8 and 3.4 [1]. The five-year survival for the period 2004 - 2008 in our country regardless of stage was 70%. According to stage the survival was Stage 1: 92%, Stage 2: 64%, Stage 3: 55%, and Stage 4: 15%. These figures look good, but we have to keep in mind that 65% of the patient data is missing [2].

In our country cervical cancer is the eighth most frequent tumour in females (2.3%) and the third most frequently occurring gynecological tumour. The majority of cervical tumours are diagnosed in Stage 1, but no significant trend is observed for these tumours over the last ten years [1].

In Belgium the recommendation to screen is adapted from the European Guidelines and foresees one Pap smear or liquid-based cytology sample for women of 25 to 64 years at a three-year interval [3-6]. In the Flemish region, cervical cancer screening program began in 1994 and in Walloon region no formal screening program is in place [3,7,8].

Currently, the screening for cervical cancer is essentially still opportunistic, which means that a smear is taken on the initiative of the woman or her clinician (general practitioner or gynaecologist). The coverage has remained stable the last 15 years. For the period 1998 – 2000 and 2007 – 2010, the coverage rate was respectively, 59% and 62%. This is still well below the aim of 85%, which was set in 1994! Furthermore the screening is still based on cytology, with only reflex HPV testing in case of ASCUS.

Cervical cancer still exists due to the fact that still around 40% of the women in Belgium are not taking part in the screening and to the fact that cytology misses almost half of all abnormal smears. The reality is that half of the women with cervical cancer are never screened and that 20% of the women with cervical cancer did have a pap smear within the last five years, but the cytology was “normal” [9].

The cancers, which are often missed by conventional cytology, are the adeno- and adenosquamous carcinomas [10, 11]. In fact there is a rise in the absolute and relative incidence of cervical adenocarcinoma (ADC) in many countries [10, 11]. The decline of cervical cancer has to be attributed to a decrease in squamous cell carcinoma (SCC). ADC currently accounts for up to 25% of all cases of cervical cancer [12]. This may again be due to the limitations of detecting ADC at screening or it could be that the incidence of ADC is truly on the rise [13].

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Human papillomavirus (HPV) has been identified as the causal factor of precancer and cancer of the cervix [14, 15]. Genital HPV is acquired through skin-to-skin contact. The best example of skin-to-skin contact is intimate genital or orogenital contact. The lifetime risk of getting infected with HPV is 80% [14, 15]. About 80 to 90% of all HPV infections are transient however and disappear within one to two years [11, 14-17]. If the HPV infection persists, then there is a significant risk of developing a precancerous lesion. The timeframe from initial infection to preinvasive and in the end invasive disease appears to be at least 10 to15 years [11]. When one uses cytology for screening, one looks for the abnormality caused by a HPV infection. The cytology screening has a sensitivity of only 53% [18]. To be sure that everyone understands this, almost 50% of all precancers and cancers are missed; perhaps an understatement but cytology has a high false negative rate. The latter is especially true for the adenocarcinomas. HPV is the causal factor for cervical (pre)cancer and it is therefore more logical to look if the HPV infection is present or not. Primary HPV screening would be a major improvement with a sensitivity of 93% [18].

The optimal screening strategy should identify those cervical cancer precursors likely to progress to invasive cancers (maximizing the benefits of screening) and avoid detection and unnecessary treatment of transient HPV infection and its associated benign lesions that are not destined to become cancerous (minimizing the potential harms associated with screening) [19].

Cervical cancer guidelines should be simple to use for the clinician and acceptable for women. Confusion among women and physicians leads to not attending the screening program, over- and under-screening, increased morbidity and mortality, and an increased cost for society without any benefits.

When to start and when to stop screening

The screening is recommended to start at 25 years and to stop at 65 years [3-8]. When you look at the distribution of smear according to age, then you notice that 10% is younger then 25 years, 82% of the women are from the target population (25-64 years) and 7% are older then 65 years [8]. The screening under 25 years and over 65 years cost the RIZIV/INAMI [20] about 12 million Euro per year. These costs are well-spent if lives are saved. In 2004, England raised the starting age of cervical screening from 20 to 25 years [21]. There is an increase of the incidence of cervical cancers in young women, but this increase in incidence is unrelated to the change in screening policy of 2004 [21]. The increase is likely to be associated with an increase in exposure to background risk including HPV [21]. The screening coverage in the women 25-29 years is declining. Efforts should be made to change this attempt.

A earlier large British study looked at odds of developing cervical cancer based on whether or not women had Pap in prior three-year interval [22]. Cervical screening in women ages 22-24 years had little or no impact on the rates of invasive cervical cancer up to age 30 years [22]. Due to the fact that women are getting older, in could be argued to increase the upper limit age to 70 years. The latter especially if you think that more women die of cervical cancer above 70 years than below 30 years. More research is needed before the upper age limit can be altered. Unfortunately this leads the screening of young women to unnecessary evaluation and potentially to treatment of pre-invasive cervical lesions that have a high probability of regressing spontaneously and that are on average many years from having significant potential for becoming invasive cancer [10, 11, 14, 19]. One of the greatest dangers of this over-treatment is premature birth [23].

Based on the first HPV vaccination trials, women below 25 years should be recommended to have a HPV vaccination [24]. The combination of HPV vaccination in adult and young adult women is expected to reduce substantially the cervical cancer disease burden in Belgium compared to screening alone [25]. Up to 40 years HPV vaccination is cost-effective in women [25].

The HPV vaccination coverage rate for a completed schedule in 12-13 year-olds in the Flemish region (Vlaanderen) is 84%, while in the Walloon region it hardly reaches 20% [26-28]. The Flemish region is the best-vaccinated region in the world. This is due to the school-based program, which started in September 2011. Instead of screening young women, they should be informed about the benefits of HPV vaccination, the risk of sexual transmitted infections, the use of condoms, and the methods of contraception. The high vaccination figures will reflect in 15 to 30 years in a substantial reduction of precancer (estimated > 50%) and cancer (estimated (> 80%) [29]. Currently vaccines against more HPV types are in trials. Already the first data of a nine-valent vaccine have been presented [30]. This vaccine is directed against the high-risk HPV infections types 16, 18, 31, 33, 45, 52, and 58 and the low-risk HPV infections, types 6 and 11. With the high efficacy rates against precancer lesions, it is to expected that this vaccine can prevent approximately 90% of all cervical cancers. A biologics license application for this vaccine (V503) to the U.S. Food and Drug Administration (FDA) is to be expected at the end of 2013 or the beginning of 2014 [31].

Table 1. — *Detection rate ratios of CIN 3 or worse: HPV vs. cytology and 95% CI.*

NTCC*	0.34 (0.15–0.75)
POBASCAM	0.39 (0.27–0.53)
ARTISTIC	0.52 (0.28–0.97)
Swedescreen	0.53 (0.29–0.98)

*in women aged 35 years or older

Table 2. — *Pooled detection rate ratio for invasive cancer from recruitment to end of follow-up: HPV vs. cytology and 95% CI*

NTCC	0.37 (0.17–0.80)
Swedescreen	0.71 (0.23–2.25)
POBASCAM	0.72 (0.40–1.27)
ARTISTIC	0.83 (0.26–2.66)
Pooled	0.60 (0.40–0.89)

Table 3. — *Pooled detection rate ratio for invasive cancer: HPV vs. cytology and 95% CI according to follow-up since entry of the study.*

≤ 2.5 years of follow-up	0.79 (0.46–1.36)
> 2.5 years of follow-up	0.45 (0.25–0.81)
End of follow-up (median 6.5 years)	0.60 (0.40–0.89)

Table 4. — *Cumulative incidence per 10^5 with 95% CI of invasive cervical cancer after a negative screenings test at entry.*

Years of follow-up	3.5	5.5
Cumulative incidence		
Negative HPV	4.6 (1.1–12.1)	8.7 (3.3–18.6)
Negative cytology	15.4 (7.9–27.0)	36.0 (23.2–53.5)

What should be done: cytology, HPV, or HPV+, and cytology triage?

Multiple meta-analyses have shown that a Pap cytology test fails to detect on average 50% of clinically significant precancers and cancers present at the time of testing [32]. The main reason why Pap smears miss almost 50% of all precancers and cancers is the fact that it is performed by humans and therefore subjective. HPV screening is superior to cytology because it is objective, reproducible, and standardized. HPV testing has a sensitivity of 40 to 45% higher than cytology. This means automatically c.q. practically a strong reduction in false negatives.

The evidence for this can be found in 24 cross-sectional studies and 11 multi-country randomized controlled trials (RCT) [32-47]. In order to have a good comparison for Belgium, we will have to look at the four RCTs performed in industrialized European countries. The four countries were Sweden (Swedescreen), the Netherlands (POBASCAM), England (ARTISTIC), and Italy (NTCC) [37, 39, 41, 44, 47]. All studies had different screening protocols.

Precancer lesions and the 4 RCTs

The relative incidence of CIN3 or worse histological findings after the first screening round was similar in all studies (Table 1) with no evidence of heterogeneity ($p = 0.681$) [37, 39, 41, 44, 47, 48]. The fact that they are similar suggests that the efficacy in prevention depends primarily on the screening test and not on the different screening protocols [47].

All these results show clearly that HPV-based screening detects persistent precancer (high-grade) lesions before cytology. This early detection will allow treatment of these lesions before that they can become invasive.

Cancer and the 4 RCTs

On an individual basis the 4 RCTs are not powered enough to measure the effect of HPV testing, as an alternative to regular cytological screening, on the incidence of invasive cancer [37, 39, 41, 44]. For this reason a follow-up study of the 4 RCTs was performed together with a pooling of the data [47].

The pooled analysis incorporated a total of 76,464 women aged 20–64 years followed up for a median of 6.5 years (1, 214,415 person-years) [37, 39, 41, 44, 47]. The study-adjusted pooled relative detection rate for invasive cervical cancer among all women from recruitment to end of follow-up are shown in Table 2 [47].

The screening methods were not significantly different for the detection of invasive cancer during the first 2.5 years of follow-up after study entry (Table 3) [47]. After 2.5 years, the HPV screening arm became significantly lower then the standard cytology arm. The pooled rate ratio for invasive cervical carcinoma among all women from recruitment to end of follow-up was 0.60 (95% CI 0.40–0.89), with no evidence of heterogeneity between the studies ($p = 0.52$) [47]. A random-effects model gave an almost identical estimate (0.61, 0.41–0.91) [47, 49]. The fact that the gain in reduction of cervical cancer started after 2.5 years, excludes prevalent cases and reflects to true gain of HPV based screening above cytological screening. The gain of HPV will only increase if the quality of cytology decreases.

Figure 1. — Flow-chart of HPV screening for women between 30-65 years of age.

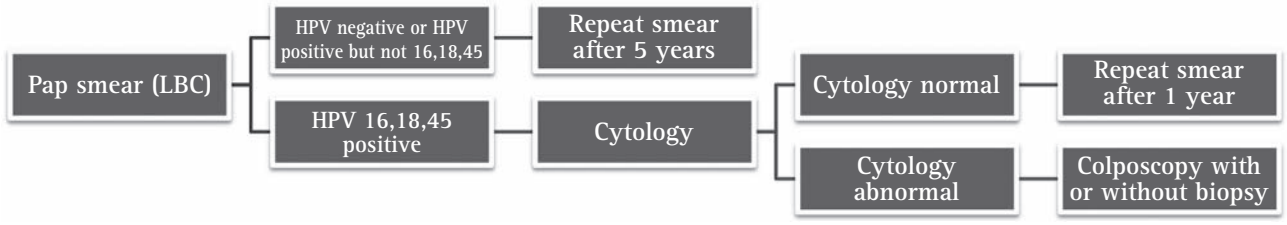

Figure 2. — Alternative flow-chart of HPV screening for women between 30-50 years of age.

In the introduction it was assumed that conventional cytology missed more often adenocarcinomas then squamous carcinoma. The key question is what will and can HPV screening achieve?

The assumption increased in validity when one looks at the pooled rate ratio for morphology. The rate ratios were lower for adenocarcinoma (0.31; 95% CI 0.14–0.69) than for squamous-cell carcinoma (0.78: 95 % CI 0.49–1.25) [47]. Especially for the young women, the increased gain is high. Because the proportion of adenocarcinomas fell by age: 40% in women younger than 30 years, 35% in those aged 30–34 years, 30% in women age 35–49 years, and 23% in those 50 years or older [47]. The rate ratios did not differ for stage. HPV testing has an even higher gain for adenocarcinomas then for squamous cancers. It cannot be emphasized enough: adenocarcinomas are often missed in the classical screening. Adenocarcinomas are in 94% due to HPV 16, 18, and 45 [29]. The introduction of prophylactic HPV vaccination (primary prevention) and HPV screening (secondary prevention) will therefore have a major impact on the incidence of these cancers [14].

What to do when a woman is high-risk (HR) HPV positive

In the POBASCAM, Swedescreen, and ARTISITC a cytological triage was performed; the NTCC HPV positive women were directly referred for colposcopy with or without biopsy [37, 39, 41, 44]. The pooled ratio showed that in case of cytological triage, there was no increase in biopsies (1.02; CI 95 % 0.97-1.07) [47]. In case of direct referral to colposcopy in case of HPV positivity (the NTCC trial), the number of biopsies were more then doubled (2.24; CI 95%, 2.09-2.39) [47]. As there is no difference in the detection rate of invasive cancer, it is to be recommended that all women who have a high-risk HPV infection should have a cytological triage. Practically this means that if a woman has a HR HPV infection a cytological analysis should be done (Figure 1). If cytology is normal the smear should be repeated after one year, and if cytology is abnormal, she should be referred for colposcopy with or without biopsy. The smear becomes a diagnostic smear instead of a screening smear.

Based on the HERACLES and SCALE trial, one can conclude that cervical cancer below 50 years is due to a HPV infection 16, 18 or 45 [50, 51]. This type-specific analysis could also be included in the triage of HR HPV positive women (Figure 2). Only women younger then 50 years of age and infected with one of these types should have reflex cytology; all the others should be rescreened after five years.

In the future this will probably alter when the current generation of vaccinated women reach the screening age. It is likely that this generation will only need a smear every 10, 15, or even 20 years. Attractive for the future is also the self-sampling in cervical screening. Women could take a sample by themselves and send it to the laboratory. If the results comes back as HPV positive, she should be invited to visit a doctor for the traditional type specific HPV screening and diagnostic cytology.

Additional staining of the smear and markers can do further fine-tuning, but current there is need for more evidence before in can be used in routine practice. It is important to do a type-specific analysis and not HR HPV positive or negative

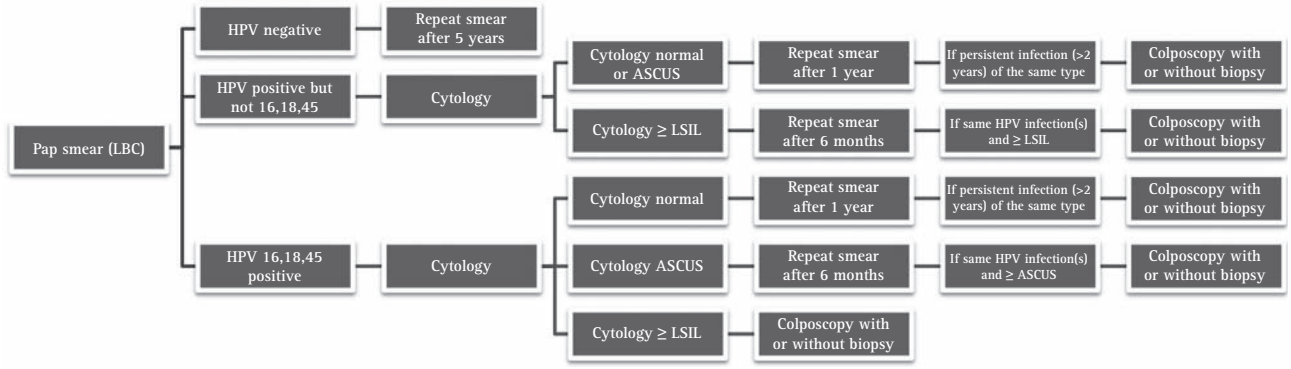

Figure 3. — Flow-chart of HPV screening for women between 25-30 years of age.

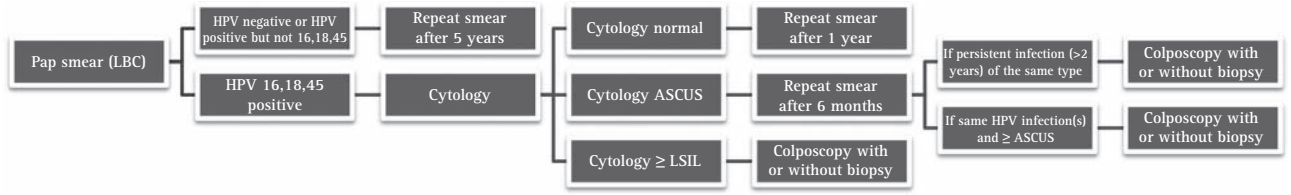

Figure 4. — Alternative flow-chart of HPV screening for women between 25-30 years of age.

test; the reason why the majority of the HPV infections are transient and will disappear within two years. Only persistent infections should be treated from a clinical point of view. This will protect women from unnecessary harm and injury. If for instance a woman who has a HPV 16 infection today and two years later a HPV 18 infection, it is not a persistent infection. She should be informed that this is normal and that she does not need any treatment. If one would have done the analysis with a HR HPV positive or negative test, the clinician would not have known that she had a transient infection on the one hand and a new infection on the other hand. This would wrongly lead to the conclusion that it is a persistent infection that needs treatment.

An additional tool in the triage is the viral load of a HPV infection [52]. As most infections will disappear, you can follow the activity of the virus. The normal pattern will be an increase in the viral load and then a decrease back to zero. If this is happening, one can wait. If a viral load stabilizes regardless of the height because it is a logarithmic scale, the clinicians should be worried because this can be regarded as a persistent infection with a risk of progression of the lesion. When applying this rule of HPV screening and cytological triage in women between 25 and 30 years, one should be very cautious. The reason is that this could lead to anxiety among the women and their clinicians, leading increased additional investigations. There is a substantial risk for over-management in case of regressive precancer lesions caught by HPV screening. At the moment there is simply not enough data for HPV screening in this age group to draw firm conclusions. The evidence for using it in this age group is thin. There is however sufficient evidence for not screening below 25 years of age. If HPV screening is done in women between 25 -30 years of age, then the algorithm of cytological triage in case of a HR HPV infection would lead to inappropriate high numbers of colposcopy and unnecessary biopsies. The number of unnecessary conisations with its associated morbidity and mortality, will undoubtedly also increase.

Especially in this age group it is necessary to perform a HPV type specific triage and an ASCUS or LSIL or more triage (Figure 3). This triage system takes in consideration the age together with the three possible HPV groups: 1) no HPV infection, 2) HPV positive not HPV types 16, 18, and 45 and 3) HPV 16,18, and 45 positive. It is complex in use, but the logically next step of acceptance. Alternatively one could also directly incorporate more rigorously all the available data in one figure (Figure 4) [50, 51]. The latter is logical and simple to use. It will however take time before everyone will accept this flow-chart and uses it.

Only in case of a persistent HPV infection of the same type for longer then two years a colposcopy should be performed. When for a LSIL an advice of colposcopy is given, this should be done very tactfully. If during a colposcopy the lesion(s) are clearly low grade or less, one should not biopsy these lesions. If there is doubt or if one does not feel comfortable, then one should take a biopsy. It is the opinion of the author that one should use common sense when reading a protocol. If the proto-

col states to take a biopsy it should not automatically mean that the clinician should take a biopsy. It is hilarious if you always follow an opinion without thinking. It is not because your are equipped with… that you should have… with every one.

The current practice of serial monogamy leads to new HPV infections (at every age) without any direct significance. It is naïve to perform only cytology below 30 years if are screening. Women, men, and clinicians should accept that more then 80% of all HPV infections will disappear (at any age) spontaneously and do not need any additional treatment. The fact that some one has a HPV infection, is a reflection that she is sexual active. There is nothing wrong in consented sex. HPV in this regard can best be compared with the common cold. Reduce anxiety and explain this to your patient and their loved ones. This will of course cost more time, but it will also increase the satisfaction of avoiding unnecessary treatment. In the past when I did premature deliveries in the middle of the night, I often wondered how many of these deliveries could be avoided if we would have had the knowledge and talked to our patients. If your are still not convinced, please go to a Neonatal Intensive Care (NIC) Unit and check how many of the premature delivers were among women with a conisation in the passed.

Which HPV test should be used? [53]

This seems a strange topic because the clinicians are generally not involved in choosing the HPV test. The clinician should however be aware that there are multiple HPV tests available and that some earlier HPV tests will miss one out of ten cancers. This is important if screening is based on HPV testing. At the end of the day the clinician is held responsible for the missed cancer. Every clinician should therefore know what the differences are between an L1 test and an E6/E7 test [53].

A HPV infection can be present in a patient in a free form (episomal), in an integrated form in the host DNA or in a mixed form which means free and integrated. From a clinical point of view the integrated viruses are important because in this form the lesions are most likely to progress to a high-grade lesion or invasive cancer. It is therefore essential that HPV tests also look at the integrated HPV types [53]. For this reason HPV tests should not only type specific but also region specific. Crucial specific regions in the HPV genome are L1, E1/E2, and E6/E7. During integration of the HPV in the human genome sometimes L1 expression is lost, but E6/E7 expression remains always present. E6/E7 are pivotal in the development of cancer (L1 negative cancers exist, but not E6 or E7 negative cancers) [53]. In other words, if one were to use an E6/E7 test all cancers would be detected, including the ones where L1 was lost. A test looking only for L1 and not for E6/E7 will miss about 10% of all invasive cancers.

In our country the most frequent used HPV tests are probably Hybrid Capture II (Qiagen) and the Cobas 4800 HPV DNA Test. To cut a long story short, if you read their labels, then you notice that these are L1 only tests. For a more detailed description I would like to refer to a previous publication titled: “Cervical cancer screening: which HPV test should be used—L1 or E6/E7?” [53].

The introduction of the first HPV testing based on L1 increased the sensitivity for screening considerable (30 to 40%). With the current knowledge of integration and progression, it is time to fine-tune these HPV tests. Nowadays a HPV test should also look at E6/E7 in order not to miss the 10% integrated HPV cancers. It will cost money to alter the HPV testing system, but from a medical legal point it is difficult to defend an L1-only test. If the right test is used at the right place, unnecessary death due to cervical cancer in women can be avoided [54]. Let us remember cervical cancer affects mainly young women with young families and the qualities years lost after a wrong test will become uncountable.

At what frequency should screening be performed

In the pooled data of the 4 RTCs, the adjusted rate ratio after a negative test on entry was 0.30 (95% CI: 0.15–0.60), with no evidence of heterogeneity ($p = 0.23$) between the studies and with an almost identical random-effects model estimate (0.34, 0.14–0.86) [37, 39, 41, 44, 47, 49]. In Table 4 the cumulative incidence of invasive cervical cancer at entry after a negative cytology and after a HPV negative test are shown. The cumulative detection rate of invasive cervical cancer eight years after enrolment was more then doubled in the cytology screen women compared to the HPV screened women, respectively, 93.6 per 10^5 (95 % CI 70.5–121.8) and 46.7 per 10^5 (95 % CI 32.1–65.5) [47]. This is a clear indication how many relevant precancers and cervical cancers are missed by cytology.

The cumulative incidence of invasive cervical cancer after a negative cytology test at 3.5 years is almost doubled the figures after a negative HPV test at 5.5 years. In other words a five-year screening interval with HPV testing is far better and safer then a screenings interval of three years with cytology. The remarks: “ Larger screenings intervals when the current vaccinated population will enter the screening age is indicated” is without a shadow of a doubt, the understatement of the next century. Shorter screenings interval of less than five years with HPV testing will only lower the specificity as most HPV infections are transient [55].

The adagio less for more should be embraced. Compared to cytology screening, screening with HPV at a five-year interval will reduce the number of smears taken, the number of colposcopies, the number of biopsies, the number of conisations, and most importantly will reduce the number of cervical cancers at a significantly lower cost. This win-win situation in an era of economical crisis should be used to speed up the integration of HPV screening.

In the vaccinated population, it seems reasonable to extend this interval to 10, 15 or even 20 years. However before this can only be introduced, the expected efficacy of the prophylactic HPV vaccination is confirmed in daily clinic. One should not rush and take too many steps at a time. This will only confuse people and make them unwilling to accept it. Every new step taken should be with sufficient evidence and pace, so that is becomes acceptable and understandable for everyone.

Current prophylactic HPV vaccination is expected to reduce cervical cancer with more then 80%. There is therefore still a need for screening. The introduction of the HPV based cervical screening will provide a 70% greater protection against invasive cervical cancer then the currently used cytology-based screening. Together HPV vaccination and screening will abandon cervical cancer to the history books. Every success comes with a price. Cervical cancer can only be eradicated if all stakeholders have the knowledge, work together and respect each other.

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