Epidemiology and Early Detection of Cervical Cancer

Peter Hillemanns  Phillip Soergel  Hermann Hertel  Matthias Jentschke

Department of Gynaecology and Obstetrics, Hannover Medical School, Hannover, Germany

Introduction

The incidence of cervical cancer was estimated at 530,000 cases worldwide in 2008. Incidence ranges from less than 6 per 100,000 in North America, Western Asia, and Australia to more than 30 per 100,000 in parts of Africa. Persistent infection with certain types of human papillomavirus (HPV) known as high risk HPV (hrHPV) is now believed to be a major causal factor in the development of cervical cancer.

Approximately 34,000 new cases of cervical cancer and 13,000 deaths due to the disease occur annually in the European Union (EU). Despite significant progress in Europe in recent decades in reducing the burden of cervical cancer (fig. 1), rates of death attributed to the disease are still high in many of the 'new' member states that joined the EU after 2003: Estimates of the annual age-standardized rates per 100,000 women in Hungary (6.9), the Slovak Republic (6.9), Poland (7.4), Latvia (8.2), Bulgaria (8.8), and Lithuania (9.8) are 5–7 times higher, and in Romania (14.2) they are 10 times higher, than in Finland (1.4) and Malta (1.2), the EU member states with the lowest rates in 2012.

Previously identified risk factors for cervical cancer include smoking, oral contraceptive use over more than 5 years, diagnosis of human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS), organ transplantation, and having a first degree relative with cervical cancer [1]. A strong causal relationship has been shown between cervical cancer and persistent infection with certain types of HPV [2], which accounts nearly for all cervical cancer cases [3].

There are over 150 different types of HPV with 30 infecting the anogenital tract. The latter types are being divided into hrHPV and low risk types (lrHPV). hrHPV are those where persistent infection is associated with an increased risk of developing cervical cancer [1]. The prevalence of HPV infection has been shown to vary between different geographic regions and between countries within those regions. Prevalence also varies according to age with the peak prevalence occurring at approximately 25 years old then declining with increasing age. This geographic variation in HPV prevalence

Keywords
Cervical cancer screening · HPV · Cytology

Summary

The new German S3 guideline ‘Prevention of Cervical Cancer’ published in 2016 is based on the latest available evidence about cervical cancer screening and treatment of cervical precancer. Large randomized controlled trials indicate that human papillomavirus (HPV)-based screening may provide better protection against cervical cancer than cytology alone through improved detection of premalignant disease in the first screening round prior to progression. Therefore, women aged 30 years and older should preferably be screened with HPV testing every 3–5 years (cytology alone every 2 years is an acceptable alternative). Co-testing is not recommended. Screening should start at 25 years using cytology alone every 2 years. The preferred triage test after a positive HPV screening test is cytology. Women positive for HPV 16 and HPV 18 should receive immediate colposcopy. Another alternative triage method is p16/Ki-67 dual stain cytology. The mean yearly participation rate in Germany is between 45 and 50%. Offering devices for HPV self-sampling has the potential to increase participation rates in those women who are at higher risk of developing cervical cancer. Regarding primary prevention, the 9-valent vaccine may provide protection against up to 85% of cervical intraepithelial neoplasia (CIN) 3 and 90% of cervical cancer, and is available in Europe as a 2-dose schedule from May 2016.
is likely to have a significant impact on the accuracy of HPV DNA testing methods when applied in different countries [4].

Screening programs for cervical cancer are now established in many parts of the world, particularly in developed countries in Europe and the USA [5]. Conventionally, screening has been based on cytological testing, commonly known as the smear test or Pap test. In conventional cytology, cellular material is sampled from the cervix using a spatula or brush and smeared directly onto a glass slide for evaluation by a cytologist. Liquid-based cytology (LBC) is a commonly used alternative whereby the sampled material is deposited in a preservative solution and transferred to a laboratory where the slide is prepared for evaluation [6]. The use of LBC has been reported to improve the so-called adequacy of the sample, i.e. the proportion of Pap smears that can be successfully evaluated by the cytologist, and to reduce the Pap smear interpretation time. The relative performance of the different techniques in terms of patient-relevant outcomes such as cancer incidence and mortality is still the subject of investigation [6]. There has been a rapid increase in HPV testing systems in the last few years. A recent review identified 125 distinct tests [7].

Cervical Cancer Screening

Evidence Based on Randomized Controlled Trials

For the German S3 guideline ‘Prevention of Cervical Cancer’, a systematic review of the clinical utility of including HPV testing in population-based screening for cervical cancer, was performed by Kleijnen et al. [8]. Inclusion criteria identified 6 relevant randomized controlled trials (RCTs). 1 of these trials was reported as 2 separate studies. The methodological quality of the included RCTs was assessed using the Cochrane Risk of Bias Tool [9]. The collective evidence base was evaluated based on the GRADE system of quality assessment for guideline development [10]. GRADE rates the quality of a complete body of evidence for a specific outcome in a specific population. Quality of evidence was assessed for risk of bias, publication bias, imprecision, inconsistency, indirectness, magnitude of effect, dose-response gradient, and the effects of any confounding [10].

The majority of these RCTs were conducted in developed countries (UK, Finland, Italy, Netherlands, and Sweden) with the exception of 1 study which was conducted in rural India. In total, 462,096 women were included across all studies with the number of participants per study ranging from 12,527 to 203,425. The age of participants ranged from 20 to 65 years although only 1 study included participants < 25 years old. The interval between screening rounds was either 3 or 5 years, with all studies reporting either 1 or 2 screening rounds.

Overall, the quality of randomization was good although allocation concealment was often poorly reported making it difficult to assess the risk of bias. 5 studies were assessed as at high risk of bias for blinding of patients and study personnel. This was typically because the clinical management of the patients differed according to which test results were available; therefore, patients and personnel could not be blinded. Quality assessments for all included studies are summarized in table 1.

There were no studies which reported overall survival, only the single study conducted in rural India reported disease-specific survival as an outcome. The aim of this study was to assess the clinical effectiveness of a single lifetime test for cervical cancer by either HPV testing alone or cervical cytology. Sankaranarayanan et al. [11] in 2009 showed that a single lifetime HPV test significantly reduced the risk of death from cervical cancer compared to a single cytology test (risk ratio (RR) 0.59, 95% confidence interval (CI) 0.39–0.91). In the group which received a single HPV test, 34/34,126 (0.1%) participants died of cervical cancer compared to 54/32,058 (0.17%) participants in the group which received a single cytology test.

The primary objective of cervical cancer screening is to detect cervical intraepithelial neoplasia (CIN) 3 early enough so that it can be treated to prevent the development of cancer. Evidence from the first screening round showed that the HPV-containing regimen detected significantly more cases of CIN 2 and CIN 3 (RR 1.51, respectively) but not of cervical cancer or CIN 3+.

In contrast, at the second screening round (table 2), in the HPV-based group, significantly fewer cases of cervical cancer (RR 0.29, 95% CI 0.11–0.73) and fewer cases of CIN 3+ (RR 0.59, 95% CI 0.44–0.80) and CIN 2+ (RR 0.65, 95% CI 0.47–0.88) were detected.

Ronco et al. [12] did a follow-up study of the 4 RCTs carried out in Sweden (Swedescreen), the Netherlands (POBASCAM), England (ARTISTIC), and Italy (NTCC) with 176,464 women aged 20–64 years to investigate direct estimates of the relative efficacy of HPV-based versus cytology-based screening for the prevention of invasive cancer in women who undergo regular screening. After a follow-up for a median of 6.5 years (1,214,415 person-years), the rate ratio for invasive cervical carcinoma among all women between HPV-based and Pap-based screening was 0.60 (95% CI 0.40–0.89), with no heterogeneity between studies (p = 0.52).
Table 1. Overview of risk of bias assessment of randomized controlled trials investigating HPV- versus Pap-based screening

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk of bias items</th>
<th>randomization</th>
<th>allocation concealment</th>
<th>patient/personnel blinding</th>
<th>outcome assessor blinding</th>
<th>incomplete outcome data</th>
<th>selective outcome reporting</th>
<th>other</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARTISTIC</td>
<td></td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Leinonen 2012</td>
<td>☐</td>
<td>☐</td>
<td>?</td>
<td>☐</td>
<td>?</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Sankaranaryanan 2009</td>
<td>☐</td>
<td>?</td>
<td>☐</td>
<td>☐</td>
<td>?</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>POBASCAM</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>?</td>
<td>?</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

☐ = Low risk of bias; ☐ = high risk of bias; ? = unclear.


Table 2. GRADE summary of findings – sensitivity analyses (S3 German Guideline Cervical Cancer Prevention, Consultation version, 2016)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks&lt;sup&gt;a&lt;/sup&gt; (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>Participants (studies), n</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>assumed risk cytology – incidence of cervical cancer</td>
<td>corresponding risk HPV test</td>
<td>RR 0.29 (0.11–0.73)</td>
<td>147,625</td>
<td>very lowb,c,d</td>
</tr>
<tr>
<td>Incidence of cervical cancer – 2nd screening round</td>
<td>20 per 100,000 (2–15)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-up: 3–5 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence of CIN 3 – 2nd screening round</td>
<td>212 per 100,000 (74–257)</td>
<td>RR 0.65 (0.35–1.21)</td>
<td>132,083 (3)</td>
<td>very lowb,d,e</td>
<td>NTCC-I, NTCC-II, POBASCAM</td>
</tr>
<tr>
<td>Follow-up: 3–5 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence of CIN 3+ – 2nd screening round</td>
<td>277 per 100,000 (122–222)</td>
<td>RR 0.59 (0.44–0.80)</td>
<td>159,962 (5)</td>
<td>moderateb,c</td>
<td>ARTISTIC, NTCC-I, NTCC-II, POBASCAM, Swedescreen</td>
</tr>
<tr>
<td>Follow-up: 3–5 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence of CIN 2+ – 2nd screening round</td>
<td>426 per 100,000 (200–375)</td>
<td>RR 0.65 (0.47–0.88)</td>
<td>159,962 (5)</td>
<td>moderateb,c</td>
<td>ARTISTIC, NTCC-I, NTCC-II, POBASCAM, Swedescreen</td>
</tr>
<tr>
<td>Follow-up: 3–5 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval (CI)) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

RR: Risk ratio.

<sup>b</sup>Blinding of participants and personnel absent or inadequate in several studies.

<sup>c</sup>Missing outcome data not accounted for in several studies.

<sup>d</sup>Widely differing estimates each with wide confidence intervals.

<sup>e</sup>Allocation concealment unclear in some studies.


Ratios did not differ by cancer stage, but were lower for adenocarcinoma (0.31, 0.14–0.69) than for squamous cell carcinoma (0.78, 0.49–1.25). The rate ratio was lowest in women aged 30–34 years (0.36, 0.14–0.94). The authors concluded that HPV-based screening provides a 60–70% greater protection against invasive cervical carcinomas compared with cytology, and data of large-scale RCTs.
support the initiation of HPV-based screening from age 30 and the extension of screening intervals to at least 5 years.

These results indicate that HPV-based screening may provide better protection against cervical cancer than cytology alone through improved detection of premalignant disease in the first screening round prior to progression. This is supported by the reduced detection of CIN3+ in the second screening round.

Evidence for Screening-Related Harms Based on RCTs

The ARTISTIC study reported screening-related harm in terms of the proportion of participants with a General Health Questionnaire (GHQ-28) score ≥ 4 [13]. GHQ-28 measures generalized psychological distress. The aim of this analysis was to investigate the increased psychological distress associated with receiving an HPV test compared to cytology only. This study showed that there was almost no difference in the proportion of participants with GHQ≥4 between those screened with HPV testing in combination with cytology compared to those screened with cytology only. This study showed that there was almost no difference in the proportion of participants with GHQ≥4 between those screened with HPV testing in combination with cytology compared to those screened with cytology only (RR 0.98, 95% CI 0.87–1.11). In the group which received the HPV + cytology combined test, 37.6% of participants (223/593) had GHQ≥4 compared to 38.3% of participants (717/1,872) in the cytology only group.

German Guidelines

In Germany, cervical cancer screening was established as an opportunistic program with Pap testing in 1971. The screening at yearly intervals starting at 20 years of age is covered by the statutory health insurances.

The German guidelines published in 3/2016 (consultation version) recommend that cervical cancer screening should start at age 25 using cytology alone every 2 years [8]. Women aged 30 and older should be screened with HPV testing every 3–5 years as the preferred option while cytology alone every 2 years is considered an acceptable alternative. Co-testing with HPV and cytology is not recommended in order to avoid an increase in the number of women with positive test results and additional colposcopies while there is little or no gain in the disease detection rate. The authors emphasize the importance of using reliable, validated HPV tests in qualified and accredited laboratories in compliance with international standards.

According to the German Cancer Screening and Registration Law (KFRG, 2013) based on the German National Cancer Plan, the so far opportunistic cervical cancer screening in Germany is to be converted into an organized screening program. The Federal Joint Committee (G-BA) as the highest decision-making body of the joint self-government of physicians, dentists, hospitals, and health insurances in Germany was appointed to organize the necessary changes for the cervical cancer screening program. The G-BA defined the cornerstones of future cervical cancer screening in Germany in March 2015 [14]. This decision was based on a benefit report by the Institute for Quality and Efficiency in Health Care (IQWiG) which is a professionally independent, scientific institute [15]. The G-BA instructed the IQWiG to draw up a letter of invitation and an information flyer for a population-based introduction of HPV testing in organized cervical cancer screening. The clinical examination for early detection of cancers of the genital area and breast in women is maintained. Women from 20 to 60 years will receive an invitation letter every 5 years from their health insurance and be informed about the cervical cancer screening program. In women aged 30 years and older, HPV testing may be performed at intervals of 5 years. For HPV-positive cases, cytology is proposed as triage method. As an alternative to this new screening strategy, women can still opt for the established annual Pap-based screening (option model). However, a combination of both screening strategies or a change before the end of the screening interval is not possible. Data will be collected for both screening strategies in a transition period of at least 6 years (or when there is sufficient data from the second round of screening). Based on the analysis of predetermined performance indicators, the G-BA will have to decide whether there is evidence for superiority or inferiority of a screening strategy, which then requires modification of the optional screening model.

US-American Guidelines

A recent systematic review for the U.S. Preventative Services Task Force (USPSTF) from 2011 found that primary HPV testing detected more cases of CIN 3 or cancer in women older than 30 years compared to cytology which is consistent with the findings of the review for the German guideline [16]. The same review also showed mixed results for the use of HPV + cytology co-testing compared to cytology alone. HPV + cytology combined testing did not detect more CIN 3+ than cytology alone; however, co-testing did detect more CIN 2+. This review led the USPSTF to recommend cervical cancer screening by cytology every 3 years for women aged 21–65 years. For women aged 30–65 years who wish to extend their screening interval beyond 3 years, screening with a combination of HPV + cytology was recommended as an acceptable alternative [17].

The guideline of the American Cancer Society (ACS), American Society for Colposcopy and Cervical Pathology (ASCCP), and American Society for Clinical Pathology (ASCP) recommends that women aged 30–65 years should be screened with combined HPV + cytology testing every 5 years as the preferred option while cytology alone every 3 years is considered an acceptable alternative [18]. This recommendation was based on an evidence review which showed that addition of HPV testing to cytology resulted in increased detection of CIN 3 in the initial screening round with a corresponding decrease in the detection of CIN 3+ in later screening rounds. This translates into a lower risk following a negative screening result thus allowing for an extended screening interval.

European Guidelines: Screening Policy and Program

Recent European guidelines from 2010 recommended that women should be invited for cervical cancer screening every 3–5 years between the ages of 25 and 65 [19]. There is significant variation in how these guidelines are implemented by individual countries with some countries initiating screening as early as 15 while...
others continue up to age 69. In Europe, the majority of countries adhere to the recommended screening interval of 3–5 years; however, in some countries (Germany, Austria, and Luxembourg) screening is carried out every year. Current European guidelines from 2015 emphasize that despite the convincing evidence for more efficacious screening using HPV primary testing, appropriate screening policy and program organization are essential to achieving an acceptable balance between benefits and harms of any screening program [20]. These principles are particularly important in HPV primary screening in order to avoid substantial increases in the number of women with positive test results leading to additional colposcopies and treatment in the absence of any additional benefit for participants. Following the recommendations in the present supplement should enable screening programs to achieve the potential benefit of HPV primary testing in cervical cancer screening while minimizing the risks.

Triage of HPV-Positive Women in Cervical Cancer Screening

Increasing HPV vaccination coverage will lead to lower disease prevalence. However, despite HPV vaccines, screening will remain essential for even decades to prevent cervical cancer. With the introduction of HPV testing alone or with cytology as an alternative to cytology screening, additional tests are required to identify women with precancerous lesions [21, 22]. The choice for a specific test algorithm should be based on the comparison of absolute risk estimates from triage tests with established clinical thresholds. A triage strategy should assure the vast majority of women being at very low risk of cervical cancer and, if positive, refer the women at highest risk for CIN 3 to colposcopy. The intermediate risk group should be small as they require continued surveillance. Currently, the most often recommended triage strategy for primary HPV screening is cytology. However, HPV genotyping for HPV 16 and HPV 18 implies a risk for CIN 3+ of more than 15% which triggers immediate colposcopy according to the clinical threshold in most Western countries [23–28]. Another alternative which is recommended in the German guidelines includes p16/Ki-67 dual stain cytology that has improved accuracy when compared to cytology based on a limited number of studies [8, 29]. The evidence for other triage methods such as host methylation and viral methylation testing is scarce.

Non-Responders to Regular Cervical Screening: HPV Self-Sampling

Population coverage for cervical cancer screening is an important determinant explaining differences in the incidence of cervical cancer between countries. In a recent study, cervical screening coverage in Germany was analyzed using a large health insurance population (AOK Niedersachsen) serving about 1 million women living in the state of Niedersachsen (Lower Saxony) for the period of 2006–2011 [30]. The overall yearly participation rate showed a rather small increase from 44.8% in 2006 to 47.6% in 2011. The highest rates occurred in women with the highest qualification level, thus leading to increasing social differences over time. There was a peak in the age group of 25–29 years with annual rates of 60.3% (2006) and 60.2% (2011) and bi-annual rates of 77 and 77.1%, with constantly decreasing rates up to the age of 60. No substantial differences occurred between a 2- and a 3-year observation period. The participation rates were significantly below the coverage observed in countries with organized screening. This may only be amended by an organized invitation-based screening program which is going to be implemented in Germany in the future. However, there will always remain a proportion of about 20–30% of women refusing to attend gynecologically driven screening. Offering devices for self-sampling to test for HPV has the potential to increase the participation rate in these difficult-to-reach women. Verdoodt et al. [31] performed a systematic review and meta-analysis to evaluate participation following an invitation including a self-sampling device (self-sampling arm) versus an invitation to have a sample taken by a health professional (control arm) sent to under-screened women. 16 randomized studies were found eligible. In an intention-to-treat analysis, the pooled participation in the self-sampling arm was 23.6% (95% CI 20.2–27.3) when self-sampling kits were sent by mail to all women versus 10.3% (95% CI 6.2–15.2) in the control arm (participation difference 12.6%, 95% CI 9.3–15.9). When women had to opt-in to receive the self-sampling device, as was the case in 3 studies, the pooled participation was not higher in the self-sampling compared to the control arm (participation difference 0.2%, 95% CI -4.5–4.9).

Increased participation was observed in the self-sampling arm compared to the control arm if self-sampling kits were sent directly to women at their home address. However, the size of the effect varied substantially among studies. Since participation was similar in both arms when women had to opt-in, future studies are warranted to identify opt-in scenarios that are most acceptable for women.

Primary Prevention: Switch to the 9-Valent HPV Vaccine

In 2006, the European Medicines Agency (EMA) endorsed the quadrivalent HPV vaccine against HPV 6/11/16/18, and in 2007, the bivalent vaccine against HPV 16/18, for the prevention of cervical cancer and other HPV-related diseases. To date, 21 of the 28 EU member states have introduced a national HPV vaccination program. Recently, EMA updated its HPV vaccines position and recommended a 2-dose regimen with increased flexibility in the interval between doses which should encourage increased vaccination coverage rates. If the vaccines are administered at an older age, the 3-dose schedule should be used. Clinical trials have shown that the prophylactic HPV vaccines are safe and highly effective against persistent vaccine-related HPV infections and anogenital precancerous lesions among women who were not infected by these types at the time of vaccination [32–34]. Indirect evidence for a population-based impact of the HPV vaccines was demonstrated with decreased HPV prevalence and decreased incidence of genital warts and high-grade cervical abnormalities after the start of vaccination programs [35, 36]. Careful and long-term assessment of the epide-
The vaccination coverage rates vary across Europe between less than 30% and more than 80% with school-based programs. Depending on good coverage, a further decrease in HPV-driven disease will be seen and screening programs will have to be adjusted accordingly.

Disclosure Statement

P.H. received research grants from GSK and Abbott, and lecture fees from SPMSD, Roche, Abbott, and Hologic. M.J. received payment for travel expenses and lecture fees from Abbott Molecular GmbH & Co. KG, Wiesbaden, Germany.

References