IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports - Commission No. S10-01

Benefit assessment of HPV testing in primary screening for cervical cancer[1]

Executive Summary

[1] Translation of the executive summary of the final report "Nutzenbewertung eines HPV-Tests im Primärscreening des Zervixkarzinoms" (Version 1.0; Status: 28.11.2011). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher:
Institute for Quality and Efficiency in Health Care

Topic:
Benefit assessment of HPV testing in primary screening for cervical cancer

Contracting agency:
Federal Joint Committee

Commission awarded on:
18.02.2010

Internal Commission No.:
S10-01

Address of publisher:
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Executive summary

Background

The Institute for Quality and Efficiency in Health Care (IQWiG) was commissioned by the Federal Joint Committee (G-BA) to conduct a benefit assessment of HPV[2] testing in primary screening for cervical cancer.

Research question

The main goal of this research was

- the comparative benefit assessment of screening strategies for cervical cancer, that is, a strategy including HPV testing alone or in combination with cytology-based testing in primary screening versus a strategy that exclusively applied cytology-based testing in primary screening.

In addition, this research aimed to compare the benefit of different primary screening strategies combining HPV- and cytology-based testing with each other.

For both goals, the term "benefit" refers to patient-relevant outcomes.

Methods

The methods of this assessment were published in a preliminary report plan (version 1.0 of 16th of August 2010) on the Internet on 23rd of August 2010 and interested parties were invited to submit comments (written hearing). After the hearing a revised report plan (version 1.0 of 29th of November 2010) was published.

The assessment was performed on the basis of randomized controlled trials on the research question stated above. For this purpose, a systematic literature search was conducted in the following databases: MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials (Clinical Trials). In addition, a search for relevant systematic reviews was conducted in the databases MEDLINE, EMBASE, the Cochrane Database of Systematic Reviews (Cochrane Reviews), the Database of Abstracts of Reviews of Effects (Other Reviews), and the Health Technology Assessment Database (Technology Assessments). The retrieved systematic reviews were scrutinized for further relevant studies. The literature search covered the period from 1990 to 1st of July 2011. Publicly available trial registries and conference proceedings of international HPV meetings were also screened. Furthermore, publications were considered that had been provided in the hearing procedure for the preliminary report plan and preliminary report. Finally, the authors of relevant study publications were contacted in order to clarify important questions.

[2] HPV = human papillomavirus

The literature screening was performed by 2 reviewers independently of one another. After an assessment of the risk of bias, the results of the individual studies for the relevant outcomes were presented.

The following patient-relevant outcomes were considered: overall survival, disease-specific (tumour-specific) survival, invasive cervical cancer, high-grade cervical intraepithelial dysplasia or in-situ cervical cancer (CIN3/CIS), CIN3+ (composite outcome of the individual components CIN3/CIS and invasive cervical cancer), harm directly or indirectly resulting from screening, health-related quality of life, as well as psychosocial aspects. In addition, the following outcomes were analysed as supplementary information: moderate-grade cervical intraepithelial dysplasia (CIN2), CIN2+ (composite outcome of the individual components CIN2, CIN3/CIS and invasive cervical cancer), sensitivity and specificity of the diagnostic test procedure insofar as they were analysed in the studies included in this benefit assessment, as well as disease-related time and effort invested by the screening participants after the initial positive test result. However, it was specified a priori that no benefit could arise solely on the basis of these supplementary outcomes.

In the assessment of cancer screening methods, the demonstration of effects on disease-specific mortality, and ideally also on overall mortality, is usually required. However, the incidence of advanced stages of cancer (but not the distribution of stages of diagnosed tumours) can also often be regarded as a patient-relevant outcome, as the reduction in disease-specific mortality can only be achieved by a reduction in advanced cancer stages. In addition, the reduction in advanced cancer stages can contribute to a reduction in morbidity and improvement in health-related quality of life.

The composite outcome CIN3+ was to be considered as long as its individual components (CIN3/CIS, invasive cervical cancer) were reported. In the interpretation of this composite outcome it is important to know whether the effects of the intervention on the individual components have the same direction.

Results

Overall 7 potentially relevant studies (8 comparisons) fulfilled the study inclusion criteria defined for this report. Five of these studies investigating 6 comparisons were included in the benefit assessment; in the following text, these comparisons are referred to as “6 studies”.

The 6 studies included in the benefit assessment were all population-based randomized controlled intervention studies with parallel groups and were conducted as multi-centre studies. A total of 235,613 women were randomized.

One study compared HPV testing plus cytology triage with cytology-based testing alone. Four studies compared a combination of HPV testing plus cytology-based testing with cytology-based testing alone. One study compared HPV testing alone with cytology-based testing alone. Four studies provided evaluable data on the second screening round; these data could

be used for the assessment of the effects of the interventions on the incidence of patient-relevant outcomes. The data on the first screening round did not distinguish between prevalence and incidence, so that a meta-analysis of cumulative event rates across both screening rounds had to be dispensed with.

The studies relevant to the conclusions of this report presented results for the patient-relevant outcomes CIN3/CIS, invasive cervical cancer, and CIN3+.

For the composite outcome CIN3+, the meta-analysis of the results of the first screening round showed an increase in diagnoses in women who underwent HPV testing alone or in combination with cytology-based testing. For the composite outcome CIN3+, the benefit assessment provides an indication that HPV testing alone or in combination with cytology-based testing leads to a reduction in this outcome.

For the outcome "invasive cervical cancer", the meta-analysis of the results of the first screening round yielded heterogeneous findings, without a recognizable direction of differences between the application of HPV testing alone or in combination with cytology-based testing. For the outcome "invasive cervical cancer", the benefit assessment provides an indication that HPV testing alone or in combination with cytology-based testing leads to a reduction in this outcome.

For the outcome CIN3/CIS, the meta-analysis of results of the first screening round showed an increase in diagnoses in women who underwent HPV testing alone or in combination with cytology-based testing. For the outcome CIN3/CIS, the benefit assessment provides a "hint" that HPV testing alone or in combination with cytology-based testing leads to a reduction in this outcome. As one study with a weighting of just above 20% did not show a group difference, the criterion for an effect in the same direction was narrowly missed. Therefore the data only provide a "hint" for the reduced incidence of CIN3/CIS.

None of the 6 studies relevant to the conclusions of this report provided evaluable data on the patient-relevant outcomes "overall survival", "disease-specific mortality", "screening-related harm", and "changes in health-related quality of life".

In the studies included in this benefit assessment, women were already being treated if they had been diagnosed with moderate-grade dysplasia (CIN2) (in one study even women with low-grade dysplasia were treated). In most cases, CIN2 regresses and only rarely progresses into invasive cervical cancer. Treatment thus means over-treatment in a great number of cases.

In 2 studies, data stratified by age groups were available for the patient-relevant outcomes CIN3/CIS, invasive cervical cancer, and CIN3+. The analysis of these data did not show an indication of different effects between subgroups (*P* value for the interaction test > 0.6 in each case).

As the screening strategies applied in the studies investigated varied greatly, no recommendation for a specific strategy that includes HPV testing can be made. The few common factors of the studies include the facts that the screening interval lasted at least 3 years and the screening programme was conducted in an organized population-based and quality assured context.

Conclusions

In primary screening for cervical cancer, this benefit assessment provides an indication of a benefit of a screening strategy including HPV testing alone or in combination with cytology-based testing versus a screening strategy including cytology-based testing alone; this benefit refers to a reduction in the composite outcome CIN3+. The data also provide an indication of a benefit regarding the incidence of invasive cervical cancer, a component of the composite outcome. In addition, the data provide a "hint" of a benefit for the component CIN3/CIS.

It should be noted that the above conclusions are based on studies that planned to treat dysplasia from moderate-grade dysplasia (CIN2) onwards. In a great number of cases, treatment of this type of dysplasia means over-treatment.

In primary screening for cervical cancer, the potential harm from HPV testing alone or in combination with cytology-based testing cannot be assessed due to a lack of data.

As the screening strategies varied greatly in the studies that our conclusions are based on, no recommendation for a specific strategy, including an algorithm for clarification of diagnosis, can be made. The few common factors of the studies include the facts that the screening interval lasted at least three years and the screening programme was conducted in an organized population-based and quality assured context.

Keywords: Uterine Cervical Neoplasms, Vaginal Dysplasia, Papillomaviridae, HPV, Pap Smear, Mass Screening, Benefit Assessment, Systematic Review

The full report (German version) is published under www.iqwig.de