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HTA-Report | Summary

Decision-analytic modeling to evaluate the long-term effectiveness and cost-effectiveness of HPV-DNA testing in primary cervical cancer screening in Germany

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Health policy

With the introduction of cervical cancer screening programmes, cervical cancer incidence and mortality rates have decreased in Western industrial countries. In Germany, annual screening using cytology with Papanicolaou technique (Pap) in women aged 20 years and older is currently recommended. Persistent infections with high-risk types of human papillomavirus (HPV) are associated with the development of cervical neoplasia. Compared to Pap cytology, HPV DNA testing is relatively more sensitive in detecting high-grade cervical cancer precursors, but with lower specificity. Introduction of HPV DNA testing in primary cervical cancer screening has the potential to improve both the long-term effectiveness and the efficiency of the screening programme when risk tailored screening with longer intervals are considered. However, as of yet no empirical screening study has evaluated the long-term effectiveness (e. g., cervical cancer incidence and mortality) of using HPV DNA testing in primary screening either alone or in combination with cytology. Given this fact and the limited nature of health resources, it is important that both the long-term effectiveness and cost-effectiveness of this new screening technology be evaluated. In this HTA report, we used decision-analytic modelling to systematically evaluate the long-term clinical and cost-effectiveness of HPV DNA testing alone or in combination with cytology in primary screening for cervical cancer. Based on the results, recommendations were derived for optimizing the cervical cancer-screening programme in Germany.

Scientific background

In Germany, currently 6,200 new cases of cervical cancer are detected each year. The 5-year survival rate for cervical cancer is 61 %. Despite the annual screening policy in Germany, cervical cancer incidence is in the upper third as compared to other European countries. Currently, an opportunistic cervical cancer-screening programme with annual Pap cytology for women aged 20 years and older is recommended in Germany. The development of cervical cancer is associated with persistent infection with high-risk carcinogenic human papillomavirus (HPV). There are two standard molecular methods for detecting HPV infections in cervical smears: the hybridization technique using the Hybrid Capture 2 (HC2) test and the amplification of the virus DNA using polymerase chain reaction (PCR). In a meta-analysis that was recently published, both methods achieved higher sensitivity than Pap cytology (relative sensitivity increase: 33 %; 95 % CI: 20 to 47 %) to detect

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high-grade cervical intraepithelial neoplasia (CIN) and invasive cervical cancer but lower specificity when compared to cytology (relative reduction in specificity: 6 %; 95 % CI: 4 to 7 %). The introduction of HPV DNA testing in primary cervical cancer screening is discussed as a potential improvement of the current cervical cancer-screening programme.

Research questions

Using a decision-analytic modelling approach, the long-term clinical and economic consequences of HPV DNA testing in primary cervical cancer screening were systematically evaluated for the German health care context.

The following research questions were examined:

1. What is the long-term clinical effectiveness (life-years gained (LYG), reduction in lifetime risk for cervical cancer) of HPV testing?
2. What is the cost-effectiveness (in Euro per LYG) of HPV testing in primary cervical cancer screening in the German health care context?
3. What is the optimal algorithm for HPV-based cervical cancer screening (i. e., test combination, start and stopping age of screening, screening interval), and which recommendations should be derived for the German health care context?

Methods

Based on the previously published and validated German Cervical Cancer Screening Model (GCCSM), we developed a decision-analytic Markov model for the natural history of HPV infection and cervical cancer that compares 18 screening strategies differing by screening interval and test combinations. Specifically, we considered the following: (1.) no screening, (2. to 5.) Pap testing alone among patients age 20 and older in intervals of one, two, three or five years, (6. to 9.) HPV testing in women aged 30 years and older in intervals of one, two, three or five years, and with annual Pap testing during age 20 to 29 years, (10. to 12.) HPV testing in women aged 30 years and older in intervals of two, three or five years and with biennial Pap testing during age 20 to 29 years, (13. to 15.) Combined HPV- and Pap testing in women aged 30 years and older in intervals of two, three or five years and with biennial Pap testing during age 20 to 29 years, (16. to 18.) HPV testing in women aged 30 years and older, in intervals of two, three or five years for HPV negative women and Pap Triage for HPV positive women and biennial Pap testing during age 20 to 29 years.

In the model, a hypothetical cohort of 15 year old women moves in annual cycles through different states including HPV-infection, cervical pre-cancer and cancer over the course of a lifetime. Transitions from one state to another are defined by annual transition probabilities derived from the published literature, and calibrated to original data from German cancer registries.

In our model, invasive cervical cancer may develop through the progression from persistent HPV-infection and the development of different stages of cervical intraepithelial neoplasia (CIN 1 to CIN 3/CIS). We did not consider heterogeneity of the population due to infections with different HPV-types. Precancerous lesions may regress to no lesions. However, regression of invasive cervical cancer to precancerous lesions was not considered. Precancerous lesions can be detected by screening only, whereas invasive

cancer cases can be detected by screening or onset of symptoms. Detected precancerous lesions and invasive cancer were assumed to be treated according to the German treatment guidelines. Women treated for precancerous lesions were assumed to have no HPV infection and no lesion, and return to the healthy state, but were still at risk for future disease. Women treated for invasive cervical cancer were assumed to have higher mortality rates than women without cervical cancer within the first five years. Stage-specific annual cervical cancer mortality rates based on original data from the Munich Cancer Registry were used. After five years, mortality was the same as for women without cervical cancer. Women were assumed to be at risk for a benign hysterectomy. Women may die from other causes than cervical cancer based on German age-specific all-cause mortality rates for females using German life tables from the Federal Statistical Office Germany.

German clinical, epidemiological and economic data for the specific model parameters were derived from the literature as well as primary data from German sources including German cancer registries (Munich, Saarland, and the Common Cancer Registry of the Federal States Berlin/Brandenburg/ Mecklenburg-Vorpommern/Sachsen-Anhalt/Sachsen/Thueringen) and German screening trials. Clinical data were derived from current guidelines for cervical cancer screening, diagnosis, and treatment and extended based on expert estimates. Age-specific screening adherence was calculated from health insurance data published in the literature. Direct annual costs were calculated based on actual reimbursement costs including frequencies of diagnostic and laboratory testing, medication, and treatment procedures related to the specific cervical cancer stages. Health resource utilisation frequencies were derived from diagnostic and treatment guidelines and a German expert panel (n=3). Costs were derived from healthcare databases and applicable pharmaceutical prices. We adjusted reimbursement prices for ambulatory care costs using a weighted average for East and West Germany as well as social and private health insurance. Inpatient costs for cervical cancer treatment procedures were based on Diagnosis Related Groups (DRG). All economic data were assessed or transformed to year 2007 Euro.

Predicted outcomes were a reduction in cervical cancer risk and mortality, life expectancy, lifetime costs, and discounted incremental cost-effectiveness ratios (ICER) expressed as Euro per life-year gained (LYG). We adopted the perspective of the third party payer and used a 3 % annual discount rate for costs and effects.

Our base case analysis examined a hypothetical cohort of women of age 15 years who had not been vaccinated for HPV. Cervical cancer screening started at age 20 years. There was no upper age limit for the end of screening. An average age-specific screening adherence rate was adopted (overall mean of 55 %). In the absence of individual data, screening adherence was modelled independently from screening history. Test accuracy data were retrieved from international meta-analyses. Sensitivity values were 47 % (CIN 1) to 72 % (CIN 2+) for Pap testing, 81 % (CIN 1) to 98% (CIN 2+) for HPV testing alone, and 82 % (CIN 1) to 99 % (CIN 2+) for combined HPV- and Pap testing. Specificity values were 95 % for Pap-, 92 % for HPV-alone, and 87 % for combined HPV- and Pap testing. In our base case analysis, we selected model parameter values conservatively, that is, against the new technology in HPV testing. Therefore, we are likely to un-

derestimate the incremental and cost-effectiveness of HPV screening strategies as compared to Pap screening. We performed sensitivity analyses to evaluate the robustness of the results and to identify future research priorities. For the sensitivity analyses, we used lower and upper 95 % confidence interval limits or ranges derived from the published literature.
The model was internally validated using epidemiologic data from German cancer registries. Additionally we performed an external model validation that compared predicted model outcomes to (1) observed epidemiologic data from German cancer registries that was not used in the model development and (2) independently-published German data. Validation outcomes were peak age (in years) of cervical cancer and its precursors (CIN 1 to 3/CIS), peak cervical cancer incidence (per 100,000 women), total cervical cancer incidence (per 100,000), the distribution of cervical cancer FIGO I to IV stages (in %), and the lifetime risks (in %) of benign hysterectomy, cervical cancer, and death due to cervical cancer. Model predictions for an unscreened population were in line with German data observed prior to the introduction of cervical cancer screening.

Results

Effectiveness

In the base case analysis, screening saved an average of 56 to 91 undiscounted life days, and resulted in 53 % to 97 % risk reduction for cervical cancer or 61 % to 99 % risk reduction for mortality due to cervical cancer, each compared to no screening. Compared to annual Pap screening, which is currently the recommended screening standard in Germany, biennial HPV testing was similarly effective (1.0 to 1.5 % lower risk reduction for cervical cancer). Among all biennial HPV screening strategies, HPV testing in women aged 30 years and older with Pap triage for HPV positives (and biennial Pap testing between 20 and 29 years) achieved the highest long-term effectiveness, followed by biennial screening with a combination of HPV- and Pap-testing in women aged 30 years and older (and annual Pap testing between 20 and 29 years) and screening with HPV testing alone in women aged 30 years and older (annual or biennial Pap testing between 20 and 29 years). The rank order was the same for the HPV strategies with 3- and 5-year screening intervals. However, compared to annual PAP testing HPV screening in 3- or 5-year intervals resulted in 7.8 % to 8.6 % or 20.5 % to 21.4 % lower long-term effectiveness with respect to risk reduction for cervical cancer. HPV screening every three years was more effective than Pap screening every two years, and HPV screening every five years was more effective than Pap screening every three years.
In the base case analysis, values for model parameters (e. g. test accuracy data, screening adherence) were selected conservatively against the new screening technology. Therefore, long-term effectiveness of (annual) Pap screening was overestimated in the base case, and incremental effectiveness of HPV as compared to Pap screening was underestimated. In a scenario analysis with test sensitivity and specificity values from a published German screening study in which Pap sensitivity was much lower than in international studies and meta-analyses (46 % for the detection of CIN 3+ compared to 72 % in the base case), HPV screening every one, two or three years was more effective than annual cytology (risk reduction for cervical

cancer: 97 %, 91 %, and 84 % versus 78 % for annual Pap). HPV screening every five years was more effective than biennial Pap screening.

Cost-effectiveness

In Germany there is no explicit cost-effectiveness threshold for a medical technology. In the literature, most often cited values for the cost-effectiveness threshold range between 50,000 and 100,000 USD or Euro per quality-adjusted life year (QALY). The National Institute for Health and Clinical Excellence (NICE) in United Kingdom recommends thresholds of 20,000 to 30,000 GBP/QALY (30,000 to 44,000 Euro/QALY).

In the base case analysis, the discounted ICER of the different non-dominated screening strategies fell between 2,600 Euro/LYG (Cytology alone every five years) and 155,500 Euro/LYG (annual cytology age 20 to 29 years, and annual HPV at age 30 years and older). Annual cytology, the current recommended screening strategy in Germany, was dominated. Biennial HPV screening in women aged 30 years and older (and biennial Pap screening in women aged 20 to 29 years) was equally effective as annual Pap screening (91 % versus 93 % risk reduction for cervical cancer) and resulted in a discounted ICER of 28,400 Euro/LYG, which should be cost-effective when compared to other well-accepted medical technologies. Biennial HPV screening in women aged 30 years and older with Pap triage for HPV positives (and biennial Pap screening in women aged 20 to 29 years) was equally effective (92 % risk reduction for cervical cancer) with an ICER of 93,700 Euro/LYG. Annual HPV screening in women aged 30 years and older (and annual Pap screening in women aged 20 to 29 years) was slightly more effective (97 % risk reduction for cervical cancer), but resulted in a discounted ICER of 155,500 Euro/LYG. With higher willingness-to-pay thresholds these strategies could be considered. Only with willingness-to-pay thresholds below 9,000 Euro/LYG less effective screening strategies with screening intervals of three or five years should be considered.

In a scenario analysis with test sensitivity and specificity values from a published German screening study, HPV screening in women aged 30 years or older in screening intervals of two or three years (and biennial Pap screening in women aged 20 to 29 years) was more effective than annual Pap screening (91 % and 83 % versus 78 % risk reduction for cervical cancer). It was also cost-effective as it had a discounted ICER of 24,200 Euro and 5,200 Euro/LYG, respectively. HPV screening in women aged 30 years every five years was less effective than annual Pap screening (71 % versus 78 % risk reduction for cervical cancer), but also cost-effective as it had a discounted ICER of 3,500 Euro/LYG.

Scenario and sensitivity analyses

In sensitivity analyses, variation in the relative sensitivity increase by HPV testing versus cytology, HPV test costs, screening adherence, screening start age, reduction in HPV incidence, and annual discount rate influenced the outcomes.

All cytology strategies were dominated by HPV testing when the relative sensitivity increase of HPV testing as compared to cytology was higher (scenario analysis with data for test accuracy from German studies). HPV testing every one, two or three years was more effective than annual cyto-

logy. Biennial HPV screening in women aged 30 years and older (and biennial Pap screening in women aged 20 to 29 years) remained the optimal strategy.

Given the doubling of HPV test costs, biennial screening with a combination of HPV- and Pap-testing in women aged 30 years and older (and biennial Pap screening in women aged 20 to 29 years) was the most efficient strategy. It had a discounted ICER of 46,800 Euro/LYG. Annual Pap cytology was not dominated as it had a discounted ICER of 90,200 Euro/LYG.
With increased screening adherence (> 75 %), a longer screening interval would be cost effective; however, with a low screening adherence (< 45 %), a shorter interval would be cost effective.
With a decrease in HPV incidence of more than 70 %, triennial HPV screening in women aged 30 years and older (and biennial Pap screening in women aged 20 to 29 years) would become the preferred strategy.
Discounted ICER increases with increasing annual discount rate. With an annual discount rate of 7 % or greater, triennial HPV screening in women aged 30 years and older (and biennial Pap screening in women aged 20 to 29 years) would be the preferred strategy.
Increasing the starting age of screening from 20 to 25 years caused no relevant loss in effectiveness but resulted in lower costs. An optimal strategy may be biennial HPV testing in women aged 30 years and older (and biennial Pap screening in women aged 25 to 29 years) with a discounted ICER of 23,400 Euro/LYG. HPV screening in women aged 30 years and older with Pap triage for HPV-positive women and Pap screening for women of ages 25 to 29 years both in two year screening interval may be cost-effective with a willingness-to-pay threshold of 87,200 Euro/LYG.

Discussion

Primary HPV screening for cervical cancer is more effective than cytology when considering long-term outcomes such as life expectancy, risk reduction for cervical cancer, and risk reduction for mortality due to cervical cancer. If HPV testing for primary cervical cancer screening were introduced in Germany, the screening interval could be extended to two years at least. The starting age of screening could be increased to 25 years without a reduction in effectiveness. Based on results from base case and sensitivity analyses, biennial HPV screening in women aged 30 years and older (and biennial Pap screening in women aged 25 to 29 years) may be the optimal screening strategy, with a discounted ICER of 23,400 Euro/LYG. With high screening adherence or low Pap sensitivity, a likely circumstance in HPV vaccinated populations or in regions with low Pap screening performance, HPV screening once every three years may be safe and cost-effective.
Our findings are consistent with the results of other published modelling studies, suggesting that HPV screening alone or in combination with cytology is effective and cost-effective with screening intervals of two or three years. However, most international studies did not include annual cytology in their evaluation. Therefore, the results of most international models were of limited use for the German decision context. Only one modelling study evaluated a screening strategy involving HPV testing and Pap triage for HPV-positive women. However, this study evaluated a combination of HPV and cytology screening and HPV screening with Pap triage for HPV-positive

women, but not HPV testing alone. Triennial HPV testing in women aged 30 years and older with Pap triage for HPV positives preceded by cytology from age 21 or 25 to 29 years was considered cost-effective as it had a discounted ICER of 78,000 or 53,000 USD/QALY gained.
As in all modelling studies our results have several limitations. First, there were no empirical quality-of-life data to use in implementing the model. Therefore, long-term effectiveness was based on life expectancy instead of quality-adjusted life expectancy. Since screening results in a relatively small gain in life expectancy, changes in quality-of-life due to psychological distress associated with screening results or adverse events of pre-cancer treatment may significantly affect the estimated cost-effectiveness ratios. Second, due to the lack of more detailed data, age-specific adherence rates were assumed to be an average adherence in every screening round independent of prior screening history. No data on adherence patterns were available. In sensitivity analyses, the screening adherence influenced the ICER of the different screening strategies. Third, our decision model did not consider heterogeneity of the population with respect to different HPV types and did not include separate states for women treated for precancerous lesions. Therefore it is of limited value in the prediction of epidemiological and clinical parameters. However, the bias is conservative in that it is against the HPV screening strategy. Fourth, modelling results evaluating the impact of an HPV vaccination on the screening programme are limited. As such, a model containing HPV type specific health states is necessary. In order to consider immunity and transmission dynamics, population based dynamic models are necessary. Fifth, clinical practice patterns were derived from guidelines and clinical expert estimations in order to consider more realistic health care data. Sixth, only direct medical costs of the health care perspective were considered. Inpatient costs were underestimated, which results in a bias against HPV screening. However, in sensitivity analyses, costs of cancer treatment had no influence on decision results.

Conclusion/recommendations

Based on our analyses and model assumptions the following conclusions were drawn:

- HPV-based primary screening for cervical cancer is more effective than cytology when considering long-term outcomes such as life expectancy, and the reduction in cervical cancer risk and mortality.
- With the introduction of HPV-based primary screening in Germany, the screening interval could be extended to two years for woman with an average risk.
- For women who undergo regular screening, the screening interval could be extended to more than two years. The same applies if the relative sensitivity increase with HPV testing is higher.
- For women with an average risk, the starting age of screening can be increased to 25 years without a relevant loss in effectiveness.
- In populations with low screening adherence, screening in short intervals is recommended.

In the German screening context and after considering effectiveness and cost-effectiveness issues an optimal screening strategy would be biennial HPV testing in women aged 30 years and older preceded by biennial cytology between ages 25 and 29 years.

Our results are based on a conservative modelling approach that is biased against HPV screening. Therefore, the incremental effectiveness and cost-effectiveness of HPV screening may be better in reality and the screening interval may be extended to three years for women who are not at high risk. However, prior to encouraging this extended interval, the effect of these longer intervals on screening adherence and attendance at gynaecological checkups should be carefully considered.

The implementation of an organised screening programme for quality-controlled introduction of HPV-screening and -vaccination with continued systematic outcomes evaluation is recommended.

Future research is necessary for gaining evidence-based information on adherence patterns, the impact of screening results on quality-of-life, as well as on decision-analytic evaluation of different integrated screening strategies in mixed vaccinated and non-vaccinated populations, and systematic evaluation of different practice patterns with respect to diagnostic work-up and treatment after initial screening results.