HPV testing: Indications of a benefit in primary screening

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Studies currently available provide indications and a "hint" that precursors of cervical cancer can be detected and treated earlier, and consequently tumours occur less often, in women who underwent testing for human papillomavirus (HPV). In this context, an HPV test can be used alone or in addition to a Papanicolaou test (Pap smear). However, both screening procedures also carry a risk of harm in the form of unnecessary treatments after testing (over-treatment). This is the result of a final report published by the German Institute for Quality and Efficiency in Health Care (IQWiG) on 24th of January 2012.

HPV testing is not reimbursed by SHI funds

In screening for cervical cancer, the German statutory health insurance (SHI) funds currently offer an annual (cytologic) examination of mucosal cells from a smear taken from the neck of the womb (cervix). This test is called a Pap smear. Since it became known that infection with HPV is the main risk factor for developing cervical cancer, experts have been discussing whether HPV testing is also a suitable screening method or is even superior to a cytologic test.

The SHI funds currently only reimburse HPV testing in exceptional cases, for example, in cases where the result of a Pap smear is unclear. The Federal Joint Committee (G-BA) therefore commissioned IQWiG to assess the benefit of HPV testing in primary screening and also to compare different screening strategies with each other.

Lower rates of cancers and their precursors are independent outcome criteria

Cancer screening is usually assessed by determining whether this procedure demonstrably contributes to the prevention of cancer-related deaths. However, in cervical cancer the fact whether or not fully developed (invasive) tumours occur less often can also be a criterion for a screening benefit. Similar to the case of colon cancer, screening for cervical cancer aims to detect and treat cellular changes (dysplasia) from which a cancerous tumour could develop, as treatment of such (advanced) precursors of cancer is far less burdensome for patients than later treatment of a tumour.

Studies with a total of 235,613 participants included

IQWiG searched for studies comparing primary screening strategies for cervical cancer based on different screening tests: a strategy including HPV testing alone or in combination with cytology-based testing and a strategy including cytology-based testing alone.

Six randomized controlled trials conducted in the United Kingdom, Finland, Sweden, the Netherlands, and Italy were included in the assessment. A total of 235,613 women had been recruited for the studies in order to be examined for precursors of invasive cervical cancer in at least two screening rounds with an interval of at least three years. However, all of these studies were susceptible to bias, which limits their informative value.

Fewer cancer diagnoses in the second screening round

In the assessment IQWiG distinguished between different outcome criteria. The composite outcome "CIN3+" was analysed, which

comprises both invasive cervical cancer and advanced precursors of cancer (high grade cervical intraepithelial dysplasia or in-situ cervical cancer, i.e. CIN3/CIS). In addition, the outcomes "invasive cervical cancer"- that is, not just the occurrence of a cancer precursor but of a tumour - as well as "CIN3/CIS" were analysed separately.

In the second screening round, the number of diagnoses for the two outcomes "CIN3+" and "invasive cervical cancer" was lower in the HPV group than in the group of women who had only been examined with a cytology-based screening strategy (e.g. Pap smear) in the first screening round. IQWiG therefore determined an indication of a benefit for these two outcomes.

If solely the advanced precursors of cancer are considered (CIN3/CIS), the data only provide a "hint" of a benefit. This is primarily due to a relatively large study that showed no difference between the HPV group and the comparator group. The new category "hint" expresses that certain minimum requirements for the available studies are fulfilled, but that conclusions on benefit and harm are only of low certainty.

No evaluable data on survival and quality of life

Conclusions on overall survival, mortality related to cervical cancer, and quality of life are not possible, as no data or no evaluable data were available for these outcomes.

Neither were evaluable data on potential screening-related harm available. For instance, unnecessary diagnostic procedures (e.g. biopsies) as a result of false-positive test results may harm patients. Moreover, the diagnosis itself can be a psychological burden, triggering anxieties or feelings of guilt.

Harm can also be caused by over-treatment. It is notable that women

with moderate grade (CIN2) or sometimes even low grade cancer precursors were also treated in the included studies; in a great number of cases these precursors regress and only rarely progress into cancer. However, it cannot be estimated on the basis of these studies how often women who underwent HPV testing and/or a Pap smear were subjected to unnecessary treatment.

No recommendation for specific screening strategy possible

The complex screening strategies applied in the studies varied greatly and can therefore hardly be compared with each other. This applies to the participants' age and the intervals between follow-up examinations, as well as to the questions in which sequence or combination the HPV or cytology test should be applied and what measures should be undertaken after certain test results.

The study results therefore do not allow a recommendation for a specific screening strategy in the German health care system. The few common factors of the studies include the fact that the screening interval lasted at least three years and the screening programme was conducted in an organized population-based and quality assured context.

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