Benefits and Risks of Cervical Cancer Screening

Pro: Karl U. Petry^a

^a Frauenklinik, Klinikum Wolfsburg, Wolfsburg, Germany

Contra: Bernhard Wörmann^b

^b Ambulantes Gesundheitszentrum, Medizinische Klinik mit Schwerpunkt Hämatologie und Onkologie, Campus Virchow Klinikum, Charité – Universitätsmedizin Berlin, Berlin, Germany

Comment: Achim Schneider^c

^c Gynäkologie und Gynäkologische Onkologie, Charité Berlin, Berlin, Germany

Cervical Cancer Screening: Pro

Karl U. Petry (Wolfsburg)

Introduction

Cervical cancer is one of the most preventable malignancies among the relevant human cancers. The genesis of this tumor depends essentially on an infection of the uterine cervix with human papillomavirus (HPV) that needs to persist for many years and decades. Oncogenic cell transformation occurs almost exclusively in a discrete cell population at the squamous columnar junction (SCJ). These peculiarities facilitate primary prevention with HPV vaccination as well as secondary prevention by detecting and treating true precursor lesions. The current screening program with annual cytology smears is effective but leads to a high number of false-positive results and unnecessary treatments. Based on the good understanding of the etiology of the disease and strong evidence from large randomized controlled trials (RCTs), further improvement in the prevention of cervical cancer by shifting to HPV screening is feasible. This could result in a further reduction in new cancer cases by 70–80% with less screening examinations and interventions, provided that well-defined patient pathways are followed and colposcopy in accordance with international quality standards is used as gold standard for the minimally invasive management of abnormal findings.

In Western countries, cervical cancer is no longer seen as a serious threat; in Germany, it is relatively rare with less than 5,000 new cases per year. In contrast to this perspective, a recent publication on the global burden of cancer showed that for women only breast cancer causes a more severe loss of life

years and quality of life than cervical cancer. In many regions of the third world, cancer of the uterine cervix even ranked number one in this negative statistic [1]. The significant reduction in cervical cancer incidence observed in industrial countries attests to the efficiency of existing screening programs. This review highlights the existing evidence for this in more detail, and gives a forecast for an optimized cervical cancer prevention program to be implemented in the near future.

No other cancer is as suitable for primary and secondary prevention as cervical cancer. The reason for the availability of effective protection from this malignancy by vaccination as well as by screening is its slow and monocausal genesis. Apart from very rare exceptions, cervical cancer is the accidental endpoint of persisting infections with HPV. The complete genesis from the initial HPV infection to persistent infection with cellular transformation to precancer to invasive cancer seems to take decades in most cases with a minimal latency period of approximately 7 years [2, 3]. The development of high-grade precursors and cervical cancer seems to depend almost exclusively on the infection of a discrete cell population located at the SCJ on the border between the ecto- and endocervix. The high susceptibility of these cells to a HPV-induced oncogenic cell transformation explains why cervical cancer is so much more common compared with primary cancers of the vagina although the exposure to HPV is identical for both the vagina and the cervix [4].

At the time of diagnosis of cervical cancer, patients are on average 50 years old, younger than for any other carcinoma. In contrast to prostate, endometrial or breast cancer, clinically meaningless cancers are rare. While the genesis of cervical cancer is slow, the clinical course is rapid with high mortality once invasive cancer is established [5].

The mechanism of secondary cancer prevention is based on the detection of precursor lesions that are surgically excised. Hereby, the natural cycle of carcinogenesis is interrupted, and development of cervical cancer is prevented actively. In the case of complete excision of precancer and all SCJ cells, the subsequent risk for invasive cervical cancer is negligible [6]. This distinguishes screening for cervical cancer fundamentally from screening concepts for breast or prostate cancer which intend to reduce mortality from these cancers. Detection of cervical precancer can be achieved with cytology-based programs implemented decades ago, or even more efficiently with HPV screening for women aged 30 years or older.

Cytology-Based Programs

In most industrial countries that introduced cytology-based prevention programs, a significant reduction in the incidence and mortality from cervical cancer was observed, while rates did not change in countries without such programs. Without screening, the life risk for cervical cancer ranges between 3–5% [7], in some regions even 6.5% [5], while it was 0.9% for Germany in the year 2004 according to the Robert Koch Institute cancer registry. Therefore, it can be concluded that the current screening concept prevents up to 2,000 new cases of cervical cancer per month. There is no grade I level of evidence for the effectiveness of cytology screening programs. Cytology programs were implemented between 1960 and 1975 without preceding high-quality studies, because scientific standards for new methods were much less ambitious then. However, a number of good cohort studies give evidence as to the success of cytology-based screening. In New Mexico, such a screening program was started for the Caucasian majority in the 1960s; the program was extended to the Hispanic population 10–15 years later, and eventually also included the native Navajos in the area. All three populations had comparable high incidences of 20–30/100,000 women, which decreased with the start of screening and the according time shift to 10/100,000 women within 20 years. This decline can only be explained by the effectiveness of the cytology-based screening program [8].

Cervical Cancer Prevention with HPV Screening

Because of the causal role of HPV in the genesis of cervical cancer, HPV testing emerged as a potential screening test in the 1990s. A negative HPV test should exclude any risk for cervical cancer for many years. The publication of six RCTs with more than a quarter million participants and up to 8 years follow-up, as well as a number of high-quality cohort studies, found that HPV screening results in a significantly better detection rate of high-grade precursors [9]. A report of the German ‘Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG)’ confirmed this better efficacy of

Fig. 1. Cytology-based screening in 1,000 women. 36 (red figures) of 1,000 women (yellow figures) will have an abnormal cytological result in annual screening. Only a minority will have true precancerous lesions (CIN3) or cervical cancer (red figures with red dots). About half of the CIN3/cancers occur in women with unsuspicious cytological results (yellow figures with red dots).

Fig. 2. HPV-based screening in 1,000 women. About 60 (red figures) of 1,000 women (yellow figures) above the age of 30 years (yellow figures) will have a positive HPV test in screening at 5-year intervals. All women with CIN3/invasive cancer will be within this group (red figures with red dots).

HPV screening compared with cytology but criticized the heterogeneity of the RCTs and could not exclude negative side effects because of unnecessary treatment of moderate (grade 2) cervical intraepithelial neoplasia (CIN2). A meta-analysis of four of the six RCTs that included more than 176,000 participants with a subtle follow-up including data of all national cancer registries was published in *Lancet*, and demonstrated significantly improved prevention of invasive cervical cancer with HPV screening reaching level I evidence [10]. Before the meta-analysis was published, IQWiG assumed that 4,800

Fig. 3. Atypical transformation zone with CIN3. After application of 3% acetic acid, white lesions become visible in the quadrants between 9 and 3 o'clock. At the site of maximal reaction in the orifice between 1 and 2 o'clock, CIN3 lesions were identified by histology.

(2,700–20,800) women would need to participate in HPV- instead of cytology-based screening with 3–5 years intervals to prevent one extra case of invasive cervical cancer. The real-life observation published in the meta-analysis showed a reduction in the cumulative incidence from 93.6 to 46.7 per 10⁵ participants, which corresponds to a number needed to screen (NNS) of 2,100. This is an extra benefit of HPV screening in addition to the cancer prevention achieved with cytology screening. Based on the incidence decline observed since the implementation of cervical cancer screening, it can be estimated that the overall NNS should range between 20 and 30 life-time participants to prevent one case of cancer. The difference between cytology- and HPV-based screening is graphically displayed in figures 1 and 2. HPV testing should be performed with licensed DNA polymerase chain reaction (PCR) tests or Hybrid Capture 2 technology (HC2, Qiagen Valencia, CA, USA). Only these tests were sufficiently validated in large screening trials and programs; the use of 'home-brewed' tests is potentially dangerous [11].

Screening Concepts

The organization of screening programs for cervical cancer in Europe is based on two different concepts. In Scandinavia, the Netherlands, the United Kingdom, and some regions of Italy, screening is centrally organized. Screening starts at age 25–30 years at 3- to 5-year intervals, findings are registered in a central database, and abnormal results are managed according to evidence-based patient pathways; screening ends at age 59–65. In the remaining European countries, women are entitled to participate in screening concepts that are regulated by law. Participation must be requested and organized by each

individual woman herself. Intervals between screening examinations are usually shorter in these high-quality opportunistic programs; in Germany and a number of other countries annual screening rounds are still recommended.

Management of Abnormal Findings and Precancer

The management of abnormal screening results depends very much on the gynecologist in charge who may prefer either repeat cytology or immediate cone biopsy without any further diagnostics in many cases. This lack of obligatory pathways leads to quite a number of unnecessary treatments as well as the development of cancers that could have been prevented [12, 13]. In organized programs, women with abnormal high-risk findings are transferred directly to colposcopy. Colposcopy allows visualization of the SCJ as the place of origin of precancer and cancer (fig. 3). This strategy avoids overtreatment, and was cost-effective in RCTs [14]. Colposcopy has experienced a transformation from medical art to standardized and evidence-based method. The management of abnormal screening results, histological assessment, and if necessary minimally invasive therapies should be performed in specialized colposcopy clinics. Colposcopists should have undergone intensive training in colposcopy and fulfill the quality parameters defined by the European Federation for Colposcopy (EFC) [15].

Screening Side Effects

Although a successful cancer prevention method without any doubt, cytology has significant disadvantages. The sensitivity for high-grade lesions is much lower than assumed, in one meta-analysis with more than 60,000 women just 53% [16]. Similarly, the rate of false-positive results is relatively high; 2–3% of all healthy participants in annual screening will receive an abnormal Papanicolaou test (Pap smear) result [17]. Protagonists of annual screening refer to a Markov model that calculated an increase in cervical cancer incidence when cytology screening intervals were extended from 1 to 3 years [18]; however, this is not the case for HPV-based screening. A long-term cohort study of 3,406 HPV-negative women who had annual Pap smears for 5 years found a 14.4% rate of false-positive cytology that resulted in unnecessary interventions and treatments, although not a single woman suffered from high-grade precancer or cervical cancer. It is noteworthy that surgical treatment of precursor lesions is associated with an increased risk of perinatal mortality and extreme premature delivery for subsequent pregnancies [19, 20]. As HPV infections are very common below the age of 30, and most of these infections will be self-limiting, HPV screening in this age group would result in a high rate of meaningless positive results. Thus, there is a consensus that HPV screening should start at age 30 with intervals of 5 years for HPV-negative

women. The German pilot project presented below shows that HPV screening shows very few side effects when this consensus is taken into account.

Therapy of Precancer

Severe dysplasia and carcinoma in situ are summarized as CIN3. The role of CIN3 as a true precancer was proven by an unethical study in a shocking way – more than 50% of untreated patients developed invasive cancers [21]. While there is little doubt that excisional treatment is obligatory for CIN3, the best treatment for the more frequent mild or moderate precursors (CIN1 und CIN2) is a matter of debate, because most of these lesions undergo spontaneous regression, especially in young women [22]. Even in well-structured screening programs, this may result in overdiagnosis and unnecessary treatments, because excisional treatment for CIN2 is mandatory for legal reasons in many countries, and even women with persisting CIN1 may finally undergo surgery.

German Pilot Project

In February 2006 in Wolfsburg, the health insurance company Deutsche BKK started a pilot project incorporating all of the elements of a modern HPV screening as highlighted in this article. All female members aged 30 years or older were offered a prevention program with cytology and HPV testing at 5-year intervals. A contract between Deutsche BKK, Klinikum Wolfsburg, and participating gynecologists in private practice defined precisely the management of abnormal screening results. Participants' data and screening results were stored in a central database at Klinikum Wolfsburg and used to monitor compliance with patient pathways. In the case of abnormal findings, patients were to be transferred for colposcopy either immediately (abnormal cytology + positive HPV test) or, in the case of persisting abnormal findings (abnormal cytology or positive HPV test), after 6–12 months. Members who had not taken part in the program after 2 years received a written invitation. After 5 years, compliance with patient pathways was excellent with 91–95%, only 3.8% of participants had to be transferred for colposcopy, while detection of CIN3 and invasive cancers was improved substantially; 95 of 172 CIN3/cancer cases were diagnosed in women with normal screening cytology. All cancers and 139/152 CIN3 were diagnosed at the first colposcopy. The rate of surgical treatments in women with less than CIN2, which is perceived as an adverse event of screening, was much lower than 15%, the value defined by the EFC for good patient management. In conclusion, the pilot project confirmed high acceptance among participants and gynecologists of a structured cervical cancer prevention program with defined patient pathways, central quality assessment, HPV testing, and extended intervals [23].

Cervical Cancer Screening: Contra

Bernhard Wörmann (Berlin)

Introduction

Cervical cancer is the twelfth most common female cancer in Germany. Cancer-specific mortality has declined since the 1970s, correlating with the introduction of screening programs using cytological smears. However, there is no formal, high-level evidence from prospective RCTs showing a positive effect of cytological screening on cancer-specific mortality. Cytological screening has a sensitivity of 50% and a specificity of >95%. Cervical cancer is caused by the persistent infection with carcinogenic HPV, transmitted via sexual contact. HPV testing of the cervical mucosa allows the distinction between high- and low-risk persons for the development of invasive cancer. It is more sensitive than cytological screening, but has not been formally introduced into the German program. The German screening program for cervical cancer does not include comprehensive quality assurance. The new law 'Gesetz zur Entwicklung der Krebsfrüherkennung und zur Qualitätssicherung durch klinische Krebsregister' (KFRG; from 3 April 2013) provides a suitable frame for the adaptation of the German program to European guidelines and for the integration of HPV testing. Future risk-benefit assessment of cervical cancer screening is influenced by the effect of HPV vaccination on the incidence of invasive cervical cancer.

Screening of asymptomatic persons for cancer is one concept of reducing the burden of cancer. Screening concepts and programs have to be evaluated under the following aspects: i) evidence-based medicine; ii) new developments; and iii) quality assurance. The results of this evaluation translate into the level of health policy and individual decision-making. Cervical cancer is the fourth most common gynecologic cancer in Germany. The number of newly diagnosed patients is estimated to amount to about 4,600 in 2014 [24]. Cervical cancer accounts for 2.1% of all newly diagnosed malignancies in women. The number of carcinomas in situ is estimated to be about 3- to 10-fold higher. The median age of newly diagnosed patients with invasive cancer in Germany is 53 years, for carcinomas in situ 34 years. Up to the 1970s, cervical cancer was the most common malignant tumor in women. Since then, the age-standardized incidence rate has dropped from about 20/100,000 in 1980 to 9.3 in 2010, with stable rates since the late 1990s [24, 25]. The cancer-specific survival rate in Germany is 69% [24]. Between 2002 and 2006, the mortality rate dropped by another 4.7%. The improvement was more pronounced in women between 55 and 64 years of age. The prognosis of patients with newly diagnosed cervical cancer is highly stage-dependent. An analysis by the German GEKID Cancer Survival Working Group for the years 2002–2006 revealed a relative age-adapted 5-year survival rate of 84.6% for localized cancer, 48.2% for locally advanced stages, and 17.9% for metastatic disease [26].

Screening for cervical cancer is based on the microscopic evaluation of cytological smears from the cervical mucosa. Its potential was first described by George Papanicolaou in 1928 and became more recognized in the 1940s [27]. Exfoliative cytology is performed in Germany by pathologists and gynecologists. When screening for cervical cancer was introduced in Europe and North America, no level IA evidence for the benefit of the program existed [28, 29]. Evidence was based on cohort studies. Even now, only one large RCT has been published. It was performed in rural India in the district of Maharashtra, and included 131,746 women aged 30–59 years [30].

Benefit

Cancer-Specific and Overall Mortality

Since the 1970s, the incidence of cervical cancer and cancer-specific mortality have decreased considerably in Northern and Central Europe [31], as well as in North America. This decrease correlated with the introduction of screening for asymptomatic women. The U.S. Preventive Services Task Force has calculated that introduction of screening reduced the incidence of cervical cancer by at least 60%, and cancer-specific mortality by 20–60% [29]. During this time, nerve-sparing and fertility-preserving surgical techniques reduced postoperative morbidity, but had no significant impact on prognosis. The therapeutic standard in the management of patients with locally advanced disease changed after the publication of five independent RCTs on the advantages of combined radiochemotherapy in 1999 [32]. Similar to most other cancer screening programs, cervical cancer screening has no significant effect on overall mortality in women.

Morbidity

Evaluations of the benefit of cytology-based screening have used cancer-specific (relative) mortality as endpoint. Other potential endpoints are reduction in the incidence of invasive cervical cancer and/or high-grade CIN3 or CIN2. Further endpoints are cancer-related morbidity and patient-reported outcome/quality of life. In a more recent trial from India, cytological screening (32,058 women) was compared to a control group (31,488 women). After 8 years of follow-up, no differences were seen with respect to incidence of cervical cancer $\geq$ stage II or cancer-specific mortality [30].

Risks

False-Positive Results

Sensitivity of cytology for the detection of intraepithelial neoplastic alterations or invasive cancer is between 30–87% with a median of 51–53% [28]. Automated interpretation was not shown to be superior to conventional microscopy [33]. The rate of false-positive results in Germany is between 2–3%. In a co-

hort study on HPV-negative women, 14.4% of the participants had at least one false-positive test within 5 years [17, 34]. A study in women referred for colposcopy showed persistent fear of cancer in 30% of the participants after 2 years [35]. Coping with a false-positive result was influenced by initial depression scores.

Overdiagnosis and Overtreatment

Precursor lesions frequently regress. In women with CIN1 and CIN2 lesions, cytological control or the performance of a HPV test is recommended in Germany. Further, minimally invasive diagnostics via colposcopy or biopsy are recommended in women with persistent pathological results. A survey by the Techniker Krankenkasse revealed an increase in the number of conizations between 2007 and 2009 without evidence of an increase in invasive cervical cancer or precancerous lesions. In addition, the age-standardized conization rate varied substantially in the different counties with numbers between 60 and 290/100,000 women [36]. Conizations are cost-intensive and increase the risk of perinatal mortality and preterm births [34, 37]. The German S2k guideline on cervical cancer from 2008 considered conization for women with CIN1 lesions as obsolete [38]. However, the degree of implementation of these guideline algorithms is unclear. The guideline is currently being updated.

Numbers Needed to Screen

Due to the lack of RCTs, the number of asymptomatic women needed to be screened for the prevention of one death from cervical cancer cannot be reliably calculated.

New Developments

Risk Factors

Almost all cases of cervical cancer can be linked to a persistent infection with cancerogenic HPV transmitted via sexual contact [39–41]. Prevalence of HPV correlates with cytological abnormalities and reaches >99% in invasive cervical cancer [42]. The majority of HPV infections regress spontaneously. More than 100 different genotypes have been identified. The most prevalent genotypes are HPV 16, 18, and 45. Other carcinogenic genotypes are HPV 31, 33, 35, 39, 51, 52, 56, 58, and 59, plus the potentially carcinogenic genotype 68 [43]. Cofactors increasing the risk of development of cancer include smoking, long-term use of hormonal contraceptives, multiparity, and human immunodeficiency virus (HIV) infection. HPV-negative women past the peak of HPV infection (i.e. 30 years or older), or women who converted from HPV-positive to HPV-negative, have a very low risk for precancerous lesions or invasive cancer [39, 41].

Changes in Incidence

The most significant breakthrough in cervical cancer has been the availability of HPV vaccines. Two preparations have been approved by the European Medicines Agency, the bivalent vaccine Cervarix® (GlaxoSmithKline, Brentford, UK) and

the quadrivalent vaccine Gardasil® (Merck & Co. Inc., Whitehouse Station, NJ, USA). Both induce long-term immune responses against the targeted genotypes and may cross-immunize against related genotypes. The vaccines cover about 80% of carcinogenic HPV genotypes. A cohort study from Australia showed a significant reduction in cytological abnormalities in young women <18 years from 0.80 to 0.42% during the observation period of 3 years [44]. Results of the pivotal vaccine trials concerning the most relevant endpoints ‘invasive cancer’ and ‘cancer-specific mortality’ have not yet been published. In 2011, the rate of vaccination in Germany was 39%. The rates vary substantially between different regions.

HPV Testing

Morbidity

Most HPV tests using material from the cervical mucosa are based on gene amplification. Different tests have been validated and approved for screening. At least six RCTs have compared HPV testing to conventional cytological screening. HPV testing had a higher sensitivity of about 95% compared to 50–55% for cytology [28, 29]. Specificity is about 95% and slightly lower than 96–98% using cytology [45]. Combination of HPV testing and cytology reaches a sensitivity of about 100%. A recent meta-analysis including four European studies compared cytology and HPV testing. With additional registry data, they calculated a 60–70% better prevention of cervical cancer using HPV testing as compared to cytological screening [10]. In the randomized study from South West India, HPV testing (34,126 women) led to a significant reduction in cancer-specific mortality after 8 years with a hazard ratio of 0.47 (0.32–0.69) in comparison with the control group (31,488 women) [30].

Mortality

Thus far, there are no mature data from RCTs using HPV testing. Thus, no studies have shown an influence of HPV testing on cancer-specific and overall mortality.

Avoidance of Unnecessary Screening Procedures

The ‘Joint European Cohort Study on the long-term predictive value of cytology and HPV testing’ showed significantly better predictive results using HPV testing. Women with a negative HPV test at first screening had a cumulative incidence of CIN3 after 6 years of 0.27% (0.12–0.45%), substantially and significantly lower than the cumulative incidence of 0.97% (0.53–1.34%) in women with initially negative cytology. In women with negative cytology but positive HPV test, the rate of CIN3 rose continuously and reached 10% after 10 years [46]. A negative HPV test had a higher predictive value against the development of invasive cervical cancer than a negative HPV test. On the basis of the recent European meta-analysis, HPV-based screening should start at age 30 and be repeated after 5 years or more [10].

Table 1. Screening programs for cervical cancer

	Germany	EU guidelines [49]
Age – lower limit, years	20	25–30
Age – upper limit, years	none	60–65
Access	opportunistic	personal invitation
Interval	annual	years

Overdiagnosis and Overtreatment

A positive HPV test cannot distinguish between transient and persistent infection [39]. Also, the current tests do not differentiate between all relevant carcinogenic genotypes. If the decision for invasive diagnostic procedures solely relied on HPV testing, overdiagnosis and overtreatment may result.

Numbers Needed to Screen

Vaccination may lead to a significant decrease in the incidence of cervical cancer, potentially also in the incidence of other HPV-associated malignancies of the penis, vulva, vagina, anus, and oropharynx. Since the effect of vaccination cannot be reliably predicted, any NNS are pure estimates.

Costs

There are only few calculations on the cost efficiency of cervical cancer screening in Germany [47]. An update including cytology, HPV testing, and morbidity is not available. The costs of HPV testing are covered by statutory health insurance after conization and as additional test in patients with mild cytological aberrations.

Quality Assurance

Screening Program in Germany

Since 1972, screening for cervical cancer has been part of cancer screening in women. Statutory health insurance providers in Germany pay for an annual cervical examination including a PAP smear starting at age 20. Rates of participation in annual screening were slightly above 50% in the 1990s [48]. Quality of cytological diagnosis is monitored via random controls. Differing from mammographic screening for breast cancer, regular reports on participation and program performance are lacking. The German screening programs differs in some respect from the EU guidelines (table 1). The first European Guideline for Quality Assurance in Cervical Cancer Screening was published in 1993. Since then, guidelines have been published on the different steps of screening, ranging from organization, quality control of cytology, algorithms for handling pathological or suspicious results, and documentation, up to the efficiency of the entire program [49]. The German screening program for cervical cancer involves no comprehensive quality control, such as implemented for mammography or colonoscopy screening. The new German KFRG law from 3 April 2013 requires the adaptation of screening

procedures to European guidelines, which also applies to cervical cancer screening. The new regulation is a suitable frame for the integration of HPV testing and the establishment of a comprehensive quality assurance program.

Cervical Cancer Screening: Comment

Achim Schneider (Berlin)

Cervical cancer is the only malignant disease in which primary and secondary prevention can be successful. This can preserve and/or restore the health of the patient. Primary prevention involves a prophylactic vaccination against high-risk HPV; secondary prevention relates to the detection and treatment of so-called precancers or CIN. Therefore, secondary prevention is not an 'early cancer diagnosis', but rather screening for high-grade CIN (CIN2 and CIN3) and thus prevention of the occurrence of cancer. Primary and secondary prevention are inextricably connected; it is not possible to discuss one without considering the other. In addition, it is necessary to consider the historical development of cervical cancer prevention. In Germany, secondary prevention was introduced in 1971, primary prevention in 2006. In the next 35 years, the number of women suffering from high-grade CIN or cancer will decrease by more than 50% due to vaccination. This development must be taken into account when considering changes in the area of secondary prevention.

In their articles, Petry and Wörmann analyze the history of, and the current situation in, secondary prevention. They also make recommendations for improvement. Both authors want to change the present screening strategy; they recommend to replace or augment cytological screening as a screening method. Since neither author wants to defend the cytological smear as a screening method, I have to take on this role – despite the fact that I, along with others, demonstrated as early as 30 years ago that HPV/DNA in cervical swabs is more sensitive than the Pap smear [50, 51]. In the following, I wish to discuss in reverse order the structure, processes, and required outcomes for the prevention of cervical cancer in our health-care system. In doing so, I will focus on secondary prevention and address the claims made by both authors.

Goals and Results

When one considers changing the present gynecological screening program, aims and expected outcomes are pivotal. With respect to a reduction in the incidence and prevalence of severe precancerous lesions and invasive cancer in the coming decades, which goals are realistic and which must be targeted? 50% of women with invasive cervical cancer did not seek gynecological prevention in the 5 years prior to diagnosis. For this reason, secondary prevention would improve the long-term outcome for these older women, if they would partici-

pate in screening. In addition, the detection method must be improved for the other half of women who did seek preventive treatment in the last 5 years before the diagnosis of cervical cancer. The goal must be to reduce the incidence of cervical cancer from the current rate of 5,000 women to 2,500 in the next 10 years. The frequency of high-grade CIN is about 10 times higher than invasive cancer. With prophylactic HPV vaccination, it is possible to reduce the occurrence of CIN3 by up to 93%. For this reason, the goal should be to reduce high-grade CIN by about 50% in the next 10 years by doubling the vaccination rate for girls and possibly boys.

Processes

Organized Invitation Process

The participation rate is crucial for the success of primary and secondary prevention. This applies to vaccination as well as to screening for high-grade CIN. The participation rate for vaccination in Germany is less than 40%; participation in cytological screening for women under 65 years of age over a 3-year period is between 60 and 80%, and between 20 and 40% for women over 65 (P. Uschold, personal communication). There is no organized invitation process in Germany to motivate non-participants to take part, neither for primary nor for secondary prevention. Organized participation in primary prevention and targeted invitation to take part in secondary prevention could result in participation rates between 80 and 90%, which reduced the incidence of cervical cancer by 80% in England. In Australia, vaccination reduced the incidence of high-grade CIN by 50% 2 years after its introduction. Whether or not these results can be transferred to the German health-care system is uncertain, however. The statutory health insurance providers in Germany report an annual participation rate in gynecological screening of approximately 50%. For mammography screening, the rate is approximately 54% (P. Uschold, personal communication). This demonstrates that, in Germany, organized mammography screening achieves results that are no better than opportunistic gynecological screening.

False-Negative Results

Molecular-biological detection of HPV has been possible for 30 years. Clinically validated tests have been available for 20 years. Despite this, HPV testing has not gained acceptance in Germany and is available only to a very limited extent as a self-paid individual healthcare option, or is covered by health insurance in the event of an inconclusive cytological smear after conization. HPV DNA detection, as has been proven, has much higher sensitivity than the cytological smear, but with lower specificity. Petry presents the advantages and disadvantages of both methods clearly in figures 1 and 2. If one considers figure 2 and assumes that, in Germany, approximately 30 million women are eligible for gynecological screening (P. Uschold, personal communication), 180,000 of these

women would be high-risk HPV-positive. Of these HPV-positive women, 49,000 would be diagnosed with high-grade CIN while 131,000 women would have a false-positive result. According to figure 1, in contrast, there are 90,000 women with a false-positive result after a cytological smear, but also 31,000 women for whom high-grade CIN or invasive cancer would not be detected by the cytological examination. At first glance, it may seem acceptable that the correct diagnosis of 31,000 women comes at the cost of 41,000 false-positive results. However, the sensitivity of the cytological examination increases from 53 to 80% in the event of 3-fold repetition over a 5-year period. In addition, only 40% of the high-grade CIN will develop into invasive cancer over a period of 15–20 years. This means that cytological screening detects severe CIN3 later than HPV screening; this does not mean, however, that the affected woman will develop invasive cancer in this lag period. In a healthcare system with higher patient compliance, it can be assumed that the majority of high-grade CIN which are not detected by a primary cytological examination will be detected in a timely manner during follow-up examinations.

HPV Tests

While cytological examination has been an established technique for over 40 years, only a few HPV detection procedures have been approved. More than 130 tests are not only based on the detection of HPV DNA, but also of HPV RNA or HPV oncoproteins. In a meta-analysis, HPV RNA detection appears to be more specific than HPV DNA detection (M. Arbyn, personal communication). So far, there is no ideal HPV test. In addition, it is unclear whether type-specific detection of HPV 16 or 18 differs in its predictive value compared to the detection of other high-risk types. Equally unclear is the significance of the diagnosis ‘marginally positive’ which occurs at a frequency of up to 20% in clinical routine, primarily with PCR-based detection methods. The legal significance of a ‘false-negative or false-positive HPV finding’ is also unclear. If one diagnoses CIN3 histopathologically and HPV detection was negative, this will be explained by a HPV type which was involved in the disease but not included in the test kit due to its rarity. If the HPV test is positive and the patient has no lesion, this is explained by a subclinical or latent infection whose biology has not been correctly defined and described as yet. In contrast, if a false-negative cytological smear occurs, this can be re-evaluated at any time and checked for the quality of the swab technique and the cytological examination. Questions of liability can be clarified using cytology, but not with a HPV result. The criticism by Wörmann that the quality of the cytological evaluation is not controlled, is only partly right: According to the cytology guidelines from 2007, the histopathological results and quality of randomly selected smears must be tested. This does not mean that no improvement is necessary. Quality control for HPV detection only occurs by way of supplied standards, whereby interlaboratory tests with clinical trials should be mandatory.

Alternative Procedures

Petry and Wörmann only discuss HPA DNA testing, and do not mention alternatives such as double stain with Ki67 and p16 on cytological preparations, for which 1 study showed significantly higher sensitivity compared to cytology (90.1 vs. 66.4%) while specificity was the same (95.3 vs. 95.4%) [52]. Compared to the cytological examination, a HPV DNA test has higher sensitivity (96.4%) but far lower specificity. In addition, the significance of double stain in the case of women below the age of 30 was equally valid as for women over 30 years of age. In two further studies, for the triaging of HPV-positive women, cytologically negative women, and women with cytological suspicion of low-grade CIN, double stain was equal or superior to HPV DNA testing [53, 54]. An additional advantage of a test system such as double stain is that the existing technological infrastructure for cytological screenings can be used and modified.

Screening Interval

As both authors correctly note, the German annual cytological screening is rather an exception in Europe, and intervals of multiple years are practiced successfully in other countries. According to calculations from the International Agency for Research on Cancer (IARC), the reduction in cumulative incidence of cervical cancer through cytological screening for women between 35 and 64 years of age compared to women who have not been screened, is 93.3% for the 1-year interval, 92.5% for the 2-year interval, and 91.4% for the 3-year interval [7]. For the situation in Germany with screening starting from age 20, these numbers are 98.7, 94.0, and 88.3%, respectively [55]. Thus, an extension of the screening interval is also justifiable for cytological screening which therefore does not necessarily have to be replaced by HPV screening. Petry demonstrated in his Wolfsburg screening cohort that an extension of the interval does not lead to lower participation rates. The success of this model is also guaranteed since compensation payment for participating physicians is adequate.

Quality Assurance

Crucial to the success of gynecological screening is quality assurance through monitoring of i) smear technology; ii) smear assessment; iii) interdisciplinary case consultations for abnormal cytological findings; iv) consideration of the wishes of the patient; v) implementation of tissue-sparing treatment techniques; and vi) interdisciplinary analysis of the surgical specimens. Whether or not the complicated cytological Munich Nomenclature III, which is currently being debated, will lead to an improvement in secondary prevention is questionable. It does seem critical that the S3 guideline ‘Prevention of Cervical Cancer’ currently being revised precisely defines the process for diagnosis and therapy. The goal should be to provide advice and treatment for women with abnormal screening findings exclusively in certified centers. In order to evalu-

ate the significance of gynecological screening, critical quality standards must be monitored centrally, and a screening registry must be synchronized with a cancer registry.

Influence of Vaccination on Gynecological Cancer Screening

As a result of the decreasing prevalence of CIN, the positive predictive value and sensitivity of the cytological examination are decreasing. The reduction in prevalence and positive predictive value for high-grade CIN depends directly on the vaccination rate: A vaccination rate of 50% leads to a reduction in positive predictive value by 40%; a vaccination rate of 90% leads to an 80% reduction [56]. The vaccination rate is likewise important for the incidence of cervical cancer: At a vaccination rate of 50%, the incidence among non-vaccinated women is twice as high as for vaccinated women after a 17-year period; if the vaccination rate is 90%, the incidence among vaccinated and non-vaccinated women is nearly identical after a 17-year period [56]. It is thus clear that the screening interval can be extended if there is a higher proportion of vaccinated women; however, an ideal screening procedure for a population with a low, moderate, or high vaccination rate has still to be identified.

Structure and Financing

The German healthcare system has a unique structure in which gynecological screening is primarily the responsibility of gynecologists and, to a lesser extent, general physicians. This separates our healthcare system from Anglo-American countries, in which smears can be taken by qualified nurses or other medical professionals. In Germany, labs or institutions led by gynecologists also perform the tests on gynecological smears. The HPV test takes place to a lesser extent in these labs, and more so in large laboratories led by lab physicians or lab companies. In this way, the examination and consultation of women or patients with respect to cytological screening lies in 'gynecological hands'. In contrast, the results of the HPV test come from a large laboratory whose test procedures are often not known in detail to the gynecologist. The results must be passed on through a gynecologist. This is particularly difficult and time-consuming when the HPV result is positive and the cytological and colposcopic findings are normal. For this reason, gynecologists are more hesitant when it comes to using the HPV test for screening and prefer to rely on a test procedure that they have known for years and learned during their training. Currently, statutory health insurance provides

EUR 380 million for the gynecological screening program (P. Uschold, personal communication). This is approximately 15 million examinations per year. Statutory health insurance provides about EUR 200 million annually for mammography screening, which is approximately 2.5 million examinations. The cost specifications for mammography screening include, apart from the primary screening test, expenses for the identification of conspicuous findings as well as for program organization. In this way, any comparison of the costs will always be limited. The costs of gynecological screening would be even higher if one were to include the costs for triaging of conspicuous findings, for example. These are difficult to estimate at this time; it is, however, a fact that must be taken into account when drawing a comparison with HPV screening, since conspicuous findings are more common here. In addition, there is the risk that costs may spiral if smear material is used for further tests with questionable clinical significance in large commercial laboratories [57]. For this reason, it is questionable whether switching to another screening method would save money.

Summary and Recommendations for Future Development in a Decreasing Order of Priority

i) Determination of goals for the medium and long term; ii) design of a documentation system which can be used to gauge the success of the measures once implemented; iii) reinforcement of primary prevention through increased participation in prophylactic HPV vaccination; iv) increase in the participation rate for gynecological screening through a reduction in the number of non-participants; v) treatment of women with abnormal findings exclusively in certified units; vi) assessment of innovative cytology-based screening procedures; vii) extension of the interval for gynecological early detection by cytological smear to 2 years above the age of 20; viii) offering additional testing for high-risk HPV at age 30, 35, and 40.

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