

Prevention of Cervical Cancer

Guideline of the DGGG and the DKG (S3 Level, AWMF Register Number 015/027OL, December 2017) – Part 1 with Introduction, Screening and the Pathology of Cervical Dysplasia

Prävention des Zervixkarzinoms

Leitlinie der DGGG und DKG (S3-Level, AWMF-Register-Nummer 015/027OL, Dezember 2017) – Teil 1 mit Einführung, Screening und Pathologie von zervikalen Dysplasien

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Key words

cervical cancer, cervical intraepithelial neoplasia (CIN),
cervical precancerous condition, HPV

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ABSTRACT

Aims Annual opportunistic screening for cervical carcinoma has been carried out in Germany since 1971. The creation of this S3 guideline meets an important need, outlined in the National Cancer Plan, with regard to screening for cervical cancer, as the guideline aims to provide important information and support for planned organized screening for cervical cancer in Germany.

Methods With the financial support of German Cancer Aid, 21 professional societies developed evidence-based statements and recommendations (classified using the GRADE system) for the screening, management and treatment of pre-

cancerous conditions of the cervix. Two independent scientific institutes compiled systematic reviews for this guideline.

Recommendations The first part of this short summary presents the pathological basis and considers various questions related to screening for cervical cancer. As also reported in earlier reviews, the meta-analysis by Kleijnen Systematic Reviews showed that HPV-based screening offers better protection against invasive cervical cancer compared to cytology-based screening. The authors of this guideline therefore recommend – in accordance with the guideline of the Joint National Committee of Germany (Gemeinsamer Bundesausschuss, G-BA) – that women aged 35 and above should be examined at regular intervals (at least every 3 years) and undergo HPV-based screening. Co-testing can also be carried out. Women between the ages of 20 and 35 should have cytological screening every 2 years.

ZUSAMMENFASSUNG

Ziele Seit 1971 erfolgt in Deutschland die jährliche, opportunistische Früherkennungsuntersuchung des Zervixkarzinoms. Durch die Etablierung dieser S3-Leitlinie wird zum einen eine wichtige Forderung des Nationalen Krebsplans zum Zervixkarzinom-Screening erfüllt. Zum anderen kann die S3-Leitlinie wesentliche Informationen und Hilfestellungen für das geplante organisierte Zervixkarzinomscreening in Deutschland geben.

Methoden Mit finanzieller Unterstützung durch die Deutsche Krebshilfe wurden durch 21 Fachgesellschaften evidenzbasierte Statements und Empfehlungen (GRADE-System) zu Screening, Management und Behandlung von Zervixkarzinom-Vorstufen erarbeitet. Zwei unabhängige wissenschaftliche Institute haben systematische Reviews für diese Leitlinie erarbeitet.

Empfehlungen Der erste Teil dieser Kurzzusammenfassung behandelt pathologische Grundlagen und Fragen zum Screening. Ähnliche wie in früheren Reviews konnte auch die Metaanalyse durch Kleijnen Systematic Reviews einen besseren Schutz vor einem invasiven Zervixkarzinom durch ein HPV-basiertes Screening im Vergleich zur Zytologie zeigen. Daher empfiehlt die Leitliniengruppe – entsprechend den Richtlinien des Gemeinsamen Bundesausschusses (G-BA) – ein HPV-basiertes Screening mit Intervallen von mind. 3 Jahren für Frauen ab 35 Jahren. Ein Co-Testing kann ebenfalls durchgeführt werden. Frauen zwischen 20 und 35 sollten ein zytologisches Screening alle 2 Jahre erhalten.

I Guideline Information

The Oncology Guidelines Program of the Association of Scientific Medical Societies in Germany (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V., AWMF), the German Cancer Society (Deutsche Krebsgesellschaft e.V., DKG) and German Cancer Aid (Deutsche Krebshilfe, DKH).

For more information, cf. the end of this article.

Citation format

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Guideline documents

The complete long version with a list of the conflicts of interest of all authors and a short version are available in German on the homepage of the Oncology Guidelines Program under: <https://www.awmf.org/leitlinien/detail/ll/015-027OL.html> or www.leitlinienprogramm-onkologie.de

Guideline authors

The German Society of Gynecology and Obstetrics (DGGG, mandate holder Prof. Dr. Peter Hillemanns, Hanover) was the lead medical society responsible for the compilation of this guideline. The guideline is issued by the Oncological Guidelines Program. Every participating medical society nominated a mandate holder, with the board of the respective society confirming the mandate in writing by. ► **Table 1** lists the societies and other organizations

► **Table 1** Participating professional societies and other organizations.

Participating professional societies and organizations	Mandate holder
German Society of Gynecology and Obstetrics [Deutsche Gesellschaft für Gynäkologie und Geburtshilfe], (DGGG)	Christian Dannecker
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International organizations	
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European Society of Gynaecological Oncology, (ESGO)***	Rainer Kimmig Martin Heubner (Deputy)

* AG-CPC, AZÄD, BVF and DGZ stepped down from participating in the compilation of the guideline on 12 May 2014. After constructive discussions by the ad-hoc committee, BVF re-joined the guideline authors on 4 September 2017.

** These international medical societies participated in the consensus process but had no voting rights.

*** Although the ESGO nominated a mandate holder and a deputy, they did not participate in the compilation of this guideline.

which participated in developing the guideline together with their respective mandated representatives. Only mandate holders nominated by participating societies and organizations were eligible to vote on a chapter-by-chapter basis during the voting process (consensus process) after they had disclosed and excluded any conflicts of interest. A patient representative was directly involved in the compilation of this guideline. Ms. Marion Gebhardt (Frauenselbsthilfe nach Krebs e.V. [Self-help for Women After Cancer]) was involved in developing the guideline right from the start and attended the consensus conferences where she had voting rights.

II Guideline Application

Purpose and objectives

The creation of this S3 guideline meets an important need, outlined in the National Cancer Plan, with regard to screening for cervical cancer. The S3 guideline provides important information and support for the planned organized screening for cervical cancer in Germany.

The old S2k German-language guideline “Prevention, Diagnosis and Therapy of HPV Infections and Preinvasive Lesions of the Female Genitalia” was consulted, with the new guideline focusing on those aspects which deal with the cervix. The guideline recommendations for primary prevention were adopted from the updated S3 guideline on HPV vaccination and supplemented by additional information regarding the impact of HPV vaccination on screening. The S3 guideline on the Diagnosis and Therapy of Cervical Cancer published in 2014 covers all aspects of invasive cervical cancer.

Targeted areas of patient care

This S3 guideline on the prevention of cervical cancer covers the prevention of cervical cancer and the diagnosis, treatment and follow-up of cervical cancer including high-grade preinvasive cervical lesions. The most important goals of the guideline were analyzing the existing data to optimize screening for cervical cancer in terms of determining the optimal test procedures, organization, investigative algorithm and treatment and considering the question of how to encourage women who refuse to go for screening to participate in the program. In addition, the guideline investigated the impact of HPV vaccination on the screening strategy for cervical cancer.

Target patient groups

This S3 guideline is aimed at all women aged 20 and above.

Target user groups/target audience

The recommendations of the guideline are addressed to all physicians and professionals involved in screening for cervical cancer, in particular gynecologists, pathologists and cytologists, as well as all healthcare professionals working in dysplasia outpatient clinics and centers.

Other target groups include:

- scientific medical societies and professional associations which are involved in screening for cervical cancer,
- women’s advocacy groups (women’s health organizations, patient and self-help organizations),

- quality assurance organizations and similar projects on national and federal state levels,
- healthcare policy institutions and decision-makers at national and federal state levels,
- payers,
- the general public to inform them about what constitutes a good medical approach.

Adoption and period of validity

This guideline is valid from 31 December 2017 through to 31 December 2020. Because of the contents of the guideline, this period of validity is only an estimate. The guideline may need to be updated if new scientific evidence appears or the methodology used in the guideline is developed further. Moreover, the key statements and recommendations of the guideline should be subjected to regular editorial checks, and the contents of the guideline should be reviewed regularly.

III Methodology

Basic principles

The method used to prepare this guideline was determined by the class to which this guideline was assigned. The AWMF Guidance Manual (version 1.0) has set out the respective rules and requirements for different classes of guidelines. Guidelines are differentiated into lowest (S1), intermediate (S2) and highest (S3) class. The lowest class is defined as a set of recommendations for action compiled by a non-representative group of experts. In 2004, the S2 class was divided into two subclasses: a systematic evidence-based subclass (S2e) and a structural consensus-based subclass (S2k). The highest S3 class combines both approaches. This guideline is classified as: S3.

Grading of evidence

The GRADE (GRADE = Grading of Recommendations Assessment, Development and Evaluation) system developed by the GRADE Working Group [1] (www.gradeworkinggroup.org) was used to evaluate the quality of evidence of the studies identified and used for this guideline (► **Table 2**).

► **Table 2** Grading of quality of evidence based on the GRADE system.

GRADE	Description	Symbol
High quality	“We are very confident that the true effect lies close to that of the estimate of the effect.”	⊕⊕⊕⊕
Moderate quality	“We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.”	⊕⊕⊕⊖
Low quality	“Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.”	⊕⊕⊖⊖
Very low quality	“We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.”	⊕⊖⊖⊖

Grading of recommendations

The methodology of the Oncology Guidelines Program requires guideline authors to assign a level of recommendation to each recommendation indicating the strength of the recommendation. The strength of each recommendation is agreed upon during a formal consensus process which requires structured consensus conferences [2]. (Details are available from the German-language Guideline Report). As part of the process, mandate holders with voting rights formally voted on the recommendations of this guideline.

This guideline includes information on the grading of the evidence of the underlying studies used for all evidence-based Statements and Recommendations and additionally shows the strength of each recommendation (level of recommendation). As outlined in the AWMF Guidance Manual [2], this guideline differentiates between three strengths or levels of recommendation, and the respective level of recommendation is reflected by the syntax used in the recommendation (► **Table 3**).

The decision criteria used to determine the level of recommendation are explained in the German-language Guideline Report for this guideline.

► **Table 3** Level of recommendation.

Level of recommendation	Description	Syntax
A	Strong recommendation	must
B	Recommendation	should
0	Open recommendation	may

Statements

Statements are expositions or explanations of specific facts, circumstances, or problems, with no direct recommendations for action. Statements are adopted after a formal consensus process using the same approach as that used when formulating recommendations and can be based either on study results or expert opinions (► **Table 4**: Level of consensus).

► **Table 4** Level of consensus.

Level of consensus	Extent of agreement in percent
Strong consensus	> 95% of participants entitled to vote agree
Consensus	> 75–95% of participants entitled to vote agree
Majority agreement	> 50–75% of participants entitled to vote agree
No consensus	< 50% of participants entitled to vote agree

Expert consensus (EC)

Statements/Recommendations which were based on the expert consensus of the guideline authors are marked as expert consensus. No symbols or letters were used to grade the expert consensus; the respective level of consensus is shown by the syntax used (must/should/may) based on the differentiation described in

► **Table 3**.

IV Guideline

1 Pathological, Cytological and Virological Basis

No.	Recommendations/ Statements	EG	LoE	Sources
3.1.	The previous (Munich II) classification of cytological findings must be switched to the new Munich III nomenclature but without including the recommendations of the new nomenclature.	EC		
1.2.	The classic 3-tiered classification into CIN 1, CIN 2 and CIN 3 will continue to be used. The 2-tiered classification used by the WHO (LSIL/HSIL) must be added in parentheses or as a comment.	EC		
1.3.	p16 immunohistochemistry should only be used to obtain a differential diagnosis to differentiate cervical findings from reactive and regenerative cervical changes which mimic intraepithelial neoplasia.	EC		

2 Epidemiology

Cervical cancer is the third most common cancer in women worldwide. The incidence and mortality rates vary considerably. Particularly in less developed countries, many women still die from cervical cancer every year.

In Germany, the incidence rate standardized for age (European standard) was 9.3 per 100 000 in 2012. The actual raw incidence rate for Germany in 2012 was 11.3 per 100 000. The introduction of cancer screening using Pap smears in 1971 contributed to a significant decrease in incidence and mortality rates in Germany. However, in recent years, incidence and mortality rates in Germany have stagnated.

Persistent infection with human papillomavirus is the main cause of cervical cancer. The prevalence of HPV is particularly high in young women under the age of 30. HPV 16 is the most common HPV type worldwide. HPV types 16 and 18 are responsible for 60 to 70% of all cervical carcinomas.

3 Primary Prevention (HPV Vaccination)

The following items from the HPV vaccination guideline 082/002 [3] represent a summary of the recommendations made by the guideline authors.

No.	Recommendations/Statements	EG	LoE	Sources
5.1.	Prior testing for HPV is not recommended as an aid to decision-making about whether to vaccinate against HPV or not. Such testing would only lead to additional costs, stresses and anxieties. Vaccination should still be carried out even in women positive for HPV because, in it is rare for women to be simultaneously be infected with all HPV types for which there are vaccines.	EC		
5.2.	All girls aged 9 years and above must be vaccinated as soon as possible against HPV. As both vaccines have been approved for use in this age group, girls of this age can be vaccinated. Early vaccination also offers protection against infections which are not transmitted through sexual contact.	EC		
5.3.	The expected benefit of vaccination may be reduced once girls begin to be sexually active. For persons who are already sexually active, the decision whether to vaccinate or not should be made on a case by case basis.	EC		
5.4.	It is not recommended to treat existing CIN or ICC with vaccination as there is no evidence that it is effective. However, there are indications that HPV vaccination can prevent recurrence after surgical therapy. HPV vaccination may be considered as part of surgical treatment to reduce the risk of recurrence.	EC		
5.5.	At the present point in time, women who are vaccinated against HPV should continue to attend screening sessions as the currently available vaccines do not prevent all forms of oncogenic HPV infection.	EC		

4 Secondary Prevention – Cytology

No.	Recommendations/Statements	EG	LoE	Sources
6.1.	A standard cytological Pap smear obtained from the uterine cervix uteri must contain sufficient epithelial cells from the transformation zone; the cells must be spread as evenly as possible across the slide and must be adequately fixed and stained.	EC		
6.2.	The collection of cells for a standard cytological Pap smear must be done using a collection instrument approved by the Cancer Screening Guideline, and cells must be fixed immediately after collection in 96% alcohol for 10 minutes or using a special fixation spray.	EC		
6.3.	When collecting cells for thin-layer cytology the recommended collection instrument must be immediately transferred into the approved fixation solution.	EC		
6.4.	There is no evidence that thin-layer cytology differs from standard Pap smear cytology in terms of its accuracy in detecting CIN 2+.	⊕⊕⊕⊕		[4–18]
6.5.	Thin-layer cytology may be used for screening. Additional tests may be carried out using the specimens collected for thin-layer cytology without having to recall the woman for a separate appointment.	EC		
6.6.	There is no evidence that computer-assisted cytology differs from standard Pap smear cytology in terms of its accuracy in detecting CIN 2+.	⊕⊕⊕⊕		[17, 19–27]
6.7.	There is no evidence that computer-assisted cytology differs from manual thin-layer cytology in terms of its accuracy in detecting CIN 2+.	⊕⊕⊕⊕		[17, 25, 28–42]
6.8.	Computer-assisted cytology may be used for screening.	EC		

5 Secondary Prevention – HPV

5.1 Suitable HPV tests

No.	Recommendations/Statements	EG	LoE	Sources
7.1.	Only HPV tests which meet the following criteria (based on Meijer et al. and Stoler et al.) must be used: <ol style="list-style-type: none"> Can detect high-risk HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68. Has at least 90% of the sensitivity of an established and validated HPV test for CIN2+. Has at least 98% of the specificity of an established and validated HPV test for CIN2+. The percentage of positive test results in a screening population consisting of women who are cytologically negative must not be higher than the percentage found with validated and established HPV tests. Single-laboratory and inter-laboratory agreement (achieved by different personnel and on different machines) should be at least 90%.	EC		
7.2.	The HPV test used for investigation must be stated on the test results.	EC		

5.2 Comparison of HPV screening alone or combined with cytology and cytological screening

No.	Recommendations/Statements	GRADE	Sources
7.3.	In women aged 30 and above, organized screening programs based on an HPV test alone or an HPV test combined with cytology and carried out at regular intervals of 3 or 5 years lead to a significant reduction in the number of new cases with cervical cancer (6/100 000) in the second round of screening after three or five years compared to organized screening programs carried out at regular intervals of 3 or 5 years which are based on cytological screening alone (20/100 000; RR 0.29).	⊕⊕⊕⊕	[15, 43 – 59]
7.4.	In women aged 30 years and above, organized screening programs carried out at regular intervals of 3 or 5 years which are based on testing for HPV alone or testing for HPV combined with cytology lead to a significant reduction in the number of new cases with CIN 3+ (82/100 000) in the second round of screening after three or five years compared to organized screening programs carried out at regular intervals of 3 or 5 years which are based on cytological screening alone (159/100 000; RR 0.59).	⊕⊕⊕⊕	[15, 48 – 61]

5.3 Potential patient-relevant disadvantages of HPV-based screening

No.	Recommendations/Statements	GRADE	Sources
7.5.	There is no evidence that there is any difference in the level of psychological stress experienced by women who have HPV-based screening compared to women who have cytological screening every 3 years.	⊕⊕⊕⊕	[60, 61]

No.	Recommendations/Statements	GRADE	Sources
7.6.	HPV-based screening and HPV test + cytology-based screening carried out every 3 or 5 years result in the detection of more cases with CIN 2 compared to cytology-based screening carried out every 3 or 5 years. This also increases the risk of overdiagnosis and overtreatment in the population being screened. This disadvantage is particularly pronounced in women under the age of 30 years. Shorter intervals between screening examinations increase the risk of overdiagnosis and overtreatment. The use of triage tests reduces overdiagnosis and overtreatment.	EC	

6 Start and End of Screening, Intervals between Screening, Special Screening Situations

6.1 Start of Screening

No.	Recommendations/Statements	GRADE	Sources
8.1.	For women under the age of 25 years, there are no indications that the benefits of organized cervical cancer screening outweigh the harm.	EC	
8.2.	Organized screening for cervical cancer can be started when women are aged 25 years. In Germany, women above the age of 20 are still entitled to have a screening test in accordance with the screening guideline (key points of the resolution regarding the Cancer Screening Guideline [KFE-RL] passed on 15 September 2016).	EC	
8.3.	Better detection rates of CIN 3+ have been reported for organized HPV-based screening in women between the ages of 25 and 30, but this also leads to a high rate of false-positive results.	⊕⊕⊕⊕	[15, 54 – 59]
8.4.	Organized HPV-based screening (HPV or HPV + cytology) should not be carried out in women under the age of 30.	⊕⊕⊕⊕ B	[15, 48 – 59]
8.5.	In Germany, women between 20 and 35 are still entitled to have organized cytology-based screening.		

6.2 Intervals between screening

No.	Recommendations/Statements	GRADE	Sources
8.6.	In women aged 30 years and above, organized HPV-based screening carried out every 3 to 5 years results in lower rates of new cases with cervical cancer compared to organized screening based on cytology alone carried out every 3 years.	⊕⊕⊕⊕	[15, 48 – 59]
8.7.	There is no evidence that cytological screening carried out annually is superior to cytological screening carried out every two years.	EC	
8.8.	In Germany, during the transition period (at least another 6 years or until sufficient data is available from the 2nd round of screening) women between the age of 20 and 35 will still be entitled to have an annual cytological examination. After the end of the transition period, the intervals between screening appointments and the screening method itself must be adapted to conform to international recommendations after the data used to monitor this age group has been taken into account. In future, women aged 35 and above will be offered a combined screening examination consisting of an HPV test and a cytological examination instead of an annual cytological examination every 3 years.		G-BA: Presse release of 16 September 2016, No. 38/2016: "Eckpunkte für zukünftiges Screening auf Gebärmutterhalskrebs geändert". Available online at: https://www.g-ba.de/institution/presse/pressemitteilungen/641 .
8.9.	If co-testing (cytology and HPV test) or HPV testing alone is done in women above the age of 30, it should be carried in the form of organized screening at intervals of least 3 years.	EC	

6.3 End of screening

No.	Recommendations/Statements	GRADE	Sources
8.10.	RCTs have only investigated women up to the age of 65. The benefit of organized screening in women aged more than 65 years is therefore not proven, irrespective of whether screening is based on HPV and/or cytology.	EC	
8.11.	Women over the age of 65 must be encouraged to continue participating in cancer screening programs. Discontinuing screening for cervical cancer may be considered for women over the age of 65 who have had multiple negative results following co-testing with a Pap smear and an HPV test.	EC	

6.4 What screening is recommended for women who have been vaccinated against HPV?

No.	Recommendations/Statements	GRADE	Sources
8.12.	Women who have been vaccinated against HPV have a lower risk of developing CIN 3+. In Germany, cancer screening is offered to women irrespective of whether they have been vaccinated or not.	EC	

6.5 What screening is recommended for women who have undergone a hysterectomy?

No.	Recommendations/Statements	GRADE	Sources
8.13.	The benefit of screening for women who have undergone total hysterectomy is not proven, irrespective of whether the screening is based on cytology or on testing for HPV.	EC	
8.14.	HPV-positive Frauen who have undergone total hysterectomy should continue to participate in organized screening programs.	EC	
8.15.	Women who have undergone supracervical hysterectomy must continue to participate in organized screening programs.	EC	

6.6 What screening is recommended for immunosuppression?

No.	Recommendations/Statements	GRADE	Sources
8.16.	Immunosuppressed women have a higher risk of developing precancerous cervical conditions and invasive cervical cancer.	EC	
8.17.	Immunosuppressed women with abnormal findings on screening must be referred to a certified dysplasia outpatient clinic/facility.	EC	

7 Biomarkers

7.1 Is primary screening with a biomarker superior to HPV DNA analysis?

No.	Recommendations/Statements	GRADE	Sources
9.1.	Cross-sectional studies have found no benefits of using biomarkers (5-type HPV mRNA, p16 ELISA, ProExC, p16/Ki-67 dual staining, protein E6) compared to high-risk HPV DNA testing.	⊕⊕⊕⊕	[62–71]
9.2.	There are currently no data from longitudinal studies of more than 3 years for the biomarkers currently being tested in large studies, meaning that these biomarkers must not be used for primary screening.	⊕⊕⊕⊕ A	[62–71]

7.2 Is primary screening with a biomarker superior to conventional cytology?

No.	Recommendations/Statements	GRADE	Sources
9.3.	Sensitivity: In cross-sectional studies, biomarkers (5-type HPV mRNA, p16 ELISA, ProExC, p16/Ki-67 dual staining, protein E6) are superior to conventional cytology with regard to sensitivity. Specificity: p16/Ki-67 dual staining is superior to conventional cytology with regard to specificity.	⊕⊕⊕⊕	[63–66, 68–70]
9.4.	Biomarkers (5-type HPV mRNA, p16 ELISA, ProExC, p16/Ki-67 dual staining, protein E6) must not be used for primary screening as long as the suitability of these procedures has not yet been verified in longitudinal studies of at least 5 years.	⊕⊕⊕⊕ A	[63–66, 68–70]

Conflict of Interest

See guideline report: https://www.awmf.org/uploads/tx_szleitlinien/015-027OLm_Praevention_Zervixkarzinom_2018-01.pdf

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