Precancerous Lesions of the Cervix, Vulva and Vagina According to the 2014 WHO Classification of Tumors of the Female Genital Tract

Systematik der präinvasiven Läsionen von Zervix, Vulva und Vagina nach der WHO-Klassifikation 2014 „Tumours of the Female Genital Tract“

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The field of medicine is subject to a continuous process of development with constant updates, meaning that classifications need to be continually re-evaluated and adapted to the current level of knowledge. Important scientific findings in recent years have led to a new WHO terminology for precancerous lesions of the cervix, vulva and vagina which are discussed below.

1 Precancerous lesions (dysplasias) of the cervix

1.1 Historical terminology

Based on studies carried out by Schauenstein, Schottländer and Kermauner in the early decades of the 20th century, the term “carcinoma in situ” (CIS) was introduced into general medical terminology by Broders in 1932 to describe precancerous lesions of the squamous epithelium. This was a revolutionary step, as most of the medical community at the time doubted the existence of a preinvasive stage for invasive carcinoma. The term “dysplasia” goes back to Reagan, who first used it in 1953 to describe all atypical and abnormal differentiations of the squamous epithelium which were less pronounced than those occurring in CIS. In 1963 Koss presented the theory, since disproved, that all cervical dysplasias, irrespective of their degree of severity (i.e., including even mild and moderate dysplasia), could progress to invasion, although the incidence of progression differed. The CIN terminology, which divides the lesions into 3 main groups and is still widely used today, was introduced by Richart in 1968. He used it to describe a continuous progression from mild (CIN 1) to moderate dysplasia (CIN 2) and finally to severe dysplasia or carcinoma in situ (CIN 3). At a workshop held in Bethesda (Maryland) in 1990, Richart transferred the already existing dual nomenclature used in cervical cytology which differentiated low-grade from high-grade changes, to the terminology used for histological classification. Since then, histology has also differentiated between two different degrees of disease in the cervical squamous epithelium: low-grade squamous intraepithelial lesions (LSIL) und high-grade squamous intraepithelial lesions (HSIL) [1].

After studying the cervical glandular epithelium, Helper went on to describe highly atypical columnar epithelium as a precursor of invasive adenocarcinoma in 1953. The term adenocarcinoma in situ (AIS) was coined by Friedell in 1953. In analogy to the CIN concept, diagnostic criteria were proposed which aimed to describe columnar epithelium with lower grade atypia than that present in AIS (e.g. endocervical glandular dysplasia), but this proved to be difficult to reproduce [1].

1.2 Current classification of WHO 2014 (Tables 1 and 2)

The current WHO classification of precancerous lesions of cervical squamous epithelium is based on new findings on HPV-related carcinogenesis; the key assumption in this context is that two early genes of HPV (E6 and E7) trigger neoplastic transformation of the squamous epithelium. This capacity to induce neoplastic transformation requires a specific expression pattern of E6 and E7, which only occurs in a small percentage of HPV infections. These types are referred to as transforming HPV infections [1].

Transforming infections are usually associated with HPV high-risk genotypes. After constant expression of E6 and E7 oncogenes the oncoproteins encoded by E6 and E7 bind to to cell cycle proteins, leading to loss of cell cycle control. Mutations gradually accumulate and cells become genetically unstable. Morphological findings are moderate or severe dysplasia of the cervical squamous epithelium (CIN 2 or CIN 3), which are subsumized in the WHO classification as HSIL. At this stage disruption of the cell cycle led to an accumulation of tumor suppressor gene p1b which

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Table 1 Terminology for HPV-associated precancerous lesions of the squamous epithelium of the cervix, vulva and vagina.

2014 WHO classification	2003 WHO classification	Synonyms
Low-grade squamous intraepithelial lesion (LSIL)	CIN 1 VIN 1 (usual type) VAIN 1 condyloma koilocytic atypia	mild dysplasia condyloma koilocytic atypia koilocytosis
High-grade squamous intraepithelial lesion (HSIL)	CIN 2 VIN 2 (usual type) VAIN 2 CIN 3 VIN 3 (usual type) VAIN 3	moderate dysplasia severe dysplasia carcinoma in situ Bowen's disease Bowenoid dysplasia

Table 2 Terminology for HPV-associated glandular intraepithelial lesions of the cervical columnar epithelium.

2014 WHO classification	Old terminology
Adenocarcinoma in situ (AIS) Syn: high grade cervical glandular intraepithelial neoplasia (HG-CGIN)*	endocervical glandular dysplasia (EGD)

* In contrast to squamous epithelial lesions, low-grade lesions of the cervical columnar epithelium are not classified.

Table 3 Terminology for HPV-negative squamous intraepithelial lesions of the vulva.

2014 WHO classification	Synonyms
differentiated VIN (dVIN)	VIN, differentiated type CIS, simplex type

can be demonstrated in an immunohistochemical examination with antibody to $p16^{ink4a}$ with overexpression of p16, when a continuous staining of all atypical epithelial cells including basal keratinocytes is observed. At colposcopy these lesions generally correspond to type 2 changes (major changes). HSIL have a significant risk of progression to invasive carcinoma [1–3].

In permissive (productive) HPV infections, expression of the viral genes E6 and E7 only occurs in basal cells in the squamous epithelium which are capable of regeneration and is therefore controlled. Permissive (productive) HPV infections can be caused by low-risk and/or high-risk HPVs. In low-risk HPV infections LSIL reveals a focal discontinuous staining with $p16^{ink4a}$ antibody (no overexpression, irrespective of the percentage of $p16^{ink4a}$ staining) as the binding affinity of low-risk HPV oncoproteins to the cell cycle proteins is significantly lower than the binding affinity of high-risk HPV oncogenes. Morphological findings are koilocytic changes and/or the development of condyloma or mild dysplasia (CIN 1). The WHO classifies these changes as LSIL. After several months T-cells generally begin to detect viral antigens, so that the majority of permissive (productive) HPV infections disappear again within one or two years. A minority of LSIL cases are caused by high-risk HPV. These lesions show overexpression of $p16^{ink4a}$ in the basal third of the epithelium. According to the current state of knowledge, the clinical procedure for $p16^{ink4a}$-positive LSIL does not need to be modified as an increased rate of progression has not been established. On colposcopy LSIL generally correspond to type 1 changes (minor changes). LSIL have only a limited risk of progression to invasive carcinoma [1–3].

The pathogenesis of carcinoma of the cervical columnar epithelium is less well understood. Not all adenocarcinomas are known to have a preinvasive stage. AIS is of considerable clinical importance, as it is considered a preinvasive precursor lesion of mucinous adenocarcinoma (differentiated into endocervical, intestinal, signet-ring cell and villoglandular subtypes) after transforming HPV infection. The term high grade cervical glandular intraepithelial neoplasia (HG-CGIN) is used synonymously for AIS (**Table 2**). In contrast to precancerous lesions of the squamous epithelium, there is no classification of low-grade lesions in the cervical columnar epithelium. The reason being, in addition to the poor reproducibility, that there do not appear to be any permissive (productive) HPV infections which affect the cervical columnar epithelium. AIS is associated with a significant risk of progression to invasive carcinoma [1,4].

Preinvasive lesions of rare subtypes of adenocarcinoma of the cervix (e.g. clear cell, serous, endometrioid, mesonephric, gastric-type, and minimal deviation adenocarcinoma) are insufficiently characterized and are therefore not classified separately [3].

1.3 Current joint classification of HPV-associated squamous intraepithelial lesions of the cervix, vulva and vagina, WHO 2014 (**Table 1**)

As the pathogenesis of HPV-related cancers in the squamous epithelium of the cervix, vulva and vagina is comparable, the current WHO terminology uses the previously mentioned diagnostic categories LSIL and HSIL to classify HPV-associated lesions in all three organs [2,5,6], (**Table 1**): LSIL therefore includes all lesions (koilocytic changes, flat condyloma, mild dysplasia) resulting from permissive (productive) HPV infection of the squamous epithelium of the cervix, vulva or vagina. Pointed condylomas are classified in the 2014 WHO classification among benign lesions of the squamous epithelium as variants of LSIL. HSIL includes moderate and severe HPV-associated dysplasias of the cervix, vulva and vagina (**Table 1**).

LSIL of the cervix, vulva and vagina have a high rate of spontaneous remission and only a low risk of progression to invasive carcinoma. HSIL of the cervix, vulva and vagina have a significant risk of progression to invasive carcinoma.

The diagnostic categories CIN 1, VIN 1 (usual type) and VAIN I can also be continued to be used synonymously for LSIL, just as CIN 2, CIN 3, VIN 2 (usual type), VIN 3 (usual type), VAIN 2 and VAIN 3 can be used synonymously for HSIL. In clinical practice, adding the individual diagnostic criteria in brackets would be very useful (e.g., HSIL [CIN 2], LSIL [condyloma], etc.), and the authors would recommend doing so because of the differences in clinical course (i.e., different progression and regression rates of CIN 2 and CIN 3).

2 Preinvasive Lesions of the Vulva

2.1 Historical terminology

In 1965 Kaufman and Gardner grouped premalignant changes of the vulva into three groups: erythroplasia of Queyrat, Bowen's disease and carcinoma simplex, first described by Abell in 1965. Since 1976 the International Society for the Study of Vulvar Disease (ISVVD) uses the terms mild dysplasia (VIN 1), moderate

dysplasia (VIN 2) and severe dysplasia (VIN 3). In 2004 the ISVVD introduced a two-part classification system, classifying lesions into HPV-positive usual-type VIN (formerly VIN 2/3) or HPV-negative differentiated VIN (dVIN)/simplex-type carcinoma in situ (CIS) [1].

2.2 Current 2014 WHO classification (Tables 1 and 3)

The WHO currently classifies vulvar lesions into two fundamentally different lesions of the squamous epithelium according to the different pathogenesis of the vulvar cancer (HPV-induced or HPV-negative): SIL and differentiated VIN (dVIN). SIL covers all HPV-associated intraepithelial lesions. In analogy to cervical and vaginal classifications, these vulvar lesions are differentiated into LSIL and HSIL. In contrast, dVIN refers to HPV-negative lesions which generally develop in the context of dermatoses (lichen sclerosus and lichen planus). In contrast to HPV-associated lesions (SIL), dVIN is not graded according to severity. Biologically dVIN corresponds to an in situ carcinoma, independently of histological differentiation. On immunohistochemical examination, dVIN typically does not overexpress $p16^{ink4a}$. Around half of dVIN show a positive immunohistochemical reaction for p53 antibodies [5].

At colposcopy the changes found with HPV-induced precancerous vulvar lesions largely correspond to those found in the cervix and vagina. The signs of dVIN on colposcopy are still insufficiently described; most commonly they correspond to those reported for leukoplakia or, in rarer cases, erythroplakia [1].

While vulvar LSIL has a high rate of spontaneous remission, vulvar HSIL and dVIN have a significant risk of progression to invasive carcinoma (see also 1.3). Compared to HPV-induced precancerous lesions, dVIN tend to progress faster to invasive carcinoma, in some cases within less than 1 year [1,5].

Genital Paget's disease is another preinvasive epithelial vulvar lesion. Melanoma in situ is a non-epithelial preinvasive lesion [1,5].

3 Current Classification of Preinvasive Vaginal Lesions, WHO 2014 (Table 1)

Preinvasive lesions of the vaginal squamous epithelium are generally associated with HPV and, as such, are currently differentiated by the WHO into LSIL and HSIL (see also 1.3). At colposcopy vaginal LSIL generally correspond to type 1 changes (minor changes), while HSIL usually present as type 2 changes (major changes). In rare cases, vaginal cancers develop independently of HPV, e.g. subsequent to lichen planus. The mechanism of HPV-independent cancers in the vaginal squamous epithelium is still insufficiently studied but is assumed to correspond to the development in the vulva. However, to date the WHO has not identified diagnostic criteria analogous to dVIN [1,6].

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Conflict of Interest

None.

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