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“

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 Kernaufer 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) and 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

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 summarized in the WHO classification as HSIL. At this stage disruption of the cell cycle led to an accumulation of tumor suppressor gene p16 which
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\(^{ink4a}\) overexpression, irrespective of the percentage of p16\(^{ink4a}\) staining is significant for the risk of progression to invasive carcinoma [1–3].

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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 p16INK4a. 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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