**Abstract**

Vulvar premalignant squamous lesions include low- and high-grade intraepithelial neoplasias. High-grade lesions include usual (classic) and differentiated (simplex) vulvar intraepithelial neoplasia (VIN). Usual VIN (uVIN), the most common, is related to human papilloma virus (HPV), occurs in younger patients, and is frequently multifocal. Differentiated VIN (dVIN), less common, is related to lichen sclerosus and other chronic vulvar dermatoses, occurs in older women, and is usually unifocal. Terminology schemes for premalignant lesions are reviewed. Invasive squamous cell carcinoma also occurs in two distinct clinicopathologic settings. Most conventional keratinizing squamous cell carcinomas arise from a background of dVIN and comprise the majority of invasive squamous tumours. Warty and basaloid invasive squamous cell carcinomas likely develop from uVIN and comprise a minority of invasive tumours. Clinical features, microscopic findings, differential diagnoses, immunoprofiles, prognosis and treatment of premalignant and malignant lesions are addressed.

**Keywords** classic; condyloma acuminatum; differentiated; HPV; human papilloma virus; lichen sclerosus; simplex; squamous cell carcinoma; VIN; vulva; vulvar intraepithelial neoplasia

**Introduction**

The premalignant squamous lesion of the vulva is designated as squamous dysplasia. The majority of vulvar dysplasias are associated with human papilloma virus (HPV) infection and are referred to as “usual” vulvar intraepithelial neoplasia (uVIN). A separate intraepithelial neoplastic proliferation with a pathogenesis unrelated to HPV, which is related to lichen sclerosus and other vulvar dermatoses is designated as “simplex” or “differentiated” VIN (dVIN). Although condyloma acuminatum (CA) is not a true premalignant lesion, like usual VIN it is HPV-associated and is considered by some to be a low-grade lesion, hence its inclusion in this review. Although carcinoma of the vulva is the fourth most common gynaecologic malignancy, it is relatively rare, accounting for only 5% of all female genital tract cancers. Over 90% of invasive vulvar tumours are squamous cell carcinomas.

The most frequent form of invasive squamous cell carcinomas (invSCC) of the vulva, conventional keratinizing squamous cell carcinoma, occurs in elderly women and is related to dVIN, lichen sclerosus (LS), and probably other dystrophic vulvar lesions including squamous hyperplasia. The less common forms of invSCC, the warty and basaloid subtypes, account for one-third of vulvar invSCC, are seen in relatively young women, are associated with HPV, and are preceded by HSIL (VIN 2 and 3).

Over the last decade much new information has shed light on the pathogenesis of vulvar precursor lesions and invSCC, leading to considerable changes in terminology for both. Therefore, before turning our attention to the individual precursor lesions, a discussion of terminology is warranted.

**Terminology**

Currently there are numerous grading systems in place, reflecting the heterogeneity of vulvar precursor lesions, and taken as whole may be complicated and confusing for the novice as well as the experienced pathologist. There are separate grading systems utilizing the (VIN) terminology and systems using the two-tiered cytology-based squamous intraepithelial lesion (SIL) terminology known as the Bethesda System.

The VIN terminology, adopted in 1986, is a three-tiered system and was devised to replace the atypia-carcinoma-in-situ terminology. It is the most widely accepted nomenclature system and was, until recently, endorsed by both the World Health Organization (WHO) and the International Society for the Study of Vulvovaginal Disease (ISSVD). This system recognizes three grades of VIN: 1, 2, and 3, where VIN 1 is defined as a low-grade lesion and VIN 2 and 3 are high-grade lesions. VIN 2/3 encompasses lesions previously classified as carcinoma in situ, Bowen disease, and Bowenoid papulosis. This system is analogous to the cervical intraepithelial neoplasia (CIN) terminology which is widely utilized for cervical precursor lesions. In addition, the VIN system is the first to recognize differentiated or simplex VIN, which by definition is a high-grade lesion.

In 1994, the WHO proposed the squamous intraepithelial lesion (SIL) system for grading vulvar precursor lesions which is based on the Bethesda System, a system that has been used for years in the reporting of cervical cytology and biopsies. The Bethesda System is two-tiered and divides dysplasia into low-grade SIL and high-grade SIL. While the VIN systems do not include condyloma acuminatum as VIN 1, the SIL terminology places condyloma in the LSIL category. In addition the 1994 WHO terminology does not include dVIN.

In 2004, ISSVD proposed a novel VIN nomenclature, a complete revision that has not been universally accepted. Essentially, the revised system eliminates the VIN 1 category and combines VIN 2 and 3 into a single category (Table 1). Thus, grading of VIN is eliminated. Instead, VIN is separated into two groups: usual (undifferentiated or classic) and differentiated (simplex) types. The usual type includes the WHO VIN categories 2 and 3. The usual type is further subdivided into warty, basaloid, and mixed (warty and basaloid) types. VIN 1 is excluded because it is deemed poorly reproducible, uncommon, and may mimic reactive changes from inflammation or differentiated VIN. The rationale for combining VIN 2 and 3 is that because of high inter-observer variability, VIN 2 and 3 cannot reliably be separated and thus should be placed in the same category. ISSVD also noted that the occasional example of VIN that cannot be placed into either of the two VIN categories (usual nor differentiated type) may be classified as “VIN, unclassified type”.

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Since the first edition of this review was published in 2010, three additional classification systems have been proposed. In 2013, the Lower Anogenital Squamous Terminology (LAST) was introduced by the American Society for Colposcopy (ASCCP) and the College of American Pathologists (CAP). The purpose of LAST was to unify the nomenclature of HPV-associated squamous lesions of the entire lower anogenital tract. This system utilizes the Bethesda System’s two-tiered LSIL and HSIL rather than the three-tiered VIN 1, 2, or 3 since it is more consistently reproducible by pathologists. However, importantly, since LAST only refers to HPV related squamous precursor lesions, it does not include dVIN which has a higher rate of progression to invasive squamous cell carcinoma than HPV-associated lesions and thus by its conspicuous absence, there is the potential it will be under diagnosed and under treated. In response, in 2015, the ISSVD adopted the most recent (2014) WHO classification system of LSIL, HSIL, and dVIN, but expanded the WHO classification with an explanation of what lesions are encompassed within the LSIL category: vulvar LSIL, flat condyloma, or HPV effect, and the HSIL category: vulvar HSIL, VIN usual type.

At our institution, we report vulvar biopsies using both the SIL and VIN terminologies if the lesion is HPV related; for example, low-grade lesions are reported as LSIL (VIN 1), and high-grade lesions as either HSIL (VIN 2) or HSIL (VIN 3). For lesions unrelated to HPV, we use the term VIN, differentiated. This is the terminology used in this paper.

### Condyloma acuminatum

#### Introduction

Condyloma acuminatum (CA) is a sexually transmitted benign squamoproliferative lesion caused by HPV, most frequently types 6 and 11. Because it is not associated with high-risk HPV subtypes, it is not a cancer precursor lesion.

#### Clinical features

CA occurs in approximately 1% of sexually active reproductive age females, usually in the early years of sexual activity. The lesion most frequently involves the external genitalia, including the vulva, introitus, perineal, and perianal skin and less frequently the vagina and cervix. CA is usually asymptomatic but may cause vulvar itching and burning. The clinical correlate to condyloma is the genital wart. Grossly, the lesion is exophytic, usually multiple, and can range in size from minute raised lesions to large cauliflower-like coalescing masses. CA has a tendency to recur, especially in immune-compromised patients.

### Classification systems for VIN

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<tr>
<td>VIN 1</td>
<td>LSIL</td>
<td>Flat condyloma, HPV effect</td>
<td>LSIL</td>
<td>LSIL</td>
<td>LSIL (vulvar LSIL, flat condyloma or HPV effect)</td>
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<tr>
<td>VIN 2, 3</td>
<td>HSIL</td>
<td>1. VIN, usual type</td>
<td>HSIL</td>
<td>HSIL</td>
<td>HSIL (vulvar HSIL, VIN usual type)</td>
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<td></td>
<td></td>
<td>a) VIN, warty type</td>
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<td>b) VIN, basaloid type</td>
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<td>c) VIN, mixed (warty/basaloid type)</td>
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<td>VIN, differentiated type</td>
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<td>VIN, differentiated dVIN</td>
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Although not life-threatening, the cosmetic and social issues relating to these lesions are not insignificant and likely influenced the decision to include HPV types 6 and 11 in some HPV vaccines.

### Microscopic findings

The classic condyloma has an exophytic branching, papillary growth pattern with stratified squamous epithelium and underlying fibrous stroma. There may be overlying parakeratosis and hyperkeratosis (Figure 1). Koilocytic atypia, which can range from subtle to conspicuous, is seen in surface layers of the infected epithelium. Koilocytic atypia includes nuclear enlargement and coarsening, nuclear membrane irregularity, binucleate forms, and perinuclear cytoplasmic halos. When mitotic figures are present, they are confined to the lower third of the epithelium.

### Differential diagnosis

Various lesions with verrucous-like squamous proliferations can be mistaken for CA. A frequent mimic is the benign fibroepithelial polyp. The distinction between the two lesions can be particularly challenging when the condyloma shows only very subtle koilocytic change. However, the fibroepithelial polyp, unlike condyloma, demonstrates atypical multineucleated stromal cells. Another frequent mimicker of condyloma is vulvar seborrheic keratosis (VSK) which is also a discrete lesion. VSK, in contrast to CA, consists of a proliferation of basaloid cells and

![Figure 1 Condyloma acuminatum with characteristic exophytic, papillary architecture (H & E, original magnification 4x).](image-url)