The incidence of human papilloma virus-related vulvar intraepithelial neoplasia is increasing worldwide. This is associated with an increasing incidence of invasive vulvar cancer in young women. Undifferentiated vulvar intraepithelial neoplasia has an invasive potential; a subset of very young patients with pigmented lesions and spontaneous regression has been described. Differentiated vulvar intraepithelial neoplasia is human papilloma virus negative and affects older women, who are at risk of invasive cancer. Chromosomal changes and angiogenesis may play a role in carcinogenesis. Immunocompromised women bear a substantial risk of vulvar intraepithelial neoplasia. These facts demand the awareness of both women and physicians, because there is evidence of diagnostic delays in patients with vulvar cancer. The standard treatment is surgical excision, which may be combined with laser treatment in extensive disease. Preliminary results of topical antiviral agents and photodynamic therapy are available, but remain to be confirmed by prospective, placebo-controlled studies. Curr Opin Obstet Gynecol 14:39–43. © 2002 Lippincott Williams & Wilkins.

Introduction
During the past two decades there have been significant changes in the epidemiology of human papilloma virus (HPV), resulting in an increasing incidence of lower genital tract neoplasia. However, the incidence of invasive vulvar cancer remained stable, and vulvar cancer was still considered to be mainly a disease of old women. The epidemiology of vulvar intraepithelial neoplasia (VIN), its relationship with invasive cancer, the standards of diagnosis, and recent developments in therapy will be described in the present review.

Epidemiology
The incidence of VIN is comparable with that of invasive vulvar cancer. The Surveillance, Epidemiology and End Results programme revealed an increase in incidence during the 1970s and 1980s. From 1973 to 1987 the age-adjusted incidence rate doubled from 1.1 to 2.1 per 100 000 women-years, surpassing the rate of invasive vulvar cancer [1]. During the same observational period, the Cancer Registry of Norway documented an increase in the age-adjusted incidence rate from 0.5 to 1.4 per 100 000 women-years [2]. A New Zealand vulvar clinic reported a significant increase in the incidence of VIN 3 in women aged less than 50 years during these decades [3]. At the University Hospital of Vienna, Austria, on average seven new cases per year presented during the period from 1985 to 1988, and there were approximately 25 new cases per year presented during the period from 1994 to 1997 [4]. Similar observations were reported from Greece. The authors calculated an increasing incidence of VIN from 1.8 to 2.8 per 100 000 women from 1986 to 1998 [5]. The worldwide increase in the incidence of lower genital tract intraepithelial neoplasia appears to be associated with HPV infection. Specific genital HPV types, in particular HPV 16, are strongly implicated in the causation of high-grade VIN. Multiple sexual partners, a history of genital warts, pre-invasive cervical cancer and smoking have been reported as risk factors for the development of VIN. In a follow-up (median 18 years) of more than 4400 women with cervical intraepithelial neoplasia (CIN) 3, who underwent cold-knife conization with clear margins at the University Hospital of Graz, Austria, 0.3% developed high grade VIN [6]. This demonstrates an increased risk for these patients when compared with the general population, the individual risk appears to be low. Women infected with human immunodeficiency virus (HIV) are approximately four times more likely to be
infected with HPV. The prevalence of VIN in HIV-infected women was reported to range from 0.5 to 37% [7]. The high rate of HIV infection among women with VIN supports the recommendation of HIV testing for women with VIN [8].

Invasive cancer and vulvar intraepithelial neoplasia

Jones and coworkers from New Zealand [9] were the first to demonstrate an increasing incidence of VIN-related invasive vulvar cancer in younger women. In an early cohort (1965–1974), only 2% of patients were younger than 50 years of age at the time of presentation, whereas in a later cohort (1990–1994), 21% were younger than 50 years of age \( (P = 0.001) \). Cigarette smoking and multiple lower genital tract neoplasia were both significantly more common in women younger than 50 years of age \( (P < 0.001) \). The authors concluded that over the observed decades, a subset of women younger than 50 years of age with squamous cell carcinoma (SCC) of the vulva associated with VIN has emerged [9]. This observation was confirmed by a retrospective study conducted at the University Hospital of Vienna, Austria. Joura et al. [4*] evaluated data of 366 women in two cohorts regarding changes in the incidence and age of VIN and vulvar SCC from 1985 to 1997. The total number with invasive vulvar cancer remained stable whereas the number of high-grade VIN (VIN 2+3) lesions tripled (Fig. 1). Analysing women aged 50 years or less, a dramatic increase in the number of cases of high grade VIN (fourfold) and of vulvar cancer (+157%) was observed. The proportion of invasive vulvar cancer in younger women increased from 5 to 16% \( (P < 0.01) \) during the observational period. Although a single peak (70–80a) was observed in the earlier cohort, a bimodal age distribution of invasive vulvar cancer has emerged with a minor peak of younger women (Fig. 2). This suggested an association with the distribution of VIN. According to the recent data of the Annual Report to the Nation published by the National Cancer Institute, vulvar cancer is one of 12 tumour entities with increasing incidence in the United States. Vulvar cancer now has an age-adjusted incidence of 1.7 per 100,000 in the United States. The incidence rates for cancer of the vulva increased 2.4% per year from 1992 to 1998. The increase occurred predominantly among women less than 65 years of age [10**].

The long-term risk of invasive cancer in women who have previously been treated for VIN is in the order of 2.5–7% [2,3,11]. The risk of untreated VIN appears to be much higher [3]. In association with vulvar cancer, high-grade VIN has been shown to be an independent prognostic factor for recurrence (relative risk 3.06) in a study of 101 patients and 33 recurrences [12]. Rouzier et al. [13*] reported 108 patients with invasive vulvar cancer, 23% of which were associated with undifferentiated VIN. In this cohort, VIN adjacent to the tumour was an independent predictor of survival [13*]. Allelic imbalance is frequently found in both VIN and invasive vulvar cancer [14]. A chromosome 17 aneusomy is frequently found in vulvar cancer tissue and associated normal skin and precursor lesions such as VIN or lichen sclerosus, but not in normal vulvar skin in non-cancer patients [15**]. In that study, the gain of chromosome 17 in lichen sclerosus-associated cancers and the loss of this chromosome in HPV-related vulvar cancers support the current concept of two different pathways of vulvar carcinogenesis at the chromosomal level, in addition to epidemiological and histological features. In a small study including 17 cases of VIN and 26 cases of vulvar cancer...
cancer [16*], vascular endothelial growth factor was found in 92% of the vulvar cancers and in 6% of VIN specimens but not in normal tissue. Angiogenesis may play a role in the transition from VIN to invasive cancer.

**Subsets of vulvar intraepithelial neoplasia**

VIN is apparently a heterogeneous condition, and the clinical features of different subsets have recently been described. Jones and Rowan [17*] reported 14 cases of women with spontaneous regression of high-grade VIN. The women were 15–27 years of age (median 19.5 years), 93% were non-white (Maori and Pacific Islanders). All women were seen initially in a sexual health clinic, and with one exception, all had been treated previously for genital condyloma acuminata. Four of the 14 cases were pregnancy associated. Half of the women were asymptomatic. The transit time to regression of VIN 2–3 was 3–30 months (median 9.5 months). All lesions were multiple and pigmented [17*].

Although warty and basaloid (undifferentiated VIN) is usually found in HPV-positive, young women, differentiated VIN is found in older women. Yang and Hart [18*] studied the clinicopathological features of 12 cases of differentiated VIN. All patients were of postmenopausal age (median 66 years). Three patients had a history of previous vulvar cancer and one had a synchronous invasive SCC of the vulva. Squamous hyperplasia was present in the adjacent epidermis in 10 patients, and lichen sclerosus was present in four patients. One patient had microinvasions (0.6 mm). Four patients subsequently developed invasive vulvar cancer. Ten out of 12 patients had positive p53 immunostaining with suprabasilar extension of p53-positive cells in each patient. In only one differentiated VIN, a p53-negative lesion, HPV was identified. All invasive cancers were of the conventional keratinizing type and were HPV negative [18*]. The results suggested that differentiated VIN has a strong association with HPV-negative vulvar SCC, and alteration of the p53 gene appears to be involved in the development of differentiated VIN.

**Diagnosis**

The standard of diagnostics remains visualization and the liberal use of biopsy. This should not be delayed by inadequate and hence ineffective topical treatments.

**Clinical diagnosis**

Lesions may be white, red, or brown in colour. White lesions are caused by hyperkeratosis. Red lesions result from increased vascularity, reflecting either an inflammatory response or increased blood vessel formation secondary to angiogenetic factors. In younger patients, high-grade VIN lesions are frequently multifocal and extensive. Colposcopy is now an accepted standard in the diagnostic assessment of pre-invasive vulvar disease. Diagnosis ultimately depends on the liberal use of directed biopsy. These are best taken with a Keyes biopsy instrument under local anaesthesia [19]. Toluidine blue or 5% acetic acid may be helpful in defining the site of biopsy [20]. In our own experience cytology has a low sensitivity and cannot replace biopsy, which is well tolerated by women. Therefore, we do not recommend it as a routine diagnostic tool for suspected VIN.

**Histology**

The current histological classification of VIN was introduced by the International Society for the Study of Vulvovaginal Disease in the late 1980s. The main histopathological features are disordered maturation and nuclear abnormalities. In VIN 1 the dysplasia is confined to the lowest third of the epithelium. In the VIN 2 lesion the dysplasia involves the lower two-thirds, and in VIN 3 the changes involve the full thickness of the epithelium. Preti et al. [21*] evaluated the inter-observer variability of the VIN diagnosis and grading system. Six consultant pathologists working at different European institutions independently reviewed 66 vulvar biopsies in a prospective design. Exact agreement between two pathologists reached 74% considering VIN 2 and 3 as a single class. Conversely, only 5% of VIN 1 diagnoses were concordant in paired analysis. The authors concluded that the current International Society for the Study of Vulvovaginal Disease terminology offers a reproducible tool in the hands of expert pathologists. Although there is good agreement on the diagnosis of high-grade VIN, the diagnostic category of vulvar intraepithelial neoplasia 1 is not reproducible [21*].

**Tumour markers and molecular markers**

The use of serum tumour markers may become a prognostic factor in invasive vulvar cancer. In VIN and the detection of occult invasion it does not play a role [22**,23]. Modesitt et al. [24] evaluated the association of Ki-67 expression and invasion in patients with VIN 3. A diffuse pattern of this nuclear marker was expressed in VIN 3, but failed to be a useful marker for occult cancer [24].

An analysis of the history of 102 women with vulvar carcinoma at a tertiary care unit provided evidence of diagnostic delays [25]. In young women, pruritus is often initially mistaken for candidiasis or minor genital warts. An adequate management appears to be a favourable prognostic factor. Against the background of the current epidemiology, a more active approach to the diagnosis (biopsy!) and management of precursor lesions may often prevent some cases of vulvar cancer in young patients [26,27]. Women should be encouraged to perform a vulvar self-examination on a monthly basis [28*], and physicians should be aware of precursing conditions and treat them adequately.
Treatment
The treatment modality of choice remains individualized surgery. Non-surgical concepts are under evaluation. Preliminary results may be promising but have to be confirmed by prospective studies.

Surgery
The treatment of VIN is aimed at the control of symptoms and prevention of progression to invasive cancer. Localized high-grade VIN lesions are best managed by local superficial excision, with a disease-free margin of at least 5 mm [19]. In young women with extensive disease, an ablative procedure using a carbon dioxide laser has to be considered. The main advantage of excision is the following histopathological investigation. Because biopsy may fail to demonstrate a focal invasion [11,29,30], laser treatment should be limited to experts for vulvar diseases. An early invasion of less than 1 mm (The International Federation of Gynecology and Obstetrics classification stage 1a) is adequately treated with wide local excision. Sideri et al. [29] reported 52 patients with VIN who were treated with laser vaporization or laser excision. Fourteen women underwent carbon dioxide laser vaporization; 11 were cured in one session (75%). Two patients who underwent more treatments eventually developed invasive SCC 5 and 7 years from the initial treatment. In 38 women, excision was performed by means of a laser. The cure rate for excision was 87%. In three cases, the pathology report on the excised specimen showed an unrecognized invasive lesion (12%), and two patients with multifocal disease experienced recurrences. Symptom relief was obtained in all patients studied with both laser vaporization and excision [29]. The study clearly demonstrates advantages and disadvantages of both the excision and destructive methods. In another series of 78 patients with biopsy confirmed VIN 3, 16 patients (20.5%) were found to have invasion, nine of them of more than 1 mm (11.5%) [30]! Infection with HIV substantially increased the risk of recurrence after treatment [8]. Ideally, the individualized treatment of VIN should be performed at multidisciplinary specialist centres.

Topical treatments
In addition to adequate treatment, the preservation of anatomical integrity and sexual function is essential. Topical treatments are under evaluation, but have not yet become clinical standard. The concept of an antiviral non-surgical treatment in young women with HPV-related disease is appealing, but only case reports exist so far. Imiquimod, an immune response modifier, has been shown to be safe and effective for the treatment of external and perianal genital warts caused by HPV. Imiquimod 5% cream was applied to four women with VIN 3 three times per week until all lesions cleared. Post-treatment biopsies showed no evidence of persis-
References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

** of special interest
*** of outstanding interest


An excellent follow-up of a large cohort of women with HPV-related disease.


An important review of Surveillance, Epidemiology and End Results data with focus on epidemiological trends in different tumour entities.


This paper focuses on the importance of epithelial changes in association with vulvar cancer.


An important paper for the understanding of the different pathways of vulvar carcinogenesis at the chromosomal level.


This paper has interesting findings regarding the possible association between angiogenesis and invasion.


An important contribution to the understanding of VIN as a heterogeneous condition.


This paper is an interesting analysis of a common subset of VIN.


This paper questions the reproducibility of the diagnosis of VIN I and confirms the utility of the present classification for high-grade VIN.


A useful review of different markers and their clinical value. Comprehensive information is given on the topic.


Very useful information for women.


The first observation of imiquimod treatment in VIN patients.


The first observation of topical cidofovir treatment in VIN patients.


An interesting study on the use of PDT. Discussion demonstrates advantages and limitations.


An interesting new therapeutic approach with the limitation of unclear effect on vulvar disease.