Vulvar and Vaginal Cancer, Vulvar Intraepithelial Neoplasia 3 and Vaginal Intraepithelial Neoplasia 3: Experience of a Referral Institute

Efraim Siegler MD[1], Yakir Segev MD[1], Lena Mackuli MD[1], Ron Auslender MD[1], Mayan Shiner PhD[2] and Ofer Lavie MD[1]

[1]Department of Obstetrics and Gynecology and [2]Serology Laboratory, Carmel Medical Center, affiliated with Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

ABSTRACT: **Background:** Vulvar and vaginal malignant and premalignant lesions are uncommon and are clinically heterogeneous diseases with two pathways of carcinogenesis: human papillomavirus (HPV) induced or non-HPV induced.

Objectives: To evaluate the demographic and clinical characteristics associated with vulvar or vaginal cancer and vulvar and vaginal intraepithelial neoplasia 3 (VIN3, VAIN3).

Methods: We conducted a retrospective chart review of 148 women with vulvar and vaginal malignancy and pre-malignancy for the period October 2004 to October 2012, and identified 59 and 19 patients with vulvar and vaginal cancer respectively, and 57 and 13 patients with VIN3 and VAIN3 respectively

Results: The median age of vulvar cancer patients was 30 years older than that of VIN3 patients. HPV was found in 60% and 66.6% of vulvar and vaginal cancer patients respectively, and in 82.3% and 84.6% of patients with VIN3 and VAIN3 respectively. A history of cervical intraepithelial neoplasia (CIN) or warts was observed in 10% and 10.5% of vulvar and vaginal cancer patients respectively, and in 57.9% and 46% of patients with VIN3 and VAIN3 respectively. In 52.6% of patients the vaginal cancer was metastases from other organs.

Conclusions: Most women with vulvar carcinoma are older than 70 years. VIN3 and VAIN3 are associated with HPV infection and the most prevalent type is HPV16. Almost half the vaginal cancers are associated with metastases from other organs and almost half of VAIN3 is associated with past cervical dysplasia or carcinoma.

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Vulvar cancer and vaginal cancer are rare gynecological malignancies, representing 3%–4% and 1% respectively of female genital cancer. In the United States the incidence of vulvar intraepithelial neoplasia (VIN) is 2.8–3.7 per 100,000 women and of vaginal intraepithelial neoplasia (VAIN) 0.2–0.4/100,000 [1]. In the U.S. during the period 1973–2004, the incidence of VIN3 tumors increased by an average of 3.5% per year (reaching a total increase of 108.5% in 21 years) compared to 1.0% per year (31%) for invasive tumors [2]. There is a strong association between human papillomavirus (HPV) and VIN3, but the correlation between HPV infection and vulvar carcinoma is weaker [3,4].

In Israel, during the period 1998–2002, the age-standardized incidence of vulvar carcinoma and vaginal carcinoma was 1.0 and 0.3 per 100,000 women respectively. Jewish women had a higher rate than non-Jewish women: 1.1 versus 0.2 for vulvar cancer and 0.3 vs. 0.2 for vaginal cancer per 100,000 women [5].

Menczer et al. [6] showed that in Israel the relative frequency (percentage) of VIN3 (carcinoma in situ) among all vulvar lesions increased from 5.4% during the period 1961–1973 to 12.8% in 1985–1994, while the relative frequency of vulvar carcinoma among all vulvar malignant and pre-malignant lesions decreased from 80.6% in 1961–1973 to 69.6% in 1985–1994. In another Israeli study HPV was detected in 64% of 14 patients with vulvar carcinoma [7]. Worldwide immunization with the quadrivalent vaccine against HPV6, 11, 16 and 18 has been shown to reduce the risk of VIN3 by 46% [8].

The aim of the present study was to evaluate the demographic and clinical characteristics associated with vulvar and vaginal cancer and VIN3 and VAIN3 in a referral medical center in northern Israel. We also examined the HPV types in some of the patients.

PATIENTS AND METHODS

We conducted a retrospective chart review of 148 women with vulvar and vaginal cancer, VIN3 and VAIN3, attending our Lower Genital Tract Clinic between October 2004 and Oct 2012. The study group included all patients (Jews and non-Jews) diagnosed with malignant and premalignant lesion of the vulva and the vagina. Study parameters included age, clinical presentation, and presence of previous or coex-

isting genital disease, other malignant or premalignant gynecological disease, or other malignancies. Past medical history, risk factors and pathological type of the lesion were recorded.

All patients underwent vaginoscopy, vulvoscopy and colposcopy (in woman with intact cervix). Histological biopsy was performed in all cases and HPV typing was performed in 46 of the 148 women (31.1%). DNA was extracted from cervical swabs using an automated extractor. HPV genotype was determined by nested polymerase chain reaction [9,10], and nucleotide sequencing was performed by Hylabs (Rehovot, Israel). Samples of undetermined genotype were analyzed by a reverse hybridization line probe assay (INNO-LiPA HPV Genotyping Extra, Innogenetics NV, Belgium). The assay enabled detection of 40 HPV types. The treatments undertaken were recorded. The study protocol was approved by the Ethical Review Committee of Carmel Medical Center (protocol # CMC 88-0069).

RESULTS

We identified 148 patients in our database. Table 1 presents their demographic characteristics. Fifty-nine women were diagnosed with vulvar carcinoma, 19 with vaginal carcinoma, and 57 and 13 patients with VIN3 and VAIN3 respectively. The median age was 72.4 years (range 26–99 years) for vulvar cancer patients and 63 years (range 36–84) for vaginal cancer patients. The median age for women diagnosed with VIN3 was 43 years (range 21–84) and 60 years (range 32–85) for women with VAIN3. Women with vulvar cancer were older: 72.9% were over 70 and only 6.7% were less than 50 years old. Of VIN3 patients, 57% were < 50 years old and only 16% were > 70 years old. Thirty-six percent of women with vaginal cancer (7/19) and 38.4% of women with VAIN3 (5/13) were over 70 years old.

Non-Jews (Moslems and Christians) comprised 13.5% (8/59) and 15.8% (9/57) of the vulvar cancer and VIN3 patients, respectively.

Past history included lichen sclerosis in 17% of women with vulvar malignancy (6/59) and 3.5% of women with VIN3 (2/57). Past history of genital warts, cervical intraepithelial neoplasia (CIN) or cervical malignancy was recorded in 10% of vulvar cancer women (10/59), in 57.9% of VIN3 women (33/57), in 47.3% of vaginal cancer patients (9/19), and in 46% of women diagnosed with VAIN3 (6/13).

A history of other malignancies (breast, colon, thyroid) was recorded in 32% of women (19/59) with vulvar cancer, 25% (5/19) of vaginal cancer patients, and 10.5% (6/57) and 38% (5/13) of women with VIN3 and VAIN3 respectively.

In 52.6% (10/19), the vaginal tumor represented metastases from other organs. The primary malignancy was endometrial cancer in four cases, ovarian cancer in two, and one case each of vulvar cancer, bladder cancer, kidney tumor and colon cancer [Table 2]. The most common pathological diagnosis was squamous cell carcinoma in 59.3% (35/59) and 31.5% (6/19) of women with vulvar and vaginal cancer respectively. Other pathologies of vulvar malignancy included Paget's disease in 13.5% (8/59), basal cell carcinoma in 11.9% (7/59), and verrucous carcinoma in 8.5% (5/19). In vaginal cancer, adenocarcinoma was found in 31.6% of the patients (6/19), and clear cell carcinoma and verrucous carcinoma in one woman each.

HPV typing was performed in 46 women (31.1%); HPV16 was the most common type, found in 47.2% of the positive patients. Other types were HPV18, 31, 33, 35, 54, 59, 67, 82,and multiple types, and in two women HPV was positive but the type could not be defined [Table 3].

The primary treatments performed in women with vulvar carcinoma were radical vulvectomy in 42% (25/59), wide local excision in 39% (23/59), and biopsy-only in 19% (11/59). Of the 19 women with vaginal cancer, 8 (42.1%) were referred to chemotherapy/radiotherapy, 4 (21%) underwent surgery and chemotherapy, and 3 (15.8%) underwent radical hysterectomy and upper vaginectomy. The remaining 4 women (21%) were followed with no specific treatment due to their poor medical condition.

Of the 57 patients diagnosed with VIN3, 61% (35/57) were treated with laser vaporization, 24% (14/57) had wide local excision, 7% (4/57) were treated with imiquimod and 7% (4/57) with interferon injections. For the 13 women diagnosed with VAIN3, vaginectomy was performed in 5 (38.5%),

Table 1. Demographic characteristics of patients with vulvar carcinoma, vaginal carcinoma, VIN3 and VAIN3

	Vulvar cancer	Vaginal cancer	VIN3	VAIN3
Total = 148	**n=59**	**n=19**	**n=57**	**n=13**
Median age	72.4	63	43	60
Age < 50 years	6.7% (4/59)	10.5% (2/19)	57.9% (33/57)	23% (3/13)
Age 50–70 years	20.3 (12/59)	52.6% (10/19)	26.3 (15/57)	38.5% (5/13)
Age > 70 years	72.9% (43/59)	36.8% (7/19)	15.8% (9/57)	38.5% (5/13)
Non-Jews (Moslems, Christians)	13.5% (8/59)	10.5% (2/19)	15.8% (9/57)	7.7% (1/13)

Table 2. Medical characteristics and past history of patients with vulvar carcinoma, VIN3, vaginal carcinoma and VAIN3

	Vulvar cancer	Vaginal cancer	VIN 3	VAIN 3
Total = 148	**n=59**	**n=19**	**n=57**	**n=13**
History of lichen sclerosis	17% (10/59)		3.5% (2/57)	
History of CIN, warts, cervical malignancy	10% (6/59)	47.3% (9/19)	57.9% (33/57)	46% (6/13)
Past history of other malignancies (non-genital organs)	32% (19/59)	25% (5/19)	10.5% (6/57)	10.5% (6/57)
Metastases	–	52.6% (10/19)		

Table 3. HPV types in vulvar and vaginal malignancy and neoplasia

HPV types	Total HPV	Vulvar cancer	Vaginal cancer	VIN3	VAIN3
HPV 16	17 (47.2%)	4	1	9	3
HPV 18	1 (2.8%)			1	
HPV 31	1 (2.8%)				1
HPV 33	1 (2.8%)		1		
HPV 35	2 (5.7%)				2
HPV 54	3 (8.5%)	1			2
HPV 59	1 (2.8%)				1
HPV 67	2 (5.7%)			1	1
HPV 82	2 (5.7%)	1	1		
HPV positive	2 (5.7%)		1	1	
Multiple types	4 (11.4%)			2	2
Total HPV-positive	36	60% (6/10)	66.6% (4/6)	82.3% (14/17)	92.3% (12/13)
HPV-negative	10	40% (4/10)	33.3% (2/6)	17.6% (3/17)	7.7% (1/13)
Total	46	10	6	17	13

laser ablation in 5 (38.5%), and combined treatment of laser + vaginectomy in 3 (23%).

DISCUSSION

The etiology of vulvar cancer in young women is different to that in older patients. In young women the cause is mainly HPV infection and the cancer typically develops slowly over time after the appearance of VIN3. This is similar to cervical cancer following CIN 2-3 lesion of the cervix. In older women, the cause is chronic vulvar lesions presenting with pruritus and irritation, i.e., untreated lichen sclerosis or other dermatoses [11,12].

Vulvar cancer has been considered a malignancy of advanced age but is becoming more common in younger women subsequent to the increasing prevalence of HPV infection and other risk factors of cervical and vulvar cancer, namely tobacco use and multiple sex partners [13]. HPV types were found in 93% of VAIN3 (n=13) and in 85.3% of VIN3 women (n=4). In vaginal cancer patients HPV types were found in only 66% of the women (n=13) and in vulvar malignancy HPV was positive in 68.8% (n=3). One-third of the patients with vaginal cancer had a history of cervical dysplasia or carcinoma [14]. The frequency of VIN3 has increased around the world [15], including Israel. The relative frequency of VIN3 and all vulvar malignant and premalignant lesions in Israel increased from 5.4% in 1961–1973 to 12.8% in 1985–1994 [6]. The greater increase in incidence was observed in the younger population. The mean age of our population with VIN3 was 43 years, which is younger than the 53.9 mean age reported by McNally et al. [15].

VAIN3 is considered a precursor of vaginal carcinoma. The mean age of women with VAIN3 in our study was 60 years, and of vaginal cancer patients 63. The mean age of women with VAIN3 was 54.3 in the study by Rhodes and team [16], while the mean age of vaginal cancer patients reported by Gunderson et al. [17] was 60. That short period of time between VAIN3 and vaginal carcinoma should raise the question regarding a different natural history and different path of pathological progression from VAIN3 to vaginal carcinoma than the progression path from CIN 3 to cervical carcinoma, or from VIN3 to vulvar carcinoma.

Metastatic carcinoma is the most common vaginal tumor [18], which concurs with our findings showing that 52.6% of the vaginal malignancies in our cohort were metastases from the endometrium, ovary, vulva, bladder, kidney or colon. According to a Finnish study [19], women with CIN have a significantly excessive risk of vulvar and vaginal cancer. Standardized incidence ratios for cancers of the vagina were as high as 9.08, and of vulva cancer 6.15 [19]. The percentage of previous CIN lesions and genital warts in our patients was 57%, higher than the 39% of coexistent or previous genital disease described by McNally et al. [15].

Although we examined HPV types in only 31.1% of our patients (46/148), the percentage of HPV positivity was similar to numbers published in the literature. HPV was found in 60% and 66.6% of our patients with vulvar cancer and vaginal cancer, respectively, compared to 40.4% and 69.9% in a previous meta-analysis [4].

In our study, HPV types were found in 82.3% and 84% of women with VIN3 and VAIN3, respectively, similar to the findings – 85.3% and 90% – described by De Vuyst et al. [4]. HPV16 was found to be the most common type in our study, detected in 47.2% of the HPV-positive women. In women diagnosed with vaginal cancer in our study, a past history of warts, cervical dysplasia, or cervical carcinoma was recorded in 47.3% (9/19), which was higher than the 22% described by Gunderson et al. [17].

In view of a report that vulvar and vaginal cancer are rare among non-Jews [5], we recorded the percentage of non-Jewish patients (Moslem and Christian) in our study. In our district non-Jews (Moslems and Christians) constitute 15%–20% of the population; among the women with vulvar carcinoma and VIN3, 13.5% and 15.8%, respectively, were non-Jews. In vulvar neoplasia the numbers of non-Jews were proportional to their percentage in the population.

The primary treatment of vulvar malignancy has been surgery, while for vaginal carcinoma less than half the patients (42.1%) were treated with chemotherapy and radiotherapy. The reason for this was that some patients presented a metastatic tumor and some had a poor general medical condition that rendered them unfit for surgery.

Our study is limited due to both its retrospective nature and

incomplete data for several parameters (HPV was measured in only a minority of the women, and data on smoking history and sexual history were frequently missing). However, our data do show that vulvar and vaginal malignant and premalignant diseases in our medical center were similar to the epidemiologic findings of studies from around the world.

Since almost half the women with vaginal cancer, VAIN3 and VIN3 had a history of warts or cervical carcinoma or CIN 3, it is imperative to follow those women meticulously and to explain to them as well as to the medical community the importance of frequent observation and examination even years after the original diagnosis of their cervical malignant or premalignant lesion. The effect of the vaccine against HPV on the incidence of vulvar and vaginal neoplasia will have to be evaluated in the future.

Vulvar and vaginal malignancy and neoplasia are rare pathologies in women's health, and larger prospective studies are needed to better understand their etiology and natural history, as well as prevention and optimal treatment of those diseases.

Correspondence
Dr. E. Siegler
Dept. of Obstetrics and Gynecology, Carmel Medical Center, Haifa 34362, Israel
Phone: (972-4) 826-0001
Fax: (972-4) 826-0001
email: siegler@netvision.net.il

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