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Review

Genetic and epigenetic changes in vulvar squamous cell carcinoma and its precursor lesions: A review of the current literature

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HIGHLIGHTS

- Vulvar cancer has two etiological pathways: an HPV-dependent pathway and an HPV-independent pathway
- This review describes the current literature on genetic and epigenetic changes in vulvar cancer and its precursor lesions
- Somatic mutations, especially *TP53* mutations, occur more often with increasing grades of dysplasia and in HPV-negative tumors

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ABSTRACT

Vulvar cancer is a relatively rare gynecologic malignancy with an annual incidence in developed countries of approximately 2 per 100,000 women. Vulvar squamous cell carcinoma (VSCC) has two etiological pathways: a high risk human papillomavirus (HPV)-dependent route, which has usual vulvar intraepithelial neoplasia (uVIN) as a precursor lesion, and an HPV-independent route, which is associated with differentiated VIN (dVIN), lichen sclerosus, and genetic alterations, such as *TP53* mutations. Research on the molecular etiology of vulvar cancer has increased in the past years, not only regarding genetic alterations, but also epigenetic changes. In genetic alterations, a mutation irreversibly changes the nucleotide sequence of the DNA, or the number of copies of chromosomes per cell is altered. In epigenetics, the nucleotide sequence remains the same but genes can be 'switched' on or off by, for example, DNA methylation or histone modification. We searched the current literature on genetic and epigenetic alterations in VSCC and its precursor lesions. Many studies have reported a higher incidence of somatic mutations in HPV-negative tumors compared to HPV-positive tumors, with *TP53* mutations being the most frequent. Allelic imbalances or loss of heterozygosity are more frequently found in higher stages of dysplasia and in invasive carcinomas, but it is not exclusive to HPV-negative tumors. A limited number of studies are available on epigenetic changes in vulvar lesions, with hypermethylation of *CDKN2A* being the most frequently investigated change. For most genes, hypermethylation occurs more frequently in vulvar squamous cell carcinomas than in precursor lesions. As most studies have focused on HPV infection and *TP53* mutations, we suggest that more research should be performed using whole genome or next generation sequencing to determine the true landscape of genetic and epigenetic alterations in vulvar squamous cell carcinoma.

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Table 1
Studies on mutations in vulvar cancer and its precursors.

Author	Year	No. of patients	Diagnosis	HPV-status	Gene	Mutation %	Technique used	Remarks
Pilotti	1993	5	verrucous VC	−	*TP53*	0%	SSCP exon 5–9 + confirmation sequencing	
Kurvinen	1994	1	CIS	+	*TP53*	0%	SSCP exon 5–9 + confirmation sequencing	
		1	VIN	+	*TP53*	0%		
		2	VSCC	−	*TP53*	0%		
		7	VSCC	+	*TP53*	0%		
Lee	1994	9	VSCC	−	*TP53*	44%	SSCP exon 5–8 and part of exon 4	
		12	VSCC	+	*TP53*	8%		
Milde-Langosch	1995	12	VIN	50%*	*TP53*	33%	PCR-TGGE	* not described in association to mutations
Pilotti	1995	7	VIN*	+	*TP53*	0%	SSCP exon 5–9	*some adjacent to reported VSCC
		12	VSCC	−	*TP53*	33%		
		4	VSCC	+	*TP53*	50%		
Kim	1996	11	VSCC	−	*TP53*	36% (25% keratinising, 100% Pagets)	SSCP exon 5–8	* 11 (8 keratinising, 1 basaloid, 2 Pagets) 7 (3 keratinising, 2 basaloid, 1 Pagets, 1 warty)
		7	VSCC	+	*TP53*	0%		
Sliutz	1997	38	VSCC	not tested	*TP53*	32%	PCR-TGGE	
Wong	1997	6	VSCC	not tested	*CDKN2A* and *CDKN2B*	0%	SSCP *CDKN2A* exon 1–3 and *CDKN2B* exon 1–2	
Flowers	1999	10*	VIN	−	*TP53*	10%		* multiple samples from same patient
		11*	VIN	+	*TP53*	9%		
		15	VSCC	−	*TP53*	29% KSC, 0% basaloid		
		15	VSCC	+	*TP53*	33% KSC, 8% basaloid		
Ngan	1999	25	VSCC	−	*TP53*	20%	SSCP exon 5–8 + confirmation sequencing	
		23	VSCC	+	*TP53*	22%		
Brooks	2000	23	VSCC	−	*TP53*	74%	SSCP exon 4–9	codon 72P/R same cohort as Marin 2000 and O'Nion 2001
		13	VSCC	+	*TP53*	31%		
Holway	2000	2*	VIN	not tested	*PTEN*	100%	SSCP exon 5–8	* same patients as VSCC
		10	VSCC	not tested	*PTEN*	60%		1 patient had PTEN mutation in VIN but not in adjacent VSCC. In 3 patients different mutations were found in VIN and VSCC
Marin	2000	36	VSCC	not tested	*TP53*	58%	SSCP exon 4–9 + confirmation sequencing	
		10	LS	−	*TP53*	70%		
		29 (3 basaloid, 26 squamous)	VC	−	*TP53*	55%		
		11 (3 basaloid, 8 squamous)	VC	+	*TP53*	45%		
Wada	2000	1	VIN	+	*TP53* + *KRAS*	0% *TP53*, 0% *KRAS*	SSCP *TP53* exon 5–8, KRAS exon 1	
O'Nions	2001	23	VSCC	−	*TP53* + *CDKN2A*	74% *TP53*, 13% *CDKN2A*	SSCP CDKN2A exon 1α +2, TP53 exon 7–9	
		13	VSCC	+	*TP53* + *CDKN2A*	31% *TP53*, 0% *CDKN2A*		
Gasco	2002	23	VSCC	−	*CDKN2A* + *Stratifin* + *TP53*	13% *CDKN2A*, 0% *Stratifin*, 73.9 % *TP53*		
		20	VIN	−	*CDKN2A* + *Stratifin* + *TP53*	0% *CDKN2A*, 0% *Stratifin*, 0% *TP53*		*CDKN2A* and *stratifin* were tested on 11 patients