Trends in the Incidence of Invasive and In Situ Vulvar Carcinoma

Patricia L. Judson, MD, Elizabeth B. Habermann, Nancy N. Baxter, MD, PhD, Sara B. Durham, MS, and Beth A. Virnig, PhD, MPH

OBJECTIVE: To characterize the incidence of vulvar carcinoma in situ and vulvar cancer over time.

METHODS: We used the Surveillance Epidemiology and End Results database to assess trends in the incidence of vulvar cancer over a 28-year period (1973 through 2000) and determined whether there had been a change in incidence over time. Information collected included patient characteristics, primary tumor site, tumor grade, and follow-up for vital status. We calculated the incidence rates by decade of age, used χ^2 tests to compare demographic characteristics, and tested for trends in incidence over time.

RESULTS: A total of 13,176 in situ and invasive vulvar carcinomas were identified; 57% of the women were diagnosed with in situ, 44% with invasive disease. Vulvar carcinoma in situ increased 411% from 1973 to 2000. Invasive vulvar cancer increased 20% during the same period. The incidence rates for in situ and invasive vulvar carcinomas are distributed differently across the age groups. In situ carcinoma incidence increases until the age of 40–49 years and then decreases, whereas invasive vulvar cancer risk increases as a woman ages, increasing more quickly after 50 years of age.

CONCLUSION: The incidence of in situ vulvar carcinoma is increasing. The incidence of invasive vulvar cancer is also increasing but at a much lower rate.

(Obstet Gynecol 2006;107:1018–22)

LEVEL OF EVIDENCE: III

From the Department of Obstetrics, Gynecology & Women's Health, Division of Gynecologic Oncology, Division of Health Services Research and Policy, Department of Surgery, Division of Colorectal Surgery, and University of Minnesota Cancer Center, University of Minnesota, Minneapolis, Minnesota.

Funded by the University of Minnesota Comprehensive Cancer Center.

Presented at the 37th Annual Meeting of the Society of Gynecologic Oncologists, Palm Springs, California, March 22–26, 2006.

Corresponding author: Patricia L. Judson, MD, Division of Gynecologic Oncology, Department of Obstetrics, Gynecology, and Women's Health, University of Minnesota, 420 Delaware Street SE, MMC 395, Minneapolis, MN 55455; e-mail: judso003@umn.edu.

ISSN: 0029-7844/06

Recently, a report in the Journal of the National Cancer Institute identified vulvar cancer as 1 of the 12 cancers rising in incidence between 1992 and 1998.[1] Combined invasive and in situ vulvar carcinoma rates increased 2.4% per year, with the increase particularly pronounced in younger women.[1] The National Cancer Institute report did not clarify whether the recent increase was due to changes in invasive, in situ, or the combination of invasive and in situ disease.

Vulvar cancer makes up 3% to 5% of all female genital cancers. The definition of vulvar cancer frequently includes both vulvar cancer and carcinoma in situ, also called vulvar intraepithelial neoplasia III. Sturgeon et al[2] identified an increasing incidence of vulvar carcinoma in situ more than a decade ago and postulated that this would result in an increase in invasive vulvar cancer.

The association between in situ vulvar carcinoma and the human papillomavirus (HPV) is established,[3,4] with HPV DNA identified in 72% of vulvar intraepithelial neoplasia lesions.[3] In contrast, HPV infection and invasive vulvar cancer appear to be less strongly correlated. Studies show HPV associated with vulvar cancer in 14–60% of cases, with most studies showing approximately 40%.[3–9] The different association between HPV infection in invasive and in situ disease is in marked contrast to squamous cell carcinoma of the cervix, where the prevalence of HPV is close to 100% for invasive disease. Although it has been shown that HPV-related cervical dysplasia can progress to cervical cancer,[10,11] the progression of vulvar carcinoma in situ to vulvar cancer has been suggested but not confirmed.[12–17]

Human papillomavirus is one of the most common sexually transmitted infections in the United States.[18] It is estimated that more than 50% of sexually active people will acquire genital HPV and that 80% of women will have acquired genital HPV by age 50 years.[19–21] Given this trend, we would expect to see a

rise in both in situ and invasive vulvar carcinoma if, in fact, both are causally related to HPV infection.

We undertook this analysis to characterize trends in the incidence of vulvar carcinoma in situ and vulvar cancer with the intent of identifying possible mechanisms underlying the trends.

MATERIALS AND METHODS

Data were obtained from the Surveillance, Epidemiology, and End Results (SEER) cancer registry database, which collects information on cancer incidence and survival from 11 population-based cancer registries; these 11 registries include about 14% of the U.S. population.[22] Seven of these registries contain records of all cancers diagnosed between 1973 and 2000: Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, and Utah. The Seattle-Puget Sound data contain the years of 1974–2000, and the Atlanta data date to 1975. Two registries, Los Angeles and San Jose-Monterey, contain cancer cases diagnosed between 1992 and 2000. The information collected by SEER includes patient characteristics, county of residence, primary tumor site, tumor grade, and follow-up for vital status.

Our population consists of 13,176 patients with vulvar carcinomas, in situ and invasive. Women were excluded if they were diagnosed with any other cancer before developing vulvar cancer. We divided the cohort into 2 age cohorts of women aged 0–49 years and women older than 50 years of age at diagnosis, roughly representing premenopausal and postmenopausal age groups. The older than 50 years cohort contained 7,579 (57.2%) women; the remaining 5,597 (42.5%) were younger than 50 years old.

We compiled a comparison cohort of women diagnosed with squamous cell cervical carcinoma. Cervical carcinoma was chosen as the comparison group, given its similarity to vulvar carcinoma in being HPV-related. Of the 110,806 women included, 81,892 (74%) were diagnosed with in situ disease, and 28,914 (26%) with invasive cancer. All in situ cases are from years before 1996, when SEER ceased reporting in situ cervical carcinoma.[22]

Incidence rates (per 100,000 female population) per year were calculated using standard SEER methodology and the SEER*Stat (National Cancer Institute, http://www.seer.cancer.gov/publicdata/access.html) and SAS (SAS Institute Inc., Cary, NC) software for vulvar carcinoma from 1973 through 2000. We evaluated rates of in situ and invasive vulvar carcinomas by age to evaluate differences in incidence over the life-span and for 3 periods: 1973–1981, 1982–1991, and 1992–2000. We used χ^2 tests to compare demographic characteristics of incident cancer cases between women aged 0–49 years and women aged 50 years and older. We determined whether rates changed over time using the Cochran-Armitage trend test with 1 degree of freedom for each stage.[23]

The study used de-identified public-use data obtained from the SEER program and are considered human subjects–exempt. Institutional review board approval was not applied for at the University of Minnesota. However, the institutional review board agreed that the activities described are exempt from review under Federal Guidelines 45CF part 46.101 (b) category #4.

RESULTS

Demographic characteristics of the patients are shown in Table 1. Two-thirds (8,786) of the women had squamous cell histology. Fifty-seven percent of the women were diagnosed with in situ disease, with the remaining diagnosed with invasive disease.

The incidence rates for in situ and invasive vulvar carcinomas are distributed differently across the age groups (Fig. 1 and 2). Similar to the pattern seen in our comparison cohort of women diagnosed with in situ cervical carcinomas (Fig. 1), in situ vulvar carcinoma incidence has a peak and then declines. This peak, however, is approximately 20 years later than the in situ cervical peak.

There is less similarity between patterns of invasive vulvar and cervical cancers than was seen for in situ disease (Fig. 2). Whereas invasive cervical cancer

Table 1. Demographic Characteristics of Vulvar Carcinoma Patients by Age

	< 50 y	≥ 50 y	Overall
Cases	5,597 (42.48)	7,579 (57.52)	13,176
Histology			
Squamous	3,711 (66.30)	5,075 (66.96)	8,786 (66.68)
Other	1,886 (33.70)	2,504 (33.04)	4,390 (33.32)
P	.428		
Stage			
In situ	4,597 (82.13)	2,863 (38.38)	7,460 (56.6)
Invasive total	1,000 (17.87)	4,716 (62.22)	5,716 (43.38)
Local	715 (12.77)	2,803 (36.98)	3,518 (26.70)
Regional	175 (3.13)	1,177 (15.53)	1,352 (10.26)
Distant	21 (0.38)	207 (2.73)	228 (1.73)
Unstaged	89 (1.59)	529 (6.98)	618 (4.69)
P	< .001		
Race			
White	4,458 (79.65)	6,742 (88.96)	11,200 (85.00)
African American	582 (10.40)	443 (5.85)	1,025 (7.78)
Other	178 (3.18)	227 (3.00)	405 (3.07)
Unknown	379 (6.77)	167 (2.20)	546 (4.14)
P	< .001		

Values are n (%).

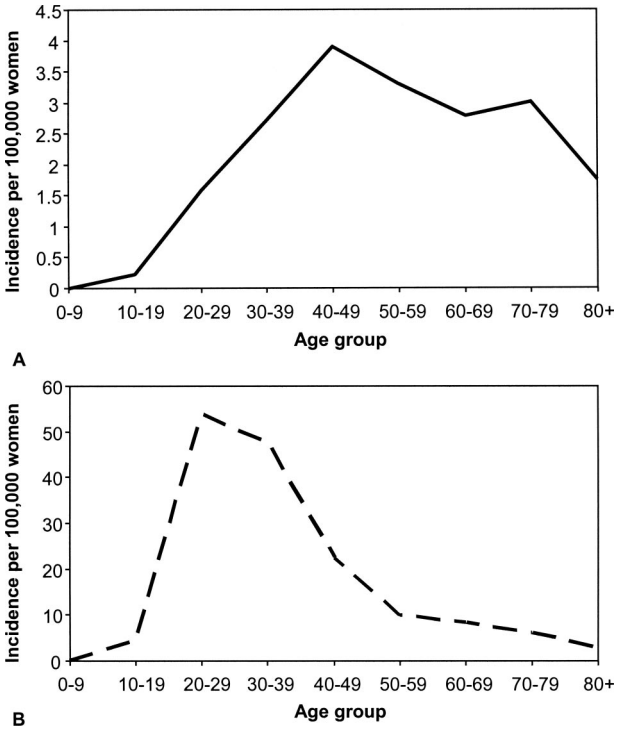

Fig. 1. Incidence of in situ vulvar and cervical carcinomas by age, 1973–2000. **A.** In situ vulvar carcinoma incidence increases until age 40–49 years, and then decreases. **B.** In situ cervical carcinoma incidence increases until age 20–29 years, and then decreases.

Judson. Incidence of Vulvar Carcinoma. Obstet Gynecol 2006.

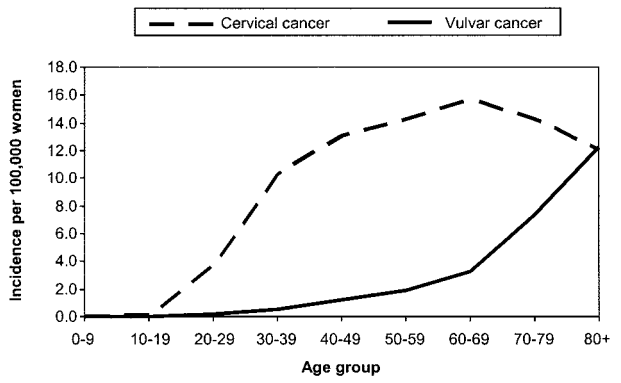

Fig. 2. Incidence of invasive vulvar and cervical cancers by age, 1973–2000. Invasive vulvar cancer risk increases as a woman ages. Invasive cervical cancer peaks at age 60 years and then decreases.

Judson. Incidence of Vulvar Carcinoma. Obstet Gynecol 2006.

peaks at age 60–69 years and then decreases, invasive vulvar cancer begins to increase more quickly after 50 years of age and never stabilizes. These patterns are consistent across all stages of invasive vulvar and cervical cancers. Age-specific patterns of vulvar cancer incidence were similar for squamous and nonsquamous histology (data not shown).

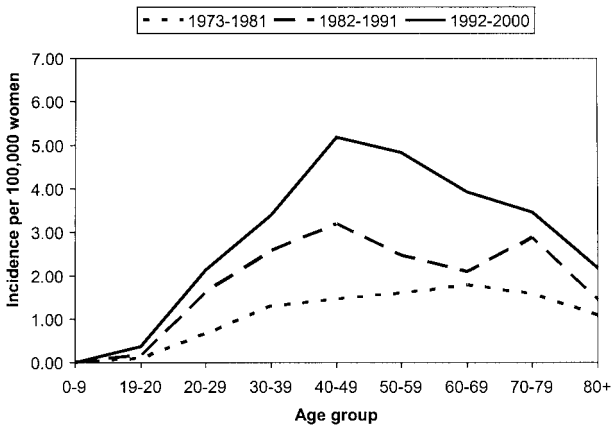

Fig. 3. Incidence of in situ vulvar carcinoma by age and diagnosis year. The incidence of in situ vulvar carcinoma increased by 411% from 1973 to 2000.

Judson. Incidence of Vulvar Carcinoma. Obstet Gynecol 2006.

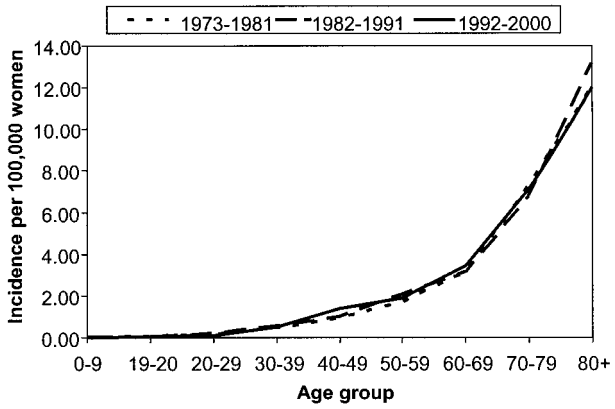

Fig. 4. Incidence of invasive vulvar cancer by age and diagnosis year. The incidence of invasive vulvar cancer increased 20% from 1973 to 2000.

Judson. Incidence of Vulvar Carcinoma. Obstet Gynecol 2006.

The incidence of in situ vulvar carcinoma and invasive carcinoma increased over the period 1973–2000 (Table 2, Fig. 3 and 4). The incidence of in situ disease increased 411%, from 0.56 cases per 100,000 women in 1973 to 2.86 per 100,000 women ($P < .001$) in 2000 (Table 2). In contrast, invasive vulvar cancer experienced only a modest 20% increase from 1973 to 2000, with little apparent change in age-specific rates. In 1973, there were 1.8 cases per 100,000, and in 2000 the rate increased minimally to 2.2 cases per 100,000 women ($P < .001$).

DISCUSSION

The increasing incidence of vulvar carcinoma in situ in America correlates with reported increases in HPV

Table 2. Incidence of Vulvar Carcinoma by Year

Rate per 100,000 Women	1973	1983	1993	2000	*P**
In situ	0.56	1.41	2.54	2.86	< .001
Invasive	1.31	1.30	1.46	1.57	< .001
Local	0.67	0.76	0.98	1.00	< .001
Regional	0.28	0.36	0.28	0.48	.012
Distant	0.04	0.06	0.05	0.03	.311
Unstaged	0.32	0.12	0.15	0.06	< .001

* Cochran-Armitage trend test.

infection and has similarly been observed in a population-based study of Norway.[24] The increase of in situ vulvar carcinoma has occurred predominantly in women younger than 65 years, with a peak incidence observed in the 40–49-year-old age group and steadily decreases thereafter. This age distribution is similar to that seen in cervical carcinoma in situ (Fig. 1). The increase of in situ vulvar carcinoma, in the SEER database, may be secondary to an increased incidence of screening, detection and reporting both by the patient and the physician.

Despite the increase of in situ vulvar carcinoma, we have observed relatively little change in the incidence of invasive vulvar cancer, particularly in women younger than 50 years. If HPV-induced in situ vulvar carcinoma progressed reliably to vulvar cancer, as in cervical cancer, we would expect to see a peak in the incidence of vulvar cancer approximately 5 to 20 years after the peak of in situ disease, as seen in cervical cancer. We also would expect to see a leveling of the incidence of invasive vulvar cancer with age as is seen with invasive cervical cancer. Instead, there is a steady increase in incidence of invasive vulvar cancer with age. The differential age distributions between invasive vulvar and cervical cancers, particularly in combination with common patterns of in situ disease suggest that factors other than HPV are related to the development of invasive vulvar cancer for at least some cases.

A possible explanation for differences in age distribution between in situ and invasive vulvar carcinoma is that in situ vulvar disease is detected and treated before its progression to vulvar cancer. In cervical disease, Pap testing and early treatment of preinvasive disease have reduced the incidence of cervical cancer, yet these have not appreciably altered the age distribution, making this explanation unlikely for vulvar carcinoma.

This study relies on data from the SEER cancer registry. Although population based, it is limited because it does not include information about patients' sexual history, tobacco use, menopausal history, or HPV and human immunodeficiency virus (HIV) status. However, the observed patterns are consistent with the interpretation that HPV infection, which is highly associated with vulvar carcinoma in situ, does not progress to vulvar cancer at the same rate as cervical carcinoma in situ progresses to cervical cancer. This finding may also be of relevance to anal intraepithelial neoplasia and invasive anal cancer, HPV-related cancers where the natural history and progression from in situ to invasive cancer is poorly understood, and should be studied further.[25]

We have demonstrated that the incidence of in situ vulvar carcinoma is increasing, similar to the increasing incidence of HPV in the population. In contrast, the incidence of invasive vulvar cancer has increased at a much lower rate, and the risk continues to increase with age. Although HPV may play a role in both vulvar cancer and cervical cancer, the development of these cancers are dissimilar. Additional factors should be evaluated.

REFERENCES

1. Howe HL, Wingo PA, Thun MJ, Ries LA, Rosenberg HM, Feigal EG, et al. Annual report to the nation on the status of cancer (1973 through 1998), featuring cancers with recent increasing trends. J Natl Cancer Inst 2001;93:824–42.
2. Sturgeon SR, Brinton LA, Devesa SS, Kurman RJ. In situ and invasive vulvar cancer incidence trends (1973 to 1987). Am J Obstet Gynecol 1992;166:1482–5.
3. Madeleine MM, Daling JR, Carter JJ, Wipf GC, Schwartz SM, McKnight B, et al. Cofactors with human papillomavirus in a population-based study of vulvar cancer. J Natl Cancer Inst 1997;89:1516–23.
4. Nuovo GJ, Delvenne P, MacConnell P, Chalas E, Neto C, Mann WJ. Correlation of histology and detection of human papillomavirus DNA in vulvar cancers. Gynecol Oncol 1991; 43:275–80.
5. Bloss JD, Liao SY, Wilczynski SP, Macri C, Walker J, Peake M, et al. Clinical and histologic features of vulvar carcinomas analyzed for human papillomavirus status: evidence that squamous cell carcinoma of the vulva has more than one etiology. Hum Pathol 1991;22:711–8.
6. Toki T, Kurman RJ, Park JS, Kessis T, Daniel RW, Shah KV. Probable nonpapillomavirus etiology of squamous cell carcinoma of the vulva in older women: a clinicopathologic study using in situ hybridization and polymerase chain reaction. Int J Gynecol Pathol 1991;10:107–25.
7. Carson LF, Twiggs LB, Okagaki T, Clark BA, Ostrow RS, Faras AJ. Human papillomavirus DNA in adenosquamous carcinoma and squamous cell carcinoma of the vulva. Obstet Gynecol 1988;72:63–7.
8. Hording U, Junge J, Daugaard S, Lundvall F, Poulsen H, Bock JE. Vulvar squamous cell carcinoma and papillomaviruses: indications for two different etiologies. Gynecol Oncol 1994; 52:241–6.
9. Monk BJ, Burger RA, Lin F, Parham G, Vasilev SA, Wilczynski SP. Prognostic significance of human papillomavirus DNA in vulvar carcinoma. Obstet Gynecol 1995;85:709–15.
10. Petersen O. Spontaneous course of cervical precancerous conditions. Am J Obstet Gynecol 1956;72:1063–71.

11. Kolstad P. Carcinoma of the cervix, stage 0: diagnosis and treatment. Am J Obstet Gynecol 1966;96:1098–111.
12. Jones RW, Rowan DM. Vulvar intraepithelial neoplasia III: a clinical study of the outcomes in 113 cases with relation to the later development of invasive vulvar carcinoma. Obstet Gynecol 1994;84:741–5.
13. Jones RW, Baranyai J, Stables S. Trends in squamous cell carcinoma of the vulva: the influence of vulvar intraepithelial neoplasia. Obstet Gynecol 1997;90:448–52.
14. Brinton LA, Nasca PC, Mallin K, Baptiste MS, Wilbanks GD, Richart RM. Case–control study of cancer of the vulva. Obstet Gynecol 1990;75:856–66.
15. Poulsen H, Junge J, Vyberg M, Horn T, Lundvall F. Small vulvar squamous cell carcinomas and adjacent tissues. A morphologic study. APMIS 2003;111:835–42.
16. Sykes P, Smith N, McCormick P, Frizelle FA. High-grade vulvar intraepithelial neoplasia (VIN 3): a retrospective analysis of patient characteristics, management, outcome and relationship to squamous cell carcinoma of the vulva 1989-1999. Aust N Z J Obstet Gynaecol 2002;42:69–74.
17. van Seters M, van Beurden M, de Craen AJ. Is the assumed natural history of vulvar intraepithelial neoplasia III based on enough evidence? A systematic review of 3322 published patients. Gynecol Oncol 2005;97:645–51.
18. Centers for Disease Control and Prevention. Table 47. Selected STDs and complications–initial vists to physicians' offices: United States, 1966–2003. Available at: http://www.cdc.gov/std/stats03/table47.htm. Retrieved March 2, 2006.
19. Ho GY, Bierman R, Beardsley L, Chang CJ, Burk RD. Natural history of cervicovaginal papillomavirus infection in young women. N Engl J Med 1998;338:423–8.
20. Koutsky LA, Galloway DA, Holmes KK. Epidemiology of genital human papillomavirus infection. Epidemiol Rev 1988; 10:122–63.
21. Myers ER, McCrory DC, Nanda K, Bastian L, Matchar DB. Mathematical model for the natural history of human papillomavirus infection and cervical carcinogenesis. Am J Epidemiol 2000;151:1158–71.
22. National Cancer Institute. SEER public use data 1973-2001. 2004 Available at: http://www.seer.cancer.gov/. Retrieved February 9, 2006.
23. Agresti A. Categorical data analysis. New York (NY): Wiley; 1990.
24. Iversen T, Tretli S. Intraepithelial and invasive squamous cell neoplasia of the vulva: trends in incidence, recurrence, and survival rate in Norway. Obstet Gynecol 1998;91: 969–72.
25. Zbar AP, Fenger C, Efron J, Beer-Gabel M, Wexner SD. The pathology and molecular biology of anal intraepithelial neoplasia: comparisons with cervical and vulvar intraepithelial carcinoma. Int J Colorectal Dis 2002;17:203–15.