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Epidemiology of Vulvar Neoplasia in the NIH-AARP Study

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Abstract

Objective—To clarify risk factors for rare vulvar neoplasms.

Methods—Within the NIH-AARP Study, among 201,469 women interviewed in 1995–1996 and followed for a mean of 13.8 years, there were 370 diagnoses of incident vulvar neoplasms, including 170 invasive and 198 vulvar intraepithelial neoplasms grade 3 (VIN3). Hazard ratios (HR) and 95% confidence intervals (CI) were calculated via multivariate logistic regression for various demographic, reproductive and lifestyle factors, with separate consideration of relations according to invasiveness, histology and age at diagnosis.

Results—Consistent with descriptive data, we found non-white women at lower risks of vulvar neoplasia than white women (HR=0.59, 95% CI 0.36–0.95). Significant risk factors for VIN3 included being divorced/separated (HR vs. currently married=1.77, 95% CI 1.24–2.51), a current cigarette smoker (3.88, 95% CI 2.64–5.72), a user of oral contraceptives (1.46, 95% CI 1.06–2.01), or a current user of menopausal hormones (1.73, 95% CI 1.24–2.41). Significant risk factors for invasive cancers were being obese (HR for BMI ≥30 vs. <25=1.62, 95% CI 1.10–2.40) or a current smoker (1.86, 95% CI 1.21–2.87). Cigarette smoking was a risk factor mainly for neoplasms shown in other investigations to be HPV-related, namely VIN3 and invasive squamous cell cancers (SCCs) occurring in the younger stratum of cases. In contrast, obesity was primarily associated with the development of invasive SCCs.

Conclusions—Our results support that vulvar neoplasia is a heterogeneous disease. VIN3 demonstrated risk factors consistent with an HPV-related etiology, while invasive cancers were additionally affected by obesity, suggesting that further attention should focus on the role of chronic inflammatory conditions.

Keywords

vulvar neoplasia; epidemiology; risk; invasive; VIN3; squamous cell carcinomas

INTRODUCTION

Although vulvar cancer accounts for only 3–5% of all female genital tract cancers in the U.S., it is the most common anogenital cancer in women over the age of 70 years (1).

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Conflict of Interest Statement:

The authors declare that there are no conflicts of interest.

Incidence rates of both invasive cancers and high-grade vulvar intraepithelial neoplasms (VIN) are higher among whites than non-whites; however, while invasive cancer rates increase with age, high-grade VIN peaks around 50–60 years (Figure 1). Because of the rarity of vulvar cancers, little is known regarding epidemiologic risk factors. The most well established risk factor is a history of a previous cervical intraepithelial neoplasia grade 3 (CIN-3) (2–4), consistent with the notion that many cases are linked to infection with the human papillomaviruses (HPV). Although it was previously assumed that approximately 40–51% of all vulvar cancers were attributable to HPV infections (5), it now appears that decreasing proportions are associated with viral infections as women age—with only 15–17% of cases in women 67 years of age or older being associated with HPV infection (6). In older women, vulvar cancers are thought to result more from chronic inflammatory skin disorders, including lichen sclerosus (7).

Most previous epidemiologic investigations of vulvar cancer have been small and have identified inconsistent risk factors (8–12). The Million Women Study (MWS), however, recently published data relevant to 898 vulvar cancers (13). In addition to a history of CIN, significant risk factors in this study included obesity (HR = 1.71 for body mass indices or BMI of 30 vs. <25) and early menopause (HR, 1.52 <50 vs. 50 years).

To shed further light on etiologic factors for rare vulvar neoplasms, we utilized data collected within the NIH-AARP Diet and Health Study, a prospective investigation of dietary and lifestyle factors that focused on older individuals. With an average age at recruitment of nearly 62 years and extended follow-up, this investigation allowed us to not only attempt verification of previous findings, but also to assess risk factors among a population of predominantly older women, whose neoplasms may be less influenced by HPV infection.

METHODS

The NIH-AARP Diet and Health Study design and methodology has been described previously (14). Briefly, the NIH-AARP Diet and Health study is a prospective cohort study of exposure and lifestyle factors on cancer risk initiated in 1995–1996. A baseline questionnaire was sent to ~3.5 million AARP members aged 50–71 years old residing in six US states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) and two metropolitan areas (Atlanta, GA and Detroit, MI). 566,399 non-duplicate and satisfactorily completed questionnaires were returned. We excluded respondents who used a proxy respondent for the baseline questionnaire (n = 15,760), men (n = 325,171), and women who self-reported a previous cancer diagnosis other than non-melanoma skin cancer (n = 23,998). The analytic population consisted of 201,469 women.

The Special Studies Institutional Review Board of the US National Cancer Institute approved the NIH-AARP Diet and Health Study, and all participants gave informed consent by virtue of completing and returning the questionnaires.

Vital status was ascertained by annual linkage to the National Death Index Plus, by cancer registry linkages, and through responses to mailings. Address changes were ascertained

through annual linkage to the National Change of Address database maintained by the US Postal Service (USPS), by receipt of USPS notification of undeliverable mail, via use of other address change update services, and by direct communication with participants.

Risk Factor Ascertainment

We used the baseline questionnaire to collect information on age at cohort entry, race, marital status, education, age at menarche, number of births, age at first birth, age at menopause, prior hysterectomy, body mass index (BMI), smoking status, alcohol use, diabetes status, oral contraceptive use, and menopausal hormone use.

Incident Vulvar Neoplasia Ascertainment

Incident cases of vulvar neoplasms were identified by probabilistic linkage to the recruitment area cancer registries and registries of common relocation areas (Arizona, Nevada, and Texas) (15). Low-grade intraepithelial lesions were not included as these are not routinely reported to cancer registries and are not considered as potentially neoplastic lesions (16). We did include all higher grades of both squamous intraepithelial and non-squamous VINs (both differentiated and undifferentiated forms, the latter of which are more likely to be HPV-associated), and classified these lesions collectively as VIN grade 3 (VIN3). Information collected from the registries included dates of diagnosis and ICD-O-3 histology codes. Of the 201,469 women in the analytic population, 370 were diagnosed with incident vulvar neoplasms. We stratified all cases to invasive (n=170) and VIN3 (n=198) based on the behavior code, the fifth digit of the ICD-O-3 code (2 cases were missing appropriate data to classify). Further, to evaluate risk factor differences in cases associated with HPV, we used histology codes to stratify cases to squamous cell carcinomas (SCCs) or squamous cell neoplasms, ICD-O-3 codes 8050–8084 and 8120–8131, the neoplasm type most associated with HPV (17), and other types of vulvar neoplasms. Twenty two cases were missing histology information (7 invasive and 15 VIN3). Of the remaining cases, 107 were classified as invasive SCC, 56 as invasive non-SCC, 176 as squamous cell VIN3, and 7 as non-squamous VIN3.

Statistical Analysis

Follow up time began the day the baseline questionnaire was scanned and ended with the first occurrence of vulvar neoplasm diagnosis, death, movement outside of registry ascertainment area, or December 31st, 2011. The frequency of cases and controls was calculated within all categories of risk factors. Cox proportional hazards regression was used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) associating possible risk factors with incident vulvar neoplasia with adjustment for age. Tests for trend were constructed for ordinal categorizations of risk factors with 3 or more categories, using the median value or mid-value (for categories with a range of values) in each level as a continuous covariate. Analyses were repeated with cases stratified according to whether they were invasive vs. VIN3, SCC vs. other histology, or younger vs. older than the median age at diagnosis within categories of invasive cancer or VIN3. Further, risk factors within the invasive cancers were assessed according to combinations of histology and age at diagnosis. Finally, given that there was some uncertainty as to whether all VIN3 cases were captured through the cancer registries, separate analyses compared risks derived from those registries

that appeared to have more complete reporting (>50% of all neoplasms comprised by VIN3) versus those possibly involving some under-reporting. All analyses were performed using SAS 9.3 (SAS Institute Inc., Cary, NC).

RESULTS

Descriptive characteristics of the 201,469 eligible NIH-AARP Study cohort members at baseline interview are shown in Table 1. The mean age at entry was 61.8 years, with the majority of women being white, married, educated beyond high school, and parous. Substantial proportions of women reported a prior hysterectomy as well as usage of either oral contraceptives or menopausal hormones. Approximately a quarter of the subjects had BMIs reflective of obesity (≥ 30 kg/m²).

After a mean of 13.8 years of follow-up, 370 women had developed vulvar neoplasia (170 invasive cancers and 198 VIN3). The mean ages at diagnosis were 71.0 years for invasive cancers and 67.5 years for VIN3.

Demographic risk factors for vulvar neoplasms are shown in table 2. Non-white women were at a significantly lower risk for developing any type of vulvar neoplasia than white women (HR=0.59, 95% CI 0.36–0.95), with similar, albeit non-significant, associations seen for both invasive cancers and VIN3. Compared to married women, divorced and separated women were at a significantly elevated risk of VIN3 (HR=1.77, 1.24–2.51). Years of education, however, was not related to vulvar neoplasia risk.

We observed no association of vulvar neoplasia risk with various menstrual factors, including ages at menarche, first birth, or menopause (Table 3). However, there was evidence of reduced risk with number of births among parous women, with the trend in risk being significant ($p=0.02$) for all neoplasms and highly significant ($p<0.01$) for VIN3. Further, women with 5 or more births were at a significantly reduced risk of VIN3 compared to nulliparous women (HR=0.45, 95% CI 0.21–0.97). Women who reported a prior hysterectomy were at a non-significantly elevated risk of invasive vulvar cancers (HR=1.30, 95% CI 0.92–1.83), with no difference in risk seen according to oophorectomy status.

A variety of lifestyle factors were also examined in relation to vulvar neoplasia risk (Table 4). There was a significant trend in risk ($p=0.02$) of invasive cancers according to BMI, with women who had BMIs of ≥ 30 being at a 62% higher risk compared to those with BMIs <25 (95% CI 1.06–2.34). This relation was not observed for VIN3. No significant relations of risk were observed for either a history of diabetes or alcohol consumption, but elevated risks were observed among smokers, as well as those who reported use of oral contraceptives or menopausal hormones. Current smokers were at the highest risk, and the risks were higher for VIN3 than invasive cancers where the strongest association was seen for current, high intensity smokers (HR for ≥ 21 or more cigarettes per day vs. never smokers=4.73, 95% CI 2.79–8.01). The elevated risk associated with menopausal hormone use was restricted to VIN3, and did not vary substantially according to currency or duration of use, with HRs in the range of 1.6–1.8 for all categorizations. In addition, significantly increased risks of VIN3 were seen among oral contraceptive users, with the highest risk seen for women who

reported extended use of oral contraceptives (HR for >10 years vs. <1 year =1.70, 95% CI 1.08–2.67). No association with either menopausal hormones or oral contraceptives were seen for invasive vulvar cancers.

A total of 65.6% of the invasive tumors with known histology were classified as SCCs and the remainder as non-SCCs (22 basal carcinoma, 15 melanoma, 13 Paget disease, 5 adenocarcinoma, 1 leiomyosarcoma). As shown in table 5, both SCCs and non-SCCs occurred more frequently among whites than non-whites, although the risks were non-significant. Being a current smoker was not associated with an elevated risk of invasive non-SCC, but was related to an increased risk of invasive SCC (HR=2.55, 95% CI 1.53–4.27). Obesity was also only a risk factor for invasive SCC (HR for BMIs ≥30 vs. <25=2.15, 95% CI 1.30–3.57).

Significant risk factors for squamous cell VIN3 (which comprised 96.2% of all VIN3 with known histologies) included being divorced or separated (HR=1.81, 95% CI 1.25–2.63), a current smoker (HR= 3.86, 95% CI 2.53–5.90), or a current user of menopausal hormones (HR=1.81, 95% CI 1.27–2.58) (Table 5). We were unable to assess risks for non-SCC VIN3 because there were only 7 of them (2 *in situ* adenocarcinoma, 5 Paget disease).

When we subdivided the neoplasms by the median age at diagnosis (71 years for invasive cancers, 68 for VIN3), cigarette smoking was a risk factor only for VIN3 and for the least oldest case group of invasive cancers (Supplementary table 1). Obesity was unrelated to VIN3 diagnosed prior to age 68, but a risk factor for all other case groups; however, the association was significant only for the invasive cancers diagnosed at 71 years of age or older.

When we further subdivided the invasive tumors by both age and histology (Supplementary table 2), we found that current cigarette smoking was associated with a particularly enhanced risk among the SCC cases diagnosed prior to 71 years of age (HR=6.07, 95% CI 2.78–13.23). In contrast, obesity (BMI ≥30) was a risk factor for invasive SCCs both among the women <71 years of age (HR=1.88, 95% CI 0.92–3.84) as well as among the older women (2.39, 95% CI 1.17–4.90), but unrelated to risk of the non-SCCs.

Analyses that separately considered risks according to the apparent completeness of reporting of VIN3 (with 62.1% of the cases deriving from registries with higher rates of reporting) showed some differences, although associations consistent with most risk factors identified for the totality of VIN3 (non-white race, being divorced/separated, multiparity, current cigarette smoking) were found in both high and low prevalence areas (data not shown). Elevated risks, however, were not identified for exogenous hormone users in the lower prevalence areas.

DISCUSSION

In agreement with recent SEER incidence trends (figure 1), findings from our NIH-AARP study that focused only on older women confirmed an increased risk of invasive vulvar cancers and VIN3 for white compared to non-white women. Reasons for the racial disparity in vulvar neoplasia are unclear, especially given trends for another HPV-related cancer--

cervical cancer--that shows higher incidence for blacks than whites. The racial trends for vulvar neoplasms may relate to a higher incidence of non-HPV related vulvar neoplasms among older white women, but it has also been suggested that enhanced screening and management of cervical disease, increased detection because of better visualization, or possibly different etiologies may be involved (18). These explanations remain speculative and require further detailed investigation.

As a rare condition, it has been difficult for epidemiologic studies to assess risk factors for vulvar neoplasia. Similar to cervical cancer, the assessment of risk is complicated by the fact that HPV appears to be an important cause of many cases, making it difficult to assess the contribution of other factors. Like most previous epidemiologic investigations of this neoplasm, we did not have information on HPV infection status. Nonetheless, by examining risks according to the histology of the tumors and ages at diagnosis, we were able to identify risk factors that differed between vulvar neoplasms that are predominantly influenced by HPV versus those that are affected by additional carcinogenic processes.

Although we did not have information on HPV infection status, we found that being separated or divorced was a significant risk factor for vulvar neoplasms, possibly indicating that sexual behaviors place this group at higher risk of being infected with HPVs. This was supported by our finding that the risk associated with being separated or divorced was most strongly related to VIN3, which are known from other investigations to be largely HPV-related. However, in the absence of having data on infection status we can only speculate on the cause of the association. Further, other unmeasured lifestyle factors could be more explanatory to our observed relations.

Consistent with an important role for HPV, an established risk factor for vulvar cancer is a past diagnosis of CIN. A previous Finnish investigation found a 4-fold increased risk of vulvar cancer following treatment for any grades of CIN, although this was based on 6 cases of vulvar cancer among 7,564 women (2). Similarly, in the MWS, a 2.7-fold increased risk of vulvar cancer was noted among women who reported CIN grade 3, although again based on only a small number of women (n=20). Thus, although we did not capture information on this potential risk factor, given its uncommon occurrence it is unlikely that failure to adjust for this would have meaningfully affected other assessed risk factors.

Of the factors that we evaluated, the exposure that was most strongly related to vulvar neoplasia risk was cigarette smoking. This link has been established in cervical cancer (19), but its role in the etiology of vulvar cancer has been less certain. A number of studies have suggested that smokers may be at an increased risk of vulvar cancers (8, 10, 20, 21); however, the latest and largest investigation of vulvar cancer, which focused only on invasive cancer, demonstrated no association with currency of smoking (duration of smoking was not evaluated) (13). In our study, we found smoking to be a risk factor for both VIN3 and invasive cancers, but among invasive cancers the association was restricted to SCCs that developed among women below the median diagnostic age of our subjects (<71 years). It is important to note that SCCs developing among older women tend most often to be differentiated tumors, which are less commonly HPV-related (6). Thus, cigarette smoking may exert its effects on vulvar neoplasia risk through an enhancement of the effects of HPV,

consistent with at least one study that noted a relation of smoking restricted to squamous vulvar cancers whose tissues harbored HPV (21).

When we analyzed all cases of VIN3, we found an increased risk associated with exposure to exogenous hormone use, including both oral contraceptives and menopausal hormones. Although there has been no consensus from previous studies regarding the effects of exogenous hormone use on vulvar cancer risk (8–10, 12), our finding is of interest given studies linking oral contraceptive usage to cervical abnormalities, including cancer (22). For cervical cancer, the relation has been postulated to reflect enhanced HPV effects given that transcriptional regulatory regions of HPV DNA contain hormone-recognition elements and that transformation of cells *in vitro* with viral DNA is enhanced by hormones (23). The restriction of our hormone associations to neoplasms that are most strongly influenced by HPV, namely VIN3, might suggest a similar relation, although further investigations are warranted—especially since our associations were only found in cancer registry states with high prevalences of VIN3, suggesting a possible role overall in our study for some selection biases.

Several early clinical observations (12, 24, 25) suggested that obesity might predispose to vulvar cancer, but some epidemiologic studies have not confirmed significant relations (8, 10, 11). However, the Metabolic Syndrome and Cancer Cohort found that a one standard deviation increase in BMI was associated with a 36% increased risk of vulvar cancer (26), while the MWS found subjects with BMIs of ≥ 30 kg/m² to be at 70% higher risk than those with BMIs < 25 kg/m² (13). We found a similar relation of invasive cancer risk with obesity, which affected women of all ages. However, similar to findings reported by the MWS, the association of obesity to vulvar cancer was restricted to the SCCs in our study. The fact that our association was not restricted to our youngest group of cases suggests that factors in addition to HPV infection might be etiologically involved. Findings that obese women have higher rates of chronic inflammatory skin disorders, such as lichen sclerosus (27), which has been related to high rates of subsequent vulvar cancer (7), would be consistent with there being a subset of vulvar cancers that arise under conditions of altered immunity. This would be consistent with linkage of vulvar cancer with alterations in immune response genes, including interleukin 2 (28).

The MWS also reported that women with early menopause were at increased vulvar cancer risk (13), an association that was not confirmed in our investigation. The divergent results may have reflected a difference in our definitions, as they considered both early natural and surgical menopause together, whereas we considered them separately. We did note a non-significant increase in invasive vulvar cancer risk associated with a prior hysterectomy, regardless of oophorectomy status, which may partially reflect prior treatment for cervical disorders. Our results, however, provide no support for an important role of early natural menopause or other menstrual factors in the etiology of vulvar neoplasia, consistent with several other studies (10–12).

Although our study had some limitations, including relatively small numbers of neoplasms among a fairly racially homogeneous population and possibly incomplete ascertainment of VIN3 cases, our results were consistent with other observations (29, 30) in demonstrating

that vulvar neoplasms are etiologically heterogeneous, with risk factors dependent on age at diagnosis and clinical characteristics, including invasiveness and histology. VIN3 was diagnosed at younger ages and for the most part demonstrated risk factors similar to those identified for cervical cancer, consistent with an etiology largely reflective of HPV infection; however, we did not specifically have information to differentiate the VIN3 cases according to HPV infection status. Although HPV was likely involved in the development of some of the invasive cancers, the increased risk associated with obesity indicates a potential role for inflammatory processes. Our findings provide directions for future research of rare vulvar neoplasms, although further etiologic insights would benefit from clarification of the role of HPV—and the types of HPV involved—in relation to other possible co-factors. However, among older women, the role of vulvar tissue alterations that might reflect the role of inflammation would also appear worthy of further pursuit.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Vulvar neoplasia is comprised of several etiologically heterogeneous conditions.
- Risk factors for VIN3 and invasive cancer included white race and cigarette smoking.
- Other risk factors for VIN3 suggested an HPV-related etiology.
- Obesity had a distinctive role in the etiology of invasive squamous cell cancers.
- Future studies should assess risk factors in relation to measurement of HPV types.

A) Invasive

B) VIN3

Figure 1.

Incidence Rates (per 100,000 women) of A) invasive vulvar cancer and B) vulvar intraepithelial neoplasia grade 3 (VIN3) by racial groups, Surveillance, Epidemiology, and End Results (SEER) Program, 2000–2013, 18 geographic areas

Table 1

Participant Characteristics at Baseline and Details of Follow-up, NIH-AARP Study Cohort

Characteristic at baseline	
Number of women	201,469
Mean age at recruitment (s.d.)	61.8 (5.4)
White (%)	90.6
Currently married (%)	44.6
Education beyond high school (%)	67.2
Parous (%)	84.8
Among parous, age at first birth >30 years (%)	6.8
Among naturally menopausal, age at menopause <45 years (%)	12.3
Prior hysterectomy (%)	41.3
Body mass index > 30 kg/m ²	23.3
Current smoker (%)	14.8
History of diabetes (%)	7.4
Ever oral contraceptive user (%)	53.1
Current menopausal hormone user (%)	44.0
Follow-up	
Women-years (1000s)	2,777.7
Mean length of follow-up (s.d.)	13.8 (3.9)
Number of women with incident invasive vulvar cancers	170
Mean age (s.d.)	71.0 (6.7)
Number of women with incident vulvar intraepithelial neoplasia grade 3 (VIN3)	198
Mean age (s.d.)	67.5 (6.6)

Table 2

Hazard Ratios of Vulvar Neoplasia for Demographic Factors, NIH-AARP Study

	All Vulvar Neoplasms (N=370)				Invasive Vulvar Cancers (N=170)				VIN3 (N=198)			
	Exp Cases	HR [/]	95% CI	Exp Cases	HR [/]	95% CI	Exp Cases	95% CI	Exp Cases	HR [/]	95% CI	Exp Cases
Race												
White	340	1.00	Referent	156	1.00	Referent	182	Referent	182	1.00	Referent	
Non-white	23	0.59	0.36–0.95	10	0.54	0.27–1.11	13	0.64	13	0.64	0.34–1.22	
Marital status												
Currently married	133	1.00	Referent	66	1.00	Referent	67	Referent	67	1.00	Referent	
Widowed	86	1.16	0.86–1.56	42	0.99	0.65–1.49	43	1.34	43	1.34	0.88–2.05	
Divorced/Separated	119	1.46	1.12–1.89	43	1.12	0.75–1.67	75	1.77	75	1.77	1.24–2.51	
Never married	28	1.45	0.94–2.24	16	1.33	0.73–2.43	12	1.57	12	1.57	0.84–2.94	
Education												
High school	128	1.00	Referent	66	1.00	Referent	61	Referent	61	1.00	Referent	
Vocational school/some college	116	0.79	0.60–1.03	52	0.80	0.55–1.17	63	0.81	63	0.81	0.55–1.17	
College graduate	103	0.83	0.63–1.10	42	0.74	0.49–1.13	61	0.94	61	0.94	0.64–1.39	
<i>P</i> for trend		0.19			0.15					0.79		

[/]HRs adjusted for age (categorical), race, marital status, body mass index (categorical), smoking status, oral contraceptive use and menopausal hormone use.

Hazard Ratios of Vulvar Neoplasia for Reproductive and Hormonal Factors, NIH-AARP Study

Table 3

	All Vulvar Neoplasms (N=370)				Invasive Vulvar Cancers (N=170)				VIN 3 (N=198)			
	Exp Cases	HR ¹	95% CI		Exp Cases	HR ¹	95% CI		Exp Cases	HR ¹	95% CI	
Age at menarche												
12	171	1.00	Referent		78	1.00	Referent		92	1.00	Referent	
13-14	156	1.10	0.87-1.38		72	1.09	0.78-1.52		83	1.09	0.80-1.50	
15	39	1.29	0.90-1.86		19	1.27	0.75-2.15		20	1.31	0.80-2.15	
<i>P</i> for trend		0.16				0.38				0.29		
Number of births												
0	61	1.00	Referent		26	1.00	Referent		35	1.00	Referent	
1	55	1.28	0.83-1.98		22	1.35	0.67-2.71		33	1.24	0.71-2.16	
2	100	0.98	0.66-1.46		42	1.07	0.57-2.02		56	0.91	0.55-1.51	
3-4	117	0.77	0.52-1.14		57	0.98	0.53-1.81		60	0.64	0.38-1.06	
5	34	0.77	0.47-1.27		23	1.22	0.60-2.46		11	0.45	0.21-0.97	
<i>P</i> for trend		0.02				0.99				<0.01		
Age at first birth												
<20	68	1.00	Referent		30	1.00	Referent		36	1.00	Referent	
20-24	155	1.01	0.74-1.38		70	1.04	0.65-1.67		85	1.02	0.67-1.55	
25-29	64	1.08	0.75-1.55		35	1.27	0.75-2.17		29	0.94	0.56-1.58	
30	19	1.00	0.59-1.71		7	0.83	0.35-1.92		12	1.21	0.61-2.41	
Nulliparous	61	1.20	0.78-1.85		26	1.06	0.53-2.10		35	1.36	0.78-2.37	
<i>P</i> for trend (parous only)		0.86				0.77				0.94		
Age at menopause												
<45	83	1.02	0.64-1.64		41	0.74	0.35-1.58		42	1.32	0.72-2.43	
45-49	25	1.24	0.89-1.73		10	1.25	0.78-2.01		15	1.23	0.77-1.97	
50-54	67	1.00	Referent		34	1.00	Referent		32	1.00	Referent	
55	21	1.18	0.73-1.90		12	1.25	0.66-2.38		9	1.07	0.52-2.22	
Premenopausal	9	0.82	0.38-1.76		2	0.68	0.15-3.02		7	0.93	0.38-2.29	
Surgical	154	1.11	0.83-1.48		70	1.13	0.75-1.71		83	1.08	0.72-1.60	
<i>P</i> for trend (natural menopause only)		0.58				0.89				0.46		

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	All Vulvar Neoplasms (N=370)				Invasive Vulvar Cancers (N=170)				VIN 3 (N=198)			
	Exp Cases	HR [/]	95% CI		Exp Cases	HR [/]	95% CI		Exp Cases	HR [/]	95% CI	
Prior Hysterectomy												
No	193	1.00	Referent		88	1.00	Referent		104	1.00	Referent	
Yes	172	1.17	0.93–1.47		80	1.30	0.92–1.83		91	1.05	0.77–1.44	
No oophorectomy	82	1.24	0.94–1.65		36	1.26	0.83–1.93		45	1.19	0.82–1.73	
Oophorectomy	87	1.08	0.81–1.44		43	1.34	0.88–2.02		44	0.89	0.60–1.33	

[/]HRs adjusted for age (categorical), race, marital status, body mass index (categorical), smoking status, oral contraceptive use and menopausal hormone use.

Table 4

Hazards Ratios of Vulvar Neoplasia for Lifestyle Factors, NIH-AARP Study

	All Vulvar Neoplasms (N=370)				Invasive Vulvar Cancers (N=170)				VIN3 (N=198)			
	Exp Cases	HR ¹	95% CI	Exp Cases	HR ¹	95% CI	Exp Cases	95% CI	Exp Cases	HR ¹	95% CI	Exp Cases
Body Mass Index												
<25.0	150	1.00	Referent	68	1.00	Referent	81	Referent	81	1.00	Referent	
25.0–29.9	121	1.21	0.94–1.55	49	1.11	0.76–1.62	72	1.31	72	1.31	0.94–1.82	
30.0	87	1.30	0.98–1.73	48	1.62	1.10–2.40	39	1.04	39	1.04	0.69–1.57	
<i>P</i> for trend		0.06			0.02					0.72		
Smoking Status												
Never	121	1.00	Referent	69	1.00	Referent	52	Referent	52	1.00	Referent	
Former	133	1.23	0.95–1.58	61	1.00	0.70–1.42	71	1.54	71	1.54	1.07–2.23	
Current	96	2.78	2.10–3.68	34	1.86	1.21–2.87	61	3.88	61	3.88	2.64–5.72	
1–10 cigs/day	21	2.04	1.26–3.29	7	1.35	0.62–2.95	14	2.92	14	2.92	1.58–5.41	
11–20 cigs/day	47	3.11	2.18–4.42	19	2.30	1.34–3.95	27	4.01	27	4.01	2.47–6.50	
21 cigs/day	28	3.10	2.04–4.70	8	1.75	0.83–3.67	20	4.73	20	4.73	2.79–8.01	
Alcohol												
0	105	1.00	Referent	58	1.00	Referent	46	Referent	46	1.00	Referent	
<0–0.5	189	0.97	0.75–1.26	87	0.92	0.65–1.32	101	1.04	101	1.04	0.71–1.51	
<0.5–1.0	24	0.79	0.49–1.27	6	0.38	0.15–0.95	18	1.21	18	1.21	0.68–2.14	
1.0	52	1.00	0.70–1.42	19	0.77	0.44–1.33	33	1.25	33	1.25	0.77–2.01	
Diabetes												
No	342	1.00	Referent	157	1.00	Referent	183	Referent	183	1.00	Referent	
Yes	28	1.15	0.75–1.76	13	1.05	0.58–1.93	15	1.26	15	1.26	0.69–2.29	
Oral Contraceptive Use												
< 1 year	203	1.00	Referent	111	1.00	Referent	91	Referent	91	1.00	Referent	
1 year	164	1.21	0.96–1.53	58	0.95	0.67–1.36	105	1.46	105	1.46	1.06–2.01	
1–4 years	68	1.13	0.83–1.53	29	1.03	0.65–1.62	39	1.25	39	1.25	0.83–1.89	
5–9 years	53	1.31	0.95–1.82	17	1.00	0.59–1.70	35	1.57	35	1.57	1.03–2.41	
10 years	43	1.24	0.86–1.79	12	0.75	0.39–1.45	31	1.70	31	1.70	1.08–2.67	
Menopausal Hormone Use												

	All Vulvar Neoplasms (N=370)			Invasive Vulvar Cancers (N=170)			VIN3 (N=198)		
	Exp Cases	HR [/]	95% CI	Exp Cases	HR [/]	95% CI	Exp Cases	HR [/]	95% CI
Never	155	1.00	Referent	87	1.00	Referent	66	1.00	Referent
Former	33	1.12	0.76–1.65	12	0.76	0.42–1.40	21	1.62	0.97–2.73
Current	182	1.25	0.99–1.58	71	0.90	0.64–1.27	111	1.73	1.24–2.41
<5 years	54	1.37	0.98–1.92	21	1.10	0.65–1.84	33	1.76	1.11–2.79
5–<10 years	44	1.16	0.80–1.66	15	0.74	0.41–1.35	29	1.69	1.05–2.70
10 years	88	1.23	0.92–1.64	35	0.88	0.58–1.36	49	1.74	1.16–2.60

[/]HRs adjusted for age (categorical), race, marital status, body mass index (categorical), smoking status, oral contraceptive use and menopausal hormone use.

Table 5

Hazard Ratios of Vulvar Neoplasia, by Histology, for Major Identified Risk Factors, NIH-AARP Study

	Invasive, SCC (N=107)			Invasive, Non-SCC (N=56)			VIN3, Squamous Cell (N=176)		
	Exp Cases	HR ¹	95% CI	Exp Cases	HR ¹	95% CI	Exp Cases	HR ¹	95% CI
Race									
White	98	1.00	Referent	51	1.00	Referent	161	1.00	Referent
Non-white	6	0.62	0.27–1.43	4	0.46	0.11–1.89	12	0.74	0.39–1.41
Marital Status									
Married	34	1.00	Referent	29	1.00	Referent	59	1.00	Referent
Widowed	31	1.36	0.81–2.29	11	0.66	0.31–1.39	37	1.33	0.84–2.09
Divorced/Separated	31	1.55	0.93–2.57	9	0.56	0.25–1.23	68	1.81	1.25–2.63
Never married	9	1.54	0.70–3.36	6	0.99	0.34–2.87	11	1.63	0.84–3.13
Body Mass Index									
<25.0	35	1.00	Referent	32	1.00	Referent	71	1.00	Referent
25.0–29.9	36	1.58	0.97–2.55	13	0.70	0.36–1.36	67	1.38	0.97–1.95
30.0	33	2.15	1.30–3.57	12	0.96	0.48–1.94	33	1.00	0.64–1.56
Smoking Status									
Never	40	1.00	Referent	26	1.00	Referent	44	1.00	Referent
Former	37	1.03	0.65–1.64	23	1.03	0.57–1.84	68	1.80	1.22–2.65
Current	27	2.55	1.53–4.27	4	0.62	0.21–1.81	51	3.86	2.53–5.90
Oral Contraceptive Use									
<1 year	72	1.00	Referent	37	1.00	Referent	82	1.00	Referent
1 year	34	0.84	0.53–1.33	19	0.93	0.50–1.72	92	1.39	0.99–1.95
Menopausal Hormone Use									
Never	54	1.00	Referent	27	1.00	Referent	58	1.00	Referent
Former	10	1.05	0.53–2.07	2	0.40	0.09–1.69	16	1.36	0.75–2.46
Current	43	0.95	0.61–1.47	27	0.97	0.54–1.75	102	1.81	1.27–2.58

¹HRs adjusted for age (categorical) and all factors shown.