Rising and Falling Trends in Incidence Rates of Vulvar and Vaginal Cancers in the United States, 2000-2016

Yang-yang Yue
Shengjing Hospital of China Medical University
Wei-li Zhou
Shengjing Hospital of China Medical University
Dong-mei Pei (peidm1111@hotmail.com)
Shengjing Hospital, China Medical University

Research article

Keywords: Incidence, Trends, Relative survival, Vaginal Cancer, Vulvar Cancer, Squamous cell carcinoma, Adenocarcinoma, SEER, Epidemiology

Posted Date: August 27th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-60446/v1

Abstract

Background: Few studies focus on incidence trends in vulvar and vaginal by histological type, race, age, and region. We aimed to evaluate the temporal incidence trends and survival for the two cancers.

Methods: Cases with primary vulvar or vaginal carcinoma from 2000-2016 were identified from the Surveillance, Epidemiology, and End Results 18 registries. Annual percent change (APC) and average APC (AAPC) were calculated to evaluated trends. Relative survival was estimated to compare survival outcomes.

Results: Vulvar cancer incidence rates were highest among non-Hispanic whites (20.9 per 1,000,000 person-years) and in the Midwest (27.7), while vaginal cancer rates were highest among non-Hispanic blacks (8.2) and in the South (6.7). Overall, vulvar cancer rate increased 0.4% annually (AAPC, 0.4%; 95% CI, 0.1% to 0.6%), but vaginal cancer rate decreased 1.4% annually (AAPC, -1.4%; 95% CI, -2.0% to -0.5%). The increased vulvar cancer rate was only observed for squamous cell carcinoma (APC, 1.0%), while the decreased vaginal cancer rate was only observed for other malignancies (APC, -1.7%). Vulvar cancer rates increased only among whites (APC, 1.2%), but vaginal cancer rates decreased only among whites (AAPC, -1.3%) and Asians (APC, -2.7%). Vulvar cancer rates increased among patients aged 50-59 (APC, 1.1%), 60-69 (APC, 1.3%), and 70-79 (APC, 1.2%) years, while vaginal cancer rates decreased among patients aged 50-59 (APC, -1.4%) and 80 (APC, -1.4%) years or older. Overall, whites had the highest five-year relative survival for both vulvar (72.22%) and vaginal (49.03%) cancers.

Conclusion: There were profound disparities in vulvar and vaginal cancer incidence rates attributable to histological type, race, age, and region. The increased vulvar cancer rates and the declined vaginal cancer rate highlights the importance of further studies to investigate the reason for the disparities.

Introduction

Vulvar and vaginal carcinomas are two rare cancers in women, accounting for nearly 10% of all gynecologic cancers, with approximately 6000 newly diagnosed cases and 5000 deaths yearly in the United States (US)(1). The histological types of these carcinomas are mainly squamous cell carcinoma (SCC, 80-90%), adenocarcinoma (ADE, 4-10%), and other histological types (hereafter referred to as other malignancies, OM)(2-4).

During 1999-2015 in the US, the incidence rate of vulvar SCC increased by 1.3% per year in women aged 50-69 years old, and the incidence rate of vaginal SCC decreased by 0.3% per year in women aged younger than 40 years and 70 years or older(5). Moreover, no studies are characterizing the incidence and survival rates of ADE and OM for vulvar and vaginal carcinomas due to their rareness. Furthermore, although the trends in vulvar and vaginal cancers have been documented, it is unclear whether these changes are equal or not when classified by histological type, race, and region. To the best of our knowledge, previous studies have not taken these features into account when evaluating the incidence and survival rates of these two cancers. Racial disparities of incidence and survival rates were well

documented in several common carcinomas such as malignant meningioma, hepatocellular carcinoma, uterine corpus carcinoma, prostate carcinoma, and pancreatic carcinoma(6-11). However, little is known about the racial disparities in the incidence and survival rates of vulvar and vaginal carcinomas.

The primary aim of this study was to evaluate the age-adjusted incidence and five-year survival of vulvar and vagina carcinomas by race, histological subtype, and region using the Surveillance, Epidemiology, and End Results (SEER) database of the US. The secondary aim was to estimate the temporal trends of incidence rate over time by race, histological subtype, and region.

Materials And Methods

Study population

We identified the incidence rates in patients with microscopically confirmed cancers of the vulva (labium majus, C51.0; labium minus, C51.1; clitoris, C51.2; overlapping lesion of the vulva, C51.8; vulva NOS, C51.9) and vagina (C52.9) diagnosed between 2000 and 2016 from the SEER 18 database, representing approximately 28% of the US population, using the third edition of the International Classification of Diseases for Oncology (ICD-O-3) codes. We included patients above 20 years old and excluded those younger than 20 years due to the rareness of these cancers in this age group. Cases were categorized by race into non-Hispanic white (hereafter referred to as whites), non-Hispanic black (blacks), non-Hispanic American Indian/Alaska Native (Indians), Non-Hispanic Asian or Pacific Islander (Asians), and Hispanics. Non-Hispanic unknown races were excluded because they had few patients. Cases were classified into three groups by histologic subtype as defined by the ICD-O-3 histology codes: SCC, ADE, and OM. The registries included in this study were San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, Atlanta, San Jose–Monterey, Los Angeles, Alaska Native Registry, rural Georgia, California (excluding San Francisco, San Jose–Monterey, and Los Angeles), Kentucky, Louisiana, New Jersey, and Georgia (excluding Atlanta and rural Georgia).

Statistical analysis

Age-adjusted overall incidence rates were calculated using SEER*Stat software (version 8.3.5) for cancer patients and then by race, histological subtype, ten-year age group (i.e., 20-29, 30-39, and continuing to 80 years or older), and region (northeast [Connecticut and New Jersey], Midwest [Michigan and Iowa], South [Georgia, Kentucky, and Louisiana], and west [California, Hawaii, New Mexico, Washington, and Utah]). Incidence rates were age-adjusted to that of the 2000 US standard population and expressed per 1,000,000 woman-years. Rate ratios were estimated, and the 95% confidence intervals (CI) were calculated using the Tiwari modification method.

Trends in incidence rates were calculated and plotted using the National Cancer Institute Joinpoint regression software (version 4.7.0.0). In Joinpoint software, we calculated annual percent changes (APCs) and 95% CIs using the Empirical Quantile method(12, 13). The software program chose the best-fitting linear regression model in a logarithmic scale based on the least-weighted Bayesian Information

Criterion to identify years when APCs significantly changed, allowing a maximum of three joinpoints, while providing a minimum number of joinpoints necessary to fit the data. In most situations, a single segment fits the data best (single APC). If more than one APC was estimated, trends were summarized by the average APC (AAPC).

We estimated overall five-year relative survival in the patients, and then by race and histological type diagnosed during 2000-2016. Cases not microscopically confirmed and had missing data of survival time were excluded. Expected survival was estimated using the Ederer II method. Cases in the survival cohort were matched to the socioeconomic, geographic, and race annual life tables (SES/Geography/Race Annual Life Tables) by age, sex, race, calendar year, and county of residence at the time of cancer diagnosis(14). Relative survival was estimated using the Actuarial method and age-adjusted to the International Cancer Survival Standard Population, which is for cancer sites with increasing incidence by age, including vulva and vagina cancers. The relative survival was defined as the ratio of the observed to the expected survival rate. All statistical tests were two-sided, and a *P*-value of less than 0.05 was considered to indicate statistical significance.

Results

Age-adjusted incidence rates (2000 to 2016)

We identified 18,681 primary vulvar cancer cases and 5,691 primary vaginal cancer cases from 2000 to 2016 in the SEER 18 database. Overall, the age-adjusted incidence rate was 18.1 per 1,000,000 woman-years for vulva carcinoma and 5.5 per 1,000,000 woman-years for vaginal carcinoma. The incidence rates varied considerably by race, with the highest vulvar cancer incidence rate in whites (20.9) and the highest vaginal cancer rates in blacks (8.2). Moreover, the lowest incidence rates for vulvar and vaginal cancers were all demonstrated in Asians (7.1 and 3.6, respectively). The incidence rate varied widely by histological type and was highest in SCC (13.7 and 3.5 for vulvar and vaginal cancers, respectively), followed by OM (4.1 and 1.1), and ADE (0.3 and 0.9) (Table 1).

The vulvar SCC incidence was significantly higher among whites (16.1) than among blacks (12.1), Indians (11.3), Hispanics (10.0), and Asians (3.5). The vulvar ADE incidence rates were similar in blacks (0.4), whites (0.3), Asians (0.3), and Hispanics (0.2). In contrast, the vaginal SCC and ADE incidence rates were higher among blacks (5.2 and 1.2, respectively) than among whites (3.4 and 0.9), Hispanics (4.1 and 0.6), Indians (3.1 and 0.6), and Asians (2.0 and 0.6). The OM incidence rate for vulvar cancer was higher among whites (4.6) but for vaginal cancer among blacks (1.8) (Table 1).

The incidence rate overall varied regionally and was highest in the Midwest for vulvar cancer (23.7), and in the South for vaginal cancer (6.7). However, after stratifying by histological type and race, no marked regional difference was observed in most subsets (Table 2).

The incidence rates increased monotonously with age and were highest among patients aged 80 years or older overall and by histological type (Table 3).

Trends in age-adjusted incidence rates overall and by histologic type and race

Overall, the age-adjusted incidence rate increased for vulvar cancer (AAPC, 0.4%; 95% CI, 0.1% to 0.6%, from 17.28 to 18.21 per 1,000,000 woman-years in 2000 and 2016, respectively) and decreased for vaginal cancer (AAPC, -1.4%; 95% CI, -2.0% to -0.5%, from 6.13 to 4.61 per 1,000,000 woman-years in 2000 and 2016, respectively) (Fig. 1).

The SCC incidence rate increased significantly by 1.0% per year for vulvar cancer (APC, 1.0%; 95% CI, 0.6% to 1.3%) but was stable for vaginal cancer (APC, -0.5%; 95% CI, -1.3% to 0.4%). The ADE incidence rate was stable for both vulvar cancer (APC, 0.6%; 95% CI, -1.5% to 2.9%) and vaginal cancer (APC, -1.0%; 95% CI, -2.4% to 0.4%). The incidence rate for OM was stable for vulvar cancer (APC, -0.6%; 95% CI, -1.5% to 0.4%) but declined significantly by 1.7% per year for vaginal cancer (APC, -1.7%; 95% CI, -3.1% to -0.4%) (Fig. 1).

When grouped by race and ethnicity, temporal trends for Indians could not be generated because of their small number. The vulvar cancer incidence rate increased significantly by 1.2% (APC, 1.2%; 95% CI, 0.8% to 1.7%) in whites but was stable in blacks (APC, -0.1%; 95% CI, -1.0% to 0.9%), Asians (APC,-0.1%; 95% CI, -1.9% to 1.8%), and Hispanics (APC, -0.1%; 95% CI, -1.1% to 1.0%). The vaginal cancer rates decreased significantly in whites (AAPC, -1.3%; 95% CI, -2.0% to -0.3%) and Asians (APC, -2.7%; 95% CI, -4.8% to -0.6%) but was stable in blacks (APC, -1.0%; 95% CI, -3.1% to 1.2%) and Hispanics (APC, -1.7%; 95% CI, -3.5% to 0.1%). For vulvar cancer, the SCC rates increased only among whites (APC, 1.8%; 95% CI, 1.3%-2.3%) but were stable among blacks, Asians, and Hispanics, while ADE and OM rates were stable among all the women. For vaginal cancer, SCC and ADE rates were stable in all groups, whereas OM rate decreased among whites (APC, -2.0%; 95% CI, -3.9%-0.2%) (Fig. 2).

The overall temporal trends and those by histological type varied widely by age. The overall vulvar cancer rate increased significantly in the 50-59 (APC, 1.1%; 95% CI, 0.5% to 1.8%), 60-69 (APC, 1.3%; 95% CI, 0.4% to 2.1%), and 70-79 (APC, 1.2%; 95% CI, 0.3% to 2.0%) age groups, while the overall vaginal cancer rate declined significantly in the 50-59 (APC, -1.4%; 95% CI, -2.6% to -0.1%), and 80 years and older (APC, -1.4%; 95% CI, -2.7% to -0.1%) age groups. After stratifying by histological type, significantly increasing temporal trends of vulvar cancer rates were seen only among those with SCC aged 50-59 (APC, 1.9%; 95% CI, 1.1% to 2.7%), 60-69 (APC, 2.1%; 95% CI, 1.0% to 3.1%) and 70-79 (APC, 1.4%; 95% CI, 0.5% to 2.3%); on the contrary, the significantly declining temporal trends of vaginal cancer incidence rates were observed only among those with OM aged 50-59 (APC, -4.0%; 95% CI, -7.5% to -0.5%), 60-69 (APC, -3.1%; 95% CI, -5.3% to -0.8%) and 80 years or older (APC, -2.2%; 95% CI, -3.8% to -0.6%)(Fig. 2).

Five-year relative survival overall and by histologic subtype and race

The overall five-year relative survival rates were 72.3% and 49.2% in women with vulvar and vaginal cancers, respectively. The five-year relative survival of women with vulvar and vaginal cancer was 69.1% and 52.4% for SCC, 63.5% and 53. 8 for ADE, and 83.6% and 37.6% for OM, respectively. The highest

relative survival rates for both vulvar (72.7%) and vaginal (50.2%) cancers were in the whites, but the pattern was inconsistent after stratifying by histological type (Table 4 and Fig. 3).

Discussion

The Principal findings of this study are that vulvar cancer incidence rates were highest and increasing among non-Hispanic whites, while vaginal cancer rates were highest and stable among non-Hispanic blacks but declining among whites and Asians. Whites have the highest five-year relative survival rate for both vulvar and vaginal cancers.

As we discovered in this study, the vulvar SCC incidence rates have been increasing, supporting previous observations evaluating vulvar SCC incidence in the United States(15, 16), consistent with the findings of previous studies suggesting increasing vulvar cancer incidence rates in Norway, Germany, and Australia(17-19). We also found that the incidence rate of vaginal OM had been declining, but the incidence rate of vulvar OM was stable, which was consistent with the findings of previous studies(20, 21). Although our research ruled out the probability that increased vulvar incidence was attributable to misclassification of vaginal cancer to vulvar cancer because of rate changes in different histological types and races for the two cancers, it remained unclear why vulvar cancer and vaginal cancer incidence rates had contrasting temporal trends. It is likely that unknown risk factors drove the increasing incidence for vulvar SCC and the decreasing incidence of vaginal OM, for example, life-style and genetic susceptibility.

Consistent with a finding reported in a previous study(5) based on the SEER database, our study confirmed the increasing incidence rates in vulvar SCC patients aged 50-59 and 60-69 years in the US during the past decades. Additionally, we observed an increased vulvar SCC incidence among patients aged 70-79 years. Moreover, we found a stable vaginal SCC incidence in all age groups, which was in contrast to a published study that identified a decreased vaginal SCC incidence in women younger than 40 years and 70 years or older(5). We found a decreased vaginal OM incidence among patients aged 50-59, 60-69, and 80 years or older.

To the best of our knowledge, this study was the first to evaluate vulvar and vaginal cancer incidence rates by histologic type among Asians and Hispanics. Although the incidence rates for the two cancers were lower in these groups, vaginal cancer incidence has decreased rapidly among Asians, which underscores the need for a study investigating the potential protective factors among those women. Another unique characteristic of this study was assessing incidence by geographic region. Overall, the vulvar incidence rate was highest in the Midwest, and the vaginal incidence rate was highest in the South. However, after stratifying by histological type and race, no significant regional difference in rates was observed within most subsets. It was likely that the small size in each subset limited the statistical efficacy.

The strength of our study is the detailed incidence rate trends by histological type, race, age, and region. The stability of this population-based cohort (SEER 18) ensured that the same geographic regions were

represented over the entire duration of the study. Further, the detailed incidence records of newly diagnosed cases, as well as an extended period covered, allowed for APC calculations and trends observation. Furthermore, a large sample size of patients aged from 20 to 80 years or older, almost complete follow-up data, and high-quality control of the SEER program, make our results generalizable. Our study was subjected to some limitations. It was a retrospective SEER-based study. SEER did not provide information on established risk factors for vulvar and vaginal cancer, such as human papillomavirus. Therefore, we could not directly assess the variation in vulvar and vaginal cancer incidence and trends between histological types, race, and geographical regions to these risk factors. Finally, although SEER registries use standardized codes and progress to classify race and ethnicity data, the initial collection of this information is carried out by health care facilities and practitioners, and misclassification in a small proportion of cases is possible.

Given the racial disparities, clinicians would pay more attention to patients in special groups with higher incidence rates and worse survival, which is in favor of making clear the reason for the disparities. The results of this study would promote policymakers to inspect whether the health care delivery needs of patients in different racial groups are fully met or not, which is of great benefit. Ongoing surveillance for the two cancers using high-quality population-based registries is crucial to monitor cancer rates and trends.

Conclusions

There were profound disparities in vulvar and vaginal cancer incidence rates attributable to histological types, race, age, and region. Overall, the vulvar cancer incidence rate increased by 0.4% annually from 2000 to 2016, and vaginal cancer incidence rate decreased by 1.4% annually in the same period. Vulvar cancer incidence only increased for SCC, while vaginal cancer incidence only decreased for OM. The vulvar cancer incidence rate was highest and increased among non-Hispanic whites, while vaginal cancer incidence rate was highest among blacks but decreased among whites and Asians. This study demonstrates the most recent and comprehensive evaluation of differences in incidence trends and survival for vulvar and vaginal cancers in the United States. Identifying the differences can provide critical information to improve survival, explore etiology, and satisfy health care delivery needs.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and material

The datasets analyzed in this study are available in the SEER database, https://seer.cancer.gov/.

Competing interests

The authors declare that they have no competing interests.

Funding

None.

Authors' contributions

YYY: Conceptualization, Methodology, Software, Validation, Visualization, Supervision, Writing-Original draft preparation, and Editing; WLZ: Conceptualization, Data curation, Formal analyses, Supervision, Writing-Original draft preparation; DMP: Methodology**,** Supervision, Writing-Reviewing, and Editing

Acknowledgments

Not applicable.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA: a cancer journal for clinicians. 2019;69(1):7-33.
2. Gadducci A, Fabrini MG, Lanfredini N, Sergiampietri C. Squamous cell carcinoma of the vagina: natural history, treatment modalities and prognostic factors. Crit Rev Oncol Hematol. 2015;93(3):211-24.
3. Di Donato V, Bellati F, Fischetti M, Plotti F, Perniola G, Panici PB. Vaginal cancer. Crit Rev Oncol Hematol. 2012;81(3):286-95.
4. Frank SJ, Deavers MT, Jhingran A, Bodurka DC, Eifel PJ. Primary adenocarcinoma of the vagina not associated with diethylstilbestrol (DES) exposure. Gynecol Oncol. 2007;105(2):470-4.
5. Van Dyne EA, Henley SJ, Saraiya M, Thomas CC, Markowitz LE, Benard VB. Trends in Human Papillomavirus-Associated Cancers - United States, 1999-2015. MMWR Morbidity and mortality weekly report. 2018;67(33):918-24.
6. Rich NE, Yopp AC, Singal AG, Murphy CC. Hepatocellular Carcinoma Incidence Is Decreasing Among Younger Adults in the United States. Clin Gastroenterol Hepatol. 2019:242-8.e5.
7. Clarke MA, Devesa SS, Harvey SV, Wentzensen N. Hysterectomy-Corrected Uterine Corpus Cancer Incidence Trends and Differences in Relative Survival Reveal Racial Disparities and Rising Rates of Nonendometrioid Cancers. J Clin Oncol. 2019;37(22):1895-908.
8. Achey RL, Gittleman H, Schroer J, Khanna V, Kruchko C, Barnholtz-Sloan JS. Nonmalignant and malignant meningioma incidence and survival in the elderly, 2005-2015, using the Central Brain Tumor Registry of the United States. Neuro Oncol. 2019;21(3):380-91.

9. Tavakkoli A, Singal AG, Waljee AK, Elmunzer BJ, Pruitt SL, McKey T, et al. Racial Disparities and Trends in Pancreatic Cancer Incidence and Mortality in the United States. Clin Gastroenterol Hepatol. 2020;18(1):171-8.e10.
10. Murphy CC, Wallace K, Sandler RS, Baron JA. Racial Disparities in Incidence of Young-Onset Colorectal Cancer and Patient Survival. Gastroenterology. 2019;156(4):958-65.
11. Dess RT, Hartman HE, Mahal BA, Soni PD, Jackson WC, Cooperberg MR, et al. Association of Black Race With Prostate Cancer-Specific and Other-Cause Mortality. JAMA Oncol. 2019;5(7):975-83.
12. Clegg LX, Hankey BF, Tiwari R, Feuer EJ, Edwards BK. Estimating average annual per cent change in trend analysis. Stat Med. 2009;28(29):3670-82.
13. Kim H-J, Luo J, Chen H-S, Green D, Buckman D, Byrne J, et al. Improved confidence interval for average annual percent change in trend analysis. Stat Med. 2017;36(19):3059-74.
14. Mariotto AB, Zou Z, Johnson CJ, Scoppa S, Weir HK, Huang B. Geographical, racial and socio-economic variation in life expectancy in the US and their impact on cancer relative survival. PLoS One. 2018;13(7):e0201034.
15. Tan A, Bieber AK, Stein JA, Pomeranz MK. Diagnosis and management of vulvar cancer: A review. J Am Acad Dermatol. 2019;81(6):1387-96.
16. Hansen BT, Campbell S, Nygard M. Long-term incidence trends of HPV-related cancers, and cases preventable by HPV vaccination: a registry-based study in Norway. Bmj Open. 2018;8(2):e019005.
17. Barlow EL, Kang YJ, Hacker NF, Canfell K. Changing Trends in Vulvar Cancer Incidence and Mortality Rates in Australia Since 1982. Int J Gynecol Cancer. 2015;25(9):1683-9.
18. Buttmann-Schweiger N, Klug SJ, Luyten A, Holleczek B, Heitz F, du Bois A, et al. Incidence patterns and temporal trends of invasive nonmelanotic vulvar tumors in Germany 1999-2011. A population-based cancer registry analysis. PLoS One. 2015;10(5):e0128073.
19. Meltzer-Gunnes CJ, Småstuen MC, Kristensen GB, Tropé CG, Lie AK, Vistad I. Vulvar carcinoma in Norway: A 50-year perspective on trends in incidence, treatment and survival. Gynecol Oncol. 2017;145(3):543-8.
20. Smith EK, White MC, Weir HK, Peipins LA, Thompson TD. Higher incidence of clear cell adenocarcinoma of the cervix and vagina among women born between 1947 and 1971 in the United States. Cancer Causes Control. 2012;23(1):207-11.
21. Pleunis N, Schuurman MS, Van Rossum MM, Bulten J, Massuger LF, De Hullu JA, et al. Rare vulvar malignancies; incidence, treatment and survival in the Netherlands. Gynecol Oncol. 2016;142(3):440-5.

Tables

Table 1 Age-adjusted incidence rates of vulvar and vaginal cancers and by histological subtype and race

Category	Vulvar cancer			Vaginal cancer		
	No. of Case	Age-adjusted Incidence (95% CI)	IRR	No. of Cases	Age-adjusted Incidence (95% CI)	IRR
Total	18681	18.1 (17.8-18.4)	NA	5691	5.5 (5.3-5.6)	NA
Histological subtype						
Squamous cell carcinoma	14146	13.7 (13.5-13.9)	Reference	3642	3.5 (3.4-3.6)	Reference
Adenocarcinoma	326	0.3 (0.3-0.3)	0.02 (0.02-0.03)	907	0.9 (0.8-0.9)	0.25 (0.23-0.26)
Other	4209	4.1 (4.0-4.2)	0.30 (0.29-0.31)	1142	1.1 (1.0-1.2)	0.31 (0.29-0.34)
Race						
Non-Hispanic white	14938	20.9 (20.6-21.3)	Reference	3848	5.3 (5.1-5.5)	Reference
Non-Hispanic black	1503	14.7 (14.0-15.5)	0.70 (0.66-0.74)	802	8.2 (7.6-8.8)	1.55 (1.43-1.67)
Indian	96	14.9 (11.9-18.4)	0.71 (0.57-0.88)	29	4.6 (3.0-6.8)	0.87 (0.57-1.28)
Asian	623	7.1 (6.5-7.7)	0.34 (0.31-0.37)	332	3.6 (3.2-4.0)	0.68 (0.60-0.76)
Hispanic	1521	13.4 (12.7-14.1)	0.64 (0.60-0.68)	680	5.8 (5.3-6.2)	1.09 (0.99-1.18)
Histologic subtype X race						
Squamous cell carcinoma						
Non-Hispanic white	11409	16.1 (15.8-16.4)	Reference	2456	3.4 (3.3-3.5)	Reference
Non-Hispanic black	1242	12.1 (11.4-12.8)	0.76 (0.71-0.80)	510	5.2 (4.8-5.7)	1.54 (1.39-1.70)
Indian	77	11.3 (8.8-14.3)	0.70	18	3.1 (1.8-5.0)	0.93

			(0.55-0.89)			(0.53-1.49)
Asian	307	3.5 (3.1-3.9)	0.22 (0.19-0.24)	185	2.0 (1.8-2.4)	0.60 (0.51-0.70)
Hispanic	1111	10.0 (9.4-10.7)	0.63 (0.59-0.67)	473	4.1 (3.8-4.6)	1.22 (1.10-1.35)
Adenocarcinoma						
Non-Hispanic white	221	0.3 (0.3-0.3)	Reference	645	0.9 (0.8-1.0)	Reference
Non-Hispanic black	43	0.4 (0.3-0.6)	1.38 (0.97-1.94)	122	1.2 (1.0-1.5)	1.36 (1.10-1.66)
Indian	0	NA	NA	4	0.6 (0.1-1.6)	0.66 (0.16-1.77)
Asian	28	0.3 (0.2-0.5)	1.03 (0.66-1.53)	58	0.6 (0.4-0.8)	0.66 (0.50-0.87)
Hispanic	34	0.2 (0.2-0.3)	0.79 (0.52-1.16)	78	0.6 (0.5-0.8)	0.68 (0.52-0.87)
Other						
Non-Hispanic white	3308	4.6 (4.4-4.8)	Reference	747	1.0 (1.0-1.1)	Reference
Non-Hispanic black	218	2.2 (1.9-2.5)	0.47 (0.41-0.54)	170	1.8 (1.5-2.1)	1.74 (1.46-2.07)
Indian	19	3.6 (2.1-5.7)	0.79 (0.47-1.25)	7	0.9 (0.3-1.9)	0.87 (0.33-1.89)
Asian	288	3.3 (2.9-3.7)	0.71 (0.63-0.81)	89	1.0 (0.8-1.2)	0.94 (0.74-1.17)
Hispanic	376	3.1 (2.8-3.5)	0.68 (0.61-0.76)	129	1.0 (0.8-1.2)	1.00 (0.81-1.21)

Abbreviations: IRR, incidence rate ratio; NA, not applicable

Table 2 Age-adjusted incidence rates of vulvar and vaginal cancers and by histological subtype, race, and region

Category	Vulvar cancer			Vaginal cancer		
	No. of Cases	Age-adjusted Incidence (95% CI)	IRR	No. of Cases	Age-adjusted Incidence (95% CI)	IRR
Region						
South	4752	22.1 (21.5-22.7)	Reference	1460	6.7 (6.4-7.1)	Reference
Northeast	3328	19.9 (19.2-20.5)	0.90 (0.86-0.94)	887	5.2 (4.9-5.6)	0.78 (0.71-0.85)
Midwest	2237	23.7 (22.7-24.7)	1.07 (1.02-1.13)	560	5.9 (5.4-6.4)	0.88 (0.79-0.97)
West	8364	15.0 (14.7-15.4)	0.68 (0.66-0.71)	2784	5.0 (4.8-5.2)	0.74 (0.69-0.79)
Histological subtype X region						
Squamous cell carcinoma						
South	3807	17.6 (17.1-18.2)	Reference	965	4.5 (4.2-4.8)	Reference
Northeast	2571	15.3 (14.7-15.9)	0.87 (0.83-0.91)	564	3.3 (3.0-3.6)	0.74 (0.67-0.83)
Midwest	1738	18.5 (17.6-19.4)	1.05 (0.99-1.11)	348	3.6 (3.3-4.1)	0.82 (0.72-0.93)
West	6030	10.8 (10.6-11.1)	0.61 (0.59-0.64)	1765	3.2 (3.0-3.3)	0.71 (0.65-0.77)
Adenocarcinoma						
South	75	0.3 (0.3-0.4)	Reference	232	1.0 (0.9-1.2)	Reference
Northeast	64	0.4 (0.3-0.5)	1.14 (0.80-1.62)	137	0.8 (0.7-1.0)	0.77 (0.62-0.96)
Midwest	31	0.3 (0.2-0.5)	0.96 (0.61-1.49)	108	1.1 (0.9-1.4)	1.10 (0.86-1.39)
West	156	0.3 (0.2-0.3)	0.83 (0.62-1.11)	430	0.8 (0.7-0.8)	0.73 (0.62-0.86)

Other						
South	870	4.1 (3.8-4.4)	Reference	263	1.2 (1.1-1.4)	Reference
Northeast	693	4.1 (3.8-4.5)	1.01 (0.91-1.12)	186	1.1 (1.0-1.3)	0.90 (0.74-1.10)
Midwest	468	4.9 (4.5-5.4)	1.20 (1.07-1.34)	104	1.1 (0.9-1.3)	0.90 (0.71-1.13)
West	2178	3.9 (3.8-4.1)	0.96 (0.88-1.04)	589	1.1 (1.0-1.1)	0.86 (0.74-1.00)
Race X region						
Non-Hispanic white						
South	3940	24.5 (23.7-25.2)	Reference	1045	6.3 (6.0-6.7)	Reference
Northeast	2802	21.4 (20.6-22.2)	0.88 (0.83-0.92)	649	4.9 (4.5-5.3)	0.77 (0.70-0.85)
Midwest	2000	25.2 (24.1-26.3)	1.03 (0.97-1.09)	445	5.5 (5.0-6.1)	0.87 (0.78-0.97)
West	6196	17.9 (17.5-18.4)	0.73 (0.70-0.76)	1709	4.9(4.7-5.1)	0.77 (0.72-0.84)
Non-Hispanic black						
South	697	15.5 (14.3-16.8)	Reference	381	9.1 (8.1-10.1)	Reference
Northeast	250	15.1 (13.3-17.2)	0.97 (0.84-1.13)	127	7.8 (6.4-9.3)	0.86 (0.69-1.06)
Midwest	194	15.9 (13.7-18.3)	1.02 (0.87-1.21)	98	8.6 (6.9-10.5)	0.95 (0.75-1.19)
West	362	12.8 (11.5-14.2)	0.83 (0.72-0.94)	196	7.1 (6.1-8.2)	0.79 (0.66-0.94)
Indian						
South	6	9.1 (2.9-21.1)	Reference	1	1.4 (0.0-8.9)	Reference
Northeast	1	4.3 (0.1-22.2)	0.47 (0.01-3.94)	1	2.7 (0.1-18.0)	1.96 (0.02-178.09)

Midwest	6	22.5 (7.4-52.3)	2.48 (0.58-10.81)	1	7.9 (0.2-35.8)	5.66 (0.07-343.18)
West	83	15.7 (12.3-19.7)	1.73 (0.71-5.53)	26	5.0(3.2-7.4)	3.56 (0.51-145.36)
Asian						
South	40	11.8 (8.0-16.6)	Reference	6	2.3 (0.7-5.3)	Reference
Northeast	45	6.4 (4.5-8.7)	0.54 (0.33-0.90)	29	4.1 (2.6-6.0)	1.75 (0.67-6.31)
Midwest	8	5.0 (2.0-10.2)	0.42 (0.15-0.97)	3	2.2 (0.4-6.5)	0.96 (0.14-5.13)
West	530	7.0 (6.4-7.6)	0.59 (0.41-0.88)	294	3.7 (3.3-4.2)	1.58 (0.68-5.35)
Hispanic						
South	69	12.7 (9.5-16.6)	Reference	27	4.6 (2.8-7.0)	Reference
Northeast	230	17.6 (15.2-20.2)	1.38 (1.02-1.91)	81	6.2 (4.8-7.8)	1.35 (0.82-2.33)
Midwest	29	19.8 (12.7-29.1)	1.56 (0.93-2.53)	13	8.7 (4.4-15.1)	1.89 (0.84-4.02)
West	1193	12.8 (12.0-13.5)	1.00 (0.76-1.35)	559	5.7 (5.2-6.2)	1.24 (0.80-2.04)

Abbreviation: IRR, incidence rate ratio

Table 3 Age-adjusted incidence rates of vulvar and vaginal cancers by age and histological subtype

Category	Vulvar cancer			Vaginal cancer		
	No. of Cases	Age-adjusted Incidence (95% CI)	IRR	No. of Cases	Age-adjusted Incidence (95% CI)	IRR
Total	18681	18.1 (17.8-18.4)	NA	5691	5.5 (5.3-5.6)	NA
Age group						
20-29	154	0.8 (0.6-0.9)	Reference	35	0.2 (0.1-0.2)	Reference
30-39	725	3.7 (3.4-3.9)	4.84 (4.07-5.80)	174	0.9 (0.8-1.0)	5.13 (3.55-7.61)
40-49	2042	9.7 (9.3-10.2)	12.87 (10.92-15.26)	539	2.6 (2.3-2.8)	14.89 (10.57-21.61)
50-59	3334	18.1 (17.5-18.8)	23.99 (20.41-28.39)	1062	5.7 (5.4-6.1)	33.51 (23.94-48.37)
60-69	3649	30.2 (29.3-31.2)	40.01 (34.04-47.32)	1367	11.3 (10.7-11.9)	66.03 (47.23-95.20)
70-79	4028	54.8 (53.1-56.5)	72.53 (61.74-85.76)	1248	17.0 (16.0-17.9)	98.87 (70.70-142.61)
80+	4749	99.4 (96.6-102.3)	131.52 (112.01-155.44)	1266	26.5 (25.1-28.0)	154.60 (110.56-222.97)
Histological subtype X age group						
Squamous cell carcinoma						
20-29	78	0.4 (0.3-0.5)	Reference	10	0.0(0.0-0.1)	Reference
30-39	559	2.8 (2.6-3.1)	7.39 (5.82-9.49)	110	0.6 (0.5-0.7)	11.42 (5.98-24.47)
40-49	1698	8.1 (7.7-8.5)	21.12 (16.83-26.85)	353	1.7 (1.5-1.9)	34.25 (18.39-72.04)
50-59	2679	14.6 (14.0-15.1)	38.12 (30.43-48.38)	687	3.7 (3.4-4.0)	76.08 (41.09-159.37)
60-69	2671	22.1 (21.3-23.0)	57.81 (46.15-	820	6.8 (6.3-7.3)	138.83 (75.06-

			73.37)			290.61)
70-79	2946	40.1 (38.7-41.6)	104.83 (83.72-133.01)	792	10.8 (10.0-11.5)	220.28 (119.08-461.16)
80+	3515	73.6 (71.2-76.0)	192.40 (153.73-244.01)	870	18.2 (17.0-19.5)	372.56 (201.49-779.69)
Adenocarcinoma						
20-29	0	NA	NA	8	0.0 (0.0-0.1)	Reference
30-39	17	0.1 (0.1-0.1)	Reference	23	0.1 (0.1-0.2)	2.97 (1.28-7.67)
40-49	29	0.1 (0.1-0.2)	1.63 (0.87-3.17)	80	0.4 (0.3-0.5)	9.72 (4.70-23.29)
50-59	59	0.3 (0.2-0.4)	3.75 (2.16-6.86)	184	1.0 (0.9-1.1)	25.33 (12.58-59.57)
60-69	92	0.8 (0.6-0.9)	8.81 (5.22-15.79)	278	2.3 (2.0-2.6)	58.98 (29.50-137.97)
70-79	64	0.9 (0.7-1.1)	10.09 (5.84-18.38)	194	2.6 (2.3-3.0)	67.47 (33.54-158.51)
80+	65	1.4 (1.1-1.7)	15.80 (9.16-28.77)	140	3.0 (2.5-3.5)	75.52 (37.26-178.36)
Other						
20-29	76	0.4 (0.3-0.5)	Reference	17	0.1 (0.0-0.1)	Reference
30-39	149	0.7 (0.6-0.9)	2.00 (1.51-2.68)	41	0.2 (0.1-0.3)	2.47 (1.37-4.64)
40-49	315	1.5 (1.3-1.7)	4.04 (3.14-5.27)	106	0.5 (0.4-0.6)	6.00 (3.58-10.69)
50-59	596	3.2 (3.0-3.5)	8.65 (6.81-11.14)	191	1.0 (0.9-1.2)	12.44 (7.57-21.81)
60-69	886	7.4 (6.9-7.9)	19.73 (15.60-25.29)	269	2.2 (2.0-2.5)	26.75 (16.40-46.61)
70-79	1018	13.9 (13.0-14.7)	37.11 (29.37-47.49)	262	3.6 (3.1-4.0)	42.57 (26.08-74.20)
80+	1169	24.5 (23.1-	65.51	256	5.4 (4.7-6.1)	64.15

	25.9)	(51.92-83.75)	(39.28-111.85)

Abbreviations: IRR, incidence rate ratio; NA, not applicable

Table 4 Five-year relative survival rate of vulvar and vaginal cancers by histological subtype and race

Category	Vulvar cancer		vaginal cancer	
	No. of Cases	% (95% CI)	No. of Cases	% (95% CI)
Total	13314	72.3(71.2-73.3)	3474	49.2(47.1-51.2)
Histological subtype				
Squamous cell carcinoma	10083	69.1 (67.9-70.3)	2175	52.4 (49.7-54.9)
Adenocarcinoma	224	63.5 (54.9-70.9)	516	53.8 (48.5-58.7)
Other	3007	83.6 (81.4-85.6)	783	37.6 (33.7-41.6)
Race				
Non-Hispanic white	10537	72.7 (71.5-73.9)	2305	50.2 (47.7-52.7)
Non-Hispanic black	1139	71.6 (68.1-74.7)	514	45.5 (40.3-50.6)
Indian	72	71.8 (53.9-83.8)	13	28.7 (7.3-55.1)
Asian	458	72.4 (66.7-77.2)	226	48.4 (40.6-55.8)
Hispanic	1108	68.4 (64.8-71.8)	416	48.5 (42.6-54.2)
Histologic subtype x race				
Squamous cell carcinoma				
Non-Hispanic white	8094	69.5 (68.1-70.8)	1456	52.3 (49.1-55.4)
Non-Hispanic black	920	71.3 (67.4-74.8)	309	51.4 (44.4-58.0)
Indian	56	67.1 (47.8-80.6)	6	17.1 (0.8-52.8)
Asian	225	63.1 (54.8-70.3)	124	56.7 (45.5-66.5)
Hispanic	788	64.1 (59.7-68.2)	280	51.9 (44.4-58.9)
Adenocarcinoma				
Non-Hispanic white	142	62.6 (51.5-71.8)	360	57.6 (51.2-63.5)
Non-Hispanic black	35	51.4 (30.7-68.8)	78	38.0 (25.5-50.4)
Indian	0	NA	2	50.6 (0.5-91.5)
Asian	21	72.1 (45.7-87.2)	38	58.7 (39.2-73.8)
Hispanic	26	79.4 (46.7-93.2)	38	42.1 (24.7-58.5)
Other				
Non-Hispanic white	2301	84.8 (82.1-87.0)	489	38.6 (33.5-43.6)
Non-Hispanic black	184	76.3 (67.4-83.0)	127	35.9 (26.4-45.4)

Indian	16	82.0 (24.6-97.2)	5	NA
Asian	212	81.8 (73.6-87.7)	64	26.1 (14.5-39.3)
Hispanic	294	78.5 (72.0-83.7)	98	41.9 (30.0-53.2)

Abbreviation: NA, not applicable

Figures

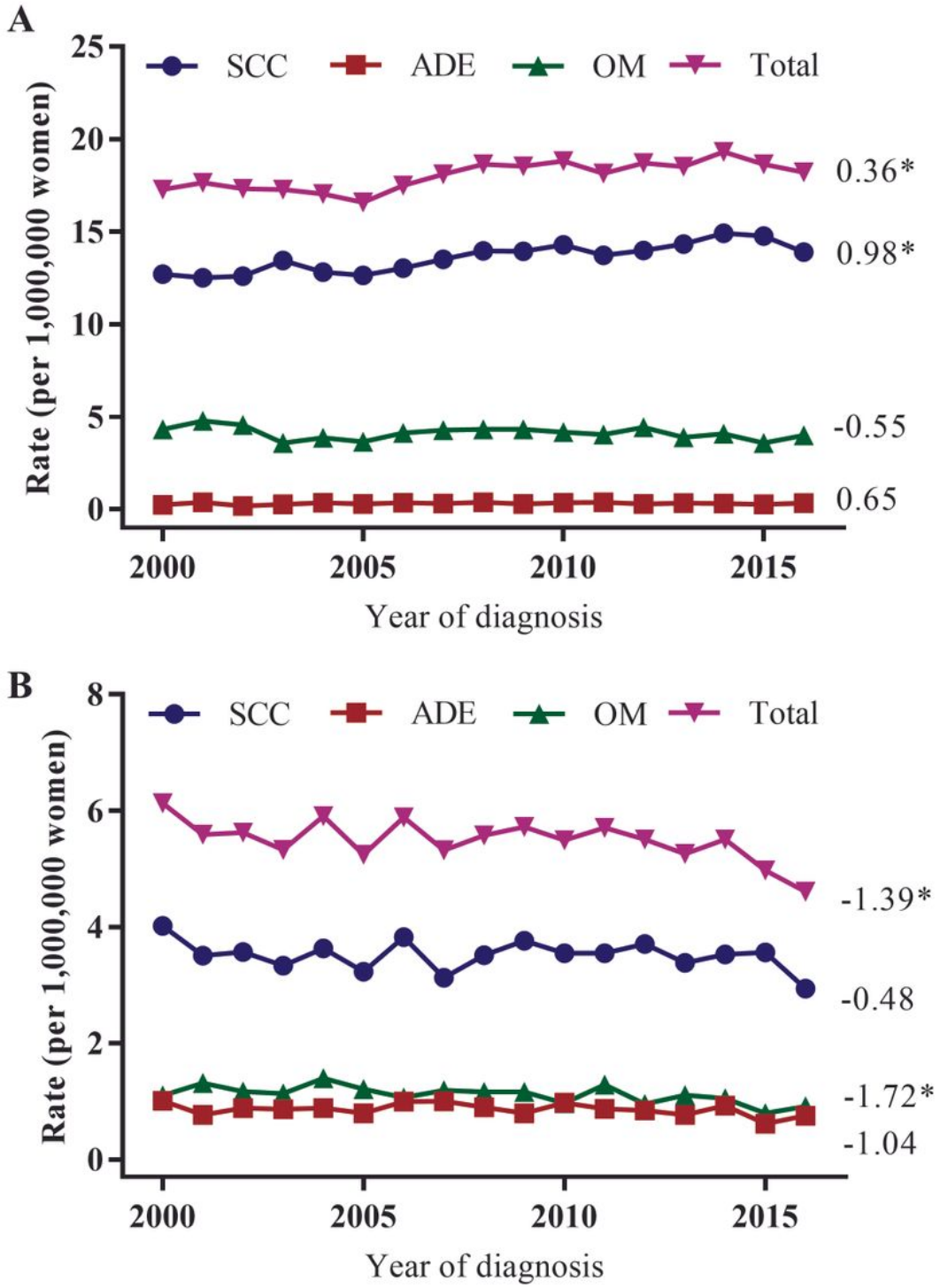

Figure 1

Incidence trends in vulvar and vaginal cancers by histological type during 2000-2016. (A) vulvar cancer; (B) vaginal cancer. All trends are summarized by a single annual percentage change estimate, except for overall rates, which are summarized by the average annual percentage change; trends for vulvar and vaginal cancer are plotted on a different scale. SCC, Squamous cell carcinoma; ADE adenocarcinoma; OM, other malignancies. (*) Significantly different than zero at P< 0.05.

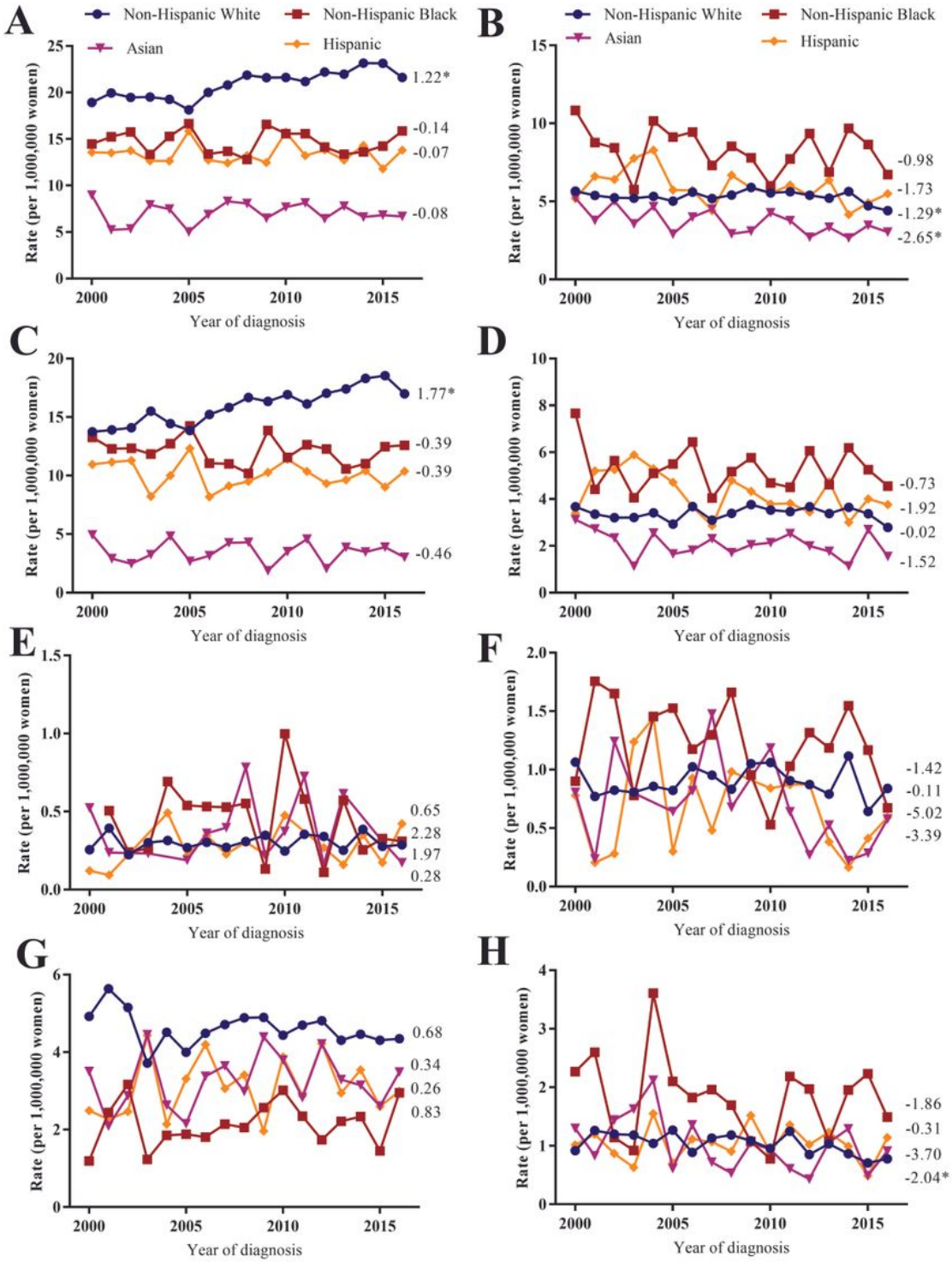

Figure 2

Incidence trends in vulvar and vaginal cancers by race during 2000-2016. (A, C, E, G) vulvar cancer; (B, D, F, H) vaginal cancer; (A, B) overall and within (C, D) squamous cell carcinoma, (E, F) adenocarcinoma, and (G, H) other malignancies subgroups. Vulvar and vaginal cancer rates for non-Hispanic whites (dot), non-Hispanic blacks (square), non-Hispanic Asians/Pacific Islanders (triangle), and Hispanics (rhombus) are shown separately. All trends are summarized by a single annual percentage change estimate, except for

squamous cell carcinoma rates among non-Hispanic whites, which are summarized by the average annual percentage change; trends are plotted on a different scale. (*) Significantly different than zero at P< 0.05.

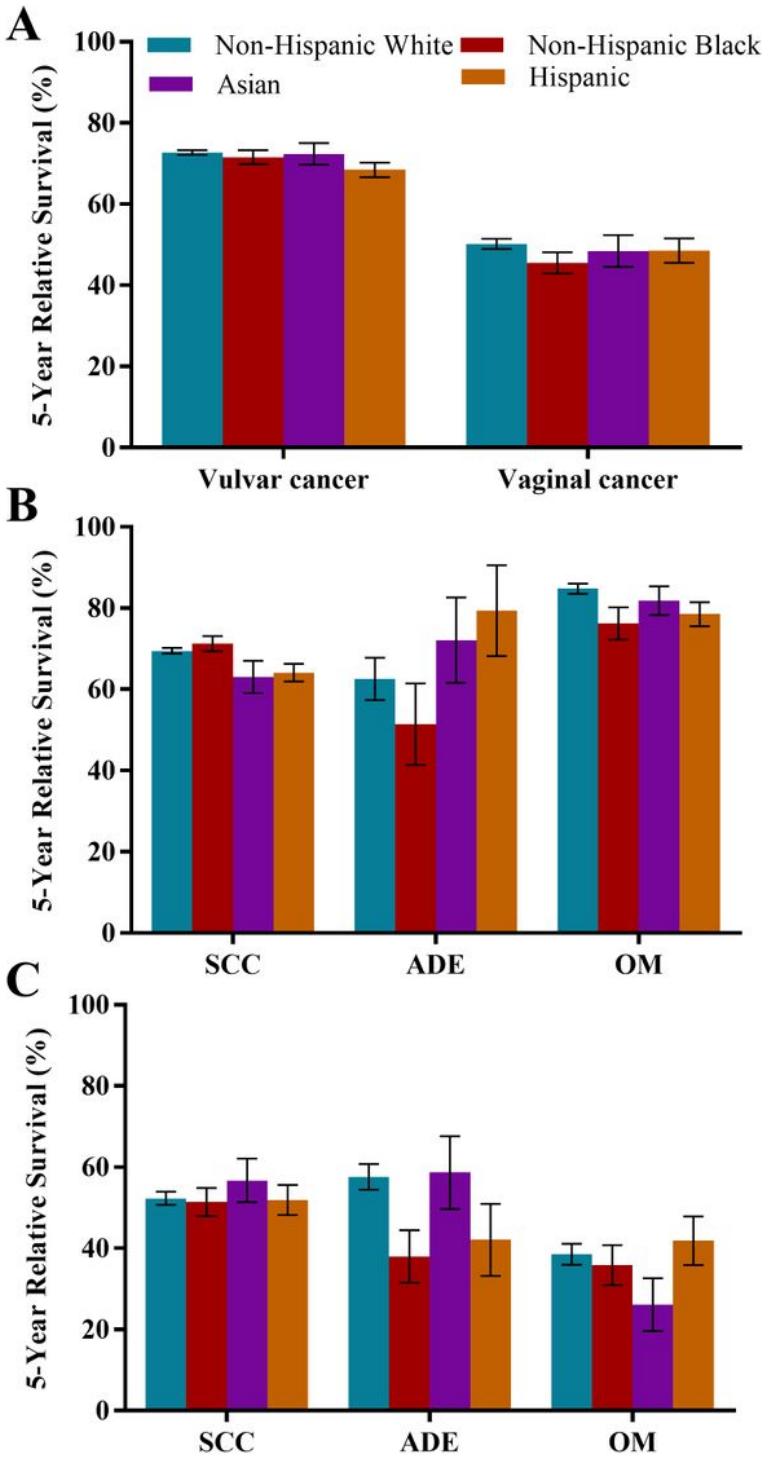

Figure 3

Five-year relative survival of vulvar and vaginal cancers by race during 2000-2016. (A) overall and by histological type in (B) vulvar cancer and (C) vaginal cancer. Expected survival for patients diagnosed

between 2000 and 2016 was estimated with the Ederer II method, and relative survival was calculated by estimating the observed to the expected survival rate using the actuarial method. Error bars indicate standard error of the mean.