Risk of Anal Cancer in a Cohort With Human Papillomavirus – Related Gynecologic Neoplasm

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Abstract

Background: To assess the development of anal cancer in women diagnosed with a human papillomavirus-related cervical, vulvar, or vaginal neoplasm.

Methods: Using data from National Cancer Institute's Surveillance, Epidemiology and End Results program from 1973 through 2007, 189,206 cases with either in situ or invasive cervical, vulvar, or vaginal neoplasm were followed for 138,553,519 person – years for the development of subsequent primary anal cancer. Standardized incidence ratios were calculated from the observed number of subsequent anal cancers compared with those expected based on age-, race- and calendar year- specific rates in the nonaffected population.

Results: Anal cancer developed in 255 women with a history of in situ or invasive gynecologic neoplasm, aggregate standardized incidence ratio of 13.6 (95% confidence interval [CI] 11.9 – 15.3), indicating a 13-fold increase in anal cancer compared with expected. The standardized incidence ratio for anal cancer incidence among women with in situ vulvar cancer was 22.2 (95% CI 16.7 – 28.4) and was 17.4 (95% CI 11.5 – 24.4) for those with invasive vulvar cancer. The standardized incidence ratio for anal cancer incidence in women with in situ cervical cancer was 16.4 (95% CI 13.7 – 19.2) and was 6.2 (95% CI 4.1 – 8.7) for women with invasive cervical cancer. The standardized incidence ratio for anal cancer incidence among women with in situ vaginal cancer was 7.6 (95% CI 2.4 – 15.6) and was 1.8 (95% CI 0.2 – 5.3) for invasive vaginal cancer.

Conclusions: Women with human papillomavirus-related gynecologic neoplasm are at higher risk for developing anal cancer compared with the general population. This high-risk population may benefit from close observation and screening for anal cancer.

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Background

Squamous cell cancer of the anus is a rare malignancy that constitutes 1-2% of all gastrointestinal tumors. The American Cancer Society estimates that 5,260 incident anal cancer cases and approximately 720 attributable deaths will have occurred in 2010 [1]. The incidence of anal cancer has increased significantly over the past 2 – 3 decades [2]. In a population-based review of the Surveillance, Epidemiology and End Results (SEER) cancer registry, a 2.8 fold increase in the incidence of anal cancer was identified from 1973 through 1998 [2]. Much of this increased incidence is thought to be attributable to infection with human papillomavirus (HPV), similar to the pathophysiology of cervical cancer. In fact, the presence of high-risk types of human papillomavirus, particularly HPV-16 or HPV-18, has been identified in a large proportion of anal cancer tissue specimens [3-6].

Prevention of anal cancer with screening has been proposed to reduce the burden of disease from this malignancy. However, general population-wide screening with anal Papanicolaou smear would not likely be cost-effective or acceptable to most patients. Recommendations for anal cancer screening that target high-risk groups are needed. Presently, men who have sex with men and immuno-compromised hosts are considered to be at high-risk for anal cancer [7]. In addition, several population-based studies report an increase in anal cancer incidence among women with invasive and in situ cervical cancer [8, 9] as well as invasive vulvar and vaginal cancer [10] . At this time, few data exist regarding the risk associated with in situ gynecologic neoplasm, and whether it differs from the risk associated with invasive gynecologic neoplasm [11]. We used the SEER registry, a large population-based cancer registry, to measure the incidence of secondary anal cancers in a

cohort of women with either in situ or invasive cervical, vulvar, or vaginal human papillomavirus-related neoplasm. We also characterized the duration between the diagnoses of the human papillomavirus-related gynecologic neoplasm and anal cancer and investigated whether radiation therapy for gynecologic cancer modifies the risk of a subsequent anal cancer.

METHODS

Data

We used data from the SEER Program for this study and included 17 registries from Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, Utah, Greater California, Kentucky, Louisiana, New Jersey, Georgia and the Alaska, Los Angeles and San Jose-Monterey [12]. Information collected by SEER includes patient characteristics, tumor site, grade, stage, first course of treatment, and follow-up for vital status [13]. We hold a data use agreement with the National Cancer Institute and our study protocols were reviewed and considered exempt by the Lahey Clinic Institutional Review Board. The SEER public access user file makes every effort to protect the identities of cancer patients. The data use agreement specifically requests that all research results must be presented or published in a manner that ensures that no individual can be identified [13]. As per our data use agreement, we have hidden all sample sizes of fewer than five patients.

Patient selection

We identified all women diagnosed with invasive cervical, vaginal, or vulvar cancer from 1973 to 2007 or in situ cervical, vaginal, or vulvar cancer from 1973 to 1995. The SEER program ceased tracking in situ tumors of the cervix after 1995. The inclusion criteria were all girls and women older than 15 years of age at the time of a primary diagnosis of invasive cervical, vulvar, or vaginal cancer that was histopathologically categorized as squamous cell carcinoma. A total of 56,876 girls and women had an invasive gynecologic neoplasm, and 7,886 were excluded because of a history of previous primary cancer. Also excluded were 22,625 women with primary gynecologic neoplasm of the following cell types: adenocarcinoma, adenosquamous carcinoma, endometrioid adenocarcinoma, serous

adenocarcinoma, and undifferentiated carcinoma. Study size was determined by number of patients who met inclusion and exclusion criteria.

Subsequent Anal Cancer

We identified all women who developed squamous cell cancers of the anus after a primary diagnosis of either in situ or invasive primary gynecologic neoplasm. Two methods were used for selection of secondary anal cancer cases: the restrictive and the inclusive methods. In the restrictive method, we limited our cases to women who developed anal cancer as the second primary cancer. If another cancer developed between the gynecologic neoplasm and anal cancer, then it was excluded in the restrictive method. In the inclusive method, anal cancer could develop as a second, third or fourth primary cancer. Standardized incidence ratios were calculated by both methods. Thirteen women who developed a second primary anal cancer within 1 year of the primary gynecologic diagnosis were also excluded to avoid potential bias of synchronous tumors, which may have made determination of time sequence difficult.

Statistical Analysis

The computation of standardized incidence ratios was conducted using indirect standardization methods applied to the person-time accumulated among individuals meeting inclusion criteria from the SEER population. Person-years at risk for the development of subsequent cancers for each woman began at 2 months after the date of diagnosis of the gynecologic cancer and ended at the date of last contact with the patient, death, or end of the study period on December 2006, whichever was earliest. The person-years and observed

cases of subsequent anal cancers were stratified according to patient age at initial gynecologic neoplasm diagnosis (5-year groups), race or ethnicity, and 5-year calendar intervals. Anal cancer incidence rates among the female population were calculated and stratified by age, race, and calendar-year group, and were multiplied by the person-years accrued by the gynecologic cancer cases to estimate the expected numbers of subsequent cancers for each stratum. The observed and expected numbers of subsequent cancers for each stratum were then summed. The standardized incidence ratio represents the ratio of the observed number divided by the expected number of subsequent cancers. Briefly, the standardized incidence ratio reports the incidence of cancer in a population at risk compared with an expected incidence of cancer in a population determined to be at average risk or "normal". For example, a standardized incidence ratio of 1.0 indicates that the observed number of anal cancer cases in those patients with a history of gynecologic neoplasm is equal to what would be the expected number of anal cancer cases from a comparison "average" population in the SEER program. A standardized incidence ratio greater than 1.0 would indicate that more cancer cases occurred than expected; thus a standardized incidence ratio of 2.0 should be interpreted as observing twice as many anal cancer cases among a population with gynecologic neoplasia than the expected number among an "average" population of women. Confidence intervals (CIs) for the standardized incidence ratios were calculated using Vandenbroucke Method [14]. Standardized incidence ratios were calculated separately for in situ and invasive cancers. SEER*STAT and SAS 9.2 were used for data analysis [13].

In an effort to assess the potential effects of radiotherapy on the subsequent development of primary anal cancers, gynecologic cancer cases were stratified by whether they received radiation therapy (yes or no) and standardized incidence ratios were calculated

as described above within these strata. A total of 1,103 women with unknown radiotherapy status were excluded from this analysis.

We also described the time period between the primary gynecologic neoplasm and subsequent anal cancer diagnosis using means and standard deviations and tested for differences between invasive and in situ neoplasm with the Student *t* test. Finally, we used Kaplan-Meier curves to characterize the risk of anal caner over the duration of follow-up.

RESULTS

Index Cohort

We identified a total of 189,206 cases: 132,330 cases of in situ human papillomavirus-related gynecologic neoplasm (124,075 cervical, 6,792 vulvar, and 1,463 vaginal) and 56,876 cases of invasive gynecologic neoplasm (43,669 cervical, 9,950 vulvar, and 3,257 vaginal). Demographic characteristics of the index cohort are presented in Table 1.

Risk of Anal Cancer

Using the inclusive method, we identified 255 cases of anal cancer, 58 anal cancers among women with invasive primary gynecologic neoplasm and 197 anal cancers after an in situ gynecologic neoplasm, during a follow-up of 138,553,519 person-years (Table 2). The aggregate standardized incidence ratio for the incidence of anal cancer in all patients with gynecologic neoplasm was 13.6 (95% CI 11.9 – 15.3). The standardized incidence ratio for the incidence of anal cancer was 6.2 (95% CI 4.1 – 8.7), 17.4 (95% CI 11.5 – 24.4) and 1.8 (95% CI 0.2 – 5.3) for women with invasive cervical, vulvar, and vaginal cancer, respectively (Table 3). The standardized incidence ratios for women with in situ gynecologic neoplasm were higher than those for women with invasive cancers. The standardized incidence ratio for the incidence of anal cancer was 16.4 (95% CI 13.7 – 19.2), 22.2 (95% CI 16.7 – 28.4), 7.6 (95% CI 2.4 – 15.6) for women with in situ cervical, vulvar, and vaginal cancer, respectively (Table 3).

The analyses were repeated using the restrictive method to remove the potential of confounding from other cancer treatment. Using this approach, the standardized incidence ratio for anal cancer was 5.1 (95% CI: 3.2 – 7.4), 14.3 (95% CI: 9.0 – 20.9) and 1.8 (95% CI

0.2 – 5.4) for women with an initial invasive cervical, vulvar, and vaginal cancer diagnosis, respectively. The standardized incidence ratio for anal cancer was 14.3 (95% CI 12.0 – 17.2), 16.1 (95% CI 11.4 – 21.6) and 6.1 (95% CI: 1.50 – 13.6) for in situ cervical, vulvar, and vaginal neoplasm, respectively.

Latency of Anal Cancer

Kaplan-Meier curves characterizing the time to anal cancer diagnosis for each gynecologic malignancy were calculated. The mean time interval between the incidence of primary gynecologic malignancy and the diagnosis of a second primary anal cancer was longest in women with in situ cervical cancer (15.7 years). In fact, the interval between diagnoses was longer for in situ compared with invasive cancers for all gynecologic neoplasm, although the small number of anal cancers observed among the vaginal cancer cases limits this conclusion (Table 4).

The effect of Radiation therapy

Radiation therapy was reported as a treatment used in 23,884 (55.6 %) women with invasive cervical cancer, 2,215 (22.7 %) women with invasive vulvar cancer, and 2,008 (63.6%) women with invasive vaginal cancer. The risk of anal cancer in women with a previous cervical cancer diagnosis was similar among women who did not receive radiotherapy (standardized incidence ratio= 3.1, 95% CI 1.6 – 4.9) compared with those who did (standardized incidence ratio= 2.9, 95% CI 1.5 – 4.6) (Table 5). The data for vulvar and vaginal cancer were inconclusive.

Discussion

We identified a significant association between gynecologic neoplasm and anal

cancer for both in situ and invasive cancers of the cervix and vulva and in situ neoplasm of the vagina. The highest risk for anal cancer was identified in those women with evidence of either in situ or invasive squamous cell cancer of the vulva. These data indicate that women with both in situ and invasive cancers of the cervix and vulva are at higher risk for developing anal cancer than the general population and may benefit from close observation and anal cancer screening.

The pathway of human papillomavirus-related malignant transformation for cervical cancer has been well established and has led to effective prevention strategies. The National Cancer Institute recommends cervical cancer screening with Papanicolaou smear at least once every 3 years, starting within 3 years of the initiation of sexual intercourse, but no later than age 21 [15]. Although randomized controlled trials demonstrating a benefit to cervical cancer screening have not been conducted, observational studies from the International Agency for Research on Cancer have shown a 91%-94% reduction in cervical cancer incidence with screening [16]. The incidence of cervical cancer decreased from 32 cases per 100,000 women in the 1940s to 8.3 cases per 100,000 women in the 1980s in the United States, and is largely attributed to increased use of cervical cytology to detect precursor lesions [17].

Although it would be impractical and not cost-effective to implement a policy of routine anal cancer screening in the United States for all sexually active adults, screening has been proposed for individuals at elevated risk for anal cancer. Given that routine Papanicolaou smear screening has significantly reduced cervical cancer incidence and mortality across many populations, it is expected that similar screening of populations at high risk for anal cancer precursor lesions will also reduce the burden of this disease [18]. To

accomplish this goal, high-risk groups must be identified to properly target those individuals who may benefit. Our data reveal that women with a previous gynecologic neoplasm represent a high-risk group, particularly those women with vulvar neoplasm.

Epidemiologic data reveal that as in cervical cancer, the majority of patients with anal squamous cell cancer have had associated infection with a similar HPV subtypes. In particular, HPV-16 is the most commonly isolated subtype from anal cancer tissue specimens (cite ref 3). Given the common precursor for anal and gynecologic squamous cell cancers, a common pathway for cancer transformation in the genitalia and anus has been proposed, thereby placing women with genital cancers at higher risk for developing anal cancer. Previous data have shown that women with cervical, vulvar, and vaginal cancers are at higher risk for anal human papillomavirus infection and anal intraepithelial neoplasia [19-22]. In addition, population-based studies reveal that the risk of anal cancer is significantly greater in women with in situ or invasive cervical cancer [8]. Our study using population-based data from the United States reports a standardized incidence ratio of 16.3 and 6.2 for women with in situ and invasive cervical cancer, respectively. The increased risk among the in situ group may be due to differences in treatment, surveillance, strain of human papillomavirus, or other host defenses. Not surprisingly, because of the proximity, the highest risk of anal cancer was noted in women with in situ vulvar neoplasm. Length of follow-up is unlikely to account for the increased risk with in situ neoplasia as our study did adjust for patient follow-up. Other possible explanations for the increased risk of anal cancer with in situ neoplasm may be related to differences in treatment, surveillance, strain of human papillomavirus, or other host defenses.

In addition to the increased risk of anal cancer with in situ neoplasm, we also

evaluated the role of radiation in modifying the association between gynecologic neoplasm and anal cancer. We hypothesized that exposure to irradiation would prevent development of anal cancer, given the therapeutic role of irradiation as a component of the Nigro protocol, consisting of 5-flurouracil, mitomycin C, and 30 Gy of radiation therapy [23]. Chaturvedi *et al* similarly examined the incidence of secondary cancers after cervical cancer and found that all women had a higher risk of developing anal cancer compared with the general population, regardless of radiation therapy status [24] Consistent with their result, we found that women with invasive gynecologic malignancy who were exposed to radiotherapy had a similar risk of anal cancer compared with those who did not receive radiotherapy. Our findings are not compatible with our hypothesis that radiation therapy sterilizes dysplasia in those areas included in the field of treatment, including the anus.

Our study has limitations related to the nature of the data used in our analyses. First, although the data are collected prospectively, we analyzed the data retrospectively, which might lead to selection or information bias. Second, migration of participants out of the states included in the SEER registry may have limited the capture of second primary tumors. Migration status is not recorded in our dataset [25] and might lead to underreporting of second primary cancers, resulting in a conservative estimate of subsequent cancer risk. Additionally, we were unable to explore the role of human papillomavirus-positive status because the tumor registry does not record this information. However, it is acknowledged that human papillomavirus infection is present in almost all cases of cervical cancer [26], and in the vast proportion of cases of vulvar, and vaginal cancer [27]. Fourth, we were unable to identify the role of HIV on the overall effect toward anal cancer development. It is clear that patients with HIV are at increased risk for squamous cell cancer of the anus, and that

infection with this virus rose substantially during the study period. A fifth limitation is that cancer patients are often under more intense medical surveillance than the general population, leading to ascertainment bias [11] and a possible inflation of the standardized incidence ratio. Notwithstanding the potential biases and caveats described, the SEER program is an excellent population-based tool that broadly characterizes cancer epidemiology and treatment, avoiding potential biases that can be introduced in hospital-based studies as a result of area referral patterns and incomplete follow-up [25].

In conclusion, our study has demonstrated that women with a wide range of primary human papillomavirus-related gynecologic neoplasm are at higher risk for developing anal cancer compared with the general population. On average, anal cancer developed between 4 and 16 years after diagnosis and thus, women with gynecologic neoplasm may benefit from early anal cancer screening. According to our data, those treated with irradiation are not protected from the development of incident anal cancer and should still be considered high risk. At this time, cost-effectiveness analyses are needed to determine the value of anal cancer screening in women with primary human papillomavirus-related gynecologic neoplasm.

Tables

Table 1. Characteristics of Cohort With Cervical, Vaginal, and Vulvar Neoplasm Using the Inclusive Method.

	Cervical		Vaginal		Vulvar	
	In situ	**Invasive**	**In situ**	**Invasive**	**In situ**	**Invasive**
Gynecologic cancer cases	124,075	43,669	1,463	3,257	6,792	9,950
Race						
White	103,314 (83.2)	33,005 (75.5)	1,194 (81.6)	2,642 (81.2)	5,956 (87.7)	8,890 (89.4)
African American	14,862 (12.0)	6,725 (15.4)	203 (13.9)	459 (14.0)	685 (10.1)	838 (8.4)
Other	5,899 (4.8)	3,939 (9.1)	66 (4.5)	156 (4.8)	151 (2.2)	222 (2.2)
Age at diagnosis (y)						
15-19	3,174 (2.6)	44 (0.1)	23 (1.6)	1 (0.03)	87 (1.3)	4 (0.04%)
20-24	18,028 (14.5)	613 (1.4)	56 (3.8)	6 (0.2)	321 (4.7)	19 (0.2)
25-29	30,675 (24.7)	2,394 (5.5)	52 (3.6)	15 (0.5)	516 (7.6)	59 (0.6)
30-34	26,490 (21.4)	4,217 (9.7)	66 (4.5)	27 (0.8)	680 (10.0)	167 (1.7)
35-39	17,039 (13.7)	5,038 (11.5)	88 (6.0)	87 (2.7)	783 (11.5)	366 (3.7)
40-44	10,497 (8.5)	5,335 (12.2)	119 (8.1)	107 (3.3)	839 (12.4)	507 (5.1)
45-49	6,078 (4.9)	4,883 (11.2)	122 (8.3)	172 (5.3)	714 (10.5)	683 (6.9)
50-54	3,397 (2.7)	4,254 (9.7)	148 (10.1)	234 (7.2)	586 (8.6)	754 (7.6)
55-59	2,386 (1.9)	3,813 (8.7)	152 (10.4)	278 (8.5)	502 (7.4)	739 (7.4)
60-64	2,050 (1.7)	3,466 (7.9)	159 (10.9)	320 (9.8)	463 (6.8)	735 (7.4)
65-69	1,805 (1.5)	3,083 (7.1)	161 (11.0)	380 (11.7)	464 (6.8)	887 (8.9)
70-74	1,228 (1.0)	2,356 (5.4)	139 (9.5)	403 (12.4)	362 (5.3)	1,125(11.3)
75-79	701 (0.6)	1,830 (4.2)	102 (7.0)	431 (13.2)	269 (4.0)	1,321(13.3)
80-84	362 (0.3)	1,254 (2.9)	53 (3.6)	366 (11.2)	124 (1.8)	1,169(11.8)
85 or older	165 (0.1)	1,089 (2.5)	23 (1.6)	430 (13.2)	82 (1.2)	1,415(14.2)
Vital Status						
Alive	109,836 (88.5)	23,981(54.9)	816 (55.9)	1,080 (33.2)	4,459 (65.7)	4,535 (45.6)
Dead *	14,239 (11.5)	19,688 (45.1)	647 (44.1)	2,177 (66.8)	2,333 (34.3)	5,415 (54.4)

Data are n or n (%)

* Patient's vital status at the date of last contact, death, or end of the study period on December 2006, whichever was earliest.

Table 2. Characteristics of Anal Cancer Patients With Initial Gynecologic Neoplasm Using The Inclusive Method.

	Cervical		Vaginal		Vulvar	
	In situ	**Invasive**	**In situ**	**Invasive**	**In situ**	**Invasive**
Number of Anal Cancer Cases	137	28	5	Fewer than 5*	55	28
Race						
White	116(84.7)	24(85.8)	4(80)		45(81.8)	22(78.6)
African American	11(8.0)	4(14.2)	1(20)	-	9(16.4)	5(17.9)
Other	10(7.3)	0	0		1(1.8)	1(3.5)
Age at anal cancer diagnosis, n (%)						
15-19						
20-24	0	0	0	-	0	0
25-29	0	0	0	-	0	0
30-34	1(0.73)	0	0	-	1(1.8)	1(3.6)
35-39	4(2.9)	0	1(20)	-	1(1.8)	2(7.1)
40-44	11(8.0)	2(7.1)	0	-	7(12.7)	1(3.6)
45-49	18(13.1)	3(10.7)	2(40)	-	1(1.8)	0
50-54	17(12.4)	0	0	-	13(23.6)	3(10.7)
55-59	26(19.0)	4(14.3)	0	-	12(21.8)	1(3.6)
60-64	24(17.5)	3(10.7)	1(20)	-	9(16.4)	9(32.1)
65-69	14(10.2)	4(14.3)	0	-	6(11.0)	3(10.7)
70-74	5(3.6)	5(17.9)	0	-	4(7.3)	1(3.6)
75-79	8(5.8)	3(10.7)	0	-	0	0
80-84	7(5.1)	1(3.6)	0	-	1(1.8)	5(17.9)
85 or older	1(0.7)	2(7.1)	0	-	0	0
	1(0.7)	1(3.6)	1(20)	-	0	2(7.1)

* These data hidden as per our data-use agreement with the Surveillance, Epidemiology, and End Results program.

Table 3. Standardized Incidence Ratio of Anal Cancer in Patients With In Situ and Invasive Gynecologic Neoplasm Divided by Race Using the Inclusive Method.

Primary Gynecologic Neoplasm	In situ vs. invasive	Race	Observed	Expected*	Standardized Incidence Ratio	95 % CI**
Cervical	***In situ***	**Total**	**137**	**8.4**	**16.4**	**13.7 - 19.2**
		White	116	6.6	17.4	14.4 - 20.7
		African American	11	1.4	7.6	3.8 - 12.8
		Other	10	0.26	38.46	18.3 – 66.0
	Invasive	**Total**	**28**	**4.5**	**6.2**	**4.1 - 8.7**
		White	24	3.5	6.8	4.3 - 9.8
		African American	<5**	0.8	5.1	1.3 - 11.2
Vulvar	**In situ**	**Total**	**55**	**2.5**	**22.2**	**16.7 - 28.4**
		White	45	2.2	20.3	14.8 - 26.6
		African American	9	0.2	37.5	17.0 – 66.0
	Invasive	**Total**	**28**	**1.6**	**17.4**	**11.5 - 24.4**
		White	22	1.5	14.8	9.2 - 21.6
		African American	5	0.1	45.5	14.3 – 94.0
Vaginal	**In situ**	**Total**	**5**	**0.7**	**7.6**	**2.4 - 15.6**
	Invasive	**Total**	**< 5*** **	**<5*** **	**1.8**	**0.2 - 5.3**

* The expected cases were calculated from Surveillance, Epidemiology and End Results 9, stratified by age, race, and calendar-year group.
** The Confidence interval was calculated using the Vandenbroucke Method.
*** These data hidden as per data-use agreement with the Surveillance, Epidemiology and End Results program.

Table 4. Time Interval Between Gynecologic Neoplasm and Anal Cancer.

Primary Gynecologic Neoplasm		Number Of Anal Cancer Cases	Mean (Median) Time Between diagnoses (y)	Minimum Time Between Diagnoses (y)	Maximum Time Between Diagnoses, (y)	*P* value*
Cervical Neoplasm						
	Invasive	28	11.4(13)	0	29	0.01
	In situ	137	15.7(16)	0	30	
Vulvar Neoplasm						
	Invasive	28	7.1(4.5)	0	23	0.24
	In situ	55	8.9(8)	0	23	
Vaginal Neoplasm						
	Invasive	<5**	4.5(4.5)	3	6	0.22
	In situ	5	11(11.5)	1	16	

*Student *t* test was used to estimate the *P* value.

**These data hidden as per data-use agreement with the Surveillance, Epidemiology and End Results program.

Table 5. Standardized Incidence Ratio of Anal Cancer Among Women With Invasive Cervical, and Vulvar Neoplasia by Mode of Treatment.*

	Cervical Neoplasm			Vulvar Neoplasm		
Mode of Treatment*	Observed	Expected	SIR (95% CI)	Observed	Expected	SIR (95% CI)
Radiotherapy	13	4.5	2.9 (1.5 – 4.6)	< 5	1.6	2.5(0.6 - 5.5)
No Radiotherapy	14	4.5	3.1 (1.6 - 4.9)	20	1.6	12.4(7.5 – 18.4)

CI, Confidence interval

* Women with unknown mode of treatment were excluded.

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Appendix I: Expanded Background

Human papillomavirus (HPV) is the most common sexually transmitted disease in the United States. HPV is a DNA virus that belongs to the papillomaviridae family, which has a great tropism for epithelial cells in the skin and mucous membranes. HPV has more than 150 types, 40 of them can infect the anogenital tract. It is classified as either high or low risk based on their oncogenic potential. Low risk HPV (HPV 6,11) can cause condylomata acuminata, whereas high risk HPV (HPV 16,18) causes cervical cancer. HPV has been implicated in the pathogenesis of other anogenital tumors, such as vulvar, vaginal, and anal tumors.

Anal squamous cell carcinoma is a rare malignancy of the gastrointestinal tract. Although it is rare, however, in the past 20 years, the incidence of anal squamous cell carcinoma is doubled [1]. In a study used the Surveillance, Epidemiology and End Results (SEER) database between 1974 through 2000, it demonstrated an increased incidence of anal cancer among females during that time period [2]. In another study that used both SEER database and the Centers for Disease Control and Prevention's National Program of Cancer Registries (NPCR), it was reported that the incidence rates of anal cancer among women increased by 2.8% per year between 1992 and 2004 [3]. There is growing evidence-linking HPV to anal cancer[4, 5]. The prevalence of HPV in anal cancer was found to be 90%, and HPV 16 was found in more than 75% of the cases [6]. A case control study conducted in Sweden and Denmark showed that 88% of patients with anal cancer had HPV DNA present in the anal cancer specimens after they were

analyzed by polymerase chain reaction (PCR) assay compared to two control groups. Furthermore, it demonstrated that 73% of the specimens were positive for HPV-16 [7]. HPV has also been found in anal intraepithelial neoplasia (AIN) [8, 9].

Both anal and cervical cancers have much in common; they share embryologic, and pathologic features, as well as the type of the oncogenic HPV. However, despite of these similarities, the full natural history of anal intraepithelial neoplasia is not fully known. AIN is classified to low grade (AIN I), and high grade AIN (AIN II or III). High grade AIN is a premalignant lesion and can progress to anal cancer. In a cohort study in HIV positive and HIV negative patients, progression from low grade AIN to high grade AIN was more common among patients who were HIV positive, who had low CD4 count, and who had infection with multiple HPV types [10].

The TNM staging system of squamous cell carcinoma of the anus is dependent on the tumor size (T), nodal involvement (N), and the presence or absence of distant metastasis (M). In a cohort study of 19,195 patients with squamous anal cell carcinoma who were identified from the National Cancer Database between 1985 and 2000, it showed that distant metastasis was present in 5.7% of patients, and nodal involvement was present in 19.5% [11]. Tumor size (T) classification was as follows: T1: 27%, T2: 44.8%, T3: 20.6%, T4: 4.5%. The 5-year survival was 68.5%, 58.9%, 43.1%, and 34.3% for T1, T2, T3, and T4 tumors [11].

The treatment of the squamous cell carcinoma of the anus has changed dramatically over the last 25 years. In the past, the standard treatment was wide local excision or abdominoperineal resection (APR). Outcomes were generally poor, with a

high rate of recurrence. A major improvement in the treatment of anal cancer happened after the introduction of the Nigro protocol in 1974 [12]. Nigro protocol consists of 3,000 rad external irradiation to the primary tumor, pelvic and inguinal lymph nodes, and systemic chemotherapy. Currently, chemotherapy and radiotherapy are the treatment strategies for these patients.

Because anal cancer and gynecologic cancers share common risk factors, anal cancer can develop in patients with primary gynecologic neoplasm. In a large Swedish cohort study among women diagnosed with grade 3 cervical intraepithelial neoplasia (CIN3), the incidence rate ratio of anal cancer was 31 among women who were between 18-29 years compared to women with no cervical lesion[13]. Another study reported a standardized incidence ratios (SIRs) of anal cancer after CIN3 and invasive cervical cancer of 5.9, and 6.3, respectively [14]. Swedish study reported SIRs of anal cancer of 3.7, and 3.9 after in situ and invasive cervical cancer, respectively [15]. Another study indicated that women with invasive cervical cancer had a relative risk of 4.6 for subsequent invasive anal cancer[16]. Another cohort study among 205 women with genital intraepithelial neoplasia, 12.2% developed biopsy proven anal intraepithelial neoplasia, and 5.9% had abnormal anal cytology [17]. A cohort study of SEER Registry data reported SIRs of anal cancer of 7.8, 6, and 4.7 after invasive vaginal, vulvar and cervical tumors, respectively [18] . This analysis also revealed a SIR for anal cancer of 17.3 after an in situ vulvar tumor diagnosis.

One of the primary aims of this study was to determine if women who are diagnosed with either in situ or invasive primary gynecologic neoplasm have a higher incidence of anal

squamous cell carcinoma compared with the general population. Since the SEER Registry does not include information on viral status, we could not evaluate the association between HPV and anal cancer risk. While there is substantial external biologic and clinical evidence supporting an HPV-anal cancer causal relationship, evaluating this relationship using epidemiologic data was not the goal of our analysis. Instead, our goal was to quantify the excess risk of anal cancer among women with a preceding gynecologic cancer diagnosis with the goal of identifying such a high-risk group. Since general population screening for anal cancer is unlikely to be efficient, there is a critical need to identify subsets of the population who might get maximum benefit from anal cancer screening.

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Appendix II: Results of the Restrictive Method

Index Cohort

Using the restrictive method, we identified a total of 181,997 cases: 129,118 cases of in situ human papillomavirus-related gynecologic neoplasm (121,843 cervical, 5,807 vulvar, and 1,458 vaginal) and 52,879 cases of invasive gynecologic neoplasm (41,793 cervical, 8,543 vulvar, and 2,543 vaginal). Demographic characteristics of the index cohort are presented in Table 6.

Risk of Anal Cancer

Using the restrictive method, we identified 206 cases of anal cancer, 46 anal cancers among women with invasive primary gynecologic neoplasm and 160 anal cancers after an in situ gynecologic neoplasm, during a follow-up of 138,553,519 person-years (Table 7). The standardized incidence ratio for the incidence of anal cancer was 5.1 (95% CI 3.2 – 7.4), 14.3 (95% CI 9.0 – 20.9) and 1.8 (95% CI 0.2 – 5.4) for women with invasive cervical, vulvar, and vaginal cancer, respectively (Table 8). The standardized incidence ratios for women with in situ gynecologic neoplasm were higher than those for women with invasive cancers. The standardized incidence ratio for the incidence of anal cancer was 14.3 (95% CI 12.0 – 17.2), 16.1 (95% CI 11.4 – 21.6), 6.1 (95% CI 1.5 – 13.6) for women with in situ cervical, vulvar, and vaginal cancer, respectively (Table 8).

Latency of Anal Cancer

Kaplan-Meier curves characterizing the time to anal cancer diagnosis for each gynecologic malignancy were calculated. The mean time interval between the incidence of primary gynecologic malignancy and the diagnosis of a second primary anal cancer was longest in women with in situ cervical cancer (16.2 years). In fact, the interval between diagnoses was longer for in situ compared with invasive cancers for all gynecologic neoplasm, although the small number of anal cancers observed among the vaginal cancer cases limits this conclusion (Table 9).

The effect of Radiation therapy

The risk of anal cancer in women with a previous cervical cancer diagnosis was similar among women who did not receive radiotherapy (standardized incidence ratio= 2,9 , 95% CI 1.5 – 4.6) compared with those who did (standardized incidence ratio= 2.2, 95% CI 1.0 – 3.8) (Table 10). The data for vulvar and vaginal cancer were inconclusive.

Appendix III: Tables of the Restrictive Method

Table 6. Characteristics of Cohort With Cervical, Vaginal, and Vulvar Neoplasm Using the Restrictive Method.

	Cervical		Vaginal		Vulvar	
	In situ	**Invasive**	**In situ**	**Invasive**	**In situ**	**Invasive**
Gynecologic cancer cases	121,843	41,793	1,458	2,543	5,807	8,543
Race						
White	101,497 (83.3)	31,588(75.5)	1,198 (82.1)	2,060 (81.0)	5,084 (87.5)	7,638 (89.4)
African American	14,571 (11.9)	6,401 (15.3)	204 (13.9)	364 (14.3)	583 (10.0)	715 (8.3)
Other	5,775 (4.7)	3,804 (9.1)	56 (3.5)	119(4.6)	140 (2.4)	190 (2.2)
Age at gynecologic cancer diagnosis (y)						
15-19	3,160 (2.5)	44 (0.1)	23 (1.5)	1 (0.04)	82 (1.4)	4 (0.05%)
20-24	17,940 (14.7)	603 (1.4)	56 (3.8)	6 (0.2)	286 (4.9)	18 (0.2)
25-29	30,431 (24.9)	2,352 (5.6)	52 (3.5)	12 (0.4)	442 (7.6)	52 (0.6)
30-34	26,195 (21.5)	4,131 (9.8)	67 (4.5)	19 (0.7)	572 (9.8)	147 (1.7)
35-39	16,777 (13.7)	4,901 (11.7)	88 (5.9)	59 (2.3)	659 (11.3)	322 (3.7)
40-44	10,242 (8.4)	5,164(12.3)	121 (8.2)	80 (3.1)	721 (12.4)	448 (5.2)
45-49	5,888 (4.8)	4,699 (11.2)	122 (8.3)	134 (5.2)	635 (10.9)	597 (6.9)
50-54	3,230 (2.6)	4,072 (9.7)	148 (10.0)	183 (7.2)	507 (8.7)	637 (7.4)
55-59	2,249 (1.8)	3,645 (8.7)	153 (10.4)	219 (8.6)	437 (7.5)	644 (7.5)
60-64	1,903 (1.5)	3,276 (7.8)	159 (10.8)	247 (9.7)	398 (6.8)	615 (7.2)
65-69	1,650 (1.3)	2,916 (6.9)	161 (10.9)	291 (11.4)	372 (6.4)	764 (8.9)
70-74	1,107 (0.9)	2,187 (5.2)	134 (9.1)	306 (12.0)	308 (5.3)	962 (11.2)
75-79	619 (0.5)	1,688 (4.0)	102 (6.9)	335 (13.1)	222 (3.8)	1,146(13.4)
80-84	310 (0.2)	1,129 (2.7)	53 (3.6)	298 (11.7)	105 (1.8)	979 (11.4)
≥ 85	142 (0.1)	986 (2.3)	24 (1.6)	353 (13.8)	61 (1.0)	1,208(14.1)
Vital Status						
Alive	108,454 (89.0)	23,130(55.3)	812 (55.6)	804 (31.6)	3,883(66.8)	3,827 (44.8)
Dead *	13,389 (10.9)	18,633 (44.6)	648 (44.1)	1,739 (68.3)	1,924 (33.1)	4,716 (55.2)

Data are n or n(%)

* Patient's vital status at the date of last contact, death, or end of the study period on December 2006, whichever was earliest.

*Table 7. Characteristics of Patients with Anal Cancer with Initial Gynecologic Neoplasm Using the Restrictive Method *.*

	Cervical		**Vulvar**	
	In situ	**Invasive**	**In situ**	**Invasive**
Anal Cancer Cases (n)	120	23	40	23
Race				
White	103(85.8)	21(91.3)	32 (80.0)	19(82.6)
African American	8 (6.7)	2(8.7)	7 (17.5)	3(13.0)
Other	9 (7.5)	0	1 (2.5)	1 (4.4)
Age at anal cancer diagnosis, n (%)				
15-19	0	0	0	0
20-24	0	0	0	0
25-29	2 (1.7)	0	0	1(4.4)
30-34	4 (3.3)	0	1 (2.5)	1 (4.4)
35-39	8 (6.7)	2 (8.7)	3 (7.5)	0
40-44	14(11.7)	2 (8.7)	0	0
45-49	24 (20.0)	0	11(27.5)	3 (13.0)
50-54	22(18.3)	4(17.4)	10 (25.0)	1 (4.4)
55-59	13(10.8)	1(4.4)	8 (20.0)	6 (26.1)
60-64	5 (4.2)	4(17.4)	3 (7.5)	3(13.0)
65-69	8 (6.7)	4(17.4)	3 (7.5)	1 (4.4)
70-74	5 (4.2)	2 (8.7)	0	0
75-79	1 (0.8)	1(4.4)	1 (2.5)	5(21.7)
80-84	1 (0.8)	2(8.7)	0	0
≥85	13(10.8)	1(4.4)	0	2 (8.7)

*****There were less than 5 patients in both, in situ and invasive vaginal cancer. These data hidden as per our data-use agreement with the Surveillance, Epidemiology and End Results program.

Table 8. Standardized Incidence Ratio of Anal Cancer in Patients With In Situ and Invasive Gynecologic Neoplasm Divided By Race Using The Restrictive Method.

Primary Gynecologic Neoplasm	In situ vs. invasive	Race	Observed	Expected*	SIR	95 % CI**
Cervical	**In situ**	**Total**	**120**	**8.4**	**14.3**	**12.0 - 17.2**
		White	104	6.7	15.6	12.7 - 18.8
		African American	8	1.4	5.5	2.3 - 10.2
		Other	9	0.2	34.6	15.4 - 61.5
	Invasive	**Total**	**23**	**4.5**	**5.1**	**3.2 -7.4**
		White	21	3.5	5.9	3.6 - 8.8
		African American	<5	0.8	2.5	0.21 - 7.4
		Other	-	-	-	-
Vulvar	**In situ**	**Total**	**40**	**2.5**	**16.1**	**11.4 - 21.6**
		White	32	2.2	14.4	9.8 – 20.0
		African American	7	0.2	29.2	11.3 - 55.4
		Other	<5	0.02	50	0 – 200
	Invasive	**Total**	**23**	**1.6**	**14.3**	**9.0 - 20.9**
		White	19	1.5	12.7	7.6 - 19.3
		African American	<5	0.1	27.2	4.9 - 67.9
		Other	<5	0.01	100	0 – 400
Vaginal	**In situ**	**Total**	**<5**	**0.66**	**6.1**	**1.5 - 13.6**
	Invasive	**Total**	**<5**	**1.1**	**1.8**	**0.2 - 5.4**

CI, confidence interval.
* The expected cases were calculated from Surveillance, Epidemiology and End Results 9, stratified by age, race, and calendar-year group.
** The CI was calculated using the Vandenbroucke Method.

Table 9. Time Interval Between Gynecologic Neoplasm and Anal Cancer Using the Restrictive Method.

Primary Gynecologic Neoplasm		Anal Cancer Cases (n)	Mean Time Between Diagnoses (y)	Minimum Time Between Diagnoses (y)	Maximum Time Between Diagnoses (y)	*P* value *
Cervical Neoplasm						
	Invasive	23	11.7	1	24	0.02
	In situ	120	16.2	1	30	
Vulvar Neoplasm						
	Invasive	23	8.3	1	23	0.27
	In situ	40	10.2	1	23	
Vaginal Neoplasm						
	Invasive	<5**	4.5	3	6	0.27
	In situ	<5**	11.25	1	16	

*Student *t* test was used to estimate P value

** These data hidden as per our data-use agreement with the Surveillance, Epidemiology and End Results Program.

*Table 10. Standardized Incidence Ratio of Anal Cancer Among Women With Invasive Cervical and Vulvae Neoplasm by Mode of Treatment Using the Restrictive Method *†*

	Cervical Neoplasm			Vulvar Neoplasm		
Mode of treatment	**Observed**	**Expected**	**SIR (95% CI)**	**Observed**	**Expected**	**SIR (95% CI)**
Radiotherapy	10	4.54	2.2 (1.0-3.8)	6	1.61	3.73 (1.3-7.30)
No Radiotherapy	13	4.54	2.9 (1.5-4.6)	19	1.61	11.8 (7.1- 17.7)

*There were less than 5 patients in both, in situ and invasive vaginal cancer. These data hidden as per our data-use agreement with the Surveillance, Epidemiology and End Results program.
†Women with unknown mode of treatment were excluded.