Published in final edited form as:

Semin Colon Rectal Surg. 2017 June ; 28(2): 97–101. doi:10.1053/j.scrs.2017.04.008.

Anal Cancer and Anal Cancer precursors in Women with a History of HPV-Related Dysplasia and Cancer

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Abstract

The epidemiology of anal cancer in the U.S. has changed over the past 3 decades. During this period the incidence of anal cancer has increased among both men and women. Of note, women with a history of anogenital HPV infection are at higher risk than the general population for anal cancer. The increased risk ranged from increased incidence rate ratios ranging from 1.82 to 6.3 in women with a history of cervical cancer, to 4.2-16.4 in women with a history of prior cervical intraepithelial neoplasia 3 (CIN 3). In addition, studies describing screening women with a previous history of anogenital HPV infection (including CIN 3) for anal HPV and anal pre-cancers demonstrate that the prevalence of anal HPV is measureable in this population. The prevalence of anal high grade squamous intraepithelial lesions (HSIL) in this population was relatively low, which may have been related to the fact that many of these studies had insufficient samples, and the numbers of patients undergoing HRA remain low. Future studies evaluating anal cancer screening strategies in this high-risk group are needed.

Introduction

Over the past 3 or more decades, the incidence of anal cancer among US women has doubled.¹ Anal cancer is strongly associated with high-risk (HR) HPV infection, and there is evidence that women with cervical HR-HPV are at increased risk for anal HR-HPV^{2,3}. Women with persistent cervical HR-HPV infection may develop pathologic changes to cervical intraepithelial neoplasia (CIN) 3 or cancer. In this review, we will summarize the data available regarding the increased risk of subsequent anal cancer in women treated for CIN3 or cervical cancer.

CIN and anal HPV, Abnormal Anal Cytology and AIN

Given the increased anal cancer risk is there a way to prevent anal cancer in these women who have already had a disease state attributed to persistent anogenital HR-HPV? Anal cancer has many similarities with cervical cancer: both are epithelial cancers that appear to

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be caused or closely associated with HR HPV (most frequently HPV16) and are frequently adjacent to full thickness intraepithelial lesions (AIN3 and CIN3 respectively). However, the median age for diagnosis with anal cancer is over a decade older than that for cervical cancer (median age 61 compared with 49 respectively).⁴ We know that cervical cancer begins with a HR-HPV infection of the cervix, commonly from adolescence, which failed to clear and instead develops into CIN3, and the CIN3 lesion if not treated has a 30% risk of developing into invasive cancer over an additional 10-20 years. There are similar data in HIV-infected men who have sex with men supporting that anal cancer developing from untreated or incompletely treated AIN3.⁵ Thus, an option for prevention is to adopt the cervical cancer prevention model—perform a screening test of the anus (e.g. anal cytology and/or anal HPV), if abnormal perform a diagnostic evaluation of the anus (high resolution anoscopy (HRA)) with directed biopsy. If biopsies show AIN2+ then treat to prevent malignant transformation. However, many women are hesitant to undergo anal evaluations as they do not consider themselves to be at risk; because they have never practiced anal sex.⁶ Of note, the impact of a history of anal sex has not consistently been shown to be an independent risk factor for anal HPV, neoplasia and cancer in studies with female subjects.²

CIN3 and Cervical Cancer: Risk factors for Anal Cancer

Table 1 reviews recent studies evaluating anal cancer risk among women with a history of CIN 3. For example, Sand et al⁷ reviewed years 1978-2012 from a Danish registry study and identified 125 incident anal cancers from 104,155 women with CIN3 and 32 from 52,135 women with CIN2. The mean age of diagnosis of women with CIN3 and CIN2 was the same at 34 years. The hazard ratios for anal cancer for woman with CIN3 and CIN2 were HR= 4.2 (95% CI, 3.4–5.0) and HR=2.9 (95% CI 2.0–4.1) respectively. The hazard ratio for anal cancer in younger women with CIN 2,3 was much higher than that for older women (compared with similarly aged unaffected population), and the calculated incidence per 100,000 person-years steadily increased over time from CIN 2,3 diagnosis. In particular, the increased risk of anal cancer began at the time of CIN3 diagnosis (regardless of the age at diagnosis), increased to 6 per 100,000 at ages 40-49 to 24 per 100,000 from age 60 and older; in this cohort, the increased risk of anal cancer continued for over 25 years following CIN2,3 diagnosis.⁷

Risk factors for incident anal cancers were delineated from the Million Women Study⁸ which recruited 1.3 million women age 50 -64 in the UK at the time of their routine mammographic screening through the NHS from 1996-2001. Although the primary aim of the trial was to determine if hormone replacement therapy use is associated with an increased risk of breast cancer, detailed reproductive, health and lifestyle data were collected and the records were linked to the women's medical records and cancer registries. After an average of 13 years of follow-up, 517 women from the Million Women Study were diagnosed with incident anal cancer.⁸ The greatest risk factor for anal cancer was a history of CIN3 with a RR= 4.03 (95% CI 2.59–6.28) after adjustment for other factors including smoking, alcohol use, BMI, age at menarche, ever use of the oral contraceptive pill, parity, tubal ligation, and lower income status.⁸

Studies utilizing cancer registries to demonstrate the increased risk for anal cancer with history of cervical cancer are summarized in table 2. In particular, the risk of anal cancer given a history of cervical cancer was evaluated from K2-France, a population-based retrospective cohort of patients diagnosed with an initial cancer between 1989 and 2004 and then followed through 2007. Of the 4234 women with cervical cancer (mean age 54), 5 were diagnosed with anal cancer, showing a significant increased risk compared with the general population (SIR = 5.42, 95% CI 1.75-12.64).⁹

Chaturvedi investigated incident second cancers diagnosed in women treated for cervical cancer by combining the data from 7 cancer registries in Europe and the US. The risk of anal cancer was increased regardless of the use of radiation treatment. However, in those treated with pelvic radiation the risk was greatest 10-29 years after diagnosis and that increased risk continued for more than 40 years. In addition women under age 40 at the time of radiation therapy were more likely to develop an anal cancer compared with women diagnosed over age 59.¹⁰

Table 3 reviews a number of cross-sectional studies that have evaluated the prevalent rates of anal HPV, abnormal anal cytology, and AIN2+ detection in women with history of cervical HPV associated disease. Women with cervical neoplasia have high rates of abnormal anal cytology, and in women who present for HRA, there are high rates of AIN2+. However, these studies illustrate significant issues with obtaining adequate specimen collection and complying with referral for HRA.

For example, in a cohort study at the Naval Medical Center at San Diego California, Lamme et al¹¹ reported on 196 HIV-negative women referred to the dysplasia clinic for abnormal cervical cytology to assess anal HPV infection and abnormal anal cytology. All participants underwent a standard colposcopy procedure with directed biopsy as indicated as well as concurrent collection of specimens for cervical HR-HPV testing and anal swabs for cytology and HR-HPV testing. Women with abnormal anal cytology were then referred for HRA. Anal HR-HPV was detected in 32.5% (95% CI 0.26-0.40) and cervical HR-HPV in 80.7% of the cohort. The prevalence of abnormal anal cytology was 17.6% (all ASCUS or LSIL); 15% of anal cytology samples were found to be insufficient. Women diagnosed with oncogenic cervical HPV were associated with a higher risk of having oncogenic anal HPV (OR 3.6, 95% CI 1.9-10.77, P<0.24). Oncogenic anal HPV indicated a higher occurrence of abnormal anal cytology result (OR 6.5, 95% CI 2.74-15.60, P<0.001).¹¹

Similarly, Robinson and et al¹² enrolled 273 HIV- women from 2012-2014 who attended an outpatient clinic at a teaching hospital for a routine gynecological exam, colposcopy or gynecological oncology visit. All women had swabs for anal HPV and cytology; women with abnormal cytology were referred for HRA. Women with a positive history of lower genital tract dysplasia or cancer had higher rates of abnormal cytology (41.2% vs 21.7%), higher rates of anal HR-HPV (20.8% vs 1.2%) and higher rates of anal HSIL (8/190 vs 0/83). Like other cross-sectional studies, this study was limited by high rates of insufficient specimens for cytology (10%) and HR-HPV testing (25%), and 40% of the women with abnormal anal cytology actually received HRA.¹³

To assess the differential effect of lower genital tract cancer and dysplasia with anal HPV and anal neoplasia Cronin et al¹⁴ conducted a cross-sectional study with 190 women, with 67 in the malignancy group (have recent history of vaginal, vulvar, or cervical cancer proven by biopsy) and 123 in the dysplasia group (h/o CIN2+, VIN2+ or VAIN2+ within past 2 years). The 2 cohorts had similar rates of HR-HPV (about 20% and abnormal anal cytology (about 40%), the rates of anal HSIL differed-- 6 women in the malignancy group had anal HSIL whereas there were 2 women who were diagnosed with anal HSIL in the dysplasia group ($p=0.03$). Note that 30-40% of the women referred did not attend HRA and that higher attendance may have changed this outcome.¹⁴

A fascinating study by Simpson et al¹⁵ attempted to assess the association among different wiping habits after urination/defecation and anal HPV associated conditions. They conducted a cross-sectional study in Australia where they recruited 163 women from colposcopy clinics in Tasmania with a history of histologically proven high-grade HR-HPV-mediated cervical, vulvar or vaginal intraepithelial neoplasia (recruited 2012-2014) and assessed the association of anal HPV and cytology with multiple risk factors including post-toilet wiping behaviors. It was found that front-to-back wiping post-urination and/or defecation were both related to increased prevalence of anal HR-HPV (1.97 (95% CI 1.24, 3.15), 1.61 (95% CI 1.02, 2.55)) abnormal anal cytology (1.73 (95% CI 1.18, 2.52), (1.99 (95% CI 1.37, 2.89)), and histological proven neoplasia 3.07 (95% CI 1.55, 6.09), 3.60 (95% CI 1.82, 7.12)) whereas there was no relation between back to front wiping and anal abnormalities¹⁵.

The above data may help to develop models assessing if anal cancer screening with detection and treatment of anal cancer precursors is cost effective. Cromwell et al¹⁶ estimated the cost-effectiveness of anal cancer screening for women with a history of CIN2/3; screening with anal cytology every 3 years with referral to HRA for abnormalities for 20 years after diagnosis was compared with no screening. Given the assumptions used, the calculated Incremental Cost-Effectiveness ratios (ICERs) was \$20,562/Life Years Gained (LYG) and the mean value of Quality-Adjusted Life Year gained (QALYs) was -0.0364 (i.e., more quality-adjusted survival was observed in the unscreened arm). However, the assumptions used for the model appear may have been underestimated by several orders of magnitude. For example, the prevalent AIN2+ in this population at year 1 of screening is likely significantly higher than the prevalence used in the Markov model for this paper of 1%. In addition, the cost of "anoscopy", which may have been HRA was \$7.55 whereas our current cost is at least 50 times that. Finally, the planned surveillance was to continue for 20 years post CIN2/3 diagnosis whereas at least 1 publication shows the increased risk of anal cancer lasting for at least 25 years.¹⁶ Further cost-effectiveness analyses are needed to address questions of optimal screening methods for women.

Conclusion

The studies identified in this review show us that 1) CIN3 is associated with an increased risk of anal cancer, and that risk persists for 25 years 2) cervical cancer is associated with an increased risk of anal cancer, regardless of whether radiation is used in treatment 3) women with cervical HPV associated disease may have high rates of anal HPV infection, abnormal

anal cytology and AIN2+. Furthermore, the high rates of insufficient specimens for both anal cytology and anal HPV in these studies strongly suggests that the existing data may be inaccurate (and likely undercalled). At this time, there are not enough prevalence, incidence and natural history data regarding anal HPV infection, anal pre-cancer and anal cancer in women with a history of previous genital HPV-related neoplastic disease.

Because anal sex has not been consistently shown to be an independent risk factor for anal HPV, neoplasia and cancer for women with previous genital HPV-related cancer or dysplasia,² and because women are often reluctant to undergo studies of their anal canal, education of clinicians and patients regarding prevention of anal cancer and anal cancer precursors is needed. Specifically, there is a rationale to screen these women for anal cancer precursors, however, the optimal screening strategy remains unclear, and guidelines are lacking. It is likely that the progression to cervical cancer and anal cancer from their respective precursors is not identical, therefore a replication of the cervical cancer model may not be ideal. Further studies are needed to get accurate measures for the prevalence and incidence of anal HPV and anal neoplasia in women with a history of CIN or cervical cancer. In addition, natural history data can be used in cost effectiveness to models to identify the optimal anal cancer prevention paradigms for these women who are at an elevated risk for anal cancer.

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Table 1

Anal cancer in women with prior cervical cancer

Study author/years	Population	Study design/data source	Total no. of patients in cohort	Number of anal cancers	Anal cancer incidence (95% CI) in women per 100,000 py	Standardized Incidence Ratio (SIR) for Anal Cancer and other Notable Findings	Mean(median) and range of years between diagnoses
Chaturvedi et al ¹⁰ Varies by country	Denmark, Finland, Norway, Sweden, US	13 population based cancer registries from 5 countries	104,760	817 (includes anus/rectum)	63.8 (no Confidence Interval reported)	SIR 1.84, CI (1.72 – 1.98)b 1.84 (1.72 to 1.98) SEER data only; (SIR = 3.12; 95% CI = 1.88 to 4.88)	Increased rectal/anal cancer 10 years if radiation Rx
Evans et al ¹⁷ 1960-1999	Women with history of invasive cervical cancer UK	Thames Cancer Registry	21,605	18	12.4	SIR 6.3 (3.7-10)	“ within 4 years or after 15 years”
Saleem et al ⁹ 1973 – 2007	Patients with either in situ or invasive cervical, US	SEER	43,669	28	n/a	SIR 6.2 (4.1– 8.7)	Mean(median) 11 (13) years; range (0-29)
Neumann et al ¹⁸	French Cancer registries, diagnosed 1989 and 2004	K2-France	4234	5	n/a	SIR 5.4 (1.75– 12.64)	Unknown

Table 2

Anal cancer in women with prior CIN3

Study author/years	Population	Study design/data source	Total no. of patients in cohort	Number of anal cancers	Anal cancer incidence (95% CI) 100,000 py	Standardized Incidence Ratio (SIR) for Anal Cancer and other Notable Findings	Mean(median) and range of years between diagnoses
Coffey et al ⁸	Women recruited 1996-2001, 13 years follow-up, UK	Million Women Study (women age 50+)	12,531	21	n/a	Relative risk: 4.03 (2.59-6.28)	Unknown.
Evans et al ¹⁷ 1960-1999	Women with history of CIN 3 UK	Thames Cancer Registry	59, 519	23	4.8 (CIN3) No CI Reported	SIR 5.9 (3.7 – 8.8) for women diagnosed with CIN 3	“only significant 10+ years after CIN3 dx.”
Edgren et al ¹⁹ 1968-2004	Women with history of CIN 3 Sweden	Sweden National Registry	36,704	131	With CIN3 vs, without Overall 6.0 vs 1.0By decade: 30-39: 1.4 vs 0.2 40-49: 4.3 vs 0.7 50-59: 8.3 vs 1.6 70-79: 17.2 vs 5.5	Adjusted Anal IRR of 4.68 (95% CI 3.87 – 5.62)	greatest risk for women with CIN3 diagnosed >10 years
Saleem et al ⁹ 1973 – 2007	Patients with in situ cervical, 1973-1995 US	SEER	124,075	137	n/a	SIR 16.4 (13.7– 19.2)	Mean(median) 16 (16) years Range 0 - 30
Sand et al ⁷	Danish Civil Registration System		104,155	125	60+ incidence 24 40-49	Overall (HR 4.2; 95% CI, HR = HR 4.8; 95% (CI), 3.3-7.0]	HR increased from year 1, 5+ levels off at 4 with small CI

NOTE. SIR, standardized incidence ratio

Table 3
HR HPV, anal cytology and AIN in women with lower genital tract neoplasia/cancer

Study author/y ears	Population	Total no. of patients in cohort	HR-HPV ANAL		Abnormal Anal Cytology				AIN		% HRA	
			%	INSUFFICIENT SPECIMEN %	% ABNL	% HSIL	% INSUF	AIN1+	AIN2+	%		
Robison et al ¹³	“high risk” dysplasia or cancer	190	21	25	41	5	10			8/190 (2.1%)	60	
	“low risk”	83	1	25	22	0	10					
Cronin et al ¹⁴	Cancer	67	15	30	39	4/67	11	4/67	10/67 (14.9%) 1 cancer	70		
	-IN2/3	123	24	22	43	5/123	9	13/123	2/123 (1.6%)	61		
Simpson et al ¹⁵	Colposcopy clinic	163	39		%				13/163 (8.0%)	50/65		
D’Haenvers et al ²⁰	Colposcopy clinic	149 (96 anal swabs)	54	53	10.8%	0	37.5 %	NR	NR	0		
Goodman et al. ²¹	Hawaii cohort “low risk”	650 (431 analswabs)	22		NR	NR	NR	NR	NR	NR		
Park et al. ²²	Colposcopy clinic	102	39	10	9	0	4 (initial, later retested)	NR	NR	NR		
Leo et al. ²³	CIN 3 and control group	40 each	35 CIN, Control 10	0	NR	NR	NR	NR	NR	NR		
Lucyntho et al ²⁴	Gyn Clinic	84 SIL, 76 controls	NR	NR	NR	NR	NR	17 SIL, 2 control	3 SIL, 0 control	100 %		
Koppe et al ²⁵	Gyn clinic	106 SIL, 74 controls	NR	NR	NR	NR	NR	10.4 SIL, 1.4 control	4.7 SIL, 0 control	100 %		
Chatti et al ²⁶	SIL (including HIV and other immunosuppression	404 immunocompetent, 31 HIV, 46 other	NR	NR	NR	NR	NR	21.8 immunocompetent, 25.8 HIV, 23.9 other	4 immunocompetent, 25.8 HIV, 8.7 other	100 %		
Valari et al ²⁷	Colposcopy clinic	253	30	6.4	NR	NR	NR	NR	NR	NR		