Received: 21 March 2022 | Revised: 19 May 2022 | Accepted: 20 May 2022

DOI: 10.1002/ijc.34143

CANCER EPIDEMIOLOGY

IJC INTERNATIONAL JOURNAL of CANCER

A nationwide longitudinal study on risk factors for progression of anal intraepithelial neoplasia grade 3 to anal cancer

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Abstract

Little is known about risk factors for progression of high-grade anal intraepithelial neoplasia (AIN) to anal squamous cell carcinoma (ASCC). In this large, population-based study, we assess the role of factors related to immune status for the risk of ASCC among individuals from the general population with a diagnosis of AIN3. Individuals diagnosed with AIN3 during 1985-2016 were identified in the Danish Pathology Registry and followed for subsequent development of ASCC. The study population was linked to the National Patient Registry, the Danish Prescription Registry and the Danish HIV Cohort Study for information on autoimmune disease, genital warts and HIV status. To study the progression rate, Cox regression models with hazard ratios (HR) and 95% confidence intervals (CI) were applied with time since AIN3 as the underlying time scale and with adjustment for age at AIN3 diagnosis, year of AIN3 diagnosis and sex. The study population comprised 1222 individuals with AIN3 contributing 12 824 person-years of follow-up. Ninety-seven individuals (7.9%) developed ASCC. Individuals registered with an autoimmune disease or genital warts before and/or after the AIN3 diagnosis had an increased rate of progression to ASCC compared to individuals without these conditions. People living with HIV had a higher progression rate than HIV-negative individuals (HR = 4.25; 95% CI: 1.87-9.65) with the highest progression rate among those with CD4 count ≤200 cells/μL. These associations may be caused by an interplay between HPV infection and immunosuppression.

KEYWORDS
anal cancer, anal intraepithelial neoplasia, progression, risk factors

Abbreviations: AIN, anal intraepithelial neoplasia; ASCC, anal squamous cell carcinoma; CI, confidence interval; HPV, human papillomavirus; HR, hazard ratio; MSM, men who have sex with men; PLWH, people living with HIV; SNOMED, systematized nomenclature of medicine.

What's new?

Anal cancer risk is strongly associated with persistent human papillomavirus (HPV) infection. However, little is known about risk factors for progression of high-grade anal intraepithelial neoplasia to anal cancer. This is the first report of an association between autoimmune disease, genital warts and/or living with HIV and the risk of developing anal cancer following an anal intraepithelial neoplasia diagnosis in the general population. The study provides new insights on potential progression pathways to anal cancer and points to an interplay between immunosuppression and HPV infection. An important long-term approach to reduce anal cancer incidence is gender-neutral HPV vaccination.

1 | INTRODUCTION

We have previously shown that the risk of anal cancer, with anal squamous cell carcinoma (ASCC) being by far the most common type, increases with increasing severity of precursor lesions, reaching almost 4% 5 years after a diagnosis of AIN3.[1]

Anal cancer risk is strongly associated with persistent infection with human papillomavirus (HPV) with nearly 90% of anal cancers being attributable to HPV.[2] The risk of anal cancer is, however, particularly high in certain population groups, including people living with HIV (PLWH), men who have sex with men (MSM) and organ transplant recipients.[3-5] Compromised immune function due to an intrinsic alteration of the immune system, immunosuppressive treatment or both is also an important risk factor for anal cancer.[4] Other risk factors include receptive anal intercourse, a history of genital warts and smoking.[5,6] Among women, a history of high-grade vulvar or cervical intraepithelial neoplasia, vulvar cancer or cervical cancer also constitute an increased anal cancer risk.[7]

Apart from studies investigating the effect of treatment of high-grade anal precursor lesions on the subsequent risk of anal cancer,[8-12] few studies have examined other factors associated with progression of high-grade AIN to anal cancer, including sex, marital status, smoking, lesion characteristics and HIV/AIDS.[8-10] Previous studies were based on a limited number of anal cancer cases and most were conducted among high-risk populations. Thus, little is known about factors associated with progression of high-grade AIN lesions to anal cancer in the general population.

This gap in knowledge prompted us to examine the role of factors related to immunosuppression, including autoimmune disease and HIV, and genital warts in the development of ASCC among individuals in the general population with a diagnosis of AIN3, using data from the unique, nationwide, population-based Danish registries.

2 | MATERIALS AND METHODS

2.1 | Data sources

From the nationwide Danish Pathology Registry, we identified individuals registered with AIN3 (including carcinoma in situ) during 1985-2016 and subsequent ASCC. The Danish Pathology Registry holds information on pathology specimens from public and private pathology departments in Denmark since 1970.[13] The diagnostic information in the Danish Pathology Registry is based on the Systematized Nomenclature of Medicine (SNOMED). The SNOMED topography codes used to identify individuals with AIN3 and ASCC included T69000, T69010, T69015, T69110, T69120, T02507, and TY1701 and SNOMED morphology codes corresponding to AIN3 and ASCC, respectively.

Information on vital status, date of death and migration to and from Denmark was obtained from the Danish Civil Registration System.[14]

From the National Patient Registry, we retrieved information on diagnoses of autoimmune disease. A history of genital warts was included as a composite measure of a diagnosis in the National Patient Registry and/or one or more filled prescriptions in the Danish Prescription Registry. The National Patient Registry holds information on diagnoses and surgical procedures for all hospitalizations for somatic conditions since 1977 and for all outpatient contacts since 1995.[15] The Danish Prescription Registry contains information on all prescription drugs sold in Danish community pharmacies since 1995. Drugs are categorized according to the Anatomic Therapeutic Chemical system.[16] Information on HIV status and measures related to HIV positivity was obtained from the Danish HIV Cohort Study. This is an open cohort with continuous enrolment of PLWH aged 16 years or older at time of HIV diagnosis seen in one of the eight Danish HIV centers since December 31, 1994. PLWH diagnosed before this date are also included in the cohort.[17]

Autoimmune disease, genital warts and HIV infection occurring before and/or after AIN3 may influence the risk of subsequent development of ASCC. We divided autoimmune disease and genital warts into three categories: "never"; "yes, before AIN3"; and "yes, only after AIN3." Due to limited power we were not able to distinguish between the effect of HIV infection before and after AIN3. Hence, HIV status was categorized as being HIV-positive before the AIN3 diagnosis or not. PLWH were further divided according to CD4 count defined as the last CD4 count registration before the AIN3 diagnosis and categorized as CD4 ≤ 200 cells/μL and CD4 ≥ 200 cells/μL.

For descriptive and adjustment purposes, we retrieved information about age and sex from the Civil Registration System, information

on education, marital status and ethnicity from registries in Statistics Denmark, which administers several nationwide demographic registries,[18] and information about treatment of AIN3 from the National Patient Registry and the Danish Prescription Registry. The exposure window for treatment of AIN3 covered the period up to 6 months after the AIN3 diagnosis and included surgical, ablative and topical treatment.

Linkage of information from the registries was done using the unique personal identification number assigned to all Danish residents.[14]

2.2 | Statistical analysis

Individuals with AIN3 were followed for subsequent development of ASCC until first occasion of ASCC, emigration, death or end of follow-up (December 2018), whichever came first. To exclude prevalent cases, the follow-up started 6 months after the AIN3 diagnosis. The median follow-up time with 95% confidence limits was estimated based on the reverse Kaplan-Meier method.[19] The absolute risk of ASCC following AIN3 as a function of time since AIN3 was stratified by autoimmune disease, genital warts and HIV status all measured at baseline. The risk was estimated nonparametrically using the Aalen-Johansen estimator taking into account competing risk from death and other histological types of anal cancer. To study the rate of progression in relation to autoimmune disease, genital warts and HIV status, Cox regression models were applied with time since AIN3 as the underlying time scale. All exposure variables were entered as time-varying variables, that is, individuals who had a diagnosis only after the AIN3 diagnosis were included in the analysis as unexposed until the change in their exposure status. We report crude hazard ratios (HR) with 95% confidence intervals (CI) and HR adjusted for age at AIN3 diagnosis as a continuous variable, year of AIN3 diagnosis as a continuous variable and sex as a stratum variable, that is, allowing for separate underlying hazards by sex. In additional analyses, we restricted the Cox regression analysis to individuals diagnosed with AIN3 from 1995 and onwards as information from the Danish Prescription Registry was not available until 1995 and adjusted for treatment of AIN3 as a dichotomous variable (yes/no). Additionally, we conducted an analysis where the effect of genital warts was further adjusted for HIV status, as HIV may be a confounding factor for the association between genital warts and ASCC. Finally, when dealing with competing risks, HRs do not directly translate into relationships between risks. To investigate this, we estimated HRs for the associations between exposure variables and competing risk outcomes (death and other histological types of anal cancer). The proportional hazards assumption was evaluated in scaled Schoenfeld residual plots and correlation tests were based on the Schoenfeld residuals.[20] The correlation tests showed some violations of the proportional hazards assumption for age, which was supported by the residual plot showing a decreasing trend in the scaled residuals with increasing age. To take this into account, age (grouped as <45, 45-65, ≥65 years) was added as a stratum variable.

TABLE 1 Characteristics of the study population at the time of AIN3 diagnosis

	Number of individuals with AIN3 (%)
Total	1222 (100.0)
Age at AIN3 diagnosis	
<45 y	427 (34.9)
45-54 y	311 (25.5)
55-64 y	221 (18.1)
65-74 y	152 (12.4)
≥75 y	111 (9·1)
Sex	
Male	293 (24.0)
Female	929 (76.0)
Year of diagnosis	
1985-1994	185 (15.1)
1995-2004	394 (32.2)
2005-2014	497 (40.7)
2015-2016	146 (11.9)
Autoimmune disease	
Never	1118 (91.5)
Yes, before AIN3[a]	53 (4.3)
Yes, only after AIN3[a]	51 (4.2)
Genital warts	
Never	812 (66.4)
Yes, before AIN3	326 (26.7)
Yes, only after AIN3	84 (6.9)
HIV-status before AIN3 diagnosis	
Negative	1171 (95.8)
Positive	51 (4.2)
CD4 count[b]	
CD4 ≥ 200 cells/μL	34
CD4 < 200 cells/μL	11

Abbreviation: AIN, anal intraepithelial neoplasia.
[a]Both before and after AIN3 diagnosis, the two most common autoimmune diseases were rheumatoid arthritis and type 1 diabetes. Note that individuals could be registered with the same disease more than once and with more than one autoimmune disease. Here only the first registration of each disease is reported.
[b]Due to missing values for CD4 count the numbers do not sum up to the total number of HIV positive individuals.

3 | RESULTS

In a previous study of anal cancer risk following benign anal disease and anal cancer precursor lesions, we identified a total of 1491 individuals registered with a diagnosis of AIN3.[1] For the purpose of the present study, we excluded those diagnosed with AIN3 before 1985 as data from the registries from which we obtained information on exposure variables were sparse before 1985. Thus, for the present

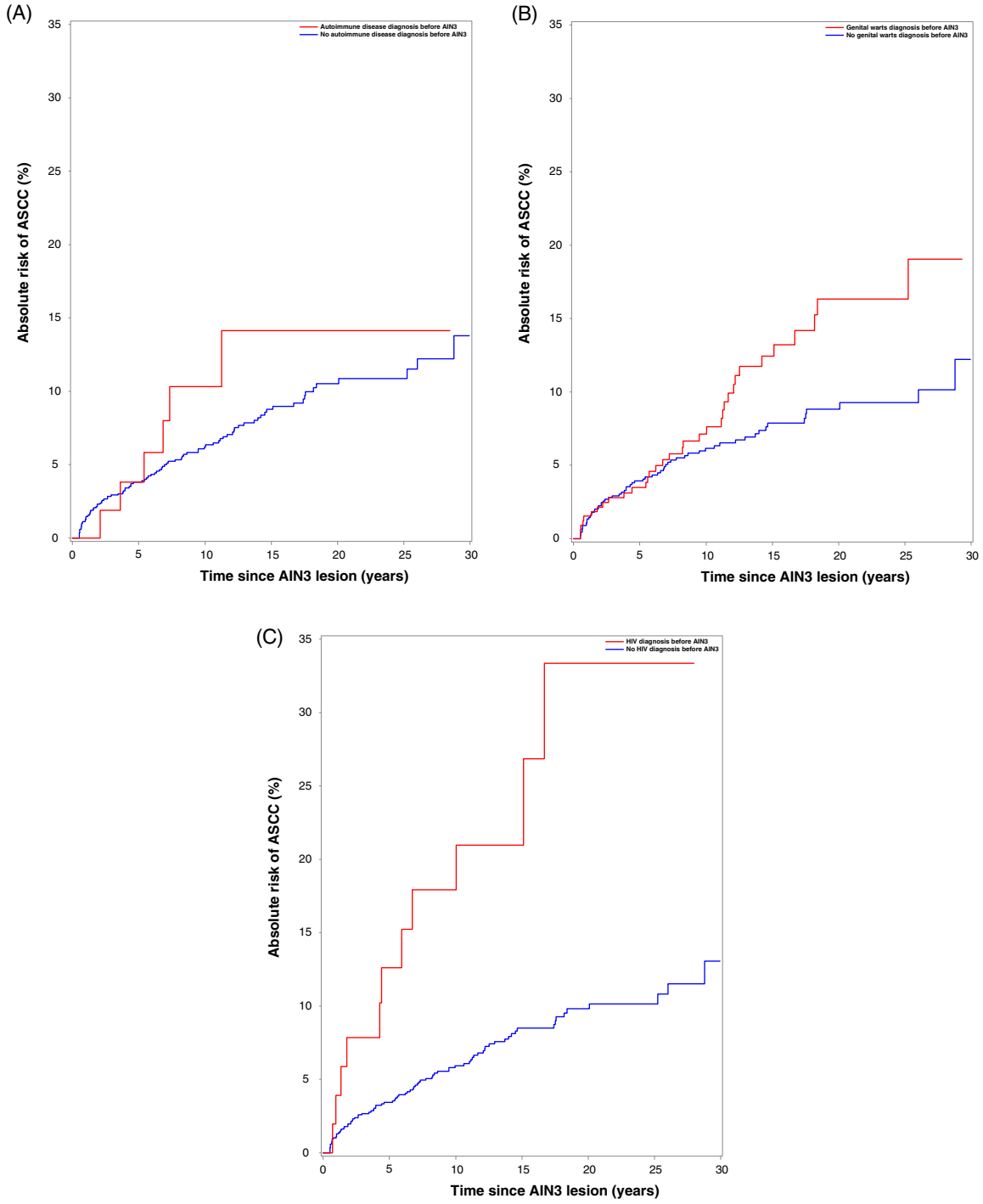

FIGURE 1 (A) Absolute risk of ASCC following AIN3 according to autoimmune disease. (B) Absolute risk of ASCC following AIN3 according to genital warts. (C) Absolute risk of ASCC following AIN3 according to HIV status [Color figure can be viewed at wileyonlinelibrary.com]

study we included 1431 individuals registered with AIN3 during 1985-2016 who were not previously registered with a diagnosis of anal cancer. To study incident ASCC we also excluded individuals who emigrated (n = 2), died or developed other histological types of anal cancer (n = 30), or developed ASCC within the first 6 months after the AIN3 diagnosis (n = 177). Hence, the final study population comprised 1222 individuals with AIN3 who were at risk of ASCC 6 months after AIN3. The maximum follow-up time was 34 years (median 12.8 years [95% CI: 12.1-13.6]), contributing 12 824 person-years of follow-up.

Characteristics of the study population at the time of AIN3 diagnosis are presented in Table 1. Approximately 60% were aged <55 years, and the majority were women (76.0%). Most AIN3's were diagnosed from 1995 and onwards (84.9%). Fewer than 9% were registered with a diagnosis of an autoimmune disease either before or during the follow-up period with the two most common diseases

TABLE 2 Hazard ratios (HR) with 95% confidence intervals (CI) of progression from anal intraepithelial neoplasia (AIN) 3 to anal squamous cell carcinoma (ASCC) among individuals at risk 6 mo after AIN3 diagnosis 1985-2016 (total number of person years = 12 824)

	Number of person years	Number of ASCC cases	Incidence per 100 person years	HR[a]	(95% CI)	HR[b]	(95% CI)
Autoimmune disease							
Never	11 994	83	0.7	Ref.		Ref.	
Yes, before AIN3	469	6	1.3	1.76	(0.77-4.03)	1.86	(0.81-4.29)
Yes, only after AIN3	361	8	2.2	3.96	(1.86-8.42)	3.37	(1.58–7.19)
Genital warts							
Never	8378	55	0.7	Ref.		Ref.	
Yes, before AIN3	3557	34	1.0	1.49	(0.97-2.28)	2.04	(1.27-3.29)
Yes, only after AIN3	889	8	0.9	1.53	(0.72-3.22)	1.88	(0.87-4.08)
HIV-status before AIN3 diagnosis							
Negative	12 368	86	0.7	Ref.		Ref.	
Positive[c]	456	11	2.4	3.40	(1.81-6.38)	4.25	(1.87–9.65)
CD4 ≥ 200 cells/μL	273	≥5	≥1.8	3.49	(1.61-7.56)	3.71	(1.44-9.55)
CD4 < 200 cells/μL	74	<5	<6.7	7.33	(2.68-20.0)	8.11	(2.76–23.8)

[a]Adjusted for time since AIN3.
[b]Adjusted for time since AIN3, age at AIN3, year of diagnosis and sex.
[c]Due to missing values for CD4 count the numbers do not add up to the total number of person years for HIV positive individuals. Due to GDPR regulations, exact numbers <5 cannot be presented.

being rheumatoid arthritis and type 1 diabetes. Approximately 35% ever had genital warts, and almost all of the study population was HIV-negative (Table 1). The main route of HIV infection was homosexual sex (74.5%) and all but one of the PLWH received antiretroviral treatment (data not shown). Fifty-five percent were registered with one or more types of treatment (ablative, surgical or topical) for AIN3, however the actual proportion is most likely higher as this information is incomplete, particularly before 1995 (data not shown).

Altogether, 97 individuals (7.9%) developed ASCC during 12 824 person-years, 295 died before/without anal cancer, five developed other histological types of anal cancer and 15 emigrated. The remaining 810 individuals were alive, living in Denmark without anal cancer at the end of follow-up. The absolute risk of ASCC following AIN3 according to autoimmune disease, genital warts and HIV status at baseline is depicted in Figure 1A-C. During the first approximately 5 years following an AIN3 diagnosis, the estimated absolute risk of ASCC seemed similar among individuals with and without an autoimmune disease, while thereafter, the risk of ASCC was highest among those registered with an autoimmune disease (Figure 1A). Likewise, no apparent difference in the risk of ASCC after AIN3 was observed between individuals with and without genital warts during the initial 10 years of follow-up, while the risk was higher after more than 10 years of follow-up among individuals registered with genital warts before AIN3, compared to individuals not having genital warts before AIN3 (Figure 1B). In contrast, PLWH individuals had a markedly higher risk of developing ASCC after an AIN3 diagnosis than HIV-negative individuals and this was evident immediately and during the entire follow-up period (Figure 1C).

Results from the Cox regression analysis on the rate of progression from AIN3 to ASCC in relation to autoimmune disease, genital warts and HIV status are presented in Table 2. The diagnosis of an autoimmune disease after the AIN3 diagnosis in individuals not previously registered with an autoimmune disease was associated with an increased rate of progression to ASCC compared to individuals not having an autoimmune disease (HR = 3.37; 95% CI: 1.58-7.19) and an incidence of ASCC per 100 person years of 2.2. A similar, although not statistically significant, association was observed for autoimmune disease before AIN3 diagnosis. Among individuals who were registered with genital warts before AIN3 there was a doubling in the progression rate from AIN3 to ASCC compared to individuals not having genital warts. A similar association was found for individuals registered with genital warts only after the AIN3 diagnosis although not reaching statistical significance. Additional adjustment for HIV status did not change the observed association for genital warts although the estimates were somewhat attenuated (data not shown). Finally, PLWH had a markedly higher progression rate than HIV-negative individuals (HR = 4.25; 95% CI: 1.87-9.65) and the rate of ASCC following AIN3 was highest among those with CD4 count <200 cells/μL (HR = 8.11; 95% CI: 2.76-23.8). Among PLWH, the incidence of ASCC per 100 person years was 2.4.

In a sensitivity analysis restricted to individuals diagnosed with AIN3 during 1995-2016, we found results similar to those from the main Cox regression analysis (Table S1). Further adjustment for treatment of AIN3 made virtually no changes to the estimates (Table S1). Finally, competing risk rates, that is, rates of death or other histological types of anal cancer, following an AIN3 diagnosis seemed to be only weakly positively associated with autoimmune

disease and no associations with genital warts and HIV infection were seen (data not shown).

4 | DISCUSSION

In this population-based study of more than 1200 individuals diagnosed with AIN3 contributing more than 12 500 person-years of follow-up, we found that having an autoimmune disease, genital warts and living with HIV were related to an increased risk of developing ASCC following an AIN3 diagnosis. Autoimmune disease and genital warts registered before as well as after the AIN3 diagnosis were associated with higher rates of ASCC. Among PLWH, the most pronounced risk of ASCC was observed among those with a low CD4 count.

Few studies have investigated factors related to progression of AIN3 to anal cancer, with only one study investigating the factors examined in the present study,[10] and one study including data from the general population.[8] Thus, we are not able to directly compare our results with previous literature.

We found an excess risk of ASCC among individuals with AIN3 who had a diagnosis of autoimmune disease. An association between autoimmune disease and ASCC was previously shown in a Danish cohort study.[4] One potential explanation for this association may be an increased susceptibility to HPV. In patients with psoriasis, a common autoimmune disease, increased risks of other HPV-related cancers have also been reported.[21] Furthermore, long-lasting perianal Crohn's disease, another common autoimmune disease, was reported in a study of anal cancer patients, suggesting that chronic inflammation may be responsible for the development of anal ASCC.[22] In accordance with this, we have previously found that benign inflammatory conditions increased the risk of anal cancer.[1] Thus, it is possible that inflammatory lesions may promote HPV-initiated carcinogenesis or facilitate access of HPV to the epithelium. In addition, another factor that could explain the increased risk associated with a diagnosis of autoimmune disease, is the immunosuppression that may result from the treatment of these diseases.

In line with the results of the present study, a large Danish cohort study found that a previous diagnosis of genital warts was strongly associated with the subsequent risk of anal cancer among both women and men, and the risk remained elevated for >10 years following the diagnosis of genital warts compared to the general population.[6] Genital warts are caused by infection with the nononcogenic HPV types 6 and 11, but coinfection with other HPV types is common.[23] Individuals with genital warts may have an increased risk of developing HPV-associated cancer due to an increased likelihood of also harboring oncogenic HPV types.[6] Immunological factors may also explain why some individuals have a reduced ability to clear HPV and thereby an increased risk of genital warts and later development of cancer.[6,24] Furthermore, the association between genital warts and anal cancer may be a marker of high-risk sexual behavior resulting in coinfection with oncogenic HPV subtypes.[5] Thus, a high number of partners and being MSM has been shown to increase the risk of both genital warts and anal cancer.[23,25]

An increased risk of ASCC associated with HIV infection is well documented,[3] and a diagnosis of AIDS has also been found to be associated with progression of perianal high-grade AIN to anal cancer in MSM.[10] Immunosuppression in PLWH may favor the development of AIN, which may potentially progress to ASCC.[3,4] Previous studies found that a low CD4 count was associated with increased risk of high-grade AIN[26] and anal cancer,[27] respectively, which is in accordance with our findings. Finally, several studies have reported an increased incidence of AIN and ASCC in PLWH after the introduction of highly active antiretroviral therapy in 1996. This has been attributed to improved survival of PLWH resulting in longer HPV persistence and thus leaving more time to develop HPV-associated cellular abnormalities and HPV-related cancer.[3,5]

We observed different time frames of progression from AIN3 to ASCC depending on the risk factor that was examined. The higher absolute risk of ASCC following immediately after AIN3 as well as the shorter time to progression among PLWH compared to women with autoimmune diseases or genital warts may indicate a higher degree of immunosuppression, making PLWH with AIN3 at higher risk of developing cancer than individuals with autoimmune disease or genital warts. This may be relevant for potential screening programs and thus needs further investigation.

The main strength of our study is the use of high-quality nationwide registries with valid information. Unlike most previous studies, the present study was conducted among women and men from the general population. Furthermore, a relatively large number of individuals with AIN3 was included, and there was virtually no loss to follow-up. However, our study also has several limitations. Anal cancer is a rare disease, and some of our analyses included small numbers, limiting our ability to draw firm conclusions. We had limited power to distinguish between effects acting before and after the AIN3 diagnosis. Furthermore, we did not have enough statistical power to perform analyses separately for women and men. With regard to the exposures that we examined, the diagnosis of autoimmune disease relied on a patient registry, which implies that only patients diagnosed or treated at hospitals were included. This may lead to under ascertainment of patients with milder disease, which could introduce bias. Similarly, information concerning treatment of AIN3, originating from the National Patient Registry, was based only on hospital admission and outpatient contacts, and was therefore not complete. In addition, information on different prescription drugs from the Danish Prescription Registry was not available until 1995. Nevertheless, most AIN3 diagnoses in our study occurred from 1995 and onwards and the analysis restricted to individuals diagnosed during 1995-2016 showed results similar to the results among the entire study population. Another limitation is that we had no information on potential confounders or other risk factors such as smoking, sexual behavior, sexual preference and HPV status. Finally, as there is no routine anal cancer screening program in Denmark, those who were detected with AIN3 may not be an entirely representative sample of all individuals with AIN3.

To prevent progression from AIN3 to ASCC and thus reduce the incidence of ASCC, treatment is an important factor, but high-risk

groups (such as PLWH and immunocompromised individuals) should be prioritized. In addition, more information is needed on the efficacy of treatment of AIN3 to prevent ASCC. The ANal Cancer/HSIL Outcomes Research (ANCHOR) study is currently being performed to address this question. Furthermore, given the high progression rate to cancer, screening among groups at the highest risk of having AIN3 is important. Routine screening of anal cancer is not offered in the general population, but it has been proposed for high-risk groups.[28] Another approach to reduce the risk of anal cancer is HPV vaccination. The HPV vaccine has been shown to be highly effective for prevention of anal cancer precursor lesions in both women and men and has been approved for prevention of anal cancer.[29,30] A high vaccine coverage and vaccination of boys, which was introduced in Denmark in 2019, could have an important long-term impact on both AIN3 and anal cancer incidence.

In conclusion, our study based on the general population shows that among individuals with a diagnosis of AIN3, autoimmune disease, ever genital warts and living with HIV, particularly with a low CD4 count, are important factors for the subsequent risk of ASCC. These associations may be caused by an interplay between HPV infection and immunosuppression. In order to decrease the incidence of ASCC, high HPV vaccination coverage and gender-neutral vaccination is essential.

AUTHOR CONTRIBUTIONS

Mette T. Faber, Kirsten Frederiksen and Susanne K. Kjaer initiated the study and contributed to the study conception and design. Kirsten Frederiksen was responsible for the data collection and data analysis. Mette T. Faber wrote the first draft of the manuscript. All authors were involved in the interpretation of the analyses and gave input to and approved the final manuscript. The work reported in the paper has been performed by the authors, unless clearly specified in the text.

ACKNOWLEDGEMENTS

We thank Niels Obel and the steering committee of The Danish HIV Cohort Study for sharing the data.

CONFLICT OF INTEREST

Joel M. Palefsky received grant support, SAB, and speaker's fee from Merck, and acted as a consultant for Antiva Biosciences, Virion Biotechnologies and Virion Therapeutics. Finally, he has stock options in Virion Therapeutics. Susanne K. Kjaer previously received speaker's fee from Merck, and a research grant through her institution from Merck. All other authors report no conflicts of interest.

DATA AVAILABILITY STATEMENT

The study is based on pseudonymized registry data located on a secure platform at Statistics Denmark, which can be accessed given the relevant data permits. Further information is available from the corresponding author upon request.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Faber MT, Frederiksen K, Palefsky JM, Kjaer SK. A nationwide longitudinal study on risk factors for progression of anal intraepithelial neoplasia grade 3 to anal cancer. *Int J Cancer*. 2022;151(8):1240-1247. doi:10.1002/ijc.34143