ORIGINAL RESEARCH

Incidence of cervical dysplasia and cervical cancer in women living with HIV in Denmark: comparison with the general population

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Objectives

Women living with HIV (WLWH) are reportedly at increased risk of invasive cervical cancer (ICC). A recent publication found that WLWH in Denmark attend the national ICC screening programme less often than women in the general population. We aimed to estimate the incidence of cervical dysplasia and ICC in WLWH in Denmark compared with that in women in the general population.

Methods

We studied a nationwide cohort of WLWH and a cohort of 15 age-matched women per WLWH from the general population for the period 1999–2010. Pathology samples were obtained from The Danish Pathology Data Bank, which contains nationwide records of all pathology specimens. The cumulative incidence and hazard ratios (HRs) for time from inclusion to first cervical intraepithelial neoplasia (CIN)/ICC and time from first normal cervical cytology result to first CIN/ICC were estimated. Sensitivity analyses were performed to include prior screening outcome, screening intensity and treatment of CIN/ICC in the interpretation of results.

Results

We followed 1140 WLWH and 17 046 controls with no prior history of ICC or hysterectomy for 9491 and 156 865 person-years, respectively. Compared with controls, the overall incidences of CIN1 or worse (CIN1+), CIN2+ and CIN3+, but not ICC, were higher in WLWH and predicted by young age and a CD4 count < 200 cells/μL. In women with normal baseline cytology, incidences of CIN1+ and CIN2+ were higher in WLWH. However, when we compared subgroups of WLWH and controls where women in both groups were adherent to the national ICC screening programme and had a normal baseline cytology, incidences of CIN and ICC were comparable.

Conclusions

Overall, WLWH developed more cervical disease than controls. Yet, in WLWH and controls adherent to the national ICC screening programme and with normal baseline cytology, incidences of CIN and ICC were comparable.

Keywords: cervical cancer, cervical intraepithelial neoplasia, highly active antiretroviral therapy, HIV, screening

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Introduction

Women living with HIV (WLWH) face a higher risk of persistent cervical infection with oncogenic human papillomavirus (HPV), the cause of invasive cervical cancer (ICC) [1].

The natural history of cervical disease has been reported to differ compared with that in non-HIV-infected women with respect to prevalence, incidence, regression and progression [2–5].

As most ICC cases occur in women who have not been appropriately screened [6], consideration of attendance at screening programmes is essential in the interpretation of cytology findings. Recognizing the increased risk of ICC in WLWH, the US Centers for Disease Control and Prevention (CDC) in 1993 declared ICC an AIDS-defining diagnosis [7] and since 1995 an intensified ICC screening programme for WLWH has been recommended, with cervical cytology tests carried out twice in the first year after HIV diagnosis and annually thereafter [8]. In Denmark, however, as few as 2.6% of WLWH have the recommended two cervical cytology tests in the first year after HIV diagnosis, and from 1999 to 2010 attendance at the annual HIV ICC screening programme was low, but steadily increasing from 29% to 46% of all WLWH [9].

In the context of the remarkably low screening attendance among WLWH in Denmark, we aimed to examine the incidence of cervical dysplasia in WLWH in Denmark compared to that in controls and to identify risk factors for dysplasia in a setting where ICC screening and treatment are readily available and free of charge. The study was carried out by linking data from a nationwide HIV cohort and a nationwide pathology data bank.

Methods

Setting

Denmark has a population of 5.6 million [10] and an estimated HIV prevalence among adults of 0.1% [11]. Treatment of HIV infection is restricted to eight specialized medical centres, where patients are seen on an out-patient basis at intended intervals of 12–24 weeks.

Medical care, including highly active antiretroviral therapy (HAART), is paid for by taxes and provided free of charge to individuals living with HIV in Denmark.

Cervical cancer screening in Denmark

The national ICC screening programme has been described elsewhere [9]. Briefly, women aged 23–49 years receive personal invitations for screening every third year and women aged 50–65 years every fifth year [12].

Since 1995, an intensified screening programme for ICC has been recommended in WLWH, with a cervical cytology test performed twice in the first year after HIV diagnosis and thereafter annually [8]. Written invitations are not implemented in this setting and screening relies on information provided by health care professionals to WLWH [9].

Registries

The Civil Registration System (CRS)

The CRS is a national registry of all Danish residents [13]. A unique, 10-digit personal identification number (PIN) is assigned to each individual at birth or immigration. We identified population controls for this study from the CRS. The PIN was used to link data from the following registries.

Danish HIV Cohort Study (DHCS)

The DHCS is a prospective, observational, nationwide, multicentre, and population-based cohort study of all individuals living with HIV seen at the Danish HIV clinics since 1 January 1995. The cohort has been described in detail elsewhere [14]. Data collection is ongoing, with continuous enrolment of both newly diagnosed residents and immigrants with HIV infection. The database is updated annually and among others contains demographic data, date of HIV diagnosis, smoking status and HAART regimen. Laboratory data include CD4 counts and HIV RNA.

The Danish Pathology Data Bank (DPDB)

The DPDB contains detailed nationwide records of all pathology specimens analysed in Denmark [15]. Data on cytology and histology were retrieved using Systemized Nomenclature of Medicine (SNOMED) codes of cervix uteri: T8x3* and T83*. Cervical cytology results were interpreted according to the 2001 Bethesda system [16]. Cytology reports of atypical squamous cells – cannot exclude high-grade squamous intraepithelial lesion (HSIL) (ASC-H) and atypical glandular cells (AGC) were categorized as HSIL. All histology reports of cervical intraepithelial neoplasia stage 1 (CIN1), CIN2, CIN3 and ICC were based on biopsies and not extrapolated from cytology reports.

The Danish Cancer Registry (DCR)

The DCR contains information on all incident cancers diagnosed in Danish citizens [17]. Diagnoses of prior ICC were obtained using the The International Classification of Diseases (ICD-10) codes C53.0 – C53.9.

Ethics

The study was approved by the Danish Data Protection Agency (2010-331-0468 and 2012-331-0082) and the DHCS is approved by the Danish Data Protection Agency

(2008-41-1781). Ethics approval and individual consent are not required by Danish legislation governing this type of study [18].

Study population
HIV-infected cohort
From the DHCS, we identified all WLWH with a Danish PIN and aged 16 years or more at the time of HIV diagnosis. The index date was defined as 1 January 1999 or the date of HIV diagnosis, the individual's18th birthday or immigration, whichever came last.

Population controls
For each WLWH, we identified 15 age-matched women without a known HIV diagnosis from the general population in the CRS who were alive on the patient's index date. The index date of the WLWH was also referred to as the index date of the respective population controls.

WLWH and controls with a history of ICC, carcinoma in situ or hysterectomy prior to the index date were excluded.

Statistical analyses

The time from the index date to the date of hysterectomy, emigration, death, loss to follow-up or 31 December 2010, whichever occurred first, was calculated. Prior screening was assessed from 1 January 1999. Three strategies were used to study incident dysplasia using the cumulative incidence function with death as a competing risk.

First, we studied overall incidence, regardless of prior screening, for the time from the index date to the first CIN1 or worse (CIN1+), CIN2 or worse (CIN2+), CIN3 or worse (CIN3+) and carcinoma. The significance of differences in the incidence of dysplasia between WLWH and controls was estimated using the log-rank test. For women diagnosed with carcinomas during the study period, we assessed prior screening attendance according to the national ICC screening programme.

Secondly, incidence was estimated in all women presenting with normal cervical cytology for the time from the first normal cervical cytology result to dysplasia.

Thirdly, to evaluate whether prior screening and cytology results had an impact on outcome, women adherent to the national ICC screening programme with a normal cytology sample at the latest test were studied for the time from the first normal cytology result to CIN/ICC.

Additionally, in this subgroup of women adherent to the national ICC screening programme prior to enrolment, the hazard ratio (HR) for the time from the index date to the first cervical cytology result of any kind was estimated and adjusted for age to see if screening behaviour (as recommended) changed after an HIV diagnosis compared with screening behaviour among controls. Percentages of women in this subgroup obtaining a cervical cytology result within the following 39 months (3 years + a 3-month grace period, as recommended in the screening guidelines) were calculated.

Cox proportional hazards models were used to estimate HRs and associated 95% confidence intervals (CIs) for risk factors of dysplasia in WLWH. Two models were developed, as CD4 count and HIV RNA are dependent covariates and could not be included in the same model. Time-updated age, mode of transmission, ethnicity and smoking status were included in both models, whereas time-updated HIV RNA was included in the first model and replaced by CD4 count in the second model. Only the HR of the CD4 count covariate is presented for the second model. To control for repeated testing, a combined *P*-value was estimated for variables spending more than one degree of freedom in the multiple analyses.

In the two models of time from a normal cytology result to dysplasia, matching of women was incomplete, as normal baseline cytology was mandatory to enter the analyses. Hence, an adjustment for age and calendar period was implemented in the calculations of HRs of risk of dysplasia comparing WLWH and controls.

Individuals with missing explanatory variables were excluded from the multivariate regression analyses. The models were tested for proportional hazards by allowing for time-dependent effects of covariates.

To evaluate whether gynaecological treatment affected the different stages of CIN found in the two cohorts, women who had undergone a cervical cone biopsy were studied. We assessed the first conization and the previous histology sample collection that led to the cone biopsy. The odds ratio (OR) for having a cone biopsy performed at CIN stages 1 and 2 versus CIN3 among WLWH and controls was estimated.

Undetectable viral load was defined as a plasma HIV RNA load of < 500 HIV-1 RNA copies/mL, which was the highest level of sensitivity for testing in the observation period. The significance level was set at 0.05 (two-sided).

The cumulative incidence function of time from index date/normal cytology to dysplasia was estimated using R-2.12.2 and the cmprsk library [19]. Calculation of time-updated variables was performed using the %stratify SAS macro [20]. SAS statistical software version 9.2 (SAS Institute, Cary, NC) was used for all other data analysis.

Results

A total of 1172 WLWH in Denmark were identified. Twenty-nine women were excluded, because of a prior history of ICC or carcinoma in situ. Further, three WLWH

Table 1 Characteristics of women living with HIV (WLWH) and controls

	WLWH	Controls
Number of individuals	1140	17 046
Follow-up (years) [median (IQR)]	9.4 (5.0–12.0)	10.9 (6.7–12.0)
Follow-up time, total (person-years)	9491	156 865
Age at inclusion (years) [median (IQR)]	33.6 (29.0–40.0)	33.6 (29.0–40.0)
Ethnicity [n (%)]		
White	546 (48.7)	–*
Asian	122 (10.8)	
Black	423 (37.7)	
Other	31 (2.8)	
Missing	(18)	
Place of HIV transmission† [n (%)]		
Denmark	434 (43.2)	–*
Europe + USA	73 (7.3)	
Africa	386 (38.5)	
Asia	103 (10.3)	
Other	7 (0.7)	
Missing	(137)	
Mode of transmission [n (%)]		
Heterosexual	883 (81.5)	–*
IDU	166 (15.3)	
Other	34 (3.2)	
Missing	(57)	
CD4 count at inclusion [n (%)]		
< 200 cells/μL	295 (27.9)	–*
200–350 cells/μL	288 (27.2)	
> 350 cells/μL	475 (44.9)	
Missing	(82)	
Hepatitis C virus coinfection [n (%)]		
Yes	237 (20.8)	–*
No	903 (79.2)	
Smoking status [n (%)]		
Current or previous smoker	490 (43.0)	–*
Never smoker	388 (34.0)	
Unknown smoking status	262 (23.0)	

*No information available.
†Self-reported geographical location at the time of HIV acquisition.
IDU, injecting drug use; IQR, interquartile range.

Table 2 Number and percentage of women living with HIV (WLWH) and controls with (i) at least one type of cervical dysplasia and (ii) at least one type of cervical dysplasia after a sample of normal cytology

		WLWH	Controls
(i) Women with at least one type of cervical dysplasia [n (%)]	CIN1 or worse	163 (14.3)	738 (4.3)
	CIN2 or worse	129 (11.3)	620 (3.6)
	CIN3 or worse	78 (6.8)	434 (2.5)
	Carcinoma	4 (0.4)	28 (0.2)
(ii) Women with at least one type of cervical dysplasia after a sample of normal cytology [n (%)]	CIN1 or worse	62 (7.4)	420 (3.8)
	CIN2 or worse	51 (6.1)	356 (3.2)
	CIN3 or worse	21 (2.5)	231 (2.1)
	Carcinoma	0 (0.0)	6 (0.1)

and their respective 45 controls were excluded because of hysterectomy prior to the index date. Finally, 54 controls were excluded because of hysterectomy prior to the index date, leaving 1140 WLWH and 17 046 age-matched female controls in the study, representing a total of 9491 and 156 865 person-years of follow-up, respectively. Basic characteristics of patients and controls are described in Table 1.

The cumulative incidence of cervical dysplasia of any kind was two- to three-fold higher in WLWH compared with controls, in spite of higher mortality in WLWH (Table 2; data on mortality not shown). This difference reached the level of significance for CIN1+ to CIN3+ (Fig. 1). Four (0.4%) WLWH developed carcinomas versus 28 (0.2%) controls ($P = 0.15$) (Table 2).

None of the four WLWH presenting with carcinomas had obtained a prior cervical cytology result; however, follow-up was too short in three women to determine

screening attendance. In comparison, 18 of the 28 controls presenting with carcinomas had had no cervical cytology tests performed in the preceding screening period, although in 10 of these women follow-up was too short to determine screening attendance. In nine of the 10 controls adherent to the national ICC screening programme, the latest cytology sample was normal and one woman presented with a prior HSIL.

In the adjusted analyses, factors associated with CIN were young age (18–30 years) and a CD4 count < 200 cells/μl (Table 3). To estimate the effect of missing values on outcome in the adjusted analyses, we performed sensitivity analyses by adding an extra category with missing values. Accordingly, low CD4 count became a predictor of CIN2+ and young age a predictor of CIN3+ (data not shown).

A total of 841 (73.8%) WLWH and 11 067 (64.9%) controls presented with normal baseline cytology at inclusion. When we compared the cumulative incidence for the time from the first normal cytology result to dysplasia, WLWH presented with higher incidences of CIN1+ and CIN2+, but not CIN3+ and carcinomas [adjusted HR 2.48 (95% CI 1.90–3.24), 2.40 (95% CI 1.79–3.22) and 1.52 (95% CI 0.97–2.38), respectively] (Fig. 2; Table 2).

Further, 144 (12.6%) WLWH and 4772 (28.0%) controls were adherent to the national ICC screening programme and presented with normal baseline cytology at inclusion. There was no significant difference in the incidences of CIN1+, CIN2+ and CIN3+ between adherent WLWH and controls in the adjusted analyses [HR 1.55 (95% CI 0.93–2.56), 1.47 (95% CI 0.79–2.73) and 0.90 (95% CI 0.33–2.48), respectively] (Fig. 3). Within 39 months from inclusion, 67% of these WLWH versus 83% of controls had obtained a subsequent cytology result [adjusted HR 0.72 (95 %CI 0.60–0.87); $P = 0.0006$]. In the latter two models for time from normal cytology to dysplasia, sample sizes were too small to estimate risk factors of dysplasia in WLWH.

Cone biopsies were performed in 132 (11.5%) WLWH and 711 (4.1%) controls during the study period. Among WLWH

CIN1 OR WORSE

CIN2 OR WORSE

CIN3 OR WORSE
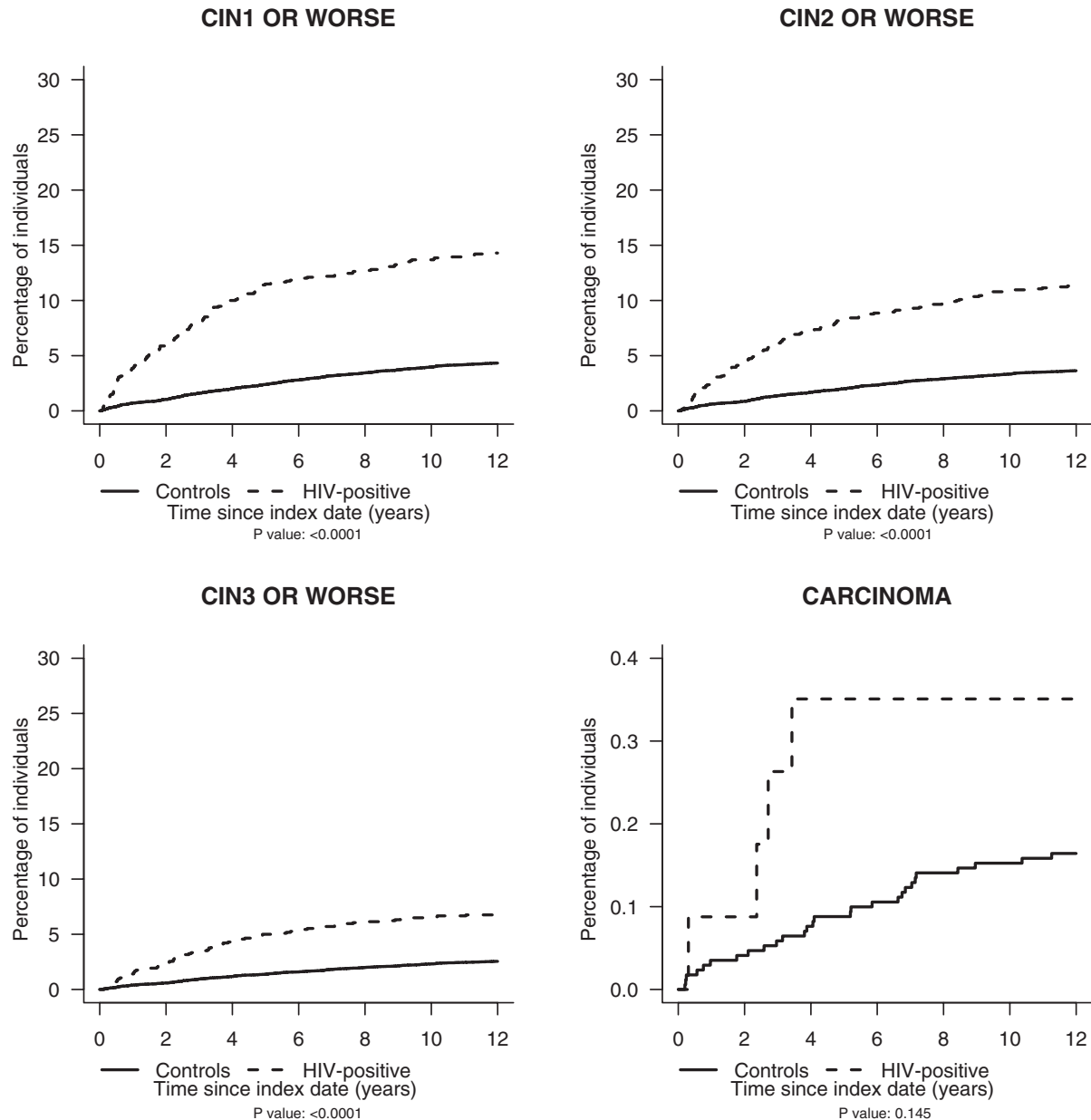
CARCINOMA

Fig. 1 The cumulative incidence function with death as a competing risk for time from inclusion to cervical intraepithelial neoplasia stage 1 (CIN1) or worse, CIN2 or worse, CIN3 or worse or carcinoma stratified by women living with HIV and their controls. Please note the different scale of the *y*-axis for carcinomas.

with a prior cone biopsy, 76 (57.6%) had the biopsy performed at CIN stages 1 and 2, whereas the corresponding proportion among controls was 278 (39.1%) [OR 2.11 (95% CI 1.45–3.08)].

Discussion

In this nationwide HIV cohort study with complete records of prior screening intensity, screening results and treatment

of cancer precursors, we found that WLWH overall developed more CIN of all stages compared with controls. In women with normal baseline cytology, incidences of CIN1+ and CIN2+ were higher in WLWH than in controls; however, in the subgroup of WLWH and controls adherent to the national ICC screening programme and with normal baseline cytology, the risks of CIN were comparable. Development of dysplasia in WLWH was predicted by young age and most recent CD4 count < 200 cells/μL. Finally, in

Table 3 Risk of cervical intraepithelial neoplasia in women living with HIV [unadjusted and adjusted hazard ratios (HRs); $n = 1140$]

Predictors of cervical dysplasia*	Unadjusted HR CIN1 or worse	CIN2 or worse	CIN3 or worse	Adjusted HR CIN1 or worse	CIN2 or worse	CIN3 or worse
Time-updated age						
18–30 years	1.00[†]	1.00[†]	1.00[†]	1.00[†]	1.00[†]	1.00
> 30–40 years	0.85 (0.57–1.26)	0.70 (0.44–1.11)	0.63 (0.36–1.12)	0.73 (0.46–1.15)	0.58 (0.34–0.98)	0.49 (0.25–0.96)
> 40–50 years	0.57 (0.35–0.94)	0.68 (0.40–1.16)	0.58 (0.29–1.14)	0.51 (0.29–0.91)	0.56 (0.30–1.05)	0.59 (0.28–1.25)
> 50 years	0.22 (0.09–0.53)	0.26 (0.11–0.64)	0.06 (0.01–0.48)	0.19 (0.07–0.52)	0.22 (0.08–0.61)	–[†]
Mode of transmission						
Heterosexual contact	1.00	1.00	1.00	1.00	1.00	1.00
Injecting drug use	0.80 (0.50–1.30)	0.92 (0.55–1.54)	1.15 (0.62–2.14)	0.97 (0.53–1.75)	1.06 (0.56–2.03)	1.39 (0.65–3.01)
Other	–[†]	–[†]	–[†]	–[†]	–[†]	–[†]
Ethnicity						
White	1.00	1.00	1.00	1.00	1.00	1.00
Asian	1.47 (0.91–2.38)	1.27 (0.73–2.21)	1.61 (0.84–3.11)	1.21 (0.70–2.15)	1.05 (0.54–2.03)	1.44 (0.65–3.19)
Black	1.16 (0.83–1.63)	1.07 (0.74–1.57)	0.97 (0.59–1.62)	0.90 (0.57–1.42)	0.89 (0.53–1.48)	0.91 (0.47–1.79)
Other	0.43 (0.11–1.75)	0.52 (0.13–2.12)	0.44 (0.06–3.21)	0.25 (0.04–1.84)	0.32 (0.04–2.31)	0.55 (0.07–4.04)
Time-updated CD4 count						
< 200 cells/μL	1.00[†]	1.00	1.00[†]	1.00[†]	1.00	1.00[†]
200–350 cells/μL	0.77 (0.48–1.24)	0.76 (0.44–1.33)	0.56 (0.28–1.12)	0.69 (0.40–1.21)	0.74 (0.38–1.44)	0.64 (0.29–1.38)
> 350 cells/μL	0.53 (0.34–0.82)	0.59 (0.35–0.97)	0.43 (0.24–0.80)	0.49 (0.30–0.82)	0.61 (0.33–1.12)	0.40 (0.20–0.82)
Time-updated HIV RNA						
In patients receiving HAART						
< 500 copies/mL	1.00	1.00	1.00	1.00	1.00	1.00
> 500 copies/mL	1.11 (0.76–1.61)	1.11 (0.73–1.70)	1.10 (0.63–1.92)	2.13 (0.87–5.26)	2.00 (0.71–5.63)	1.64 (0.45–5.94)
In patients *not* receiving HAART						
< 500 copies/mL	1.00	1.00	1.00	1.00	1.00	1.00
> 500 copies/mL	1.20 (0.16–9.16)	0.93 (0.12–7.30)	0.24 (0.05–1.22)	1.06 (0.69–1.63)	1.08 (0.66–1.76)	1.02 (0.54–1.91)
Smoking status						
Current or previous smoker	1.00	1.00	1.00	1.00	1.00	1.00
Never smoker	1.13 (0.81–1.59)	1.08 (0.74–1.58)	1.02 (0.63–1.67)	1.04 (0.70–1.57)	1.08 (0.68–1.72)	0.96 (0.53–1.76)

CIN, cervical intraepithelial neoplasia; HAART, highly active antiretroviral therapy.
*Two models are shown in the table: mode of transmission, ethnicity and calendar period were included in both models, whereas time-updated HIV RNA was included in the first model and replaced by time-updated CD4 count in the second model. We only present the HR of the CD4 count from the second model. HRs of carcinomas could not be estimated because of the limited number of events.
[†]The combined *P*-value is significant.
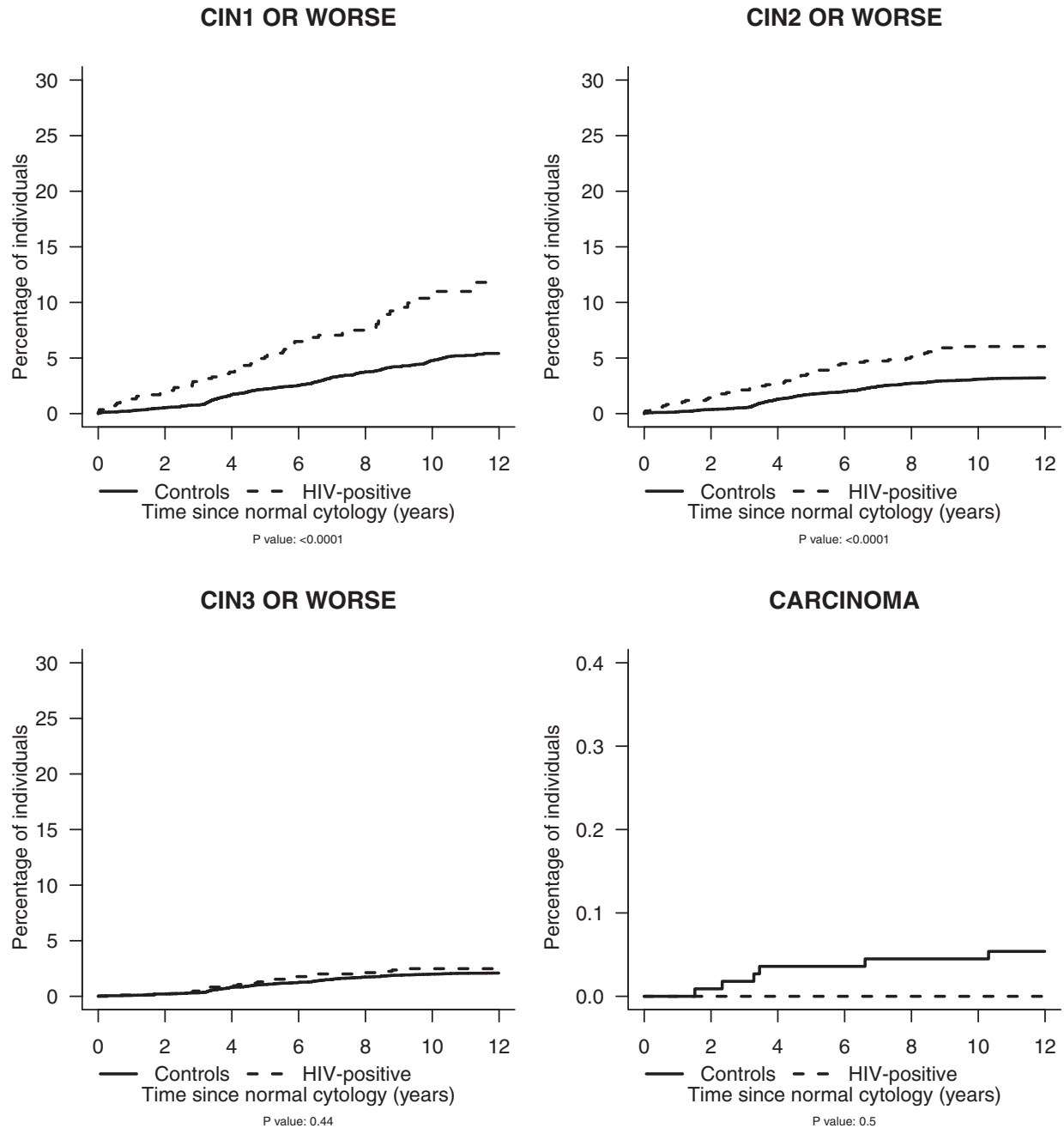[†]Data could not be estimated because of a limited number of events.

WLWH having had a cone biopsy, the intervention was more likely at earlier CIN stages than in controls.

A comparable median three-fold increase in the incidence of any squamous intraepithelial lesion (SIL) [4] was found in a recent review comprising 15 cohort studies (seven were based on cytology only). The studies were predominantly European, normal baseline cytology was mandatory, and patients were followed up every 6–12 months. Notably, the study outcome was SIL and not ICC. In the US Women's Interagency HIV Study, where study participants receive semi-annual cervical cytology tests, similar risks of cervical precancer and ICC were found between WLWH and controls who were oncogenic HPV negative and had normal baseline cytology at enrolment [21]. Although screening intensity was higher and HPV co-testing was implemented, the outcome was comparable to that in our subgroup of adherent WLWH with normal baseline cytology.

The impact of HAART on ICC and other HPV-associated neoplasias remains controversial [1,4,5,8,22–24]. In contrast to decreasing incidences of opportunistic infections, the introduction of HAART has been associated with a stable incidence of ICC and increased incidences of both oropharyngeal tumours [24] and anal cancer [1,23–25]. The stable incidence of ICC may partly be explained by the fact that persistent cervical HPV infection precedes ICC by decades [1]. Immune reconstitution and death act as competing risks in ICC development. A cumulative HPV exposure secondary to increased longevity of individuals living with HIV might have a proportionally greater impact on risk of HPV-related cancers than the partial reversal of immunosuppression following initiation of HAART [1]. Further, HIV infection and ICC share common sexual risk factors [24]. Unlike some [22,26,27], but in accordance with other reports [28–30], we found no protective effect against dysplasia of being on HAART with a suppressed viral load. Along with others [31], we question retaining ICC as an AIDS-defining cancer in the era of HAART. The division of cancers into infection-related and infection-unrelated cancers, as done by Borges *et al.* [32], seems more appropriate.

CIN1 OR WORSE

P value: <0.0001

CIN2 OR WORSE

P value: <0.0001

CIN3 OR WORSE

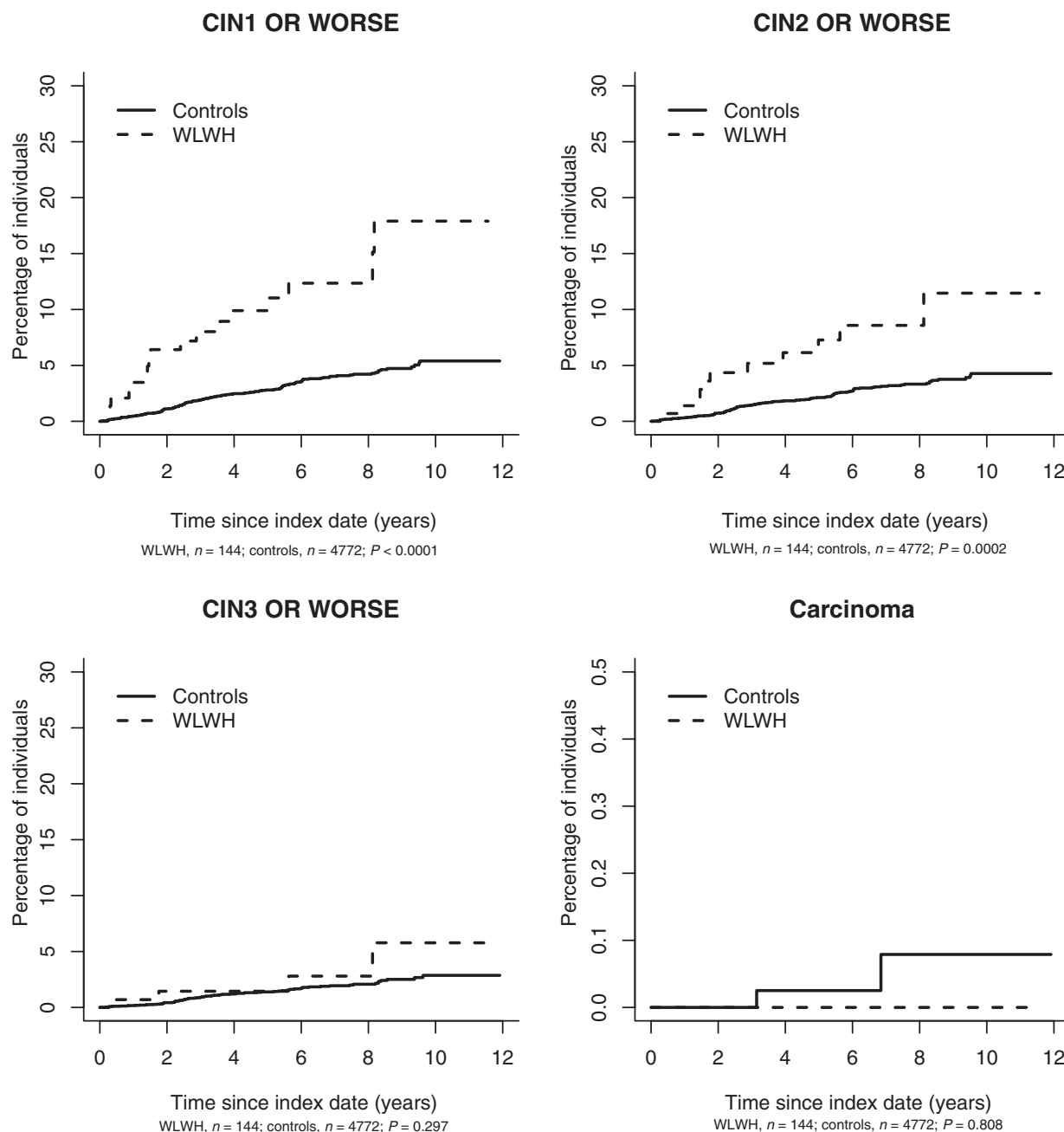P value: 0.44

CARCINOMA

P value: 0.5

Fig. 2 Incidence of cervical dysplasia in women presenting with normal cervical cytology at inclusion. The cumulative incidence function was calculated with death as a competing risk for time from first normal cytology result to first cervical intraepithelial neoplasia stage 1 (CIN1) or worse, CIN2 or worse, CIN3 or worse or carcinoma stratified by women living with HIV and their controls. Please note the different scale of the *y*-axis for carcinomas.

A CD4 count > 350 cells/µL was protective against CIN, which is in agreement with the findings of others [22,27,33]. The decreased risk of persistent HPV infection following immunoreconstitution [1] provides a plausible explanation for this. In the multivariate analysis, the only independent predictor of CIN3+ was a low CD4 count, emphasizing the importance of maintaining high CD4 counts in WLWH.

In addition to host immunity, screening behaviour offers another explanation for the connection between low CD4 counts and cervical dysplasia. Poor adherence to HAART,

CIN1 OR WORSE

CIN2 OR WORSE

CIN3 OR WORSE

Carcinoma

Fig. 3 Incidence of cervical dysplasia in women adherent to the national cervical cancer screening programme and with a normal cytology sample as the latest test before inclusion. The cumulative incidence function was calculated with death as a competing risk for time from first normal cytology result to first cervical intraepithelial neoplasia stage 1 (CIN1) or worse, CIN2 or worse, CIN3 or worse or carcinoma stratified by women living with HIV and their controls. Please note the different scale of the *y*-axis for carcinomas.

resulting in low CD4 counts, and consequent regular visits to HIV centres might act as proxies for suboptimal self-care and low adherence to recommended screening programmes. In accordance with earlier reports [6,34], the majority of women diagnosed with ICC had a history of nonadherence to screening recommendations. WLWH in Denmark (including the subgroup of WLWH adherent to the national ICC screening programme at inclusion in the present study) display lower attendance at the national ICC screening programme [9], and therefore the overall higher

incidences of CIN in the present study cannot be explained by a higher screening intensity.

An elevated ICC incidence among WLWH in the younger age groups relative to the general population has been suggested [33], but data are scarce. In the present study, CIN was predicted by young age, potentially because of the higher prevalence of HPV in younger women [22].

According to guidelines, management of dysplasia in WLWH should not differ from that in the general population [5]. Excisional treatment is associated with increased risk of preterm labour [35], but expectant management might be an unsuitable approach in some WLWH [2,31]; those of low socioeconomic status, particularly, might be poorly motivated to seek regular medical follow-up [2]. However, too frequent screening can lead to over-referral, high costs and adverse events associated with overtreatment [6]. Further, higher recurrence rates post-treatment are found in WLWH [2]. More than 10% of WLWH in Denmark had a cone biopsy performed as opposed to about 4% in the general population. In WLWH having had a cone biopsy performed, the intervention was carried out at earlier CIN stages than in controls. This might explain some of the reduced difference in the incidence of CIN3 and carcinoma between WLWH and controls and contribute to the low number of carcinomas seen in WLWH. Most evidence concerning ICC is limited to detection of CIN3 [6,33], but as only a minority of CIN3 cases regress [36] and CIN3 is an indication for treatment, we find this a fair proxy for cancer.

The comparable risks of cervical disease seen in our subgroup of adherent WLWH and controls with normal baseline cytology and the similar findings in the WIHS cohort [21] raise the question of whether intensified screening programmes are necessary for all WLWH. Recent guidelines from the European AIDS Clinical Society (EACS) suggest that longer screening intervals may be appropriate if prior cervical cytology findings are repeatedly negative [37]. Moreover, as the oncogenic HPV DNA test concurrent with cervical cytology is increasingly available, a more individualized approach might be implemented in HIV ICC screening programmes, including both prior cervical cytology and HPV results.

The major strength of our study is the nationwide population-based design, linking the nationwide registers DHCS and CRS, resulting in low loss to follow-up [38], and the DPDB, which has complete nationwide records of all cervical cytology and histology specimens, ensuring that data are not subject to recall bias. We were not limited by 'selection by indication', as women were included in our analyses regardless of prior screening behaviour and attendance at HIV centres. Moreover, our ability to integrate data on prior hysterectomy, ICC screening and results and intervention optimized the accuracy of the results. Finally, histopathology was used as a hard endpoint instead of cytology, as it serves as the gold standard [39].

Some limitations need to be considered. HPV testing of patients was implemented gradually over the study period and was not included in the analyses. Data on sexually transmitted diseases (STDs) were not available and therefore not included in the analyses, and neither was the ethnicity of controls. Screening was not evenly distributed between WLWH and controls and therefore estimates of CIN in WLWH might be conservative.

In conclusion, WLWH overall had higher incidences of all stages of CIN. The higher incidence of CIN in WLWH displaying low CD4 counts and nonadherence to the ICC screening programmes reinforces the need to improve ICC screening attendance in high-risk patients. Yet, the comparable risks of cervical disease in WLWH and controls adherent to screening with normal baseline cytology call for individualized screening recommendations, including prior cervical cytology and HPV results, in future HIV ICC screening guidelines.

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