Cancer burden and risk factors among women with HIV: a multi-regional study from the D:A:D and RESPOND cohort collaborations

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Summary

Background Data on cancer incidence and associated risk factors among women with HIV are limited. We investigated cancer burden among women with HIV.

Methods We included all women ≥18 years from the two large multicentre observational cohort collaborations (D:A:D and RESPOND). The primary outcomes were incidence of all cancers, HPV-related and common individual cancers including breast cancer, lung cancer, and non-Hodgkin lymphoma (NHL) from 2006 to 2021. Baseline was defined as the latest date of entry into local cohort enrolment and 1st January 2006 for D:A:D and 1st January 2012 for RESPOND. Participants were followed from baseline until the date of first cancer, final follow-up or administrative censoring—whichever occurred first. We assessed risk factors using multivariable Poisson regression by applying robust standard errors and determined a population attributable fraction (PAF) for key risk factors for cancers.

Findings Among 17,512 women included, median age at baseline was 39.5 years (interquartile range, IQR 32.5–46.0). Over 141,404 person-years (PYS) and a median 9.2 (5.5–10.1) years of follow-up, 832 women were diagnosed with any cancer; incidence rate 5.9 (95% CI 5.5–6.4)/1000 PYS, 163 HPV-related cancers (1.1

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[1.0–1.3]/1000 PYS), 150 breast cancers (1.1 [0.9–1.2]/1000 PYS), 94 lung cancers (0.7 [0.5–0.8]/1000 PYS) and 72 NHL (0.5 [0.4–0.6]/1000 PYS). Older age (≥45 vs. <45 years), Southern Europe (vs. Western Europe) and smoking were associated with an increased risk of overall cancers. Lower pre-ART nadir CD4, time-updated CD4, and a prior AIDS diagnosis were associated with lung- and HPV-related cancer. In PAF analysis, smoking and HIV-related factors such as lower current CD4, nadir CD4 and HIV viremia significantly contributed to cancer risk.

Interpretation Our findings suggest that women with HIV older than 45 years, past or current immunosuppressed or current smokers could be candidates for intensified cancer screening and prevention.

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Keywords: Women with HIV; Cancer incidence; HPV; Modifiable risk factors; Observational cohort study

Research in context

Evidence before this study

We searched PubMed for full articles, systematic reviews, and meta-analyses published up to May 31, 2025, in any language, using the terms "HIV", "women", "cancer", "incidence", and "risk factors". While several studies have addressed specific cancers such as cervical and breast cancer in HIV-positive women, there remains a relative paucity of large-scale cohort studies that comprehensively assess the overall cancer burden and associated risk factors in this population. There are limited data specifically addressing cancer incidence, risk factors, and attributable burden in women with HIV, particularly from large international cohort collaborations.

Added value of this study

This study provides comprehensive data on cancer burden and risk factors among 17,512 women with HIV across two major international cohort collaborations, D:A:D and RESPOND. With over 141,000 person-years of follow-up, we identified key risk factors—including older age, smoking, and HIV-related immunosuppression—for overall, HPV-related and common individual cancers. Importantly, we estimated population attributable fractions (PAFs) to quantify the relative contribution of modifiable and HIV-specific risk factors, highlighting modifiable targets for prevention.

Implications of all the available evidence

Our findings underscore the need for intensified cancer screening and prevention strategies among women with HIV, particularly those over 45 years, those with a history of low CD4 counts, or those who smoke. These data support the integration of cancer prevention into routine HIV care for women and reinforce the importance of early HIV diagnosis, sustained viral suppression, and smoking cessation efforts in reducing cancer risk.

Introduction

While the risk of death from AIDS-related-cancers has decreased due to efficient antiretroviral therapy (ART), mortality rates from non-AIDS-cancers have increased,[1–5] and projections suggest that the incidence of these cancers in people with HIV will continue to rise.[6] The rates of cancers overall and infection-related cancers, such as cervical and anal cancers associated with human papillomaviruses (HPV) or Epstein–Barr virus (EBV)-associated lymphomas, are also considerably higher in people with HIV compared to the general population.[7–9] A recent combined RESPOND and D:A:D analysis has demonstrated increasing trends over time for the rates of smoking- and obesity-related cancers.[2] Other similar studies, also reporting age-standardised incidence rates, have suggested increases in cancer rates for both men and women with HIV.[10,11] Due to the smaller proportion of women generally participating in clinical studies, particularly in regions with a male-predominant HIV epidemic, research on the burden of specific cancers and the associated risk factors among women with HIV remains limited.[12,13]

Although women in the general population, especially from many low- and middle-income countries, continue to experience rising rates of specific cancers such as breast, lung and anal cancers,[14–16] the specific risk factors contributing to these malignancies among women with HIV remain inadequately explored and are the subject of limited research. To date, research has focused on HPV-related dysplasia or single cancers such as cervical and anal cancers without providing an overview of the overall cancer burden in women with HIV.[17,18] While several studies have consistently shown a significantly elevated risk of cervical cancer in women with HIV,[19–21] fewer large-scale multi-regional studies focused on the incidence and risk factors of other HPV-associated cancers, such as oropharyngeal, anal, vulvar and vaginal cancers in this population. This is despite the increasing incidence of oropharyngeal cancers associated with HPV in the general population in many developed countries, including the European region.[22,23]

In this study, we examine the incidence and risk factors for all, HPV-related cancers and individual common cancers among women with HIV attending routine clinical care using combined data from two large multi-regional cohort studies—the RESPOND and D:A:D collaborations—collected between 2006 and 2022.

Methods

Study design and study population

The D:A:D (https://chip.dk/Research/Studies/DAD) and RESPOND (https://chip.dk/Research/Studies/RESPOND) studies are large-scale, prospective, multi-cohort collaborations from across Europe, Australia and the United States of America (USA), including more than 49,000 people with HIV from 11 cohorts in D:A:D (1999–2016), and more than 35,000 people from 17 cohorts in RESPOND (2017-ongoing). Detailed descriptions of both studies and participating cohorts and countries have previously been published.[2,24–27] Both the D:A:D and RESPOND collaborations follow similar methodologies and collect harmonized data. In each, demographic and clinical information is obtained during routine clinical care, recorded at enrolment, and updated annually thereafter. For RESPOND, retrospective data for up to five years prior to enrolment, and earlier where available, are also collected. In both studies, clinical events, including cancers, are prospectively collected through specific case event forms. Reported events undergo central validation by study physicians at the coordinating centre, using a pre-established algorithm, during the respective validation periods (D:A:D: from 2004 onwards; RESPOND: from 12 months prior to the last local cohort visit before RESPOND enrolment onwards). All cancer events are additionally reviewed by an external oncologist.[2]

Cisgender women with HIV (female sex assigned at birth) who were 18 years or older were eligible, with an additional criterion for RESPOND, where participants were excluded if they did not have a CD4 count and VL measurement either 12 months prior to or within three months after baseline (n = 2482). For individuals with a history of cancer before baseline, only incident cases of cancers of a different type occurring during follow-up were considered, and women with unknown prior cancer type were excluded. Eligible participants were followed from baseline until the validated diagnosis of a cancer event of interest during follow-up, death, date of last follow-up, or administrative censor date (1st February 2016 for D:A:D and 31st December 2022 for RESPOND)—whichever occurred first. Baseline was defined as the date of cohort entry (in D:A:D, the latest of date of cohort entry or 1 Jan 2006; in RESPOND, the latest of cohort enrolment or 1 Jan 2012). For D:A:D participants, the date of last follow-up was defined as 6 months after the last clinic visit, or the end date of D:A:D (1st February 2016), to account for possible delays in event reporting after study closure.[28] The date of last follow up for RESPOND was defined as the latest of the most recent CD4 count, VL measurement, drop out date, or date of death. For participants enrolled in both collaborations, data from D:A:D were utilized up to the date of the RESPOND baseline, after which data from RESPOND were used.

Study outcomes

The primary study outcomes were the incident cancer diagnoses by the following groupings.

i. All cancers reported in both cohorts, irrespective of site or histological type, were included, except for non-melanoma skin cancers and a relapse of or metastases from a primary cancer.
ii. HPV-related cancers—HPV-related cervical, vulvar, vaginal, anal, and oropharyngeal cancers.
iii. Most common individual cancers—breast cancer, lung cancer and non-Hodgkin lymphoma (NHL)

There was one additional anal cancer in the "HPV-related cancers" group but not in the "All cancers" because one participant had >1 cancer during follow-up and the follow-up time was censored at the cancer event of interest for each group. We excluded pre-malignant conditions for cancers such as anal and cervical cancers in the groups. Additionally, incident analyses also considered for other common individual cancer types with sufficient events to ensure statistical power, including cervical, head and neck, anal and other non-cervical gynaecological cancers.

The cancer types included in all cancer group and HPV-related cancer groups are listed in Supplementary Table S1. For head and neck cancers, we considered all

	Overall (N = 17,512)		All cancers (N = 832)		HPV-related cancers (N = 163)		Breast cancer (N = 150)		Lung cancer (N = 94)		Non-Hodgkin's lymphoma (N = 72)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Total	17,512	100	832	4.8	163	0.9	150	0.9	94	0.5	72	0.4
Age group (years)												
<45	12,584	71.9	441	53	60	36.8	46	30.7	9	9.6	40	55.6
45–55	3505	20	259	31.1	74	45.4	71	47.3	41	43.6	22	30.6
>55	1423	8.1	132	15.9	22	13.5	20	13.3	31	33	10	13.9
Ethnicity[a]												
White	8411	48	477	57.3	93	57.1	86	57.3	70	74.5	32	44.4
Black	3992	22.8	114	13.7	22	13.5	25	16.7	1	1.1	14	19.4
Other	871	5	25	3.0	8	4.9	4	2.7	2	2.1	4	5.6
Unknown	4238	24.2	216	26.0	40	24.5	35	23.3	21	22.3	22	30.6
BMI (kg/m^2)												
<18.5	1192	6.8	85	10.2	17	10.4	10	6.7	19	20.2	2	2.8
18.5–<25	7845	44.8	393	47.2	81	49.7	74	49.3	58	61.7	30	41.7
25–<30	1464	8.4	54	6.5	6	3.7	13	8.7	5	5.3	6	8.3
30+	2837	16.2	136	16.3	33	20.2	29	19.3	3	3.2	10	13.9
Unknown	4174	23.8	164	19.7	26	16	24	16	9	9.6	24	33.3
Geographical Region[b]												
Western Europe and USA	7830	44.7	400	48.1	63	38.7	83	55.3	55	58.5	32	44.4
Southern Europe	3024	17.3	185	22.2	46	28.2	30	20	17	18.1	15	20.8
Northern Europe and Australia	4472	25.5	189	22.7	35	21.5	25	16.7	20	21.3	22	30.6
Eastern and east central Europe	2186	12.5	58	7.0	19	11.7	12	8	2	2.1	3	4.2
HIV acquisition mode												
Heterosexual	12,903	73.7	209	25.1	108	66.3	115	76.7	50	53.2	17	23.6
IDU	2781	15.9	551	66.2	45	27.6	20	13.3	40	42.6	44	61.1
Other	678	3.8	36	4.3	8	4.9	5	3.3	3	3.2	30	8.3
Unknown	1150	6.6	36	4.3	2	1.2	10	6.7	1	1.1	5	6.9
ART treatment history												
ART Naive	4750	27.1	159	19.1	23	14.1	27	18	15	16	30	41.7
ART Experienced, VL < 200 cp/mL	9163	52.3	446	53.6	92	56.4	90	60	62	66	17	23.6
ART Experienced, VL ≥ 200 cp/mL	2959	16.9	194	23.3	45	27.6	28	18.7	15	16	21	29.2
ART Experienced, unknown VL	640	3.7	33	4.0	3	1.9	5	3.3	2	2	4	4.5
Smoking status												
Never	6064	34.6	226	27.2	30	18.4	62	41.3	4	4.3	27	37.5
Current	5219	29.8	350	42.1	75	46	45	30	63	67	25	34.7
Previous	2314	13.2	136	16.3	31	19	29	19.3	20	21.3	3	4.2
Unknown	3915	22.4	120	14.4	27	16.6	14	9.3	7	7.4	17	23.6
HCV[d]												
No	10,988	62.7	464	55.8	90	55.2	109	72.7	40	42.6	36	50
Yes	3884	22.2	273	32.8	58	35.6	22	14.7	48	51.1	22	30.6
Unknown	2640	15.1	95	11.4	15	9.2	19	12.7	6	6.4	14	19.4
HBV[e]												
No	14,275	81.5	701	84.3	138	84.7	127	84.7	85	90.4	55	76.4
Yes	643	3.7	36	4.3	10	6.1	5	3.3	1	1.1	3	4.2
Unknown	2594	14.8	95	11.4	15	9.2	18	12	8	8.5	14	19.4
Hypertension[f]												
No	14,588	83.3	665	79.9	131	80.4	130	86.7	78	83	55	76.4
Yes	1831	10.5	139	16.7	30	18.4	20	13.3	15	16	10	13.9
Unknown	1093	6.2	28	3.4	2	1.2	0	0	1	1.1	7	9.7

(Table 1 continues on next page)

	Overall (N = 17,512)		All cancers (N = 832)		HPV-related cancers (N = 163)		Breast cancer (N = 150)		Lung cancer (N = 94)		Non-Hodgkin's lymphoma (N = 72)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
(Continued from previous page)												
Diabetes[g]												
No	17,106	97.7	791	95.1	160	98.2	143	95.3	90	95.7	71	98.6
Yes	406	2.3	41	4.9	3	1.8	7	4.7	4	4.3	1	1.4
Prior AIDS												
No	13,875	79.2	576	69.2	104	63.8	120	80	52	55.3	53	73.6
Yes	3637	20.8	256	30.8	59	36.2	30	20	42	44.7	19	26.4
Prior cancer												
No	16,585	94.7	779	93.6	153	93.9	137	91.3	88	93.6	71	98.6
Yes	569	3.2	40	4.8	8	4.9	5	3.3	5	5.3	1	1.4
Unknown	358	2	13	1.6	2	1.2	8	5.3	1	1.1	0	0
Dyslipidaemia[h]												
No	7600	43.4	265	31.9	52	31.9	44	29.3	22	23.4	38	52.8
Yes	9912	56.6	567	68.1	111	68.1	106	70.7	72	76.6	34	47.2
Prior comorbidity[i]												
No	5239	29.9	166	20	34	20.9	27	18	15	16	30	41.7
Yes	10,647	60.8	614	73.8	120	73.6	112	74.7	75	79.8	37	51.4
Unknown	1626	9.3	52	6.2	9	5.5	11	7.3	4	4.3	5	6.9
Prior non-AIDS comorbidity[j]												
No	8876	50.7	422	50.7	93	57.1	57	38.0	57	60.6	49	63.1
Yes	7010	40.0	358	43.0	61	37.4	82	54.7	33	35.1	18	25.0
Unknown	1626	9.3	52	6.3	9	5.5	11	7.3	4	4.3	5	6.9
Prior exposures to INSTI												
No	17,125	97.8	824	99.0	163	100	150	100	92	97.9	71	98.6
Yes	387	2.2	8	1.0	0	0	0	0	2	2.1	1	1.4
Prior exposures to PI												
No	8679	49.6	321	38.6	64	39.3	56	37.3	27	28.7	39	54.2
Yes	8833	50.4	511	61.4	99	60.7	94	62.7	67	71.3	33	45.8
Prior exposures to NNRTI												
No	9172	52.4	385	46.3	61	37.4	65	43.3	40	42.6	48	66.7
Yes	8340	47.6	447	53.7	102	62.6	85	56.7	54	57.4	24	33.3
Continuous variables												
Age, years	39.5	(32.5, 46.0)	44.5	(39.0, 50.5)	42.5	(37.3, 47.1)	43.1	(38.5, 49.0)	49	(43.8, 55.8)	43.9	(37.2, 48.4)
Pre-ART CD4 nadir, cells/mm^3[c]	223	(110.0, 363.0)	172.5	(70.0, 300.0)	127	(55.0, 248.0)	211	(135.0, 320.0)	163	(68.0, 280.0)	144	(58.0, 295.0)
Baseline CD4, cells/mm^3	458.2	(306.0, 654.0)	421	(257.5, 631.0)	340	(172.0, 630.0)	490	(351.0, 714.0)	451	(269.5, 640.5)	293.5	(100.0, 503.0)
Viral load at baseline, copies/mL	50	(40.0, 4720.0)	50	(40.0, 6597.0)	50	(49.0, 2650.0)	50	(49.0, 2000.0)	50	(39.0, 1720.0)	8531.5	(122.0, 95,819.0)

Abbreviations: BMI, body mass index; IDU, injection drug use; ART, antiretroviral therapy; VL, viral load; AIDS, acquired immune deficiency syndrome; HCV, hepatitis C virus; HBV, hepatitis B virus; INSTI, integrase strand transfer inhibitor; PI, protease inhibitor; NNRTI, non-nucleos(t)ide reverse transcriptase inhibitor. [a]Data on ethnicity/race are not available for several participating cohorts. [b]Due to small numbers, Australia was combined with Northern Europe, USA was combined with Western Europe, and Eastern Central Europe combined with Eastern Europe. [c]CD4 count was taken as the lowest CD4 cell count prior to baseline. If no CD4 cell count was measured, the first measurement within 12 weeks after baseline was used. [d]HCV coinfection was time-updated and defined as: HCV antibody-negative, HCV-positive (anti-HCV positive, HCV-RNA positive, or on HCV medication), or resolved HCV (anti-HCV positive/HCV RNA-negative). [e]HBV co-infection was time-updated and defined by HBsAg-positive, HBeAg-positive, or HBV-DNA positive test. [f]Hypertension was defined two consecutive systolic blood pressure (SBP) measurements ≥140 mmHg and/or diastolic blood pressure (DBP) measurements ≥90 mmHg, performed on different days; one single SBP measurement ≥140 mmHg and/or DBP measurement ≥90 mmHg with the use of antihypertensive medication within six months of this measurement; or the initiation of antihypertensives without a recorded high BP. [g]Diabetes was defined by a reported diagnosis, use of anti-diabetic medication, glucose ≥11.1 mmol/L, and/or HbA1c ≥ 6.5% or ≥48 mmol/mol. [h]Dyslipidaemia was defined as total cholesterol >239.4 mg/dL or HDL cholesterol <34.7 mg/dL or triglyceride >203.55 mg/dL or use of lipid-lowering treatments. [i]Comorbidity was defined as a combine endpoint of prior AIDS-defining and non-AIDS defining cancers, AIDS events, CKD, CVD, hypertension, diabetes, dyslipidemia. [j]Non-AIDS comorbidity was defined as all comorbidities excluding AIDS events and AIDS-defining cancers.

Table 1: **Baseline demographics and characteristics of women with HIV overall and by cancer types.**

oropharyngeal cancers (n = 9) as HPV-related cancers, based on evidence showing high-risk oncogenic HPV strains in approximately 50–80% of people with HIV,[29] consistent with other studies.[30,31] Other head and neck cancers such as those of the oral cavity (including lip), hypopharynx, salivary gland, larynx and nasal cavity—were not included in HPV-related cancer grouping. Cervical, vaginal, and vulval cancers were classified as

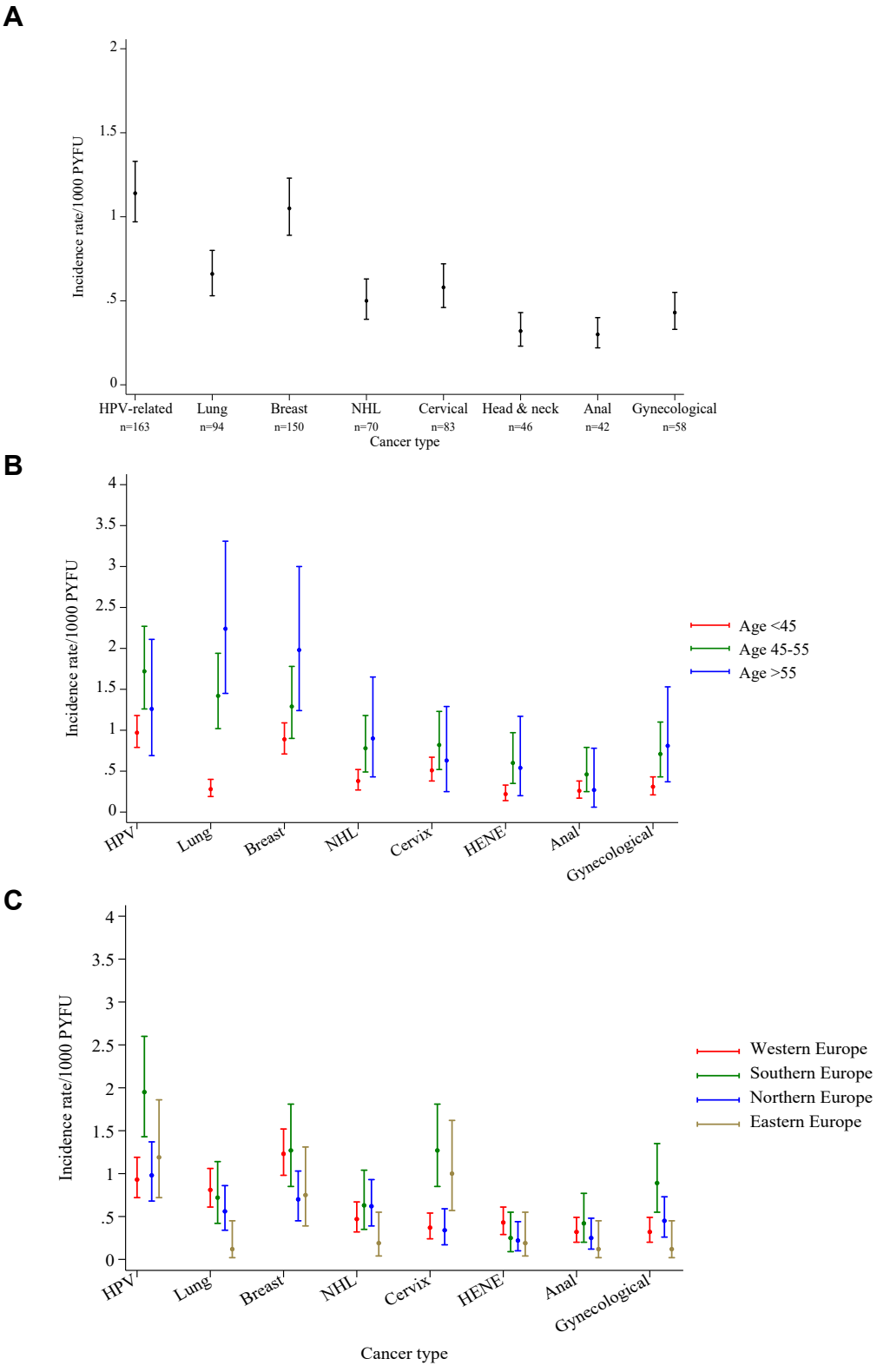

Fig. 1: **Cancer incidence among women with HIV in RESPOND and D:A:D among all women with HIV (A) and, stratified by age groups (B) and regions (C).** *Other gynaecological cancers exclude cervical cancers. HPV-related cancer group included 43 anal, 83 cervical, 28 other

HPV-related, while all other gynaecological cancers were considered HPV-unrelated.

Statistical analysis

Baseline characteristics were summarized for each cancer group or type. Crude incidence rates (IR) (and 95% confidence intervals, CI) of any cancer type and each cancer group were determined. We calculated the incidence rates stratified by key subgroups: age group (<45, 45–55, and >55 years), geographical regions (Western Europe/US, Southern Europe, Northern Europe/Australia and Eastern/Central Europe) and calendar period (2006–2014 and 2015–2022). Due to the small number of female participants in some cohorts, Australia was combined with Northern Europe, the USA was combined with Western Europe, and Eastern Central Europe combined with Eastern Europe, consistent with previous analyses.[2]

Multivariable Poisson regression with robust standard errors was used to assess the factors associated with incident cancer outcomes. We adjusted potential confounders as a *priori*. Baseline covariates included: race/ethnicity, geographical region, mode of HIV acquisition (heterosexual, injection drug use, others, unknown), pre-ART nadir CD4 count, a prior AIDS event (including cancer and non-cancer AIDS event) and a prior cancer event. We also included the following time-updated covariates: age, HIV-1 viral load (VL), CD4 count, calendar period (≥2015 vs. <2015) chronic hepatitis C virus (HCV) infection, chronic hepatitis B virus (HBV) infection (definitions included in Table 1 footnotes), body mass index (BMI) (<18.5, 18.5–<25, 25–<30 and ≥30 kg/m^2) and smoking status (current, former, or never smoker). Cumulative exposure to integrase strand transfer inhibitors (INSTIs), protease inhibitors (PIs), nucleo (s/t)ide-analogue reverse transcriptase inhibitors (NRTIs), and non-nucleoside RTIs (NNRTIs) were also included as time-updated covariates. We also adjusted for RESPOND or D:A:D cohort as a covariate in the models to account for any differences in data collection methods or reporting across the collaborations. No adjustment for multiple comparisons was made, as analyses intended to identify potential risk factors. Overdispersion was assessed using the Cameron–Trivedi test. The test did not reach statistical significance (p = 0.46), suggesting that Poisson regression was appropriate for these data. We calculated the population attributable fraction (PAF) for modifiable and HIV-related risk factors contributing to the cancer risks for all cancers, HPV-related cancers, and common individual cancers such as breast and lung cancers using the methods described by Laaksonen et al.[32] The calculations considered the time-updated variables (ever smoking [vs. never smoke], BMI [≥30 vs. <30 kg/m^2], CD4 count [<350 vs. ≥350 cells/mm^3], HIV-1 VL (≥200 vs. <200 copies/mL), AIDS diagnosis, HBV and HCV), and baseline nadir CD4 count, and additionally adjusted for age, geographical region, mode of HIV acquisition, calendar year and RESPOND/D:A:D cohort in the models that estimated PAFs and 95% CI.

P-values reported are two-sided, with a p-value <0.05 defined as statistically significant. Data management and statistical analyses were performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA) and Stata software version 18.0 (Stata Corp., College Station, TX, USA). Forest plots were generated using the ggplot2 package in R (R Foundation for Statistical Computing, Vienna, Austria).

Sensitivity analyses

We conducted several sensitivity analyses: i. excluding participants with any cancer diagnosed prior to baseline and including only centrally validated cancer events (cancers in RESPOND are validated only after 2017), ii. applying the same inclusion criteria of RESPOND to the D:A:D cohort (i.e., excluding those without a CD4 count and VL measurement either 1 year prior to or within 12 weeks after baseline), iii. fixing the covariates at baseline when investigating the main exposure of interests (e.g. time-updated CD4 count as main exposure of interest and fixing other covariates at baseline) to mitigate the potential bias in the causal pathway, and iv. using 12-month lagged time-updated CD4 count instead of latest CD4 count to evaluate the impact of potential reverse causation on the primary analysis results.

Ethics

Participants are consented to share data with RESPOND according to local requirements. Participants are pseudonymised at enrolment by assigning a unique identifier by the participating cohort before data transfer to RESPOND. According to national or local requirements, all cohorts have approval to share data with RESPOND. Ethical approvals are obtained, if required, from the relevant bodies for collection and

non-cervical HPV-related gynaecological cancers (3 vaginal and 25 vulval cancers) and 9 head and neck cancers (all were oropharyngeal cancers). The incidence rate was 5.9 (95% CI: 5.5, 6.4)/1000 PYS for all cancers (n = 832), 1.1 (1.0, 1.3)/1000 PYS for HPV-related cancers (n = 163), 0.7 (0.5, 0.8)/1000 PYS for lung cancer (n = 94), 1.1 (0.9, 1.2)/1000 PYS for breast cancer (n = 149), 0.5 (0.4, 0.6)/1000 PYS for NHL (n = 70), 0.6 (0.5, 0.7)/1000 PYS for cervical cancer (n = 80), 0.3 (0.2, 0.4)/1000 PYS for head and neck cancers (HENE) (n = 46), 0.3 (0.2, 0.4)/1000 PYS for anal cancer (n = 42) and 0.4 (0.3, 0.5)/1000 PYS other gynaecological cancers (n = 59). **Abbreviations**: HENE, head and neck; NHL, non-Hodgkin lymphoma.

	Person-years (PYS)	All cancers		Person-years (PYS)	HPV-related cancers		Person-years (PYS)	Breast cancer		Person-years (PYS)	Lung cancer		Person-years (PYS)	Non-Hodgkin lymphoma	
		No.	Incidence rate/1000 PY (95% CI)		No.	Incidence rate/1000 PYS (95% CI)		No.	Incidence rate/1000 PYS (95% CI)		No.	Incidence rate/1000 PYS (95% CI)		No.	Incidence rate/1000 PYS (95% CI)
Overall	14,0311	832	5.9 (5.5, 6.4)	142,794	163	1.1 (1.0, 1.3)	142,901	150	1.1 (0.9, 1.2)	143,379	94	0.7 (0.5, 0.8)	143,307	72	0.5 (0.4, 0.6)
Age at baseline, years															
<45	102,326	441	4.3 (3.9, 4.7)	103,665	101	1.0 (0.8, 1.2)	103,798	92	0.9 (0.7, 1.1)	104,084	29	0.3 (0.2, 0.4)	104,008	40	0.4 (0.3, 0.5)
45–55	27,229	259	9.5 (8.4, 10.7)	27,978	48	1.7 (1.3, 2.3)	28,012	36	1.3 (0.9, 1.8)	28,132	40	1.4 (1.0, 1.9)	28,139	22	0.8 (0.5, 1.2)
>55	10,757	132	12.3 (10.3, 14.6)	11,151	14	1.3 (0.7, 2.1)	11,090	22	2.0 (1.2, 3.0)	11,164	25	2.2 (1.5, 3.3)	11,160	10	0.9 (0.4, 1.7)
Region[a]															
Western Europe	66,313	400	6.0 (5.5, 6.7)	67,598	63	0.9 (0.7, 1.2)	67,524	83	1.2 (1.0, 1.5)	67,778	55	0.8 (0.6, 1.1)	67,616	32	0.5 (0.3, 0.7)
Southern Europe	23,096	185	8.0 (6.9, 9.3)	23,614	46	2.0 (1.4, 2.6)	23,686	30	1.3 (0.9, 1.8)	23,775	17	0.7 (0.4, 1.1)	23,765	15	0.6 (0.4, 1.0)
Northern Europe and Australia	35,084	189	5.3 (5.1, 5.6)	35,596	35	1.0 (0.7, 1.4)	35,666	25	0.7 (0.5, 1.0)	35,758	20	0.6 (0.3, 0.9)	35,701	22	0.6 (0.4, 0.9)
Eastern and central Europe	15,818	58	3.7 (2.8, 4.7)	15,986	19	1.2 (0.7, 1.9)	16,025	12	0.8 (0.4, 1.3)	16,069	2	0.1 (0.02, 0.4)	16,079	3	0.2 (0.04, 0.6)
Calendar period															
2006–2014	87,934	513	5.8 (5.3, 6.4)	89,031	110	1.2 (1.0, 1.5)	89,115	90	1.0 (0.8, 1.2)	89,321	57	0.6 (0.5, 0.8)	89,269	50	0.6 (0.4, 0.7)
2015–2022	52,375	319	3.6 (3.2, 4.0)	53,763	53	1.0 (0.7, 1.3)	53,786	60	1.1 (0.9, 1.4)	54,058	37	0.7 (0.5, 0.9)	54,035	22	0.4 (0.3, 0.6)

[a]Due to small numbers, Australia was combined with Northern Europe, USA was combined with Western Europe and Eastern Central Europe combined with Eastern Europe.

Table 2: **Cancer incidence for all cancer, HPV-related cancers, lung cancer, breast cancer and non-Hodgkin lymphoma.**

sharing of data. Data are stored on secure servers at the RESPOND coordinating centre in Copenhagen, Denmark, in accordance with current legislation and under approval by The Danish Data Protection Agency (approval number 2012-58-0004, RH-2018-15, 26/1/2018), under the EU General Data Protection Regulation (2016/679).

Role of the funding source

As per RESPOND governance, funders of the study were also academic collaborators, and employees or associates could be included as co-authors if they met the International Committee of Medical Journal Editors criteria. However, funding bodies (including employees and associates hereof), were not able to veto study design, data collection, data analysis, data interpretation, or writing of the manuscript.

Results

Participants' characteristics

A total of 17,512 adult women with HIV met the inclusion criteria. The median age was 39.5 (IQR, 32.5, 46.0) years and 48%, 23%, and 5% were White, Black and Other race/ethnicity, respectively. Approximately 25% had unknown race/ethnicity as the reporting of race/ethnicity is prohibited by law in several cohorts. Most of the participants were recruited from Western Europe cohorts (43%), followed by Southern Europe (26%) and Northen Europe (17%). The median baseline CD4 count was 458 (IQR, 306–654) cells/mm^3 and the median pre-ART nadir CD4 count was 223 (IQR, 110–363) cells/mm^3, while 21% had an AIDS event (of which 14% were AIDS-defining malignancies) documented prior to baseline. The median BMI at baseline was 22.4 (IQR, 20.2–25.4) kg/m^2 with 8.4% classified as overweight (25–<30 kg/m^2) and 16.2% obese ($\geq$30 kg/m^2). Approximately 30% of women were current smokers, and 22% and 4% were living with chronic HBV and HCV co-infection. Baseline characteristics and missing data are summarized in Table 1. Of 17,512 participants, 8056 (46%) were complete cases with no missing values in any variable included.

Cancer incidence during follow-up

The most common cancers were breast (n = 150), lung (n = 94), cervical (n = 83), NHL (n = 70), other non-cervical gynaecological cancers (n = 58), head and neck cancers (n = 46) and anal (n = 42) (Supplementary Table S1). Cervical cancers made up the majority (51%) of the HPV-related cancer group (n = 163), which also included 43 (26%) anal cancers, 9 (5.5%) head and neck cancers (all oropharyngeal cancers), and 28 (17%) non-cervical gynaecological

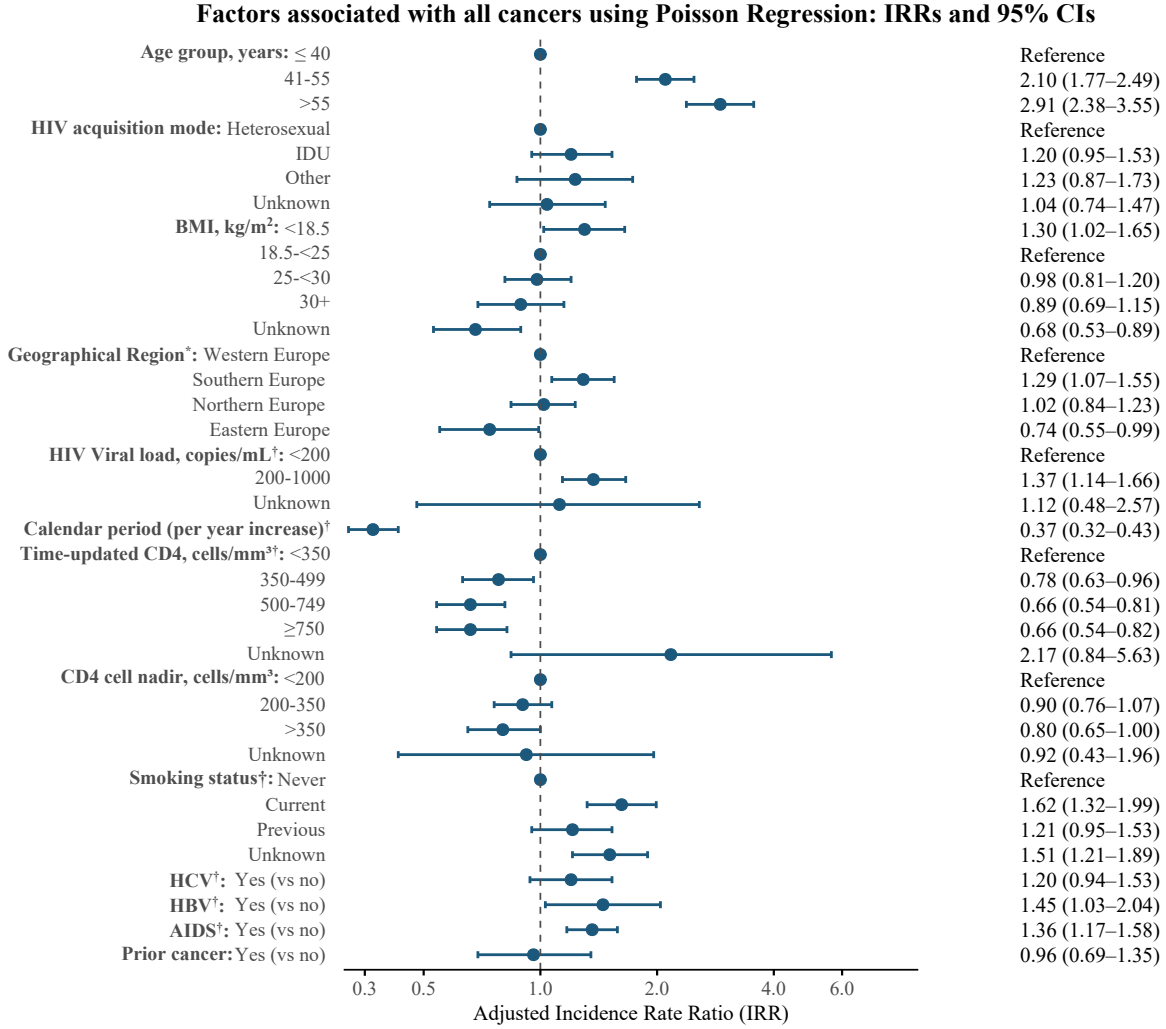

Fig. 2: **Forest plot illustrating factors associated all cancers (n = 832)**. *Due to small numbers, USA was combined with Western Europe, Australia was combined with Northern Europe, and Eastern Central Europe combined with Eastern Europe. † Time-updated variables. ‡ Ethnicity was not included in the multivariable model due to large number of missing values. **Abbreviations:** BMI, body mass index; IDU, injection drug use; HCV, hepatitis C virus; HBV, hepatitis B virus; INSTI, integrase strand transfer inhibitor; PI, protease inhibitor; NNRTI, non-nucleos(t)ide reverse transcriptase inhibitor.

cancers (3 vaginal and 25 vulval cancers). Baseline characteristics between women with HIV with and without cancers are also summarized in the Supplementary Tables S2–S3.

Over 141,404 person-years (PYS) of follow-up, there were 832 cancer diagnoses including 163 HPV-related cancers, corresponding to IRs of 5.9 (95% CI 5.5–6.4) and 1.1 (1.0–1.3) per 1000 PYS, respectively (Fig. 1). The IR of the individual cancer types of lung cancer, breast cancer, NHL, cervical cancer, head and neck cancer, anal cancer and other non-cervical gynaecological cancers are described in Fig. 1. The IR stratified by age groups, regions and calendar periods are presented in Table 2. The cancer IR was generally higher among women of older age groups, except for HPV-related cancers. Southern Europe consistently had higher IR for most cancer groups, and especially for cervical cancers, compared to other geographical regions (Fig. 1C and Supplementary Table S4).

Factors associated with cancer incidence in women with HIV

In multivariable Poisson regression, older age (vs. <45 years, 45–55: incident rate ratio [IRR] 2.10, 95% CI 1.77–2.49, and >55: IRR 2.91, 95% CI 2.38–3.55), participation in a cohort from Southern Europe (vs. Western Europe, IRR 1.29, 95% CI 1.07–1.55), time-

updated HIV VL ≥ 200 copies/mL (vs. <200 copies/mL, IRR 1.37, 95% CI 1.14–1.66), current smokers (vs. never smoke, IRR 1.62, 95% CI 1.32–1.99), and a prior AIDS-defining diagnosis (IRR 1.36, 95% CI 1.17–1.58) were associated with an increased risk of overall cancer. A reduced risk was observed in women with higher time-updated CD4 counts, higher nadir CD4 counts, and with follow-up in 2015 or later (Fig. 2).

For HPV-related cancers, after adjustment for confounders, older age (45–55 vs. <45 years: IRR 1.39, 95% CI 1.01–1.97), participation in a Southern European cohort (vs. Western European, IRR 2.21, 95% CI 1.48–3.32), current smoking (3.09, 95% CI 1.91–5.02), HBV co-infection (2.57, 95% CI 1.32–4.88), and having a prior AIDS diagnosis (1.95, 95% CI 1.41–2.71) were significantly associated with an increased risk. Conversely, a reduced risk of HPV-related cancers was observed in women with higher time-updated CD4 counts and higher nadir CD4 counts (Fig. 3).

Among the individual cancer types, older age and earlier calendar periods were associated with an increased risk of breast cancer, while time-updated CD4 counts, and smoking were not associated with a heightened risk (Fig. 4). For lung cancer, older age (45–55 vs. <45 years: 4.30, 95% CI 2.13–8.67 and > 55: 11.4, 95% CI 5.60–23.1), current (15.17, 95% CI 4.33–53.16) or previous smoking (9.84, 95% CI 2.88–33.58) compared to those who never smoked, and having a prior AIDS diagnosis (2.30, 95% CI 1.48–3.55) were associated with an increased risk.

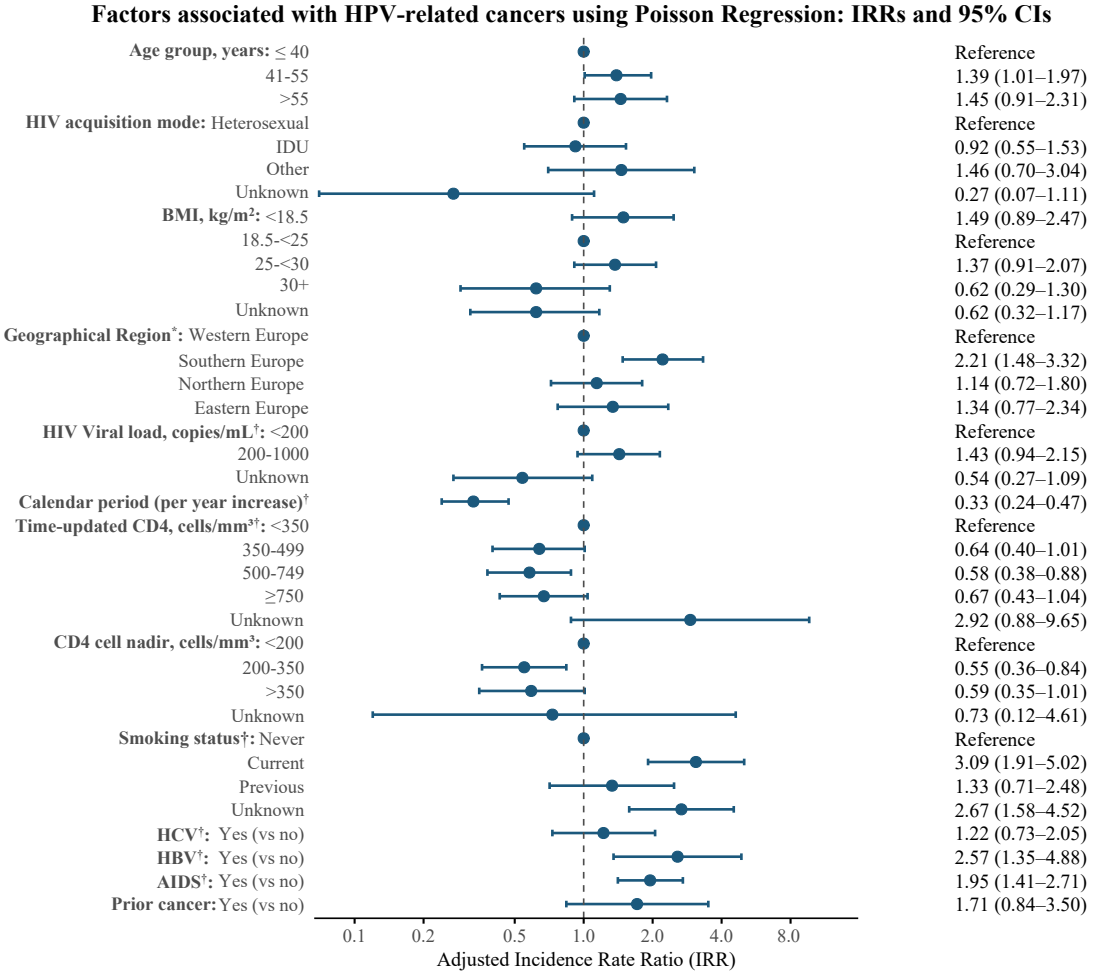

***Fig. 3*: Forest plot illustrating factors associated HPV-related cancers (n = 163).** * Due to small numbers, USA was combined with Western Europe, Australia was combined with Northern Europe, and Eastern Central Europe combined with Eastern Europe. † Time-updated variables. ‡ Ethnicity was not included in the multivariable model due to large number of missing values. **Abbreviations:** BMI, body mass index; IDU, injection drug use; HCV, hepatitis C virus; HBV, hepatitis B virus; INSTI, integrase strand transfer inhibitor; PI, protease inhibitor; NNRTI, non-nucleos(t)ide reverse transcriptase inhibitor.

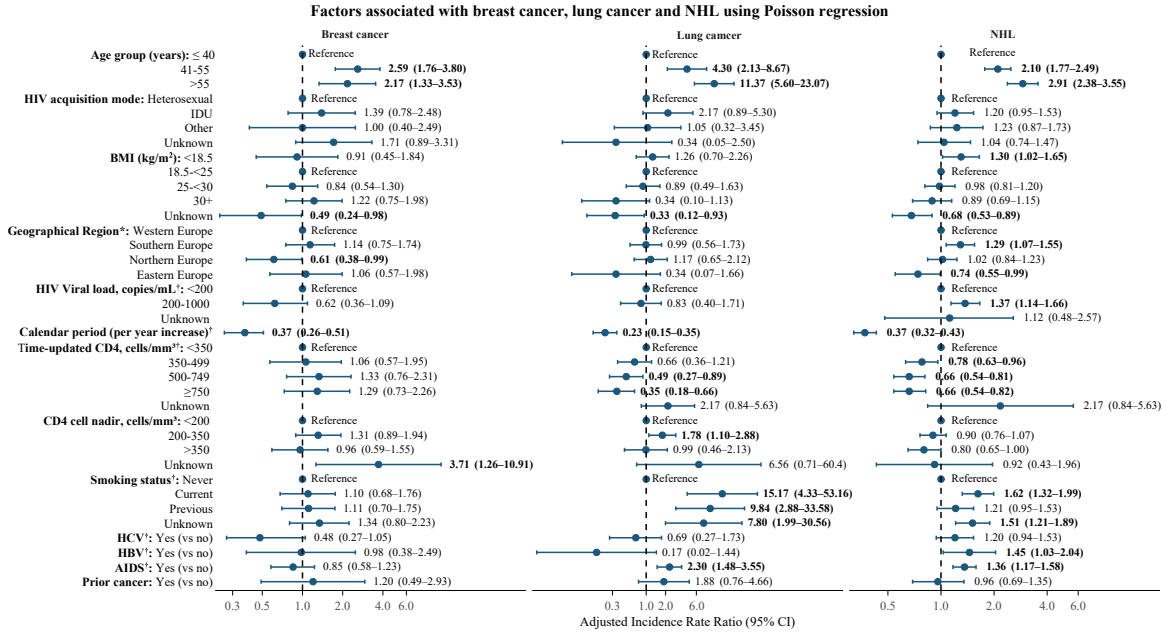

Fig. 4: **Forest plot illustrating factors associated with breast cancer (n = 150), lung cancer (n = 94) and non-Hodgkin lymphoma (n = 72).** * Due to small numbers, USA was combined with Western Europe, Australia was combined with Northern Europe, and Eastern Central Europe combined with Eastern Europe. † Time-updated variables. ‡ Ethnicity was not included in the multivariable model due to large number of missing values. **Abbreviations:** BMI, body mass index; IDU, injection drug use; HCV, hepatitis C virus; HBV, hepatitis B virus; INSTI, integrase strand transfer inhibitor; PI, protease inhibitor; NNRTI, non-nucleos(t)ide reverse transcriptase inhibitor.

Higher time-updated CD4 counts (500–749 vs. <350 cells/mm^3: 0.49, 95% CI 0.27–0.89, ≥750: 0.35, 95% CI 0.18–0.66), higher nadir CD4 counts (200–350 vs. <200 cells/mm^3: 1.78, 95% CI 1.10–2.88), and later calendar periods of follow-up (≥2015 vs. <2015: 0.23, 95% CI 0.15–0.35) were significantly associated with a reduced lung cancer risk. Current smoking (2.41, 95% CI 1.30–4.46), underweight or overweight time-updated BMI (<18.5 kg/m^2 vs. 18.5–<25 kg/m^2: 2.36, 95% CI 1.20–4.65 and 25–<30 kg/m^2: 1.79, 95% CI 1.01–3.20) and being from a Southern European cohort (3.58, 95% CI 2.05–6.25, vs. Western Europe) were strongly associated with an increased cervical cancer risk. Conversely, higher time-updated CD4 counts (500–749 vs. <350 cells/mm^3, IRR: 0.38 [0.20, 0.72]) were associated with a significantly lower risk (IRR 0.38, 95% CI 0.20–0.72) (Fig. 4).

Population attributable fraction (PAF) for modifiable and HIV-related risk factors contributing to cancers risk

For overall cancers, modifiable/preventable risk factors such as ever smoking (vs. never) (22.2%, 95% CI 11.6–31.6) and a prior AIDS diagnosis (10.6%, 95% CI 5.4–15.5) had the largest PAF followed by low time-updated CD4 <350 cells/mm^3 (vs. ≥350) (8.1%, 95% CI 4.2–11.9) and detectable HIV-1 VL ≥ 200 copies/mL (vs. <200) (5.6%, 95% CI 2.1–8.9) (Fig. 5A). For HPV-related cancers, ever smoking had the highest PAF (45.8%, 95% CI 22.5–62.0), followed by low nadir CD4 count <200 cells/mm^3 (vs. ≥200) (29.4%, 95% CI 10.0–44.5), AIDS diagnosis (24.4%, 95% CI 11.6–35.3), low time-updated CD4 count (12.3%, 95% CI 2.2–21.3) and detectable HIV-1 VL (7%, 95% CI 1.0–15.0) (Fig. 5B).

While there were no statistically significant PAF (all p-values >0.05) for breast cancer risk factors (Fig. 5C), for lung cancer, ever smoking yielded the greatest PAF (88%, 95% CI 64.4–96.3), followed by a prior AIDS diagnosis (32.0%, 95% CI 14.2–46.1) and time-updated CD4 counts <350 (vs. ≥350 cells/mm^3) (16.2%, 95% CI 3.6–27.1) and the effect of nadir CD4 was not prominent (Fig. 5D).

Sensitivity analyses

The findings from the sensitivity analyses were largely consistent with the primary analyses. In sensitivity analyses which included only centrally validated cancers (from 2017 onwards) (n = 727 for all cancers, n = 86 for HPV-related cancers, and hence had less statistical power), the direction of association of nadir CD4 count was consistent with the main analysis, although estimates were attenuated and not statistically significant

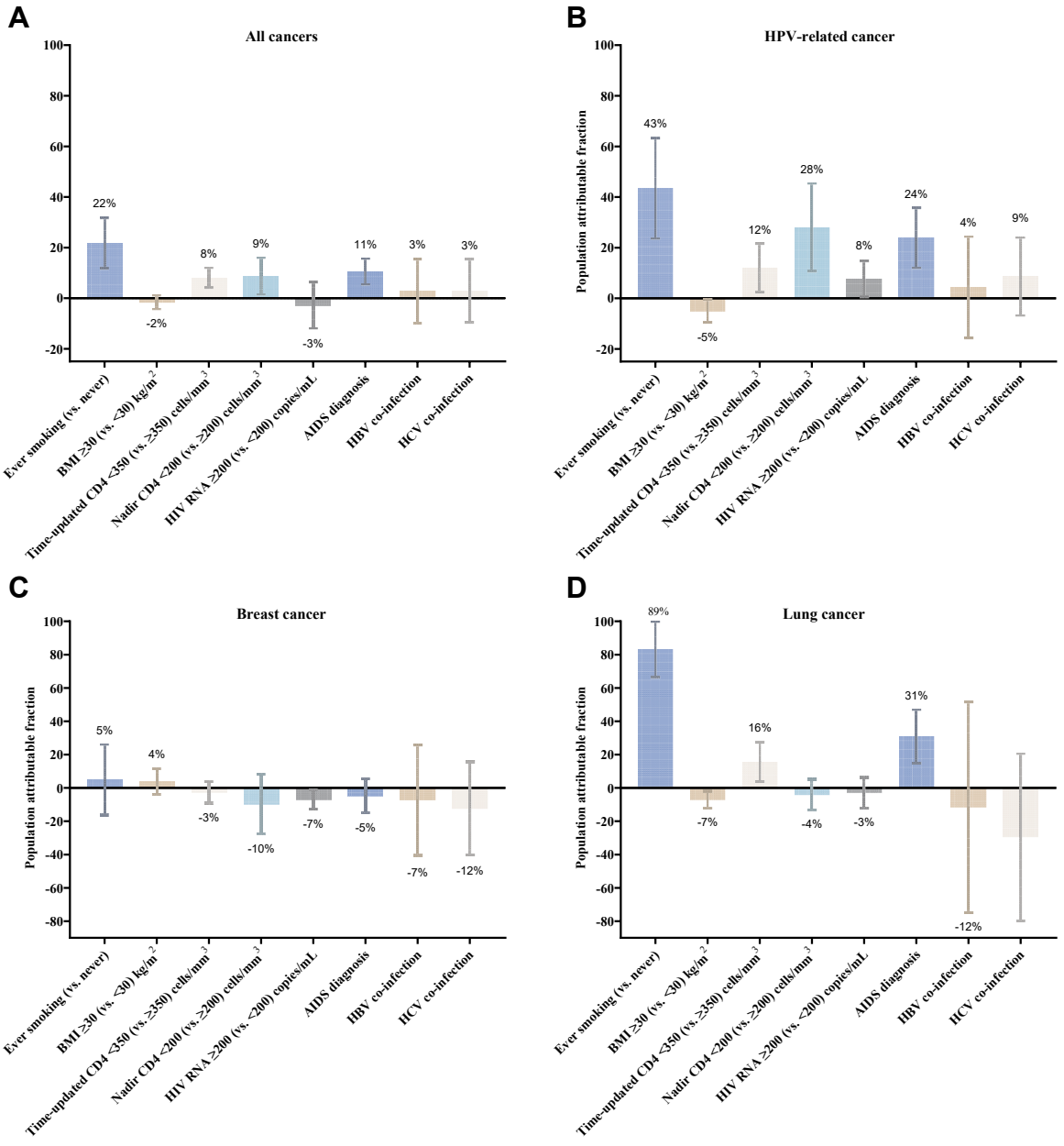

Fig. 5: **Population attributable fractions for modifiable risk factors for cancer risk for (A) all cancers, (B) HPV-related cancers, (C), breast cancer, and (D) lung cancer**. The population attributable fraction is calculated while accounting for time-varying risk factors. Error bars represent 95% confidence intervals. **Abbreviations**: BMI, body mass index; AIDS, acquired immune deficiency syndrome; HBV, hepatitis B virus; HCV, hepatitis C virus.

(Supplementary Tables S5–S7). Moreover, the associations between 12-month lagged time-updated CD4 and the risk of overall cancers, HPV-related cancers and lung cancer were consistent with the primary analyses (Supplementary Table S8). We also repeated the analyses combining countries with small numbers into a single "other" category and the results remain robust (Supplementary Table S9).

Discussion

In this study including adult women with HIV from two large multi-cohort collaborations across different regions, traditional risk factors such as older age and smoking, and HIV-related factors such as a prior AIDS event, lower current CD4 counts and detectable HIV-1 VL were associated with increased cancer risks. There were regional differences in the overall cancer

incidence and HPV-related cancers group, as well as for cervical cancers. Among the modifiable risk factors, there was variability in the estimated PAF, with smoking and a prior AIDS diagnosis contributing a greater PAF for overall cancers, as well as HPV-related and lung cancers, while low time-updated and nadir CD4 counts also contributed to HPV-related and lung cancers. These findings highlight the importance of integrating management of traditional cancer risk factors such as tabaco use and persistent HPV infection, which are particularly important in women with HIV, through screening, prevention, and intervention. Such efforts, alongside long-term HIV care to support good immune status and sustained HIV viral suppression, are essential to reduce cancer incidence in this population.

In our study, increasing age and smoking were found to contribute significantly to the burden of cancers including HPV-related cancers and lung cancers. However, smoking was not associated with breast cancers. In general, cigarette smoking is more prevalent among people living with HIV compared to those without HIV in many regions, and studies from North America and Europe have demonstrated its substantial role in the elevated cancer risk in this population.[3,33,34] The smoking prevalence among women with HIV in Europe, where most of our participants reside, is higher than that of the general population in the region.[35] While data on smoking and cancer incidence in women with HIV in this region are limited, studies from US cohorts have shown women with HIV have a higher risk of smoking-related cancers than men with HIV.[3,36] Previous studies have suggested that biological sex differences may influence cancer susceptibility and progression,[37,38] and variations in in immune response between men and women[39] could contribute to differences in cancer development. Additionally, environmental exposures such as indoor/outdoor air pollution and second-hand smoke, could also contribute to the observed differences in cancer incidence. Nevertheless, we were unable to adjust for these unmeasured confounders in our analysis.

We also found that HIV-related factors such as lower time-updated CD4 counts, prior AIDS diagnosis and detectable HIV VL contributed significantly to certain cancers, including the most common cancers, HPV-related cancers, lung cancer and cervical cancer. However, non-HIV-related factors such as smoking accounted for a larger contribution to cancer development (i.e., higher PAFs for non-HIV-related factors than HIV-related factors). In our study, immunodeficiency, as indicated by lower time-updated and nadir CD4 counts, and prior AIDS diagnosis was strongly associated with HPV-related cancers and individual cancer types including cervical and lung cancers. In a recent prior analysis of the combined D:A:D and RESPOND cohorts, we showed that poor immune recovery despite a minimum of 2 years of continuous viral suppression is associated with an increased risk of incident cancers.[27,40] These findings suggest that prolonged periods of immune suppression may increase susceptibility to oncogenic processes, potentially through reduced control of viral infections such as HPV and impaired tumor immune surveillance and pro-oncogenic influences on cellular environments that facilitate genetic mutations.[41,42] Similarly, immune suppression could amplify the effects of traditional cancer risk factors, such as smoking, which is more prevalent among women with HIV, thereby increasing cancer susceptibility in this population.

Significant regional variations remain in access to health care, socioeconomic factors, screening and prevention programs for vaccine preventable cancers such as cervical cancer. While the burden of cervical cancers due to the oncogenic HPV strains such as HPV-16 or HPV-18 has been drastically reduced by the efforts of HPV vaccination campaigns and cervical cancer screening programs, regional differences remain in terms of the incidences and mortality from these cancers.[43] For women with HIV, such regional disparities may also affect prevention and screening strategies for other common cancers, such as breast cancer. However, large cohort studies providing data on the impact of regional variations in cancer screening, prevention, and outcomes among women with HIV are limited.

In our study, women enrolled in Southern European cohorts had an increased risk for cancers compared to Western European cohorts. This was especially evident for cervical cancers, but not breast cancer, lung cancer or other HPV-related cancers such as anal cancer and oropharyngeal cancers. While we do not have data on vaccination status, we consider it unlikely that differences in HPV vaccination coverage fully explain our findings, as most women in our cohorts would not have been eligible for these relatively recent programmes. Nonetheless, differences in historical HPV vaccination coverage and cervical cancer screening practices and prevention strategies[44–46] may still contribute to the observed differences. Other region-specific factors such as migration patterns,[47,48] socioeconomic, behavioural or healthcare-related factors including limited access to healthcare, cultural differences, and lack of awareness, may also contribute to the increased burden of cervical cancer in this population. To our knowledge, no studies among women with HIV have explored how regional differences in screening and vaccination programs influence cancer outcomes. Further research incorporating detailed data on these factors is needed to clarify the underlying drivers of these observations.

Our study has several limitations to be acknowledged. Despite the large sample size of the study the number of incident cases of specific cancer types was still limited, so due to statistical power limitations, we were able to evaluate the most common individual cancers. Another important limitation is that we were

unable to consider the impact of other confounders such as lifestyle, diet and physical activity. Additionally, migration status, which was not collected in most cohorts, could also have contributed to the observed differences in cancer risks due to potential disparities in healthcare services faced by migrant women with HIV including cervical cancer screening or vaccination programs.[49] Because approximately two-thirds of follow-up person-years were contributed by the D:A:D study (ending in 2016), while RESPOND contributed more recent data through 2022, observed temporal trends and exposure patterns may partly reflect differences between cohorts rather than changes over time alone. Although cohort membership was included as a covariate in all analyses, differences in calendar time, data capture, and population composition may have influenced the observed associations and should be considered when interpreting these results. Nonetheless, this is one of the largest studies to date with more than 15 years of follow-up investigating the incidence of cancers among women with HIV. Our findings are likely generalizable to women with HIV engaged in care in Europe, Australia and other similar settings, although they may not fully capture the experience of those not linked to care or those living in regions such as sub-Saharan Africa. Our study, which incorporates both regression analysis investigating the risk factors associated with cancer risk and the PAF approach evaluating the contribution of modifiable traditional risk factors and HIV-related factors, demonstrates the interplay between these risk factors.

In summary, our study demonstrates the significant contributions of traditional risk factors, and HIV-related factors to cancer risk in women with HIV. Women with current and past immunosuppression, older age, or those who smoke may particularly require intensified cancer prevention and screening where available. These findings underscore the importance of addressing modifiable risks, such as smoking cessation and improving immune status by reducing late diagnosis of HIV and more timely initiation of ART, to reduce the cancer burden in this population.

Contributors

WMH, BN, AT, LG, LR and KP conceived the idea and developed the project proposal and a statistical analysis plan. All authors reviewed the proposal and contributed to the revised proposal and analysis plan. WMH performed the statistical analysis and wrote the analysis report, which was reviewed and commented on by all authors. WMH developed the first draft of the manuscript and revised the subsequent drafts. WMH, BN, AT, LG, LR and KP reviewed all manuscript versions and interpreted the data. MK, MC, IA, CM, CM, FW, CS, AC, AA, WE, FB, MS, CC, AH, NW, VV, FR, LY, and SR contributed to the interpretation of the data and reviewed and provided input into the final draft of the manuscript. WMH and KP accessed and verified the data. All authors were permitted to access the primary data and final analysed datasets. All authors approved and had responsibility for the decision to submit for publication.

Data sharing statement

The RESPOND Scientific Steering Committee (SSC) encourages the submission of concepts for research projects. Online research concepts should be submitted to the RESPOND secretariat (respond.rigshospitalet@regionh.dk); for guidelines on how to submit research concepts, see the RESPOND governance and procedures point 6. The secretariat will direct the proposal to the relevant Scientific Interest Group, where the proposal will initially be discussed for scientific relevance before being submitted to the SSC for review. Once submitted to the SSC, the research concept's scientific relevance, relevance to RESPOND's ongoing scientific agenda, design, statistical power, feasibility, and overlap with already approved projects will be assessed. Upon completion of the review, feedback will be provided to the proposer or proposers. In some circumstances, a revision of the concept might be requested. If the concept is approved for implementation, a writing group will be established consisting of the proposers (up to seven people who were centrally involved in developing the concept), representatives from RESPOND cohorts, and representatives from the Statistical Department and Coordinating Center. All individuals involved in the process of reviewing these research concepts are bound by confidentiality. All data within RESPOND from individual cohorts are de-identified. The present RESPOND data structure and a list of all collected variables and their definition can be found online. For any inquiries regarding data sharing, please contact the RESPOND secretariat (respond.rigshospitalet@regionh.dk).

Editor note

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Declaration of interests

MC has received research grants from Gilead Sciences and received honoraria from MSD, Gilead Sciences and ViiV Healthcare, all paid to his institution. CC has received fees from GSK/ViiV, Gilead Sciences and MSD paid to her institution, as well as unrestricted Nordic Fellowship Grant from Gilead Sciences Nordic, not related to this study. CS has received honoraria for the preparation of educational materials and for participation in speaker panels from Gilead Sciences, ViiV Healthcare and MSD. FWNMW has participated on advisory board for ViiV Healthcare, all paid to his institution. AC has received consultancy fees and honoraria from MSD, Gilead Sciences, Jannsen Cilag and ViiV Healthcare. CS has received honoraria from Gilead Sciences, ViiV Healthcare and MSD. FB has received research grants and consultation fees from Gilead Sciences, ViiV Healthcare, and MSD, all paid to his institution and has received honoraria from Gilead Sciences, ViiV Healthcare, and MSD. IAA has received project grants from Gilead Sciences, not related to this study and a travel grant from Gilead Sciences. LR has received unrestricted support to the RESPOND consortium from participating cohorts, CHIP, ViiV Healthcare, Gilead Sciences and MSD, all paid to her institution. VV, FR, LY are employees of ViiV Healthcare, Gilead Sciences and MSD, respectively. KP has received unrestricted research grants from ViiV Healthcare and Gilead sciences, all paid to her institution. The content of RESPOND publications is solely the responsibility of the authors and does not necessarily represent the official views of any of the listed institutions or funders.

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Appendix A. Supplementary data

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