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The interaction between smoking status and highly active antiretroviral therapy (HAART) use on the risk of Kaposi's sarcoma (KS) in a cohort of HIV-infected men

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Background: Although the independent effects of smoking status and HAART are reported as lower risks against KS, their combined effects have not been explored. We examined whether there is an interaction between smoking status and HAART use on the risk of KS development in an on-going US cohort of HIV-infected men.

Methods: Cox proportional hazards regression was used to analyse a total sample of 2736 participants of the Multicenter AIDS Cohort Study (MACS).

Results: We identified 530 incident KS cases with a total follow-up time of 26 594 person-years (incidence rate: 2.00 out of 100 person-years). Current smoking status and HAART use were independently associated with a lower risk of KS development (hazard ratio – HR = 0.56, 95% CI: 0.35–0.90, $P = 0.02$ and HR = 0.27, 95% CI: 0.16–0.48, $P < 0.0001$, respectively). There was no evidence of multiplicative interaction between current smoking status and HAART use on KS risk (HR = 2.14, 95% CI: 0.97–4.73, $P_{interaction} = 0.06$). Lower effect of smoking was only present among those not on HAART (HR = 0.57, 95% CI: 0.35–0.92, $P = 0.02$).

Conclusion: The inverse association of cigarette smoking on KS risk may be limited to those not on HAART. The biological mechanism of smoking in KS carcinogenesis should be elucidated.

Kaposi's sarcoma (KS) is caused by human herpesvirus-8 (HHV-8) (Chang *et al*, 1994) and is one of the most common cancers in HIV-infected persons (Beral, 1991; Grulich *et al*, 2007). Highly active antiretroviral therapy (HAART) is reported to decrease KS incidence, (Jacobson *et al*, 2000; Portsmouth *et al*, 2003; Shiels *et al*, 2011) and to prolong time to treatment failure (Bower *et al*, 1999). Recently, an inverse association between cigarette smoking and infection with HHV-8 or KS development has also been reported (Goedert *et al*, 2002; Nawar *et al*, 2005; Mbulaiteye *et al*, 2006; Anderson *et al*, 2008). However, the biological mechanism of smoking in the pathogenesis of KS has not yet been defined. From the Multicenter AIDS Cohort Study (MACS), Hoover *et al.* (1993) reported that cigarette smoking is a protective factor against the risk of KS development in HIV-infected men and hypothesised that smoking induces inflammatory cytokines that lower the risk of AIDS-associated KS.

Although the independent roles of cigarette smoking and HAART have been reported, the interaction between them has not been examined, to our knowledge. The current analysis aimed to determine whether there is an interaction between smoking status and HAART use on the risk of KS development in a cohort of HIV-infected men who have sex with men (MSM) in the United States.

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MATERIALS AND METHODS

Study population. The current analysis used a public dataset obtained from the MACS, an on-going cohort study of HIV-infected and HIV-uninfected MSM in the United States (Kaslow *et al*, 1987). Briefly, a total of 6972 participants were recruited from four USA cities (Baltimore, MD; Chicago, IL, USA; Pittsburgh, PA, USA and Los Angeles, CA, USA) over three enrolment periods from April 1984 to August 2003: 4954 between 1984-1985, 668 between 1987–1991, and 1351 from 2001–2003. At the baseline visit and follow-up visits every 6 months, study participants were interviewed with a standardized questionnaire by trained interviewers, were examined by a clinician, and also consented to donate blood for various laboratory tests, including confirmation of HIV status (Kaslow *et al*, 1987; Lazo *et al*, 2007; Desquilbet *et al*, 2011). The Institutional Review Board of each participating institution approved the MACS protocol. Moreover, all MACS participants agreed to provide written consent.

Variables of interests and measurement

Outcome variable. The outcome of interest was KS development. Cancer ascertainment and classification were described in detail elsewhere (Seaberg *et al*, 2010). In the current analysis, the ICD-O-3 code 9140.4 was used to identify KS cases (World Health Organisation – WHO, 2000). We defined KS incident cases as men who did not have KS at the baseline visit or at the seroconversion visit (if HIV-negative at baseline) but developed KS subsequently.

Independent variables. Two independent variables were used for the current analysis: current smoking status (yes/no) at baseline and subsequent visits from the standardized questionnaire and HAART use (ever/never), according to the 2008 DHHS/Kaiser Panel on Clinical Practices for the Treatment of HIV infection guidelines (Supplementary File 1).

Statistical analysis. The current analysis included 2736 participants (HIV-seropositive or seroconverters) as we excluded 3514 HIV non-infected participants and 722 participants in enrolment 3. As there were only four incident cases of KS in enrolment period 3 and all cases in enrolment period 3 received HAART, it was not possible to examine the interaction. Overall time of follow-up was from April 1, 1984 to October 1, 2005 (cutoff of the dataset). The follow-up time was defined as the time from the entry date (HIV-infected men) or the seroconversion date (HIV-seroconverters) to the KS diagnosis date for subjects who developed KS or to the last recorded visit date for subjects who did not develop KS. In the current analysis, those who died before the development of KS were censored.

As CD4+ cell count and HIV viral load were significantly associated (i.e, collinearity – $P<0.0001$), we did not include both of them in the adjusted model. Current smoking status at baseline visit and HAART ever-use were included because these variables did not change over time. The covariates included in the adjusted models as categorised in Table 1 were: age, race/ethnicity, employment status, education level, individual gross income, CD4 cell count, and enrolment period (D'Souza *et al*, 2008; Desquilbet *et al*, 2011). CD4 cell count was treated as a time-dependent variable in adjusted models. Enrolment period was adjusted for because there was difference in HAART adherence between whites and African Americans between the two enrolment periods (Lazo *et al*, 2007).

We used Cox proportional hazards regression to determine the interaction between smoking status and HAART use on KS development. The interaction between current smoking status and HAART use-ever was a product of these two binary variables. In the modelling process, besides the interaction terms, both current smoking status and HAART use-ever were also presented. We also performed stratified analyses to determine the relationship between current smoking status and KS risk by HAART use and the relationship between HAART use and KS risk by current smoking status. All statistical analyses were performed using SAS 9.2 (Cary, NC, USA) (SAS Institute 2000–2008). All tests were two-sided, and $P=0.05$ was used as the significance level.

Table 1. Baseline sociodemographic characteristics of the MACS HIV-infected men in the current study

Characteristics	HIV-seropositive (n, %)	HIV-seroconverter (n, %)
Age (years)		
⩽29	220 (10.0)	33 (6.1)
30–39	805 (36.7)	131 (24.3)
40–49	756 (34.4)	208 (38.5)
50–59	350 (15.9)	141 (26.1)
60–69	59 (2.7)	24 (4.4)
⩾70	6 (0.3)	3 (0. 6)
Race/ethnicity		
Caucasian American	1868 (85.2)	494 (91.5)
African American	234 (10.7)	39 (7.2)
Others	90 (4.1)	7 (1.3)
Employed		
No	554 (25.3)	134 (24.9)
Yes	1632 (74.7)	405 (75.1)
Education level		
⩽12 years	357 (16.5)	64 (12.0)
College level	1220 (56.3)	314 (58.8)
Graduate level	588 (27.2)	156 (29.2)
Individual gross income		
⩽$20 000	278 (27.8)	95 (26.3)
$20 000–$39 999	357 (35.7)	132 (36.6)
$40 000–$59 999	322 (32.2)	125 (34.66)
⩾$60 000	42 (4.2)	9 (2.5)
Current smoking		
No	1259 (57.6)	302 (55.9)
Yes	927 (42.4)	238 (44.1)
Packs smoked when smoked most		
Never smoked	64 (4.9)	19 (5.7)
<Half pack per day	111 (8.41)	31 (9.3)
1/2–<1 pack per day	153 (11.6)	37 (11.1)
1–<2 packs per day	448 (33.9)	108 (32.3)
⩾2 packs per day	544 (41.2)	139 (41.6)
HAART use-ever		
No	1688 (76.9)	321 (59.4)
Yes	508 (23.1)	219 (40.6)
Enrolment		
1 (period 1984–1985)	1814 (82.6)	514 (95.2)
2 (period 1987–1991)	382 (17.4)	26 (4.8)
CD4 cell count (mean ± s.d.)	359 ± 272.0	523.2 ± 343.6
HIV viral load (mean ± s.d.)	49 945 ± 102 422	151 978 ± 675 845

Table 2. The association between HAART use and incidence of Kaposi's sarcoma of the MACS HIV-infected men in current study, stratified by current smoking status and HAART use

	KS incidence cases	Follow-up [b] (person-years)	Unadjusted model			Adjusted model [a]		
			HR	95% CI	*P*-value	HR	95% CI	*P*-value
Current Smoking: no	336	15 609						
HAART ever use								
No			Ref.			Ref.		
Yes			0.08	0.06–0.12	<0.0001*	0.28	0.16–0.49	<0.0001*
Current Smoking: yes	192	10 949						
HAART ever use								
No			Ref.					
Yes			0.13	0.08–0.20	<0.0001*	0.60	0.28–1.12	0.10
HAART use: no	55	13 094						
Current smoking								
No			Ref.			Ref.		
Yes			0.78	0.64–0.94	0.01*	0.57	0.35–0.92	0.02*
HAART use: yes	473	13 164						
Current smoking								
No			Ref.			Ref.		
Yes			1.20	0.71–2.05	0.50	1.09	0.52–2.92	0.82

Abbreviations: CI: confidence interval; HR = hazard ratio; Ref. = Reference category.
[a]The model was adjusted for age, race/ethnicity, employment status, education, individual gross income, enrolment, and CD4 cell count.
[b]The follow-up time was for both KS and non-KS incidence cases.
*: *P*-value < 0.05.

RESULTS

More than 40% of participants were current smokers. The proportion of ever HAART use was 23 and 41% among HIV-seropositive and HIV-seroconverters, respectively (Table 1). We identified 530 incident KS cases with a total follow-up time of 26 594 person-years. The incidence rate was, therefore, 2.00 out of 100 person-years (2.40 out of 100 person-years in HIV-seropositive persons and 0.88 out of 100 person-years in HIV-seroconverters; data not shown). Although current smoking status and HAART use were independently associated with a lower risk of KS development (HR = 0.56, 95% CI: 0.35–0.90, $P = 0.02$ and HR = 0.27, 95% CI: 0.16–0.48, $P < 0.0001$, respectively), there was no evidence of interaction on the multiplicative scale between current smoking status and HAART use on the risk of KS (HR = 2.14, 95% CI: 0.97–4.73, $P_{\text{interaction}} = 0.13$) (data not shown).

HAART use showed a protective effect in lowering the risk of KS development in non-current smokers (HR = 0.28, 95% CI: 0.16–0.49, $P < 0.0001$). In stratified analyses by HAART use (Table 2), the inverse association with smoking was only present among those not using HAART (HR = 0.75, 95% CI: 0.35–0.92, $P = 0.02$).

DISCUSSION

In this analysis, we found that current smoking status and HAART use were independently associated with a lower risk of KS development, and there was no evidence of multiplicative interaction between current smoking status and HAART use. However, we also found that the inverse association of smoking was only present among those who had never been on HAART. The inverse association between HAART use and the risk of KS found in our analysis is consistent with previous literature (Jones *et al*, 2000; Carrieri *et al*, 2003). The importance of immunosuppression in KS carcinogenesis is highlighted by these findings. HIV seropositivity among HHV-8 infected persons seems to facilitate cytokine production that induces angiogenesis, stimulates the growth of endothelial cells, and promotes the growth of KS spindle cells (Albini *et al*, 1995; Fiorelli *et al*, 1995; Gallo, 1998).

Our finding on the independent inverse association of current smoking status on the risk of KS development is also consistent with previous studies (Hoover *et al*, 1993; Goedert *et al*, 2002; Nawar *et al*, 2005; Anderson *et al*, 2008). For example, Hoover *et al.* (1993) found that in HIV-infected men, KS was 30–39% less likely among smokers than among non-smokers and hypothesised that smoking regulates key inflammatory cytokines, thus reducing KS risk among AIDS patients. In fact, Nouri-Shirazi and Guinet (2003), and Nouri-Shirazi *et al.* (2007) reported that nicotine influences the immune system by modifying the differentiation of dendritic cells (DCs) into atypical DCs. Specifically, the DCs alter the regulation of interleukin (IL)-10, 12 and interferon-γ-producing effector cells as well as the stimulation of antigen-presenting cell-dependent T-cell responses. Although the biological mechanism of smoking on carcinogenesis is not fully understood, this evidence provides a rationale for further investigation of the role of cigarette-smoking (i.e., nicotine) on KS risk.

We also observed that the inverse association of smoking was only present among those not on HAART. As Hoover *et al.* (1993) found the impact of smoking status on KS incidence before the HAART era, we thought that the potential protective effects on KS development by smoking and HAART use might be due to separate biological mechanisms and deserve to be studied further.

The major strength of our study is the use of MACS, a well-designed large cohort study of HIV-infected men in the United States, to accurately identify KS cases. The main limitation in our analysis is that because most MACS participants are Caucasian males, we cannot generalise our findings to HIV-infected women or to other racial/ethnic groups. Another limitation is that we could not analyse specific HAART regimens individually due to the change of its definition over time. Although there were no associated found (data not shown) between smoking intensity as measured by the 'number of packs smoked per day when smoked most', >25% of subjects were missing data on smoking duration. Therefore, a more accurate representation of smoking intensity measured in pack-years could not be calculated.

To our knowledge, this is the first attempt to determine the possible interaction between smoking status and HAART use on KS risk. We also thought that if this interaction is true, the underlying biological or statistical mechanism deserves further investigation. We found independent associations between current smoking status and HAART use with a lower risk of KS development but no evidence of multiplicative interaction between current smoking status and HAART use. However, the inverse association between cigarette smoking and KS risk may be limited to those not using HAART. Our findings should be interpreted cautiously, given the negative impact of smoking on general health and the null results from a previous clinical trial examining nicotine use on KS development (Goedert *et al*, 2008). We, however, still think that to fully appreciate the impact that this finding might have on KS incidence among HIV-infected populations, the comprehensive biological mechanism of smoking in KS carcinogenesis needs to be elucidated.

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DISCLAIMER

The contents of this publication are solely the responsibility of the authors and do not necessarily represent the official views of the National Institutes of Health or the Cancer Prevention and Research Institute of Texas.

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