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Prevalence of non-HIV cancer risk factors in persons living with HIV/AIDS: a meta-analysis

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Abstract

Objective—The burden of cancer among persons living with HIV/AIDS (PLWHA) is substantial and increasing. We assessed the prevalence of modifiable cancer risk factors among adult PLWHA in Western high-income countries since 2000.

Design—Meta-analysis.

Methods—We searched PubMed to identify articles published in 2011-2013 reporting prevalence of smoking, alcohol consumption, overweight/obesity, and infection with human papillomavirus (HPV), hepatitis C virus (HCV) and hepatitis B virus (HBV) among PLWHA. We conducted random effects meta-analyses of prevalence for each risk factor, including estimation of overall, sex-specific, and HIV-transmission-group-specific prevalence. We compared prevalence in PLWHA with published prevalence estimates in US adults.

Results—The meta-analysis included 113 publications. Overall summary prevalence estimates were current smoking, 54% (95% confidence interval (CI) 49%-59%) versus 20-23% in US adults; cervical high-risk HPV infection, 46% (95% CI 34%-58%) versus 29% in US females; oral high-risk HPV infection, 16% (95% CI 10%-23%) versus 4% in US adults; anal high-risk HPV

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infection (men who have sex with men), 68% (95% CI 57%-79%), with no comparison estimate available; chronic HCV infection, 26% (95% CI 21%-30%) versus 0.9% in US adults; and HBV infection, 5% (95% CI 4-5%) versus 0.3% in US adults. Overweight/obesity prevalence (53%; 95% CI 46%-59%) was below that of US adults (68%). Meta-analysis of alcohol consumption prevalence was impeded by varying assessment methods. Overall, we observed considerable study heterogeneity in prevalence estimates.

Conclusions—Prevalence of smoking and oncogenic virus infections continues to be extraordinarily high among PLWHA, indicating a vital need for risk factor reduction efforts.

Keywords

HIV infections; Acquired Immunodeficiency Syndrome; neoplasms; cancer risk factors; cancer prevention; high-income countries

Introduction

Cancer is a leading cause of death among persons living with HIV/AIDS (PLWHA) in the United States and Europe [1-4]. Furthermore, incidence of both AIDS-defining and specific non-AIDS-defining-cancers is elevated in PLWHA compared with the general population [5-13] (Table 1). Both impaired immune function and high prevalence of modifiable non-HIV cancer risk factors contribute to this substantial cancer burden [6, 14-17]. In this meta-analysis, we estimated the prevalence of cancer risk factors (smoking, alcohol consumption, overweight/obesity, and infection with human papillomavirus [HPV], hepatitis C virus [HCV], and hepatitis B virus [HBV]; Table 1) [18-37] among adult PLWHA in Western high-income countries (US, Canada, Western Europe, Australia) in recent years (2000-2013) from cohort, cross-sectional, case-control, and experimental studies and compared these prevalence estimates with those among US adults; we also compared prevalence estimates between PLWHA and uninfected comparison groups from the same study when such comparison groups were available.

Methods

Study selection

We searched PubMed/MEDLINE to identify relevant references published in English during 2011-2013 and available in PubMed as of April 17, 2014. We cross-referenced Medical Subject Heading (MeSH) terms for each risk factor (Table 2) with MeSH terms “HIV infections” or “Acquired Immunodeficiency Syndrome” and “Adult.” One author (RUHR) screened abstracts to remove clearly-ineligible studies. Two authors (RUHR and RD) then independently performed full-text review of the remaining articles for eligibility, with discrepancies resolved by discussion.

We restricted prevalence estimates to those based on data collected during 2000-2013 (to reflect experience in the modern antiretroviral therapy [ART] era) with ≥100 adult PLWHA living in the US, Canada, Western Europe, or Australia. We included prospective or retrospective cohort, cross-sectional, case-control, and experimental studies. We excluded publications for which severe selection bias could be anticipated (e.g., estimation of HBV

prevalence among hepatocellular carcinoma patients). When eligibility was uncertain we queried authors for clarification.

If the prevalence of a risk factor from a given study was reported in more than one publication, in general we used the following hierarchy to decide which publication to include: 1) availability of a comparison prevalence estimate from uninfected subjects; 2) availability of prevalence estimates by sex or high-risk behavior (i.e., men who have sex with men [MSM] and injection drug users [IDU]); and 3) sample size. If more than one publication from a given study each presented unique information (e.g., sex-specific prevalence estimates in one publication, and an overall, unstratified prevalence estimate with a larger overall sample size in another publication), each publication contributed to the relevant meta-analysis (e.g., female, male, overall).

Data extraction

Three authors conducted data extraction (RUHR, RD, and LSP), with independent extraction by a pair of these authors for each data element and with discrepancies resolved by discussion. For prevalence estimates, our denominator was the number of persons with known status for the risk factor. If an article presented a prevalence estimate that included unknowns in the denominator, we re-calculated the prevalence estimate, excluding unknowns. We examined eligible publications identified from each specific risk factor search for the presence of prevalence estimates for other risk factors and included these estimates in our analyses (e.g., if a publication identified in the smoking search, but not in the HCV search, reported HCV prevalence, we included the HCV prevalence estimate).

We extracted prevalence estimates for study samples unrestricted by sex or HIV transmission category (henceforth called the “overall” group), as well as estimates for the following demographic groups: female, male (unrestricted by HIV transmission category), MSM, and IDU. We extracted prevalence estimates for internal uninfected comparison groups when available. For eligible publications (meaning that the publication included ≥100 adult PLWHA), we imposed no sample size restriction for demographic sub-groups or uninfected comparison groups.

We extracted data on country(ies), study design, prevalence estimate calendar year(s), sampling frame (e.g., clinic/hospital-based; geography-based), sex, age, race, HIV risk group, CD4+ count, ART, and method of measurement/definition of risk factors. For each risk factor reported in each publication, we assessed four indicators of potential for bias: whether or not 1) the aim of the study was to measure the prevalence of the risk factor or the risk factor was a predictor, outcome, or covariate in the study; 2) exclusion criteria might cause selection bias; 3) subjects were excluded due to missing information on the risk factor; and 4) there were included subjects with missing information on the risk factor. For the latter three indicators, we calculated the proportion excluded/missing, if known. We then classified a prevalence estimate to have higher potential for bias if the study did not aim to measure the risk factor and the risk factor was not a predictor, outcome, or covariate (indicator 1); or if the total of the proportions excluded/missing across indicators 2-4 was known to be >10%, or if any of these proportions was unknown.

We extracted prevalence estimates for the adult civilian noninstitutionalized population of the United States (henceforth called “US adults”) from the National Health Interview Survey (NHIS) [38, 39], National Health and Nutrition Examination Survey (NHANES) [40-49], and Behavioral Risk Factor Surveillance System (BRFSS) [50-52], each during a calendar period between 2000 and 2010 for which data were reported. In NHANES, HIV prevalence was 0.5% in the age group 18-49 years during 2003-2006 [53]; there were no data from NHIS or BRFSS.

Statistical analysis

For each risk factor, we conducted a meta-analysis of prevalence for each demographic group with at least two individual study prevalence estimates. The summary prevalence estimate (sPrev) for each group was based solely on individual study prevalence estimates for that group. Thus, sPrev for “overall” did not include individual study prevalence estimates from studies restricted according to sex or HIV transmission category. Using the Stata 12.1 metaprop module [54], we calculated sPrev and 95% confidence intervals (CI), as well as I^2 values and Q statistic p-values to assess study heterogeneity [55]. To stabilize variances, we transformed individual study prevalence estimates using the Freeman-Tukey double arcsine transformation [56, 57]. We used random-effects models [58] because we expected substantial study heterogeneity. Therefore, each sPrev estimate should be interpreted as an average prevalence across studies with true differences in target population prevalence, not a common prevalence across studies with the same target population prevalence [59]. If only one study reported a particular risk factor prevalence for a given group, we presented that individual estimate and Wilson score 95% CI. In sensitivity analyses, we calculated sPrev estimates excluding studies classified as having higher potential for bias. Finally, we assessed bias in study selection for each risk factor/group with ≥10 individual studies [60] through visual inspection of funnel plots and the Egger [61] and Begg [62] tests.

Results

We identified 1,573 unique references from the PubMed queries. After initial review of abstracts, we performed full-text review of 717 articles and found 113 eligible publications [63-175] (Table 2). Supplemental Table S1 presents characteristics of each eligible publication. The study design distribution was prospective cohort, 49; retrospective cohort, 10; cross-sectional, 46; case-control, 2; and experimental, 6. Most (87%) study samples were clinic/hospital-based; only one study sample was population-based. Among the 113 publications, the median number of subjects was 388 (interquartile range [IQR], 192-905). The geographic location distribution was United States, 59; Western Europe, 46; Canada, 4, and Australia, 4. Of 104 publications that reported sex distribution, the median percent male was 75.4% (IQR, 65.0%-85.4%). Of 91 publications that reported mean or median age, the median of the mean or median was 44.0 years (IQR, 41.6- 46.5). Of 63 publications that reported mean or median CD4+ count, the median of the mean or median was 487.0 (IQR, 426.0-513.3). Of 75 publications that reported percent on ART, the median was 84.0% (IQR, 73.0%-93.9%). Fewer than 60% of publications reported race or HIV transmission group.

Table 3 presents results for each risk-factor-specific, group-specific meta-analysis. Forest plots for key meta-analyses are presented in Supplemental Figure S1. Individual study prevalence estimates are presented in Supplemental Tables S2-S7.

Smoking

Forty-five publications reported smoking prevalence [63-107], but most (84%) presented frequencies for "current," "former," and/or "ever" smoker without precisely defining these terms (e.g., ever smoker: at least 100 cigarettes lifetime) (Supplemental Table S2). Overall current smoking sPrev was 54% (95% CI 49%-59%; I^2=99%), about 2.5 times the prevalence among US adults (Table 3) [39, 41, 51]. The majority of studies with uninfected comparison groups found higher smoking prevalence in PLWHA (Table 4). The highest current smoking sPrev was among IDU (74%; 95% CI 60%-85%; I^2=89%) (Table 3).

Alcohol consumption

Twenty-six publications reported hazardous alcohol consumption prevalence [63, 65, 66, 71, 73, 76, 84, 91, 94, 101, 103, 104, 108-121]. Meta-analysis of hazardous alcohol consumption prevalence was hampered by the wide range of definitions over varying time spans (e.g., past 30 days, past 6 months) (Supplemental Table S3). Definition-specific meta-analyses yielded small numbers of studies and sPrev estimates with wide 95% CIs. We therefore chose not to stratify but to estimate sPrev of "hazardous alcohol consumption" regardless of definition. Overall hazardous alcohol consumption sPrev was 24% (95% CI 15%-33%; I^2=100%) (Table 3) compared with 5-15% prevalence among US adults, depending on the definition [39, 42, 52]. Hazardous alcohol consumption prevalence did not meaningfully differ between PLWHA and uninfected comparison groups (Table 4).

Overweight/obesity

Eighteen publications reported overweight (BMI: 25.0-29.9 kg/m^2) and/or obesity (BMI: ≥30.0 kg/m^2) prevalence [68, 69, 72, 73, 75, 77, 78, 90, 101, 104, 105, 118, 122-127]. In all publications, weight and height were directly measured; we therefore restricted our comparison with US adults to NHANES, the only nationally representative survey with directly measured weight and height. Overall overweight sPrev (32%; 95% CI 29%-35%; I^2=88%) was similar to the prevalence in US adults (34%), but obesity sPrev (17%; 95% CI 14%-21%; I^2=98%) was lower than the prevalence in US adults (34%) [43], as was overweight/obesity sPrev (53%; 95% CI 46%-59%; I^2=98%, versus 68%) (Table 3). Prevalence of overweight/obesity was consistently higher in uninfected comparison groups compared to PLWHA (Table 4).

Human papillomavirus infection

Eighteen publications reported HPV infection prevalence [91-93, 95, 96, 98, 128-139]. The number of HPV types tested varied from 15 to 47; the number of high-risk HPV types tested varied from 11 to 22 (Supplemental Table S5). Cervical HPV sPrev was 64% (95% CI 25%-95%; I^2=99%), compared with 43% prevalence among US females [44] (Table 3); cervical high-risk-type HPV sPrev was 46% (95% CI 34%-58%; I^2=96%) compared with 29% prevalence in US females [45]. Overall oral HPV sPrev was 34% (95% CI 26%-42%;

I^2=68%), about five times the prevalence in US adults (7%) [46]; high-risk-type oral HPV sPrev was 16% (95% CI 10%-23%; I^2=71%), compared with 4% prevalence in US adults [46, 47] (Table 3). Most studies of anal HPV prevalence were among MSM (sPrev=91%; 95% CI 87%-95%; I^2=93% for any type and sPrev=68%; 95% CI 57%-79%; I^2=98% for high-risk types) (Table 3); prevalence was similarly high in all groups. PLWHA generally had significantly higher oral and anal HPV prevalence than uninfected comparison groups (Table 4).

Hepatitis C virus infection

Sixty-three studies reported HCV infection prevalence [63-65, 69, 72, 73, 75, 77, 79-84, 88, 90, 102-104, 107, 109, 110, 114, 117-119, 123, 127, 133, 140-173]. We calculated sPrev for HCV-exposed, defined in 69% of individual studies as positive by HCV antibody test, and for chronic HCV infection, defined in 80% of studies as positive by HCV antibody and HCV RNA tests (see Supplemental Table S6 for all definitions). Overall HCV-exposed sPrev was 28% (95% CI 23%-33%; I^2=100%), compared with just 1.3% prevalence in US adults [48] (Table 3). Overall chronic HCV infection sPrev (26%; 95% CI 21%-30%; I^2=99%) was also much higher than the prevalence in US adults (0.9%) [48]. HCV sPrev was relatively low among MSM (HCV-exposed sPrev=8%; 95% CI 6%-11%; I^2=93% and chronic HCV sPrev=5%; 95% CI 2%-10%; I^2=94%), but was extremely high among IDU (HCV-exposed sPrev=80%; 95% CI 68%-89%; I^2=97% and chronic HCV sPrev=71%; 95% CI 55%-86%; I^2=94%). HCV prevalence was consistently higher in PLWHA than uninfected comparison groups (Table 4).

Hepatitis B virus infection

Twenty-six publications reported HBV infection prevalence [63, 65, 69, 71, 79-81, 89, 102, 106, 110, 123, 141, 144, 147, 150, 151, 154, 157, 159, 162, 165, 170, 172, 174, 175]. HBV infection was defined in 72% of individual studies as positive by HBV surface antigen test (see Supplemental Table S7 for all definitions). Overall HBV sPrev was 5% (95% CI 4%-5%; I^2=87%) compared to just 0.3% in US adults [49] (Table 3).

Potential for bias

Across all risk factors summed over all publications, we classified 39% as having higher potential for bias, including smoking, 30%; alcohol, 42%; overweight/obesity, 37%; HPV, 49%; HCV, 38%; and HBV, 42%. Furthermore, across all risk factors summed over all publications we found that the study did not aim to measure the risk factor and the risk factor was not a predictor, outcome, or covariate in 8% of cases; there were exclusion criteria that might cause selection bias in 17%; there were excluded subjects due to missing information on the risk factor in 8%; and there were included subjects with missing information on the risk factor in 33% (only 13% with >10% missing information).

In sensitivity analyses excluding studies with higher potential for bias, the change in sPrev was both meaningful (i.e.,$|sPrev_{exc} - sPrev_{all}|/sPrev_{all}$>15%) and statistically significant (i.e., p-value for difference between $sPrev_{\text{lower potential for bias}}$ and $sPrev_{\text{higher potential for bias}}$ <0.05) for former smoker among females (15% for all studies, 18% for studies with higher potential for bias excluded); hazardous alcohol consumption among females (15% versus

18%) and among MSM (25% versus 32%); overweight/obesity among females (64% versus 44%) and males (55% versus 44%); cervical HPV, any type (64% versus 44%); and oral HPV, any type, among males (27% versus 40%).

We observed some funnel plot asymmetry (Supplemental Figure S2) for hazardous alcohol consumption (overall), with a deficit of smaller studies with higher prevalence; and for overweight/obesity (overall) and chronic HCV infection (overall), each with deficits of smaller studies with lower prevalence. The Egger test for chronic HCV infection was the only statistically significant test for bias in study selection (p=0.008).

The PLWHA and uninfected comparison groups in Table 4 generally had similar demographic characteristics. Exceptions that might have influenced comparisons included Morano *et al.* (2013) for alcohol and HCV (IDU: 43% in PLWHA, 14% in uninfected; mean age: 43.8 years in PLWHA; 35.9 years in uninfected); Raymond *et al.* (2012) for HCV (IDU: 32% in PLWHA, 12% in uninfected); and Wieland *et al.* (2011) for smoking (100% MSM in PLWHA; uninfected group was males, not restricted to MSM).

Discussion

To our knowledge, this is the first comprehensive meta-analysis of the prevalence of cancer risk factors among PLWHA. There is one meta-analysis published on cervical HPV prevalence in PLWHA [176]. Our analyses quantified the continuing high prevalence of smoking and HPV, HCV, and HBV infections among PLWHA. Prevalence of overweight/obesity was lower than in US adults. Assessment of alcohol consumption was hampered by variability in assessment methods.

Overall, about half of PLWHA were current smokers, a prevalence 2.5 times higher than in US adults. This high prevalence often reflected the high prevalence in demographically similar uninfected persons, where, for example, IDU smoking prevalence was high, regardless of HIV status (Table 4). The prevalence of high-risk HPV infections remained distressingly high, with cervical sPrev of 46% (1.6 times the prevalence in US adults); oral prevalence of 10-16% (2.5-4 times the prevalence in US adults); and anal sPrev around 70% (no nationally representative prevalence estimate in US adults available). More than one quarter of PLWHA were infected with HCV (12-40 times higher than in US adults) and about 5% were infected with HBV (10-25 times higher than in US adults). Furthermore, 70-80% of IDU were infected with HCV, accounting for the fact that in the US, about half of liver cancer cases among PLWHA occur in IDU [177], who constitute 22% of PLWHA [178].

With the introduction of ART and greater control of HIV wasting syndrome, the prevalence of overweight/obesity among PLWHA has increased [179, 180]. However, our results showed that PLWHA have not yet reached the overweight/obesity prevalence of US adults (53% versus 68%) or of demographically similar uninfected persons. Finally, results for alcohol consumption were difficult to interpret due to considerable heterogeneity in measurement. Although the overall prevalence of hazardous alcohol consumption (regardless of definition) was 24%, roughly 1.5-4 times higher than in US adults, direct

comparisons of PLWHA with demographically similar uninfected comparison groups, using the same definition, showed no differences.

We observed considerable study heterogeneity in prevalence estimates, with the majority of I^2 values >90%. This result was not surprising in our "overall" group, which could vary across studies by sex and MSM and IDU status distribution, or in our male group, which could vary by MSM and IDU status distribution. However, heterogeneity was generally high even within our more narrowly defined demographic groups (females, MSM, IDU). Potential sources of heterogeneity included differences in study design, geographic location, sex, age, race/ethnicity, prevalence estimate calendar year(s), and risk factor measurement method/definition. Differences in CD4+ count [181] or number of HPV types tested could be sources of heterogeneity for HPV prevalence, and differences in amount of time on ART could be a source of heterogeneity for overweight/obesity [182].

Our goal was to provide a broad overview of cancer risk factor prevalence in PLWHA. Our random effects models, which appropriately penalized the precision of our estimates in the context of high study heterogeneity, provided reasonable approximations of average prevalence estimates. Future research focused on identifying risk-factor-specific sources of heterogeneity could identify high prevalence sub-groups to target for risk factor reduction efforts.

Our study had limitations. First, the individual study PLWHA samples were primarily clinic/hospital-based samples that may not have been representative of the overall PLWHA population. However, samples from a broad range of well-established cohorts and HIV treatment centers were represented in this meta-analysis (Supplemental Table S1), suggesting that our results provide robust estimates of cancer risk factor prevalence among PLWHA receiving HIV care.

Second, risk factors often are included in descriptions of baseline characteristics or are used as covariates, without being central to the study and therefore without being indexed in PubMed. This phenomenon is illustrated by the fact that 42% of our publications reported the prevalence of one or more risk factors that were not identified in the searches for those risk factors. Recognizing that there most likely were other articles that reported the prevalence of one or more risk factors but were not identified in any of the searches, we aimed for a robust representation of publications indexed in PubMed, with the limitation that we would not identify all of them. Inspection of funnel plots provided limited evidence for bias in study selection for hazardous alcohol consumption, overweight/obesity, and chronic HCV infection; however, the only significant statistical test was the Egger test for chronic HCV infection.

Third, although our sensitivity analyses suggested that our sPrev estimates were not heavily distorted by bias, because most studies did not report participation rates, we were unable to include participation rates in our potential for bias measure.

Fourth, in our extraction of prevalence estimates we excluded unknowns from the denominator. This approach is valid if the prevalence of the risk factor is similar among the knowns and unknowns, but otherwise is biased. However, the alternative of including the

unknowns in the denominator always underestimates prevalence unless the risk factor is absent in all of the unknowns. Fortunately, only 13% of risk factor-publication combinations had >10% of subjects with missing values.

Finally, we need to consider the possibility of information bias in the individual studies. We know little about the smoking definitions. Determination of overweight/obesity should be accurate because weight and height were directly measured. There was variability in the number of HPV types tested; studies testing for fewer types might underestimate prevalence. Similarly, studies with narrower definitions of HCV or HBV infection (e.g., positive by HBV DNA test versus positive by DNA test or HBV surface antigen test) might underestimate prevalence.

Despite these potential sources of bias, the general consistency between comparisons of our sPrev estimates among PLWHA with prevalence estimates among US adults and comparisons of prevalence estimates among PLWHA and uninfected comparison groups from the same study (Table 4) provides validation for our essential findings.

Interventions to reduce the high prevalence of smoking and oncogenic virus infections among PLWHA can play a critical role in reducing the high cancer burden. Specific interventions include smoking cessation [183, 184], HPV [185-188] and HBV vaccination [189, 190], and HCV [191, 192] and HBV [189, 193] treatment. Research is needed to develop effective, tailored smoking cessation interventions, including for sub-populations (e.g., IDU, MSM), to effectively address the high prevalence of co-occurring risk factors, to identify potential adverse interactions between pharmacologic interventions and ART [184, 189, 194-196], and to overcome impaired immunogenicity [189, 190, 197, 198] of or non-adherence [199] to vaccine regimens. Finally, epidemiologic studies to estimate the population attributable risk percent for various cancer types due to cancer risk factors among PLWHA would help guide both research and practice.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Cancer risk factors and cancer types with elevated risk among PLWHA, by cancer type [5-13, 18-37][a]

	(✓ = elevated risk; ? = possible elevated risk)						
	Risk factor						Cancer types with elevated risk among PLWHA
Cancer type	**Smoking**	**Hazardous alcohol consumption**	**Obesity**	**Human papillomavirus**	**Hepatitis C virus infection**	**Hepatitis B virus infection**	
Oral cavity/pharynx	✓	✓		✓			✓
Digestive							
Esophagus							?
Esophagus, adenocarcinoma	✓	✓	✓				
Esophagus, squamous cell carcinoma	✓	✓		?			
Stomach	✓						✓
Gastric cardia	✓		✓				
Colorectal	?	✓	✓				
Anus				✓			✓
Liver	?	✓	?		✓	✓	✓
Gallbladder			?				?
Pancreas	✓		✓				
Respiratory							
Larynx	✓	✓		?			✓
Lung	✓						✓
Skin							
Squamous cell carcinoma	?			?			✓
Breast							
Postmenopausal breast		✓	✓				
Premenopausal breast							
Genital							
Cervix	✓			✓			✓

	(✓ = elevated risk; ? = possible elevated risk)						
	Risk factor						Cancer types with elevated risk among PLWHA
Cancer type	Smoking	Hazardous alcohol consumption	Obesity	Human papillomavirus	Hepatitis C virus infection	Hepatitis B virus infection	
Endometrium			✓				
Vagina				✓			✓
Vulva				✓			✓
Penis				✓			✓
Urinary							
Bladder	✓						
Kidney	✓		✓				✓
Endocrine							
Thyroid			?				
Hematopoietic and lymphoid							
Non-Hodgkin lymphoma			?		?	?	✓
Multiple myeloma			?				✓
Leukemia			?				✓
Acute myeloid leukemia	✓		?				

[a] Cancer-type-specific risk factors was based on data from HIV-uninfected populations.

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Table 2

PubMed Medical Subject Heading (MeSH) search terms and number of articles identified and contributing to the meta-analysis, by cancer risk factor

Cancer risk factor/MeSH terms	Specific risk factor search results				Total articles that contributed to the respective meta-analysis[b]
	Identified articles	Full-text review	Excluded after full-text review, with reasons for exclusion[a]	Contributed to the meta-analysis	
Smoking	130	75	55	20	45
Tobacco products			Age: 2		
Tobacco			Geographic location: 5		
Smoking			N<100: 7		
			Calendar years: 17		
			No prevalence estimate: 17		
			Redundant article: 7		
Hazardous alcohol consumption	226	64	53	11	26
Alcohol drinking			Age: 3		
Alcoholism			Geographic location: 3		
Alcohol-related disorders			N<100 : 1		
Alcoholic intoxication			Calendar years: 16		
			Severe selection bias: 3		
			No prevalence estimate: 21		
			Redundant article: 6		
Overweight/obesity	236	102	91	11	18
Overweight			Age: 3		
Obesity			Geographic location: 18		
Body mass index			N<100: 15		
Body weight			Calendar years: 12		
			No prevalence estimate: 41		
			Redundant article: 2		
Human papillomavirus infection	190	83	65	18	18
Papillomavirus infections			Age: 1		

Cancer risk factor/MeSH terms	Specific risk factor search results				Total articles that contributed to the respective meta-analysis[b]
	Identified articles	Full-text review	Excluded after full-text review, with reasons for exclusion[a]	Contributed to the meta-analysis	
Papillomaviridae			Geographic location: 9 N<100: 8 Calendar years: 5 Severe selection bias: 1 No prevalence estimate: 34 Redundant article: 7		
Hepatitis C virus infection	725	374	322	52	63
Hepatitis C			Age: 2		
Hepacivirus			Geographic location: 24		
Hepatitis C, chronic			N<100: 15		
			Calendar years: 43		
			Severe selection bias: 2		
			No prevalence estimate: 224		
			Redundant article: 12		
Hepatitis B virus infection	311	107	96	11	26
Hepatitis B			Age: 2		
Hepatitis B virus			Geographic location: 20		
Hepatitis B, chronic			N<100: 3		
			Calendar years: 15		
			Severe selection bias: 4		
			No prevalence estimate: 50		
			Redundant article: 2		
Total unique articles[c]	1,573	717	604	113	113

[a] One reason per article; many articles had more than one reason for exclusion.

[b] Articles identified from the specific risk factor search plus articles identified from other risk factor searches that also included a prevalence estimate for this risk factor.

[c] Articles identified in more than one specific risk factor search only counted once.

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Table 3

Meta-analysis and single study prevalence estimates, 95% confidence intervals (95% CI), I^2 values, and number of studies (N) for cancer risk factors among adult persons living with HIV/AIDS in Western high-income countries and US adult prevalence estimates

Risk factor/demographic group	Prevalence estimate				US adult prevalence (%)[a]		
	Prevalence (%) (95% CI)	I^2, Q statistic p-value	N	References	NHIS	NHANES	BRFSS
Smoking							
Random effects meta-analysis							
Current							
Overall[b]	54 (49-59)	99%, <0.001	28	[63-90]	20	23	20[c]
Female	48 (36-60)	97%, <0.001	10	[67, 70, 71, 86, 87, 91-95]	18	20	19[c]
Male[d]	58 (39-76)	98%, <0.001	6	[67, 70, 71, 86, 87, 96]	23	26	22[c]
MSM	38 (29-47)	93%, <0.001	7	[67, 70, 86, 96-99]			
IDU	74 (60-85)	89%, <0.001	3	[70, 86, 100]			
Former							
Overall[b]	20 (16-25)	98%, <0.001	7	[64, 65, 67, 73, 76, 77, 86]	21		
Female	15 (8-23)	87%, <0.001	5	[67, 86, 92, 94, 95]	18		
Male[d]	25 (14-39)	92%, <0.001	3	[67, 86, 96]	25		
MSM	31 (21-42)	92%, <0.001	3	[86, 96, 97]			
IDU	22 (1-58)	94%, <0.001	2	[86, 100]			
Ever							
Overall[b]	67 (61-72)	99%, <0.001	13	[64, 65, 67, 73, 76, 77, 86, 101-106]	42		
Female	66 (54-76)	95%, <0.001	7	[67, 86, 92, 94, 95, 101, 107]	36		
Male[d]	70 (61-79)	95%, <0.001	4	[67, 86, 96, 101]	48		
MSM	64 (54-74)	89%, <0.001	3	[86, 96, 97]			
IDU	94 (91-97)	0%, 0.84	2	[86, 100]			
Hazardous alcohol consumption[e]							
Random effects meta-analysis							

Risk factor/demographic group	Prevalence estimate				US adult prevalence (%)[a]		
	Prevalence (%) (95% CI)	I^2, Q statistic p-value	N	References	NHIS	NHANES	BRFSS
Overall[b]	24 (15-33)	100%, <0.001	21	[63, 65, 66, 71, 73, 76, 84, 101, 103, 104, 108-118]	5[f], 9[g]		5[h] 15[i]
Female	15 (4-33)	99%, <0.001	8	[66, 71, 94, 101, 111, 112, 116, 119]	4[f], 4[g]	3[j]	4[h], 10[i]
Male[d]	33 (14-56)	100%, <0.001	7	[66, 71, 101, 111, 112, 116, 120]	6[f], 15[g]	8[j]	6[h] 21[i]
MSM	25 (10-44)	98%, <0.001	4	[66, 91, 111, 121]			
Single study[k]							
IDU	42 (28-57)	-	1	[66]			
Overweight/obesity							
Random effects meta-analysis							
Obesity							
Overall[b]	17 (14-21)	98%, <0.001	12	[68, 69, 72, 73, 75, 78, 90, 104, 105, 118, 122, 123]		34	
Female	47 (17-77)	95%, <0.001	2	[78, 101]		36	
Male[d]	25 (11-44)	94%, <0.001	2	[78, 101]		32	
Overweight							
Overall[b]	32 (29-35)	88%, <0.001	10	[68, 69, 75, 78, 90, 104, 105, 118, 122, 123]		34	
Overweight/obesity							
Overall[b]	53 (46-59)	98%, <0.001	13	[68, 69, 75, 77, 78, 90, 104, 105, 118, 122-125]		68	
Female	64 (27-93)	92%, <0.001	2	[78, 124]		64	
Male[d]	55 (35-75)	85%, 0.009	2	[78, 124]		72	
Single study[k]							
Obesity							
MSM	12 (10-15)	-	1	[126]			
IDU	18 (15-23)	-	1	[127]			
Overweight							
Female	17 (9-30)	-	1	[78]		29	

Risk factor/demographic group	Prevalence estimate				US adult prevalence (%)[a]		
	Prevalence (%) (95% CI)	I^2, Q statistic p-value	N	References	NHIS	NHANES	BRFSS
Male[d]	30 (22-39)		1	[78]		40	
MSM	42 (39-45)	-	1	[126]			
IDU	28 (23-33)	-	1	[127]			
Overweight/obesity							
MSM	54 (51-58)	-	1	[126]			
IDU	46 (41-51)	-	1	[127]			
Human papillomavirus infection[l]							
Random effects meta-analysis							
Cervical							
Any type							
Female	64 (25-95)	99%, <0.001	2	[92, 128]		43[m]	
High-risk types							
Female	46 (34-58)	96%, <0.001	5	[92, 93, 95, 128, 129]		29[n]	
Oral							
Any type							
Overall[b]	34 (26-42)	68%, 0.046	3	[130-132]		7[o]	
Female	34 (28-41)	0%, 0.74	2	[91, 131]		4[p]	
Male[d]	27 (7-53)	94%, <0.001	2	[96, 131]		10[o]	
MSM	27 (16-39)	94%, <0.001	5	[91, 96, 131, 133, 134]			
High-risk types							
Overall[b]	16 (10-23)	71%, 0.031	3	[130-132]		4[q]	
Female	10 (0.2-29)	87%, 0.005	2	[91, 131]		2[q]	
Male[d]	15 (12-18)	1%, 0.32	2	[96, 131]		6[q]	
MSM	12 (6-19)	90%, <0.001	5	[91, 96, 131, 133, 134]			
Anal							
Any type							

Risk factor/demographic group	Prevalence estimate				US adult prevalence (%)[a]		
	Prevalence (%) (95% CI)	I^2, Q statistic p-value	N	References	NHIS	NHANES	BRFSS
Male[d]	84 (61-98)	98%, <0.001	2	[96, 135]			
MSM	91 (87-95)	93%, <0.001	6	[96, 98, 133, 135-137]			
High-risk types							
Overall[b]	75 (58-89)	93%, <0.001	2	[130, 138]			
Male[d]	66 (63-69)	0%, 0.44	2	[96, 135]			
MSM	68 (57-79)	98%, <0.001	7	[96, 98, 133, 135-137, 139]			
Single study[k]							
Anal							
Any type							
Overall[b]	84 (80-87)	-	1	[130]			
Female	90 (83-94)	-	1	[92]			
IDU	93 (86-97)	-	1	[135]			
High-risk types							
Female	85 (78-90)	-	1	[92]			
IDU	68 (57-78)	-	1	[135]			
Hepatitis C virus infection							
Random effects meta-analysis							
Exposed[r]							
Overall[b]	28 (23-33)	100%, <0.001	36	[65, 69, 72, 73, 75, 80, 82-84, 88, 90, 102-104, 110, 114, 118, 140-158]		1.3[s]	
Female	28 (22-35)	95%, <0.001	8	[88, 107, 114, 118, 148, 151, 152, 159]		0.7[s]	
Male[d]	23 (17-30)	98%, <0.001	6	[88, 114, 118, 148, 151, 152]		1.9[s]	
MSM	8 (6-11)	93%, <0.001	10	[114, 118, 133, 151, 152, 160-164]			
IDU	80 (68-89)	97%, <0.001	7	[88, 114, 118, 127, 148, 151, 152]			

Risk factor/demographic group	Prevalence estimate				US adult prevalence (%)[a]		
	Prevalence (%) (95% CI)	I^2, Q statistic p-value	N	References	NHIS	NHANES	BRFSS
Chronic infection[t]							
Overall[b]	26 (21-30)	99%, <0.001	23	[63-65, 77, 79-81, 109, 117, 123, 140, 142, 153, 157, 158, 165-172]		0.9[u]	
Female	33 (21-47)	92%, <0.001	7	[63, 80, 119, 166, 168, 169, 171]			
Male[d]	35 (24-46)	93%, <0.001	6	[63, 80, 166, 168, 169, 171]			
MSM	5 (2-10)	94%, <0.001	6	[80, 163, 168-170, 173]			
IDU	71 (55-86)	94%, <0.001	6	[80, 119, 169-171, 173]			
Hepatitis B virus infection[v]							
Random effects meta-analysis							
Overall[b]	5 (4-5)	87%, <0.001	24	[63, 65, 69, 71, 79-81, 89, 102, 106, 110, 123, 141, 144, 147, 150, 151, 154, 157, 165, 170, 172, 174, 175]		0.3[w]	
Female	5 (2-10)	94%, <0.001	4	[71, 151, 154, 159]		0.2[w]	
Male[d]	4 (4-8)	77%, 0.012	3	[71, 151, 154]		0.4[w]	
MSM	5 (2-9)	94%, <0.001	3	[151, 154, 162]			
IDU	7 (5-9)	0%, 0.80	2	[151, 154]			

Abbreviations: BRFSS, Behavioral Risk Factor Surveillance System; CI, confidence interval; IDU, injection drug users; MSM, men who have sex with men; NHANES, National Health and Nutrition Examination Survey; NHIS, National Health Interview Survey.

[a] Respective references as follows: NHIS: smoking, alcohol [39]; NHANES: smoking [41], alcohol [42], overweight/obesity [43], human papillomavirus (HPV) [44-47], hepatitis C virus (HCV) [48], hepatitis B virus (HBV) [49]; BRFSS: smoking [51], alcohol [52].

[b] "Overall" refers to study samples unrestricted by sex or HIV transmission category.

[c] Median prevalence among all 50 US states and the District of Columbia.

[d] "Male" refers to male study samples unrestricted by HIV transmission category.

[e] Definition of hazardous alcohol consumption varied across studies (see Supplemental Table S3).

[f] On average >7 drinks per week for women, >14 drinks per week for men (each in the past year) [39].

[g] At least 12 episodes of >4 drinks in 1 day in the past year [39].

[h] >1 drink per day for women, > 2 drinks per day for men (each in the past month); median prevalence among all 50 US states, the District of Columbia, the Commonwealth of Puerto Rico, Guam, and the US Virgin Islands [52].

[i] >3 drinks during one occasion for women, >4 drinks during one occasion for men (each in the past month); median prevalence among all 50 US states, the District of Columbia, the Commonwealth of Puerto Rico, Guam, and the US Virgin Islands [52].

[j] >3 drinks in a day for women, >4 drinks in a day for men (each measured by dietary recall of the previous day) [42].

[k] Prevalence results for demographic groups with only one study that reported the cancer risk factor prevalence.

[l] The number of HPV types defined as “any type” varied across individual studies from 15 to 47; the number of HPV types defined as “high-risk” varied across studies from 11 to 22. See Supplemental Table S5 for the definition in each individual publication.

[m] Positive for any of 37 HPV types among females aged 18-59 years [44].

[n] Positive for any of 23 high-risk types among females aged 14-59 years [45].

[o] Positive for any of 37 HPV types among persons aged 14-69 years [46].

[p] Positive for any of 37 HPV types among females aged 18-59 years [44] or 14-69 years [46].

[q] Positive for any of 18 high-risk types among persons aged 14-69 years [46, 47].

[r] Defined in 69% of individual studies as positive by HCV antibody test. See Supplemental Table S6 for the definition in each individual publication.

[s] Positive by HCV antibody test among persons aged 6 years or older [48].

[t] Defined in 80% of individual studies as positive by HCV antibody and RNA tests. See Supplemental Table S6 for the definition in each individual publication.

[u] Positive by HCV antibody and RNA tests among persons aged 6 years or older [48].

[v] Defined in 72% of individual studies as positive by HBV surface antigen test. See Supplemental Table S7 for the definition in each individual publication.

[w] Positive by HBV surface antigen test among persons aged 6 years or older [49].

Table 4

Prevalence of cancer risk factors among adult persons living with HIV/AIDS (PLWHA) compared with uninfected comparison groups from the same study

Risk factor Author (Publication year) Country	Demographic group	Category	PLWHA		Uninfected		
			N	Prevalence (%)	N	Prevalence (%)	p-value
Smoking							
Beachler *et al.* (2012) US [91]	Female	Current	186	46	93	48	0.75
	MSM	Current	191	33	172	18	0.0011
Fitch *et al.* (2013) US [74]	Overall[a]	Current	166	62	152	33	<0.0001
Freiberg *et al.* (2013) US [73]	Overall[a]	Current	25,510	60	50,876	54	<0.0001
		Former	25,510	13	50,876	16	<0.0001
		Ever	25,510	73	50,876	70	<0.0001
Galli *et al.* (2012) Italy [75]	Overall[a]	Current	4,249	31	9,148	26	<0.0001
Marshall *et al.* (2011) US [100]	IDU	Current	312	84	740	86	0.48
		Former	312	10	740	9	0.83
		Ever	312	94	740	95	0.41
Sharma *et al.* (2011) US [107]	Female	Ever	245	70	219	76	0.15
Wieland *et al.* (2011) Germany [99]	MSM	Current	210	44	239[b]	22	<0.0001
Hazardous alcohol consumption							
Beachler *et al.* (2012) US [91][c]	MSM		187	8	168	12	0.21
Crystal *et al.* (2012) US [119][d]	Female		905	4	434	7	0.027
Devlin *et al.* (2012) US [109][e]	Overall		115	50	72	44	0.49
Freiberg *et al.* (2013) US [73][f]	Overall[a]		27,350	14	55,109	13	0.0004
McGinnis *et al.* (2013) US [120][g, h]	Male[i]		444	22	393	20	0.48
Morano *et al.* (2013) US [114][j]	Overall[a]		552	20	6,921	18	0.26
Overweight/Obesity							

Risk factor Author (Publication year) Country	Demographic group	Category	PLWHA		Uninfected		
			N	Prevalence (%)	N	Prevalence (%)	p-value
Bauer *et al.* (2011) US [124]	Overall[a]	Overweight/ obesity	102	44	68	59	0.06
	Female	Overweight/ obesity	43	44	35	60	0.17
	Male[i]	Overweight/ obesity	59	44	33	58	0.21
Freiberg *et al.* (2013) US [73]	Overall[a]	Obesity	26,872	14	53,539	39	<0.0001
Galli *et al.* (2012) Italy [75]	Overall[a]	Obesity	1,306	5	7,464	13	<0.0001
		Overweight	1,306	24	7,464	41	<0.0001
		Overweight/ obesity	1,306	30	7,464	54	<0.0001
Salter *et al.* (2013) US [127]	IDU	Obesity	322	18	869	23	0.055
		Overweight	322	28	869	32	0.16
		Overweight/ obesity	322	46	869	55	0.004
Human papillomavirus infection							
Beachler *et al.* (2012) US [91]	Female	Oral, any type[k]	187	35	93	18	0.0033
		Oral, high-risk[l]	187	18	93	9	0.037
	MSM	Oral, any type[k]	192	45	173	28	0.0008
		Oral, high-risk[l]	192	23	173	17	0.15
Goldstone *et al.* (2012) US [138]	Overall[a]	Anal, high-risk[m]	132	83	160	61	<0.0001
Read *et al.* (2012) Australia [134]	MSM	Oral, any type[n]	249	19	251	7	<0.0001
		Oral, high-risk[o]	249	8	251	2	0.0019
Swedish *et al.* (2011) US [139]	MSM	Anal, high-risk[m]	386	79	558	57	<0.0001
Hepatitis C virus infection							
Crystal *et al.* (2012) US [119]	Female	Chronic[p]	905	20	434	10	<0.0001
	Female IDU	Chronic[p]	246	64	74	45	0.0025

Risk factor Author (Publication year) Country	Demographic group	Category	PLWHA		Uninfected		
			N	Prevalence (%)	N	Prevalence (%)	p-value
Devlin *et al.* (2012) US [109]	Overall[a]	Chronic[p]	115	37	72	13	0.0003
Freiberg *et al.* (2013) US [73]	Overall[a]	Exposed[q]	27,350	35	55,109	16	<0.0001
Morano *et al*. (2013) US [114]	Overall[a]	Exposed[r]	601	33	7,710	7	<0.0001
	Female	Exposed[r]	214	27	3,094	7	<0.0001
	Male[i]	Exposed[r]	338	40	3,827	9	<0.0001
	IDU	Exposed[r]	239	71	996	44	<0.0001
	MSM	Exposed[r]	44	27	145	8	0.0005
Raymond *et al.* (2012) US [173]	MSM	Chronic[s]	108	16	358	1	<0.0001
	MSM IDU	Chronic[s]	35	23	42	10	0.11
Salter *et al.* (2013) US [127]	IDU	Exposed[r]	346	93	869	81	<0.0001
Sassoon *et al.* (2012) US [155][t]	Overall[a]	Exposed[r]	118	36	66	26	0.17
Sharma *et al.* (2011) US [107]	Female	Exposed[r]	245	36	219	33	0.56

Abbreviations: IDU, injection drug users; MSM, men who have sex with men.

[a] "Overall" refers to study samples unrestricted by sex or HIV transmission category.

[b] Uninfected comparison group was males, not restricted to MSM.

[c] >14 drinks per week in the past 6 months.

[d] >14 drinks per week.

[e] Kreek-McHugh-Schluger-Kellogg Scale.

[f] History of alcohol abuse or dependence, based on International Classification of Diseases, Ninth Revision (ICD-9) codes.

[g] Composite International Diagnostic Interview-Substance Abuse Module (CIDI-SAM) diagnosis of alcohol abuse or dependence in the past year or >14 drinks over any consecutive 7-day period or >4 drinks in 1 day based on 30-day Timeline Follow Back.

[h] Only included subjects who reported having at least one drink in the past year.

[i] "Male" refers to male study samples unrestricted by HIV transmission category.

[j] >1 drinks per day for women or >2 drinks per day for men in the last 30 days.

[k] Positive for any of 36 types.

[l] Positive for any of 14 high-risk types.

[m] Positive for any of 13 high-risk types.

[n] Positive for any of 37 types.

[o] Positive for any of 11 high-risk types.

[p] Hepatitis C virus (HCV) antibody positive and HCV RNA positive.

[q] HCV antibody positive or at least 1 inpatient or 2 outpatient ICD-9 code diagnoses.

[r] HCV antibody positive.

[s] HCV antibody positive with a signal-to-cutoff ratio of at least 5.

[t] 53% of PLWHA were alcoholics compared with 100% of uninfected comparison group.