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A meta-analysis of the incidence of non-AIDS cancers in HIV-infected individuals

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Abstract

Objective—To estimate summary standardized incidence ratios (SIRs) of non-AIDS cancers among HIV-infected individuals compared to general population rates overall and stratified by gender, AIDS and highly active antiretroviral therapy (HAART) era.

Design—A meta-analysis using SIRs from 18 studies of non-AIDS cancer in HIV-infected individuals.

Methods—SIRs for non-AIDS cancers in HIV-infected individuals and 95% confidence limits (CL) were abstracted from each study. Random effects meta-analyses were used to estimate summary SIRs. Modification by gender, AIDS and HAART era were estimated with meta-regression.

Results—4,797 non-AIDS cancers occurred among 625,716 HIV-infected individuals. SIRs for several cancers were elevated. In particular, cancers associated with infections, such as anal (SIR=28; 95% CL 21, 35), liver (SIR=5.6; 95% CL 4.0, 7.7) and Hodgkin lymphoma (SIR=11; 95% CL 8.8, 15), and smoking, such as lung (SIR=2.6; 95% CL 2.1, 3.1), kidney (SIR=1.7; 95% CL 1.3, 2.2) and laryngeal (SIR=1.5; 95% CL 1.1, 2.0). AIDS was associated with greater SIRs for Hodgkin lymphoma, leukemia, lung, brain and all non-AIDS cancers combined.

Conclusions—HIV-infected individuals may be at an increased risk of developing non-AIDS cancers, particularly those associated with infections and smoking. An association with advanced immune suppression was suggested for certain cancers.

Keywords

AIDS; Cancer; HIV; Meta-analysis; Epidemiology

INTRODUCTION

Kaposi's sarcoma, non-Hodgkin's lymphoma and cervical cancer incidence rates in HIV-infected individuals are significantly greater than rates in the general population[1], and are considered to be AIDS-defining illnesses by the Centers for Disease Control and Prevention[2]. However, less is known about the incidence of non-AIDS-defining cancers among those infected with HIV. Standardized incidence ratios (SIRs) comparing rates of all non-AIDS cancers combined in HIV-infected individuals to the general population have ranged from

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essentially null to almost three[3–14]. Additionally, the SIRs of specific types of non-AIDS cancers among HIV-infected individuals have been examined in several studies, though these estimates are often imprecise with a limited number of cases of each cancer site. A recent meta-analysis of incident non-AIDS cancers in HIV-infected individuals compared to the general population included seven studies and examined specific cancers[15]. The SIRs were found to be elevated among HIV-infected individuals for many cancer sites, particularly for those with a confirmed or suspected infectious etiology. Our study includes an additional six studies (not included in the prior meta-analysis) to examine SIRs from 13 studies for each cancer site, and for all non-AIDS cancers combined. We also present stratified SIRs for non-AIDS cancers to examine differences by gender, AIDS and highly active antiretroviral therapy (HAART) era.

METHODS

Search Strategy and Inclusion Criteria

Published articles were eligible for inclusion if they met two criteria. First, the article had to include a comparison of the incidence of non-AIDS cancers in HIV-infected individuals and the general population, estimated by SIR. The general population data was obtained from either a cancer registry or Surveillance Epidemiology and End Results (SEER). Second, the article had to provide data that did not overlap with other published studies. The search terms "HIV" or "AIDS," and "cancer," and "SIR" or "incidence", as well as specific cancer sites (i.e., "lung," "anal," "prostate") were used to identify potential articles in PubMed and EMBASE. Additionally, the references of articles identified as relevant were searched for studies that may have been missed. Searches were conducted between November 2007 and March 2009.

Statistical Analysis

SIRs and their 95% confidence limits (CLs) for all non-AIDS cancer sites among HIV-infected individuals compared to the general population were abstracted from each study. Some of the studies[3, 4, 6, 7, 12–14, 16–18] only reported SIRs and 95% CLs to one decimal place, perhaps limiting our ability to faithfully represent the existing evidence to a small extent by the introduction of rounding error. In three studies, SIRs were reported stratified by gender, calendar period or gender and calendar period without a combined estimate[4, 8, 10, 19], and were treated as separate stratum-specific studies in our analysis. Study-specific standard error estimates for the natural logarithm of the SIR were obtained as $\sigma_j = (\ln a_j - \ln SIR_j)/1.96$, where a_j is the upper 95% CL, respectively, and j = 1 to J indexes the studies. A funnel plot (of $1/\sigma_j^2$ by $\ln(SIR_j)$) for each cancer site was created to graphically assess the potential for publication bias. We analyzed asymmetry in the funnel plot by calculating *P*-values for the departure of the intercept from zero in a regression of $1/\sigma_j$ on $\ln(SIR_j)/\sigma_j$, as described by Egger et al.[20], and for the rank correlation between the study-specific SIRs and their variances, as described by Begg and Mazumdar[21]. Funnel plot asymmetry was also examined with Duval and Tweedie's trim and fill method[22], a simple imputation method that assumes that any asymmetry is due to publication bias. Heterogeneity between studies was examined by calculating a *P*-value for Cochran's Q, namely $\sum_{j=1}^{J}(1/\sigma_j^2)\left[\ln(SIR_j) - \ln(\bar{SIR})\right]^2$, where $\ln(\bar{SIR})$ is the inverse-variance weighted average log SIR, and is distributed as χ^2 with J-1 degrees of freedom.

We estimated a random-effects summary SIR and 95% CL for each cancer site and all non-AIDS cancers combined. Empirical Bayes estimates of each SIR were then calculated by using hierarchical shrinkage to reduce overall error[23]. Additionally, stratum-specific random effects SIRs were estimated separately for men and women, those with and without AIDS, and for the pre-HAART and HAART eras. Modifications of the SIR (ratio of SIRs and 95% CLs) by these variables were estimated in separate models by meta-regression of gender, AIDS and HAART era on the ln(SIR) using random-effects inverse-variance weighted linear regression with the among-study variance estimated by restricted maximum likelihood. Only those studies that reported estimates stratified by or restricted to one strata of gender[4, 6, 10, 12, 14, 19, 24, 25], AIDS[6, 7, 11, 14, 26] or HAART era[3–5, 8, 12, 17–19, 24] were included in stratum-specific SIRs and meta-regression models. Though mean age was reported in most of the publications, it was inconsistently reported as either the mean age of those with cancer or the mean age of the entire HIV-infected cohort, thus we were unable to include age as a covariate in meta-regression. Additionally, we were unable to include gender, AIDS and HAART era in the same model, as the studies did not provide results stratified by all three factors.

All analyses were carried out using STATA version 8.2 and all graphs were generated in SAS version 9.1.

RESULTS

Forty-two studies were identified for potential inclusion. Twenty-six studies were excluded due to their data overlapping with either a larger study or more recently published study[5, 7, 9, 12, 24–47]. One study was excluded for using comparison data from a source other than SEER or cancer registries [35], two other studies were excluded for not presenting SIRs[48, 49], and the remaining 13 were included in the overall meta-analysis. An additional five studies excluded from the overall meta-analysis were included in the stratified analyses for gender[12, 25] AIDS status[7, 26], and HAART era[5]. Though the data from these three studies overlapped with data from larger studies[4, 8, 14] these studies presented stratum-specific estimates which the original publications did not, and thus were not included in these stratum-specific meta-analyses and meta-regressions.

Of the 18 studies included in these analyses, nine were carried out in Europe[3–7, 10, 14, 16, 19], seven in the United States[8, 12, 17, 18, 24–26], one in Australia[11], and one in Uganda[13] (table 1). The mean age of study participants ranged from 28 to 48 years. Most results were for both genders combined, with men predominating (33–94%). Five studies were confined to women[10, 12, 19, 25, 49] and four to men[10, 19, 25, 49]. Data on HIV-infected individuals were obtained from AIDS registries in five studies[4, 7, 8, 10, 25], HIV/AIDS registries in six studies[3, 11, 13, 14, 24, 26], prospective cohorts in six studies[5, 6, 12, 16–18], and a hospital database in one study[19]. Three studies used SEER data to calculate the number of expected cases[12, 17, 18], and the remaining studies used data from country-specific cancer registries. All of the studies used age- and sex-specific population incidence estimates. Additionally, several studies used race-[8, 12, 17, 18, 25, 26], calendar year/period-[3–6, 8, 13, 18, 26, 33], registry-[6, 8, 26] or region-specific[10, 25, 33] incidence rates.

Funnel plot asymmetry was not indicated by visual inspection, the tests of Eggar et al. or Begg and Mazumdar, or Duval and Tweedie's trim and fill method for the majority of cancer sites (table 1). However, funnel plot asymmetry was suggested for the following cancer sites: pancreatic cancer (p-values: 0.2 and 0.05, respectively), prostate cancer (p-values: 0.1 and 0.05, respectively), rectal cancer (p-values: 0.3 and 0.05, respectively), melanoma (p-values: 0.2 and 0.07, respectively) and multiple myeloma (p-values: 0.05 and 0.05, respectively) by the tests of Eggar et al. and Begg and Mazumdar. Additionally, the trim and fill method imputed hypothetical missing results for the following cancer sites: lung, prostate, brain, multiple myeloma, pancreas, penis and small intestine. With the imputed studies included, the changes in each SIR did not change inferences. Most studies had a change in SIR of <0.4 (range: 0.06 to 0.36), with the exception of penile cancer (change in SIR: 1.68). Pronounced heterogeneity was observed in well over half of the cancer sites. For example, for all non-AIDS cancers combined this heterogeneity (Cochran's Q=115; p-value<0.001) is illustrated by the ability to find three separate estimates with no overlap among their 95% confidence intervals (e.g., the estimate for women on HAART from Herida et al.[19] and the estimates for both genders combined from Grulich et al.[11] and Clifford et al.[6]).

In over one million person-years of follow-up from the 13 studies, a total of 4,797 non-AIDS cancer cases were identified for inclusion in the overall meta-analysis. The most frequently observed non-AIDS cancer type was lung cancer (n=847), followed by Hodgkin lymphoma (n=643), and anal cancer (n=254). Many types of cancer were found to be substantially elevated among HIV-infected individuals when compared to the general population (table 2). In particular, many cancers associated with infections were observed to be elevated among HIV-infected individuals, including cancers of the anus (SIR=28; 95% CL 21, 35), oropharynx (SIR=1.9; 95% CL 1.4, 2.6), liver (SIR=5.6; 95% CL 4.0, 7.7), stomach (SIR=1.7; 95% CL 1.2, 2.5), and Hodgkin lymphoma (SIR=11; 95% CL 8.8, 15). The incidence rates of certain, but not all, cancers associated with cigarette smoking, such as lung (SIR=2.6; 95% CL 2.1, 3.1), kidney (SIR=1.7; 95% CL 1.3, 2.2) and laryngeal cancers (SIR=1.5; 95% CL 1.1, 2.0) were also observed to be elevated among HIV-infected individuals. Additionally, HIV-infected individuals were observed to have substantially lower rates of breast (SIR=0.74; 95% CL 0.56, 0.97) and prostate (SIR=0.69; 95% CL 0.55, 0.86) cancers, when compared to the general population. Overall, twice as many non-AIDS cancers were observed among those who were HIV-infected, compared to the general population (SIR=2.0; 95% CL 1.8, 2.2).

When the ln(SIRs) for each cancer site were regressed on gender, the SIRs for lung cancer (ratio of SIRs: 0.54; 95% CL 0.27, 1.1), kidney cancer (ratio of SIRs: 0.41; 95% CL 0.17, 1.01), laryngeal cancer (ratio of SIRs: 0.26; 95% CL 0.11, 0.58), leukemia (ratio of SIRs: 0.43, 95% CL 0.20, 0.92) and multiple myeloma (ratio of SIRs: 0.38; 95% CL 0.18, 0.80) appeared to be less elevated among men than women (figure 1; appendix 2). However, the SIRs for all non-AIDS cancers combined (ratio of SIRs: 1.59; 95% CL 1.23, 2.06) was greater among men than women.

When ln(SIRs) were regressed on AIDS status, relative to those without AIDS, those with AIDS had dramatically increased SIRs for leukemia (ratio of SIRs: 8.02; 95% CI 3.52, 18.25) and brain cancer (ratio of SIRs: 4.86; 95% CI 1.22, 19.34) (figure 2; appendix 3). Those with AIDS were observed to have three times the SIR of Hodgkin lymphoma (ratio of SIRs: 2.77; 95% CL 1.43, 5.37), lung cancer (ratio of SIRs: 3.01; 95% CL 1.69, 5.38), and all non-AIDS cancers combined (ratio of SIRs: 3.17; 95% CL 1.42, 7.09), when compared to those without AIDS. The SIRs for liver and laryngeal cancers also appeared to be more elevated among those with AIDS than among those without AIDS. No difference was seen in SIRs by AIDS status for anal cancer, non-melanoma skin cancer, melanoma, pancreatic cancer, or prostate cancer. The AIDS case definition in the U.S. varies from the AIDS case definitions in Europe and Australia, thus we examined the results stratified by AIDS with and without the U.S. study[26]. As the stratified results were similar regardless of whether the U.S. study was included, only the results including this study were presented.

Finally, when ln(SIRs) were regressed on HAART era, the SIRs for kidney cancer (ratio of SIRs: 1.56, 95% CL 0.96, 2.54) and breast cancer (ratio of SIRs: 1.48; 95% CL 0.98, 2.23) were observed to be increased in the HAART era compared to the pre-HAART era (figure 3; appendix 4). The SIRs did not appear to be different for the remaining cancer sites by HAART era, including for all non-AIDS cancers combined (ratio of SIRs: 0.94; 95% CL 0.59, 1.49).

DISCUSSION

We combined data from 18 studies (13 studies in overall meta-analysis, and 5 additional studies included in stratified analyses) to estimate the relative incidence of specific non-AIDS cancers among HIV-infected individuals, compared to the general population. HIV-infected individuals had twice the risk of a non-AIDS cancer than the general population. SIRs for all non-AIDS cancers were greater among men than women and among those with AIDS than those without AIDS; however, no substantial difference was observed by HAART era. The random-effects SIRs showed a substantial increase in the incidence rate of many individual cancer sites among those with HIV when compared to the general population. Additionally, the SIRs for certain cancers seemed to be modified by gender, AIDS and HAART era. These differences do not by themselves imply that the incidence rate of specific cancers is different by gender, or HAART era, as the reference group of general population non-AIDS cancer incidence may differ in these strata.

Though the body of research supporting an increased risk of non-AIDS cancers among HIV-infected individuals continues to expand, explanations for this increase have not yet been well-elucidated. HIV-associated immune suppression may increase susceptibility to cancers that are caused by oncogenic viruses. Indeed, we observed the greatest SIRs to be in cancer sites that have an infectious etiology. Anal, vaginal, penile, nasopharyngeal, laryngeal and oral cancers are all associated with infection with human papillomavirus (HPV), and were all found to occur at a greater rate among those infected with HIV than in the general population. Additionally, liver cancer is associated with hepatitis B (HBV) and hepatitis C (HCV) virus, and nasopharyngeal cancer and Hodgkin lymphoma are both associated with Epstein-Barr virus (EBV); the incidence rates for these three cancer sites were all substantially higher in those with HIV than in the general population. HIV-infected persons may be disproportionately infected with oncogenic viruses. For example, in a study of homosexual men, HIV-infected men were found to have 1.5 times the risk of anal HPV infection as HIV-uninfected men[50], and in a study of women at high risk for HIV, HIV-infected women were found to have 1.8 times the risk of anal HPV infection as HIV-uninfected women[51]. Conversely, several cancers without strong evidence for an infectious etiology, such as colorectal and pancreatic cancers, had summary SIRs that were near null. Decreased immune function paired with increased incidence of these infections may be responsible for the increased rates of virally-associated cancers among those infected with HIV. The association between decreased immune function and increased risk of anal cancer, Hodgkin lymphoma and liver cancer is further supported by our observation that the SIRs of these cancers were increased among those with AIDS compared to those without AIDS. Furthermore, rates of anal cancer, Hodgkin lymphoma, and liver cancer, as well as other cancers associated with oncogenic viruses have been found to be elevated among organ transplant recipients, providing support for the role of suppressed immunity in their etiology[15].

HIV-infected individuals may also have a higher prevalence of other cancer risk factors (e.g., cigarette smoking) than the general population. One study reported the prevalence of cigarette smoking to be 59% among persons with HIV/AIDS in New York State, which is three times the prevalence in the general population[52]. Another study reported the prevalence of smoking among all participants of the Swiss HIV Cohort Study to be 72%, and as high as 96% among injection drug users in the cohort[38]. We observed elevated summary SIRs for several smoking-related cancers, including lung, kidney, stomach, laryngeal and oral cancers. While some studies suggest that the increased risk of lung cancer among HIV-infected individuals is likely explained by differences in smoking[6, 12], other studies have shown an increase in lung cancer, even after accounting for differences in smoking[40, 53]. The SIRs for most smoking-related cancers (lung, kidney, laryngeal, and stomach cancers) were observed to be greater among women than men. Perhaps the greater SIR observed among women is due to a greater relative increase in smoking among HIV-infected women compared to the general population compared to HIV-infected men, though we did not have data to examine the prevalence of cigarette smoking among men and women in each study. Interestingly, the SIR for lung cancer was observed to be greater among those with AIDS than those without AIDS, suggesting that immune suppression may play a role in the development of lung cancer among those who are

HIV-infected. It has been hypothesized that HIV-associated suppression of the immune system may lead to reduced tumor surveillance, allowing tumors of the lung to continue to develop when they otherwise would be destroyed by the immune system[54, 55].

We observed the incidence of breast and prostate cancer to be lower among HIV-infected women and men compared to the general population. This may suggest a potential protective effect of HIV on the development of these cancers, perhaps through changes in hormone levels[42]. However, the decreased incidence of these cancers among HIV-infected individuals may also be due to differential screening by HIV status[27, 42]. Those with HIV, particularly injection drug users and the poor, may be less likely to be regularly screened for cancers. For example, the Women's Interagency HIV Study found women with HIV and at high risk for HIV were significantly less likely to have a mammogram than women in the general U.S. population[56]. Therefore, more sub-clinical disease may be detected among those without HIV, which would result in an increased incidence.

Our analyses were limited to the information provided by each of the included studies. We were unable to look at other factors that may modify the association between HIV and non-cancer AIDS, such as age, likely route of transmission, smoking status, or race/ethnicity. We observed notable between-study heterogeneity; this heterogeneity may be due to differences in study design, populations studied, or in unmeasured characteristics that may vary across studies. Indeed, it is likely that one or more of these factors explains a portion of the observed between-study heterogeneity. Additionally, we observed departures in symmetry for the funnel plots of a few cancer sites, which may be due to publication bias.

The use of general population comparisons is a limitation of the literature, and thus of our review of that literature. In occupational epidemiology, such external comparisons with general populations are generally considered inferior to internal comparisons within employed populations. The biases have been grouped under such rubrics as the "healthy worker" and "healthy worker survivor" biases. The analog of internal comparisons in occupational studies would be to compare HIV-infected individuals with and without AIDS directly, or to compare HIV-infected men and women directly, rather than to compare the comparisons with the general population.

Another limitation is the examination of effect-measure modification for ratio effect measures. It may have been preferable to examine modification of rate differences[57]. Fortunately, the indications are of a greater elevation of rate ratios in groups with higher baseline rates (HIV-infected men and AIDS patients). In this case, positive rate ratio modification implies positive rate difference modification.

Finally, for some cancer sites, our meta-analyses were based on very few cases from few studies. Summary SIRs for nasopharyngeal, eye, bone, small intestine and gall bladder cancers were all based on 10 cases or fewer, and summary SIRs for nasopharyngeal, eye, small intestine, lip, oral and pharyngeal, oropharyngeal, gall bladder and rectal cancers were based on results from only two or three studies. Thus, the estimates for these cancer sites are particularly imprecise.

This work expands upon a previous meta-analysis that presented summary SIRs for non-AIDS cancers among HIV-infected individuals[15]. In addition to the seven studies included in the prior meta-analysis, we included six studies that have presented SIRs for non-AIDS cancers. Additionally, our study differs from the prior meta-analysis in that we examined whether SIRs differed by gender, AIDS status and HAART era, while the previous study did not. These stratified analyses highlight differences in SIRs of non-AIDS cancers, relative to the general population, that may be associated with gender, immune suppression and HAART use.

This study found an increased general-population SIR for many types of non-AIDS cancers. It remains unclear whether HIV-infected individuals are truly at a greater risk for non-AIDS-defining cancers, or if confounding by unadjusted cancer risk factors may be responsible for the apparent elevated incidence. Future pooling projects (rather than meta-analyses) that compare HIV-infected to HIV-uninfected individuals will be better able to elucidate the effect of HIV infection on the development of non-AIDS cancers.

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Appendix

Appendix 1

SIRs and (95% confidence limit)s for each study included in the overall meta-analysis.

	Oropharynx	Lip, oral & pharynx	Nasopharynx	Head & neck	Esophagus	Stomach	Small Intestine	Colon	Rectum
Cooksley	---	---		---	---	---	---	0.9 (0.4, 1.5)	---
Grulich	2.74 (0.33, 9.89)	---	---	---	2.11 (0.43, 6.16)	0.61 (0.07, 2.2)	2.69 (0.07, 15.0)	0.33 (0.07, 0.96)	0.64 (0.17, 1.64)
Herida (men/1996–99)	---	0.93 (0.61, 1.36)	---	---	0.58 (0.19, 1.35)	1.19 (0.51, 2.35)	---	---	---
Herida (men/1992–95)	---	2.82 (2.05, 3.78)	---	---	0.22 (0, 1.22)	4.81 (2.85, 7.61)	---	---	---
Herida (women/1996–99)	---	---	---	---	---	1.49 (0.02, 8.30)	---	---	---
Herida (women/1992–95)	---	---	---	---	7.14 (0.09, 39.74)	11.43 (3.07, 29.26)	---	---	---
Dal Maso	---	---	---	---	---	2.2 (1.0, 4.4)	---	0.9 (0.2, 2.5)	2.3 (0.7, 5.4)
Allardice	---	---	---	1.6 (0.04, 8.8)	---	2.9 (0.07, 15.9)	---	---	---
Clifford	---	4.1 (2.1, 7.4)	---	---	---	1.7 (0.2, 6.4)	---	---	---
Newnham	1.1 (0.4, 2.3)	---	5.0 (1.4, 12.8)	---	---	0.4 (0.1, 1.5)	3.4 (0.4, 12.4)	---	---
Mbulaiteye	---	---	4.2 (0.8, 12)	---	1.6 (0.2, 5.6)	1.5 (0, 8.2)	---	---	---
Engels (1980–1989)	1.2 (0.5, 2.3)	---	---	---	0.4 (0, 2.5)	1.2 (0.3, 3.2)	---	---	---
Engels (1990–1995)	2.4 (1.8, 3.1)	---	---	---	1.5 (0.8, 2.5)	0.9 (0.5, 1.6)	1.8 (0.5, 4.7)	---	---
Engels (1996–2002)	2.1 (1.4, 3.0)	---	---	---	1.9 (0.9, 3.5)	1.8 (1.0, 3.0)	1.9 (0.4, 5.5)	---	---
Galceran (men)	---	---	---	---	---	---	---	---	---
Galceran (women)	---	---	---	---	---	---	---	---	---
Serraino	---	---	---	1.2 (0.6, 2.1)	---	1.8 (0.5, 4.5)	---	0.3 (0, 1.6)	---
Patel	---	---	---	---	1.8 (0.8, 3.5)	1.3 (0.6, 2.4)	---	---	---
Long	---	---	---	5.1 (2.8, 8.6)	5.2 (1.1, 15.1)	2.4 (0.3, 8.8)	---	---	---
Dal Maso (1986–1996)	---	---	---	1.4 (0.5, 3.0)	---	1.9 (0.7, 4.1)	---	0.5 (0, 1.9)	2.5 (0.8, 5.9)
Dal Maso (1997–2004)	---	---	---	1.8 (0.2, 9.1)	2.5 (0.2, 9.1)	1.6 (0.6, 3.4)	---	1.4 (0.7, 2.7)	2.3 (0.9, 4.7)

	Colorectal	Anus	Liver	Gall Bladder	Pancreas	Larynx	Lung	Bone	Melanoma
Cooksley	---	---	---	---	---	0.9 (0.3, 2.4)	0.7 (0.4, 1.1)	---	0.6 (0.2, 1.3)
Grulich	---	37.1 (17.8, 68.3)	2.72 (0.56, 7.94)	1.60 (0.04, 8.91)	1.55 (0.32, 4.52)	0.6 (0.02, 3.34)	1.44 (0.84, 2.30)	---	1.34 (0.93, 1.86)
Herida (men/1996–99)	---	---	---	---	---	1.00 (0.46, 1.90)	2.12 (1.67, 2.65)	---	1.10 (0.44, 2.27)
Herida (men/1992–95)	---	---	---	---	---	0.83 (0.22, 2.12)	1.13 (0.71, 1.72)	---	2.01 (0.86, 3.95)
Herida (women/1996–99)	---	---	---	---	---	---	6.59 (3.40, 11.52)	---	0.63 (0.07, 2.29)
Herida (women/1992–95)	---	---	---	---	---	---	1.08 (0.01, 5.98)	---	1.07 (0.12, 3.86)
Allardice	---	---	22.0 (2.7, 80.2)	---	---	---	4.1 (1.3, 9.5)	9.1 (0.23, 50.5)	---
Clifford	---	33.4 (10.5, 78.6)	7.0 (2.2, 16.5)	---	2.7 (0.3, 9.9)	---	3.2 (1.7, 5.4)	---	1.1 (0.3, 2.8)
Newnham	0.9 (0.5, 1.5)	23.1 (13.7, 36.5)	5.6 (3.0, 9.6)	---	0.8 (0.2, 2.3)	2.0 (0.7, 4.8)	2.2 (1.6, 3.1)	0.9 (0.02, 4.9)	0.2 (0.02, 0.6)
Mbulaiteye	---	---	2.1 (0.4, 6.0)	---	---	---	5.0 (1.0, 15)	8.8 (1.0, 32)	---

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	Colorectal	Anus	Liver	Gall Bladder	Pancreas	Larynx	Lung	Bone	Melanoma
Engels (1980–1989)	0.9 (0.4, 1.6)	18.3 (9.1, 32.7)	2.4 (0.5, 7.1)	---	0.8 (0.1, 3.0)	1.7 (0.5, 3.9)	2.5 (1.9, 3.3)	1.8 (0, 9.8)	1.2 (0.5, 2.3)
Engels (1990–1995)	0.8 (0.5, 1.1)	20.7 (15.5, 27.0)	4.0 (2.6, 5.8)	---	0.6 (0.2, 1.4)	1.7 (1.0, 2.8)	3.3 (2.9, 3.8)	1 (0.1, 3.6)	1.2 (0.8, 1.8)
Engels (1996–2002)	1.0 (0.7, 1.4)	19.6 (14.2, 26.4)	3.3 (2.0, 5.1)	---	0.7 (0.2, 1.7)	2.7 (1.6, 4.4)	2.6 (2.1, 3.1)	---	1.0 (0.5, 1.8)
Galceran (men)	---	---	13.13 (1.24, 48.30)	---	---	---	3.88 (1.01, 10.02)	---	---
Galceran (women)	---	---	---	---	---	---	---	---	---
Serraino	---	33 (11, 76)	9.4 (4.7, 16.9)	---	2.3 (0.3, 8.3)	---	1.7 (0.9, 2.8)	---	1.2 (0.1, 4.2)
Patel	2.3 (1.8, 2.9)	42.9 (34.1, 53.3)	7.7 (5.7, 10.1)	---	0.8 (0.3, 1.8)	---	3.3 (2.8, 3.9)	---	2.6 (1.9, 3.6)
Long	0.5 (0.1, 1.9)	39.0 (18.7, 71.7)	16.5 (8.8, 28.2)	---	1.0 (0.03, 5.7)	---	5.5 (3.7, 8.0)	---	4.0 (1.1, 10.1)
Dal Maso (1986–1996)	---	35.5 (12.8, 77.7)	2.1 (0.4, 6.4)	---	1.7 (0.2, 6.3)	---	2.1 (1.2, 3.3)	2.5 (0, 14.0)	0.9 (0.2, 2.6)
Dal Maso (1997–2004)	---	44.0 (21.8, 78.9)	6.4 (3.7, 10.5)	3.9 (0.4, 14.5)	1.1 (0.1, 4.1)	---	4.1 (2.9, 5.5)	2.6 (0, 14.6)	0.6 (0.1, 1.7)

	Skin (non-melanoma)	Female breast	Uterus	Ovary	Vagina	Penis	Prostate	Testis	Kidney
Cooksley	6.4 (4.4, 8.9)	---	---	---	---	---	---	---	---
Grulich	4.17 (0.50, 15.1)	1.13 (0.23, 3.30)	---	3.26 (0.08, 18.2)	---	---	1.06 (0.53, 1.90)	1.46 (0.70, 2.69)	0.79 (0.16, 2.31)
Herida (men/1996–99)	---	---	0.48 (0.01, 2.69)	---	---	---	0.52 (0.21, 1.08)	---	2.18 (1.16, 3.74)
Herida (men/1992–95)	---	---	---	---	---	---	0.30 (0.03, 1.07)	---	0.95 (0.19, 2.77)
Herida (women/1996–99)	---	0.43 (0.24, 0.73)	---	0.9 (0.10, 3.27)	---	---	---	---	---
Herida (women/1992–95)	---	0.25 (0.07, 0.65)	3.03 (0.61, 8.85)	---	---	---	---	---	2.86 (0.04, 15.09)
Dal Maso	1.5 (0.8, 2.5)	0.7 (0.1, 2.0)	---	4.4 (0.8, 13.2)	---	---	1.2 (0.1, 4.3)	1.1 (0.3, 2.8)	1.1 (0.2, 3.2)
Allardice	2.8 (1.04, 6.2)	---	---	---	---	---	---	0.7 (0.02, 3.75)	---
Clifford	3.2 (2.2, 4.5)	1.4 (0.5, 3.4)	---	---	---	---	1.4 (0.3, 4.3)	1.6 (0.6, 3.5)	2.0 (0.2, 7.5)
Newnham	19.6 (15.3, 24.8)	0.8 (0.4, 1.4)	---	1.0 (0.1, 3.7)	---	3.9 (0.8, 11.5)	0.9 (0.3, 2.0)	1.1 (0.6, 1.7)	1.1 (0.4, 2.5)
Mbulaiteye	4.9 (1.0, 14)	1.9 (0.8, 3.7)	5.5 (1.5, 14)	3.3 (0.9, 8.5)	10 (0.1, 57)	---	2.9 (0.3, 11)	25 (0.3, 140)	16 (1.8, 58)
Engels (1980–1989)	---	---	---	1.9 (0, 10.4)	---	---	0.9 (0.4, 1.8)	2 (1, 3.5)	1.6 (0.6, 3.5)
Engels (1990–1995)	---	0.4 (0.2, 0.6)	0.7 (0.1, 2.1)	0.5 (0.1, 1.9)	4.2 (0.9, 12.3)	5.6 (1.8, 13.1)	0.5 (0.4, 0.7)	1.5 (0.9, 2.2)	1.2 (0.7, 1.9)
Engels (1996–2002)	---	0.8 (0.5, 1.2)	0.5 (0.1, 1.7)	0.3 (0, 1.9)	4.4 (0.9, 12.8)	8 (2.2, 20.6)	0.5 (0.4, 0.7)	0.7 (0.2, 1.6)	1.8 (1.1, 2.8)
Galceran (men)	1.4 (0.13, 5.15)	---	---	---	---	---	---	---	---
Galceran (women)	---	---	---	---	---	---	---	---	---
Serraino	---	0.8 (0.3, 1.9)	---	---	---	---	---	---	---
Patel	---	0.9 (0.6, 1.3)	---	---	21.0 (11.2, 35.9)	---	0.6 (0.4, 0.8)	1.6 (0.9, 2.7)	1.8 (1.1, 2.7)
Long	---	0.6 (0.1, 1.8)	---	---	---	24.2 (0.6, 134.7)	0.6 (0.2, 1.5)	---	2.9 (1.0, 6.8)
Dal Maso (1986–1996)	2.1 (1.2, 3.3)	0.8 (0.1, 2.2)	---	1.7 (0, 9.7)	24.6 (2.3, 90.6)	---	1.3 (0.1, 4.7)	1.4 (0.5, 3.4)	1.2 (0.2, 3.6)
Dal Maso (1997–2004)	1.8 (1.2, 2.6)	0.6 (0.2, 1.4)	1.5 (0, 8.3)	---	24.3 (4.6, 71.8)	---	---	0.7 (0.1, 2.5)	0.7 (0.1, 2.2)

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	Bladder	Eye	Brain	Thyroid	Hodgkin Lymphoma	Multiple Myeloma	Leukemia	All non-AIDS cancers
Cooksley	---	---	---	---	5.6 (3.6, 8.4)	1.4 (0.3, 4.4)	1.4 (0.6, 2.7)	---
Grulich	1.06 (0.29, 2.71)	1.73 (0.04, 9.64)	1.82 (0.73, 3.75)	0.56 (0.01, 3.12)	7.85 (4.40, 13.0)	4.15 (1.34, 9.67)	3.38 (1.80, 5.78)	1.63 (1.42, 1.87)
Herida (men/1996–99)	0.63 (0.23, 1.36)	---	1.05 (0.54, 2.24)	---	31.66 (25.79, 38.47)	---	---	1.91 (1.71, 2.13)
Herida (men/1992–95)	1.19 (0.43, 2.58)	---	2.97 (1.62, 4.98)	---	22.75 (17.27, 29.40)	---	---	2.36 (2.09, 2.69)
Herida (women/1996–99)	2.33 (0.03, 12.94)	---	1.71 (0.34, 5.01)	---	14.29 (6.84, 26.27)	---	---	1.06 (0.81, 1.37)
Herida (women/1992–95)	4.55 (0.06, 25.29)	---	3.92 (1.06, 10.04)	---	9.62 (3.10, 22.44)	---	---	1.19 (0.83, 1.67)
Dal Maso	0.4 (0, 1.5)	---	4.4 (2.2, 8.0)	---	16.2 (11.8, 21.7)	4.8 (0.9, 14.3)	5.3 (2.8, 9.2)	2.3 (2.0, 2.7)
Allardice	4.2 (0.5, 15.0)	---	3.3 (0.4, 12.0)	---	3.6 (0.4, 13.1)	---	2.2 (0.06, 12.4)	1.8 (1.1, 2.6)
Clifford	---	---	2.9 (0.8, 7.6)	2.9 (0.6, 8.7)	17.3 (10.2, 27.4)	5.5 (0.5, 20.4)	1.8 (0.2, 6.7)	2.8 (2.3, 3.3)
Newnham	0.5 (0.1, 1.5)	---	1.0 (0.4, 1.8)	0.4 (0.01, 2.3)	5.6 (4.0, 7.7)	2.7 (1.0, 5.9)	2.5 (1.5, 3.9)	2.5 (2.3, 2.8)
Mbulaiteye	---	3.7 (1.3, 8.0)	4.4 (0.1, 24)	5.7 (1.1, 16)	5.7 (1.2, 17)	8.5 (0.1, 47)	15 (0.2, 80)	2.8 (2.1, 3.6)
Engels (1980–1989)	---	---	3.7 (2, 6.4)	1.9 (0.5, 4.7)	7 (4.5, 10.4)	2.7 (0.7, 7.0)	---	2.0 (1.7, 2.3)
Engels (1990–1995)	0.7 (0.3, 1.3)	---	0.4 (0.1, 0.9)	0.3 (0.1, 0.9)	8.1 (6.4, 10.1)	2.2 (1.2, 3.6)	---	1.8 (1.7, 1.9)
Engels (1996–2002)	---	---	0.5 (0.1, 1.5)	0.5 (0.1, 1.4)	13.6 (10.6, 17.1)	2.2 (1.1, 3.9)	---	1.7 (1.6, 1.9)
Galceran (men)	---	---	---	---	28.44 (10.23, 62.30)	---	---	2.32 (1.40, 3.63)
Galceran (women)	---	---	---	---	---	---	---	1.79 (0.34, 5.29)
Serraino	0.7 (0.1, 2.4)	---	1.7 (0.4, 5.1)	---	10.8 (6.4, 17.0)	---	1.7 (0.4, 5.1)	---
Patel	0.5 (0.2, 1.1)	---	---	0.6 (0.2, 1.5)	14.7 (11.6, 18.2)	1.4 (0.6, 2.9)	2.5 (1.6, 3.8)	---
Long	4.1 (1.1, 10.5)	---	---	---	9.8 (4.2, 19.2)	3.0 (0.4, 10.7)	---	---
Dal Maso (1986–1996)	0.7 (0.1, 2.0)	---	3.5 (1.5, 7.0)	---	18.0 (13.2, 23.9)	5.5 (1.0, 16.4)	4.9 (2.4, 8.8)	2.4 (2.0, 2.8)
Dal Maso (1997–2004)	0.3 (0, 1.2)	---	3.2 (1.4, 6.3)	---	20.7 (14.6, 28.5)	3.9 (1.0, 10.0)	1.1 (0.2, 3.3)	2.2 (1.9, 2.5)

Appendix

Appendix 2

Random effects SIRs and ratio of SIRs by sex for non-AIDS cancers among HIV-infected individuals compared to the general population.

		Number of Studies	SIR	95% CL
Anus	Men	4	32	(22, 46)
	Women	3	24	(12, 48)
	Ratio of SIRs		1.33	(0.60, 2.97)
Skin Cancer	Men	5	5.7	(2.5, 13)
	Women	4	3.9	(2.0, 7.7)
	Ratio of SIRs		1.45	(0.39, 5.46)
Hodgkin Lymphoma	Men	7	15	(8.3, 26)
	Women	6	8.4	(4.8, 15)
	Ratio of SIRs		1.79	(0.83, 3.88)
Stomach	Men	4	1.3	(0.55, 3.2)
	Women	3	3.8	(1.2, 12)
	Ratio of SIRs		0.35	(0.09, 1.34)
Lung	Men	7	1.9	(1.4, 2.7)
	Women	6	3.8	(2.5, 5.9)
	Ratio of SIRs		0.54	(0.27, 1.1)
Kidney	Men	4	1.2	(0.75, 1.9)

		Number of Studies	SIR	95% CL
	Women	4	3.0	(1.3, 6.7)
	Ratio of SIRs		0.41	(0.17, 1.01)
Leukemia	Men	4	1.5	(0.88, 2.7)
	Women	4	3.8	(2.5, 5.7)
	Ratio of SIRs		0.43	(0.20, 0.92)
Larynx	Men	4	1.2	(0.84, 1.8)
	Women	2	4.9	(2.5, 9.5)
	Ratio of SIRs		0.26	(0.11, 0.58)
Melanoma	Men	5	1.1	(0.68, 1.7)
	Women	3	1.3	(0.62, 2.6)
	Ratio of SIRs		0.84	(0.36, 1.99)
Brain	Men	4	1.8	(1.2, 2.8)
	Women	3	2.7	(1.7, 4.4)
	Ratio of SIRs		0.66	(0.33, 1.33)
Multiple Myeloma	Men	4	2.2	(1.4, 3.2)
	Women	2	5.6	(2.9, 11)
	Ratio of SIRs		0.38	(0.18, 0.80)
Thyroid	Men	2	1.9	(0.31, 12)
	Women	3	0.96	(0.51, 1.8)
	Ratio of SIRs		2.31	(0.69, 7.69)
Colon	Men	3	0.71	(0.55, 0.91)
	Women	2	1.5	(0.24, 9.9)
	Ratio of SIRs		0.47	(0.23, 0.94)
All non-AIDS cancers	Men	6	2.3	(2.0, 2.7)
	Women	7	1.5	(1.1, 1.8)
	Ratio of SIRs		1.59	(1.23, 2.06)

Appendix

Appendix 3

Random effects SIRs and ratio of SIRs by AIDS status for non-AIDS cancers among HIV-infected individuals compared to the general population.

		Number of Studies	SIR	95% CL
Anus	No AIDS	5	20	(10, 38)
	AIDS	4	31	(19, 52)
	Ratio of SIRs		1.61	(0.65, 4.02)
Skin Cancer	No AIDS	3	2.9	(1.4, 5.8)
	AIDS	3	6.6	(0.40, 108)
	Ratio of SIRs		2.77	(0.20, 37.71)
Hodgkin Lymphoma	No AIDS	4	5.9	(3.3, 10)
	AIDS	5	16	(12, 21)
	Ratio of SIRs		2.77	(1.43, 5.37)
Liver	No AIDS	2	3.9	(2.6, 5.6)
	AIDS	5	6.5	(3.6, 12)
	Ratio of SIRs		1.67	(0.82, 3.42)
Lung	No AIDS	5	1.5	(0.82, 2.6)
	AIDS	5	5.1	(4.0, 6.4)
	Ratio of SIRs		3.01	(1.69, 5.38)
Leukemia	No AIDS	3	0.9	(0.48, 1.9)
	AIDS	3	7.5	(4.7, 12)
	Ratio of SIRs		8.02	(3.52, 18.25)
Larynx	No AIDS	2	2.1	(1.3, 3.6)
	AIDS	3	3.6	(1.7, 7.6)
	Ratio of SIRs		1.70	(0.69, 4.18)
Pancreas	No AIDS	2	1.0	(0.14, 7.2)
	AIDS	3	2.2	(0.92, 5.4)
	Ratio of SIRs		1.13	(0.41, 3.15)
Prostate	No AIDS	2	1.1	(0.57, 2.0)
	AIDS	2	1.4	(0.27, 6.8)
	Ratio of SIRs		1.29	(0.33, 5.09)
Melanoma	No AIDS	2	0.39	(0.04, 4.1)
	AIDS	2	0.44	(0.12, 1.7)
	Ratio of SIRs		0.99	(0.07, 13.56)
Brain	No AIDS	2	0.8	(0.27, 2.4)
	AIDS	2	3.9	(1.6, 9.6)
	Ratio of SIRs		4.86	(1.22, 19.34)

		Number of Studies	SIR	95% CL
All non-AIDS cancers	No AIDS	4	1.2	(0.66, 2.0)
	AIDS	4	3.7	(2.0, 6.8)
	Ratio of SIRs		3.17	(1.42, 7.09)

Appendix

Appendix 4

Random effects SIRs and ratio of SIRs by HAART era for non-AIDS cancers among HIV-infected individuals compared to the general population.

		Number of studies	SIR	95% CL
Anus	Pre-HAART Era	4	37	(19, 75)
	HAART Era	5	47	(22, 100)
	Ratio of SIRs		1.25	(0.48, 6.49)
Head and Neck	Pre-HAART Era	3	1.6	(0.91, 2.9)
	HAART Era	3	2.5	(1.1, 5.6)
	Ratio of SIRs		1.54	(0.56, 4.29)
Hodgkin Lymphoma	Pre-HAART Era	7	9.7	(6.2, 15)
	HAART Era	6	19	(13, 27)
	Ratio of SIRs		1.90	(1.11, 3.27)
Liver	Pre-HAART Era	4	6.0	(2.8, 13)
	HAART Era	5	7.5	(4.2, 14)
	Ratio of SIRs		1.25	(0.49, 3.24)
Stomach	Pre-HAART Era	4	3.0	(1.2, 7.5)
	HAART Era	4	1.6	(1.1, 2.3)
	Ratio of SIRs		0.55	(0.21, 1.44)
Lung	Pre-HAART Era	6	2.0	(1.2, 3.3)
	HAART Era	6	3.5	(2.6, 4.6)
	Ratio of SIRs		1.78	(0.99, 3.22)
Kidney	Pre-HAART Era	3	1.2	(0.81, 1.8)
	HAART Era	4	1.9	(1.3, 2.8)
	Ratio of SIRs		1.56	(0.96, 2.54)
Larynx	Pre-HAART Era	3	1.3	(0.78, 2.1)
	HAART Era	2	1.7	(0.64, 4.4)
	Ratio of SIRs		1.45	(0.54, 3.92)
Esophagus	Pre-HAART Era	2	1.4	(0.30, 6.1)
	HAART Era	4	1.8	(0.77, 4.4)
	Ratio of SIRs		1.38	(0.26, 7.46)
Bladder	Pre-HAART Era	4	1.3	(0.66, 2.6)
	HAART Era	3	1.2	(0.35, 3.8)
	Ratio of SIRs		0.82	(0.22, 3.11)
Colorectal	Pre-HAART Era	2	1.4	(0.46, 4.3)
	HAART Era	3	1.2	(0.63, 2.2)
	Ratio of SIRs		0.82	(0.25, 2.75)
Prostate	Pre-HAART Era	4	0.49	(0.32, 0.75)
	HAART Era	5	0.56	(0.44, 0.72)
	Ratio of SIRs		1.14	(0.77, 1.69)
Melanoma	Pre-HAART Era	5	1.2	(0.86, 1.6)
	HAART Era	6	1.5	(0.90, 2.4)
	Ratio of SIRs		1.29	(0.71, 2.32)
Breast	Pre-HAART Era	5	0.43	(0.31, 0.59)
	HAART Era	6	0.64	(0.50, 0.82)
	Ratio of SIRs		1.48	(0.98, 2.23)
Testis	Pre-HAART Era	4	1.4	(1.0, 1.9)
	HAART Era	3	1.0	(0.49, 2.2)
	Ratio of SIRs		0.74	(0.39, 1.32)
Brain	Pre-HAART Era	3	1.9	(0.66, 5.7)
	HAART Era	3	1.0	(0.63, 1.7)
	Ratio of SIRs		0.56	(0.16, 1.91)
Multiple Myeloma	Pre-HAART Era	3	2.5	(1.3, 4.6)
	HAART Era	3	2.6	(1.7, 4.1)
	Ratio of SIRs		1.11	(0.60, 2.05)
Uterus	Pre-HAART Era	2	1.5	(0.35, 6.2)
	HAART Era	3	0.65	(0.28, 1.5)
	Ratio of SIRs		0.46	(0.10, 2.03)
All non-AIDS cancers	Pre-HAART Era	4	1.9	(1.6, 2.4)
	HAART Era	3	1.7	(1.4, 2.1)

	Number of studies	SIR	95% CL
Ratio of SIRs		0.89	(0.62, 1.28)

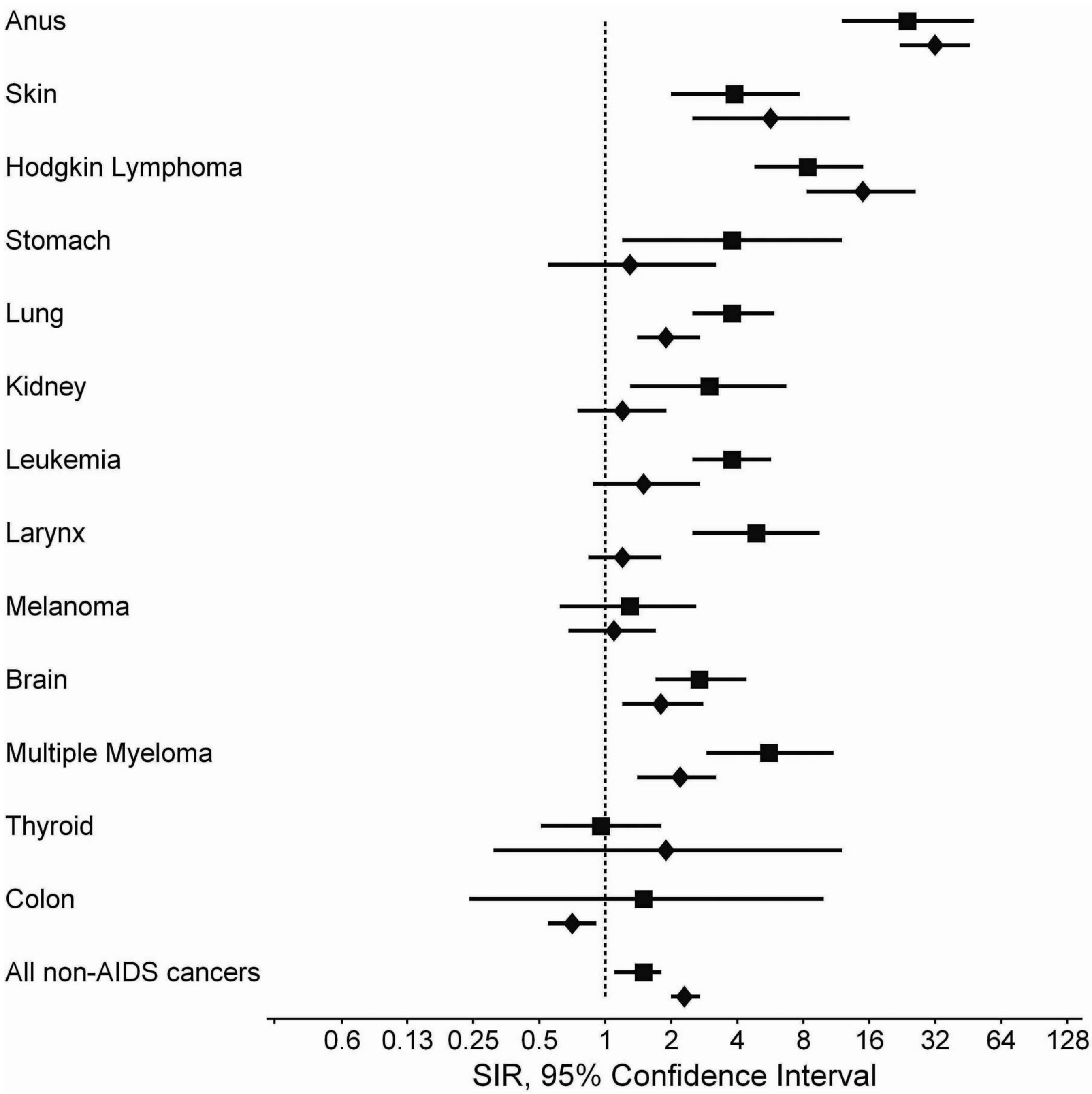

Figure 1.

Summary standardized incidence ratios (SIRs) and 95% confidence limits for specific types of non-AIDS cancer, by gender.

Women

men

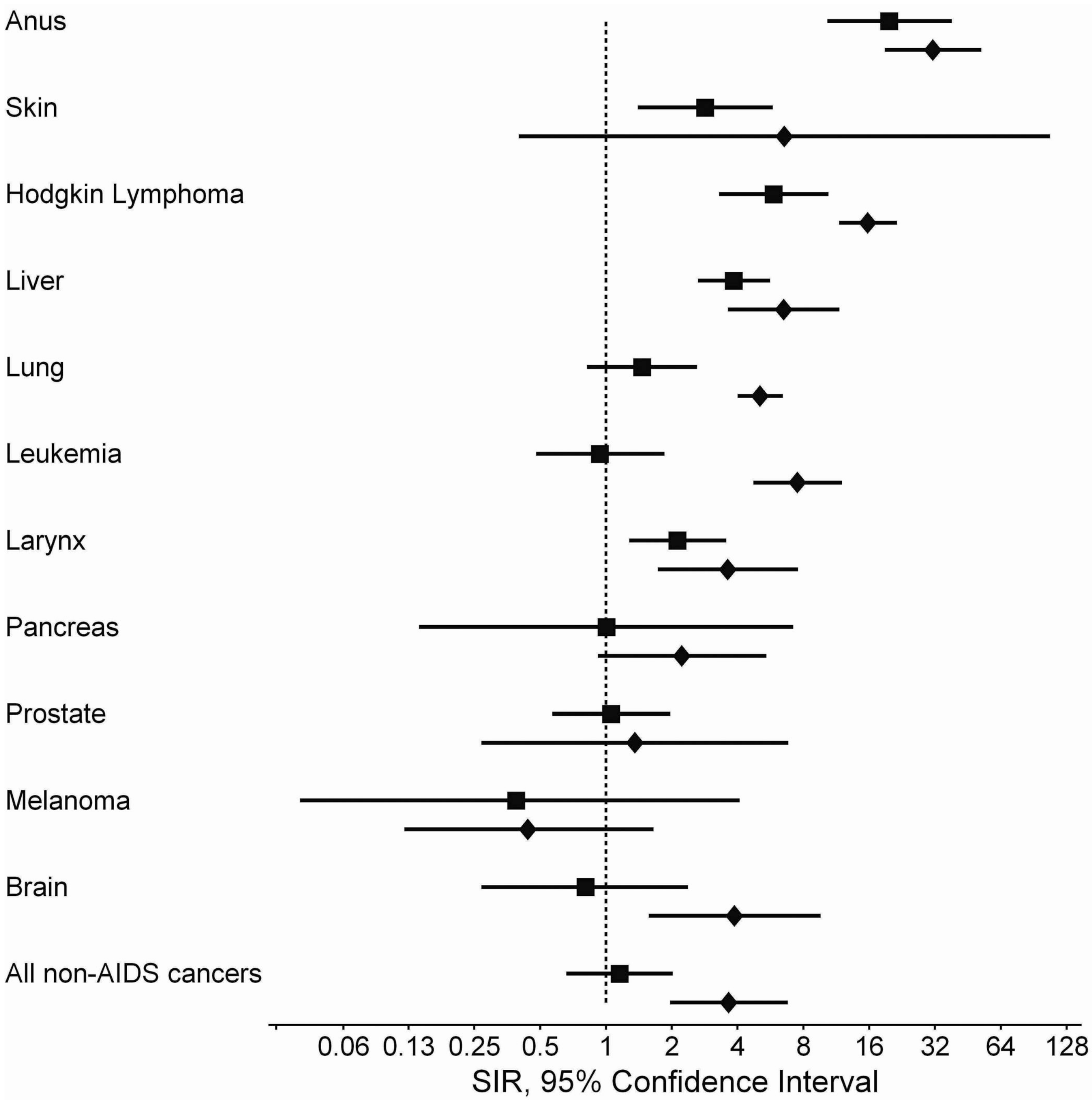

Figure 2.

Summary standardized incidence ratios (SIRs) and 95% confidence limits for specific types of non-AIDS cancer, by AIDS status.

No AIDS

AIDS

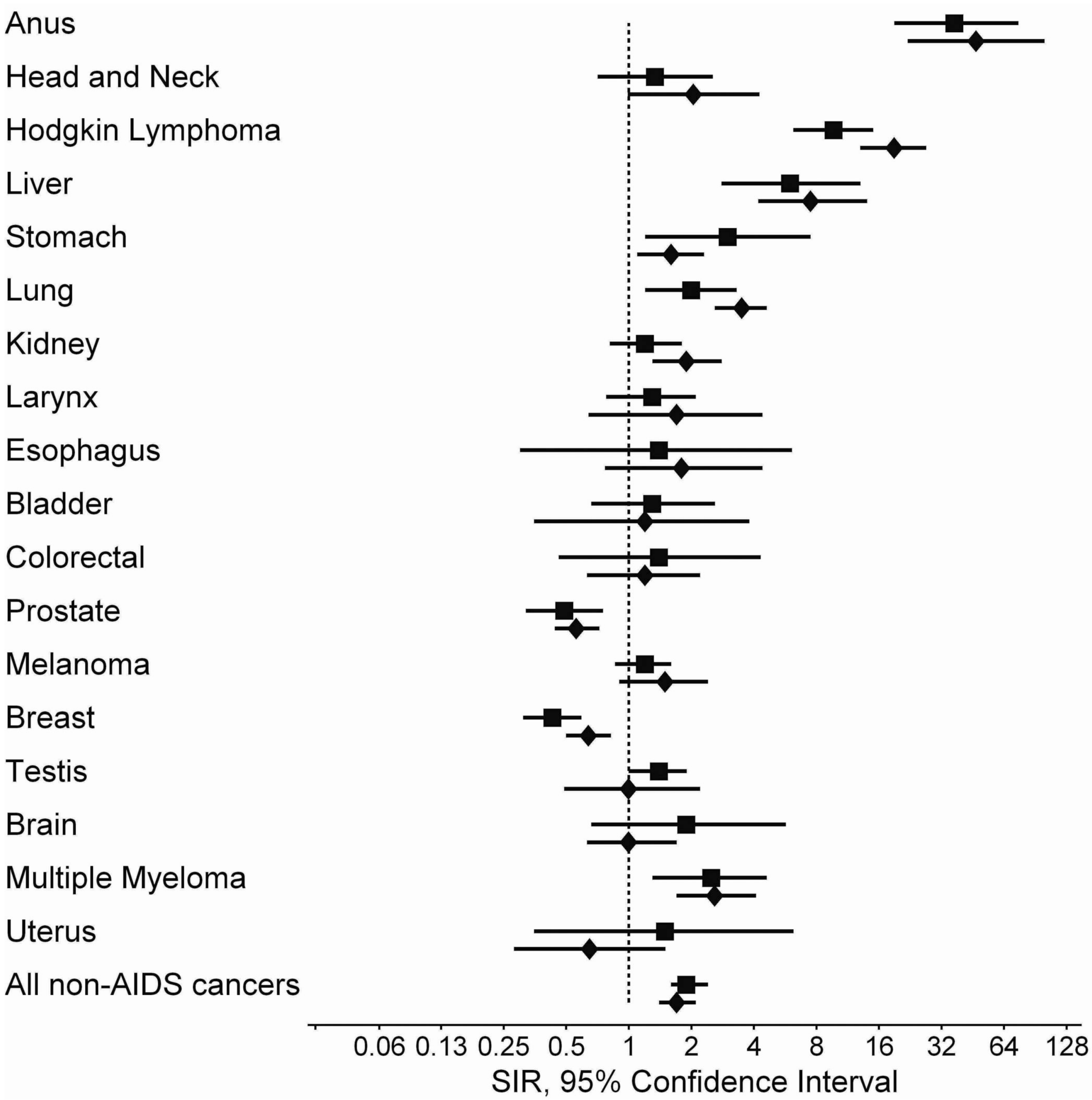

Figure 3.

Summary standardized incidence ratios (SIRs) and 95% confidence limits for specific types of non-AIDS cancer, by Highly Active Antiretroviral Therapy (HAART) era.

No HAART

HAART

Table 1

Characteristics of 18 studies of the incidence of non-AIDS cancers among HIV-infected populations when compared to the general population.

First author	Years	Country	Population comparison	Non-AIDS cancer cases
Cooksley[24]	1981–1984	United States	Cancer Registry	330
Gallagher*[25]	1981–1994	United States	Cancer Registry	1,569
Grulich[11]	1985–1998	Australia	Cancer Registry	196
Herida[19]	1992–1999	France	Cancer Registry	651
Dal Maso**[7]	1985–1998	Italy	Cancer Registry	170
Allardice[3]	1981–1996	Scotland	Cancer Registry	24
Hessol*[12]	1993–2001	United States	SEER	22
Clifford[6]	1985–2002	Switzerland	Cancer Registry	132
Newnham[14]	1985–2001	England	Cancer Registry	442
Mbulaiteye[13]	1989–2002	Uganda	Cancer Registry	60
Engels[8]	1980–2002	United States	Cancer Registry	1,627
Galceran[10]	1981–1999	Spain	Cancer Registry	22
Serranio[16]	1985–2005	Italy and France	Cancer Registry	107
Long[18]	1996–2005	United States	SEER	115
Patel[17]	1992–2003	United States	SEER	708
Engels**[26]	1991–2002	United States	Cancer Registry	461
Powles***[5]	1983–2007	England	Cancer Registry	156
Dal Maso[4]	1986–2004	Italy	Cancer Registry	383

* Data included in gender-stratified meta-analysis only.

** Data included in AIDS-stratified meta-analysis only.

*** Data included in HAART era-stratified meta-analysis only.

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Table 2

Random effects SIRs and 95% CL for non-AIDS-defining cancers among HIV-infected individuals compared to the general population with results from tests of heterogeneity and funnel plot asymmetry.

	Studies	Cases	SIR	95% CL	Cochran's Q statistic (p-heterogeneity)	Begg & Mazumdar Test p-value	Eggar's Test p-value	Studies imputed by Trim and Fill
Lung	13	847	2.6	(2.1, 3.1)	117 (<0.001)	1.0	0.4	1
Hodgkin Lymphoma	13	643	11	(8.8, 15)	196 (<0.001)	0.4	0.1	0
Anus	8	253	28	(21, 35)	33 (<0.001)	0.9	1.0	0
Colorectal	4	174	1.1	(0.69, 1.7)	40 (<0.001)	0.7	0.2	0
Liver	11	171	5.6	(4.0, 7.7)	49 (<0.001)	1.0	0.7	0
Melanoma	10	161	1.2	(0.88, 1.6)	44 (<0.001)	0.2	0.07	0
Skin Cancer	7	160	3.5	(1.8, 6.8)	181 (<0.001)	0.6	0.2	0
Prostate	9	159	0.69	(0.55, 0.86)	18 (0.08)	0.1	0.05	3
Female Breast	11	142	0.74	(0.56, 0.97)	30 (0.003)	0.9	0.7	0
Kidney	9	109	1.7	(1.3, 2.2)	24 (0.04)	1.0	0.8	0
Oropharynx	3	108	1.9	(1.4, 2.6)	7.0 (0.1)	0.5	0.3	0
Leukemia	10	102	2.6	(1.9, 3.5)	16 (0.06)	0.8	0.4	0
Stomach	11	96	1.7	(1.2, 2.5)	49 (<0.001)	1.0	0.4	0
Testis	8	96	1.4	(1.1, 1.9)	18 (0.05)	0.8	0.7	0
Lip, oral and pharynx	2	84	2.2	(1.0, 4.7)	26 (<0.001)	1.0	0.9	0
Brain	9	75	1.8	(1.2, 2.7)	41 (<0.001)	0.8	0.3	2
Multiple Myeloma	9	72	2.6	(1.5, 4.5)	12 (0.4)	0.05	0.05	4
Larynx	5	62	1.5	(1.1, 2.0)	11 (0.1)	0.4	0.08	0
Esophagus	8	51	1.5	(0.99, 2.3)	25 (0.01)	0.8	0.6	0
Bladder	9	48	1.1	(0.72, 1.7)	28 (0.005)	0.4	0.2	0
Head and Neck	4	42	2.0	(1.1, 3.6)	16 (0.003)	1.0	0.6	0
Pancreas	9	39	1.0	(0.74, 1.4)	7.7 (0.7)	0.2	0.05	3
Colon	4	26	0.81	(0.48, 1.4)	7.4 (0.1)	0.5	0.1	0
Vagina	4	25	9.4	(4.9, 18)	13 (0.02)	0.7	0.4	0
Thyroid	6	24	1.1	(0.56, 2.3)	25 (0.001)	0.8	0.5	0
Penis	4	16	6.8	(4.2, 11)	4.4 (0.4)	0.2	0.2	2
Rectum	2	16	1.5	(0.54, 4.2)	5.6 (0.06)	0.3	0.05	0
Ovary	6	14	1.4	(0.78, 2.4)	10 (0.2)	0.5	0.3	0
Uterus	4	14	1.5	(0.68, 3.4)	16 (0.008)	0.3	0.2	0
Small Intestine	3	10	2.2	(1.4, 3.3)	0.73 (0.9)	0.3	0.3	1
Bone	5	7	2.6	(1.3, 5.0)	9.3 (0.2)	0.4	0.9	0
Eye	2	7	3.1	(1.6, 5.9)	0.63 (0.4)	---	---	0
Nasopharynx	2	7	4.1	(2.1, 7.9)	0.06 (0.8)	---	---	0
Gall Bladder	2	3	2.6	(1.1, 6.4)	0.65 (0.4)	1.0	0.1	0
All non-AIDS Cancers	9	3,513	2.0	(1.8, 2.2)	115 (<0.001)	1.0	0.7	0