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Lung Cancer in HIV Infection

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Abstract

Lung cancer is the most prevalent non-AIDS-defining malignancy in the HAART era. Smoking plays a significant role in the development of HIV-associated lung cancer, but the cancer risk is 2–4 times greater in HIV-infected persons than in the general population, even after adjusting for smoking intensity and duration. Lung cancer is typically diagnosed a decade or more earlier among HIV-infected persons (mean age, 46 years) compared to those without HIV infection. Adenocarcinoma is the commonest histological subtype, and the majority of patients are diagnosed with locally advanced or metastatic carcinoma. Since pulmonary infections are common among HIV-infected individuals, clinicians may not suspect lung cancer in this younger patient population. Surgery with curative intent remains the treatment of choice for early stage disease. Although there is increasing experience in using radiation and chemotherapy for HIV-infected patients who do not have surgical options, there is a need for prospective studies for this population frequently excluded from participating in cancer trials. Evidence-based treatments for smoking-cessation with demonstrated efficacy in the general population must be routinely incorporated into the care of HIV-positive smokers.

INTRODUCTION

HIV-associated morbidity and mortality have declined dramatically since the mid 1990s as a result of highly active antiretroviral therapy (HAART), consisting of multiclass antiretroviral regimens, becoming widely available.[1,2] With HIV-infected persons now living well into middle age and beyond, there is a renewed public health and clinical interest in long-term morbidities, including malignancies that occur disproportionately in this population.[3]

Kaposi's sarcoma (KS), intermediate and high-grade peripheral non-Hodgkin's lymphoma (NHL), primary central nervous system NHL, and cervical cancers are AIDS-defining

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malignancies (ADMs) based on the Center for Disease Control and Prevention (CDC) case definition of AIDS.[4] HIV-infected individuals also have an elevated risk for other malignancies which are not ADMs including lung cancer, head and neck cancer, liver and anal neoplasms, and Hodgkin's disease.[5,6] The increased risk for non-ADMs is most likely related to high prevalence of co-infection with various oncogenic viruses including human papillomavirus, hepatitis B and C viruses, and exposure to carcinogens.[5,7] The U.S. AIDS population expanded four fold from 1991–2005, largely because of an increase in the number of people with AIDS surviving past the age of 40 years old. Though the estimated number of ADMs decreased by greater than three-fold during this period, the number of patients with of non-ADMs increased by a similar three fold during the same interval.[8]

Lung cancer is the commonest cause of cancer mortality worldwide for both men and women, causing approximately 1.2 million deaths each year.[9] It is also the third commonest malignancy among HIV-infected persons, preceded only by KS and NHL in incidence.[8.10,11] In this article, we will briefly review the emerging epidemiologic data that suggests that lung cancer risk is 2–4 times greater in HIV-infected persons than in the general population, even after adjusting for other factors such as smoking intensity and duration.[12–16] We will also review reasons why the risk of lung cancer may be greater in this group than the general population, then focus on clinical features of the disease, treatment recommendations and cigarette smoking prevention.

EPIDEMIOLOGY

In 1984, Irwin and colleagues were the first to describe a case of metastatic non-small cell lung cancer in an HIV-infected man.[17] Since then, a number of studies carried out either exclusively before the HAART era or both before and during the HAART era have suggested that lung cancer risk is greater among HIV-infected individuals compared to the general population (Table 1).[11,12,17–32] Though some of the largest studies included only patients with an AIDS-defining diagnosis[11,18,21,22] several cohort and registry linkage studies, which have included HIV-positive patients with and without AIDS, have also consistently demonstrated an increased risk of lung cancer.[19,23,27,28–30,33] In a meta-analysis of seven reports of HIV-associated cancer risk and published between 2002 and 2006, 444,172 people with HIV/AIDS were identified, of whom 1,297 were diagnosed with lung cancer.[34] The lung cancer standardized incidence ratio (SIR) of 2.72 (95% confidence interval [CI]: 1.91–3.87) among HIV-infected individuals was comparable to the SIR of lung cancer in immunosuppressed organ transplant patients (SIR 2.18; 95% CI, 1.85–2.57).

The risk of lung cancer in the setting of HIV infection appears to have remained relatively stable in the HAART era. Engels and colleagues reviewed the trends in cancer risk among people with AIDS in the pre-HAART, early HAART and recent HAART era. The relative risk of lung cancer occurring during the time periods of 1980–1989, 1990–1995 and 1996–2002 were 2.5 (95% CI, 1.9–3.3), 3.3 (95% CI, 2.9–3.8) and 2.6 (95% CI, 2.1–3.1), respectively.[11] In a prospective observational cohort study involving 54,780 HIV-infected persons in the Adult and Adolescent Spectrum of HIV Disease Project and the HIV Outpatient Study, the incidence rates for lung cancer in the pre-HAART (1992 to 1995), early HAART (1996 to 1999), and recent HAART (2000 to 2003) era were also not significantly different (91.9, 93.8 and 84.9 per 100,000 prospective person-years respectively; p=0.29).[33]

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RISK FACTORS

Smoking

Cigarette smoking is the dominant risk factor for lung cancer and the elevated lung cancer risk among HIV-infected patients is, in part, attributed to heavy smoking. Among HIV-infected individuals, prevalence estimates of smoking range from 35–70% compared to approximately 20% in the general U.S. population.[35–37] Tobacco use may be even more common among HIV-seropositive intravenous drug users. Among those followed in the AIDS Link to the Intravenous Experience (ALIVE) study cohort, over 85% of the participants are current smokers.[38] Furthermore, the data regarding tobacco use among HIV-infected patients, as documented in the medical records, is often incomplete or inaccurate. In a recent survey of 200 HIV-infected patients in a U.S. Veterans hospital, 82% reported tobacco use, but the electronic medical records suggested smoking in only 49% of patients.[39]

Over 90% of all HIV-positive patients with lung cancer are smokers (Table 2). In a recent multi-institutional and retrospective chart review of 75 HIV-infected lung cancer patients, smoking histories were available for 71 of the patients, of whom 70 (99%) were described as current or former smokers.[40] The median pack-year smoking history was 41 among the HIV-infected patients compared to 14 for a reference group of HIV-infected individuals without lung cancer.

There are only a limited number of epidemiologic studies which have attempted to estimate the effect of HIV infection on lung cancer risk after accounting for smoking habits. In a registry linkage study, the observed incidence of lung cancer in people with AIDS was compared to general population rates and rates from a lung cancer prediction model for smokers.[12] Though actual smoking behavior data were unavailable for people with AIDS in this study, under plausible smoking assumptions of duration and intensity, the observed incidence of lung cancer was significantly higher than predicted among 40- to 49- and 50- to 59-year-old men with AIDS (observed/predicted = 5.03 and 1.43, respectively) and 40- to 49-year-old women with AIDS (observed/predicted = 1.88). In this analysis, lung cancer risk was substantially elevated in people with AIDS compared to the general population, and smoking did not entirely account for the observed elevation, especially among younger adults. Two additional studies which indirectly adjusted for smoking reported that, despite assuming a prevalence of smoking of 100%, there was still a 2–4 times greater lung cancer incidence among HIV-infected individuals compared to the general population.[13,.14]

In contrast, in the ALIVE cohort, smoking behavioral data available as information about smoking intensity and duration was collected through semiannual questionnaires from a cohort of HIV-infected and HIV-uninfected intravenous drug users. Twenty nine cases of lung cancer were noted among the 2,495 participants with at least 2 years of follow-up. In this study, HIV infection was associated with greater than twice the risk of lung cancer after adjustment for average number of packs of cigarettes smoked per day and other covariates.[16]

HIV-Related Factors

The increased risk of lung cancer in HIV-infected persons is not fully explained by smoking; several other mechanisms are likely important in promoting lung cancer. These factors include the potential oncogenic role of HIV, recurrent pulmonary infections, HIV-induced immunosuppression and HIV-associated decrease in immune surveillance. HIV could also mediate increased susceptibility to tobacco carcinogens.[15]

In vitro the HIV *tat* (transactivator of transcription) gene product increases the expression of a number of proto-oncogenes including c-myc, c-fos and c-jun. *Tat* also down regulates the

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tumor suppressor gene p53 in lung adenocarcinoma cell lines.[41] Furthermore, downregulation of the HIV-*tat* interacting protein (TIP30) promotes metastatic progression of lung cancer in vitro and in nude mice.[42,43] Microsatellite alterations, which reflect widespread genomic instability, are six fold greater when lung cancer is associated with HIV infection. However, the absence of integrated HIV genomes in the microdissected tumor samples from HIV-infected lung cancer patients argues against a direct role for HIV infection in the promotion of lung cancer.[44]

HIV infection is also associated with altered innate pulmonary immunity.[45] In the bronchoalveolar lavage fluid of HIV-infected individuals, there are increased concentrations of lysozyme, immunoglobulins and chemokine ligand 5.[46] In HIV-positive patients, oxidative stress is significantly higher than in seronegative control subjects as determined by elevated plasma lipid peroxide concentrations and breath-alkane output. The increase in lipid peroxidation is associated with lower plasma concentrations of various antioxidant micronutrients including Vitamin C, α-tocopherol, β-carotene and selenium.[47] The chronic inflammation arising from pulmonary infections may potentiate the effects of smoking in increasing lung cancer risk.[48–50]

Unlike the prototypical ADMs, KS and NHL, where the risk increases as immunosuppression becomes more pronounced, lung cancer may occur at any point in the course of HIV infection. The risk of HIV-associated lung cancer is generally not closely linked to a low CD4+ cell count or to an elevated HIV viral load, although analyses of a French cohort with over 52,000 HIV-positive individuals showed a rate ratio of 2.2 (95% CI, 1.3–3.6) for lung cancer in patients with CD4+ counts between 350–500 cells/μL and 8.5 (95% CI, 4.3–16.7) in patients with CD4+ counts <50 cells/μL when compared to HIV-positive patients with CD4+ counts >500 cells/μL.[51] Prolonged moderate immunosuppression as seen in the HAART era may further contribute to lung cancer risk.

CLINICAL CHARACTERISTICS

Lung cancer is typically diagnosed a decade or more earlier among HIV-infected persons (mean age, 46 years) compared to those without HIV infection (Table 2).[40,52–62] Yet, in a recent registry linkage study, the difference in the age at diagnosis of lung cancer was relatively modest between persons with AIDS and the general population (50 vs. 54 years) after adjusting for the underlying population structures.[31] In HIV-infected patients with lung cancer, men are significantly overrepresented compared to women, with a male-female sex ratio of 5–10:1. This likely reflects the epidemiology of lung cancer, as well as HIV/AIDS; in developing countries, both diseases affect men disproportionately compared to women. The median CD4+ count at HIV-associated lung cancer diagnosis is often over 200 cells/μL.

The majority of patients with HIV-associated lung cancer are symptomatic at diagnosis. This is likely due to the advanced stage of disease by the time lung cancer is diagnosed. Respiratory complaints are particularly frequent and most notably include cough (40–86%), chest pain (25–75%) and dyspnea (10–57%).[21,40,58,59,63] Fatigue is ubiquitous, and as many as 10–30% of patients will also have hemoptysis. The signs and symptoms of lung cancer among HIV-infected persons mirror those of age-matched lung cancer controls.[40,64] As many as 70–90% of HIV-lung cancer patients are diagnosed with locally advanced or metastatic carcinoma (Stage IIIB or IV).

Only a handful of small studies have focused on the radiological characteristics of HIV-associated lung cancer patients.[64–67] Among 15 such patients, parenchymal masses and nodules were the commonest features (67%) on chest radiographs and computerized tomography (CT).[65] Masses were peripheral in 11 cases (73%) and were located in the upper lobes in 10 cases (67%). Enlarged lymph nodes were present in 60% and distant

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metastases in 30% of patients. Another study showed a higher frequency of mediastinal adenopathy (6/7 vs. 7/14) and pleural effusion (4/7 vs. 4/14) in HIV-infected patients compared to a sex-matched control group of HIV-negative patients with adenocarcinoma of the lung, though these differences did not reach statistical significance.[64]

Since pulmonary infections are common among HIV-infected individuals, clinicians may not suspect lung cancer in this younger patient population. Thirty of 32 (94%) HIV-lung cancer patients identified at Johns Hopkins University had chest radiographs to evaluate pulmonary complaints within 12 months prior to their cancer diagnosis.[59] The majority of these chest radiographs (60%) were reported as either normal (30%) or abnormal with nonspecific infiltrates (30%) but without an obvious finding to trigger a concern for neoplasm. Twenty-six of the 32 (87%) patients had a chest radiograph within one month of diagnosis, of which 10 (31%) radiographs were reportedly without neoplasm. In their analysis, the authors concluded that a low clinical suspicion for malignancy and over reliance on non-diagnostic chest radiographs resulted in delayed diagnosis of lung cancer in HIV-positive individuals.

In the non-lung cancer setting, positron emission tomography (PET) scans often upstage cancer diagnosis among HIV-positive individuals owing to an increased likelihood of reactive lymphadenopathy among this group.[68–70] The role of PET in the evaluation of HIV-associated malignancies, including lung cancer, needs to be better defined.

Pathological Findings

Non-small cell lung cancer represents 86–94% of cases in HIV-infected patients, with adenocarcinoma being the commonest histological type (30–52%), similar to age-matched lung cancer control groups.[14,40,54–60] With the exception of two retrospective studies, squamous cell cancer is the second commonest histological type (19–36%) in HIV-lung cancer patients, comparable to the 25% squamous cell cancer reported in HIV indeterminate individuals in the SEER data set.[49,53] The predominance of adenocarcinoma among HIV-infected individuals mirrors the changes in the distribution of the histological types of lung cancer seen in the general population. In the 1990s, adenocarcinoma surpassed squamous cell carcinoma as the leading histology associated with lung cancer in the U.S. and in other industrialized nations.[71]

TREATMENT AND OUTCOME

No specific recommendations exist for the management of HIV-associated lung cancer. Traditionally, such individuals have been excluded from clinical trials participation.[72] Surgery with curative intent remains the treatment of choice for localized disease[73], and there is increasing experience in using radiation therapy and systemic chemotherapy for patients who do not have surgical options.

Data on the management of HIV-associated lung cancer is principally derived from uncontrolled retrospective analyses rather than prospective clinical trials. Studies from the pre-HAART era and early years of the HAART era reported shorter survival times among HIV-lung cancer patients than HIV-indeterminate or negative lung cancer patients (Table 3).[40, 52–55,59,74] In a representative analysis, only 5% of the 38 patients with AIDS and lung cancer in the 1980s survived 24 months; whereas, 10% of 97 such persons survived 24 months in 1996 through 2000.[75] By comparison, 31% of lung cancer patients without AIDS survived 24 months. In persons with AIDS, the adjusted death hazard ratio of 2.5 in 1996 through 2000 showed no significant reduction from earlier hazard ratios. However, in the most recent of studies performed later in the HAART era, these two groups appear to have comparable survival times.[40,58,74] In a recent retrospective review of 75 patients with HIV-

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associated lung cancer, the median survival of those with advanced cancer was 9 months and was similar to the median survival of SEER lung cancer participants.[40]

The direct influence of HAART on survival remains unanswered, although encouraging findings are emerging. In a multivariate analysis of 49 HIV-positive individuals with non-small cell lung cancer, HAART, ECOG performance status ≤1, weight loss <10% and disease stage I–II were good prognostic factors for survival.[61] HIV-associated lung cancer patients who were receiving HAART lived longer than individuals not receiving HAART (9 vs. 4.5 months). In a retrospective analysis of 52 patients with HIV-infection and non-small cell lung cancer, a performance status <2, a CD4+ count ≥ 200 cells/μL at diagnosis and use of HAART after lung cancer diagnosis were associated with increased survival.[76] For the individual with HIV-associated lung cancer, the benefits of taking HAART are protean and likely include minimizing risk of opportunistic infections and maintaining a better performance status. Perhaps these patients are better able to tolerate more active chemotherapy than in the pre-HAART era.[60,77,78]

There are potential drug-drug interactions and cumulative toxicity concerns when HAART is combined with systemic chemotherapy. Etoposide, taxanes, vinca alkaloids and anilinoquinazolines erlotinib and gefitinib are metabolized by cytochrome P450.[79–81] All protease inhibitors inhibit CYP4503A4, but ritonavir is the most potent inhibitor in the class, even at low doses.[82] Also, ritonavir inhibits the P-glycoprotein efflux pump protein, driving chemotherapeutic agents like vinca alkaloids and taxanes outside the cells.[83] Nucleoside analogs like zidovudine can exacerbate myelosuppression.[84] Among 40 HIV-positive patients with non-small cell lung cancer, 20% of various chemotherapy combinations were complicated by grade 4 hematological toxicity; protease inhibitor use was significantly associated with hematological toxicity.[76]

Prospective Studies

The interplay between HAART and chemotherapy becomes more important as we increasingly employ the same treatment regimens for HIV-associated lung cancer patients with adequate CD4+ cell counts and suppressed HIV viral loads as we do for HIV seronegative individuals with lung cancer. The Intergroupe Francophone de Cancerologie Thoracique has recently initiated a phase II, multicenter, nonrandomized, open-label study evaluating the combination of pemetrexed plus carboplatin in HIV-positive patients with lung cancer (NCT01296113).[85]

The AIDS Malignancy Consortium (AMC), in response to the lack of prospective trials for HIV-infected persons with non-ADMs, is conducting phase I and pharmacokinetics studies to investigate the interplay between HAART and chemotherapy and biological therapies and to establish tolerable doses in this underserved patient population. AMC-078 is a phase I study of vorinostat in combination with paclitaxel and carboplatin in solid tumors (with focus on upper aerodigestive cancers) in persons with HIV infection (NCT01249443).[86] In addition to evaluating the safety and tolerability of vorinostat in combination with paclitaxel (175 mg/m^2, IV) and carboplatin (AUC 6, IV) administered in 3 week cycles, the study will evaluate the pathological characteristics of non-ADMs of the aerodigestive tract and the effects of study therapy on patient immune status and HIV viral load. Physician support and patient accrual to these prospective trials should be strongly encouraged.

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PREVENTION

Smoking Cessation

There are no unique clinical practice guidelines to implement smoking cessation efforts among HIV-positive person and so evidence-based treatments with demonstrated efficacy in the general population must be incorporated into the care of HIV-positive smokers.[86]

U.S. Public Health Service guidelines recommend brief individual smoking cessation counseling with five components (known as the "5 A's") at each clinical encounter.[88] Providers are advised to systematically *a*sk about tobacco use, *a*dvise smokers to quit, *a*ssess willingness to quit, *a*ssist with quitting, and *a*rrange follow up. Smokers' telephone quit lines are cost-effective interventions with broad reach and demonstrated efficacy for long-term smoking cessation. Motivational interviewing is effective in increasing quit attempts.[89] Cognitive behavioral interventions, designed to modify critical cognitions and actions that maintain behaviors such as smoking by promoting the thoughts and skills necessary to create behavioral change, are additional strategies to help smokers quit or reduce cigarette smoking.[90,91]

Medications approved by the U.S. Food and Drug Administration for smoking cessation include nicotine replacement therapy (patch, lozenges, inhalers, gum and nasal spray), bupropion and varenicline.[88] There are no known interactions between nicotine replacement therapy and HAART. Bupropion is metabolized by the hepatic cytochrome P450 CYP2B6 system, and its metabolism has been shown to be inhibited by protease inhibitors (nelfinavir, ritonavir), and a non-nucleoside reverse transcriptase inhibitor (efavirenz) in vitro.[92] Short-term ritonavir administration does not significantly alter bupropion pharmacokinetics in healthy volunteers[93] and no medication-associated adverse events were observed in a case series of 10 HIV-positive persons using either ritonavir, nelfinavir, or efaverinz with bupropion.[94] The results and tolerance recorded for varenicline in HIV-positive individuals are similar to those published in relation to seronegative patients and no drug interactions have been described to date with HAART and varenicline.[95] Both bupropion and varenicline are associated with serious neuro-psychiatric symptoms including behavioral changes, hostility, agitation, depressed mood, suicidal ideation and attempted suicide. These symptoms have occurred in patients without pre-existing psychiatric illness.[96]

Thirty-four HIV-positive individuals, who were part of the Swiss HIV cohort study, received smoking cessation interventions consisting of counseling sessions and nicotine replacement therapy. In this prospective evaluation, self-reported smoking abstinence for 12 months was 38% (13 of 34) in the intervention group and 7% (27 of 383) in the control group (odds ratio 6.2, 95% CI 2.8–14.3).[97] Two other smaller studies in HIV-positive smokers with smoking cessation interventions including nicotine replacement therapy and counseling sessions showed similar outcomes, with abstinence rates of 44% and 63% at the end of nicotine replacement therapy.[98,99]

HIV-positive persons often have a complex range of psychiatric, social, economic, and medical concerns and may benefit from smoking cessation interventions specifically tailored to their unique needs. Smoking cessation interventions should be specifically built to take into account depression and codependencies in addition to nicotine dependence and motivation. In a randomized trial of a proactive cellular telephone intervention for smokers living with HIV/AIDS, 95 active smokers from a large, inner city HIV/AIDS care center were recruited and randomized to receive either usual care (brief physician advice to quit smoking, targeted self-help written materials and nicotine replacement therapy) or a cellular telephone intervention.[100] The cellular telephone intervention consisted of 8 counseling sessions delivered via telephone in addition to the usual care components. At 3-month

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follow up, the point prevalence smoking abstinence rate was 10% for the usual care group and 37% for the cellular telephone group; participants who received the phone intervention were 3.6 times (95% CI, 1.3–9.9) more likely to quit smoking compared with participants who received usual care.

Despite the high prevalence of smoking and significant barriers to quitting among those with HIV, many are interested in quitting and have made quit attempts. Studies have reported that between 40% to 63% of HIV-positive smokers are contemplating quitting or preparing to quit smoking[35,101,102] similar to smokers in the general population.[103] Approximately 70% of HIV-positive smokers have made a previous quit attempt, with an average of 2.8 quit attempts since their HIV diagnosis. That somewhere between 69% and 84% of HIV-positive smokers are interested in smoking cessation programs or nicotine replacement therapy means that we cannot be content to focus on non-detectable HIV viral loads or improved CD4+ cell counts as the only metrics of good health. The importance of stopping smoking needs to be an ever present message during our clinical encounters.[35,102]

SCREENING

Lung cancer screening is a rapidly evolving field, with potential to significantly reduce the burden of lung cancer.[104] Early randomized control trials in lung cancer screening evaluated chest radiography with or without sputum cytology and showed no reduction in lung cancer mortality.[105–109]

The lack of a clear result from chest x-ray screening and the refinement of CT scanning techniques have led to the evaluation of CT for lung cancer screening. The National Lung Screening Trial (NLST), a randomized national trial involving more than 53,000 current and former heavy smokers ages 55 to 74 with at least a 30-pack-year smoking history, compared the effects of low-dose helical CT and standard chest X-ray on lung cancer mortality and found 20% fewer lung cancer deaths (354 vs. 442) among trial participants screened with low-dose helical CT.[110] Preliminary data from the NLST trial were released in November 2010, and screening recommendations based on these findings will await publication of the full trial report.[111] The possible disadvantages of helical CT include the cumulative effects of radiation from multiple CT scans; surgical and medical complications in patients who prove not to have lung cancer but who need additional testing to make that determination; and risks from additional diagnostic work-up for findings unrelated to potential lung cancer, such as liver or kidney disease.[111–113] The high prevalence of infectious and inflammatory conditions in HIV infected patients can generate suspicious findings and increase the false positive rate, resulting in significant anxiety and expense. Also, the NLST study population, while ethnically representative of the high-risk U.S. population of smokers, was a highly motivated and primarily urban group that was screened at major medical centers. Hence the results may not accurately predict the effects of recommending low-dose helical CT scanning for other populations including HIV-infected individuals.[111] With this in mind, the recently activated HIV-CHEST study in France is recruiting HIV-positive individuals and seeks to determine the prevalence of lung cancers detected by low-dose CT.[114]

Currently, per the U.S. Preventive Services Task Force (USPSTF), the evidence is insufficient to recommend for or against screening asymptomatic persons for lung cancer with either low-dose CT, chest x-ray, sputum cytology, or a combination of these tests.[115]

Though the CDC recommends HIV testing in all health care settings calling for standard non-targeted “opt-out” HIV screening, for a variety of reasons, routine opt-out HIV testing is still not widely done in the United States. Such an approach to HIV testing for all patients diagnosed with cancer may improve clinical outcomes by facilitating appropriate HIV management during cancer treatment for individuals who are found to be HIV positive.[116]

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CONCLUSION

Lung cancer risk is 2–4 times greater in HIV-infected persons than in the general population, even after adjusting for smoking intensity and duration. HIV-associated lung cancer is typically diagnosed a decade or more earlier among HIV-infected persons. The distribution of histological types and tumor stage is similar to that observed in the general population, with adenocarcinoma being the commonest histological type and the majority of patients diagnosed with locally advanced or metastatic disease (stage IIIB or IV). As pulmonary infections are common among HIV-infected individuals, clinicians may not suspect lung cancer in this patient population, and this may lead to a delay in the cancer diagnosis. Surgery with curative intent remains the treatment of choice for localized disease, and there is increasing experience in using radiation therapy and systemic chemotherapy for patients who do not have surgical options. Though retrospective studies conducted during the pre- and early HAART era reported shorter survival times among HIV-lung cancer patients than HIV-indeterminate or negative lung cancer patients, in the most recent of studies performed in the HAART era, these two groups appear to have comparable survival times. A few prospective clinical trials are currently enrolling HIV-infected persons with advanced lung cancer, and physician support and patient accrual to these prospective trials should be strongly encouraged. Screening with low-dose CT is not yet advised in this high risk population. As smoking plays a significant role in the development of HIV-associated lung cancer, people with HIV should be reminded of the hazards of smoking and encouraged to stop. Smoke cessation strategies with demonstrated efficacy in the general population must be routinely incorporated into the care of HIV-positive smokers.

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Table 1

The Relative Risk of HIV-related Lung Cancer

Reference	Time Period	N	RR/SIR	95% CI
Engels et al[11]	1980–1989	49	2.5	1.9–3.1
	1990–1995	233	3.3	2.9–3.8
	1996–2002	111	2.6	2.1–3.1
Chaturvedi et al[12]	1980–2002	1489	3.8	3.6–4.1
Parker et al[13]	1990–1995	36	6.5	4.5–8.9
Frisch et al[18]	1980–1996	808	4.5	4.2–4.8
Allardice et al[19]	1981–1996	5	4.1	1.3–9.5
Gallagher et al[20]	1981–1994	217	3.3	2.86–3.75
Dal Maso et al[21,22]	1985–1996	17	10.7	6.2–17.2
	1997–1998	4	14.1	3.7–36.4
Newnham et al[23]	1985–2001	39	2.2	1.7–3.1
Clifford et al[24]	1985–2002	14	3.2	1.7–5.4
Grulich et al[25]	1985–1999	17	1.44	0.84–2.30
Serraino et al[26]	1985–2005	14	1.7	0.9–2.8
Bower et al[27]	1986–1996	2	0.8	0.2–1.4
	1997–2002	9	6.7	3.5–9.9
Herrida et al[28]	1992–1995	22	1.13	0.71–1.72
	1992–1999	77	2.12	1.67–2.65
Long et al[29]	1996–2005	29	5.5	3.7–8.0
Silverberg et al[30]	1996–2007	54	1.9	1.4–2.5
Engels et al[31]	1991–2002	109	2.6	2.1–3.1
Shiels et al[32]	1996–2007	605	3.0	2.8–3.2

N = Number of HIV-infected patients with lung cancer; RR = relative risk; SIR = standardized incidence ratio; CI = confidence interval

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Table 2

Clinical Characteristics of HIV-infected patients with Lung Cancer

Reference	N	Age (Median)	Males	Smokers	Pack years	MSM	IVDU	Median CD4 Count (cells/μL)
Engels et al[14]	33	46	67%	97%	37	-	57%	>200
D'Jaen et al[40]	75	50	83%	99%	41	47%	21%	340
Vyzula et al[52]	16	44	94%	100%	30	38%	56%	184
Sridhar et al[53]	19	48	48%	93%	93	32%	21%	121
Tirelli et al[54]	36	38	89%	94%	-	17%	69%	150
Alshafie et al[55]	11	49	82%	90%	-	-	82%	200
Flores et al[56]	19	47	100%	-	-	31%	21%	-
Spano et al[57]	22	45	86%	95%	-	45%	23%	364
Ruiz et al[58]	16	49	61%	100%	20	-	50%	211
Brock et al[59]	92	46	67%	99%	30	-	58%	305
Hakimian et al[60]	34	44	68%	100%	25	-	86%	>200
Lavole et al[61]	49	46	86%	100%	31	37%	35%	350
Jung et al[62]	40	51	58%	95%	-	-	-	213

MSM = men who has sex with men; IVDU = intravenous drug user

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Table 3

Comparison of survival rates in HIV-positive and HIV-negative persons with lung cancer

Author	HIV-positive N	Median Survival In months/HIV+	HIV-negative N	Median Survival in months/HIV−
D'Jaen et al[40]	75	9	160,091*	9
Vyzula et al[52]	11	7.5	49	11
Sridhar et al[53]	16	3	32	10
Tirelli et al[54]	36	5	102	10
Alshafie et al[55]	11	4	116	7
Brock et al[59]	92	6.3	4973	9.4
Powles et al[74]	9	4	28	4

*SEER data set (HIV-negative or HIV-indeterminate)