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HIV-associated lung cancer: ambiguities and challenges

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Lung cancer is a major challenge for people with HIV/AIDS, their clinicians, and the researchers who are working to improve their plight. Research on lung cancer with HIV has been reviewed by Kirk and Merlo [1]. Because lung cancer is common and lethal, the impact on HIV-associated morbidity and mortality is substantial. As highlighted by Sigel *et al.* [2] in the current issue, and previously described by others [3–9], the incidence of this malignancy is increased 1.7-fold with HIV infection and at least 3-fold among people with AIDS compared to demographically similar populations. Given the lack of effective treatment options [10–12], the search is on for lung cancer risk factors and markers, especially those that might be amenable to intervention for people with HIV/AIDS. Cigarette smoking is the main culprit, but smoking prevalence is only slightly higher in HIV-positive patients compared to HIV-negative individuals [2].

Clues may come from the consistent observation that lung cancer risk increases with the transition from asymptomatic HIV infection to AIDS. A recently low CD4 lymphocyte count was strongly predictive of lung cancer in a large study in France [8], but results from several other studies have implied that CD4 lymphocyte count is irrelevant [2,6,7,9,13]. Rather than systemic immunity, the lung itself is likely to be the locus of the entire carcinogenic process. Presumably this process involves an interaction between the effects of smoking and HIV. Sigel *et al.* confirmed that lung cancer was 1.5-fold higher following a diagnosis of bacterial pneumonia, but not following diagnosis of tuberculosis or *Pneumocystis jirovecii* pneumonia [2,14]. Chronic obstructive pulmonary disease increased the risk by nearly two-fold [2], as it does without HIV [15]. Implicitly, carcinogenesis may hinge on bronchopulmonary inflammation and a direct or, more likely, indirect effect of HIV on carcinogenic pathways, such as increasing genomic instability or DNA methylation of bronchopulmonary cancer-suppressor genes [16,17]. The current study and its predecessors have been too small and too heavily weighted with smokers to identify the postulated interaction between HIV and smoking [2,9,13].

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AIDS appears to accelerate development of lung cancer. Incidence before age 50 was elevated 4.7-fold with AIDS, but it was elevated only 1.5-fold with AIDS after age 60 [6]. Moreover, lung cancer cases among persons with AIDS (PWA) were significantly younger by 4 years (median age 50) compared to lung cancer cases in the age-adjusted general US population [18]. No other cancer except anal cancer occurred at a younger age in the AIDS population [18]. Given that the incidence of AIDS and death is accelerated with high HIV load and is reduced with control of HIV replication by effective antiretroviral therapy (ART), the same would be expected for lung cancer. In support, the incidence rate of lung cancer in the AIDS population declined during 1993–2005 [19]. However, this falling incidence cannot be readily attributable to ART-mediated control of HIV replication. Except in one study [5], lung cancer risk has been unrelated to receipt of ART and lower HIV load [2,8,9]. The possibility that ART directly affects lung neoplasia has not been reported. Alternatively, effects of HIV virions or proteins on bronchopulmonary cells, without infecting them, might be entertained. This model appears to affect breast cancer risk [20].

Antiretroviral therapy-mediated survival and aging of the HIV/AIDS population are steadily increasing the burden of lung cancer cases [19]. More and more patients require care for lung cancer. The vast majority of HIV-associated lung cancer presents at stage 3 or 4, resulting in substantial mortality [6,10,11,21–24].

Through year 2000, 24-month survival with lung cancer was only 10% among PWA, compared to 31% in the general population [25]. In Italy during 1999–2005, median survival was only 9 months with lung cancer and AIDS [26]. Likewise in Baltimore, median survival was only 6 months; tumor stage largely accounted for survival differences; and 92% of the deaths in these cases were due to lung cancer [11]. Chest radiography failed to detect lung cancer at an early stage [11]. Thus, surgical excision was attempted in only 14% of the cases and 24% of these patients received no cancer treatment, mostly because of poor performance status [11]. Identification and management of drug interactions between ART and cancer chemotherapy regimens have been based on very limited data and experience [10,12]. Treatment with epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors has modestly increased survival for general population patients whose tumors have EGFR mutations [27], but there are no published data relevant to people with HIV/AIDS.

Although there is statistical evidence for an effect of HIV that is independent of smoking, there remains a nagging concern for residual confounding because associations with CD4 cell count, HIV load, and ART use are ambiguous, because smoking is such a potent lung carcinogen, and because all of the published studies lacked direct data on smoking or lacked relevant details such as smoking intensity and age at initiation [2–9]. One wonders if the extraordinarily high risk before age 50 merely reflects smoking initiation at a very young age [6,18]. One also wonders if people with HIV have grown up and continue to live in homes with high levels of exposure to second-hand smoke, which increases lung cancer risk by about 1.24-fold [28]. Irrespective of HIV, lung cancer prevention always returns to smoking cessation, which cuts the risk in half within 5–10 years, albeit with a residual risk for another decade especially for former heavy smokers [29,30]. Smoking addiction is potent and insidious, but control efforts are starting to result in lower lung cancer incidence

and mortality in the USA [31]. It is hard, but the benefit for the successful patient is enormous.

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