Lung cancer in the Swiss HIV Cohort Study: role of smoking, immunodeficiency and pulmonary infection

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BACKGROUND: Immunodeficiency and AIDS-related pulmonary infections have been suggested as independent causes of lung cancer among HIV-infected persons, in addition to smoking.

METHODS: A total of 68 lung cancers were identified in the Swiss HIV Cohort Study (SHCS) or through linkage with Swiss Cancer Registries (1985–2010), and were individually matched to 337 controls by centre, gender, HIV-transmission category, age and calendar period. Odds ratios (ORs) were estimated by conditional logistic regression.

RESULTS: Overall, 96.2% of lung cancers and 72.9% of controls were ever smokers, confirming the high prevalence of smoking and its strong association with lung cancer (OR for current vs never = 14.4, 95% confidence interval (95% CI): 3.36–62.1). No significant associations were observed between CD4+ cell count and lung cancer, neither when measured within 1 year (OR for < 200 vs > 500 = 1.21, 95% CI: 0.49–2.96) nor further back in time, before lung cancer diagnosis. Combined antiretroviral therapy was not significantly associated with lung cancer (OR for ever vs never = 0.67, 95% CI: 0.29–1.52), and nor was a history of AIDS with (OR = 0.49, 95% CI: 0.19–1.28) or without (OR = 0.53, 95% CI: 0.24–1.18) pulmonary involvement.

CONCLUSION: Lung cancer in the SHCS does not seem to be clearly associated with immunodeficiency or AIDS-related pulmonary disease, but seems to be attributable to heavy smoking.

Keywords: lung cancer; HIV; AIDS; immunodeficiency; smoking; case–control study

Lung cancer is one of the most common non-AIDS-defining cancers to occur among HIV-infected persons (Dal Maso et al., 2009; Franceschi et al., 2010; Shiels et al., 2011), and shows two- to seven-fold excess risks in comparison with the general population (Grulich et al., 2007; Shiels et al., 2009). In the Swiss HIV Cohort Study (SHCS) subjects, lung cancer risk is three times that in the general Swiss population (Franceschi et al., 2010). A large part of this excess can be explained by the high proportion of heavy smokers among HIV-infected persons (Giordano and Kramer, 2005), particularly among intravenous drug users (IDUs) (Clifford et al., 2005; Dal Maso et al., 2009).

However, HIV infection has been suggested to be associated with increased lung cancer incidence even after controlling for individually collected (Shiels et al., 2010) or hypothetically modelled (Engels et al., 2006; Chaturvedi et al., 2007) smoking history data. Further suggesting a link between lung cancer and HIV-related immunodeficiency, large cohorts of HIV-infected persons (Patel et al., 2008; Guiguet et al., 2009; Reekie et al., 2010) have recently reported strong associations between declining CD4+ counts and lung cancer risk. Nevertheless, other record linkage studies of cancer registries with cohorts of HIV-infected persons (Clifford et al., 2005) and/or AIDS registries (Chaturvedi et al., 2007; Polesel et al., 2010) have failed to observe any link between CD4+ cell counts and lung cancer risk, or any change in risk between the pre-combined antiretroviral therapy (cART) and cART era.

Although HIV is not considered to have any direct carcinogenic effects (Bouvard et al., 2009), it has been hypothesised that HIV-associated inflammation in the lungs might predispose to
smoking-related lung damage (Engels et al., 2006), and lung cancer in HIV-infected persons has been associated with a history of AIDS-related pulmonary diseases (Kirk et al., 2007; Shebl et al., 2010), which are themselves related to immunodeficiency.

Our aim was to disentangle the independent effects of smoking, HIV-related immunodeficiency and AIDS-related pulmonary diseases on lung cancer among HIV-infected persons in Switzerland.

**MATERIALS AND METHODS**

The SHCS is an ongoing study that has been enrolling HIV-infected persons since 1984 from seven large hospitals in Switzerland (http://www.shcs.ch) (Swiss HIV Cohort Study et al., 2010), including 103,000 person-years (py) of follow-up until December 2009. Women contribute 31% of py and representation of HIV-transmission categories are balanced between men having sex with men (MSM), IDU and heterosexual/other (35, 29 and 36% of py, respectively). Detailed information on all AIDS-related disease, CD4+ cell count and HIV-related treatments are collected at the time of enrolment, and at each 6-month follow-up visit. Detailed information on smoking history (in number of pack-years) has been routinely collected from all HIV-infected persons under active follow-up in the SHCS since April 2000, for whom current smoking intensity, as well as number of cigarettes smoked per day, is also recorded at each 6-month follow-up visit.

A total of 107 lung cancer cases were identified in SHCS participants, of which 84 were identified from the SHCS database, and 23 additional cases were identified through record linkage with 8 Swiss Cantonal Cancer Registries (Franceschi et al., 2010). In all, 10 patients with Kaposi sarcoma (KS) and 13 with lymphoma localised in the lung were excluded. In addition, 6 prevalent cases occurring before, or within 1 month of, SHCS enrolment and 10 diagnosed >6 months after the last SHCS follow-up date were excluded, leaving 68 eligible incident cases occurring during active SHCS follow-up (median follow-up from SHCS enrolment to lung cancer diagnosis = 7 years; interquartile range, 3–12 years). Confirmation of histological subtype was available for 65 (94%) of the 68 cases, including 21 adenocarcinoma (International Classification of Disease in Oncology morphology codes (ICD-O) codes 81403; 82523; 82533; 84813), 15 large cell carcinoma (80123; 80203; 80313; 80823), 14 squamous cell carcinoma (80703; 80713; 80723), 8 small cell carcinoma (80413) and 7 other specified carcinomas (80463; 84303).

For each lung cancer case, five control subjects were matched at random from eligible SHCS participants without lung cancer. Eligible controls had at least the same length of follow-up as did matched cases. Matching criteria were: (1) SHCS centre; (2) gender; (3) HIV-transmission category (IDU, MSM, heterosexual/other); (4) age at enrolment (as close as possible, up to a maximum of 9 years difference); (5) year at reference date (as close as possible, up to a maximum of 9 years difference); (6) smoking intensity, as well as number of cigarettes smoked per day, and duration of smoking were matched, leaving 337 controls for this study (Table 1).

| Centre       | Lung cancer | Controls |
|--------------|-------------|----------|
| Basel        | 11          | 55       |
| Bern         | 9           | 42       |
| Geneva       | 15          | 75       |
| St Gallen    | 7           | 35       |
| Vaud         | 13          | 65       |
| Zurich       | 13          | 65       |
| Gender       |             |          |
| Male         | 54          | 270      |
| Female       | 14          | 67       |
| HIV-transmission category | | |
| MSM          | 19          | 95       |
| IDU          | 25          | 125      |
| Het/other    | 24          | 117      |
| Age at lung cancer (years) | | |
| 25–44        | 24          | 132      |
| 45–54        | 26          | 122      |
| 55–64        | 13          | 61       |
| > 65         | 5           | 22       |
| Duration of follow-up before lung cancer (months) | | |
| <24          | 11          | 55       |
| 24–59        | 13          | 65       |
| >60          | 44          | 217      |
| Calendar period at lung cancer | | |
| 1985–1991    | 3           | 15       |
| 1992–1995    | 6           | 30       |
| 1997–April 2000 | 6    | 31       |
| May 2000–2005 | 28     | 146      |
| 2006–2010    | 25          | 115      |

Abbreviations: Het = heterosexual; IDU = intravenous drug user; MSM = men having sex with men. *Or reference date for controls (date after a similar length of follow-up in the SHCS as matched cases). †Truncation in mid-2000 to match for availability of smoking information.

**Table I** Distribution of 68 lung cancer cases and 337 controls, according to matching variables

For any marker of immunodeficiency was available during any one time period, that closest to the reference date was used. Matching was not retained in the long-term comparison and numbers of cases and controls obviously decreased substantially as follow-up went back in time. The nadir CD4+ cell count, defined as the lowest ever reported CD4+ cell count while under active SHCS follow-up, was also extracted for each subject.

Here, cART use was defined as the prescription of at least three antiretroviral drugs, including a protease inhibitor or a non-nucleoside reverse transcriptase inhibitor or three nucleosides, including abacavir. Only persons who had used cART for >1 month before the reference date were classified as users.

The definition of AIDS-related pulmonary disease includes recurrent bacterial pneumonia, pulmonary tuberculosis (TB), or Pneumocystis jiroveci pneumonia, recorded at any time before the reference date.

This study was approved by the local ethical committees of the seven SHCS sites and of the International Agency for Research on Cancer. Written informed consent was obtained from all SHCS participants.

**Statistical analysis**

Logistic regression, conditioned on matching variables, was used to calculate odds ratios (ORs) and corresponding 95% confidence
intervals (95% CIs). Models were also adjusted for smoking status (never/former, current with <30 pack-years, current with ≥30 pack-years, unknown).

RESULTS

Table 1 shows the distribution of the 68 lung cancer cases and controls by matching variables. A majority of lung cancer cases were male (79.4%), had been followed up in the SHCS for >5 years before lung cancer diagnosis (64.7%) and were diagnosed after 1996 (86.8%). Intravenous drug users accounted for 36.8% of cases. As a result of matching on these criteria, these proportions were similar among controls. Lung cancer occurred at a mean age of 50 years. Of the 64 lung cancer cases with follow-up post-cancer, 2000), of whom 96.2% (11.5% former, 84.6% current) of lung cancer cases and 72.9% (24.0% former, 48.9% current) of controls (77.7%) (i.e., those followed up in the SHCS after April 2000), of whom 96.2% (11.5% former, 84.6% current) of lung cancer cases and 72.9% (24.0% former, 48.9% current) of controls were male (79.4%), had been followed up in the SHCS for 5 years. Of the 64 lung cancer cases with follow-up post-cancer, only 9 (14%) were still alive 2 years after lung cancer diagnosis.

The associations of smoking, cART use, AIDS and nadir CD4+ cell count with lung cancer risk are shown in Table 2. Smoking status was known for 52 lung cancer cases (76.5%) and 262 controls (77.7%) (i.e., those followed up in the SHCS after April 2000), of whom 96.2% (11.5% former, 84.6% current) of lung cancer cases and 72.9% (24.0% former, 48.9% current) of controls were smokers. Among controls, the prevalence of smoking was 96.0, 60.0 and 66.4% among IDU, MSM and heterosexual/other, respectively. Lung cancer risk was very strongly associated with current smoking (OR vs never = 14.4, 95% CI: 3.36–62.1), and was also elevated, although not significantly so, among the few former smokers (OR vs never = 3.22, 95% CI: 0.63–16.6). Former smokers were at significantly lower risk than current smokers (OR = 0.22, 95% CI: 0.08–0.59). Odds ratios were slightly higher among current smokers who had smoked ≥30 (OR vs never = 15.9, 95% CI: 3.67–69.1) than <30 (OR vs never = 11.5, 95% CI: 2.42–54.6) pack-years. History of cART use was not significantly associated with lung cancer risk (OR for ever vs never = 0.67, 95% CI: 0.29–1.52). History of AIDS-related diseases, whether with pulmonary disease (OR = 0.49, 95% CI: 0.19–1.28) or without pulmonary disease (OR = 0.53, 95% CI: 0.24–1.18), was not more frequent among cases than controls. Three, three and zero cases of recurrent bacterial pneumonia, P. jiroveci pneumonia and TB, respectively, were previously diagnosed among lung cancer cases. No significant associations or trends with lung cancer were observed for nadir CD4+ cell count (OR for <50 vs ≥200 = 0.73, 95% CI: 0.34–1.55).

The associations of various measures of immunodeficiency with lung cancer risk are shown in Table 3, measured at two different time periods with respect to lung cancer diagnosis (within 1 year and 1–2 years before), and according to two statistical models (unadjusted and adjusted for smoking). No significant associations were observed between lung cancer and CD4+ cell counts, neither when measured within 1 year (OR for <200 vs ≥500 = 0.49–2.96) or 1–2 years (OR = 0.96, 95% CI: 0.41–2.24) before lung cancer diagnosis. Similarly, no significant associations or trends with lung cancer were observed for CD8+ cell counts (Table 3). A CD4+/CD8+ ratio lower than 25 within 1 year of lung cancer diagnosis showed an association with lung cancer risk of borderline statistical significance (OR = 2.15, 95% CI: 1.00–4.59), but this relationship was not seen at 1–2 years before lung cancer diagnosis (OR = 1.07, 95% CI: 0.49–2.36). Although data on HIV viral load were available for a smaller number of cases (n = 54, 79%) and controls (n = 269, 80%), no evidence of an association of lung cancer with higher viral load was observed within 1 year of lung cancer diagnosis (OR for ≥10,000 vs <500 = 1.10, 95% CI: 0.44–2.75).

Adjustment for smoking had no material effect on any of the above findings (Table 3), nor did a sensitivity analysis excluding

Table 2  Relative risk for lung cancer by selected characteristics at reference datea

| Characteristic                          | Lung cancer | Controls | ORb (95% CI) | Smoking-adjusted ORc (95% CI) |
|----------------------------------------|-------------|----------|--------------|------------------------------|
| Overall                                | 68          | 337      |              |                              |
| Smoking status                         |             |          |              |                              |
| Never                                  | 2           | 3.8      | 71           | 27.1                         |
| Former                                 | 6           | 11.5     | 63           | 24.0                         |
| Current                                | 44          | 84.6     | 128          | 48.9                         |
| Unknown                                | 16          | 1.6      | 75           |                              |
| Pack-yearsd                            |             |          |              |                              |
| <30                                    | 16          | 36.4     | 62           | 50.8                         |
| ≥30                                    | 28          | 63.6     | 60           | 49.2                         |
| Unknown                                | 0           |          | 6            |                              |
| History of cART use                    |             |          |              |                              |
| Never                                  | 18          | 26.5     | 77           | 22.8                         |
| Ever                                   | 50          | 73.5     | 260          | 77.2                         |
| History of AIDS-defining disease       |             |          |              |                              |
| No                                     | 54          | 79.4     | 229          | 68.0                         |
| Yes, without pulmonary diseasea        | 8           | 11.8     | 62           | 18.4                         |
| Yes, with pulmonary diseasea           | 6           | 8.8      | 46           | 13.6                         |
| Nadir CD4+ cell count, cells per µl    |             |          |              |                              |
| ≥200                                   | 31          | 45.6     | 142          | 42.4                         |
| 50 – 199                               | 26          | 38.2     | 124          | 37.0                         |
| <50                                    | 11          | 16.2     | 69           | 20.6                         |
| Unknown                                | 0           |          | 2            |                              |

Abbreviations: cART = combined antiretroviral therapy; CI = confidence interval; OR = odds ratio. aSee the ‘Materials and Methods’ section for definition of reference date. bConditioned upon matching variables. cConditioned upon matching variables and adjusted for smoking status (never/former, current with <30 pack-years, current with ≥30 pack-years, unknown).
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Table 3 Relative risk of lung cancer, by markers of immunodeficiency at two different time periods before cancer diagnosis

|                     | One to two years before lung cancer* | Within one year before lung cancer* |
|---------------------|-------------------------------------|------------------------------------|
|                     | N  | %  | ORb (95% CI) | N  | %  | ORb (95% CI) |
| **Lung cancer**     |    |    |              |    |    |              |
| Overall             | 68 | 337|                | 68 | 337|                |
| **CD4+ cell count, cells per μl** |   |    |              |    |    |              |
| ≥500                | 23 | 39.0|              | 20 | 29.4|              |
| 200–499             | 26 | 44.1| 0.76 (0.41–1.43) | 16 | 24.1| 0.59 (0.30–1.16) |
| <200                | 10 | 16.9| 0.96 (0.41–2.24) | 10 | 14.7| 0.97 (0.40–2.34) |
| Unknown             | 9  | 14  |                | 0  | 0   |                |
| **CD8+ cell count, cells per μl** |   |    |              |    |    |              |
| ≥1000               | 28 | 47.5|                | 26 | 38.2|                |
| 500–999             | 25 | 42.4| 0.84 (0.46–1.53) | 35 | 51.5| 1.05 (0.55–1.98) |
| <500                | 6  | 10.2| 0.64 (0.25–1.67) | 7  | 10.3| 0.57 (0.20–1.58) |
| Unknown             | 9  | 14  |                | 0  | 0   |                |
| **CD4+/CD8+ ratio, %** |   |    |              |    |    |              |
| ≥0.50               | 25 | 42.4| 1.25 (0.43–4.00) | 22 | 24.1| 1.01 (0.53–1.90) |
| 0.25–0.49           | 22 | 37.3| 0.78 (0.39–1.55) | 26 | 38.2| 0.78 (0.39–1.55) |
| <0.25               | 12 | 20.3| 0.92 (0.40–2.09) | 20 | 29.4| 0.92 (0.40–2.09) |
| Unknown             | 9  | 14  |                | 0  | 0   |                |
| **HIV viral load, copies per ml** | |   |              |    |    |              |
| <500                | 37 | 68.5| 0.79 (0.38–1.67) | 40 | 72.7| 0.79 (0.38–1.67) |
| 500–999             | 12 | 22.2| 1.79 (0.83–3.86) | 8  | 14.5| 1.79 (0.83–3.86) |
| ≥10 000             | 5  | 9.3 | 0.66 (0.24–1.79) | 7  | 12.7| 0.66 (0.24–1.79) |
| Unknown             | 14 | 24  |                | 13 | 24  |                |

Abbreviations: CI = confidence interval; OR = odds ratio. *Or before the reference date in controls (see the ‘Materials and Methods’ section for definition). †Conditioned upon matching variables. ‡Conditioned upon matching variables and adjusted for smoking (never/former, current with <30 pack-years, current with ≥30 pack-years, unknown).

Figure 1 Box plots of CD4+ cell counts at yearly intervals prior to reference date‡, among lung cancer cases and controls. *Horizontal lines in box plots represent 10th, 25th, 50th (median), 75th and 90th (percentiles). ‡See Materials and Methods section for definition of reference date.

DISCUSSION

Our carefully matched case–control study within the SHCS suggests no evidence for a significant effect of HIV-related immunodeficiency on lung cancer risk in this high-risk population (Franceschi et al, 2010). None of the classic markers of HIV-related immunodeficiency, including low CD4+ cell counts, high HIV viral load nor history of AIDS or AIDS-related pulmonary disease, showed any clear association with lung cancer in the SHCS. A strong relationship between declining CD4+ cell counts and lung cancer risk was recently reported by the French Hospital HIV Database (FHVD) (Guiguet et al, 2009), with a relative risk of 4.8 (95% CI: 2.8–8.0) for 100–199 vs >500 latest CD4+ cell counts. Similarly strong relationships with CD4+ cell counts have been reported in two additional studies from the United States and Europe (Patel et al, 2008; Reekie et al, 2010). Although the CIs around our risk estimates are not entirely compatible with those of previous studies, the findings from the SHCS show no or little association. The reasons for these inconsistencies are unclear, but not all previous studies were supplemented by data linkage with cancer registries to the same extent of the SHCS. Indeed, the FHVD has since been estimated to be only 67% complete with respect to lung cancer diagnosis (Lanoy et al, 2011). Thus, in HIV cohorts that do not obtain comprehensive cancer ascertainment, the more immunosuppressed patients may be overrepresented among lung subjects of unknown smoking status (e.g., smoking adjusted OR for <200 vs >500 CD4+ cell counts at 1–2 years before lung cancer = 0.93, 95% CI: 0.31–2.76). Among controls, there were no significant correlations between any of the markers of immunodeficiency with smoking status (data not shown).

Figure 1 shows mean CD4+ cell counts from 10 years to <1 year before the reference date in lung cancer cases and controls. There was no evidence of any difference in CD4+ cell counts between cases and controls in any time period before the reference date.

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cancer cases as a consequence of investigations of AIDS-related pulmonary diseases. Alternatively, the inability to completely rule out KS and lymphoma localised in the lung, which contributed up to 50% of lung neoplasms in the pre-cART era (Parker et al., 1998), could lead to erroneous interpretations, given the strong associations of these two AIDS-defining cancers with declining CD4+ cell counts. In this study, histological verification allowed the exclusion of 10 lung KS and 13 lung lymphomas. Otherwise, the distribution of histological types were similar to those reported in other series of HIV-positive lung cancer, as well as in age-matched series of HIV-negative cases (Lavelle et al., 2006).

Although confirmed as a very strong risk factor for lung cancer (16-fold increase in risk for ≥30 pack-years), smoking behaviour was not consistently related to markers of immunodeficiency in the SHCS and hence would appear not to be a strong confounder of the association between these markers and lung cancer. However, confounding by smoking behaviour is more problematic when comparing lung cancer between HIV-positive and HIV-negative subjects (Engels et al., 2006; Chaturvedi et al., 2007; Shielis et al., 2010; Ensgis et al., 2011). In the face of such a strong relationship, even with adjustment for smoking measures at an individual level (Levine et al., 2010; Shielis et al., 2010), there remains potential for residual confounding through unmeasured differences in the patterns (e.g., duration of the habit and time since quitting among former smokers) of tobacco use between HIV-positive and HIV-negative ever smokers. A two-fold excess risk of lung cancer is also consistently seen among immunosuppressed kidney transplant recipients (Scully et al., 2007; van Leeuwen et al., 2010) which might suggest a role of immunodeficiency. However, smoking is also associated with indications for kidney transplant, so that confounding by smoking history is also difficult to rule out in this scenario (Wen et al., 2008).

History of AIDS-related pulmonary disease, and in particular recurrent pneumonia, was recently linked to an increase in lung cancer risk in the large HIV/AIDS Cancer Match study (Shebl et al., 2010), suggesting that HIV-related chronic inflammation might potentiate the carcinogenic effects of smoking in the lung (Engels et al., 2006). However, this study had to use hypothetical scenarios to address the problem of confounding by smoking behaviour (Shebl et al., 2010), which is a risk factor for both pulmonary infections (notably TB (Lin et al., 2007; Gajalakshmi and Peto, 2003)) and lung cancer. Although a sample size which was very much smaller, we were unable to reproduce evidence of such an effect in the SHCS, where only 8.8% of lung cancer cases had a history of AIDS-related pulmonary disease (and none with TB). This proportion was actually slightly lower than among matched controls, as was the proportion of patients with a history of AIDS.

In agreement with the lack of association with CD4+ cell counts and history of AIDS, there was no evidence for an effect of cART use on lung cancer in the SHCS. Although other studies have suggested that lung cancer incidence is increasing in the era of cART (Bower et al., 2003), this phenomenon may be largely an artefact of the increased survival of HIV-infected persons and the inability to fully adjust for ageing and corresponding exponential increase in lung cancer by age (Franceschi et al., 2010). Indeed, other studies have suggested that the age-standardised incidence of lung cancer is decreasing over time in persons infected with HIV (Silverberg et al., 2009; Shiels et al., 2011).

If confirmed, the lack of an effect of immunodeficiency on lung cancer risk would not lend support to a role of infection in lung cancer aetiology. Although infection with human papillomavirus has been suggested to have a role in lung cancer, recent large studies in non-HIV infected persons have provided evidence against this hypothesis, particularly among smokers (Simen-Kapeu et al., 2010; Koshiol et al., 2011).

The SHCS has many strengths, including the duration and regularity of follow-up and comprehensiveness of clinical and laboratory information. Approximately half of HIV-infected persons in Switzerland have been enrolled in the SHCS, and both genders and different risk categories are well represented. The supplementation of cancer diagnoses through linkage with cancer registries (Clifford et al., 2005) meant a more comprehensive registration of lung cancer, and the availability of histological and/or cytological confirmation for a majority of cases. The use of a nested case–control approach allowed careful matching for many important correlates of lung cancer risk, smoking and immune status. The principal weakness of the study is the relative small number of lung cancer cases that have accrued in the SHCS, which limits the extent to which small effects of HIV-related immunodeficiency can be ruled out.

As repeatedly noted in HIV-infected cohorts, we observed a high prevalence of smoking in the SHCS (73% among matched controls), and the expected large increased risks for lung cancer among smokers. However, an important finding of this study was the confirmation that, although the lung cancer risk for former smokers did not disappear, it was considerably less than that among current smokers, as seen previously in a cohort of HIV-infected females (Levine et al., 2010) and a number of large studies in the general population (IARC, 2007). Thus, the beneficial effects of quitting smoking appear, in relative terms, as important in HIV-infected persons as in the general population (Peto et al., 2000), although more important in absolute terms on account of their heavy burden of lung cancer.

As HIV-infected persons live longer in the era of cART, it can be expected that smoking will increasingly manifest its long-term oncogenic potential and that this lethal cancer becomes an increasingly important cause of death. Focusing on ways to help to quit smoking (Eki et al., 2006) would be effective in reducing lung cancer in this high-risk population.

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Conflict of interest

The authors declare no conflict of interest.

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