Cessation of cigarette smoking and the impact on cancer incidence in HIV-positive persons: The D:A:D Study

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Summary of article

This study of 35,442 HIV-positive people found the incidence of lung cancer was 10-fold higher 5 years after smoking cessation compared to never smokers; the incidence of other smoking-related cancers returned to levels of non-smokers 2-3 years after smoking cessation.

Abstract

Background

Cancers are a major source of morbidity and mortality for HIV-positive persons on combination antiretroviral therapy, while the clinical benefits of smoking cessation are not well established.

Methods

Participants were followed from 1 January 2004 until first cancer diagnosis, death, or 1 February 2016. Smoking status was defined as ex (<1,1-2,2-3,3-5,≥5 years since stopping), current, and never smokers. Outcomes considered were any cancer, lung cancer, other smoking-related excluding lung and smoking-unrelated cancers. Adjusted incidence rate ratios (aIRR) were calculated using Poisson regression, adjusting for demographic and clinical factors.

Results

35442 persons from the D:A:D study contributed 309803 person years of follow-up. At baseline, 49% of people were current smokers, 21% were ex-smokers, 30% had never smoked. Incidence of all cancers combined (N=2183) was highest <1 year after smoking cessation compared to never smokers (aIRR: 1.66 95%CI: 1.37, 2.02) and not significantly different from never smokers 1-2 years after cessation. Lung cancer incidence (N=271) was elevated <1 year after cessation (aIRR: 19.08 95%CI: 8.10, 44.95) and remained 8-fold higher 5 years after smoking cessation (aIRR: 8.69 95%CI: 3.40, 22.18). Incidence of other smoking-related cancers (N=622) excluding lung was elevated in the first year after cessation (aIRR: 2.06 95%CI: 1.42, 2.99) and declined to a level similar to non-smokers thereafter. Incidence of smoking-unrelated cancers (N=1290) was unrelated to smoking status.

Conclusion

Lung cancer incidence remained elevated for more than 5 years after smoking cessation. Deterring uptake of smoking and smoking cessation efforts should be a priority to reduce the future risk of cancer.

Introduction

Cancers are a major source of morbidity and mortality in people living with HIV (PLWH) in the context of available and effective antiretroviral treatment (cART), likely due to a combination of ongoing inflammation, reduced immune function, life style related factors, and longer life expectancy [1, 2] However, the relative contribution of life style related risk factors, such as smoking, towards elevated cancer risk, is not clear [3]. Studies of PLWH often find higher prevalence of current smoking (between 40–70%) than similar HIV-negative populations [4-6] and PLWH on cART lose more life years due to smoking rather than due to HIV infection [6, 7]. Furthermore, the risk of death from any cause in those who smoke was found to be 2–4-fold higher than never smokers in PLWH on cART [6, 7].

In the general population, tobacco smoking is an established risk factor for many cancers and the leading causes of preventable cancer worldwide [8]. Current smokers are on average 2-3 times more likely to die from any cause than those who have never smoked mainly due to smoking related diseases in high income countries [9, 10]. It has been estimated that smokers lose on average a decade of life compared with non-smokers in the general population [9, 11]. The benefits of smoking cessation in the general population are well established and include reduced mortality and incidence of cancers (particularly lung) relative to those who continue smoking [12]. It has been estimated that the benefits of cessation on the incidence of lung cancer take between 5–9 years to become apparent, and increase with longer time since cessation [13, 14].

The incidence of most cancers, including lung, increase with older age [15]. Therefore, as PLWH age [16] and the burden of these cancers are expected to increase [17, 18], smoking becomes a critically important evidence-based modifiable risk factor [19]. Despite the well characterised harms of smoking in PLWH, the clinical benefits of smoking cessation on cancer risk have not previously been reported in large epidemiological studies. The aim of this study was to estimate cancer rates after smoking cessation in PLWH from the D:A:D study.

Methods

Study design and participants

The Data Collection on Adverse events of Anti-HIV Drugs (D:A:D) Study is a prospective multinational cohort collaboration established in 1999 with more than 49000 HIV-1-positive people followed in Europe, the USA, and Australia [20]. Data for routine clinical care, including demographic factors, HIV treatment, laboratory values, and AIDS-defining events (including AIDS-defining cancers, collected in real-time and centrally validated since January 1 , 2014)) are collected at enrolment and annually thereafter. Non-AIDS-defining cancers (NADC) have been prospectively collected in real time in the D:A:D study since 1 January 2004. Detailed information on all NADCs is collected via a designated case report form (for details see http://www.chip.dk/Studies/DAD/Study-Documents), supported by additional source documentation (such as imaging results and hospital records). All events are centrally validated by a physician at the D:A:D coordinating center, with a proportion of events selected for review by an external oncologist. Events are regularly monitored for accuracy, with random monitoring at participating sites to ensure complete case ascertainment.

Inclusion criteria

Baseline was defined as the latest of date of study entry or 1 January 2004, and people were followed from baseline until the earliest of their first cancer diagnosis, last visit plus 6 months, death, or 1 February 2016. There were 42334 PLWH with follow up after the 1 January 2004. We excluded a total of 6892 people (of which 7 had no recorded gender, 2442 people had a prior cancer diagnosis, 16 had a first diagnosis of metastasis, and 4463 had no smoking information during follow-up) leaving 35442 people available for analysis.

Outcomes

Four main outcomes were assessed. (1) The first diagnosis of any cancer during prospective follow-up (2) first diagnosis of lung cancer, and (3) any smoking related cancer excluding lung cancer (including cancers of the head and neck, oesophagus, stomach, pancreas, liver, bladder, kidney and urinary, colon and rectal, cervical, ovary, acute myeloid leukaemia and chronic myeloid leukaemia [21]). All remaining cancers not included in (2) or (3) were considered to be smoking unrelated (4). The cancers

considered to be smoking related were selected based on the IARC Monographs on the Evaluation of Carcinogenic Risks to Humans [22].

Smoking status and time since cessation

xmoking status was time-updated in all analyses presented and categorised into 8 mutually exclusive categories; never smokers, current smokers, ex-smokers at baseline (for whom time since cessation could not be calculated as date of stopping was not recorded), and ex-smokers who stopped smoking during prospective follow-up, categorised as those who stopped <1 year, 1–2, 2–3, 3–5, and ≥5 years prior. If they restarted smoking during follow-up and were an ex-smoker at baseline, they would move from the ex-smokers at baseline to the current smokers category at that date. A person restarting smoking who was an ex-smoker who stopped during follow-up would move from one of the ex-smokers during follow-up categories to the current smokers category. If they ceased smoking again, they would move back to the ex smokers who stopped during follow-up category and their time since cessation would restart. . Smoking information is reported in the D:A:D Study as current smoker (yes/no) and ever smoker (yes/no) at each visit, but more specific information, such as cigarette or pipe smoking, or intensity of smoking, is not available. Change in smoking behaviour was attributed to the midpoint of the time between visits. If smoking information was missing, previous smoking information was carried forward. Duration of smoking was calculated as the cumulative number of years spent as a current smoker during active follow-up.

Statistical analysis

Incidence rates per 1000 person years of follow-up (PYFU) of each outcome were calculated according to smoking status. Poisson regression models were used to explore the association between smoking status and each outcome separately. Models were adjusted for baseline factors (gender, HIV transmission group, ethnicity, calendar year of baseline) and time varying factors (age, body mass index (BMI), current CD4 cell count, current HIV-Viral load (HIV-VL), hepatitis B (positive HBsAG surface antigen test or presence of detectable HBV DNA) and C virus co-infection (positive HCV surface antibody test), AIDS-diagnosis (excluding cancers), cardiovascular disease (CVD, including myocardial infarction, stroke and invasive cardiovascular procedures), diabetes (diagnosis, receiving diabetes medication), cART use (using ≥1 protease inhibitor [PI] or ≥1 non-nucleoside reverse transcriptase inhibitor [NNRTI]), and duration of smoking after enrolment in the D:A:D Study (years). Lung cancer subtypes were classified as small cell (SCLC), non-small cell lung cancer (NSCLC; Adenocarcinoma,

squamous cell carcinoma, large cell carcinoma, and unclassified NSCLC), other lung cancer subtypes, and unknown subtypes (20%).

All statistical tests were two sided and a type I error rate of 5%. All statistical analyses were performed using SAS 9.4 (Statistical Analysis Software, Cary NC, USA).

Results

There were 35442 PLWH included in the analysis who contributed 309803 PYFU with a median follow-up of 9.9 (IQR: 6.7, 12.0) years per person and a median of 2.4 (IQR: 0.9, 4.7) following smoking cessation. Of the 35442 people included, 2183 people developed a cancer during follow-up (incidence rate [IR]=7.05, 95%CI: 6.76, 7.35/1000 PYFU). Of these, 271 (12%, IR: 0.88, 95%CI: 0.78, 0.99/1000 PYFU) were lung cancers. 160 (59%) of these were NSLCC, where adenocarcinomas were the most common subtype (n=86, 32%), followed by squamous cell (n=40; 15%), and unclassified NSCLC (n=34; 13%). SCLC and other subtypes accounted for 31 (11%) and 26 (10%) of all lung cancers diagnosed, respectively. The subtype was not recorded for 54 (20%) of lung cancers. There were 622 (28%, IR: 2.01, 95%CI: 1.86, 2.17/1000 PYFU) other smoking related cancers (excluding lung), and 1290 (59%, IR: 4.16, 95%CI: 3.94, 4.40/1000 PYFU) were smoking unrelated cancers.

Baseline characteristics

Baseline characteristics of the study population, as well as those who developed cancer during follow are shown in Table 1. Overall, 16.6% of people were aged ≥50 years at baseline with a median age of 40 (IQR 34, 46) years, 72.6% were of male gender, 53.2% were of white ethnicity (37.1% had unknown ethnicity), and 41.9% acquired their HIV through sex between men. Just over half were on cART (52.0%) at baseline, 40.6% had a HIV-VL of ≤ 50 copies/mL and a median CD4 cell count of 444 (294,632) cells/mm^3.

The distribution of smoking status at baseline is shown Figure 1. Of the 35442 people included, 49% were reported to be current smokers at baseline, 21% were ex-smokers and 30% were never smokers. A similar distribution is demonstrated in those who developed any cancer, smoking related cancers (excluding lung) and smoking unrelated cancers during follow-up. In those who developed lung cancer, a higher proportion were reported as current smokers at baseline (72%) and a lower proportion were reported as never smokers (6%).

Crude incidence rates by smoking status

The crude incidence of each outcome by smoking status is shown in Figure 2 and Supplementary Table 1. The graphs are on different scales in order to clearly display the associations. The incidence of all cancers was highest within the first year of smoking cessation (Figure 2A), after which the incidence declined to a similar level to current smokers and remained stable thereafter (unadjusted P for trend

<0.01). Lung cancer incidence was negligible in those who never smoked (Figure 2B), with <1 event per 10000 PYFU, but was highly elevated in current smokers. Incidence was highest within the first year of smoking cessation after which the incidence declined to a similar level to current smokers and remained stable thereafter (P for trend=0.02, P trend excluding first year after cessation=0.13). Incidence of smoking related cancers (excluding lung) was highest in the first year after cessation, and declined thereafter (P for trend =0.31, Figure 2C). Incidence of smoking unrelated cancers was stable for the first 3 years following smoking cessation, with a slight decline in incidence thereafter (P for trend = 0.01, Figure 2D).

Adjusted incidence rate ratios

The adjusted incidence rate ratios (IRRs) of each cancer outcome for smoking status are shown in Figure 3 and Supplementary Table 1. The graphs are on different scales in order to clearly display each association. After adjustment, the incidence of all cancer combined was 1.28 (95%CI: 1.10, 1.49)-fold higher in current smokers relative to never smokers. A similarly elevated incidence was observed within one year of cessation relative to non-smokers, which declined with increasing time since cessation (P for trend=0.03). Lung cancer incidence was 13-fold higher in current smokers relative to never smokers (aIRR: 13.13; 95%CI: 5.83, 29.55). In those who ceased smoking during follow-up, the incidence was 19-fold higher (aIRR: 19.08 95%CI: 8.10, 44.95) in the first year following cessation, however, the incidence then quickly reduced to 11-fold higher (aIRR: 11.37 95%CI: 4.32,29.92) after 1–2 years of cessation and remained stable thereafter. With only 12 events and 12986 PYFU in those who ceased smoking > 5 years, we were not able to investigate this group in more detail. Although the P for trend was significant (P=0.02), this was driven by the increase in the first year and there was no evidence of a decline thereafter (P trend excluding first year after cessation=0.14). Incidence of smoking related cancers (excluding lung) was highest within the first year of smoking cessation (aIRR: 2.06 95%CI: 1.42, 2.99) but was no longer significantly different to never smokes after 1-2 year of smoking cessation (aIRR: 1.32 95%CI: 0.82, 2.12), albeit with wide confidence intervals. However it should be noted that the magnitude of association in this group was similar to that of current smokers (aIRR: 1.32 95%CI: 0.97,1.78). Incidence of smoking unrelated cancers did not vary according to smoking status (global P=0.05). There was no evidence that the association between smoking status and cancer incidence differed according to CD4 cell count (all P for interaction> 0.05).

Discussion

To our knowledge, this is the first study to investigate the impact of smoking cessation on cancer incidence in PLWH, within a large observational study with a relatively large number of prospectively collected cancers. Lung cancer incidence remains highly elevated in PLWH at a level similar to current smokers >5 years after cessation. Lung cancer incidence fell after the first year of cessation, however, no decline was evident thereafter and incidence remained more than 8-fold higher than among never smokers. In contrast, incidence of other smoking related cancers (excluding lung) declined after 1 year of smoking cessation. As expected, no association between smoking behaviour and smoking unrelated cancer was shown.

The peak in lung cancer and other smoking related cancers (excluding lung) in the first year following cessation observed is likely driven by existing disease [23]. This may include people who quit smoking because they feel unwell either because of their undiagnosed (subclinical) cancer or because of another condition (such as chronic obstructive pulmonary disease), which may subsequently lead to a cancer diagnosis due to increased intensity of medical surveillance [24]. We used the midpoint between visits to define the date of smoking cessation, which may have resulted in some misclassification bias, although we would assume this would affect all categories including duration since smoking cessation equally. It is possible that the increase in cancer incidence in the first year following cessation may reflect a larger impact of reverse causality in PLWH, possibly due to higher frequency of contact with care and because of an elevated risk of other comorbidities [25].

The mechanisms for the non-declining lung cancer incidence in PLWH are unknown, and longer follow-up may be need to see evidence of a declining incidence with time since cessation. We were limited by only 12 lung cancers in those who had >5 years since smoking cessation, and were not able to investigate this key group further.it is well known that smoking rates are often higher in PLWH compared to HIV-negative people, and some studies also indicate that lung cancer may develop with less smoking exposure [26]. HIV infection may contribute to increased susceptibility of lung cancer through reduced immune surveillance, increased systemic and pulmonary inflammation, and elevated risk of lung infections [27, 28]. It has also been proposed that HIV viral proteins may have some direct oncogenic activity [29], and the lung may serve as a compartment in which HIV activity may not reflect systemic viral suppression [30]. Histological subtypes of lung cancer have different risk factors including smoking. The greatest increased risk of cancer with smoking is seen for small cell and

squamous cell carcinoma with a smaller, but raised risk for adenocarcinoma . Studies have noted a higher than expected number of adenocarcinomas in HIV+ people, which may contribute to our results [31]. Alternatively, studies have suggested that the elevated lung cancer risk in PLWH could reflect more intensive medical evaluations in people with HIV, particularly after an AIDS-defining event [24, 32]. Furthermore, disparities could reflect differences in intensity, duration, of historical smoking, or age at cessation in PLWH compared to HIV-negative people [33].

Smoking prevention and cessation are the most effective ways to prevent lung cancers. Cessation tools, including behavioural interventions and nicotine replacement therapy, have been shown to be effective for smoking cessation for smokers in PLWH [34, 35]. In addition, it is important to keep in mind that the benefits of smoking cessation are not restricted to cancers, but can have beneficial all smoking related diseases and also lengthen life [22, 36]. This is particularly important in PLWH who are known to have higher risk of many diseases which can be exacerbated by smoking, including CVD, renal complications, bone fractures and metabolic bone diseases, COPD, pulmonary infections, and pneumonia [37, 38]. Further, population attributable fractions associated with smoking have been demonstrated to be around 20% for all cancers in PLWH and 9% for non-smoking related cancers [39]. Studies in PLWH have shown a lower risk of AIDS-defining events, CVD, non-AIDS-defining cancers, and pneumonia in those who cease smoking [37, 38, 40].

The major strengths of this study are the availability of data from a large, heterogeneous study population with a relatively large numbers of prospectively collected and centrally validated cancers, for which there is also access to individual level patient and clinical information. All non-AIDS cancers are centrally validated according to robust criteria including the requirement of histological evidence of cancer and/or other applied diagnostic methods, and evaluated externally and monitored. However, some limitations need to be taken into account. Smoking information in the D:A:D Study is updated at the clinic visit, therefore, exact start and stop dates of smoking episodes, intensity, number of cigarettes smoked, and lifetime duration were not available. This is an important limitation as the possible impacts of smoking duration and intensity cannot be assessed. Furthermore, smoking information is collected according to physician inquiry and smoking (and possibly restarting of smoking after cessation) may be underreported. However, a previous D:A:D analysis found a decline in CVD following cessation to that of never smokers after 3 years [37], which was similar to results from the general population. This provides some evidence of validity of the smoking information in the D:A:D

Study. Another limitation is that although median follow-up was 10 years this is comparatively short relative to studies in the HIV-negative population with follow-up of 30 years or longer.

In conclusion, incidence of lung cancer incidence in PLWH was more than 8-fold higher than never smokers several years after cessation, at a similar level to current smokers, and with no evidence of a decline after the first year. This suggests that the oncogenic potential for smoking is not reduced for lung cancer in the time frame that we have investigated. This is in contrast with similar studies in HIV-negative people, which show a consistent decline in lung cancer incidence with increasing time since cessation. Deterring uptake of smoking and smoking cessation efforts should be a priority to reduce the risk of cancer, however, monitoring and awareness of lung cancer should continue in those who stop smoking. Studies following PLWH throughout their lifetimes are needed to determine when the benefit of cessation will be seen.

Tables and figure captions

Table 1 Baseline characteristics

Figure 1 Smoking status at baseline

Figure 2 Crude incidence rate (IR) of (A) all cancers, (B) lung cancers, (C) smoking related cancers (excl. lung), and (D) other smoking related cancers, by smoking status P-for trend refers to testing trend among time since smoking cessation.

Figure 3 Adjusted* incidence rate ratio (aIRR) according to smoking status with never smokers as the reference category. P-for trend refers to testing trend among time since smoking cessation.

Footnote to Figure 3. *Adjusted for baseline factors (gender, HIV transmission group, ethnicity, calendar year of baseline) and time varying factors (age [<40, 40-49, >50 year], body mass index (BMI; <18, 18-26, 27-30, >30 and unknown]), current CD4 cell count [<100, 100-199,200-299, 300-399, 400-499, ≥500, unknown), current HIV-Viral load (HIV-VL; <50, 50-1000, >1000, unknown copies/ml]), age, body mass index (BMI), current CD4 cell count, current HIV-Viral load (HIV-VL), hepatitis B (positive HBsAG surface antigen test or presence of detectable HBV DNA) and C virus co-infection (positive HCV surface antibody test), AIDS-diagnosis (excluding cancers), cardiovascular disease (CVD, including myocardial infarction, stroke and invasive cardiovascular procedures), diabetes (diagnosis, receiving diabetes medication), cART use (using ≥1 protease inhibitor [PI] or ≥1 non-nucleoside reverse transcriptase inhibitor [NNRTI]), and duration of smoking after enrolment in the D:A:D Study (years).

Conflicts of Interest

Dr. Law reports grants from Boehringer Ingelhiem, Gilead Sciences, Merck Sharp & Dohme, Bristol-Myers Squibb, Janssen-Cilag, ViiV HealthCare, personal fees from Gilead Sciences, Sirtex Pty Ltd, outside the submitted work. Dr. Petoumenos reports grants from pharmaceutical consortium - ViiV Healthcare Australia, Gilead Sciences Australia; MSD Australia; Janssen Asia Pacific, outside the submitted work. Dr. Sabin reports grants from The D:A:D Oversight Committee, during the conduct of the study; personal fees from Gilead Sciences, personal fees from ViiV Healthcare, personal fees from Janssen-Cilag, outside the submitted work. Dr. Bonnet reports personal fees from Gilead, ViiV Healthcare, Janssen, MSD, non-financial support from Gilead, ViiV Healthcare, Janssen, MSD, grants from Gilead, Janssen, outside the submitted work. Dr. Reiss reports grants from Gilead Sciences, grants from ViiV Healthcare , grants from Janssen Pharmaceutica, grants from Merck&Co, other from Gilead Sciences, other from ViiV Healthcare, other from Merck&Co, other from Teva Pharmaceutical Industries, other from Janssen Pharmaceutica, outside the submitted work. Dr. Pradier reports personal fees from GILEAD, outside the submitted work. Dr. Mocroft reports grants from DAD Oversight Commitee, during the conduct of the study; personal fees from ViiV and Gilead, outside the submitted work. Authors not mentioned report no conflict of interest.

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