Time to first cigarette and lung cancer risk in Japan

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Background: Cigarette smoking is the major cause of lung cancer (LC). Although the time to first cigarette (TTFC) of the day is a distinct indicator of nicotine dependence, little information is available on its possible relation to LC.

Patients and methods: This case–control study includes a total of 1572 incident LC cases and 1572 non-cancer controls visiting for the first time the Aichi Cancer Center Hospital between 2001 and 2005. We estimated the odds ratio (OR) and 95% confidence interval (CI) for TTFC using a logistic regression model after adjustment for several potential confounders.

Results: TTFC was inversely associated with the risk of LC. This association was consistent across histological subtypes of LC. For all LCs considered among ever smokers and after accurate allowance for smoking quantity and duration, besides other relevant covariates, compared with TTFC > 60 min, the adjusted ORs were 1.08 (95% CI, 0.73–1.61) for TTFC of 31–60 min, 1.40 (0.98–2.01) for 6–30 min and 1.86 (1.28–2.71) for within 5 min (Ptrans.< < 0.001). Statistically marginally significant heterogeneity by histological subtype was observed (P heterogeneity, 0.002).

Conclusions: Nicotine dependence, as indicated by the TTFC, is associated with increased risk of LC and is therefore an independent marker of exposure to tobacco smoking.

Key words: nicotine dependence, smoking, addiction, lung cancer

Introduction

The association between cigarette smoking and lung cancer (LC) risk was firmly established in the 1950s [1], and the direct associations of risk with younger age at smoking initiation, greater number of cigarettes per day (CPD), longer duration of cigarette smoking and the inverse one with years since quitting smoking, have been well established [2–7].

The time to first cigarette (TTFC) after waking is a specific indicator of nicotine dependence [8–13] and is also associated with other aspects of smoking behavior, including difficulty in smoking cessation, smoking relapse, and tolerance. It is one of...
the six items of the Fagerstrom Test for Nicotine Dependence (FTND) [14–16] and one of the two items of the Heavy Smoking Index (HSI) [14], which have been shown to provide a reliable measure of nicotine dependence [17, 18]. In addition, a shorter TTFC was recently associated with higher levels of cotinine in active current smokers [19]. Nicotine and its metabolite, cotinine, have been associated with LC promotion in vitro and in rodents [20], but the issue of carcinogenicity of nicotine remains open to discussion [21]. Furthermore, high correlations between urinary levels of cotinine and 4-(methyl nitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) and 1-hydroxypyrene (1-HOP), which are respectively the metabolites of tobacco-specific carcinogens 4-(methyl nitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and polycyclic aromatic hydrocarbons (PAH), were observed [22]. Therefore, TTFC may be an indicator of smoking exposure as well as of nicotine dependence, and thus a shorter TTFC could be associated with increased risk of smoking-related cancers. However, there are only a few studies evaluating this association [23–26].

Here, we investigate the association between TTFC and LC risk in a Japanese population, using data from a large case–control study.

**materials and methods**

**study population**

Incident LC cases (n = 1552) and non-cancer controls (n = 1552) were selected from the database of the Hospital-based Epidemiologic Research Program at Aichi Cancer Center (HERPACC) enrolled between 2001 and 2005 [27, 28]. Both case and controls had no cancer or history of neoplasia. Among the subjects, 903 cases and 1143 controls were ever smokers. The controls were selected randomly and individually matched to cases by 5-year age category and sex, with a control-to-case ratio of 1:1 from the 14 329-control pool. A total of 3144 participants (1572 cases and 1572 controls) were included in the study. The study was approved by the Institutional Ethical Committee of Aichi Cancer Center. Detailed description of subjects is given in supplemental methods, available at *Annals of Oncology* online.

**information on time to the first cigarette of the day**

Information on TTFC was collected at the first visit of the participants using a self-administered questionnaire. TTFC was asked with the following four options: ≤5 min, 6–30, 31–60 and >60 min.

**evaluation of other lifestyle factors**

We obtained smoking status (nonsmoker, former smoker and current smoker) with duration (years) and CPD. We defined nonsmokers as those who smoked less than 100 cigarettes in their lifetime and former smokers as those who had quit smoking at least 1 year. We also obtained other lifestyle factors, including alcohol drinking, consumption of fruits and vegetables (FV), occupation and socioeconomic status. Details are described in the supplemental materials, available at *Annals of Oncology* online.

**data analyses**

To assess the association between the TTFC and the risk of LC, we estimated the odds ratios (ORs) and 95% confidence intervals (CIs), using logistic regression models. First, we evaluated impacts of TTFC among current and former smokers separately, relative to never smokers, by using all the subjects adjusted for confounders. To allow for differences in smoking intensity and duration across levels of TTFC, we evaluated TTFC excluding never smokers. For this analysis, we used unconditional logistic regression models adjusted for the same covariates of the overall analyses after further allowance for smoking status, number of CPD and duration of smoking. We conducted stratified analyses by histological subtype. Heterogeneity across strata of confounders and across strata of histological subtypes was assessed by likelihood-ratio-tests. Mean numbers of cigarettes smoked per day were derived from analysis of variance (ANOVA) and were adjusted for confounders. We applied χ²-test when appropriate. The details of data analysis are given in supplemental method, available at *Annals of Oncology* online.

**results**

Demographic characteristics and selected lifestyle habits of the participants are shown in Table 1 and supplementary Table S1, available at *Annals of Oncology* online. Age and sex were matched by design. The proportion of current smokers was higher in cases than in controls. Cases smoked more CPD and for longer time, with significant trends in risk. Compared with controls, cases ate fewer portions of FV, and were more frequently blue-collar workers.

Table 2 presents the association between TTFC in former and current smokers and LC, overall and across histologies. In the analysis of LC overall, compared with never smokers, the ORs for TTFC of >60, 31–60, 6–30 and ≤5 min were 1.15 (95% CI, 0.76–1.78), 1.63 (1.09–2.42), 2.42 (1.74–3.35) and 2.76 (1.94–3.92) for former smokers, and 1.65 (0.94–2.87), 2.67 (1.73–4.11), 4.05 (3.02–5.43) and 6.57 (4.87–8.85) for current smokers. For the stratified analyses by histological subtype, the point estimates were greater in squamous (SQ)/small-cell carcinoma (SM) combined (SQ/SM) than in adenocarcinoma (AD).

When the analysis was restricted to ever smokers (Table 3) and allowance was made for smoking status plus quantity and duration of smoking, compared with TTFC of >60 min after waking, the ORs for overall LC were 1.08 for 31–60 min, 1.40 for 6–30 min and 1.86 for within 5 min. With reference to specific histological subtypes, the inverse association with TTFC was stronger for SQ/SM than for AD and the estimates between the two histological subtypes were heterogeneous (P_{heterogeneity} = 0.002). The ORs for TTFC within 5 min, compared with >60 min, were 1.35 (95% CI, 0.81–2.24) for AD and 3.28 (1.56–6.91) for SQ/SM. When the analysis was further restricted to current smokers, compared with TTFC of >60 min, the ORs for overall LC were 1.14 for 31–60, 1.40 for 6–30 min and 2.07 for within 5 min. The corresponding values for TTFC of within 5 min compared with that of >60 min were 1.42 (95% CI, 0.65–3.09) for AD and 3.41 (1.02–11.4) for SQ/SM, in the presence of significant heterogeneity between these two histological subtypes. This association was consistently observed in stratified analyses by covariates (supplementary Table S2, available at *Annals of Oncology* online).

We also investigated an association between TTFC and the smoking intensity expressed in the number of cigarettes smoked per day and observed a TTFC dosage effect with the mean number of cigarettes smoked per day (supplementary Table S1, available at *Annals of Oncology* online). The mean number of cigarettes smoked per day was negatively correlated with TTFC among ever smokers. Data not shown, we did not observe any
significant association between TTFC and smoking duration, which is one of the components of pack-years.

discussions

In the first large case–control study in an Asian population, we found that TTFC was independently associated with the risk of
LC after adjustment for smoking status, quantity and duration of smoking. A shorter TTFC is associated with increased risk with a significant trend in risk. While this inverse association was observed for two specific histological subtypes, AD and SQ/SM, the association for SQ/SM was stronger than that for AD. Moreover, the association was consistent across most strata of potential confounders, suggesting robustness of results.

Epidemiologic studies have shown a dose–response relationship between the number of CPD and the LC risk [14]. However, a level of inter-individual variability exists in the way smokers regulate their nicotine intake per cigarette [29]. Moreover, the correlation between the frequency of smoking and cotinine level is moderate in light smokers and low in heavy smokers [19]. Muscat et al. recently reported that the plasma and urine levels of cotinine showed different patterns of increase with increasing number of CPD between light smokers and heavy smokers [31]. Although the changes in cigarette design and smoking behavior may have led to changes in cigarette design and smoking behavior may have led to changes in tobacco smoke exposure, the strength of the association with smoking risk remains consistent across most strata of potential confounders, suggesting robustness of results.

<table>
<thead>
<tr>
<th>Combined categories of smoking dependence and smoking status</th>
<th>LC over all</th>
<th>Adenocarcinoma (AD)</th>
<th>Squamous/small-cell carcinoma (SQ/SM)</th>
<th>P for heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Former smokers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;60</td>
<td>75</td>
<td>141</td>
<td>Reference</td>
<td>48</td>
</tr>
<tr>
<td>31–60 min</td>
<td>126</td>
<td>160</td>
<td>1.08 (0.73–1.61)</td>
<td>68</td>
</tr>
<tr>
<td>6–30 min</td>
<td>392</td>
<td>308</td>
<td>1.40 (0.98–2.01)</td>
<td>184</td>
</tr>
<tr>
<td>≤5 min</td>
<td>529</td>
<td>262</td>
<td>1.86 (1.28–2.71)</td>
<td>249</td>
</tr>
<tr>
<td>Current smokers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;60 min</td>
<td>28</td>
<td>41</td>
<td>Reference</td>
<td>19</td>
</tr>
<tr>
<td>31–60 min</td>
<td>64</td>
<td>58</td>
<td>1.14 (0.60–2.14)</td>
<td>34</td>
</tr>
<tr>
<td>6–30 min</td>
<td>257</td>
<td>175</td>
<td>1.40 (0.80–2.46)</td>
<td>123</td>
</tr>
<tr>
<td>≤5 min</td>
<td>409</td>
<td>158</td>
<td>2.07 (1.16–3.69)</td>
<td>185</td>
</tr>
</tbody>
</table>

ORs were calculated by an unconditional logistic regression model adjusted for age, alcohol consumption, fruit and vegetable intake and socioeconomic status. Heterogeneity test was carried out by likelihood-ratio test after estimations by an unconditional logistic regression model adjusted for age, sex, CPD, duration of smoking, smoking status, alcohol consumption, fruit and vegetable intake and occupation, except for a stratifying factor. Missing values for covariates were excluded in the ANOVA models.

Muscet al. found that TTFC was significantly inversely associated with the risk of LC in a case–control study among ever smokers [23]. Using data from the same database, similar associations were reported for the risks of upper aerodigestive tract (UADT) cancers among ever smokers [24, 25]. In addition, we found a similar association between TTFC and UADT cancer risk in a large case–control study here in Japan [26]. The findings of this study confirm these previous observations that TTFC is a risk factor of smoking-related cancers, independent from other indicators of tobacco consumption, including the duration of smoking, and the number of CPD. Moreover, our findings and previous observations suggest that TTFC is an indicator of tobacco dependence impacting on cancer risk that is not adequately measured by the other aspects of smoking, which is supported by evidence that TTFC is highly correlated with the cotinine level [19] and in turn, the cotinine level correlates with tobacco-related carcinogens [22].

To the best of our knowledge, ours is the first study investigating the association between TTFC and LC risk by histological subtypes. The level of cotinine in plasma and urine was significantly and highly correlated with the metabolites of NNK and PAH, namely NNAL and 1-HOP [19], which have been related to AD and squamous cell carcinoma (SQ) of the lung, respectively [30]. That may explain our finding that TTFC was associated with the risk of major histological subtypes, AD and SQ/SM. The strength of the association with smoking appears, however, to differ by histological subtype due to different exposure of tobacco smoke particles to sites that are more peripheral in the respiratory tract. Compared with AD located in the peripheral sections of the lung, SQ/SM occurs mainly in the large central bronchi, an area highly exposed to large particles from tobacco smoking [31]. Although the changes in cigarette design and smoking behavior may have led
to a stronger association of AD with smoking than in the past, through an increase in the dose of NNK [32] and smoker compensation [33], the relative risk for smoking is highest in SM, followed by SQ and lowest in AD [2]. This may also explain the heterogeneity by histological subtype observed in our study.

Our study has several strengths. First, the size of the study was large enough and the participation rate was almost complete for both cases and controls, and the questionnaire including smoking was satisfactorily valid and reproducible [34–36]. In addition, control participants were selected from the same hospital and almost all participants lived in the same area, it is likely that they would refer to ACCH for cancer treatment or diagnosis. We previously confirmed that the questionnaire-based lifestyle characteristics in this population are similar to those of the general population in Nagoya City [28], warranting generalizability of our findings to Japanese. Second, potential confounding by sex, alcohol drinking, fruit and vegetable intake and SES was considered by individual matching and statistical confounding by sex, alcohol drinking, fruit and vegetable intake and SES was considered by individual matching and statistical adjustment in the analyses. Potential limitations of our study are described in supplementary discussion, available at Annals of Oncology online.

In conclusion, our case–control study found that TTFC is a risk factor for LC, independent of other conventional smoking exposure measurements.

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disclosure

The authors have declared no conflicts of interest.

references

Talactoferrin alfa versus placebo in patients with refractory advanced non-small-cell lung cancer (FORTIS-M trial)

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Background: Talactoferrin alfa is an oral dendritic cell (DC)-mediated immunotherapy (DCMI). We tested whether talactoferrin was superior to placebo in advanced non-small-cell lung cancer (NSCLC).

Patients and methods: An FORTIS-M trial was an international, multicenter, randomized, double-blind comparison of talactoferrin (1.5 g p.o. BID) versus placebo BID, in patients with stage IIIB/IV NSCLC whose disease had failed two or more prior regimens. Treatment was administered for a maximum of five 14-week cycles. The primary efficacy end point was overall survival (OS); secondary end points included 6- and 12-month survival, progression-free survival (PFS), and disease control rate (DCR).

Results: Seven hundred and forty-two patients were randomly assigned (2:1) to talactoferrin (497) or placebo (245). The median OS in the intent-to-treat (ITT) population was 7.66 months in the placebo arm and 7.49 months in the talactoferrin arm [hazard ratio (HR), 1.04; 95% CI, 0.873–1.24; P = 0.6602]. The 6-month survival rates were 59.9% (95% CI, 53.4% to 65.8%) and 55.7% (95% CI, 51.1% to 59.9%), respectively. The 12-month survival rates were 32.2% (95% CI, 28.3% to 38.2%) and 30.9% (95% CI, 26.8% to 35%), respectively. The median PFS rates were 1.64 months and 1.68 months, respectively (HR, 0.99; 95% CI, 0.835–1.16; P = 0.8073). The DCRs were 38.4 and 37.6%, respectively. The 6-month survival rates were 59.9% (95% CI, 53.4% to 65.8%) and 55.7% (95% CI, 51.1% to 59.9%), respectively. The 12-month survival rates were 32.2% (95% CI, 28.3% to 38.2%) and 30.9% (95% CI, 26.8% to 35%), respectively. The median PFS rates were 1.64 months and 1.68 months, respectively (HR, 0.99; 95% CI, 0.835–1.16; P = 0.8073). The DCRs were 38.4 and 37.6%, respectively [stratified odds ratio (OR), 0.96; 95% CI, 0.698–1.33; P = 0.8336]. The safety profiles were comparable between arms.

Conclusions: There was no improvement in efficacy with talactoferrin alfa in patients with advanced NSCLC whose disease had failed two or more previous regimens.

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