Time to First Cigarette and Upper Aerodigestive Tract Cancer Risk in Japan

Keitaro Matsuo, Silvano Gallus, Eva Negri, Daisuke Kawakita, Isao Oze, Satoyo Hosono, Hidemi Ito, Shunzo Hatooka, Yasuhisa Hasegawa, Masayuki Shinoda, Kazuo Tajima, Carlo La Vecchia, and Hideo Tanaka

Abstract

**Background:** Cigarette smoking is the major cause for upper aerodigestive tract (UADT) cancers. The time to first cigarette (TTFC) of the day is a distinct indicator of nicotine dependence, but scanty information is available on its possible relation with UADT cancers (oral, oropharyngeal, hypopharyngeal, laryngeal, nasopharyngeal, and esophageal cancers).

**Methods:** This case–control study includes a total of 1,009 incident UADT cancer cases and 3,027 age- and sex-matched noncancer controls admitted to the Aichi Cancer Center (Nagoya, Japan) between 2001 and 2005. We estimated OR and 95% confidence intervals (CI) for TTFC using logistic regression models after adjustment for several potential confounders.

**Results:** TTFC was inversely related to the risk of UADT cancer, and this association was consistent across subtypes of head and neck cancer and esophageal cancer. For all UADT cancers considered among ever smokers and after accurate allowance for smoking quantity and duration, besides other relevant covariates, compared with TTFC more than 60 minutes, the adjusted ORs were 1.40 (95% CI: 0.93–2.11) for 31 to 60 minutes, 1.76 (95% CI: 1.20–2.58) for 6 to 30 minutes, and 2.43 (95% CI: 1.64–3.61) for within 5 minutes. No significant heterogeneity was found in strata of sex, age, alcohol consumption, fruit and vegetable intake, and occupation for overall and site-specific analysis.

**Conclusion:** Nicotine dependence, as indicated by the TTFC, is associated with increased risk of UADT cancers and is therefore an independent marker of exposure to smoking.

**Impact:** Our result indicates more detailed risk evaluation of UADT cancers that is enabled by the TTFC.

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inverse associations with TTFC were independent from other established indicators of tobacco consumption, including pack-years, duration of smoking, and number of cigarettes per day. Thus, TTFC might reflect not only nicotine dependence (5, 11–15) but also intensity of smoking, not satisfactorily measured by conventional measures of smoking exposure.

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

Materials and Methods

Study population

The case participants were 1,009 patients with no prior history of cancer who were histologically diagnosed with UADT cancer (257 with oral cavity cancer, 72 oropharyngeal, 80 hypopharyngeal, 92 laryngeal, 51 nasopharyngeal cancer, 23 with cancer of the oral cavity–oropharynx–hypopharynx not otherwise specified, and 434 esophageal cancers) between January 2001 and December 2005 at Aichi Cancer Center Hospital in Nagoya, Japan. Esophageal cancer cases are mixture of squamous cell carcinoma (more than 90%) and other histologic subtype. All participants were recruited within the framework of the hospital-based Epidemiologic Research Program at Aichi Cancer Center (Nagoya, Japan) with written informed consent (16–18). UADT cancers were defined according to the following codes of the International Classification of Diseases and Related Health Problems (ICD-10): oral cavity (C00.3–C00.9, C02.0–C02.3, C03, C04, C05.0, and C06), oropharynx (C01, C02.4, C05.1–C05.2, C09, and C10), hypopharynx (C12, C13), oral cavity–oropharynx–hypopharynx not otherwise specified (C02.8, C02.9, C05.8, C05.9, and C14), larynx (C32), nasopharynx (C11), and esophagus (C15).

The controls were 3,027 first-visit outpatients during the same period who were confirmed to have no cancer and no history of neoplasms. Noncancer status was confirmed by medical examinations, including radiographic examinations, with participants suspected of having UADT cancer first examined by physical or endoscopic inspection, and subsequently radiographically, if indicated. Controls were selected randomly and individually matched by age (±4 years), sex (male, female), and cancer subsite, with a case–control ratio of 1:3. A total of 4,036 participants (1,009 cases and 3,027 controls) were included in the study. Response rate was more than 95% for both cases and controls. The study was approved by the Institutional Ethical Committee of Aichi Cancer Center.

Information on time to the first cigarette of the day

Information on TTFC was collected from first-visit outpatients ages 20 to 79 years using a self-administered questionnaire. Each participant was asked at the time of first visit to our hospital about lifestyle factors concerning environmental exposures before the current symptoms developed that made them visit our hospital. We asked TTFC with following 4 options: 5 minutes or less, 6 to 30, 31 to 60, and more than 60 minutes. Responses were checked by trained interviewers.

Evaluation of other lifestyle factors

Information on smoking status was obtained in the 3 categories of nonsmoker, former smoker, and current smoker, with former smokers defined as those who had quit smoking at least 1 year before the study enrolment. Cigarette consumption was categorized into less than 15, 15 to 24, and 25 or more cigarettes per day. For the present analyses, lifetime alcohol consumption of various common beverages (Japanese sake, beer, shochu, whiskey, and wine) was determined in terms of the average number of drinks per day, which was then converted into a Japanese sake (rice wine) equivalent (180 mL), which contains 23 g of ethanol. Drinking status was classified into the 3 categories of never drinker, light-moderate drinker (<5 days per week or ≥5 days per week, <2 g per day), and heavy drinker (≥5 days per week, ≥2 g per day). Consumption of fruits and vegetables was determined using a food frequency questionnaire (FFQ), including 43 single food items with 8 frequency categories (19). The FFQ was validated using a 3-day weighed dietary record as standard, which showed that reproducibility and validity were satisfactory (20, 21). Participants were divided into 3 groups based on the distribution of fruit and vegetable consumption among controls (tiles). Participants were also asked about their occupation as a measure of socioeconomic status (SES), and were categorized into 3 groups, that is, white collar, blue collar, or others, including workers at part time job, housewives, students, unemployed, retired, and inactive.

Data analyses

To assess the association between TTFC and the risk of UADT cancer, we estimated the OR and the corresponding 95% confidence intervals (CI) using multiple logistic regression models. First, we evaluated impacts of TTFC among current and former smokers separately relative to never smokers by using all the subjects. For this analysis, conditional logistic regression models included terms for smoking status (ex- and current smokers), number of cigarettes per day (<15, 15–24, and ≥25), and duration of smoking (<20, 20–29, 30–39, and ≥40 years). Missing values for covariates were treated as dummy variables in the models. Consistency across subtypes of head and neck cancer and esophageal cancer and across strata of confounders was assessed by likelihood ratio tests between models with and without interaction term for corresponding confounding. All analyses were conducted using STATA SE version 11.2 (STATA Corp).
Results

Demographic characteristics and selected lifestyle habits of participants are shown in Table 1. Age and sex were appropriately matched. The proportion of smokers and drinkers was higher in cases than in controls. Cases smoked more cigarettes per day and for longer time, with significant trends in risk. Compared with controls, cases ate less vegetables and fruits and were more frequently blue collar workers.

Table 2 presents the association between FTTC in former and current smokers and UADT cancer, overall and according to specific cancer subsite. In analysis of UADT cancer overall, compared with never smokers, ORs for more than 60, 31 to 60, 6 to 30, 5 or less minutes were 1.03 (95% CI: 0.64–1.64), 1.38 (95% CI: 0.92–2.07), 2.01 (95% CI: 1.44–2.81), and 2.37 (95% CI: 1.66–3.39) for former smokers and 1.30 (95% CI: 0.72–2.36), 2.11 (95% CI: 1.42–3.13), 2.80 (95% CI: 2.11–3.73), and 4.47 (95% CI: 3.38–5.91) for current smokers, respectively. Although ORs for current smokers were larger than those for former smokers, ORs for shorter FTTC were consistently associated with increased UADT cancer risk. Although the point estimates fluctuate, the inverse association with FTTC was consistently observed across separate subsites, that is, oral cavity cancer, oropharyngeal cancer, hypopharyngeal cancer, laryngeal cancer, nasopharyngeal cancer, and esophageal cancer. Supplementary Table S1 shows only age-adjusted ORs in the similar pattern as Table 2 and indicating FTTC confounded with factors adjusted in the multivariate model.

When the analysis was restricted to ever smokers (Table 3) and accurate allowance was made for smoking status plus quantity and duration of smoking, compared with FTTC more than 60 minutes after waking, the ORs for all UADT cancers were 1.40 (95% CI: 0.93–2.11) for 31 to 60 minutes, 1.76 (95% CI: 1.20–2.58) for 6 to 30 minutes, and 2.43 (95% CI: 1.64–3.61) for within 5 minutes. With
Table 2. Associations between TTFC combined with smoking status and UADT cancer risks stratified by subsite.

<table>
<thead>
<tr>
<th>Site</th>
<th>Overall</th>
<th>Oral cavity</th>
<th>Hypopharyngeal</th>
<th>Laryngeal</th>
<th>Nasopharyngeal</th>
<th>Esophageal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Case Control OR (95%CI)</td>
<td>Case Control OR (95%CI)</td>
<td>Case Control OR (95%CI)</td>
<td>Case Control OR (95%CI)</td>
<td>Case Control OR (95%CI)</td>
<td>Case Control OR (95%CI)</td>
</tr>
<tr>
<td>Never smokers</td>
<td>7.45 (2.31–23.5)</td>
<td>2.04 (1.06–3.92)</td>
<td>4.92 (1.10–20.1)</td>
<td>1.58–6.04</td>
<td>1.75 (0.89–3.43)</td>
<td>2.70 (0.52–14.3)</td>
</tr>
<tr>
<td>Former smokers</td>
<td>5.71 (9.33)</td>
<td>2.40 (0.87–6.49)</td>
<td>3.29 (0.74–14.1)</td>
<td>4.82 (1.16–18.6)</td>
<td>6.14 (1.57–23.5)</td>
<td>1.91 (0.62–6.04)</td>
</tr>
<tr>
<td>&gt; 60 minutes</td>
<td>2.04 (1.06–3.92)</td>
<td>1.65 (0.86–3.15)</td>
<td>3.09 (95% CI: 0.69–14.3)</td>
<td>4.18 (95% CI: 0.12–14.3)</td>
<td>3.09 (95% CI: 0.69–14.3)</td>
<td>3.09 (95% CI: 0.69–14.3)</td>
</tr>
<tr>
<td>31–60 minutes</td>
<td>5.71 (9.33)</td>
<td>3.29 (0.74–14.1)</td>
<td>2.40 (0.87–6.49)</td>
<td>6.14 (1.57–23.5)</td>
<td>1.91 (0.62–6.04)</td>
<td>1.91 (0.62–6.04)</td>
</tr>
<tr>
<td>9–30 minutes</td>
<td>2.40 (0.87–6.49)</td>
<td>4.18 (95% CI: 0.12–14.3)</td>
<td>3.09 (95% CI: 0.69–14.3)</td>
<td>3.09 (95% CI: 0.69–14.3)</td>
<td>3.09 (95% CI: 0.69–14.3)</td>
<td>3.09 (95% CI: 0.69–14.3)</td>
</tr>
<tr>
<td>5 or less minutes</td>
<td>1.91 (0.62–6.04)</td>
<td>1.91 (0.62–6.04)</td>
<td>1.91 (0.62–6.04)</td>
<td>1.91 (0.62–6.04)</td>
<td>1.91 (0.62–6.04)</td>
<td>1.91 (0.62–6.04)</td>
</tr>
</tbody>
</table>

NOTE: ORs were calculated by conditional logistic regression model adjusted for alcohol consumption, fruit and vegetable intake, and SES. NE, not estimated.
In the low-dependent group, whereas in the high-dependent group, cotinine levels increased linearly between "low-" and "high-

dependent groups defined by TTFC (23). In that study, cotinine levels increased linearly with the numbers of cigarettes per day, showing a plateau around 30 cigarettes per day (22). This might indicate that the levels of nicotine uptake differ by the levels of nicotine intake.

**Table 4.** Stratified analysis for TTFC less than 5 minutes compared with TTFC greater than 60 minutes among ever smokers.

<table>
<thead>
<tr>
<th>Stratified by</th>
<th>UADT Cancer</th>
<th>Head and Neck Cancer</th>
<th>Esophageal Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Case</td>
<td>Control (OR [95%CI])</td>
<td>P heterogeneity</td>
</tr>
<tr>
<td>(IATC overall)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>374</td>
<td>542</td>
<td>2.43 (1.64-3.61)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>342</td>
<td>516</td>
<td>2.35 (1.56-3.56)</td>
</tr>
<tr>
<td>Female</td>
<td>32</td>
<td>26</td>
<td>4.26 (0.95-19.2)</td>
</tr>
<tr>
<td>Age category</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60</td>
<td>175</td>
<td>250</td>
<td>2.29 (1.24-4.24)</td>
</tr>
<tr>
<td>60 or more</td>
<td>199</td>
<td>292</td>
<td>2.40 (1.41-4.06)</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>0.463</td>
<td></td>
<td>0.055</td>
</tr>
<tr>
<td>Non</td>
<td>30</td>
<td>120</td>
<td>1.48 (0.52-4.18)</td>
</tr>
<tr>
<td>Light−moderate</td>
<td>142</td>
<td>271</td>
<td>2.68 (1.51-4.76)</td>
</tr>
<tr>
<td>Heavy</td>
<td>196</td>
<td>144</td>
<td>2.76 (1.39-5.47)</td>
</tr>
<tr>
<td>Fruits and vegetables</td>
<td>0.854</td>
<td></td>
<td>0.6312</td>
</tr>
<tr>
<td>Intake</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lowest tertile</td>
<td>192</td>
<td>229</td>
<td>3.81 (1.94-7.50)</td>
</tr>
<tr>
<td>Middle tertile</td>
<td>114</td>
<td>180</td>
<td>1.91 (0.97-3.75)</td>
</tr>
<tr>
<td>Highest tertile</td>
<td>59</td>
<td>120</td>
<td>2.10 (0.94-4.70)</td>
</tr>
<tr>
<td>Occupation</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>White collar</td>
<td>148</td>
<td>204</td>
<td>3.25 (1.53-6.87)</td>
</tr>
<tr>
<td>Blue collar</td>
<td>76</td>
<td>147</td>
<td>1.32 (0.65-2.67)</td>
</tr>
<tr>
<td>Other</td>
<td>147</td>
<td>190</td>
<td>3.03 (1.59-5.77)</td>
</tr>
</tbody>
</table>

NOTE: ORs were calculated by unconditional logistic regression model adjusted for age, sex, cigarette per day, duration of smoking, smoking status, alcohol consumption, fruit and vegetable intake, and occupation except for a stratifying factor.
dependence measured by TTFC. Although we do not have data on the association between nicotine levels in plasma/urine and TTFC in this study, our results confirmed the observation (8, 9) that TTFC is an independent indicator of UADT cancer risk.

It is of interest, what is the mechanism behind TTFC shows increased risk of UADT cancer risk. One possibility is that TTFC is an indicator of tobacco dependence impinging on cancer risk that is not adequately measured by other variables used in epidemiologic studies like cigarette per day or duration of smoking. Supporting this, TTFC is highly correlates with cotinine levels (23) and cotinine levels correlate with tobacco-related carcinogens and polycyclic aromatic hydrocarbons (24). In addition, genetic polymorphisms on chromosome 15, which are associated with risk of lung cancer (25) and UATC cancer in female (26), showed a significant correlation with smoking dependence (27), supporting TTFC as a phenotype reflecting cancer susceptibility. A significant association even after adjustment of usual smoking-related indicators in this study and formers may partially support this view (8–10).

Our study had several methodologic strengths. First, potential confounding by age, sex, alcohol drinking, fruit and vegetable intake, and SES was considered by individual matching and statistical adjustment in the analyses. Second, the size of the study was large, participation was almost complete for both cases and controls, and the FFQ was satisfactorily valid and reproducible (17, 18). Potential limitations of our study also warrant mention. First, measurement of FTTC might be affected by the status of cases at recruitment. To avoid this, we asked about FTTC when the participants were healthy or before the current symptoms developed. Second, the control participants were selected among noncancer patients at our hospital. Because cases and controls were selected from the same hospital and almost all patients lived in the Tokai area of central Japan, the internal validity of this case–control study is likely to be acceptable (16). In addition, to dilute any bias that might have resulted from the inclusion of a specific diagnostic group that is related to the exposure, we did not set eligibility criteria for control diseases. Third, as the lifestyle factors considered as potential confounders were based on self-report, it is difficult to rule out some information bias. If present, however, the effect of such misclassification in relation to possible underadjustment would be limited, also considering consistency of results across stratified analysis by several potential confounders. Finally, residual confounding by unmeasured factors such as HPV infection cannot be ruled out. This, however, would have a selective impact on oropharyngeal cancer only (28), whereas we observed strong inverse association with FTTC for all the head and neck cancers considered.

In conclusion, our case–control study has shown that TTFC is a risk factor for UADT cancers, head and neck, and esophageal cancers, independent of conventional smoking exposure measurement.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Conception and design: K. Matsuou, K. Tajima, C.L. Vecchia
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Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): K. Matsuou, C.L. Vecchia
Writing, review, and/or revision of the manuscript: K. Matsuou, S. Gallus, E. Negri, I. Oze, K. Tajima, C.L. Vecchia
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): K. Matsuou, H. Ito, M. Shinoda, C.L. Vecchia, H. Tanaka
Study supervision: H. Tanaka

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