Tobacco smoking and the risk of subsequent primary cancer among cancer survivors: a retrospective cohort study

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Background: Smoking is a well-known risk factor for cancer; however, there is little evidence as to whether the smoking status of cancer survivors has any risk for subsequent primary cancer (SPC) incidence, regardless of the first cancer sites.

Patients and methods: In total, 29,795 eligible patients with a first cancer between 1985 and 2004 were examined for SPC until the end of 2006, using a record linkage between hospital-based and population-based cancer registries. The association between smoking at the time of the first cancer diagnosis and three SPC groups (i.e. specific SPC, smoking-related SPCs, and all SPCs) was calculated by Poisson regression.

Results: Ever smokers had 59% and 102% higher risk for all SPCs and smoking-related SPCs, respectively, than never smokers. Cancer survivors who had recently stopped smoking had 18% and 26% less risk, respectively, for these SPCs than those who smoked at the diagnosis. We also found that, compared with those who had never smoked, cancer survivors who had ever smoked had a significantly elevated risk of oral/pharyngeal, esophageal, stomach, lung, and hematological SPCs, regardless of the first cancer sites.

Conclusions: These findings indicate that smoking increases not only the first cancer but also a second or SPC. Moreover, the results from recent quitters versus current smokers suggest that smoking cessation may decrease the risk for SPC, especially for smoking-related SPCs in cancer survivors. Preventive measures are necessary to reduce not only SPC incidence but also tobacco use.

Key words: tobacco smoking, subsequent primary cancer, cancer survivors, Japan

introduction

Tobacco smoking is the most attributable risk factor for cancer incidence and adult mortality in Japan and worldwide [1, 2]. Approximately 50% of males and 40% of females in Japan will develop a cancer during their lifetime [3]. Owing to prolonged survival times for cancer patients and population aging, it is estimated that 5–15% of cancer patients develop a subsequent primary cancer (SPC) [4, 5]. Although risk of SPC among cancer survivors may be strongly associated with smoking behaviors [6], insufficient direct investigation of the relationship between smoking behavior and SPC incidence has been conducted owing to the lack of information in population-based cancer registries. Furthermore, to date, most studies that examined the association between smoking (and/or smoking cessation) and SPC incidence were conducted according to each first cancer, not a comprehensive list of cancers [7–14]. This study comprised a retrospective cohort study which estimated the risk for SPC incidence according to smoking behaviors at the first cancer diagnosis among a comprehensive group of cancer survivors. We used record linkage between a hospital-based cancer registry and the Osaka Cancer Registry (OCR), one of the largest population-based cancer registries [15]. We aimed to provide not only information for advancing tobacco control, but also insights into preventive measures for clinical oncologists and other health professionals [16].

methods

data

Study subjects were all eligible patients initially diagnosed with a first cancer, excluding in situ carcinomas and benign intracranial tumors, from 1985–2004 at the Osaka Medical Center for Cancer and Cardiovascular Diseases (OMCC), and who had survived for at least 3 months. Subjects were restricted to those living in Osaka and aged 20–79 years at the time of diagnosis. Those with a history of cancer or who developed synchronous SPC within 3 months were excluded. Subjects were identified from the hospital-based cancer registry, which has collected information on cancer
diagnosis, clinical stage, first course of treatment, and lifestyle factors including smoking behavior, since 1963. They were followed up using medical records or resident offices, for up to 10 years, and the follow-up was 99% complete. Their files were collated with the OCR files to obtain other information on SPC incidence, by means of a semi-automated record linkage using patients’ surname, given name, birth-year and birth-month. The study was approved by the OMCC institutional review board.

smoking behaviors

Information on smoking behaviors was collected through an integrated common questionnaire across all departments at the time of the first cancer diagnosis. The following definitions were used: ever smokers were persons who had smoked tobacco regularly either before or at diagnosis, including current smokers, recent quitters, and former smokers. Never smokers were those who had never smoked regularly. Current smokers were those who smoked cigarettes regularly at diagnosis. Recent quitters were those who had stopped smoking up to 3 years before diagnosis. Former smokers were those who stopped smoking ≥3 years before diagnosis.

The smoking behavior variable was used in two ways. First, never smoker was used as a reference category to examine whether cancer survivors who had ever smoked or who currently smoked were more likely to develop SPCs than those who currently smoked. The latter was based on a clinical perspective, suggesting a reversible effect of smoking have lower risk for SPC than those who currently smoked. The latter was used as a reference category to examine whether cancer survivors who had recently stopped smoking have lower risk for SPC than those who currently smoked. The former was used as a reference category to examine whether cancer survivors who had ever smoked or who currently smoked were more likely to develop SPCs than never smoked. Secondly, current smoker was used as a reference category to examine whether cancer survivors who had ever smoked or who currently smoked were more likely to develop SPCs than never smokers.

outcomes: SPC definitions

Metachronous SPC was defined as that diagnosed between 3 months and 10 years after the first cancer diagnosis. The incidence of three SPC groups (i.e. specific SPC, smoking-related SPCs, and all SPCs) was examined up to the end of 2006 for a maximum of 10 years after the first cancer diagnosis. Each cancer was categorized into 16 selected major groups and the others according to ICD-10, corresponding to the specific SPC sites. Smoking-related cancer sites comprised the mouth/pharynx, esophagus, stomach, colorectum, liver, gall-bladder, pancreas, larynx, lung, and kidney/urinary tract/bladder [19]. A cancer survivor can contribute to several outcomes (SPCs), provided these SPCs fit the eligibility criteria. In other words, these events have been assumed to be independent of one another. For more details on outcomes and SPC definitions, please see supplementary data, available at Annals of Oncology online.

statistical analyses

To estimate the risk for SPC, person-years at risk were calculated as the time from 3 months after the first cancer diagnosis until: 31 December 2006; date of SPC diagnosis; date of death; or 10 years after the first cancer diagnosis, whichever came first [5]. The expected number was calculated according to stratified person-years with all, smoking-related and site-specific cancer incidence rates among Osaka residents (from OCR) stratified for sex, age group (5 years), and calendar period (5 years). The observed number of SPCs was compared with the expected number, according to smoking behaviors, sex, age group, calendar period, clinical stage, smoking-related first cancer site, and follow-up interval. A standardized incidence ratio (SIR) was then obtained by dividing the observed number of SPCs by the expected number. Another indicator is the excess absolute risk (EAR), which is the absolute number of excess cancer cases, obtained by subtracting the expected number from the observed number of SPC. The EAR may be of interest for clinical and public health purposes. The SIR and EAR are used to estimate the risk of a cancer patient developing SPC compared with the incidence of cancer among the general population. The statistical significance and 95% confidence intervals (CIs) for the SIRs were tested by Poisson distribution analysis. For more details on statistical analysis, see supplementary data, available at Annals of Oncology online.

We used Poisson regression analysis to estimate the incidence rate ratio (IRR) and 95% CIs for SPC in cancer survivors according to their smoking behaviors. These ratios were adjusted for potential confounding factors: sex and age at the first cancer diagnosis. They were additionally adjusted for stage, calendar period, follow-up interval, and smoking-related first cancer site, using the expected number of cancer incidence in the general population as an offset [20, 21].

Probability values for statistical tests were two-tailed, and P < 0.05 was regarded as statistically significant. All statistical analyses were carried out using the SAS statistical package version 9.2 (SAS Institute, Inc., Cary, NC, USA) with macros [22].

results

There were 29 795 study subjects after excluding those with a missing value for smoking behaviors (n = 4). When recent quitters were used, subjects with missing cessation age were excluded (n = 649). Distribution of cancer sites in Osaka, Japan, and this study (OMCC) is shown in supplementary Table S1, available at Annals of Oncology online. During the follow-up (median follow-up duration: 4.5 years, mean: 5.2 years), SPCs were found in 1721 subjects (5.8%) as the second cancer, 122 (0.4%) as the third cancer, 18 (0.1%) as the fourth cancer, and 1 (0.003%) as the fifth cancer. Smoking-related SPCs were found in 1161 (3.9%) as the second, third, or fourth primary cancer.

Most patient characteristics were associated with the risk of SPC (supplementary Tables S2 and S3, available at Annals of Oncology online). Table 1 shows IRRs for SPC according to smoking behaviors from Poisson regression analyses. In the fully adjusted model, ever or current smokers had 59% and 76% higher risk for all SPCs, respectively, than never smokers. Cancer survivors who recently stopped smoking had 18% less risk for developing all SPCs than current smokers. For smoking-related SPCs, ever and current smokers had 102% and 136% higher risk, respectively, than never smokers. Recent quitters had 26% less risk than current smokers.

Table 2 shows SIRs and EARs for specific SPCs according to dichotomized smoking behaviors (ever versus never smokers). Although never smoker cancer survivors had significantly high SIRs of 2.92 and 3.04 for prostate and thyroid SPC, respectively, never smokers had a significantly lower SIR of 0.67 for lung SPC. Ever smoker cancer survivors had significantly high SIRs for oral/pharyngeal, esophageal, stomach, laryngeal, lung, prostate, kidney/urinary tract/bladder, and thyroid SPCs. EARs in SPCs of the esophagus, stomach, and lung were >50. In the fully adjusted Poisson regression model, ever smoker cancer survivors had significantly elevated risk for oral/pharyngeal, esophageal, stomach, lung, and hematological SPCs, compared with never smokers. A tendency toward an IRR of >1.0 was observed in other smoking-related SPCs. Although fully adjusted IRR for laryngeal SPC among ever smokers was non-significant (8.08) with a wide 95% CI, it was significant among current smokers (see supplementary Table S4, available at Annals of Oncology online). Supplementary Table S5, available at Annals of Oncology online, shows SIRs, EARs, and
**Table 1.** IRRs for SPC incidence according to smoking behaviors, Poisson regression analyses

<table>
<thead>
<tr>
<th>Smoking behaviors at the first cancer diagnosis</th>
<th>Number (%) of cancer survivors</th>
<th>All SPCs</th>
<th>Smoking-related SPCs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted IRRs (95% CI)</td>
<td>Age- and sex-adjusted IRRs (95% CI)</td>
<td>Fully adjusted IRRs* (95% CI)</td>
</tr>
<tr>
<td></td>
<td>Unadjusted IRRs (95% CI)</td>
<td>Age- and sex-adjusted IRRs (95% CI)</td>
<td>Fully adjusted IRRs* (95% CI)</td>
</tr>
<tr>
<td>Tobacco control perspective</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoker (reference)</td>
<td>13 007 (43.7)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Ever smoker</td>
<td>16 788 (56.4)</td>
<td>1.43 (1.29–1.59)</td>
<td>1.59 (1.39–1.82)</td>
</tr>
<tr>
<td>Necker smoker (reference)</td>
<td>13 007 (43.7)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Former smoker</td>
<td>3661 (12.6)</td>
<td>1.14 (0.98–1.32)</td>
<td>1.28 (1.08–1.52)</td>
</tr>
<tr>
<td>Recent quit</td>
<td>2645 (9.1)</td>
<td>1.31 (1.10–1.56)</td>
<td>1.44 (1.19–1.74)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>9833 (33.7)</td>
<td>1.61 (1.44–1.80)</td>
<td>1.76 (1.53–2.02)</td>
</tr>
<tr>
<td>Clinical perspective</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker (reference)</td>
<td>9833 (33.7)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Recent quit</td>
<td>2645 (9.1)</td>
<td>0.82 (0.69–0.96)</td>
<td>0.82 (0.69–0.96)</td>
</tr>
<tr>
<td>Former smoker</td>
<td>3661 (12.6)</td>
<td>0.71 (0.62–0.81)</td>
<td>0.73 (0.63–0.84)</td>
</tr>
<tr>
<td>Never smoker</td>
<td>13 007 (43.7)</td>
<td>0.62 (0.55–0.70)</td>
<td>0.57 (0.49–0.65)</td>
</tr>
</tbody>
</table>

*Adjusted for age groups and calendar periods at the first cancer diagnosis, sex, stage, smoking-related first cancer site and follow-up interval.

**IRR, incidence rate ratio; SPC, subsequent primary cancer; CI, confidence interval.**

**Discussion**

We found that ever smoker cancer survivors showed a significantly elevated risk of SPC, especially for smoking-related SPCs, compared with never smokers. Smoking was an independent risk factor for several specific SPCs, such as oral/pharyngeal, esophageal, stomach, lung, and hematological cancers, after adjusting for confounding factors such as age and smoking-related factors (e.g., duration of smoking and smoking cessation). This finding provides information for tobacco control measures in the future. Tobacco control measures that are applicable to prompt quitters among cancer survivors. There is, however, a clinical chance that patients who stop smoking immediately after cancer diagnosis or continue smoking until cancer diagnosis will have a risk for developing SPCs, especially for smoking-related SPCs. Therefore, a clinical chance that patients who stop smoking immediately after cancer diagnosis or continue smoking until cancer diagnosis will have a risk for developing SPCs, especially for smoking-related SPCs. Therefore, smoking cessation decreases subsequent cancer incidence.

After all, preventive measures are necessary not only to reduce the occurrence of SPC but also to promote the reduction of tobacco use. However, there is a clinical chance that patients who stop smoking immediately after cancer diagnosis or continue smoking until cancer diagnosis will have a risk for developing SPCs, especially for smoking-related SPCs. Therefore, smoking cessation decreases subsequent cancer incidence.
**Table 2.** SIRs, EARs, and Poisson regression results for specific SPC according to smoking behaviors (ever smoker versus never smoker)

<table>
<thead>
<tr>
<th>Site of SPC</th>
<th>Never smoker</th>
<th>Ever smoker</th>
<th>Poisson regression results for ever smoker versus never smoker</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of SPC</td>
<td>Person-years at risk</td>
<td>SIRs (95% CI)</td>
</tr>
<tr>
<td>Mouth/pharynx</td>
<td>9</td>
<td>71 870.2</td>
<td>1.11 (0.48–1.99)</td>
</tr>
<tr>
<td>Esophagus</td>
<td>10</td>
<td>73 244.1</td>
<td>0.87 (0.40–1.53)</td>
</tr>
<tr>
<td>Stomach</td>
<td>71</td>
<td>64 324.4</td>
<td>0.98 (0.73–1.18)</td>
</tr>
<tr>
<td>Colorectum</td>
<td>68</td>
<td>67 593.7</td>
<td>1.02 (0.75–1.23)</td>
</tr>
<tr>
<td>Liver</td>
<td>56</td>
<td>71 329.4</td>
<td>1.02 (0.73–1.26)</td>
</tr>
<tr>
<td>Gall-bladder</td>
<td>20</td>
<td>73 460.1</td>
<td>1.18 (0.68–1.73)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>29</td>
<td>73 216.3</td>
<td>1.38 (0.88–1.89)</td>
</tr>
<tr>
<td>Larynx</td>
<td>1</td>
<td>73 455.9</td>
<td>0.38 (0.01–2.02)</td>
</tr>
<tr>
<td>Lung</td>
<td>44</td>
<td>69 821.5</td>
<td>0.67 (0.46–0.85)</td>
</tr>
<tr>
<td>Breast (female)</td>
<td>38</td>
<td>35 747.7</td>
<td>1.28 (0.86–1.67)</td>
</tr>
<tr>
<td>Uterus (female)</td>
<td>15</td>
<td>65 706.7</td>
<td>0.86 (0.46–1.35)</td>
</tr>
<tr>
<td>Ovary (female)</td>
<td>15</td>
<td>51 498.6</td>
<td>1.64 (0.87–2.57)</td>
</tr>
<tr>
<td>Prostate (male)</td>
<td>15</td>
<td>58 601.7</td>
<td>2.92 (1.78–4.13)</td>
</tr>
<tr>
<td>Kidney/urinary tract/bladder (male)</td>
<td>27</td>
<td>71 292.6</td>
<td>1.54 (0.96–2.12)</td>
</tr>
<tr>
<td>Thyroid</td>
<td>19</td>
<td>70 706.4</td>
<td>3.04 (1.74–4.51)</td>
</tr>
<tr>
<td>Blood</td>
<td>24</td>
<td>69 299.7</td>
<td>1.12 (0.68–1.58)</td>
</tr>
<tr>
<td>Others</td>
<td>16</td>
<td>71 063.7</td>
<td>0.72 (0.39–1.11)</td>
</tr>
</tbody>
</table>

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**Notes:**
- Smoking-related cancer sites, excluding uterine cervix and acute myeloid leukemia because of unavailable expected number and coding rules.
- Adjusted for age groups and calendar periods at the first cancer diagnosis, sex, stage, smoking-related first cancer site, and follow-up interval.
- SIR, standardized incidence ratio; EAR, excess absolute risk; SPC, subsequent primary cancer; IRR, incidence rate ratio; CI, confidence interval.
- Boldface indicates statistical significance of $P < 0.05$. 

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interpretation difficult, especially in the case of smoking cessation. Cessation decreased risk for SPC among small-cell lung cancer patients, but not among non-small-cell lung cancer patients in a small-scale sample [9, 14, 26, 27]. In the current study, although recent quitters did not show significant IRRs for SPC among lung cancer patients (marginal significance for all SPCs; see supplementary Table S6, available at Annals of Oncology online), smoking behaviors, including recent cessation, showed a clear and significant trend of risk for SPC among total cancer survivors (see Table 1). Since the risk for SPC did not largely differ by the first cancer sites (see supplementary Tables S6–S8, available at Annals of Oncology online), an analytical design, not limited to the first cancer site, might be appropriate and solve the small-sample-size problem.

strengths of this study
Although this is an institution-based cohort, the large sample size is a strength of this study. Also, while a few studies have compared SPC risk in former smokers with that of current smokers, this is the first to compare ‘recent quitter’ with ‘current smoker’ and include comprehensive cancer survivors. Although more is known about the impact of smoking on the risk of lung cancer than any other cancer, research on smoking cessation and SPC risk is very scarce, even in the field of lung cancer. According to a previous review, only observational studies that examined the association between smoking cessation and SPC incidence were available [14]. A randomized intervention study is required to validate the hypothesis that smoking cessation decreases SPC among cancer survivors. Nevertheless, such an intervention may be unrealistic because of the low incidence rate of SPCs, ethical problems, and difficulties of studying smoking cessation [29]. Therefore, observational study may provide the best evidence in this field of research.

limitations of the study
There are several limitations of this study. First, smoking status at diagnosis was used without a measure of amount smoked (such as pack-years) and follow-up smoking assessment. This may have mixed the true exposure status, which is likely to have underestimated the benefits of cessation as quitters are more likely to relapse [30]. Secondly, the results are based on observational data. Quitting behavior may be determined by unmeasured factors. For example, patients who stop smoking may be more likely to access other cancer prevention care, perhaps overestimating the effect of quitting [29]. Thirdly, our study combined different types of cancer patients. Although limited significance was found in specific SPCs, it remains possible that other categorization methods may reveal different results. The small number of some specific SPCs makes it necessary to interpret the results with some caution.

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disclosure
The authors have declared no conflicts of interest.

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