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Original Research Article

Smoking cessation and subsequent risk of cancer: A pooled analysis of eight population-based cohort studies in Japan

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ABSTRACT

Background: Although East Asia is one of the largest tobacco-epidemic regions in the world, only a few prospective studies from Asia have investigated the impact of smoking and cessation of smoking on cancer. We aimed to assess the effect of cessation of smoking on the risk of cancer using eight population-based cohort studies in Japan.

Methods: We analyzed pooled data from eight population-based prospective cohort studies in Japan with more than 320,000 participants to assess the effect of smoking cessation on the risk of total cancers and smoking-related cancers.

Results: After adjustment for potential confounders, cancer risks in men with > 21 years of smoking cessation before baseline were found to decrease to the same level as never smokers for total cancer (never smokers: reference; former smokers with ≥21 years since smoking cessation: HR, 1.01; 95%CI: 0.91, 1.11). Even men who are heavy smokers (more than 20 pack-years) reported a reduced risk of total cancer (never smokers: reference; former smokers with ≥21 years since smoking cessation: HR, 1.06; 95%CI: 0.92, 1.23). In women, the risk of total cancer did not differ from that of never smokers after 11 years of smoking cessation before baseline (never smokers: reference; former smokers with ≥11 years since smoking cessation: HR, 0.96; 95%CI: 0.74, 1.23).

Conclusions: Our study suggests that longer duration of smoking cessation may attenuate the risk of cancer in both men and women, and that even heavy smokers (more than 20 pack-years) were found to benefit from quitting smoking.

1. Introduction

Cigarette smoking is the most important and best-established risk factor for many diseases [1,2]. Smoking-attributable cancers remain a major disease burden worldwide, accounting for the death of more than 1.2 million middle-aged adults every year [3]. Japan is ranked as the fifth largest tobacco-consuming country in East Asia, and one of the largest tobacco-epidemic regions; around 30% of men are cigarette smokers [4]. Smoking-attributable deaths remain the major cause of mortality in Japan, responsible for around 25–28% of the total male

Abbreviations: JPHC Study, the Japan Public Health Center based Prospective Study; JACC, the Japan Collaborative Cohort Study; MIYAGI-I, the Miyagi Cohort Study; MIYAGI-II, the Three-Prefecture Cohort Study in Miyagi; AICHI, the Three-Prefecture Cohort Study in Aichi; TAKAYAMA, the Takayama Study; OHSAKI, the Ohsaki Cohort Study

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mortality [5,6] and around 120,000–130,000 deaths in men and women combined [5–7]. The greatest impact of smoking is on cancer, with smoking accounting for around 39% of total cancer mortality in Japanese men [5].

Reversing the tobacco epidemic in the region is markedly dependent on the availability of strong evidence on the benefit of smoking cessation. Quitting smoking has been reported to play a major role in reducing smoking-associated health risks [8,9]. The risk of long-term abstaining smokers approaches that of never smokers for total mortality [10,11] and for cardiovascular disease mortality [12]. Further, smoking cessation (compared to continuing smoking) is associated with lower risks of incidences ot lung [13–15], pancreatic [16], head and neck [17], gastric [18], colorectal [19], cervical [20] and bladder cancers [21]. However, these results derive mainly from the US and Europe, and only a few prospective studies from Asia have investigated the impact of smoking and cessation of smoking on cancer mortality [11,22–26] or on cancer incidence [15,18]. Even with the existing studies in Asia, the number of cancer cases among former smokers was too small to allow substantial analysis by years of smoking cessation.

Here, we assessed the effect of smoking cessation on the risk of total cancer and smoking-related cancers using pooled results for eight population-based cohort studies in Japan.

2. Materials and methods

2.1. Study population

Criteria for inclusion in this study were as follows: the study was a population-based cohort study conducted in Japan; study commencement was between the mid-1980s and mid-1990s; more than 30,000 participants were enrolled; a validated questionnaire or similar method was used for the baseline survey on smoking; and incidence data for all cancers and smoking-related cancers were collected during the follow-up period. Eight large-scale population-based cohort studies met the criteria and their data were accordingly used, namely: (1) the Japan Public Health Center-based Prospective Study (JPHC-I) [27], (2) the Japan Public Health Center-based Prospective Study (JPHC-II) [27], (3) the Japan Collaborative Cohort Study (JACC) [28], (4) the Miyagi Cohort Study (MIYAGI-I) [29], (5) the Three-Prefecture Cohort Study in Miyagi (MIYAGI-II) [30], (6) the Three-Prefecture Cohort Study in Aichi (AICHI) [30], (7) the Takayama Study (TAKAYAMA) [31] and (8) the Ohsaki Cohort Study (OHSAKI) [32]. Subjects who had a past history of cancer and those without information on smoking status, sex, age and study area (only for JPHC-I, JPHC-II and JACC) were excluded from the analysis. A total of 321,501 participants were included in the current pooled analysis. All studies were approved by the institutional review boards of their respective study centers.

2.2. Exposure assessment

In each study, duration (years) of smoking cessation was assessed using a self-administered questionnaire at baseline. Although the wording of the questions varied among studies, each study was able to calculate current smoking status (never, former and current); years of smoking cessation among former smokers at the time of the baseline survey; and the average number of cigarettes smoked per day. Male subjects were classified for smoking status into seven groups, including never smokers, current smokers, and former smokers (by years of smoking cessation: 0–5 years, 6–10 years, 11–15 years, 16–20 years, and ≥21 years). In women, former smokers were classified into two groups (by years of smoking cessation: 0–10 years and ≥11 years) because of the limited number of former smokers. Intensity of smoking in former smokers was evaluated by pack-years in men, which was defined as: (years of smoking x average number of cigarettes smoked per day)/20. In a sensitivity analysis comparing the effect of years since smoking cessation on cancer risk in former smokers and relapsed smokers, former smokers were defined as subjects who answered “quit smoking” at the time of the baseline and answered the same at the 5-year and 10-year follow-up study, while relapsed smokers were defined as subjects who answered “quit smoking” at the time of the baseline but “currently smoking” at the 5-year or 10-year follow-up study in the JPHC-I and JPHC-II.

2.3. Case ascertainment

Participants were followed from the time of the baseline survey (JPHC I: 1990, JPHCII: 1993–1994, JACC: 1998–1990, MIYAGI: 1990, MIYAGI-II: 1984, AICHI: 1985, TAKAYAMA: 1992, OHSAKI: 1994). Residential status, including survival, was confirmed in each study by examination of the residential registry. Information on cancer diagnosis was collected for all study participants, and cases were identified from population-based cancer registries. In the JPHC study, incident cancers were identified through active patient notification from major local hospitals and through linkage with population-based cancer registries. Cases were coded according to the International Classification of Diseases for Oncology, Third Edition [33]. Each study also collected information on the cause of death using death certificates and coded it according to the International Classification of Diseases and Health Related Problems, Tenth Revision (ICD-10) [34], which was used to supplement the cancer registry data when information on cancer patients was not available from the registry system. The quality and completeness of the cancer registry system in Japan has been described previously [35]. In the JPHC study, the proportion of cases for which information was available from a death certificate only was 3.7% [36]. In the JACC, we used data from 22 of 45 study areas, since these were the only areas with available cancer diagnosis information. The study outcome was defined as the incidence of all cancers (ICD-10: C00-C97). To assess tobacco-associated cancer risks, we selected cancer sites based on the assessment of the available evidence in the Japanese population, which is reviewed periodically by the Development and Evaluation of Cancer Prevention Strategies in Japan research group [37]. This research group concluded that cancer sites with a convincing level of association with smoking were clustered as tobacco-related cancers, namely: lip, oral and pharyngeal (C00–C14), nasal cavity and paranasal sinuses (C30–C31), larynx (C32), esophagus (C15), stomach (C16), pancreas (C25), lung (C33–C34), cervix uteri (C53), bladder, renal pelvis and ureter (C65–C67), and liver (C22.0) [38–44]. In addition, among the tobacco-related cancer sites, esophagus, stomach, pancreas, lung, bladder/renal pelvis/ureter, and liver were independently assessed in relation to years of smoking cessation and cancer risk.

2.4. Statistical analysis

Person-years of follow-up were calculated from the date of the baseline survey for each study until the date of diagnosis of the first primary cancer, migration from the study area, death, or end of follow-up, whichever occurred first. Each study estimated the hazard ratios (HRs) and their two-sided 95% confidence intervals (95%CIs) for cancer incidence associated with smoking status and years of smoking cessation using a Cox proportional hazards model, with never smokers as the reference category. Because the model estimates time since baseline to cancer incidence as an outcome, change in years of smoking cessation after baseline for continued cessation is inherent in the analysis. The studies estimated three types of HR: model 1, with adjustment of age at baseline (years, continuous) and study area (only for JPHC-I, JPHC-II and JACC); model 2, with adjustment of alcohol consumption (men: never/former, < 1 times/week, regular (g/d) (< 23, 23 to < 46, 46 to < 69, 69 to < 92, ≥92; women: never/former, < 1 time/week, regular (g/d) < 23, ≥23), body mass index (< 18.5, 18.5 to < 25, 25 to < 30, ≥30), and pack-years (continuous) in addition to adjustment in model 1; and model 3, with exclusion of incident cancer cases within 5 years of baseline. We also conducted a stratified analysis by smoking