



Title	Association of the age at smoking initiation and cessation on all-cause and cause-specific mortality : The Japan Collaborative Cohort Study [an abstract of dissertation and a summary of dissertation review]
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学位論文内容の要旨
(Summary of Dissertation)

博士の専攻分野の名称 博士 (医学)
(Degree conferred: Doctor of Philosophy)

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学位論文題名 (Dissertation Title)

**Association of the age at smoking initiation and cessation on all-cause
and cause-specific mortality: The Japan Collaborative Cohort Study**

(喫煙開始年齢と禁煙年齢の全死亡及び死因別死亡に対する関連: JACC 研究)

【Background and Objectives】 Tobacco use is a significant public health concern worldwide and is one of the major causes of death and disability in both developed and developing countries. According to the World Health Organization (WHO) 2019 report, tobacco use is currently responsible for more than 8 million and 1.2 million deaths yearly, due to active and passive smoking, respectively, and these numbers are likely to increase over the coming decades because of the increased use of tobacco in the developing world. Reducing the global mortality burden of tobacco smoking requires comprehensive measures to prevent smoking initiation and to increase cessation rates among current smokers at an earlier age.

Japan is the fourth largest tobacco-consuming country in the world and tobacco smoking remains a leading cause of deaths, especially among men. Although the proportion of regular male smokers has markedly decreased to 27.1% in 2019 from roughly half the proportion in 1989, when it peaked at 55.3%, smoking prevalence in Japan remains higher than that in other high-income countries, including the United States and several European countries. Increasingly, there is evidence that quitting smoking contributes to the reduction of risk of total mortality, and the age at which an individual starts or stops smoking is a determinant factor for whether individuals are prone to premature death. The importance of quitting smoking at an early age has been highlighted in many studies. However, these studies focused on the association of age at cessation alone or years since cessation with all-cause mortality, and studies on all-cause and cause-specific mortality with regard to age at both initiation and cessation are limited.

【Objectives】 The aims of this study was to evaluate the association between smoking initiation and cessation age with the risk of all-cause, cancer, and CVD mortality among Japanese men in a large cohort study.

【Materials and Methods】 The data was analyzed from the dataset of the Japan Collaboration Cohort Study for Evaluation of Cancer Risk which was established from 1988 to 1990 and followed until the end of 2009. A total of 110,585 participants (46,395 men and 64,190 women) aged between 40 and 79 years were enrolled from 45 study areas across Japan and completed a questionnaire on lifestyle and medical history at baseline. The present analysis was restricted to male participants because of the limited number of female ex-smokers (only 963). Of the 46,395 initial male participants at baseline, we excluded (4,684) individuals who did not provide data on smoking-related variables and remained with (41,711) individual for analysis. Cox proportional hazard models were used to derive hazard ratios and corresponding 95% confidence intervals for deaths of current and former smokers, with never smokers as the reference. Three models were constructed: Model 1 was adjusted for age at baseline and stratified by study area; Model 2 was further adjusted for current and past illnesses (diabetes, CVDs, hypertension, and/or cancer); and Model 3 was further adjusted for marital status, children, education, occupation, exercise, walking, BMI, passive smoking, drinking habit, and number of cigarettes smoked per day. All analyses were conducted using Statistical Package for the Social Science (SPSS) version 26, and $p < 0.05$ was considered statistically significant.

【Results】 During a total of 658,470.4 person-years of follow-up, a total of 13,429 all-cause deaths occurred (including 3,682 from CVDs and 4,999 from cancers). A dose-response relationship was detected between mortality and the age at smoking initiation among current smokers specifically, compared with never smokers.

Participants who started smoking at <20 years of age had the highest HR for all-cause (HR, 1.84, 95% CI, 1.72–1.98), cancer (HR, 2.19, 95% CI, 1.95–2.45), and CVD mortality (HR, 1.70, 95% CI, 1.48–1.95). The HR for cancer mortality was consistently higher than that for CVD mortality. Former smokers demonstrated a lower risk of all-cause and cause-specific mortality than current smokers even when quit smoking at ≥ 50 years: all-cause (HR, 1.34, 95% CI, 1.17–1.54), cancer (HR, 1.43, 95% CI, 1.12–1.84), and CVD mortality (HR, 1.32, 95% CI, 1.03–1.70). However, among former smokers who quit smoking in their 50s or above, the risk of mortality remained high and showed dose dependency with regard to the age at smoking initiation, where the highest HR was detected in those who started smoking at <20 years of age: all-cause (HR, 1.51, 95% CI, 1.29–1.77), cancer (HR, 1.68, 95% CI, 1.27–2.23), and CVD (HR, 1.48, 95% CI, 1.12–1.96), mortality. Among former smokers who quit smoking when younger than 50 years, although the risk for all-cause or CVD mortality was absent or negligible, regardless of the age at smoking initiation, the risk for cancer mortality remained significantly high among those who quit smoking at 40–49 years of age (HR, 1.44, 95% CI, 1.03–2.01). The results of sensitivity analysis and the participants who were limited to those aged 50 years and above were similar to those described above.

【Discussion】 In this population-based prospective study in Japan, our main findings are as follows. First, smoking cessation is beneficial, regardless of the age at smoking initiation, as former smokers demonstrated a lower risk for all-cause and cause-specific mortality compared to current smokers, with a clear tendency of the reduction being greater when cessation occurred at lower ages. Second, among former smokers who quit smoking in their 50s or above, the mortality risk remained elevated and showed dose dependency with the age at smoking initiation, where the highest HRs were detected in those who started smoking at lower ages.

These results have important public health implications. The first finding suggests that former smokers who initiate smoking when younger but quit smoking earlier in life can gain the largest benefit from cessation. However, even participants who quit smoking during their 50s or when older had, despite higher risks than never smokers, a substantially decreased mortality risk compared to the participants who continued to smoke. This result suggests that smokers will benefit from cessation even later in life, which provides evidence that all smokers should be encouraged to quit smoking, regardless of their age at smoking initiation. Furthermore, our study suggests that the decline in mortality risk due to smoking cessation is different for cancer and CVD mortality. Although the CVD mortality risk was seemingly totally eliminated by smoking cessation at <40 years of age, the cancer-related mortality risk remained higher than in never smokers even among former smokers who quit smoking at <50 years of age. This suggests that, to prevent cancer, smoking cessation should occur as early as possible and preferably at lower ages.

【Conclusion】 In this study former smokers demonstrated a lower risk for all-cause and cause-specific mortality than current smokers, with the risk reduction being greater among smokers who quit smoking at a lower age. Furthermore, the results showed that smoking cessation at <40 years of age leads to a reduction in CVD mortality; however, the cancer-related mortality risk persisted even when cessation occurred before the age of 50. These findings imply that all smokers should be encouraged to quit smoking earlier in life regardless of their age at smoking initiation.