論文の内容の要旨

Consumption of coffee and antioxidant vitamins and risk of lung cancer in Japan

（日本人におけるコーヒーおよび抗酸化ビタミン摂取と
肺がんリスクに関する研究）

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Background: Smoking is the principal cause of lung cancer whereas not all cases of lung cancer occur in smokers or former smokers, indicating the importance of exploring non-smoking-related factors. Dietary antioxidants have been hypothesized to protect against the malignancy but the results from preceding studies are inconsistent. Moreover, limited evidence is available from Japanese or even Asian population. Hence, the associations between consumption of antioxidant-rich diet namely coffee and antioxidant vitamins and risk of lung cancer on the Japanese population were examined.

Methods: The Japan Public Health Center-based prospective (JPHC) Study, which began in 1990 for Cohort I and 1993 for Cohort II, is an ongoing cohort study with 140,000 participants living in municipalities of 11 public health centers across the country. Two analytic cohorts were generated from the JPHC Study; a total of 87,079 Japanese men (41,727) and women (45,352) aged 40-69 years and 79,705 men (38,207)

and women (41,498) aged 45-74 years were included in the analyses of coffee and antioxidant vitamins, respectively. A food frequency questionnaire was used to collect information on consumption of coffee and antioxidant vitamins namely retinol, vitamin C, vitamin E, alpha-carotene and beta-carotene. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated by multivariable-adjusted Cox proportional hazards models with further analyses by histological type of lung cancer (adenocarcinoma, small cell carcinoma, squamous cell carcinoma, other types) and smoking status.

Results: During an average follow-up of 17.0 years, 1,668 lung cancer cases (1,227 cases in men and 441 cases in women) were newly diagnosed in the analysis of coffee. Of histologically confirmed cases, 43.7% were adenocarcinoma. Compared with non-drinkers, coffee drinkers were much more likely to smoke cigarettes. In the model adjusted for age and public health center area, coffee consumption was associated with an increased risk of lung cancer incidence (HR, 1.88; 95% CI, 1.39-2.54; p_{trend} = <0.001 for men; HR, 2.06; 95% CI, 1.16-3.67; p_{trend} = 0.253 for women; comparing non-drinkers with ≥5 cups/day). In the multivariate analysis adjusting for smoking and other confounding factors, while coffee consumption was not associated with overall lung cancer risk, there was a significant increase in the risk for small cell carcinoma (HR, 3.52; 95% CI, 1.49-8.28; p_{trend} = <0.001; comparing non-drinkers with ≥5 cups/day). This finding was consistent with majority of the previous studies in which risk estimates were attenuated after adjusting for smoking.

In the analysis of antioxidant vitamins, 1,690 cases (1,237 cases in men and 453 cases in women) were newly identified as lung cancer during an average follow-up of 15.5 years. More than half of the histologically confirmed cases were adenocarcinoma. Participants with higher intakes of antioxidant vitamins tended to drink and smoke less, and consumed more vegetables and fruits overall. In the multivariate analysis, higher retinol intake was positively associated with overall lung cancer risk in men (HR, 1.26; 95% CI, 1.05-1.51; p_{trend} = 0.003; comparing the lowest with the highest intake) and the estimates were more evident with small cell carcinoma (HR, 1.92; 95% CI, 1.13-3.24; p_{trend} = <0.001). Mean retinol intake in the highest category in this study (1,121 mcg for men and 1,183 mcg for women) was much higher than that in previous studies with dietary retinol intake and somewhat comparable to the highest group in a study with retinol supplementation. No associations were observed for other antioxidant vitamins or in women.

Conclusion: While this prospective study suggests that habitual consumption of coffee is not associated with an increased risk of overall lung cancer incidence, a significant increase in the risk of small cell carcinoma was observed. Findings in this study are likely explained by residual confounding by smoking as adjustment for tobacco use was imperfect and the positive associations were evident with smoking-related subtype and among smokers, although a possibility of other explanations still remains. Higher consumption of retinol may be associated with an increased risk of lung cancer in men, especially with small cell carcinoma, although confirmation is required. Further studies

that capture more detailed quantitative information on tobacco smoking would help clarify the impact of antioxidant-rich diet and residual confounding on lung carcinogenesis. While smoking still has a substantial effect on lung cancer incidence and on mortality worldwide, studying the non-smoking-related factors not only highlights the significant price of smoking but also plays a part in understanding the mechanisms that might reduce lung cancer morbidity and mortality.

Key words: lung cancer, diet, coffee, antioxidant vitamins, cohort study