［課程－２］

審査の結果の要旨

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Antioxidants have been hypothesized to play a role in carcinogenesis of the lung but the association between dietary antioxidant intake and lung cancer risk has not been elucidated. The existing evidence is inconsistent and limited, especially from Asian population. The key research question of my thesis was: What is the association between consumption of antioxidant-rich diet namely coffee and antioxidant vitamins and lung cancer risk in Japan? The main objectives of my study were 1) to investigate basic characteristics of consumption of coffee and antioxidant vitamins – retinol, vitamin C, vitamin E, alpha-carotene and beta-carotene – with lung cancer risk factors, 2) to assess lung cancer risk by levels of coffee and antioxidant vitamin intake, and 3) to examine risk differences by gender, histological type of lung cancer and smoking status.

The key findings from my thesis are as follows:

1. A total of 1,668 lung cancer cases (1,227 cases in men and 441 cases in women) were newly diagnosed among 87,079 Japanese men (41,727) and women (45,352) aged 40-69 years during an average follow-up of 17.0 years in the analysis of coffee. Of histologically confirmed cases, 43.7% were adenocarcinoma. Two thirds of the study participants reported drinking coffee routinely while one third was non-drinkers. Compared with non-drinkers, coffee drinkers were much more likely to smoke cigarettes.

2. Coffee intake was positively associated with the risk of small cell carcinoma when analyzed in totality through multivariable Cox proportional hazards regression models (HR, 3.52; 95% CI, 1.49-8.28; p_{trend} = <0.001; comparing non-drinkers with ≥5 cups/day). A higher level of coffee intake among male heavy smokers who had ≥20.0 pack-years of tobacco exposure was associated with an increased risk of lung cancer (HR, 1.30; 95% CI, 1.04-1.63; p_{trend} = 0.014, comparing non-drinkers

with ≥3 cups/day), whereas no substantial effect modification by smoking status was observed in both men and women ($p_{interaction}$ = 0.266 for men; $p_{interaction}$ = 0.243 for women).

3. In the analysis of antioxidant vitamins, a total of 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 among 79,705 men (38,207) and women (41,498) aged 45-74 years. More than half (54.0%) of histologically confirmed cases were adenocarcinoma. Participants with a higher intake of antioxidant vitamins tended to drink and smoke less, and consumed more vegetables and fruits overall.

4. A higher level of 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) in multivariable models. This leaves a possibility of conflicting effects of the antioxidant at supranutritional level. No associations were observed for other antioxidant vitamins or in women.

In conclusion, this is the first and largest study in Japan to find that a higher consumption of retinol was positively associated with the risk of lung cancer in men while coffee intake was associated with an increased risk of small cell carcinoma in both men and women. Habitual coffee consumption and intake of other types of antioxidant vitamins were not associated with overall lung cancer risk. Differing risk estimates across histological type of lung cancer and smoking status in this study highlights the importance and necessity of stratified analyses in studies analyzing the associations between antioxidant-rich diet and lung cancer risk. As tobacco use is the predominant risk factor for lung cancer, residual confounding by smoking remains as the critical issue. These findings will not only contribute to accumulation of evidence from Japanese and Asian population but also to the better understanding of the mechanisms with different histological type of lung cancer and smoking exposure. Hence, the Review Committee agrees that this thesis has satisfied the requirements of the University for conferment of a doctoral degree.