

審査の結果の要旨

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The research question of this study was to determine the association between body-mass index (BMI) and the risk of gastric cancer among a Japanese population. There were four objectives for this study; first to identify the basic characteristics of BMI and gastric cancer risk factors; second to determine gastric cancer risk by BMI categories recommended for Asian population by the World Health Organization (WHO) expert consultation; third to determine the association between BMI and gastric cancer subsites (proximal and distal); and finally to determine the association between BMI and gastric cancer risk considering *Helicobacter pylori* (*H.pylori*) and atrophic gastritis status into consideration. She used the data obtained from the Japan Health Center-based prospective Study (JPHC-Study) to assess the association.

The key findings of her study are as follows:

1. During an average follow-up of 18.0 years, 2,860 gastric cancer cases (2,047 men, 813 women) were newly diagnosed among 92,056 study participants (44,122 men, 47,934 women). Out of 2,860 gastric cancer cases, 307 cases were proximal (upper third of the stomach) gastric cancer (244 men, 63 women), and 1,967 cases were distal (lower two-third of the stomach) gastric cancer (1,405 men, 562 women). Over half of the men who participated in the study smoked, while the majority (92%) of women were never smokers. For both men and women, percentage of current smokers were highest in lowest BMI category ($<19 \text{ kg/m}^2$; 64.5% for men, 10.1% for women). Prevalence of habitual drinkers were highest in $\geq 23 - 25 \text{ kg/m}^2$ for men (41.6%), and $<19 \text{ kg/m}^2$ for women (2.5%).
2. When a multivariable Cox proportional hazards regression models using attained age as the time scale was used to analyze the association between BMI and risk of gastric cancer, among Japanese men who were BMI $\geq 27 \text{ kg/m}^2$, we observed a significant increase in the risk for overall gastric cancer (hazards ratio (HR) 1.23, 95% confidence interval (CI), 1.00 – 1.53), compared to men who were BMI $\geq 23 - 25 \text{ kg/m}^2$.
3. There were no statistically significant association between BMI and gastric cancer risk among women.
4. For both men and women, a non-statistical, but an increase in the risk was observed for proximal gastric cancer at low ($<19 \text{ kg/m}^2$) and high ($\geq 27 \text{ kg/m}^2$) ends of the BMI categories (men: $<19 \text{ kg/m}^2$: HR 1.85, 95% CI 0.85 – 4.02; $\geq 27 \text{ kg/m}^2$: HR 1.53, 95% CI 0.84 – 2.80; women: $<19 \text{ kg/m}^2$: HR 1.56, 95% CI 0.43 – 5.69; $\geq 27 \text{ kg/m}^2$: HR 1.73, 95% CI 0.70 – 4.27).
5. These associations did not change even when we excluded those who developed gastric cancer within five years from the baseline survey

6. When *H.pylori* infection and atrophic gastritis status were considered for the association between BMI and gastric cancer risk, a significantly higher risk for proximal gastric cancer was observed among BMI ≥ 27 kg/m² subjects who were *H.pylori* anti-body seropositive (HR 6.38, 95% CI 1.19 – 33.32), atrophic gastritis positive (HR 4.84, 95% CI 1.13 – 20.77), or tested positive to either or both *H.pylori* antibody or atrophic gastritis (HR 4.57, 95% CI 1.07 – 19.49).

This study supports the evidence from previous epidemiological studies that suggested the highest risk contributor for gastric cancer in Japan is *H.pylori* infection and its associated symptoms. The results from this study also do suggest the possibility of association between BMI and gastric cancer risk among a Japanese population. While gastric cancer incidence associated with *H.pylori* infection is declining globally, the incidence of gastric cancer associated with obesity is increasing in regions previously known for low incidence of gastric cancer. With the decline in the prevalence of *H.pylori* infection in regions with high gastric cancer incidence, obesity related gastric cancer incidence may rise in those regions as well. It is possible that the risk factor attributing to the burden of gastric cancer may change. The pathogenesis of gastric cancer associated with BMI is less established compared to the pathogenesis of gastric cancer associated with *H.pylori* infection. Previous studies from the Western countries only found an association between obesity and gastric cancer. However, in this study, she also observed a potential increase in the risk among those who are underweight, highlighting the possible risk difference among Asian and Western population. Furthermore, no previous study has considered *H.pylori* infection status, an important confounder, for the association between BMI and gastric cancer risk.

Because of the limited evidence available on the association between BMI and gastric cancer particularly from Asian population, this study adds a valuable evidence to the body of knowledge that exists currently. Given the reasons above, the committee considers that this thesis is worthy of a doctoral degree.