最終試験の結果の要旨

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主査および副査の５名は、平成 27 年 12 月 17 日、学位申請者 Soroush Hassani 君に面接し、学位申請論文の内容について説明を求めると共に、関連事項について試問を行った。具体的には、以下のような質疑応答がなされ、いずれについても満足すべき回答を得ることができた。

Q1: What is the most common cancer among men in India?
A: According to IARC's GLOBOCAN 2012, the most common cancer among men in India is lung cancer.

Q2: What are the proportions of early and advanced stage of gastric cancer in this population or India?
A: According to a study in northeastern India, early gastric cancer was present in 7.6% cases and majority (62.7%) had locally advanced gastric cancers.

Q3: What is the natural history of gastric cancer by histologic types, intestinal and diffuse types?
A: Intestinal type tumor characterized by well differentiated cells grows slowly and tends to form glands, and it is the end-result of an inflammatory process. Intestinal metaplasia and dysplasia are pre-cancerous status. This tumor is observed more often in men and older people. Diffuse type tumor is characterized by poorly-differentiated cells, and they diffusely infiltrate the gastric wall rather than forming glands. These tumors are more aggressive and occur equally among men and women and develop at younger ages than those with intestinal-type tumors.

Q4: What is the difference between WHO and Lauren's classification of gastric cancer?
A: The WHO classification recognizes 4 major types: tubular, papillary, mucinous, and poorly cohesive (including signet ring cell carcinoma). The Laurén classification has proven useful in evaluating the natural history of gastric carcinoma, especially with regard to its association with environmental factors, incidence trends and its precursors, while the WHO classification is more precise for clinical decision making.

Q5: What is the most important carcinogen in bidi tobacco?
A: Among over 60 carcinogens in tobacco smoke, nitrosamines and other nitroso compounds are most important.

Q6: What is the difference in carcinogenic components among various types of tobacco?
A: Carcinogenic elements in bidi is as same as cigarette. One of the important thing is that bidi does not have a filter. Thus, bidis produce 3 times more carbon monoxide and nicotine and 5 times more tar than cigarettes. Chewing tobacco includes betel nut and slaked lime in addition to tobacco. Betel nut is also contains alkaloids which is carcinogenic. Slaked lime increases the bioavailability of nicotine by increasing pH and the carcinogenicity of tobacco especially in oral mucosa.

Q7: There is no difference in the effects of bidi smoking on gastric cancer risk by cigarette smoking status. Furthermore, both cigarette and bidi smokers showed a lower risk of gastric cancer than exclusively bidi smokers. How do you explain this result?
A: Cigarette smokers in our study population smoke cigarettes far less than those in other countries because of economic reasons. That might be the reason why we could not see the effect of cigarette smoking. For smokers of both bidi and cigarettes, smoking cigarette might reduce the number of bidis. It is also possible that we could not fully adjust the effects of confounding factors including socioeconomic status of bidi and cigarette smokers.

Q8: Why did former cigarette smokers show a higher risk of gastric cancer than current smokers?
A: They might have stopped smoking because of their clinical symptoms due to precancerous changes in the stomach.

Q9: When we consider the risk of smoking-related cancer, exposure factors should be taken account. What did you include in your analysis?
A: We examined the association of age at starting smoking and the number and duration of smoking with gastric cancer risk. Using the number of bidis or cigarettes smoked per day and duration of smoking, the cumulative effect of smoking was evaluated. Although some studies examined the amount of tar in cigarettes, is was not possible for bidis because there is no such an information on its label.

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Q10: What is your explanation for the increase of gastric cancer risk by early start of smoking?
A: It can be the cumulative effect of smoking. The duration of being exposed to the carcinogens increases in people who start smoking early. Another explanation is a high susceptibility to carcinogens in younger ages.

Q11: Is chronic inflammatory mucosa caused by smoking?
A: The mechanism of the gastric carcinogenesis of tobacco smoking is not completely understood, but some studies have shown that smoking increased the risk of transition of the mucosa to dysplasia and intestinal metaplasia.

Q12: What is the *Helicobacter pylori* (*H. pylori*) infection rate in India?
A: Recent reports from India indicate that around 80% of the population are infected with *H. pylori*.

Q13: What is your hypothesis in the association between bidi smoking and *H. pylori* infection?
A: To my knowledge, there is no study investigating the association of bidi smoking and *H. pylori* infection. Since previous studies have shown no association between cigarette smoking and *H. pylori* infection, we could assume that *H. pylori* infection may not affect the association between bidi smoking and gastric cancer risk.

Q14: Isn't it over-interpretation to mention the interaction between bidi smoking and *H. pylori*-infection in your paper without the results of *H. pylori* infection?
A: The thesis was revised as follows: "the present study could not settle the question of whether *H. pylori* infection modifies the association between bidi smoking and gastric cancer risk since we do not have any information on *H.pylori* infection in the present study population".

Q15: Why did you choose this study population?
A: Karunagappally cohort and the regional cancer registry in this area were established to study health effects of high natural background radiation, due to thorium containing monazite sand, in the coastal area of Kerala State. Because of this right conditions, we have conducted series studies of various cancers in this population.

Q16: Is radiation associated with gastric cancer risk?
A: The previous studies of Karunagappally cohort found no association between the high background radiation and different cancers including gastric cancer.

Q17: Why did you exclude female subjects? What is the incidence of gastric cancer among females in India?
A: Because the number of female smokers is very small in India, less than 1%. Gastric cancer incidence for women in Karunagappally is 2.5/100,000 person years which is also lower than that of men (6.9/100,000 person years).

Q18: Why did you exclude the specific workers, labors at rare earth factory?
A: We excluded those subjects because of some potential occupational exposures which may increase the cancer risk.

Q19: What is the main cause of death in this area?
A: Coronary heart disease is the major cause of death in Kerala State.

Q20: How was the association between salt intake and gastric cancer risk?
A: Since we did not have the information on salt intake, we used the information on dry fish consumption as a surrogate variable for salt intake. It seems to be the only dietary item with high salt concentration in this population. We found no increase in gastric cancer risk with dry fish consumption.

Q21: What is the proportion of household having a refrigerator in this area?
A: We have not obtained that information for our study subjects. According to several reports, 95% of households in Kerala state have electricity, which is the highest among other states of India.

Q22: Regarding the distribution of family income, the income of the study subjects is relatively low. Is this a low-income area in India?
A: Yes, it is. Kerala state is one of the low-income states comparing to other states in India. However, the standards of living (health indicators, education, access to electricity and so on) are high compared to other states, which might be because of socialistic government in this state.

Q23: Wliat is the mechanism of the increase of gastric cancer risk by lower education?
A: Lower education might lead to lower awareness of health and healthier lifestyle. Lower education can also lead to lower income, poor dietary habits, and less access to healthcare facilities. Education can be an indicator of socioeconomic status and hygiene in childhood which could be risk factors of infectious agents such as *H.pylori*.

Q24: What are current activities and the tobacco-control programs in India?
A: WHO Framework Convention on Tobacco Control has been implemented in India: Smoking bans in public places, including workplaces, public transport, and restaurants; Health warnings on tobacco products and at point of sale; Bans on tobacco advertising, including in all media and in community settings; Bans on sales of tobacco to children (under 18); No sale of tobacco products within a 100-yard radius from schools.

以上の結果から、５名の審査委員は申請者が大学院博士課程修了者としての学力・識見を有しているものと認め、博士（医学）の学位を与えるに足る資格を有するものと認定した。