最終試験の結果の要旨

報告番号	総研第 418 号		学位申請者	Tran Thanh Long
審査委員	主査	嶽崎俊郎	学位	博士（医学・歯学・学術）
	副査	有田和徳	副査	河野嘉文
	副査	大脇哲洋	副査	堀内正久

主査および副査の５名は、平成30年 1月 10日、学位申請者 Tran Thanh Long 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。

1. Are the guardians of control children the workers of nuclear power plants?
A: What we could know from the database was the exposure dose for the parents. According to that information, a part of fathers in the control group, around 20%, were workers of nuclear power plants.

2. The gestational age category used in Table 4 was not corresponded to the clinical definition of full-term birth which is between 37 and 41 gestational weeks. Please explain the reason why you did not follow this definition?
A: Since gestational age (GA) is a potential confounding factor in the present study, we wanted to examine more detailed GA effects on childhood cancer risk. Since more than 80% of subjects were born in 37-41 weeks, we divided this category into two groups according to the control distribution.

3. Gestational diabetes or maternal overweight are also related to high birth weight of children. Are there any studies reporting the association between these factors and child cancer risk?
A: There are a few reports on the association between gestational diabetes or maternal overweight and childhood cancer risk. A population-based study conducted in California found no significant association between gestational diabetes and childhood cancer risk.

4. In general, high birth weight, > 4,000g, is not a major concern in Japan. What is the proportion of high birth weight in Asia?
A: A retrospective cohort study in 2005 reported 13% of high birth weight in Tianjin, China. On the other hand, more recent study in Shanghai reported 6.9% which is similar to those in Vietnam, 5-6.3%.

5. What is the fourth most frequent CNS tumor among children?
A: According to the review by Christian et al., the fourth most frequent CNS tumor was craniopharygioma.

6. The origin of craniopharyngioma is different from that of the most common CNS tumors such as medulloblastoma and astrocytoma. What is the risk factor of craniopharyngioma?
A: According to the review on CNS tumors in children (Patricia AM, 2005), the causes of childhood CNS tumors are largely unknown, and risk factors for craniopharyngiomas have not been identified.

7. Can you explain the reason of discrepancy in the magnitude of odds ratios for CNS tumor risk between the present study and previous studies?
A: The present study found larger ORs for CNS tumors than those reported by the previous studies. Although we tried to figure out the reason for this discrepancy in the magnitude of ORs, we don't have any good explanations so far.

8. In Table 4, the risk of CNS tumor is low among the children who were born after 40 weeks of pregnancy. Please explain this reason.
A: It is because that I used the subjects born in 37-39 weeks as a reference group. If I take the subjects born in 40-41 weeks as the reference, which shows the lowest OR, the OR of the group >41 weeks will be greater than the unity. In fact, it is 1.3 (95%CI: 0.5, 3.6) and it would be more reasonable for the interpretation.

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9. Is the number of brain cell at birth related to birth weight? If so, what kind of brain cell is affected?
A: In the animal experiment, the birth weight was positively associated with the proliferative potential of neurosphere progenitor cells and their differentiation rates to astrocytes and neurons in newborn rats (Mina et al, 2011).

10. In the present study, you examined very old database, although the lifestyle, environment and hygiene have been changed since then. Why didn't you examine more recent data?
A: One of the advantages of this database was reliable information of birth weight and clinical diagnosis of cancers because the original study obtained these information from official or medical records. In addition, this data contains a good enough number of children with high birth weight for the analyses. We could not find other open data set with a high quality and satisfied conditions.

11. Was the benign CNS tumor included in your study?
A: According to the original report by Sever et al., the authors did not mention whether benign tumors were included or not, and there is no information of tumor histology in the database. However, one of the source for the case ascertainment was cancer registry. Although it is a matter of the speculation, the original study might have recruited malignant cases only.

12. You describe that "birth weight is strongly related to gestational age" but previous studies, except California study, could not find this relationship. What do you think about this issue?
A: This statement was referred to the evidence from a well-designed prospective cohort study published in Am J Obst Gynecol (2016), and I think it is generally accepted. In California study, the authors examined the association between gestational age and CNS tumor risk but it was not statistically significant. That study did not report the association between birth weight and gestational age.

13. Why did you fail to detect the association between birth weight and the risk of leukemia? Is there any other reason rather than sample size?
A: So far, what I could conceive of the reason is a small sample size of leukemia cases. Since the magnitude of OR for leukemia risk in the present study (OR=1.4) is similar to that reported by another meta-analysis (OR=1.35), our sample size was too small to detect the statistical significance.

14. Is the birth weight related to the cellular component?
A: As long as I know, it is not well-understood whether there is a relationship between birth weight and cellular component.

15. What was the study objective of the original study of the database used for the present study?
A: The original study was conducted to examine the association between childhood cancer risk and paternal preconception occupational radiation exposure in the populations living near Department of Energy facilities.

16. How does the IGF-1 reach to the brain? Can it pass through the blood-brain barrier?
A: According the study by Weihong et al., IGF-1 is able to enter the CNS by a saturable transport system at the blood-brain barrier, which functions in synchrony with IGF binding proteins in the periphery to regulate the availability of IGF-1 to the CNS.

17. How will you apply your finding for the prevention of childhood cancer?
A: Regarding the prevention of childhood cancer, I think, it is very important to control mothers' body weight properly during the pregnancy, which has been introduced in Japan and the US.

18. Is the increase trend of childhood cancer observed in both developed and developing countries?
A: A recent study, reported by Steliarova-Foucher et al., revealed that the incidence of childhood cancer from 2001 to 2010 has increased since the 1980s in all regions except sub-Saharan Africa, and the highest increase was observed in Southeast Asia.

19. Is there any correlation between childhood cancer incidence and birth weight trend?
A: In Japan, average birth weight tends to decrease from 1975 to 2005. This is also true in the US although the incidence of childhood cancer has increased over the years. Thus, ecological findings do not support the association between high birth weight and childhood cancer risk, but such a contradiction in the ecological study is frequently observed in other cases.

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。