International Cancer of the Head and Neck, Genetics and Environment (InterCHANGE) Study

First Study Group Meeting
Cancer Institute & Hospital, Chinese Academy of Medical Sciences, Beijing
March 4-5, 2009

MINUTES

March 4, 2009 (Wednesday)

1. Welcome and opening (Min Dai & Paolo Boffetta)
The objectives of the meeting are: 1) to discuss the feasibility of a large-scale, multicentric study of molecular and genetic epidemiology of head and neck cancer in China and other East Asian countries, 2) to agree on study hypotheses, study design, process to prepare the common study protocol, and 3) to devise a plan for the next 12 months (finalization of protocol, ethical approval, feasibility studies, grant applications).

Recent progress in head and neck cancer (chaired by Zuo-Feng Zhang)

2. Burden of head and neck cancers (Zuo-Feng Zhang)
There are over half a million cases of head and neck cancer diagnosed and over 300,000 deaths due to head and neck cancer each year worldwide. There is a high smoking prevalence in males and a low smoking prevalence in females in China. However the incidence rate of oral cancer in China is low. Low incidence of oral cavity cancer is observed in the green tea drinking regions (Zhejiang, Jiangsu, Shanghai).

3. Lifestyle risk factors (Paolo Boffetta)
Tobacco and alcohol are the major risk factors for head and neck cancers. Additional established risk factors include betel quid chewing, and HPV infection. Other risk factors include body mass index, diet, family history of cancer.

4. Genetics and biomarkers (Qingyi Wei)
With the current advances in genetic research, the study of gene-environment interactions on the risk of various diseases is a promising area. The promises of molecular epidemiology include individualized risk assessment, individualized early diagnosis and individualized treatment and therapies. The hapmap project and the resulting genome-wide association studies have yielded interesting results for cancer and other diseases.

5. HPV (Min Dai)
The results from the IARC monograph on HPV was reviewed. In summary, there is sufficient evidence in humans for the carcinogenicity of HPV16 in the oral cavity and oropharynx. However, there is limited evidence in humans for the carcinogenicity of: 1) HPV16 in the larynx, 2) HPV18 in the oral cavity and larynx, and 3) HPV6 and 11 in the larynx.
6. Nonsmoker/nondrinkers (Mia Hashibe)
Nonsmokers and nondrinkers are a difficult subgroup to study in head and neck cancer patients because they are quite rare. Approximately 11% of head and neck cancer patients are never smokers and 16% are never drinkers. In the INHANCE consortium, the priority was to examine this rare subgroup with a data pooling project. Tobacco and alcohol may account for a smaller proportion of head and neck cancers in young subjects and for varied proportions across geographic regions.

7. HNC epidemiology in China (Ni Li)
The national center for cancer registry was founded in 2002 and covers 6% of China’s population. There are 43 cancer registries and the number is expected to rise to nearly 100 by the end of this year. Trends in head and neck cancer incidence were presented for the registries that were included in the Cancer Incidence in Five Continents volumes. A few studies indicated that some important risk factors for head and neck cancer in China may include tobacco, alcohol, poor oral hygiene, air pollution, x-rays, stress, and possibly HPV infection.

Collaborative studies at IARC

8. Overview of collaborative studies at IARC (Paolo Boffetta)
The collaborative studies at IARC include multicentric studies and consortia. The central Europe multicenter case-control study on lung, head and neck, and kidney cancers was presented. The international lung cancer consortium (ILCCO, http://ilcco.iarc.fr) was also presented.

9. INHANCE Consortium (Mia Hashibe)
The International Head and Neck Cancer Epidemiology (INHANCE) Consortium projects were presented. The major topics of interest included data pooling projects on never smokers and never drinkers, estimating population attributable risks for tobacco and alcohol, understanding risks for family history of cancer, involuntary smoking, diet and SNPs. Future directions include a post-genome wide project and project on HPV serology among cases and controls.

10. IARC multicentric study on cancers of oral cavity and oropharynx (Min Dai)
The results on HPV in the IARC multicentric study on oral cavity cancer was presented. All HPV markers were most frequently detected in cancer of the tonsils. The association with anti-HPV seropositivity was much stronger for E6/E7 ab (marker of viral oncogens) than for L1 ab (marker of infection). The effect of HPV and smoking/chewing was additive, rather than multiplicative. Additionally, a paired matching analysis was done by comparing the frequency and type of TP53 mutations in patients with cancers positive for HPV 16 DNA and HPV-negative cancers. There was an inverse association between the presence of TP53 mutations and HPV16 infection.
12. Nanjing (Hongbing Shen)
For this study, incident cases will be recruited with accurate diagnosis, clinical information, samples before treatment and the questionnaire. Controls will be from the population. Three hospitals have been contacted thus far; a 4th will be contacted. Approximately 80-100 oral cavity cases and 80-100 laryngeal cancer cases may be diagnosed per year. Blood sample collection is feasible but tissue samples will be difficult. Paraffin embedded tissue is kept in the pathology department.

13. Jiangsu Province CDC (Ming Wu)
Jiangsu is one of the highest cancer incidence areas in China. Cancer has been the first leading cause of deaths since the 1970s. Cancer mortality is approximately 50% higher than the national average. Data for cancer mortality from a cause of death retrospective survey were presented. The four leading cancers are liver, lung, stomach and esophageal cancer. High cancer incidence areas of total cancer mortality are located in Lixiahe area (Middle Jiangsu) and some areas around the Tai Lake. For head and neck cancer mortality, the highest percentage was nasopharyngeal (40.76%), followed by laryngeal cancer (20.43%) and oral cavity cancer (15.48%). The risk factor intervention project, screening project, cancer registration and risk factor surveys were also presented.

14. Inner Mongolia (Min Dai)
Huhehaote is the capital of Inner Mongolia Autonomous Area. Its population is 1.8 million, with more than 30 minor ethnic groups such as Mongolian, Hui. The dominant cancers in Huhehaote are lung cancer, breast cancer, stomach cancer, colorectal cancer, leukemia, oesophageal cancer and liver cancer. Prevalence of risk factors for cancers is high in Huhehaote including high smoking rate (70-80% in men), high alcohol drinking rate, high animal meet intake, less vegetable & fruit intake, etc. Currently, CIHCAMS and the Inner Mongolia Medical College Affiliated Hospital are establishing a cancer registration system and a cohort of 200,000 people aged 35-60 years. Hospital based case-control studies will be carried out on lung, breast, stomach, colorectal, esophageal, liver and pancreatic cancers. There may be an opportunity for the head and neck cancer study to be carried out in this population.

15. Oral epithelial dysplasia and p16 methylation (Dajun Deng)
Results on oral epithelial dysplasia and p16 methylation were presented. The results are unpublished, thus the slides will not be available.

16. Shanghai (Xiaoyan Zhou)
At the Fudan University Cancer Hospital, there are 11 clinical departments and 8 diagnostic departments including head and neck surgery and radiation oncology. In 2008, there were 2576 head and neck surgeries and 1149 cases (957 thyroid, 192 nonthyroid - 16 pharynx, 13 oral cavity and 26 larynx). In the radiation oncology department there were 1102 head and neck cancer cases (853 nasopharynx, ~100 for oral cavity, pharynx and larynx). The tissue bank in the hospital was also presented.
17. Tianjin (Kexin Chen)
The Tianjin Cancer Registry was established in 1978. It is one of the largest cancer register centers in China, covering a population of approximately 4 million. It includes data on 170,000 cancer cases from 1981 to present. From 1981-2002, there were a total of 1400 oral cavity cancer cases (C00-09), 1395 pharyngeal cancer cases (C10-14) and 2258 laryngeal cancer cases (C32). The age-standardized incidence rates of HNC decreased for males and females. Different patterns of age distribution between males and females was found for laryngeal cancer. The tissue bank in Tianjin includes 18,000 tissue samples and 5100 blood samples.

18. Yunnan (Kaining Zhang, Jackson Tung)
The Yunnan province includes people from 52 ethnic minority groups (38.07%). Urgent needs for cancer research in the area includes mining in Gejiu and indoor air pollution in Xuanwei. The Yunnan cancer hospital was presented - the hospital includes the Cancer Research Institute as well as the 8 provincial research centers. The research center includes a head and neck cancer research center. In Dayao, blue asbestos is an environmental hazard that needs to be further studied.

19. Hainan (Hong Zhou)
Hainan is an island province in the south with a population of approximately 8 million. It is home to 38 ethnic minority groups. According to a literature review, there was a survey of prevalent status of malignant tumors in 2 counties of Hainan in 2004. The five main malignant tumors were liver cancer, lung cancer, carcinoma of stomach, nasopharyngeal carcinoma. In 2005, there was another paper published on ‘Smoking and drinking pattern among residents of Li ethnic minority villages in Hainan, China’. The prevalence rates of tobacco and alcohol use in Li male villagers are higher than those of the national average and other ethnic minorities in China.

20. Zhejiang Provincial CDC (Weiwei Gong)
Surveillance system in Zhejiang Province covers 30 counties and approximately 16.05 million people. For the cancer surveillance, follow up is conducted actively by phone and passively with death certificates. For quality control, the county CDC conducts surveys for the under-reported cases in hospitals twice a year. The six leading causes of cancer incidence are lung, colorectal, stomach, breast, liver and esophageal cancer. The smoking prevalence is 27.81% in Zhejiang Province in 2007. For alcohol drinking, 42.50% subjects were ever drinkers in the past 12 months before the survey.

21. Seoul, Korea (Ae-sun Shin)
For head and neck cancer incidence in Korea in 2005, there were 1132 laryngeal cancers, 884 oral cavity cancers, 270 oropharyngeal cancers, 331 hypopharyngeal cancers. At the national cancer center in Seoul, there were approximately 110 oral cavity and pharyngeal cancer cases in 2007 (C00-C14). The source of control subjects includes a cancer screening cohort of 24,000 men and women as of December 2008. This screening population undergoes a questionnaire with simple FFQ, and provides biological material (blood, spot urine, cervical exfoliated cells).

22. Taiwan (Li-yu Wang)
Oral cavity and pharyngeal cancers (C00-C14) are the 4th leading cause of cancer death in Taiwan for the year 2005 among males. Oral cavity cancer death rates increased from 4.7 per
100,000 in 1986 to 15.6 in 2007 for males. Oral cavity and pharyngeal cancers are also the 4th most common cancer in 2005 among males. The incidence rate has more than doubled for women from the 1981-5 to 2000-5 (from 1.43 to 3.21). The community based cohort of cancer screening participants was also presented. The residents were required to be aged 30-65 years in select regions from 1990-1992. From approximately 100,000 residents who were eligible, 25,000 subjects were enrolled. Data linkage with the national cancer registry system resulted in 104 incident cases of head and neck cancer (excluding salivary and nasopharynx) and 7 deaths. Alcohol, betel quid chewing and cigarette use (ABC) were all associated with the risk of head and neck cancer.

March 5, 2009 (Thursday)

1. Presentation of protocol for new study (Mia Hashibe)
   The aims for the new study include: high quality biological samples (blood for DNA, tumor tissue), follow up of cancer cases with high quality information on treatment and outcomes, repeated sampling, targeting a large series of cases/controls, and shortened lifestyle questionnaire. The study design is a multi-center case-control study with hospital or population controls depending on the center. Controls will be frequency-matched by sex, 5 year age group, ethnicity and residence area. A lifestyle questionnaire will be administered at diagnosis. Follow up questionnaires on comorbidity and quality of life may be administered 1 year later, 3 years later and 5 years later for cases only. IARC will provide access databases for computer assisted interviews or for data entry if paper questionnaires are preferred at the center. Log sheets will be used to track biological sample collection, patient information and non-participants. A pilot study will be carried out to assess the feasibility of the study in each center.

**Discussion of protocol**

2a. Cancer sites
   The study group discussed the possibility of including esophageal, nasopharyngeal and thyroid cancers. There was agreement to start with the oral cavity, pharynx and larynx sites first and then to consider nasopharyngeal or other sites later. Since the other cancer sites (nasopharynx and thyroid) are much more common than head and neck cancer, inclusion of these sites may eclipse the original study questions and aims.

   There was a suggestion that oral disease hospitals should be contacted. The principal investigator of each study center will be responsible for assessing the best hospitals to approach for their region or city.
2b. Target number of cases
Some estimates for the number of head and neck cancer cases per year were discussed:

- 100 Beijing - Cancer Institute and Hospital of Chinese Academy of Medical Sciences
- 100 Tianjin - Tianjin Cancer Hospital
- 200 Nanjing
- 100 Shanghai - Shanghai Cancer Hospital
- 70-80 Yunnan - Yunnan Cancer Hospital
- 100 Wuhan - Hubei Oral Cavity Diseases Hospital
- 100? Taiwan
- 100 Korea
- 300 Peking Union Medical College Hospital

= approximately 1280 eligible cases per year

2c. Controls
The ratio of controls to cases will be dependent on the center, but 1:1 was preferred by most of Chinese centers. For centers that may recruit small numbers of cases, 3 controls will be recruited per case (Ex. Korea). Community based controls must be considered with caution since the risk factor distribution appears to be different from the base population. Control disease list should be restricted to disease not related to tobacco or alcohol. Each center should propose the source of controls and the ratios to the overall study group for consideration.

2d. Questionnaire
For diet, a food frequency questionnaire that is already available in Chinese (from Prof Zuo-Feng Zhang) was proposed. Other additions suggested: physical activity, indoor air pollution, occupational, sexual history, weight 2 years ago and at age 20, years of education, water pipe use, involuntary smoking on all subjects (not just never smokers) and family history of cancer. Centers are requested to propose additional local habits (ex. Smoking bamboo in Yunnan). For the date of birth, it was noted that some people will report in lunar year calendars.

2e. Follow up
Possibilities for follow up of cancer patients will be assessed with a questionnaire to the study center principal investigators.

3. Biosamples (Qingyi Wei)
Possible biosamples for collection include blood, buccal cells, saliva, biopsies, fresh-frozen tissue, paraffin-embedded tissue. Laboratory analysis includes genetics (resequencing, GWAS, replication/validation), biomarkers (exposure, dietary, immunologic), HPV (serology, tumor tissue detection).

The study group discussed the difficulties of collecting large volumes of blood. The overall consensus was to aim for 15 ml of blood in 2 10-ml tubes.

Viable lymphocyte collection will be optional for the centers. The protocol will be provided from MD Anderson.
Central storage is proposed to initially be in the CIHCAMS for the Chinese centers. Prof Min Dai will investigate the possibilities. The study center should keep approximately half of the samples - storage at 2 sites will ensure backup samples are available.

4. Ethical approval
Ethical approval application will be submitted centrally at IARC. Study centers should start to apply for ethical approval with the updated protocol and questionnaire. The IARC approval will be forwarded to centers. The IARC approval is final only when local approvals are final.

The consent form in the appendix should be considered a guideline. Each center may translate this or use consent forms from previous studies. The consent form should be provided to IARC.

5. Grants
Previous IARC multicenter studies have been funded on a combination of national and central funds. The Chinese NSF application is approximately 300,000 yuans and the result will be available around September 2009. It may also be possible to apply for the department of science and technology in China from IARC, with help from Drs. Qingyi Wei, Min Dai and Zuxun Lu. This application does not have a deadline.

US National Institutes of Health (NIH) and European Commission grants will require some preliminary data (pilot study). It is anticipated that the first central grant can take place in early 2010.

6. Action plan

1. **Center questionnaire:** IARC will circulate a questionnaire to the study centers regarding the study design details specific to the center, such as the hospitals to be included, the control source, local habits, etc. **due in 2 months.**

2. **Protocol:** IARC will update the protocol and questionnaire with the study meeting comments

3. **Ethical approval:** Study centers should start to apply for ethical approval with the updated protocol and questionnaire. Ethical approval application will also be submitted centrally at IARC.

4. **Funding:** Study centers should consider applying for local funding for the pilot study if there are opportunities.

5. **Next meeting:** A second study group meeting will be planned just after the pilot study completion (9-10 months from first study meeting). Site visits are expected over the next year.
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