

Progress Report
AML and NHL Case-control Study
Activities through December 2005

Prepared by:
Otto Wong, Sc.D.
Applied Health Sciences, Inc.
181 Second Avenue, Suite 628
San Mateo, CA 94401
USA

Tel: 1 (650) 347-7898 USA
Fax: 1 (650) 344-6887 USA
ottowong@aol.com
ottowong@shmu.edu.cn

January 23, 2006

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Patient Enrollment

- The number of participating hospitals has increased to 31 (from 29 in 2004). The majority of participating hospitals are municipal hospitals (17), followed closely by district hospitals (12). The remaining two are occupational hospitals.
- As of November 2005, approximately 4000 patients have been interviewed. These patients included both cases and controls in the case-control study of AML and NHL as well as subjects in the disease progression study. Among the cumulative number of 4000 patients, approximately 3890 questionnaires were entered and verified.
- In terms of the case-control study of AML and NHL, the case enrollment rates for both AML and NHL patients during the last 6 months appeared to be quite encouraging. According to the numbers provided by the JCML (Dr. Richard Irons), the cumulative numbers of AML and NHL patients are as follows (as of November 2005):
 - 353 acute myeloid leukemia patients
 - 380 lymphoid cancer (WHO) patients
 - 251 "NHL" patients (part of lymphoid cancer above)

- If the current rates of patient enrollment can be maintained through 2006, we will likely end up with the following number of cases by the end of the year (end of data collection):
 - 500-600 acute myeloid leukemia case
 - 500-600 lymphoid cancer (WHO definition) cases
 - 350-400 "NHL" cases (part of lymphoid cancer above)
- In general, compared to previous years, case identification by the Clinical Coordinators at participating hospitals has been relatively timely and consistent. This is particularly true for AML patients. By comparison, the enrollment of NHL patients still fluctuates from time to time. Most of the NHL patients come from the Shanghai Tumor Hospital. In 2005 the team at Fudan made periodic reminders to the Clinical Coordinators at the Shanghai Tumor Hospital for timely submission of NHL patients. These periodic reminders seem to be working well.

Selection of Controls

- The selection of controls for both AML and NHL patients seemed to be working properly. In 2005, there were only a few minor isolated problems.
- At a couple of small hospitals with limited number of patients, finding appropriate controls in the right age range, especially when the cases were either very young or very old, could be difficult. There was some confusion as to whether the age matching requirement was ± 5 or ± 10 years. This point was subsequently clarified: ± 5 years should be attempted first and, if none available, ± 10 years will be accepted.
- The participation rate among eligible cases or controls has been extremely high. As of November 2005, only 6 cases or controls refused to participate in the study.
- We have been able to select two controls for every case.
- We continue to monitor the distribution of controls by diagnostic category to ensure that there will be no over-representation of any diagnostic category, which in turn may be associated with certain socio-economic class, occupation or lifestyle. The table below shows the distribution of controls by major diagnostic category, which seems to be in agreement with that of the general population of patients in Shanghai.

Diagnostic category	Percent
Cancers	13.91%
Nutritional & metabolic diseases	7.49%
Neurological system diseases	9.75%
Circulatory system diseases	12.60%
Respiratory system diseases	9.75%
Digestive system diseases	14.86%
Urinary system diseases	10.58%
Musculoskeletal diseases	11.30%
Blood & hematopoietic diseases	0
Mental diseases	0

Please note that, as specified in the protocol, patients with "blood & hematopoietic diseases" or "mental diseases" are not eligible.

Exposure Assessment

- Based on preliminary exposure assessment, a total of 259 patients were either definitely or potentially exposed to benzene, representing an overall benzene exposure rate of 7%. The exposure frequency (7%) is slightly lower than that used for power calculation (10%) in the study design.
- The distribution of benzene-exposed patients by major industry is as follows:

Industry	Percent
Painting	32%
Machine maintenance	20%
Rubber	14%
Home remodeling	13%
Shoe making	12%
Printing	9%

- Based on preliminary exposure assessment, some benzene exposure data of study subjects (cases and controls) are presented in the table below:

Earliest exposure	1936
Occupations/industries with highest exposure	rubber plank manufacture, brush & spray painting
Highest maximum exposure	515.7 ppm *
Highest minimum exposure	12.1 ppm *
Highest typical exposure	161.9 ppm *
Longest exposure	40 years

* preliminary estimates

- In addition to the patients identified to have been exposed to benzene, approximately 2800 patients were identified to have been exposed to other substances in a variety of industries. The largest category is farming with potential exposure to agricultural chemicals. Other frequently encountered chemicals are toluene and xylene.
- We continue to encounter difficulties in accessing the Shanghai Municipal IPHS's historical exposure database. Future arrangements with the Shanghai Municipal IPHS are under negotiation (handled by Dr. Richard Irons).
- As discussed in our last progress report dated July 24, 2005, several problems in interpreting the data in the Shanghai Municipal IPHS's database were identified; such as large number of zero values in the database and incomplete reporting by the district IPHS to the Shanghai Municipal IPHS. These issues are being addressed by the exposure assessment team under Tom Armstrong's direction.
- Plans have been underway to develop exposure profiles for 8 to 10 key industries using data from the 5 or 6 most industrialized districts of Shanghai. For example, the exposure assessment team has been working in close collaboration with the Yang Pu District IPHS and has been given access to the exposure records maintained at the local IPHS.
- The exposure assessment team continues to develop exposure data/estimates using the "sector analysis" approach. The analysis for two commonly encountered industries (shoe and rubber) has been completed.

- Exposure data from other sources are being collected, including published literature. According to Professor Liang, who heads the literature review task, preliminary exposure data for the following occupations/industries have been completed: shoemakers, painters, paint manufacturers, printers, dyers, and rubber workers. These literature data will supplement the Shanghai Municipal IPHS database and district IPHS data in the development of job-exposure matrix (JEM).

QA/QC

- At the beginning of 2005, a full-time person, Zhu Shoumin, was assigned to QA/QC, who reported to Zhou Yimei. He was responsible for QA/QC of questionnaire data, control selection, data entry and initial exposure assessment. The decision of one person dedicated to QA/QC turned out to be a good one. Zhu Shoumin prepared routine monthly QA/QC reports, which were shared by all senior investigators. Recently, however, these monthly reports were interrupted because of personnel changes. A new person, Pei Xiaodan, has replaced Zhu Shoumin. I have been reassured by Zhou Yimei that monthly reports will be resumed shortly.
- A recent QA/QC of questionnaires taken between December 2004 and August 2005 indicated that 92.1% of primary questionnaires sampled for review were "qualified" (i.e., no problems were found) and 98.2% of secondary questionnaires were "qualified." We have discussed with Chen Xiaobao, who is in charge of interviews, ways to further improve the quality of primary questionnaires.
- The overall data entry error from December 2004 to August 2005 was 2.6%, which is acceptable.
- In December 2005 I conducted an *ad hoc* QA of 15 matched set of questionnaires (45 questionnaires in total) taken in late November. I identified only 1 minor mistake in these questionnaires (with literally thousands of items/entries).

Project Management

- Communication with the Fudan team in Shanghai remains a high priority item. In addition to email and telephone calls, I made 6 trips to Shanghai in 2005.

- An estimated timeline for the completion of the case-control study is as follows. Based on a discussion with the team in Shanghai, Tom Armstrong and Zhou Yimei, the current projection is that case enrollment will be completed by December 2006. Final diagnoses, control selection, interviews and data entry will most likely be completed by the end of the first quarter of 2007. Exposure assessment of newly enrolled patients (cases and controls) will be conducted in the first and second quarters of 2007. Assuming that both diagnostic and exposure data for all patients will be finalized and available by June 2007, we will be performing epidemiologic analyses of the final data in the third quarter of 2007.

To facilitate data transfer/linkage and to develop plans for statistical analyses, however, we will need relatively large and representative samples of exposure estimates and diagnoses of study subjects by mid-2006 (see table below). These samples will allow us to develop plans for data transfer/linkage and to test-run analysis programs. Discussions are now underway to obtain these samples on a timely basis.

Time	Activities
July 2006	Samples of exposure estimates (from the Exposure Assessment Team) and diagnoses of study subjects (from JCML) provided to AHS.
3Q & 4Q 2006	Case-control study data management and plans for statistical analyses (based on samples provided).
December 2006	End of case enrollment.
1Q & 2Q 2007	Selection of controls. Interviews, final diagnosis and exposure assessment of last group of patients.
June 2007	Final diagnosis and exposure assessment of all patients completed.
2Q & 3Q 2007	Final data editing/auditing. Analysis and report preparation.