POLICY AND PRACTICE

Korean Multi-center Cancer Cohort Study including a Biological Materials Bank (KMCC-I)

Keun-Young Yoo[1], Hai-Rim Shin[2], Soung-Hoon Chang[3], Kun-Sei Lee[3], Sue Kyung Park[3], Daehee Kang[1], Duck-Hee Lee[4] for the KMCC Study Group

Abstract

Cohort studies of human populations have provided the most convincing evidence of links between exposure to specific agents and cancer. The Korean Multi-center Cancer Cohort (KMCC-II) is a multi-center prospective cohort designed to investigate the relationship between exposures to environmental factors, lifestyle factors, host factors and the risk of cancer in Korea. Data on general lifestyle, physical activity, diet, reproductive factors, and agricultural exposures have been collected by direct interview since 1993. Anthropometric measurements and some clinical laboratory findings have also been recorded. This cohort is characterized by the exclusion of cancer cases at the time of recruitment through cancer screening by physicians. The number of cancer-free subjects in the cohort at present totals some 35,692 men and women aged over 35 (121,856 person-years as of December 2000). Of the KMCC-II, 11,045 subjects who have donated their blood and/or urine sample were classified as the KMCC-I. In order to provide an opportunity to incorporate various biomarkers of exposure and the effect of exposure, as well as information on genetic susceptibility, a biological materials bank with blood (plasma, or serum buffy coat, packed erythrocytes) at -70°C and urine supernatants at -20°C has been established for future studies on cancer etiology. The total number of the KMCC-I is 10,694 for the blood bank and 8,907 for the urine bank (total number of observation in person-year = 47,002). Follow-up for cancer incidence has commenced based on an active surveillance system conducted mainly through telephone interview by health personnel or through diagnosis by physicians in each district, and a passive surveillance system through record linkages between the national cancer registry, the national death certificate system, and health insurance medical records databases in Korea. Moreover, this cohort study is expected to play a significant role in assessing the role of genes in the etiology of cancer. These include the determination of the cost-efficiency and reliability of the nested case-control approach, using the cohort, for exploring gene-disease associations and gene-environmental interactions using reduced sample sizes. Along with other cancer cohorts, the KMCC study could eventually provide convincing evidence on new etiologies of cancer in the Asian-Pacific region.

Key Words: Biologic materials bank - cancer - cohort study - molecular epidemiology - risk factors

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Introduction

One of the most important roles of cancer epidemiology is the investigation of the causes of cancer, or of its natural history, such knowledge can lead to the introduction of preventive measures. The growth of cancer epidemiology did not begin until the results of two important cohort studies were published; the British Doctor's Study, and the Japanese Atomic Bomb Survivor Study in Hiroshima and Nagasaki. Cohort studies of human populations have provided the most convincing evidence of links between exposure to specific agents and cancer.

The origin of the cohort study can be traced back to studies on life span in the 19th century (Silvia, 1999). During the 1940s and '50s, several landmark prospective cohort studies were implemented; the Framingham study, the

Seoul National University College of Medicine[1]; National Cancer Center Research Institute[2]; Konkuk University College of Medicine[3] and Kosin Univesity College of Medicine[4]

[1]Address for correspondence : Department of Preventive Medicine, Seoul National University College of Medicine, 28 Yongon-dong, Chongno-gu, Seoul 110-799, Korea. Tel : 82-2-740-8324 Fax : 82-2-3673-3540 E-mail : kyyoo@plaza.snu.ac.kr

investigation of the atomic bomb survivors in Hiroshima and Nagasaki, and the Doll and Hills' British Doctors cohort on smoking and lung cancer are outstanding examples. During the 1960s, many prospective and retrospective cohort studies were conducted to determine the relationships between particular diseases and specific causative agents, i.e., asbestos and lung cancer, aniline dye and bladder cancer. The current era of large-scale prospective cohort studies dates back to the 1970s. Particularly noteworthy as an advance in the design of such studies, was that serum was stored, so that serologic markers could be examined as predictors of disease risk in many cohorts, i.e., the Washington County Cohort, the Nurses' Health Study, and the EPIC study in the 1990s (Samet and Munoz, 1998).

Methodological advances have been motivated by the complexity of data analysis in cohort studies. The book by Breslow and Day pioneered design and analysis of longitudinal cohort studies on cancer (Breslow and Day, 1987). A key advance in study design was the development of sampling methods, i.e., the nested case-control or the case-cohort designs.

The Korean Multi-center Cancer Cohort(KMCC-II) is a multi-center prospective cohort designed to investigate the relationship between exposures to environmental factors, lifestyle factors, host factors and the risk of cancer in Korea. Of the KMCC-II, participants who have donated their blood and/or urine sample were classified as the KMCC-I.

The KMCC- I was constructed in 1993 (Yoo et al., 1998). The KMCC-I involves the collaboration of about 15 epidemiologists from several research institutions, i.e., Seoul National University, Dong-A University, Konkuk University, Dongkuk University, Kosin University, and the National Cancer Center in Korea. A research grant from the the Seoul National University Hospital was awarded for this cohort study in 1992. Since 1993, the Korean Electric Power Corporation has been providing, in part, research grant for this project. During 1995-97, a grant from the Korean Ministry of Health and Welfare, and in 2001, the Korean Human Genome Project sponsored by the Ministry of Science and Technology offered a long-term grant to the KMCC-I cohort. In addition, local government has provided administrative support for health surveys conducted in each area, and the National Cancer Institute - USA also gave technical advice concerning the establishment of a tissue bank for the KMCC-I cohort.

The goals of this program were to establish a large prospective cohort that could be easily followed for 10 years or more, with the aim of assessing the relationship between life-styles and cancer occurrence in the population, and of evaluating the role between both biological and chemical agents and the development of cancers, for example, stomach, liver, lung, colorectal cancer, and uterine cervix and breast cancer in women. The research design provides an opportunity to incorporate various biomarkers of exposure and the effects of exposure, as well as genetic susceptibility, which may enable us to test new hypothesis on the etiologies of cancers in the future.

Study Population

The choice of a study population for any given cohort, in general, depends on two factors, i.e., the hypothesis under investigation, and the practical constraints in terms of easy of recruitment and follow-up. The general population cohort is known to offer the advantages of both generalized study results and the ability to assess a wide variety of factors on the risk of multiple outcomes.

Recruitment of the Cohort

Eligible subjects were adults, male and female, who were voluntary participants in a cancer screening survey in each area. Men and women aged over 35, in the geographically defined areas, have been invited through cross-sectional surveys for cancer screening since 1993. Voluntary participants in the screening for cancer detection were eligible as members of the study population for this multi-center cohort.

The choice of study area for cohort construction was largely influenced by the practicalities of obtaining the full participation of study subjects and of ensuring long-term follow-up. As can be seen in Fig. 1, the KMCC-I cohort is based on four-geographically-defined urban and rural areas in Korea, which allows a large number of common exposures to be related to a large number of outcomes, and this is one of the great advantages of the population-based cohort. The study areas include; Haman County in Kyungnam Province since 1993, Choongju City in Chungbuk Province since 1996, Uljin County and Pohang City in Kyungbuk Province since 1994. Subjects from at least 4 different communities will be newly added into the present cohort every year since 2001 in collaboration with the National Cancer Center in Korea. For the KMCC-II, six other areas, including Yonchon County and Gapyong County in Kyunggi Province, Kori County and Kijang County in Kyungnam Province, etc., were additionally included. Inhabitants of these areas are mainly farmers and fishermen, whereas study subjects living

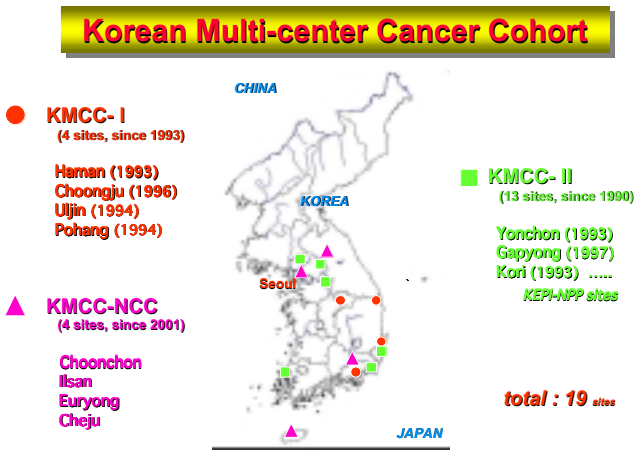

Figure 1. Sites of Centers Participating in the Korean Multi-center Cancer Cohort-I project

in Choongju, Pohang, and Kijang represent mixed urban and rural populations

Selection of Cancer-free Population

The great advantage of the cohort design is that the passage of time can be incorporated into the design of the cohort. The cohort is assembled, first, data is collected on the risk factors, and then the entire population is followed-up in time. Therefore, the disease-causing actions of exposures and modifying factors may be formulated as antecedents to the occurrence of an outcome. In order to meet this requirement, the study population should be free of cancer initially. The cohort then allows comparisons of the incidence of disease in exposed and non-exposed groups during follow-up.

The KMCC-I is characterized by a cancer-free cohort through the active screening for cancer at the time of recruitment. To perform this, field surveys were conducted in each area using a standardized cancer screening protocol. Each participant was tested for common blood cell count, urine analysis, liver function tests, blood sugar, blood pressure, visual acuity, and chest X-ray. Physical examination by physicians was performed for the cancer screening. Serologic tests for hepatitis markers, some tumor markers, and lipid profiles were performed selectively using standard methods in some of the participants.

Of the eligible subjects, persons with abnormal laboratory findings, positive for tumor markers, those that had been recommended for cancer diagnosis after physical examination by physicians, and those with a high risk of malignancy based on information provided by the questionnaire, were referred to the regional hospitals in each area in order to determine the presence of any malignancies. Finally, those with confirmed malignancies were excluded from the eligible population in order to make a cancer-free cohort. As a result, the detection rate of cancer cases by the primary and secondary screening procedures, i.e., the proportion of cancer patients among those examined, was around 0.1%.

Baseline Survey

Measurement of exposure is a crucial aspect of cohort design.

Questionnaire for Life-Style Information

For the questionnaire survey, each subject completed a detailed questionnaire by direct interview with well-trained interviewers (mainly medical college students or nursing school students). The questionnaire provided information on demographic characteristics, past medical history, family history of cancer, dietary habit, smoking and alcohol drinking habits, physical activity, occupational history, medication history, exposure history to hazardous chemicals including pesticides, exposure to electro-magnetic fields, reproductive history for female, and other factors related to cancer development.

Each item in the questionnaire was reviewed by a senior interviewer just after the interview, and the missing information, if found, was collected by telephone interview with the same person on the same day. All the information obtained from the interviewee at the direct interview was computerized in a standard manner, after the completing the verification procedure. The data warehouse was regularly backed up with database files from each site.

Anthropometric Measurements

Various anthropometric indices were measured directly using standard methods at the time of the physical examination, e.g., height, weight, abdominal and hip circumferences. A Bioelectrical Impedance Fatness Analyzer (GIF-891DX) was used to assess the body fat composition of each participant.

Serologic Tests for Biomarkers

Clinical laboratory tests for both cancer screening and baseline information were also applied to some of the participants. Of those, hepatitis markers (e.g., HBsAg, anti-HBs, IgM anti-HBc, and anti-HCV), some tumor markers (e.g., aFP, CEA, etc.), sister chromatid exchange as an exposure marker to pesticides, and lipid profile (e.g., total cholesterol, triglyceride, HDL-cholesterol, LDL-cholesterol, etc.) were also measured in some of the cohort population (Yoo et al. 1991). Stool specimens were also tested to assess the relationship between clonorchiasis and liver cancer from some members of the Haman cohort population, in whom the incidence of liver cancer is likely to be high (Shin et al., 1996).

Biological Materials Bank

If biological specimens are stored, before the occurrence of disease in a cohort subject, then, a historical approach might be successful, as up-to-date laboratory techniques can then be used to measure past exposure (Rothman et al., 1995; Toniolo et al., 1997). For this purpose, a biologic materials bank has been included in this cohort since 1993.

In order to provide an opportunity to incorporate various biomarkers of exposure and the effect of exposure, as well as information on genetic susceptibility, a biological materials bank with blood (plasma or serum, buffy coat, and packed erythrocytes) and spot urine samples has been established for future studies on cancer etiology (Fig. 2).

Each participant provided 20ml blood and 50ml of spot urine. The blood sample was fractionated into plasma, buffy-coat (as a rich source of DNA), and packed erythrocytes (as a source of cell membrane). The plasma samples were aliquoted into six Eppendorf tubes of 0.5ml, the WBC samples placed in two tubes of 0.5ml, and RBC samples in four tubes of 0.5ml. All are stored in a standardized manner at a temperature of -70^{o}C. The urine samples are stored in two centrifuge tubes of 10ml at -20^{o}C.

Two separate sets of specimens have been prepared, and these are stored separately in different location; one set is stored in each area, and the other set is stored in the central lab in the Seoul National University. This bank has been

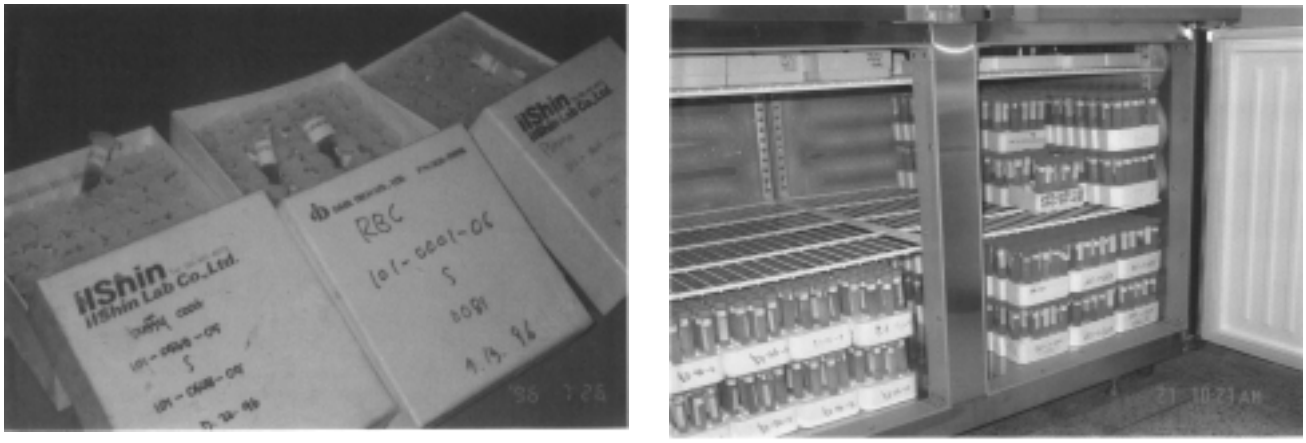

Figure 2. Biologic Materials Bank of the Korean Multi-center Cancer Cohort-I

registered as one of the biological materials bank with the Directory of On-Going Research in Cancer Prevention of the International Agency for Research on Cancer (in Red cells or red cell membranes / Serum or Plasma / Urine / White cells, buffy coat, non-viable) since 1997 (Sankaranarayanan et al., 1996).

Because a large portion of cancer etiology cannot be fully explained by risk factors identified by conventional epidemiological studies, biological materials banks enable us not only to minimize inaccuracies in past exposure measurements, but also to provide an insight into inherited differences in individual susceptibilities to human cancer. A good example is provided by the relationship between breast cancer and the inherited metabolic capacity of glutathione S-transferase, which plays an important role in the detoxification of endogenous and exogenous toxicants, and may also have a role in the metabolism of lipids and the DNA products of oxidative stress (Park et al., 2000).

We have also established an executive committee, which manages the use of specimens in the biological materials bank, and which is required to test specific hypothesis on cancer etiology, if sizable numbers of cancer cases should occur in the future.

Informed consents: questionnaire and biologic specimen

Seoul National University Hospital has an ethical committee to review studies related to human investigation and genomic tests. This study has been approved by the committee for the questionnaire and the biologic specimen (#740-C508, Nov. 13, 2001).

Number of Subjects Recruited in the KMCC

As of December 2000, 35,692 persons had completed the KMCC questionnaire, and the total number of observations exceeded 120,000 person-years for the KMCC-II. Of the KMCC-II, 10,694 subjects who have donated their

Table 1. Number of Subjects Recruited in the Korean Multi-center Cancer Cohort-I Study (as of Dec. 2000)

Project area	Study period	Questionnaire[a]	Biologic materials bank[b]		Person-years
			blood[c]	urine[d]	
Haman	1993-1999	5,093	4,974	4,236	22,682
Choongju	1996-2000	4,808	4,617	4,617	16,312
Uljin-Pohang	1994	1,144	1,103[e]	-	8,008
Total of KMCC-I (until 2003)		11,045 ~30,000	10,694 ~30,000	8,907 ~30,000	47,002 ~100,000
Total of KMCC-II[f]		35,692	10,694	8,907	121,856

[a] Number of subjects who completed the questionnaire on life-style (duplicate cases excluded). Subjects from at least 4 different communities will be newly added into the present cohort every year since 2001.

[b] Number of subjects who donated blood or urine sample (duplicate cases excluded). The total number of subjects in the tissue bank is expected to be more than 30,000 by the end of 2003.

[c] Biologic materials bank contains plasma (n=9,315)or serum (n=2,295), buffy coat (n=8,637), and packed erythrocytes (n=8,552) at 2000.

[d] Biologic materials bank contains spot urine sample.

[e] Serum only.

[f] Number of subjects who completed the questionnaire only without donation of biologic specimen in the six other areas were added to the KMCC-I. The total number of subjects in the KMCC-II is expected to be more than 55,000 by the end of 2003.

Table 2. Age and Sex Distribution of the Subjects in the Korean Multi-center Cancer Cohort-I Study (as of Dec. 2000)

Age in years	Haman	Choongju	Uljin-Pohang	Total
Male				
35 - 39	88	209	48	345
40 – 49	473	318	66	857
50 – 59	627	466	83	1,173
60 – 69	635	627	110	1,372
70 – 79	228	244	53	525
80 +	21	38	12	71
Subtotal	2,072	1,902	372	4,346
Female				
35 – 39	146	344	190	680
40 – 49	700	587	108	1,395
50 – 59	952	839	186	1,977
60 – 69	862	869	170	1,901
70 – 79	328	238	101	667
80 +	33	29	17	79
Subtotal	3,021	2,906	772	6,699
Total	5,093	4,808	1,144	11,045

blood and/or urine sample were classified as the KMCC-I (Table 1). Age and sex distribution of the cohort population can be seen in Table 2. This cohort will continue to expand by the total number of 30,000 persons until the end of 2003. An effective sample size determination showed that the number involved in the KMCC cohort is sufficient, even at this moment, to draw valid conclusions upon current hypotheses on cancer etiology when nested case-control comparisons within the cohort are applied using biomarkers of both exposure and outcome.

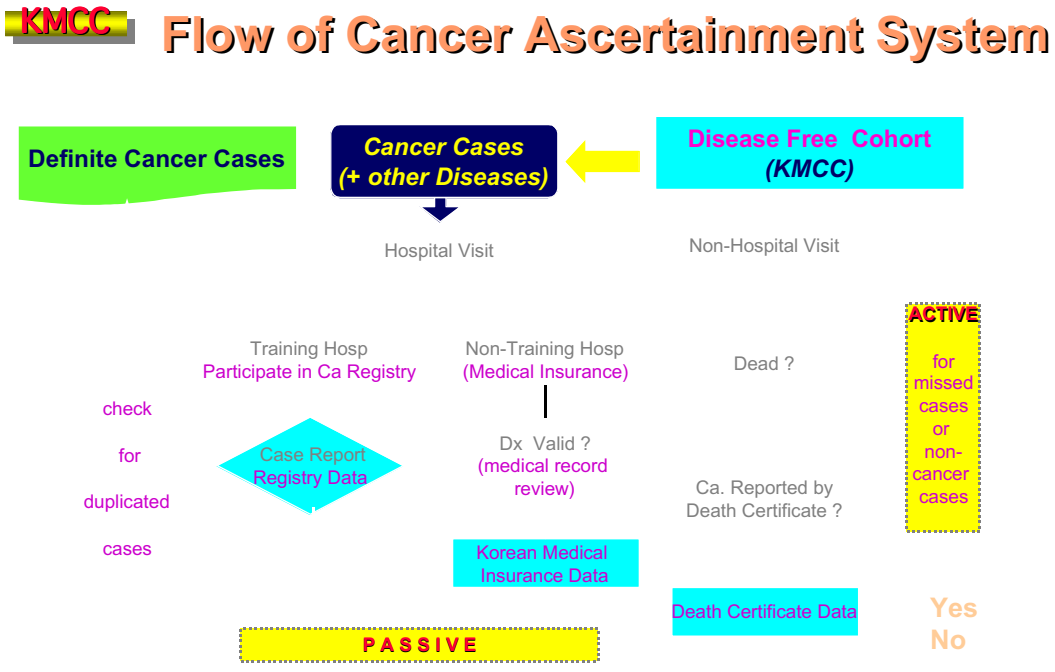

Figure 3. Active and Passive Surveillance System for Cancer Occurrences of the KMCC Study

Table 3. Results of Cancer Screening in Order for Cancer-free Population and the Interim Results of Follow-up of Cancer Occurrence in some Selected Areas of the KMCC-II (as of December 2000)

Project area	Person-years[a]	Cancer cases in screening	Incidence Cases[b]	Rates
Yonchon	19,776	0	22	
Haman	13,876	5	38	
Choonju	3,730	0	26	
Gapyong	1,992	0	0	
Kori	22,435	8	30	
Uljin	9,921	3	19	
Kijang	2,395	1	1	
Pohang	6,950	7	10	
Overall	81,075	24	146	180.1

[a] Prevalent cases identified at the time of baseline were excluded. Cancer cases and deaths (cancer and other causes) were contributed as 0.5 unit year to the observation period in person-year.
[a] Common sites of cancer identified during the observation period were as follows (male/female, interim results as of December 2000); stomach (20/13), lung (18/6), uterine cervix (0/19)liver (10/7), colon (7/6), breast (0/6),pharynx (3/1), leukemia (1/2), etc.

Ascertainment of Cancer Occurrence

The measurement of outcome is another important aspect since one of the major advantages of a cohort study is that it enables the examination of the effects of specific exposures on multiple outcomes. Many cohort studies make use of existing routine surveillance systems to ascertain the outcome of interest. In order to avoid selection bias that may rise from follow-up losses, the KMCC uses two surveillance systems to ascertain cancer occurrence. The first one is an active surveillance system in each project area, which encompasses a mailed morbidity questionnaire survey, a direct telephone interview by health personnel, and a cancer diagnosis by physicians at hospitals. The second is a passive surveillance system through record linkages between the national cancer registry, the national death certificate system, and health insurance medical records databases. Very fortunately for epidemiologists, there is a unique ID (identification number) system in Korea. Every Korean has his/her own ID number from birth, which enables epidemiologists very easily and very accurately to capture-and-recapture cancer patients all around the country using record-linkages with databases from various sources of medical information. The most efficient way of following-up for cancer occurrence at a community level has already been established for this cohort. Fig. 3 shows the passive and the active surveillance follow-up system in this cohort.

Follow-up Results and Statistical Analysis

In cohort studies, participants are followed up over time by the end of the observation period, by observing outcomes using surveillance systems. As of December 2000, 146

Figure 4. The KMCC-I Study Group (Soung-Hoon Chang, MD, Daehee Kang, MD, Kun-Sei Lee, MD, Sue Kyung Park, MD, Hai-Rim Shin, MD and Keun-Young Yoo, MD, from the left

cancer patients were finally identified by the active and passive surveillance, showing an overall incidence rate of 180.1 / 100,000 (Table 3). To calculate the incidence rate, prevalent cases at baseline were excluded, and cancer cases, cancer deaths and deaths due to other causes were contributed to 0.5 unit year of person-year observation in the denominator.

Perhaps the most critical problem of cohort study is that study factors, i.e., participants' ages, are continually changing during the follow-up, and even the exposure itself may start, stop, increase, or decrease. This dynamic nature of risk factors and their relations in time to disease occurrence can only be seen in cohort design. Therefore, a re-examination of changes associated with potential risk factors is necessary for the cohort population. Moreover, many challenges of temporally varying exposures and disease risks need new statistical methods and modern epidemiological approaches for design and analysis based on cohort study.

Nested case-control design is an example of the advances in the design and analysis of sampling methods in modern epidemiology (Samet and Munoz, 1998). In contrast to the traditional cohort study, a cohort is followed up until a sufficient number of cases develop, then by comparing cases with controls from the remainder of the cohort, at the time of the cases develop, relevant information can be obtained. This type of study is called a nested case-control study, and is an example of a particularly useful, though complex and expensive procedure, which is supported by the existence of the biologic specimen bank.

A report from the Shanghai cohort provides a good example of a nested case-control study (Ross et al., 1992). To test the hypothesis of an association between urine aflatoxin and liver cancer, the authors utilized about 18,000 cohorts. The total number involved in the follow-up was about 35,000 person-years, and 22 liver cancer cases were found. Using matched controls within the cohort, they successfully demonstrated the association between the aflatoxin metabolite and liver cancer.

Conclusion

Prospective cohort studies consume much time, cost and effort. On the other hand, they provide us with very solid credible results and often clarify cause-effect relationships. By taking advantage of the new advances in molecular epidemiology, cohort studies will undoubtedly play a significant role in assessing the role of genes in the etiology of cancer, i.e., of gene-disease / gene-environmental interactions. Beyond these more evident merits of cohort studies, nested case-control studies within the cohort may effectively reduce sample sizes, particularly when supported with biomarkers from a biological materials bank.

Langholz et al. (1999) in their review article showed a list of the worlds major prospective cohort studies involving comprehensive questionnaires and the blood sampling. Recently, the KMCC-I was certified to be listed in a table listing prospective cohort studies that have collected blood or some other source of genomic DNA, some version of a food frequency questionnaire, and have enrolled or will be enrolled at least 10,000 subjects in the world. The KMCC-I, along with other population-based cancer cohorts in the Asia-Pacific region, i.e., The Japanese Collaborative Cohort Study, The Japanese Public Health Center-based Cohort Study, and the Shanghai Women's Health Study, will eventually provide convincing evidence on the etiology of cancer using markedly reduced sample sizes in the near future (Alavanja et al., 1993; Aoki, 1993; Riboli and Kaaks, 1997; Yoshigana et al., 2001).

Acknowledgements

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Personal Profile : Keun-Young Yoo

Keun-Young Yoo was born in Seoul, Korea, on June 1954. He learned medicine at Seoul National University College of Medicine (1978), and trained Epidemiology for five years (1978-1982) in the same Medical College. In 1979-81, he has taken a Master of Public Health at the Seoul National University Graduate School of Public Health, and was awarded a Philosophical Degree at Seoul National University in 1985. Since 1986, he has been committed to cancer epidemiologic research as a faculty of the Department of Preventive Medicine at Seoul National University, and currently has been taking charge of Chairman of the same Department (since 2000). He spent a year for his career in cancer epidemiologic research as a Visiting Researcher at the Department of Epidemiology and Public Health at Yale University in 1989, and was a Visiting Scientist at the Division of Epidemiology at Aichi Cancer Center Research Institute in 1990-1991 under the sponsorship by the WHO.

His major interest is female cancer epidemiology; occurrence, descriptive statistics, risk factors, genetic susceptibility, and preventive measures. Since 1992, he has vigorously conducted a multi-center collaborative study to make a large-scale community-based prospective cohort, which is now known and characterized by several points; comprehensive questionnaire by direct interview, cancer-free cohort at the time of recruitment, complete surveillance system of cancer occurrence, and biologic materials bank. He is nominated as an Editor-in-Chief of both the Korean Journal of Epidemiology and the Journal of Korean Association of Cancer Prevention.