Cohort Profile

# Cohort Profile: Community-based prospective cohort from the National Cancer Center, Korea

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## Why was the cohort set up?

Over 30 years, cancer has been ranked as the number one killer in Korea, and its incidence and mortality have increased dramatically.[1] Therefore, many researchers have focused on identifying the causes and finding preventive measures to decrease the burden caused by cancer, one of the major health issues in Korea.

As epidemiological studies with a prospective follow-up design could provide comprehensive and strong scientific evidence on the aetiology and prevention of cancer, the Korean National Cancer Center (KNCC) Community Cohort, a community-based prospective cohort study designed to investigate the relationships in Korea between the risk of cancer and various environmental factors, lifestyle factors and host factors, was established.

The origin of this cohort can be traced back to the Korean Multi-center Cancer Cohort (KMCC) which was created in 1993.[2,3] The KMCC involves the collaboration of about 15 epidemiologists from several research institutions, such as Seoul National University, Dong-A University, Konkuk University, Dongkuk University, Kosin University and the National Cancer Center in Korea. The KNCC Community Cohort was begun as a part of the KMCC in 1993 and has been continuously developed and funded by the National Cancer Center since 2001. The objectives are to establish a large prospective community-based cohort that enables studies on risk factors, biomarkers of exposures and effects, genetic susceptibility and gene-environmental interactions in prevalent cancers in Korea, including liver cancer.

## Who is in the cohort?

The KNCC Community Cohort is based on four geographically defined urban and rural areas in Korea. The KNCC Community Cohort participants are residents of Haman-gun, Sancheong-gun and Changwon-si in Kyungnam Province located in the southern parts of the Korean peninsula, Chungju-si in Chungbuk Province in the middle part and Chuncheon-si in Gangwon Province in the northern part (Figure 1). Haman and Sancheong counties are rural areas and the majority of the residents engage in agriculture. Changwon, Chungju and Chuncheon cities are mixed areas of rural and urban cultures. Given the limitations of resources and different situations of each region, the baseline survey was done by regions and areas between 1993 and 2010, after an initial survey to determine the feasibility of the planned approach in each different region. Men and women aged over 30 who lived in the geographically defined study areas were eligible. As one of the main aims of the study is to investigate risk factors related to liver cancer, eligible participants were invited from all towns in Haman and Sancheong. In Changwon, Chungju and Chuncheon, eligible participants from one to three towns

were invited using random cluster sampling. Announcements and invitation letters were delivered by public health centre workers and community leaders in the targeted towns. Participation in the questionnaire survey and health examinations was voluntary. From the baseline survey, a total of 16 304 males and females were voluntarily recruited in the cohort. The participation rate and absolute number of participants were highest in Haman (7286 participants among 35 287 eligible residents, participation rate = 20.6%). Year of baseline survey, number of participants and participation rate according to study area are described in Table 1, and also in Appendix 1 (available as Supplementary data at *IJE* online). Compared with the general population of Korea, cohort participants were more likely to be female, older, less educated and non-drinkers, reflecting the characteristics of rural Koreans. The prevalences of *Clonorchis sinensis* (i.e. Chinese liver fluke) infection, high blood pressure and hypercholesterolaemia in the cohort participants were higher than in the general population (Table 2).

All cohort participants provided written informed consent before the baseline survey. The study protocols were

**Figure 1**. Map of the study area of the KNCC Community Cohort.

**Table 1.** Number of study participants, study area and year of baseline study of the KNCC Community Cohort

| Study area | Year of baseline survey[a] | Eligible population in target area[b] | Population in invited community | Number of participants | Participation rate, % |
|---|---|---|---|---|---|
| Haman | 1993–2003 | 35 287 | 35 287 | 7286 | 20.6 |
| Sancheong | 2004–2010 | 24 299 | 24 299 | 4633 | 19.1 |
| Changwon | 2004–2007 | 270 437 | 26 718 | 1703 | 6.4 |
| Chungju | 2003–2004 | 122 403 | 16 770 | 1099 | 6.5 |
| Chuncheon | 2003–2004 | 148 648 | 31 079 | 1583 | 5.1 |

[a]Recruited around 1000 men and women every year in each study area.
[b]Number of men and women aged over 30 reported by the 1995 census for Haman and 2005 census for Sancheong, Changwomen, Chungju and Chuncheon.

approved by the Institutional Review Board of the Seoul National University Hospital (IRB number: 740-C508) and the National Cancer Center of Korea (IRB number: NCCNHS02-007; NCCNHS03-081-1; NCCNCS-07-080).

## How often have they been followed up?

The cohort has been followed up annually to identify new cancer cases and deaths from the date of the baseline survey. It has been an exclusively register-based passive follow-up without re-contacting the participants. Using national personal identification numbers, the cohort data were linked to the Korea National Cancer Incidence Database of the Korean Central Cancer Registry[1] and Cause of Death Database of Statistics Korea.[4] The cancer registry data are very reliable at 97.7% completeness[1] and include date of diagnosis, primary cancer site, morphology and diagnostic method. Cause of death data include date and cause of death. Cancer cases and causes of death were classified according to the International Classification of Diseases, 10th edition (ICD-10). Excluding 297 subjects who had a cancer history before cohort enrolment, 1523 cancer incident cases (940.3 per 100 000) were identified in the study population, with an average of 10.1 years of follow-up on 31 December 2012. The most common cancer site was the stomach, and followed by lung, liver, colon-rectum, bile duct and gall bladder (Table 3).

## What has been measured?

Cohort participants completed a questionnaire and provided blood and urine samples during a health examination at the baseline survey. Written protocols for questionnaires, anthropometric measurements and collection, delivery and storage of biospecimens were developed and strictly enforced in the baseline surveys.

### Questionnaires

Through a face-to-face interview by well-trained interviewers using the structured questionnaire, information on demographic characteristics, past medical history, family history of cancer, history of medical use, dietary habits, smoking and alcohol drinking habits, physical activity, occupational history, history of exposure to acupuncture and blood transfusion, history of exposure to pesticides and electromagnetic fields and reproductive history for women were provided (Table 4).

### Anthropometric measurements

Height, weight, waist circumference and systolic/diastolic blood pressure were measured by trained personnel using standard methods.[10] Body mass index was calculated from the height and weight (Table 4).

### Clinical laboratory examinations

For each participant, 20 ml of venous blood (into a 10-ml serum separator tube and a 10-ml anticoagulant EDTA-coated tube), 50 ml of spot urine and 3 g of stool were taken after at least 6 h overnight fasting, for clinical laboratory tests and also for biorepository.

Routine haematology (i.e. red blood cells, white blood cells, haemoglobin, haematocrit and platelets) and chemistry (total protein, albumin, alanine aminotransferase, aspartate aminotransferase, gamma-guanosine triphosphate, creatinine, total cholesterol, triglyceride, high-density lipoprotein, uric acid and blood urea nitrogen) tests were performed. Hepatitis B surface antigen (HBsAg), antibodies against hepatitis B surface antigen (anti-HBs) and antibodies against hepatitis C virus (anti-HCV) were identified using an enzyme immunoassay (AxSYM, Abbott Laboratories, Abbott Park, IL, USA). Fasting blood glucose (FBS) was measured with the hexokinase method (in Haman, Chungju and Chuncheon between 1993 and 2004)[5] or ACCU-CHEK ACTIVE (Roche Diagnostics,

**Table 2.** Summary of measurements in baseline survey of the KNCC Community Cohort participants and comparison with the general population in Korea

| Variable | Cohort participants (n = 16 304) | | General population[a] (n = 21 556) | |
|---|---|---|---|---|
| | Men | Women | Men | Women |
| Sex, % | 38.7 | 61.3 | 47.6 | 52.4 |
| Age, % | | | | |
|   < 35 y | 3.4 | 4.8 | 15.9 | 14.9 |
|   35–44 y | 9.7 | 10.4 | 33.4 | 31.3 |
|   45–54 y | 19.9 | 20.1 | 22.5 | 20.5 |
|   55–64 y | 31.9 | 30.2 | 15.9 | 15.9 |
|   65–74 y | 28.2 | 28.5 | 9.0 | 11.3 |
|   ≥ 75 y | 7.0 | 5.9 | 3.4 | 6.1 |
| Mean age in years, SD | 58.6 ± 12.4 | 57.7 ± 13.3 | 48.3 | 50.0 |
| Marital status | | | | |
|   Married | 91.4 | 66.1 | 87.0 | 75.7 |
|   Single[c] | 8.6 | 33.9 | 13.0 | 24.3 |
| Education level, % | | | | |
|   No education | 11.7 | 31.3 | 4.1 | 14.2 |
|   Primary and middle school | 60.7 | 57.5 | 26.8 | 36.3 |
|   High school or higher | 27.5 | 11.2 | 69.1 | 49.5 |
| Smoking status, % | | | | |
|   Never smoker | 20.9 | 91.1 | 19.2 | 93.2 |
|   Ex-smoker | 31.7 | 2.6 | 20.4 | 1.3 |
|   Current smoker | 47.5 | 6.4 | 60.4 | 5.5 |
| Alcohol drinking, % | | | | |
|   Non-drinker | 27.2 | 80.5 | 13.7 | 43.9 |
|   Ex-drinker | 12.0 | 2.7 | 5.8 | 1.5 |
|   Current drinker | 60.7 | 16.7 | 80.5 | 54.6 |
| Body mass index, % | | | | |
|   < 25.0 kg/m$^2$ | 73.8 | 63.8 | 65.8 | 66.8 |
|   25–29 kg/m$^2$ | 24.6 | 31.6 | 31.7 | 29.2 |
|   ≥ 30 kg/m$^2$ | 1.6 | 4.6 | 2.5 | 4.0 |
| Physical activity | | | NA | NA |
|   Inactive | 21.3 | 23.5 | | |
|   Minimally active | 63.1 | 66.0 | | |
|   Health-enhancing physical activity | 15.6 | 10.5 | | |
| Family history of cancer | 22.0 | 22.7 | NA | NA |
| HBsAg seropositivity, % | 5.0 | 4.1 | 5.2 | 4.7 |
| Anti-HCV seropositivity, % | 3.0 | 3.2 | NA | NA |
| *C. sinensis* egg positivity, % | 34.5 | 22.4 | 3.2[b] | 1.6[b] |
| Hypercholesterolaemia[d], % | 9.4 | 15.5 | 8.6 | 10.1 |
| High blood pressure[e], % | 42.9 | 40.4 | 34.4 | 26.5 |
| High fasting blood sugar[f], % | 5.8 | 4.5 | 9.8 | 8.2 |
| Blood transfusion history | 7.8 | 9.9 | NA | NA |
| Acupuncture history | 68.5 | 77.9 | NA | NA |
| Ever having raw freshwater fish intake | 26.2 | 15.8 | NA | NA |
| Atopy | 4.6 | 6.8 | NA | NA |
| Athma | 3.1 | 3.2 | 1.5 | 1.7 |
| Exposure to pesticides | 78.6 | 60.4 | NA | NA |

SD, standard deviation; y, years; NA, not available.

[a]Source: Ministry of Health and Welfare. *2001 National Health and Nutrition Examination Survey (KNHANES)*. Seoul, 2002. [https://knhanes.cdc.go.kr].The KNHANES randomly sampled the general Korean population and the results in this table showed distributions among adults (aged ≥ 30).

[b]Source: Ministry of Health and Welfare, Korea Association of Health Promotion. *Prevalence of Intestinal Parasitic Infection in 2004*. 7th report. Seoul: Ministry of Health and Welfare, 2005.

[c]Unmarried, divorced and widowed.

[d]Hypercholesterolaemia, serum cholesterol ≥ 240 mg/dl.

[e]High blood pressure, systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg.

[f]High fasting blood sugar, ≥ 126 mg/dl or having treatment drug.

Germany), a portable glucose meter (in Sancheong and Changwon between 2004 and 2010). Semi-quantitative urinalysis for pH, occult blood, protein and glucose was performed with spot urine. Cotinine and a tobacco-specific nitrosamine [4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol, NNAL] were also measured in urine. *Clonorchis sinensis* eggs were detected and counted using the formalin-ether sedimentation method (in Haman, Chungju and Chuncheon between 1999 and 2004)[6,7] or using the Kato-Katz method (in Sancheong and Changwon between 2004 and 2010)[8] (Table 4).

**Table 3.** Cancer incidence and mortality of the KNCC Community Cohort in 2012

| KNCCC | *N* |
|---|---|
| Number of participants | 16 007 |
| Person-years | 161 961 |
| Follow-up years (mean) | 10.1 |
| Incident cancer cases, total | 1523 |
|   Stomach | 313 |
|   Lung | 267 |
|   Liver | 215 |
|   Colorectum | 185 |
|   Gallbladder and biliary tract | 99 |
|   Thyroid | 73 |
|   Prostate | 67 |
|   Breast | 49 |
|   Pancreas | 43 |
|   Oesophagus | 31 |
| Number of deaths | 2463 |
| Deaths by cancer | 814 |

The KNCCC was followed from 1993 until 31 December 2012 through linkage with the Korea National Cancer Incidence Database of the Korean Central Cancer Registry, and Cause of Death Database of Statistics Korea. Among 16 304 cohort participants, 297 subjects with previous cancer history were excluded from the analysis.

## Biorepository

Subsequent laboratory processes, separation and yielding aliquots of serum, plasma, buffy coat, packed erythrocytes and urinary samples were performed in a laboratory on site. All the frozen specimens were transported to and stored at the biorepository. Samples collected between 1993 and 2004 (in Haman and Sancheong) were separated into two sets and stored separately for safety reasons at a biorepository in Yang Pyeong-gun managed by the Seoul National University and a biorepository in the National Cancer Center.[3] Samples collected between 2003 and 2010 (in Sancheong, Changwon, Chungju and Chuncheon) were stored in a biorepository in the National Cancer Center only. The blood samples collected between 1993 and 2008 were stored at a temperature of $-70°C$ in a deep freezer, and the samples collected between 2009 and 2010 were stored at $-140°C$ in a nitrogen tank. The urine samples were stored at $-20°C$ in a refrigerator (Appendix 2, available as Supplementary data at *IJE* online).

## What has it found? Key findings and publications

This cohort focused on cancer risk appraisal and intervention. Liver cancer is highly prioritized for research with the data from the cohort, because it is one of the most common cancers in Korea (age-standardized incidence and mortality rates of liver cancer were 21.1 and 14.4 per 100 000 in 2012, respectively)[1] and furthermore the prevalence is highest in the southern part of Korea, where most participants were recruited. In this context, the prevalence of infection with hepatitis viruses and liver flukes (i.e. *C. sinensis*) and their relationships with liver cancer have been primary investigative questions. In addition, the effects of intervention programmes for *C. sinensis* infection, the

**Table 4.** Questionnaire items and clinical measurements in the KNCC Community Cohort

| Category | Measurements |
|---|---|
| Questionnaire | Demographic characteristics (age, sex, marital status, education etc.), past medical history (including cancer and other chronic diseases), family history of cancer, history of preventive medicine (including cancer screening and vaccination against hepatitis B virus), dietary habit (26 food items including raw freshwater fish), smoking and alcohol drinking habits, physical activity, occupational history, history of exposure to acupuncture and blood transfusion, history of exposure to pesticides and electromagnetic fields, reproductive history for women (menarche, menopause, oral contraceptive use, pregnancy, parity, breast feeding etc.) |
| Anthropometric | Height, weight, waist circumference, blood pressure |
| Laboratory tests | CBC: RBC, WBC, haemoglobin, haematocrit, platelets; Serology: total protein, albumin, ALT, AST, -GTP, creatinine, total cholesterol, triglyceride, HDL, uric acid, BUN, fasting blood sugar, HBsAg, HBsAg, anti-HCV; Urinalysis: pH, occult blood, protein, glucose, cotinine, NNAL; Helminth parasite: *Clonorchis sinensis* |

CBC, blood cell counts; RBC, red blood cells;WBC, white blood cells; ALT, alanine aminotransferase; AST, aspartateaminotransferase; -GTP, gamma-guanosine triphosphate; HDL, high-density lipoprotein; BUN, blood urea nitrogen; HBsAg,hepatitis B surface antigen; HBsAb, antibodies against hepatitis B surface antigen; anti-HCV, antibodies against HCV; NNAL, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol.

effects of metabolic syndrome on the elevation of serum liver enzyme levels, and the relationships between *C. sinensis* infection and allergies have been investigated.

## Hepatitis virus infection and hepatocellular carcinoma

The KNCC Community Cohort study showed high prevalence of hepatitis B and hepatitis C infection (Table 2): in Haman, seroprevalences of HBsAg and anti-HCV were 5.2% and 5.6%, respectively.[9] Incidence of hepatocellular carcinoma in the study population was 79.2 per 100 000 person-years, with an average of 9.4 years of follow-up.[9] The most important risk factor for hepatocellular carcinoma in the study area was infection with hepatitis viruses. Relative risks (RR) of hepatocellular carcinoma by HBsAg positivity, anti-HCV positivity and hepatitis B and C co-infection were 13.3, 6.7 and 115.0, respectively.[9] Hepatitis C virus genotype 2 (mostly 2a) was more prevalent but showed a higher risk (RR = 29.7) of hepatocellular carcinoma than genotype 1 (mostly 1b, RR = 2.2).[9] History of repeated acupuncture and blood transfusion were identified as major risks, since both are routes of transmission of the hepatitis C virus.[10,11]

## *C. sinensis* infection and cholangiocarcinoma

The KNCC Community Cohort study provided population-based prevalence data of *C. sinensis* infection (Table 2) with geographical variation: prevalence of *C. sinensis* eggs was 2.1% in Chuncheon, 7.8% in Chungju, 31.3% in Haman[7] and 28.2% in Sancheong and Changwon.[12] Area, male sex, raw freshwater fish intake and alcohol consumption were identified as risk factors for *C. sinensis* infection.[6,7] Known areas of *C. sinensis* endemicity showed high incidences of cholangiocarcinoma.[7,12] The KNCC Community Cohort study first showed adult worms of *C. sinensis* recovered from infected persons by praziquantel treatment and purgation,[13] as well as showing correlation between discharged worms and faecal egg counts in human clonorchiasis.[14] Three intervention arms for controlling of clonorchiasis (praziquantel treatment for infected subjects, health education focusing on risk of raw freshwater fish intake for individuals and education for community leaders) were compared. With the dramatic decrease in *C. sinensis* infection prevalence (25.2% at baseline to 8.9% at 3-year follow-up after intervention), education for community leaders was suggested as the most effective way to control *C. sinensis* infection in endemic areas.[8]

## Others

We evaluated the association between clonorchiasis and atopy or allergic diseases in adults in endemic areas of clonorchiasis, because an inverse association between them has been suggested but not consistently found. From the cross-sectional findings, clonorchiasis was positively associated with atopy [odds ratio (OR), 1.86; 95% confidence interval (CI), 1.20-2.87] and high levels of total serum IgE (OR, 1.46; 95% CI, 1.05-2.02). However, there were no associations with wheezing, AHR, asthma or allergic rhinitis.[15]

On the other hand, we investigated the independent and combined effects of alcohol consumption, cigarette smoking and metabolic syndrome on abnormal liver function; i.e. the elevation of serum liver enzyme levels. The combination of metabolic syndrome and either alcohol consumption or cigarette smoking conferred supra-additive effects on elevated serum liver enzyme levels. The combined effect of any level of alcohol consumption and cigarette smoking was also supra-additive on the elevation of gamma-glutamyl transferase (GGT) level.[16]

Some other studies with the data from the cohort suggested the effect of social networks and social support on smoking behaviours[17] and the association of socioeconomic and psychosocial factors with obesity.[18]

## What are the main strengths and weaknesses?

The KNCC Community Cohort study has several strengths. First, this is a population-based cohort in Korea with a wide spectrum of data. The KNCC Community Cohort study provides data to investigate potential risk factors for cancer, including environmental factors and genetic factors, and has the possibility of expanding to investigate other chronic diseases in the Korean population. Second, the Korea National Cancer Incidence Database of the Korean Central Cancer Registry and Cause of Death Database, which are reliable registries covering the entire population, are available to identify outcomes. Third, biospecimens (i.e. serum, plasma, buffy coat, packed erythrocytes and urinary samples) provided by each cohort participant have been stored in biorepositories and can be used for assessing the role of genes in the aetiology of cancer and for identifying potential biomarkers of cancer.

The KNCC Community Cohort study also has several weaknesses. The main weakness is the relatively small size of the cohort (*n* = 16 307). In 2011, a total of 1334 cancer incident cases were identified in the cohort, but the numbers of site-specific cancer cases were fewer than 100, with the exception of the most common cancer sites in Korea (i.e. stomach, lung, liver and colorectum). In addition, the cohort is not representative of the general population in Korea, as it includes only a few counties and cities and participation in the cohort was voluntary. Findings from this cohort study should therefore be interpreted and

generalized with caution. The second weakness is that the cohort has no information with repeated measurements. The possibility of effects of changed behaviours, environmental factors and clinical information on cancer cannot be ruled out. Third, the cohort collected information on dietary habits using the food frequency questionnaire (FFQ). However, only information on frequency of food intake, not amount, was available and it is difficult to calculate total food intakes.[19]

## Can I get hold of the data? Where can I find out more?

All data sets are stored electronically in anonymous form. Biospecimens including serum, plasma, buffy coat, packed erythrocytes and urinary samples, were aliquoted and banked at under −70°C (−20°C for urinary samples). Currently, these data are available only to members of the research team, although our research committee will welcome any enquiries regarding collaboration or data sharing for further investigation. Currently, releasing the data and biospecimens to the other researchers is under institutional consideration. Potential collaborators are invited to contact the principal investigator of the KNCC Community Cohort, Min Kyung Lim [mickey@ncc.re.kr].

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**KNCC Community Cohort profile in a nutshell**

The KNCC Community-based Cohort was designed to investigate the relationships between the risk of cancer and a variety of environmental, lifestyle and host factors in the Korean population.

Between 1993 and 2010, a total of 16 304 males and females aged over 30 years, and residing in five geographically defined urban and rural areas located in the northern, middle and southern parts of Korea, were recruited into the cohort.

The cohort has been followed up annually to identify new cancer cases and deaths from the date of the baseline survey. Using national personal identification numbers, the cohort data were linked to the Korea National Cancer Incidence Database of the Korean Central Cancer Registry and Cause of Death Database of Statistics Korea.

The cohort offers information on socio-demographic factors, lifestyle factors, environmental factors and clinical examinations results from the baseline questionnaire survey and health examination. The biorepository includes serum, plasma, buffy coat and urine.

Potential collaborators will be invited to contact the principal investigator, Min Kyung Lim [mickey@ncc.re.kr].

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