Review Article

Asia Cohort Consortium: Challenges for Collaborative Research

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ABSTRACT

In this era of chronic diseases, large studies are essential in investigating genes, environment, and gene–environment interactions as disease causes, particularly when associations are important but not strong. Moreover, to allow expansion and generalization of the results, studies should be conducted in populations outside Western countries. Here, we briefly describe the Asia Cohort Consortium (ACC), a collaborative cancer cohort research project that was first proposed in 2004 and now involves more than 1 million healthy individuals across Asia. There are approximately 50 active members from Bangladesh, China, India, Japan, Korea, Malaysia, Singapore, Taiwan, Thailand, the United States, and elsewhere. To date, the work of the ACC includes 3 articles published in 2011 on the roles of body mass index, tobacco smoking, and alcohol consumption in mortality, diabetes, and cancer of the small intestine. Many challenges remain, including data harmonization, resolution of ethical and legal issues, establishment of protocols for biologic samples and transfer agreements, and funding procurement.

Key words: Asia; cohort; consortium

INTRODUCTION

Prospective cohort studies provide the best level of observational evidence on disease causation. Furthermore, prospective cohort studies have specific strengths over clinical trials, which are often regarded as more powerful than observational studies in the hierarchy of evidence. For instance, in situations where it is unethical to design an experimental study (eg, in situations involving exposure to tobacco, alcohol, or obesity), observational studies are the only way to undertake research. Further, unlike clinical trials, cohort studies can assess multiple outcomes for any 1 exposure or multiple exposures for a specific outcome. Chronic diseases are on the rise worldwide, and Asian countries face a growing disease burden and the many important health challenges that result.1 The patterns and causes of diseases may differ among populations, yet much remains unknown about the causes of diseases in Asians, who account for most of the global population.2,3 Approximately 95% of genome-wide association studies have been undertaken among people of European origin. Thus, the findings may not apply to other populations and the resulting genomic medicine might benefit only the few. Hence, a wider spectrum of populations should be investigated.4

Since the completion of the Human Genome Project, epidemiologic studies encompassing genetics have prospered, and the importance of prospective cohorts has been more widely recognized.5 Moreover, a sufficiently large cohort or a population laboratory is essential for understanding the roles of genetic variation, environmental exposures, and the interaction between genes and exposures in the development of a disease.6 Analyses of gene–environment interactions in complex diseases with small interaction odds ratios or of genome–environment-wide interactions require even larger sample sizes to confirm associations.7,8 Potter has suggested that a cohort of at least 1 000 000 ethnically diverse individuals (“the Last Cohort”) is essential to discover disease susceptibility, early-detection biomarkers, and more-precise phenotypes.9

Combining existing cohorts is a strategy to achieve the desired results more quickly, more cheaply, and with similar scientific validity.10,11 Consortia are being established in and across many nations and research groups in order to produce expedited results and better understand the extent of international ethnic variation.10,12 One example is the Cohort Consortium of the National Cancer Institute (NCI), a collaboration of 43 high-quality cohorts consisting of more than 4 million people.13 The Cohort Consortium...
includes 4 signature initiatives that are actively producing valuable results: the Body Mass Index (BMI) and All Cause Mortality Pooling Project; the Breast and Prostate Cancer Cohort Consortium (BPC3); the Pancreatic Cancer Cohort Consortium; and the Vitamin D Pooling Project (VDPP). Through such collaborations, the complex process of identifying disease causes in relation to various genetic determining factors can be approached systematically.

**HISTORY AND ORGANIZATION OF THE ACC**

The Asia Cohort Consortium (ACC) is another large consortium of cohort-based studies in Pacific Rim countries, with approximately 50 active members from China, India, Bangladesh, Japan, Korea, Malaysia, Singapore, Taiwan, Thailand, the United States, and elsewhere (Table 1). The ACC was first proposed in November 2004 at a meeting in Seoul, Korea, and nearly all researchers at the meeting agreed on the need to establish a large consortium of cohorts. By establishing a cohort of at least 1 million healthy individuals around the world who will be followed until various disease endpoints, the ACC seeks to identify associations of diseases with genetics, environmental exposures, and their interaction, and to discover early-detection biomarkers. The ACC aims “(i) to serve as a platform for cross-cohort collaborative projects and combined analysis and (ii) to act as an incubator for new cohorts.” Led by co-chairs John Potter of the Fred Hutchinson Research Center, USA and Dahee Kang, Department of Preventive Medicine, Seoul National University College of Medicine, Korea, the ACC investigators meet biannually to update progress on existing and new cohorts in each country, to share ideas on data harmonization and development of common protocols, and to prepare collaborative projects. The ACC Coordinating Center (ACC CC) is located at the Fred Hutchinson Cancer Research Center. The ACC second meeting was held in April 2005 at the Fred Hutchinson Cancer Research Center. At that meeting, the Steering Committee was established, consisting of principal investigators from various cohort studies in each participating country. The ACC CC is located at the Fred Hutchinson Cancer Research Center and offers support for scientific collaboration, operations management, statistical and data management, and communications infrastructure and tool development. The activities of the ACC CC are described in detail elsewhere.

**Table 1. Summary of members of the Asia Cohort Consortium**

| Country | Cohort | No. of subjects | Date of enrollment | Mean follow-up period | Mean age at entry |
|---------|--------|----------------|--------------------|-----------------------|-------------------|
| India   | Mumbai Cohort Study | 146,820 | 1991–1997 | 5.2 | 50.8 |
|         | Trivandrum Oral Cancer Screening Trial (TOCS) | 129,097 | 1995–2002 | 7.5 | 49.5 |
| Bangladesh | Health Effects of Arsenic Longitudinal Study | 11,452 | 2000–2002 | 6.6 | 37.1 |
| Mainland China | China National Hypertension Survey Epidemiology Follow-up Study (CHEFS) | 154,737 | 1990–1992 | 7.2 | 55.4 |
|         | Shanghai Cohort Study (SCS) | 18,100 | 1986–1989 | 16.3 | 55.3 |
|         | Shanghai Men’s Health Study (SMHS) | 61,379 | 2001–2006 | 3.1 | 54.9 |
|         | Shanghai Women’s Health Study (SWHS) | 74,873 | 1996–2000 | 8.6 | 52.1 |
|         | Linxian Cohort | 29,459 | 1984–1987 | 18.5 | 51.9 |
| Taiwan | Community-based Cancer Screening Project (CBCSP) | 23,763 | 1991–1992 | 15.2 | 47.3 |
|         | Cardiovascular Disease Risk Factor Two-Township Study (CVCFACTS) | 5,129 | 1990–1993 | 14.9 | 47.0 |
| Singapore | Singapore Chinese Health Study (SCHS) | 63,242 | 1993–1999 | 11.5 | 56.5 |
| Japan | Three-Prefecture Cohort Study, Aichi (3-Pref Aichi) | 32,210 | 1985 | 11.6 | 56.2 |
|         | Ibaraki Prefectural Health Study | 97,578 | 1993–1994 | 11.5 | 58.8 |
|         | Japan Collaborative Cohort Study (JACC) | 86,671 | 1988–1990 | 12.7 | 57.6 |
|         | Japan Public Health Center-based Prospective Study 1 (JPHC1) | 42,771 | 1990–1992 | 14.4 | 49.6 |
|         | Japan Public Health Center-based Prospective Study 2 (JPHC2) | 55,712 | 1992–1995 | 11.5 | 54.2 |
|         | Three-Prefecture Cohort Study, Miyagi (3-Pref Miyagi) | 29,525 | 1984 | 11.6 | 56.9 |
|         | Miyagi Cohort Study | 44,867 | 1990 | 12.8 | 52.0 |
|         | Ohasaki National Health Insurance Cohort Study | 47,670 | 1995 | 9.9 | 60.1 |
| Korea | Korea Multi-center Cancer Cohort (KMCC) | 16,013 | 1993–2004 | 6.5 | 55.6 |
|         | Seoul Male Cohort | 13,953 | 1992–1993 | 14.7 | 49.2 |
Currently, consortium members are collaborating on projects examining body mass index (BMI) and various outcomes; rare cancers, including cancers of the small intestine and pancreas, which are infrequent and thus difficult to study in single studies; and biospecimen use across existing Asian cohorts.

Proposals initiating a collaborative project can be submitted throughout the year. Before every biannual meeting, all proposals are reviewed by the Executive Committee (EC) and ACC members. Proposals from anyone interested in initiating a collaborative project can be submitted. Larger grant proposals are currently being under review. Larger grant proposals are currently being drafted.

The first cross-cohort collaborative project, BMI in Asian populations, has yielded 3 articles to date (Table 2).17–19 The first article published by the group was a pooled analysis of BMI and risk of death among more than 1.1 million persons from 19 cohorts in Asia.17 We reported a U-shaped association between BMI and mortality in East Asians that subtly differed from the associations observed in studies of North American and European populations. These observations were possible largely because, in Asia, we were able to study the association between very low BMI and mortality, an opportunity that has not existed in populations of European origin for many decades. A U-shaped association was also reported in a 2011 pooled analysis of 7 large-scale cohort studies in Japan.20 In contrast, among Indians and Bangladeshis, there was no elevated risk of death in high BMI groups. These results provide important new public health data, as few previous studies have been conducted on BMI and overall risk of death in Asian populations, which account for more than 60% of the world’s population. The second article was a pooled cross-sectional analysis of BMI and self-reported diabetes that included more than 900,000 individuals from 18 cohorts.18 As was the case for BMI and mortality, the overall impact of BMI on diabetes risk had not been adequately studied in an Asian population. This study encompassed 7 Asian countries and established the shape and strength of the association between BMI and diabetes. Similar to the previous results, a positive association between BMI and diabetes prevalence was shown in all analyzed cohorts and all subgroups of the study population. The third, and most recent article, published by the ACC reported the findings of a study of the association of cancer of small intestine with BMI, tobacco smoking, and alcohol drinking, using a pooled analysis of over 500,000 individuals from 12 cohorts.19 The analysis of 134 incident cases showed a trend toward an increased hazard ratio of 1.50 (95% CI, 0.76–2.96) in the high BMI (BMI >27.5 kg/m²) group. Although the results were not statistically significant, they support the hypothesis that elevated BMI is a risk factor for cancer of the small intestine. No association was observed for tobacco smoking or alcohol drinking.

**PROGRESS AND RESULTS**

ACC participants are self-funded, and individual projects usually require a grant proposal to secure funding. The ACC has 2 funded grant proposals from the US NCI on rare cancers and BMI and on BMI and mortality, as well as other projects under review. Larger grant proposals are currently being drafted.

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**FUTURE PLANS**

Many challenges remain for the ACC. The first is harmonizing data from legacy cohorts. For instance, some questions on exposures were asked differently and demand more careful standardization. Even more complex is the need for new infrastructure, such as the establishment of an Asian nutrient database. Much work is left to be done in the field of nutrition, especially when using data from multiple countries.21,22 Furthermore, standardizing and harmonizing new and continuing cohorts, and incorporating them into the existing study in a valid way, is similarly complex and time-consuming. Phenotypic measures, specific measurement tools, and other areas may be discordant across studies.11 Biospecimens

| Table 2. Publications of the Asia Cohort Consortium |
|--------------------------------------------------|
| No. of individuals included in analysis | No. of cohorts used in analysis | Exposure | Outcome | Main result | Ref |
|------------------------------------------|-------------------------------|----------|---------|-------------|-----|
| 1 141 609                               | 19                            | BMI      | Total mortality and cause-specific mortality | BMI ≤ 1.50 HR = 2.8 (1.9–4.1)² | 17  |
| 934 154                                 | 18                            | BMI      | Self-reported diabetes | BMI < 15.0 OR = 0.6 (0.3–0.8)³ | 18  |
| 527 726                                 | 12                            | BMI, tobacco smoking, alcohol drinking | Incidence of cancer of small intestine | BMI > 27.5 HR = 1.5 (0.8–3.0)³ | 19  |

Abbreviation: BMI, body mass index; HR, hazard ratio; OR, odds ratio. Reference BMI categories: ²22.6–25.0, ³22.5–24.9, ⁴22.6–25.0. ⁵95% CI.
present unique challenges. The quality of samples collected and stored under different protocols and for varying periods may differ among cohorts. Sample transfer between countries is sometimes a problem. Ethical and legal issues regarding informed consent of study participants and the use of their information for international studies are other areas that need to be resolved. To fulfill the collective enthusiasm and talent of workers in the ACC, funding is a constant necessity. We have begun well, but there is a great deal left to do.

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