
COMMENTARY

ASEAN Cancer Cohort Consortia? - Learning from History and Possible Roles for National Cancer Centers/Institutes

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Abstract

Cancer epidemiology, with the focus clearly on populations, has particular advantages to gain from cohort studies, especially where consortia can be established covering differing ethnic and cultural groups. While there have been efforts in the past to establish cooperative efforts within the region, as exemplified by the Asian Cohort Consortium, the Asian Pacific Cohort Studies Collaboration and the ACTION study within South-East Asia, there is still scope for meaningful expansion. Japan and Korea are two countries in Asia with extensive experience of multi-institutional cohorts with cancer as one disease outcome. Their examples might be emulated within the Association of South-East Asian Nations (ASEAN). In addition to the general population, special attention might be given to nurses and doctors within South-East Asia and with a standard protocol, hospital-based case and control 'cohorts' could reward investment. The fact of considerable cultural and ethnic variation within ASEAN, along with major differences in individual cancer incidence rates, could be exploited to provide novel approaches to a better understanding of risk and prognostic factors pertinent to the particular populations within the region. Actual establishment of cohorts, however, will require a great deal of investment and cooperation between different institutions. Financial considerations mean that sponsors are essential. Political 'will' would need to be generated, with concerted action of important players. One focus might be on National Cancer Centers/Institutes wishing to enhance their impact by cooperation in leading such an effort.

Key Words: Cancer - cohorts - international cooperation - ASEAN - academia - research institutes

Introduction

Growth of cancer epidemiology as a discipline did not really become established until the results of important cohort studies were published, like for example the British Doctor's Study focusing on smoking and lung cancer (Doll and Hill, 1954). Cohort studies of human populations, without the limitations of standard case-control approaches, have thus provided what is regarded as the most compelling evidence of associations between specific cancers and exposure to specific agents. The origin of the cohort study can be traced back to studies on life span in the 19th century. During the 1940s and '50s, several landmark prospective cohort studies were launched, an outstanding example being the Framingham Heart Study study, followed in the 1960s by many prospective and retrospective cohort studies were conducted to determine the relationships between particular diseases and specific causative agents, like asbestos and lung cancer, and aniline dyes 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. While most cohorts were limited to single countries or

populations, the benefits of international cooperation with appropriate financial and logistic support are evidenced by the European Prospective Investigation of Cancer (EPIC) started in the 1990s (Riboli, 1992; Riboli and Kaaks, 1997), which has resulted in more than one thousand publications in international journals (see Table 1). In Thailand, Supanne Sriamporn/Promthet was pioneering in setting up a Khon Kaen Cancer Cohort which has given rise to a considerable number of nested case-control studies (Sriamporn et al., 2005). Here the authors wish to consider possible avenues to explore for establishment of new ASEAN cancer cohort consortia by focusing on multi-institutional experience already gained within Japan, South Korea and Asia using different approaches and population sources.

Japan

Japan has a long history of establishment of cohorts (Aoki, 1993). Starting in the late 1980s a major collaborative effort was carried out to increase knowledge about factors contributing to mortality from cancer and circulatory disease. This Japan Collaborative Cohort Study (JACC Study), sponsored by the Ministry of Education, Science, Sports and Culture of Japan with

Table 1. Cancer ‘Cohorts’ of Interest

Name	Start	Papers*
ACTION		
Asian Cohort Consortium	2004	7
Asian Pacific Cohort Studies Collaboration	1999	11
EPIC ¹	1992	1,321
Japan		
Collaborative Cohort Study	1988	183
HERPACC ²	1988	29
Public Health Center-based Prospective Study	1990	258
Korea		
KMCC- I ³	1993	32
Thailand		
Khon Kaen Cohort	1990	11

*Relevant to cancer research; ¹European Prospective Investigation into Cancer and Nutrition; ²Hospital-based Epidemiologic Research Program at Aichi Cancer Center; ³Korean Multi-center Cancer Cohort

contributions from 45 areas of the country, covered more than 100,000 participants (Tamakoshi et al., 2008). To collect epidemiological information at baseline, a self-administered questionnaire was used covering: past medical history; family medical history; health condition one year prior to entry; exercise/sports activities engaged in; frequency of food intake and preference for salty and fatty foods; smoking and alcohol drinking status; health check-up history; occupation; residential area; education; behavioral attitude/stress; and reproductive history for women. Dates and causes of death were annually or biannually confirmed, with the permission of the director- general of the Prime Minister’s Office (Ministry of Public Management, Home Affairs, Post and Telecommunications).

Beginning in 1990, the Japan Public Health Center-based Prospective Study (JPHC Study) covering 140,000 residents aged 40 to 69 years living within 11 public health center-based areas nationwide in 1990-1994 was launched (Tsugane and Sobue, 2001). Subsequently the Japan Public Health Center-based Prospective Study for the Next Generation (JPHC-NEXT) was started in 2011 (Sawada et al., 2019). A self-administered questionnaire was distributed to all registered residents aged 40-74 providing informed consent, mainly concerning lifestyle factors, such as socio-demographic situation, personal medical history, smoking, alcohol and dietary habits. .

A number of other smaller cohorts have also been established and under the auspices of the Research Group for the Development and Evaluation of Cancer Prevention Strategies in Japan, they coordinate their activities, for example in looking at smoking cessation and subsequent risk of cancer (Saito et al., 2017) .

One very practical, to our knowledge unique ‘cohort’ study which deserves particular attention is the Hospital-based Epidemiologic Research Program at Aichi Cancer Center (HERPACC) (Tajima et al., 2000). In this (see Figure 1), first visit outpatients are invited to participate and with consent, a questionnaire is administered, included items on occupation, smoking and drinking habits, dietary habits, sleeping habits, and physical exercise. More recently, DNA samples have also been collected

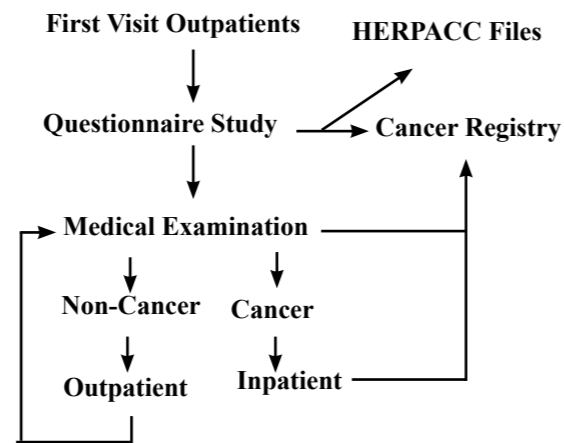


Figure 2. Flow Chart of Systematic Data Collection in the Hospital-based Epidemiologic Research Program at Aichi Cancer Center (HERPACC)

to allow investigation of gene-environment interactions and polymorphism studies (Hamajima et al., 2001). After providing questionnaire data, patients undergo medical examination and are subdivided into cancer and non-cancer cases, the latter being considered appropriate as ‘controls’ for comparison purposes (Inoue et al., 1997). Follow up is facilitated by use of the population-based cancer registry for Aichi.

South Korea

The Korean Multi-center Cancer Cohort (KMCC- I) was constructed in 1993 (Yoo et al., 1998), involving the collaboration of epidemiologists from Seoul National University, Dong-A University, Konkuk University, Dongkuk University, Kosin University, and the National Cancer Center in Korea. A research grant from Seoul National University Hospital was awarded in 1992 and since 1993, the Korean Electric Power Corporation has been providing, in part, research grants for this project. During 1995-97, a grant was received 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.

The goals of the 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-style and cancer occurrence in the population, and of evaluating roles of both biological and chemical agents. 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.

The Korean National Cancer Center (KNCC) Community Cohort (Oh et al., 2015), was begun as a part of the KMCC in 1993 and has been continuously

developed and funded by the National Cancer Center (NCC) since 2001. It is based on four geographically defined urban and rural areas located in the southern, middle and northern parts of the Korean peninsula. The authors note in particular the direct NCC involvement as an example for possible emulation.

Asian/Asian Pacific/ASEAN

As an early cooperative effort within Asia, the Asia Pacific Cohort Studies Collaboration (APCSC) was set up in order to provide high-quality evidence for the effects of risk factors on cardiovascular disease and cancer specifically for Oriental populations (Zhang et al., 1999). The idea was to pool subjects from a number of ongoing prospective cohorts meeting set criteria (Woodward et al., 2006). Ultimately this led to the inclusion of 44 studies, 16 from mainland China, 14 from Japan, 8 from Australia, 2 from Taiwan, 2 from Singapore, and 1 each from Hong Kong, New Zealand, South Korea, and Thailand. Altogether, APCSC includes over 600,000 subjects and has given rise to many papers on cancer, although the main target was cardiovascular disease (Woodward et al., 2012).

The Asian Cohort Consortium (ACC), first proposed in November 2004 in Seoul, is a consortium of cohort-based studies in Pacific Rim economies (Rolland et al., 2011). The aim is to understand relationships among genetics, environmental exposures, and the etiology of disease, with a two-fold mission to serve as a platform for cross-cohort collaborative projects and combined analysis and act as an incubator for new cohorts. The ACC now has approximately 50 active members, representing countries across Asia and the United States, as well as major cancer research organizations such as the National Cancer Institute (NCI) in Washington, DC. All members are involved in some way with building cohorts in Asia. Members are faculty at their institutions and some hold appointments in their national health ministries. These investigators, from China, India, Bangladesh, Japan, Korea, Malaysia, Singapore, Taiwan, and the United States meet on a biannual basis to report on the progress of the new and existing cohorts.

Initially only one cohort from ASEAN was included, the Singapore Population Health Studies (blog.nus.edu.sg/sphs/singapore-health-studies) (Song et al., 2012) but the Malaysian Cohort Study (www.ukm.my/mycohort), the Cohort study on clustering of lifestyle risk factors and understanding its association with stress on health and wellbeing among school teachers in Malaysia (CLUSTER) (Moy et al., 2014) and the Singapore Chinese Health Study (www.sph.nus.edu.sg/research/schs) are now included (http://www.asiacohort.org, accessed 1.3.19). Of especial note, the domain name was considered an important signal to the group of legitimacy and desire to continue to grow the ACC. Creation of email lists of “all members” was also aimed specifically at developing a community spirit.

Very high profile publications have resulted from the Asia Cancer Consortium, but this is basically a USA-led effort, with most Asian colleagues from Japan, Korea and China, as evidenced by the author list of one recent

paper (Chen et al., 2017). The sum total of the accredited contribution to the overview paper of the Global Burden of Disease Cancer Collaboration (2017), was one author from Viet Nam, and none at all from any of the other countries of South-East Asia, in a list of almost 200 scientists.

A specifically South-East Asian project, the ACTION (Asean CosTs In ONcology) Study, was undertaken by the George Institute for Global Health of Sydney, Australia, in collaboration with the ASEAN Foundation (aseanfoundation.org) and Roche Asia Pacific Regional office (Jan et al., 2012; Kimman et al., 2012). The aim was to assess the socioeconomic impact of cancer on patients in ASEAN communities, and factors that might impact on outcomes. A major focus was on catastrophic costs (The ACTION Study Group, 2015; 2017). This cooperation involved many players from Cambodia, Indonesia, Laos, Malaysia, Myanmar, the Philippines, Thailand and Viet Nam. Of particular interest, included were the National Cancer Centre in Cambodia, the Dharmais Cancer Center Hospital in Indonesia, the Lao Cancer Center, and the National Cancer Institute of Thailand. The focus is now on how this can be continued or expanded, which research questions will be given priority, and with what leadership.

What Type of Cohort?

Many of the most successful cohorts have focused on particular groups like Doctors (Doll and Hill, 1954; Doll and Peto, 1976) or nurses (Belanger et al., 1978). Women are usually the primary caregivers and women’s healthcare issues clearly need to be prioritized. In Asia, nurses’ cohort studies have been initiated in Japan (Hayashi et al., 2007), Korea (Kim et al., 2017) and Thailand (www.thainursecohort.org), for example. Whether multi-institutional doctor, nurse or particular student group cohorts could be considered is a question for discussion. Students are readily accessible for cross-sectional studies but whether they can feasibly be followed-up is less clear. The same is naturally true of general populations, where recourse is generally to use areas with good population-based cancer registration coverage (Sriamporn et al., 2005). Many problems need to be addressed when establishing a general cohort, including how to minimize bias and ensuring representative participation.

As with the ACTION study and HERPACC, a focus on actual cancer cases can overcome many difficulties, especially with active follow-up. With a multi-institutional network, specific questions might be rapidly answered with rapid patient case accrual. One good example of the benefits from cooperation is exemplified by the three plus one country stomach cancer study headed by Shinkan Tokudome, including Viet Nam (high incidence), Thailand (medium incidence) and Indonesia (very low incidence), compared with Japan (very high incidence). This resulted in the conclusion that rare *Helicobacter pylori* infection may explain low stomach cancer incidence (Tanaka et al., 2016). With a network, members could group together for specific projects in this fashion.

While the EPIC study and many of those conducted in the more developed countries of the region have focused a great deal of attention on genetic factors requiring

Table 2. Questionnaire Items and Measurements

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 (eg awareness education, cancer screening and vaccination), Dietary habits (principal component analysis) Smoking and alcohol drinking habits Physical activity, occupational history Exposure to pesticides and electromagnetic fields Reproductive history for women (menarche, menopause, oral contraceptive use, pregnancy, parity, breast feeding etc.)
Anthropometric	Height, weight, waist/hip circumference, blood pressure

sophisticated laboratory testing, this might not be feasible across all of ASEAN. In order to allow compatibility and conformity emphasis might better be placed on questionnaire items and easily performed physical measurements (see Table 2). However, this would clearly depend on the intended research and would need ad hoc discussion.

The essential questions are leadership and financial support. Many of the international efforts for cohorts involving ASEAN have been driven by teams from the USA and Australia. Their efforts have gratefully been cited below. Is there consensus that independent programs could now be established? If the National Cancer Centers/Institutes in the region were to work together more closely, as has been envisaged for the Asian National Cancer Centers Alliance, it might be possible to generate a network capable of establishing ASEAN Cancer Cohort Consortia which would attract the attention of national and international donors. Clearly, all of the local contributors to the ACTION study might also have opinions on how to best proceed.

Acknowledgements

Malcolm Moore would gratefully like to acknowledge the opportunities offered by Kazuo Tajima, Shinkan Tokudome and Suminori Kono of Japan, and Mark Woodward of Australia, to participate in many of the efforts described in the article.

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