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International strategy in cancer epidemiology: Japan's involvement in global projects and future role

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Abstract: In recent years, collaboration among researchers in the field of cancer epidemiology has been accelerating in various forms. Here, we review recent trends in international collaborative research activities in the cancer epidemiology field in Japan. These include not only support for other countries with less developed cancer statistics infrastructures, but also large-scale compilations and international comparisons through collaborative studies, as well as integration with analytical epidemiology and clinical research. Formation of international cohort consortia and estimates of cancer and risk factors in each country have contributed to raising the skill levels of cancer epidemiologists as well as to expanding research networks and activities among cancer epidemiologists. Molecular and genome epidemiological studies on cancer have progressed over decades and these continue to increase in size and dimension. Application of evidence from this area in prevention is still underway and needs further effort. Japanese epidemiologists have great potential to assume international leadership roles by taking advantage of the uniqueness, originality and characteristics of Japanese cohorts.

***Keywords*:** cancer, epidemiology, international collaboration

Introduction

Because of the major regional and global disease burden of cancer, cancer epidemiology has grown in importance and now covers a wide range of research aimed at both identifying the causes of cancer and preventing cancer at the population level. To achieve these, it is essential to understand the geographical distribution of cancer and its time trends, and to clarify the risk factors for prevention. Specifically, population-based cancer registration is an inevitable basis for descriptive statistics of cancer while analytical epidemiological research is crucial to elucidating the causes of cancer. Genomic epidemiological methods have attracted attention in recent years. These different research approaches will be bridged with health policy and practice using individual epidemiological evidence, systematic review and meta-analysis, pooled analysis, and evidence-based cancer prevention methods, as well as research into the dissemination and implementation of their findings.

Epidemiological research on cancer is no longer irrelevant to globalization, and the identification and control of risk factors is a common issue both domestically and overseas. In recent years, collaboration among researchers in the field of cancer epidemiology has accelerated in various forms. Achieving cancer prevention now requires the creation of high-impact evidence, and large-scale research collaboration platforms have emerged for that purpose. Japan is no exception; the quality of epidemiological research and researchers has improved dramatically in the last few decades. Considered in terms of the evidence-building required to realize effective cancer control policy, the cancer epidemiology field in Japan has, in a sense, entered a mature stage.

Here, we introduce recent trends in international collaborative research activities in the cancer epidemiology field in Japan, including current achievements and future prospects.

International collaborative activities in the field of descriptive epidemiology in cancer

The development of cancer registries and mortality statistics is proceeding at a rapid pace all over the world. The first population-based cancer registry (PBCR) was launched in Germany in 1929, followed by the US and Denmark (Table 1). In Japan, the first PBCR was organized by Miyagi prefecture in 1955, followed by Hiroshima city, Nagasaki city, and Aichi, Osaka

Table 1. History of population-based cancer registry and related events

Year	Population-based cancer registry in the world	Population-based cancer registry and related events in Japan
1899		The Vital Statistics Survey began to be conducted centrally using individual votes
1929	Germany (Hamburg)	
1940	USA (New York State)	
1941	USA (Connecticut)	
1942	Denmark	
1944	Canada (Saskatchewan)	
1945	England and Wales (SW)	
1948	England and Wales (Liverpool)	
1948	New Zealand	
1950	Canada (Manitoba)	
1929	Slovenia	
1950	Canada (Alberta)	
1951	USA (El Paso)	
1951		PBCR in Miyagi (the first regional PBCR)
1957		PBCR in Hiroshima city
1958		PBCR in Nagasaki city
1968		PBCR in Aichi and Osaka
1970		PBCR in Kanagawa
2006		Enforcement of the Cancer Control Act
2013		PBCR in Miyazaki (the 47th regional PBCR out of the 47 prefectures)
2016		Enforcement of the Act on Promotion of Cancer Registries

and Kanagawa prefectures. PBCRs covered the entire population in 2013. The development of mortality statistics goes back a long way, and the Vital Statistics in Japan was started in 1899. The role of descriptive epidemiology is to plan cancer control measures based on an understanding of the actual status of cancer burden. In many low- and middle-income countries (LMICs), cancer statistics do not exist, and evidence-based cancer control measures cannot be implemented, even though the burden of cancer is increasing. The global initiative for cancer registry development, launched in 2011 and led by the International Agency for Research on Cancer (IARC), has established hub centers in five continents. The fruit of almost 10 years' activities includes 167 site visits, 17 agreements and 89 training courses to date. The initiative has been deemed a success. Japan is involved in this project as a collaborating center in Asia, supporting the hub center at the Tata Memorial Cancer Center, Mumbai, India, and working to develop cancer statistics in Southeast Asian countries. Vital Strategies, a U.S. consulting firm, is developing a project called Civil Registration and Vital Statistics for Asian countries, which provides support for the collection of mortality information (*https://www.vitalstrategies.org/programs/civil-registration-and-vital-statistics*). In parallel, the World Health Organization (WHO) is implementing the Global Initiative for Childhood Cancer project (*1*), with the aim of reaching a survival rate for children with cancer of at least 60% by 2030, and statistics on childhood cancer are becoming more accurate. In this manner, through collaboration among international organizations, the private sector, and academia, certain results have been achieved. In Southeast Asian countries such as Vietnam and Myanmar, high-level cancer statistics have been developed in the space of only a few years. In previous years it typically took at least 10 years from the time a cancer registry was launched to achieving stable operations, but this has been shortened to 3 to 4 years. In addition, even in a country with a huge population like China, more than 600 cancer registries have been established to provide accurate cancer statistics for use in active cancer control (*2*).

Through these support efforts, cancer statistics have been developed in many countries, and accurate cancer statistics can be compared across more regions (*3*). Epidemiological data are available from WHO and IARC for incidence (Cancer Incidence in Five Continents), mortality (Mortality Database), and survival (SURVMARK and SURVCAN). Estimates have also been calculated for regions where actual data are not available in the GLOBOCAN project (*4*). GLOBOCAN 2020 estimates that there were 19,292,789 new cases of cancer worldwide, 9,958,133 deaths from cancer, and 50,550,287 5-year prevalent cases in 2020. Lung is the most common cancer in men (14.3%) and breast in women (24.5%). In addition to international organizations, acadamia have also started large-scale international descriptive epidemiological studies. With regard to survival, the University of London is leading the CONCORD Study (*5*), and the RARECAREnet study is focused on rare cancers, mainly under the direction of the National Cancer Institute in Milan, Italy. For rare cancers in Asia, the RARECAREnet Asia study has been initiated, led by the National Cancer Center Japan, with the participation from Japan, Korea, Taiwan, Thailand, Malaysia and India (*6*). The proportion of rare cancers in overall incidence was 16.3% in Japan, 23.7% in Korea, 24.2% in Taiwan and 22.2% in the EU. Numbers of newly diagnosed rare cancer cases in 2015 were 140,188 in Japan, 52,071 in Korea, and 24,147 in Taiwan. A

new barrier to international research is the exchange of medical information; in a sense, overreaction to the promulgation of the General Data Protection Regulation (GDPR) has made it difficult to aggregate and exchange individual cancer data in many countries. For this reason, attempts have been made in the last couple of years to create statistical models which aggregate data without taking individual data out of the country that produced it (*7*). This method, called Distributed Learning or Federated Learning, outputs only the coefficients of the equation, and no personally identifiable information leaves the local computer or storage area outside the facility.

In many developed countries, descriptive epidemiology on cancer is not limited to the calculation of cancer statistics and their use in cancer control. Rather, it is also being integrated with analytical epidemiology and clinical research fields, and has begun to influence the identification of cancer risk factors and determination of medical treatment policies. These attempts aim to sublimate the strengths of descriptive epidemiological information, such as population-based cancer registries and mortality statistics, into analytical epidemiology through linkage between databases, while taking advantage of their completeness, risk population identification, unbiasedness, and standardized collection items. Interdisciplinary integration is often carried out by merging socioeconomic databases, such as census data for risk factors of cancer incidence and mortality, with cancer registries and mortality statistics for outcomes, or by adding detailed medical information to cancer registries and mortality statistics. In the Netherlands and Scandinavian countries, multiple cancer-related databases have already been linked in real time for several decades, and the boundary between descriptive and analytical epidemiology has effectively vanished. In Norway and Denmark, studies with these designs which linked census data and data from cancer registries to analyze the relationship between occupational exposure to carcinogens and cancer incidence were conducted as early as the 1980s (*8*). Moreover, a number of studies in the Netherlands have added clinical information to cancer registry data (*9*).

Descriptive epidemiology on cancer is now a standardized and accurate way to determine the cancer burden worldwide, and international collaborative research has been conducted through the cooperation of many countries. The development of technology to promote research while ensuring the protection of personal information is also remarkable. On a more granular level, analytical epidemiological approaches which integrate cancer statistics with other statistics have been taken. Behind all these trends is the rapid spread of computers and the development of high-speed networks that can be used by everyone. In Japan, integrating databases that were developed independently is extremely difficult, and these stand like an urban landscape of inconsistent buildings. LMICs should take advantage of their latecomer status by learning from these negative lessons and moving forward with a firm focus on the development of integrated cancer statistics.

To summarize, various aspects of international research collaboration have been activated over a number of decades in the field of descriptive epidemiology of cancer. These have aimed to support countries, especially LMICs, which have yet to develop a robust cancer statistics infrastructure; conduct large-scale compilation and international comparisons through collaborative studies; and integrate with analytical epidemiology and clinical research.

Research collaboration platform: cohort consortia and risk factor burden analysis

Evidence from epidemiological studies on the association between lifestyle and cancer risk has increased in the last few decades, and understanding of cancer etiology continues to grow. Notable recent trends in large-scale cohort studies are the formation of cohort consortia and the active progress of pooled analyses. To make efficient use of existing cohort studies around the world and to achieve more precise estimates, cohort consortia with major risk factors and major outcomes have been established, mainly under the leadership of the US and Europe. The Pooling Project of Prospective Studies of Diet and Cancer (DCPP) ($n \approx 800{,}000$) (*10*) centered around Harvard University has pooled cohorts mostly from the US and Europe, as well as some from Asia, including Japan, to analyze the association between dietary factors and cancer (*11*). The European Prospective Investigation into Cancer and Nutrition (EPIC) study (*12*) ($n \approx 500{,}000$) is a large-scale cohort consortium across European countries which is unique for its multiple cohorts which were each established using a common protocol from the planning stage.

In Asia, the Asia Cohort Consortium (ACC) (*13*), established in 2004 by cancer epidemiologists across the Asian region, has expanded its contribution to collaborative research across the Asian region in the cancer epidemiological research field (*14*) (Figure 1). It aims to understand the association of genetic and environmental factors with the onset of disease using cohorts from Asian countries with a total healthy population of over one million, and to utilize this cohort data to provide reliable scientific evidence on emerging health issues and causes in Asia. The ACC has two missions: to serve as a platform for cross-collaborative projects and combined analysis in Asia, and to act as an incubator for new cohorts. The latter is unique to ACC in that it has the role of not only conducting pooled analyses, similar to many cohort consortia in Europe and the US, but also of providing intellectual support (methodology and common research materials) - albeit not funding - to the creation of new cohorts. Particularly

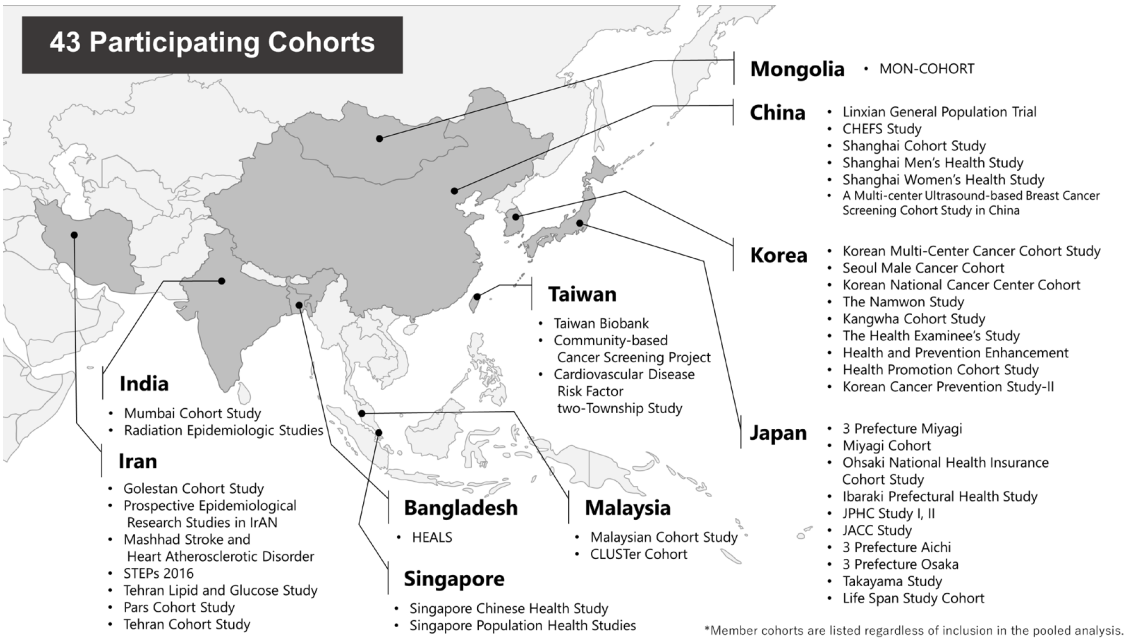

Figure 1. Participating cohorts of the Asia Cohort Consortium (as of April 2021) (*https://www.asiacohort.org/index.html*) (*13*).

in countries still developing their epidemiological resources, both human and non-human, this type of "regional" incubation is inevitable. Currently, 10 large-scale cohorts in Japan have joined to conduct pooled analyses, providing the largest population size among countries in the ACC. The ACC coordinating center is located in the National Cancer Center Japan and is in charge of the administrative work necessary to facilitate the various research activities conducted to fulfil the missions of the ACC.

The major strength of cohort consortia is large sample size. Larger sample sizes allow the investigation of uncommon or multiple types of exposure, rare diseases, and variation among population subgroups or races due to the greater statistical power provided over individual studies (*11*). Additionally, collection of individual data from each cohort allows reanalysis using standardized common confounding factors. This method supplements the limitations of meta-analyses from the published literature, which summarize risk estimates obtained for heterogeneous exposure categories with differing adjustment for potential confounders (*15*).

It is also noteworthy that studies into the attributable causes of cancer - estimated using population attributable fraction (PAF) in each country - are being widely promoted in many countries. Attributable causes for cancer differ between western countries and Japan. For example, PAF in the UK in men and women is 17.7% and 12.4% for smoking, followed by overweightness and obesity at 5.2% and 7.5% (*16*). In Japan, in contrast, tobacco smoking has the highest PAF (29.9%) followed by infectious agents (22.8%) in men, while infectious agents have the highest PAF (17.5%) followed by tobacco smoking (6.2%) in women (*17*). These discrepant findings highlight the importance of broad geographical confirmation of risk factors in multiple studies with large sample sizes.

The PAF estimates require the national representative prevalence of target risk factors; summary relative risk values from systematic reviews, meta-analyses, and/or pooled analyses; and nationwide cancer incidence and mortality statistics. Until now, PAF estimates on cancer have been reported from different countries and regions, including the US (*18*), Nordic region (*19,20*), UK (*16,21*), France (*22,23*), South Korea (*24*), China (*25*), Australia (*26*), Canada (*27*), Germany (*28*), and Brazil (*29*), as well as Japan (*17*), facilitated by the sharing of methodology. Research into the attributable causes of cancer through estimation of PAF provides evidence that has a direct impact on the health policy of the reporting country.

In addition, vigorous research into the global burden of disease is now underway for various diseases. The Global Burden of Diseases (GBD) (*30*) is the largest project; this estimates the global burden of disease from various perspectives by accumulating all available health-related data from each country into the Institute for Health Metrics and Evaluation (IHME), located at the University of Washington in Seattle. The burden of disease, globally and in each country, is estimated from various perspectives. With substantial research funding enabling independent operation, the GBD has become a huge consortium project with more than 3,600 experts from 160 countries around the world. The results from this project are published in The Lancet on a topic-by-topic basis and are influencing global health policymaking.

In summary, recent trends in the establishment of international cohort consortia and estimates of cancer and risk factors among countries have contributed to increasing the skill level of cancer epidemiologists,

as well as to expanding and strengthening research networks and activities among cancer epidemiologists.

Participation in cohort studies collaboration

Beginning in the 1980-90s, a number of large-scale population-based cohort studies with populations of more than 30,000 subjects in each cohort have been established in Japan. Currently, these cohort studies have follow-up times of 20-30 years, and most have reached the fruitful period in which they are able to yield epidemiological evidence of cancer. These cohort studies have also contributed to collaborative analyses in various research consortia platforms of cancer. To give one example, the Japan Public Health Center-based Prospective Study (JPHC Study), launched in 1990, consists of over 100,000 residents aged 40-69 years across Japan who have provided information on lifestyle habits and health conditions in multiple follow-up surveys. The study has participated in several international cohort consortia (*31*).

Although international cohort consortia have larger sample sizes, their simple aggregation into a single dataset is not feasible without the application of vast amounts of ingenuity. For example, two-stage analysis is opted for in the DCPP (*11*), one of the cohort consortia mentioned above. In the first step, these investigators calculate study-specific relative risks. In the second step, they conduct pooled analyses using a random- or mixed-effects model. An author in the DCPP mentioned the following in a methods paper (*11*): "Although combining the data from all studies is one way to take advantage of differences in the distributions of the exposure variable across studies, it assumes that the exposure was measured in comparable ways across studies. Because the distributions of dietary variables may differ across studies due to true differences in actual intake and due to differences in the dietary assessment methods used (and other study-specific sources of error), this assumption may not be reasonable, except for nutrients that come from a small number of food sources (*e.g.*, alcohol). In addition, combining the studies into one data set assumes that there is no between-studies heterogeneity in the associations of the outcome with the exposure or any of the covariates." This group has conducted both pooled and aggregated analyses and confirmed that the results were substantially comparable. Due to difficulties in testing the assumption, however, they generally conducted two-stage analysis. Although international cohort consortia have larger samples, it is necessary to consider differences in diet habits or assessment between countries or studies.

We recognize, however, a unique advantage in cohorts established in the Japanese population, because of differences between countries. Several examples may be cited. One example is in the presence of substantial differences in the traditional diet. The Endogenous Hormones, Nutritional Biomarkers and Prostate Cancer Collaborative Group (EHNBPCCG), which conducts collaborative analyses of individual participant data from prospective studies on the association of circulating hormone and nutritional biomarker levels with risk of prostate cancer. Several epidemiological studies reported that soy and isoflavone intake are possible preventive risk factors of prostate cancer (*32*). To examine the association between prediagnostic concentrations of circulating isoflavones and the risk of prostate cancer, two Japanese and five European prospective studies provided blood level data, including the JPHC Study. These showed large differences in circulating isoflavone concentrations between Japanese and European populations; for example, the mean genistein concentration in controls in Japanese studies (294.0-454.4 nmol/L) was more than 50 times higher than in European studies (5.19-5.61 nmol/L). It was therefore not possible to analyze these together; rather, the association of isoflavone concentration and prostate cancer was analyzed separately in Japanese and Europeans. Results showed no association in European men, but a high equol concentration was associated with a lower risk in Japanese men, with an OR in the highest quartile (95% confidence interval) compared with the lowest of 0.61 (0.39-0.97)). This international cohort consortium has suggested that further research is necessary in populations with high isoflavone intake (*33*). Further, this experience suggests that the presence of an association between a unique habit and several cancers can only be analyzed in the country or countries in which the habit is unique.

Another example is the existence of different incidence rates. The Biliary Tract Cancers Pooling Project consisted of 27 prospective cohorts with over 2.7 million adults, including the JPHC study. Biliary tract cancer incidence rates are subject to large worldwide variation. Rates are low in several European countries and the United States, but relatively high in Latin America and Asia, including Japan. Age-standardized incidence rates per 100,000 (world standard population) of gallbladder cancer and extrahepatic bile duct cancer - a subtype of biliary tract cancer - are 9.3 and 0.5 in Chile (men) and 2.4 and 3.7 in Japan (men) versus 0.3 and 0.4 in the UK (men) and 0.5 and 0.6 in the US (men), respectively (*34*). In fact, the Biliary Tract Cancers Pooling Project showed that the incidence rate of gall bladder cancer is much higher in the JPHC (10.4 per 100,000 person-time) than in European (EPIC, 2.0 per 100,000 person-time) and USA cohorts (NIH-AARP, 3.1 per 100,000 person-time). Japan's participation contributed to this project (*35*). Additionally, the association between body mass index and extrahepatic bile duct cancer was similar between this international cohort consortium (*35*) and a single report from the JPHC (*36*), with both showing that obesity may increase the risk of extrahepatic bile duct cancer. This suggests it is possible to provide sufficient evidence from one

country by taking advantage of the characteristics of each of the involved countries. Since infection is a major attributable cause of cancer in Japan, and the incidence of infection-related cancer, such as gastric cancer and liver cancer, is relatively high in Japan compared with Western countries, it may be advisable for Japan to take international leadership for these cancers.

In summary, although combining results from different cohorts is not a simple matter and should be done with caution, a larger sample size is one of the most important advantages of international cohort consortia. The resulting evidence - derived from populations around the world - is robust, and useful for ensuring the health of each of the populations involved. Experience with the JPHC Study indicates that Japanese cohorts have unique characteristics which differentiate them from other populations, namely in exposure distributions, such as dietary habits and prevalence of infections, and outcome features, including cancer types, and that investigators familiar with them may be candidates for leadership positions in international consortia.

Molecular and genome epidemiology research network

Molecular and genome epidemiological studies offer the possibility of investigating the impact of gene-environment interaction on ordinary environmental factors. These have recently been initiated as one area of oncology epidemiology with the aim of clarifying carcinogenic processes (*37*). These studies have helped clarify the significance in humans of findings from histopathological and experimental findings in carcinogenesis models in animals. Hypothesis-based research approaches, such as the association between functional ALDH2 polymorphisms and risk of drinking on esophageal cancer (*38*), have been favored. In terms of study design, the invariance of genetic factors has led to the reinstatement of the case-control study design, which was losing popularity in the evaluation of environmental exposures.

Advances in human genetic measurement techniques in the last 20 years, such as scanning gene polymorphisms array or next-generation sequencing and arrays, have significantly changed the approach of research in this area. It has lowered prices and enabled larger study sizes to be examined, and further resulted in the explosive enrichment of genetic information - examples include the Human Genome Project (*39*), International Hap-Map Project (*40*), and ENCODE projects (*41*). Based on these, research approaches have noticeably changed, from a hypothesis-based approach to a genome-wide, non-hypothesis-based one. For example, Genome-wide Association Studies (GWASs) of lung cancer made it possible to find genes such as telomerase, which cannot be found with a hypothesis-based approach (*42*). On the other hand, it was also interesting to discover genes that are likely to appear even in hypothesis-based studies, such as gene polymorphisms in the nicotine-like cholinergic receptor gene group on chromosome 15 (*43*). Most of the susceptibility loci identified from GWASs are on genes which might never have been identified through a conventional hypothesis-based approach, warranting the effectiveness of this approach, to a certain extent at least.

GWASs may be characterized as large-scale research employed to find gene polymorphisms with high prevalence but low effect size. The formation of a consortium centered on case-control studies of lung cancer, pancreatic cancer, breast cancer, head and neck cancer, ovarian cancer, pancreatic cancer, etc., which had been underway at that time played a major role in this. As one example, the University of Cambridge-led breast, ovarian, and prostate cancer consortium formed COGS (*44*). This consortium, based on a custom array called the COGS chip, was a hugely successful exemplar of so-called "big science", and led to the GAME-ON initiative (*45*). Each consortium in GAME-ON still aims to expand the extent of collaboration. More recently, the International HundredK+ Cohorts Consortium (IHCC) was established in 2018. This consortium aims to create a global network for translational research that utilizes large cohorts to enhance understanding of the biological and genetic basis of disease and improve clinical care and population health (Table 2) (*46*).

In this trend to increasing scale, attention has focused on the uniqueness of research into other populations, beyond Caucasians in Europe and the United States, such as those of Asian and African descent. For example, a GWAS meta-analysis of pancreatic cancer identified a GP2 gene polymorphism which is prevalent only in East Asians (*47*), and it has become clear that new ones can be found by changing the population. This shows the importance of creating a framework for collaboration among research groups from countries that have not previously formed such consortia.

Also noteworthy is the subdivision of diseases. Risk factors - especially genomic factors - that take account of the characteristics of tumors are being investigated, such as driver mutations in the EGFR gene for lung cancer (*48,49*) and the presence or absence of estrogen receptors in breast cancer (*50*). The need for larger-scale research to carry out these activities is increasing, and this trend will continue in the future.

In summary, molecular and genome epidemiological studies have progressed over the past few decades and continue to gain in size and dimension. Although outside the scope of this review, the application of evidence from this area to prevention is still underway, and further effort is required.

Conclusion

In this review, we introduced recent trends in

Table 2. Participating cohorts of the International HundredK+ Cohorts Consortium (IHCC) (*https://ihccglobal.org/membercohorts*) (*46*)

Cohort Name	Country/Region
23 and Me	USA
45 and Up Study	Australia
Africa Health Research Institute (AHRI) Population Cohort	South Africa
Apolipoprotein MORtality RISk study (AMORIS)	Sweden
Biobank Japan	Japan
BioVU Vanderbilt	USA
California Teachers Study (CTS)	USA
Canadian Partnership for Tomorrow's Health (CanPath)	Canada
Cancer Prevention Study II (CPS-II)	USA
Cancer Prevention Study II Nutrition Cohort	USA
Children's Hospital of Philadelphia (CHOP) Biorepository	USA, Europe, South America, Canada, Saudi Arabia, Australia
China Kadoorie Biobank	China
China PEACE (Patient-centered Evaluative Assessment of Cardiac Events) Million Persons Project	China
Constances Project	France
Danish National Birth Cohort	Denmark
East London Genes and Health	UK
ELSA-Brasil	Brazil
Environmental influences on Child Health Outcomes (ECHO) Cohort	USA
EPIC (European Prospective Investigation into Cancer, Chronic Diseases, Nutrition and Lifestyle)	UK, Italy, France, Germany, Norway, Nether-lands, Denmark, Spain, Greece, Sweden
EpiHealth	Sweden
Estonian Genome Project	Estonia
Finnish Maternity Cohort Serum Bank	Finland
Geisinger Cohort - MyCode Community Health Initiative	USA
Generations Study (GS)	UK, England, Scotland, Wales, Northern Ireland, Isle of Man, Channel Islands
Genomics England / 100,000 Genomes Project	England
German National Cohort (NAKO)	Germany
Golestan Cohort Study	Iran
Healthy Nevada	USA
Israel Genome Project	Israel
Japan Public Health Center-based Prospective Study (JPHC)	Japan
Japan Public Health Center-based Prospective Study for the Next Gen-eration (JPHC-NEXT)	Japan
Kaiser Permanente Research Program on Genes, Environment, and Health	USA, California
Korea Biobank Project	Republic of Korea
Korean Cancer Prevention Study (KCPS-II Biobank)	Korea
Korean Genome and Epidemiology Study (KoGES)	South Korea, Vietnam, Cambodia, Japan, China
LifeGene (and sister cohort, EpiHealth)	Sweden
LIFEPATH (Lifecourse biological pathways underlying social differences in healthy aging)	Europe, Australian, USA
Malaysian Cohort	Malaysia
Maule Cohort (MAUCO Study)	Chile
Mexico City Prospective Study	Mexico
Million Veteran Program	USA
Million Women Study	England, Scotland
Multiethnic Cohort Study (MEC, NCI)	USA, Hawaii, California
Netherlands Twin Registry	Netherlands
Newfoundland 100K Genome Project/Sequence Bio	Canada, Province of Newfoundland and Labrador
NHS (Nurses' Health Study, NCI)	USA
NHSII (Nurses' Health Study II, NCI)	USA
NICCC	Israel
Northern Sweden Health and Disease Study	Sweden
Norwegian Family Based Life Course Study	Norway
Norwegian Mother and Child Cohort Study (MoBa)	Norway
Pakistan Genomic Resource (PGR)	Pakistan
PERSIAN Cohort Study	Iran
PLCO (Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial, NCI)	USA
Qatar Genome Project	Qatar
SAPRIN (South African Population Research Infrastructure Network)	South Africa
Saudi Human Genome Program	Saudi Arabia
Saudi National Biobank	Saudi Arabia
Shanghai Men and Women's Health Study (2 cohorts)	Shanghai, China
Singapore National Precision Medicine Program	Singapore
South(east) Asian Cohorts - NETWORK	Bangladesh, Malaysia, Sri Lanka
Taiwan Biobank	Taiwan
Trøndelag Health Study (HUNT)	Norway
U.S. Precision Medicine Initiative/All of Us	USA
UK Biobank	England, Scotland, Wales
UK Blood Donor Cohorts	UK
UKLWC (UK Collaborative Trial of Ovarian Cancer Screening) Longi-tudinal Women's Cohort UKLWC	England, Wales, Northern Ireland
Vorarlberg Health Monitoring and Promotion Programme (VHM&PP)	Austria
WHI (Women's Health Initiative)	USA

international collaborative research activities in the cancer epidemiology field in Japan. The field of cancer epidemiology has not only activated support for other countries where cancer statistics infrastructure is not well developed, but also large-scale compilation and international comparison through collaborative studies, and integration with analytical epidemiology and clinical research. Formation of international cohort consortia and estimates of cancer and risk factors in individual countries have not only contributed to improving the skills of cancer epidemiologists but also to expanding research networks and activities among them. Molecular and genome epidemiological studies on cancer have progressed over decades, and continue to do so in both size and dimension. Application of evidence from this area in prevention is still underway and requires further effort. Moving forward, Japanese epidemiologists have a major opportunity to take a leadership role in international collaborative research activities, especially in those focusing on major cancer types or exposure characteristics unique to the Japanese population.

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